

Good medical practice is based on the integration of in vivo and in vitro laboratory findings with a carefully performed history and physical examination. However, in some patients, diagnosis of allergic disease and recommendations for allergy injection treatment have been made by laboratories remote from the patient examination. This report describes a comparison of such approaches with usual medical practice in the same patients, as evaluated by highly respected observers.

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A prospective assessment of the remote practice of allergy: Comparison of the diagnosis of allergic disease and the recommendations for allergen immunotherapy by board-certified allergists and a laboratory performing in vitro assays

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The remote practice of allergy may be defined as diagnosing allergic disease, recommending therapy (including allergen immunotherapy), and providing allergen extract for immunotherapy in the absence of direct contact with the patient.¹ In the most common arrangement the referring physician, usually a nonallergist, submits a serum specimen to a laboratory accompanied by a completed form which is provided by the laboratory and contains information from the history and physical examination. The laboratory performs in vitro assays of total and allergen-specific IgE. On the basis of the results of these tests and the data provided on the patient information form, a diagnosis of allergy and specific recommendations for treatment are made by the laboratory. The recommendations to the referring physician include the specific components of an allergen extract for immunotherapy, if this form of treatment has been suggested.

It has been proposed that proper clinical interpretation of both in vitro and in vivo tests used for the diagnosis of allergy requires that a physician personally perform or supervise these tests and interpret the results in light of the patient's history and physical examination. Diagnostic procedures, either in vivo or in vitro, would then serve a confirmatory role in dictating appropriate environmental control, pharmacotherapy, immunotherapy, and other therapeutic procedures.¹ If this position is correct, then the remote evaluation and diagnosis of putative allergic disease and/or formulation of plans for treatment would not provide optimal patient care.

There has been, to our knowledge, no direct comparison of the results of patient evaluations made by direct physician contact with those made by a "remote practice" laboratory. The present study was designed to examine such a comparison.

SELECTION OF PHYSICIANS

Fourteen practicing allergists were selected on the basis of certification by the American Board of Allergy and Immunology and broad geographic distribution throughout the continental United States. The physicians were asked to participate in a study "designed to examine the accuracy of the IgE determinations made by *in vitro* laboratories related to the diagnosis and treatment of allergic diseases." The participating physicians

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were not informed of the total purpose of the study, which included comparison of specific diagnoses and therapeutic recommendations.

All who agreed to participate were asked: (1) to enroll 30 consecutive patients seen by them for evaluation of rhinitis and/or bronchial asthma, (2) to complete a form that asked for information regarding each patient's history, physical examination, diagnosis, and the allergist's recommendations for therapy, (3) to provide a copy of the patient's skin test record and a serum specimen. The protocol under which this study was conducted was approved by the Practice Standards Committee and the Executive Committee of the American Academy of Allergy and Immunology and the Institutional Review Board of the National Jewish Center for Immunology and Respiratory Medicine. Patients signed an approved volunteer agreement before completing the history form and donating blood.

SELECTION OF PATIENTS

From the 30 sets of patient data and serum specimens submitted by each participating allergist, sera from 10 patients were selected for submission to the participating laboratory. The sera to be tested were selected by one of the authors to represent a balance between the diagnoses of rhinitis and bronchial asthma and among positive prick, positive intradermal only, and negative skin test results. The same author extracted from the data provided by the allergist the necessary information required to complete the patient information form provided by the laboratory, which was sent with the accompanying serum sample.

SELECTION OF LABORATORY

Only one national laboratory (Roche Biomedical Laboratories, Raritan, N.J.) that would meet the operational definition of a "remote practice laboratory" could be identified. Specifically, the laboratory was required to provide an allergy diagnosis, as well as specific recommendations for immunotherapy, on the basis of a form containing information from the patient's history and physical examination, completed by the referring physician, and the analysis of a serum specimen for total and allergen-specific IgE. The laboratory was informed that a study comparing the results of skin testing by various allergists to the results of in vitro analysis of serum specimens from the same patients was underway.

