

Screening for IgE-Mediated Allergy

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Atopic allergy affects approximately one-third of people under 30 years of age who live in industrialized countries. It is also a problem in nonindustrialized countries, but its extent is less well documented. The most common diseases associated with atopy are asthma, rhinitis, and eczema, but other skin and even gastrointestinal complaints may also be atopic in nature. However, it has to be recognized that these diseases have nonatopic counterparts (i.e., IgE antibodies do not participate in their pathogenesis).

It is rare for allergic attack to prove fatal, but drugs, venoms, or foods can provoke anaphylactic reactions. However, allergy is usually incapacitating and results in considerable inconvenience due to lost time at work, school, and play. In the USA, 35 million people (17% of the population) are affected at a cost per annum of \$1.5 billion, and as a result 5 million working days are lost each year (1). Similar figures for probable direct and indirect costs are available from Europe and Japan. Moreover, recent surveys from all over the world conclude that more people are dying from asthma than 20 years ago. The remedy for this situation is not readily at hand, because the number of allergies requiring diagnosis and attention is much larger than the number of clinicians adequately trained in the subject. Consequently, the introduction of procedures that can be used by other clinicians as well as by allergists should help to reduce the burden of recognizing and diagnosing allergy. This is a worthwhile objective.

We discuss the importance of three screening procedures: clinical history taken by questionnaire and analyzed with computer assistance, serum total IgE, and the multiallergen screening tests for commonly inhaled allergens. A combination of all three tests is more powerful than any individual one, because each has its limitations.

Keywords: Atopy; Allergens; In vitro tests; IgE antibody; Total IgE; Clinical history; AlaTOP; Phadiatop; Medical computer diagnoses.

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Introduction

Why do we need allergy testing? Fatalities linked to allergic reactions are rare, but there is no doubt that the quality of life is often impaired (2). Even so, some

clinicians regard testing as unnecessary because, they argue, very little can be done to avoid allergens known to trigger allergic symptoms. Consequently, these clinicians rely on treating symptoms with drugs such as antihistamines, cromoglycate, and steroids, and if one proves inadequate they prescribe another. Fortunately, most clinicians appreciate that although drugs have their place, they are not the complete answer to the problem. Nobody wants a patient to take drugs for the foreseeable future if it can be avoided. An allergist will try to reduce the patient's symptoms and hence minimize the usage of drugs by identifying causative allergens. Exposure to some allergens can be reduced to subclinical amounts, while for others that can be difficult to avoid, like pollens, hyposensitization may reduce the requirement for drugs, if not completely then to an acceptable level.

When more than one severe adverse reaction has taken place, for example following a bee sting, or if the symptoms are seasonal, it is usually enough for an allergist to make a provisional diagnosis. However, in cases where there is no past history of such reactions, or if the symptoms are perennial, a provisional diagnosis cannot be made without more information. For example, it is often difficult to distinguish on clinical grounds between mold and mite allergies. Even patients who have been stung may be unsure whether it was by a bee or a wasp, and when a food allergy is known the allergen may be "hidden" in the recipe, e.g., peanut-fortified meats and sauces.

Skin-prick testing with extracts of allergens is commonly used by allergy specialists to confirm the clinical history. However, there are instances when skin testing is inappropriate. Most commonly these are either when introducing an allergen could provoke an anaphylactic response, or when the patient is taking a long-acting antihistamine that would inhibit any positive skin test. The usefulness of in vitro tests for allergen-specific IgE antibodies in these situations is obvious. In addition, in vitro tests are often used when there is a need to identify efficiently atopic patients who are not consulting an allergy specialist. This situation arises frequently because the number of allergies requiring diagnosis and attention is much larger than the number of clinicians adequately trained in the

subject. Such consultations might include visits to a general practitioner, an occupational health officer, an ear, nose and throat surgeon, or a dermatologist specializing in contact allergies. Usually the provision of sufficient volume of a specimen is no problem, but there are situations where only a small specimen sample is available. This can happen in research and epidemiological surveys and also when the specimen is a tear, nasal or bronchial secretion, or a blood stain. Multiallergen tests require only a small volume of specimen to establish whether it came from an atopic person. Our purpose is to discuss these and other allergy-screening tests that are available to clinicians who are not allergy specialists.