IN VITRO METHOD AND INTERPRETATION OF RESULTS

The laboratory used a radioimmunoassay with allergen-coated discs. Initially, a multiallergen inhalant screen was performed against major seasonal and perennial allergens. If results of this screen were negative, no further tests were performed. If positive, a total IgE and 10 individual allergen-specific IgEs were assayed. This panel was common to all patients irrespective of history or geographic location. Most patients had further allergy tests, on the basis of history provided and region of residence. The following range of interpretations was provided:

1. If the inhalant screen was negative: "a negative result is strong evidence that the symptoms are not atopic in origin."
2. If RAST results were only class 1 and the history was not suggestive of allergic disease: "The patient appears to have little or no atopic problems." No immunotherapy prescriptions were provided for these patients.
3. If the patient had a positive history suggestive of allergy and confirmatory RAST results, but total IgE was within the normal range: "The patient's low atopic index indicates unpredictable results with injection therapy." A suggested immunotherapy prescription was provided.
4. If the history did not suggest a specific allergen as the cause of the symptoms, but RAST results were positive and total IgE elevated: "The patient is a likely candidate for immunotherapy if medication is not effective in maintaining seasonal symptom relief." This statement regarding "seasonal symptom relief" was used even when recommended allergens included or consisted only of perennial allergens.
5. When the history and the RAST for specific allergens correlated: "The patient is a probable candidate for immunotherapy."

For purposes of analysis the first two responses were not considered recommendations for immunotherapy, but the last three were, because suggested allergen immunotherapy prescriptions were provided.

In addition, the following modifications to the recommendations for immunotherapy were routinely provided by the in vitro laboratory. (1) "Positive animal/food allergens are usually not treated by injection and should be initially treated by avoidance." (2) "Foods and animal danders

are excluded from treatment sets unless specifically requested by ordering physician."

ANALYSIS OF RESULTS

Diagnosis

It was recognized at the initiation of the study that no "gold standard" was available by which to determine an "absolute" diagnosis of allergic disease and that recommendations for immunotherapy were even less susceptible to objective evaluation. Two of the authors (HSN, RR) established a working diagnosis for the presence or absence of allergic disease on the basis of three considerations. First, the subject must have a pattern of symptoms that would be explained by sensitivity to that allergen. Second, the subject must have exposure to that allergen. Third, the subject must be sensitive to the allergen as determined by skin or in vitro testing. In view of the disagreement as to the clinical significance of reactivity to intradermal tests after a negative prick test result, the diagnoses of allergy supported only by positive intradermal test results were listed separately. All evaluation forms from the participating allergists and the laboratory were reviewed. An overall assessment of the probability of an allergic component to the patient's condition was made and was compared with the assessments by the individual allergists and the laboratory performing the in vitro tests.

Immunotherapy

Each patient's history form was reviewed for the following items: (1) presence of perennial symptoms of rhinitis and/or asthma; (2) presence of seasonal symptoms of rhinitis and/or asthma (by month of occurrence); (3) history of frequent exposure to cats, dogs, or other indoor pets; and (4) complaint of increased symptoms in damp buildings. A list of "essential allergens for immunotherapy" was determined on the basis of evidence of significant immunologic sensitivity as indicated on the patient's skin test sheet either by a skin prick test reaction reported as at least 2 + or a wheal of at least 3 mm in diameter or an intradermal skin test reaction reported as 3 or 4 + or a wheal of at least 10 mm in diameter or by the laboratory report of a RAST class of II or greater. In addition, in the presence of perennial symptoms, house dust mite was considered significant only in geographic areas of prevalence, pets only if there was a history of frequent exposure, *Aspergillus* or *Penicillium* species only if there was a history of increased symptoms on exposure to

damp buildings. The relevant major aeroallergens for each season and for each region were determined with the use of standard references.^{2, 3} For these allergens to be significant, the patient's symptoms should have been increased above the perennial level during the season of exposure. On the basis of these criteria "critical allergens" were identified for each patient. This list was subsequently compared with the allergens recommended for immunotherapy by the allergists and those recommended by the laboratory to assess the completeness of the prescribed allergen extract. In assessing whether the recommended immunotherapy extract contained critical allergens, consideration was given to cross-reacting allergens. Thus because of extensive cross-allergenicity either *Dermatophagoides pteronyssinus* or *D. farinae* was considered adequate for treatment of house dust mite allergy, and commercial house dust extracts, which have been shown to contain large amounts of house dust mite and cat and dog allergens,⁴ were accepted as a substitute for these extracts. The same information was also used to determine the appropriateness of the recommendation for immunotherapy.

Statistical analysis

To a large extent this report is descriptive. However, when applicable, the results of the diagnostic tests, the diagnosis of the presence of allergy, and the recommendations for immunotherapy were compared by means of the McNemar symmetry chi square test. The completeness of the immunotherapy recommendations were compared by means of Yates' correction for continuity.

COMPARISON OF THE RESULTS OF SKIN TESTS AND RASTS

All 14 board-certified allergists agreed to participate; 12 submitted complete information and sera from 30 patients, and of these 360 specimens, 118 with the accompanying data forms were submitted to the laboratory performing in vitro assays.

At least one positive skin prick test result was present in 62 of 118 subjects (53%) as compared with 56 of 118 (47%) who had at least one positive class II or greater RAST result (Table I). Nine of the 12 allergists performed intradermal skin tests to some or all of the allergens, which had produced negative results on skin prick testing. There was at least one positive intradermal test result in 19 of those patients who did not have any positive

TABLE I. Comparison of skin prick test and in vitro test results

Allergists' skin test results	In vitro laboratory		
	Negative	Class 1	Class 2-4
Negative	32	2	3
ID only positive	18	0	1
Prick positive	9	1	52

For each patient the most positive skin test or RAST result for any allergen is recorded. The differences are not significant for skin prick tests versus class 2 or greater RAST results. For all skin tests and all classes of RAST, the number of subjects with positive skin test results is significantly greater ($p < 0.001$).

ID, Intradermal.

TABLE II. Number of patients with allergic disease diagnosed by allergists and laboratory

Protocol diagnosis	Allergists		In vitro laboratory	
	Allergic	Nonallergic	Allergic	Nonallergic
Allergic (prick or RAST)	56	2	50	8
Allergic (ID only)	8	1	3	6
Nonallergic	10	41	6	45
Total	74	44	59	59

Comparison of the number of patients in whom a diagnosis of allergic disease was made by the Board Certified Allergists and by the laboratory. Those in whom the diagnosis was based on the presence of only positive intradermal test results are listed separately from those in whom the diagnosis was supported by relevant positive prick skin tests or class 2 or greater RAST. Neither allergists nor laboratory differ significantly from the protocol diagnosis.

ID, Intradermal.

skin prick test results; in one of these 19 there was also a positive RAST result. Overall, there was good agreement between the results of the skin prick tests and RAST results of class II or greater. Fifty-two patients had negative reactions in both assays, and 52 had definitely positive results in both assays. Discordant results were encountered in only 12 patients. When intradermal test and class I RAST results were also considered, however, 27 patients had positive skin test and negative RAST results; five patients had positive RAST and negative skin test results, and the difference was significant ($p < 0.001$).

COMPARISON OF THE DIAGNOSIS OF CLINICAL ALLERGY

The agreement between the authors', the allergists', and the laboratory's assessment of the presence of an allergic component to the patients' rhinitis or asthma is shown in Table II. Overall, a diagnosis of allergy was made in 74 of 118 patients (63%) by the allergists and in 59 of 118 patients (50%) by the laboratory. The 59 patients who were diagnosed as allergic by the laboratory corresponded to the 56 who had at least one 2-4 + in

vitro test result and three subjects with only a 1 + test result who were deemed allergic on the basis of a fit between history and the test results. The higher number of patients diagnosed as allergic by the allergists reflects in part the greater number of positive skin test reactions when intradermal testing was performed. In a relatively small number of patients there was disagreement regarding the presence of allergy either between the allergists or the laboratory and the assessments made by the authors. Allergists differed in more often making a diagnosis of allergy, whereas the laboratory differed in less often making a diagnosis of allergy; however, neither difference was statistically significant.

RECOMMENDATIONS FOR IMMUNOTHERAPY

The laboratory recommended at least consideration of allergy immunotherapy for the 56 patients who had any class II or greater in vitro test results and for the three with class I reactions (Table III). The allergists, although they had made the diagnosis of allergy more frequently, recommended allergy immunotherapy for only 35

TABLE III. Comparison of recommendations for immunotherapy by allergists and laboratory

	Allergists	
	Yes	No
In vitro laboratory*		
Yes	28	31
No	7	52

*The laboratory recommended immunotherapy more often ($p < 0.001$).

patients. This represented 30% of all patients studied and 47% of those for whom they made a diagnosis of allergy. There were discordant recommendations in 38 patients, 32% of the total group, with the laboratory recommending immunotherapy in 31 patients in whom it was not recommended by allergists and the converse in seven patients. The difference between allergists' and laboratory recommendations was significant ($p < 0.001$).

INCLUSION OF CRITICAL ALLERGENS IN IMMUNOTHERAPY

The extent to which the critical allergens were contained in allergy immunotherapy recommendations is tabulated in Table IV. The larger number of agreements and nonagreements in the laboratory recommendations reflects their more frequent recommendation for immunotherapy. Overall, however, it is evident that the allergists more often included what had been selected as critical allergens by the authors. Allergists included all critical allergens in 28 of 35 (80%) of recommended extracts (Table V), whereas the laboratory included all critical allergens in only 29 of 59 (49%) of extracts ($p = 0.002$).

In a number of patients immunotherapy was recommended with extracts that did not contain any critical allergens. This was the case in two extracts containing house dust mite, which were recommended by allergists for treatment of perennial symptoms in patients who had intradermal wheal and flare reactions to house dust mite of less than 10 mm in diameter. The laboratory recommended eight allergen extracts, which were considered to be inappropriate. For seven patients they recommended treatment with an extract containing only one or more pollens; these patients had perennial symptoms and no seasonal exacerbation. In the other patient they recommended treatment with cat dander alone, although this patient denied frequent exposure to cats.

COMMENT

In this prospective study we have compared the results of allergy evaluations of 118 patients by a group of practicing board-certified allergists and a laboratory that performs in vitro tests and offers allergy diagnosis and recommendations for immunotherapy. Both the allergists and the laboratory were aware that they were participating in a study, but the full details were not discussed with either. It was particularly desired not to influence in any way the allergists' decision-making; therefore, to avoid any preselection bias, each allergist was asked to submit information and sera from 30 consecutive patients, and of these, only one third were actually employed for the study.

The allergists followed their normal practice patterns. They were supplied with a form requesting information regarding history, physical examination, skin test results, diagnosis, and therapeutic recommendations. Information for this form was obtained from their own individual records. No attempt was made to standardize the skin testing procedure among the participating allergists. The one laboratory that participated in the study had a preprinted form, which requested information regarding the history and physical examination. Obviously the in vitro test was performed in a similar fashion for all sera. In the initial stages of this study, attempts were made to find other laboratories that could participate, with the goal of including at least three. By the time the study was underway, no other laboratories that met the study criteria could be identified.

There were four components of this study in which the allergists and the laboratory could be compared. These were the results of skin tests and in vitro tests, the diagnosis of clinical allergic disease, the recommendations for immunotherapy, and the inclusion of specific allergens in the immunotherapy treatment.

Overall, there was fairly substantial agreement between the results of skin prick tests and RAST results of class II and greater (Table I). This finding was not unexpected because the results of various in vitro tests for IgE have been compared with results of skin prick testing, usually with good agreement.⁵ Skin prick testing with concentrated extracts is generally more sensitive than the results obtained by RAST, whereas intradermal testing is even more sensitive, although the clinical relevance of the degree of sensitization revealed by intradermal tests in the presence of negative skin prick test results has been questioned.⁶ This study confirms the approximately

TABLE IV. Comparison of inclusion of critical allergens in extracts for immunotherapy as recommended by allergists and laboratory

Skin tests included	Allergists		In vitro laboratory	
	Included	Not included	Included	Not included
Seasonal allergens				
Prick positive	68	2	77	47
ID only positive	11	0	7	7
Perennial allergens				
Prick positive	18	2	33	5
ID only positive	7	1	2	2

In determining whether critical allergens were included, credit was given for house dust mites if either *D. pteronyssinus* or *D. farinae* was included, and house dust extract was accepted as a substitute for house dust mite or dog or cat extract because it is known to contain all of these allergens in high concentration.

ID, Intradermal.

equal results of skin prick testing, as commonly practiced, and in vitro testing for eliciting evidence of IgE antibody.

The diagnosis of allergic disease was made more often by the allergists than by the laboratory, largely because of the greater sensitivity of intradermal skin tests used by the allergists. When the diagnosis was based on predetermined criteria prepared by the authors (which included clinical symptoms, evidence of exposure to a specific allergen, and the documentation of allergen-specific IgE), the diagnosis was made with a frequency intermediate between that of the allergists and the laboratory.

The laboratory made recommendations for immunotherapy more often than the allergists. It is perhaps in this area that the laboratory is at the greatest disadvantage. The laboratory's diagnosis is based on the history form and documentation of presence of allergen-specific IgE. What is lacking in any questionnaire is the ability to clarify answers or further explore areas suggested by the responses. Furthermore, although information was requested, it is not clear, as discussed below, to what extent this information was utilized. Any final clinical therapeutic decision requires discussion with patients in which alternative approaches such as use of medication and allergen avoidance are fully explored. All allergists use immunotherapy as part of their normal practice patterns. It was hard to provide more objective data regarding the specific reasons for allergists not recommending immunotherapy in those patients who had allergic symptoms and a diagnosis of IgE-mediated disease.

The problem with the questionnaire approach is further brought out when one looks at the recommendations for specific allergens to be in-

TABLE V. Adequacy of allergen prescription

	Allergists		In vitro laboratory	
	Included	Not included	Included	Not included
Complete	28	29		
Incomplete	5	22		
Inappropriate	2	8		
Not recommended	83	59		

Comparison of the number of recommended allergen extracts, which included all critical allergens. The difference between board certified allergists and the laboratory is significant ($p = 0.002$).

cluded in immunotherapy. The laboratory appears to have depended primarily on the results of antibody analysis, and in at least some instances information on the history forms was ignored. A notable example was the group of seven patients with a history of perennial rhinitis without seasonal exacerbation for whom the laboratory recommended an extract containing only pollens. In about 50% of the patients overall the recommendations for inclusion of specific allergens by the laboratory were either inappropriate or incomplete.

Although it would be desirable to compare the cost and outcome for the patients between the therapeutic approaches recommended by the allergists and the laboratory, this would be a monumental undertaking. Nevertheless, the results of this study suggest to us that the appropriate diagnosis and treatment of allergic disease is best done by a trained physician. Although the laboratory performing in vitro tests can provide reasonably good results for detection of allergen-specific IgE, this information alone or accompanied by an information form should not be used for therapeutic recommendations.

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