For the purpose of this discussion, we use the immunological definition of atopy as referring to a person who is readily triggered to produce IgE antibodies after inhalation of common environmental allergens (3,4). We are careful to use the term "atopy" in its immunological sense, because it can happen that some people are atopic but currently suffer no symptoms.

Screening tests

Clinical history taken by questionnaire and analyzed with computer assistance: This is a key feature of any allergy investigation, and we believe that a simple questionnaire should be completed whenever a blood sample is taken for analysis. The history synopsis will be useful both for guiding the laboratory investigations and for interpreting the results. It will not take much of the clinician's time as patients can usually complete the questionnaire unaided. This is feasible since most of them can describe their allergic symptoms and know when and where they occur. We recognized that the task of processing questionnaires is labor-intensive and so set about computerizing it (5,6). The program devised to score histories utilized a database of 1,500 patients who had answered a detailed questionnaire and whose total IgE level and IgE antibodies for 13 inhalant allergens (by radioallergosorbent test—Phadebas® RAST) had been determined. These patients were assigned into four groups according to their IgE antibody profiles: nonatopic, seasonal atopic, perennial atopic, and seasonal plus perennial atopic. Each questionnaire was analyzed to see how often the various answers (usually "yes," "no," or "don't know") slotted into each of the four groups. Algorithms were then constructed using Bayes theorem and approximately independent clusters (7). This enabled a patient's history to be scored according to the increasing probability of finding IgE antibodies in his or her serum. The program also used a set of rules, based on the knowledge of when and where allergens are found, to predict which allergens should be tested. When the probability scores for seasonal and

perennial atopies were high, the number of seasonal and perennial allergens cited for testing was increased to include the "less likely ones." The program was tested prospectively on a group of 554 patients, each of whom had answered the questionnaire, and had their total IgE and specific IgE levels measured as described above. More than 75% of seasonal histories were scored either as strongly positive or strongly negative, compared with about 40% of perennial histories (Fig. 1). Perennial history scores were evenly distributed through the probability rankings; this demonstrates how much easier it is to diagnose a seasonal allergy than a perennial one. Nevertheless, the predictive value of the probability scoring was almost as good for perennial as for seasonal histories (Fig. 2). We think this is because the program is able to accumulate a large number of small indicators into a positive history. The scoring of the clinical history is a diagnostic test, but its sensitivity and specificity will always be better when used in conjunction with an IgE antibody test to distinguish the atopic patients with symptoms similar to the nonatopic ones, e.g., in cases of perennial rhinitis.

Total IgE estimations: IgE differs from other immunoglobulins in being able to combine through its Fc region with high-avidity receptors on mast cells and basophils. It has the shortest half-life—2.5 days (8)—and circulates in the lowest concentration of any immunoglobulin. There is an international reference standard for total IgE, and immunoassay results are usually reported as kU/L where 1 unit is approximately 2.4×10^{-9} g (9). Circulating levels are raised in atopic allergy. The serum total IgE test is useful for completing the atopic picture, and we advocate its rou-

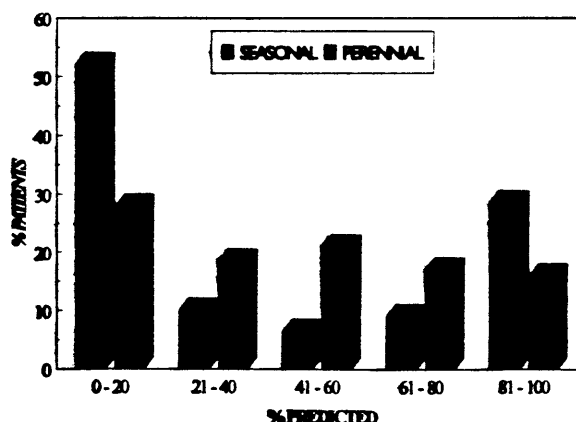


Fig. 1 Distribution of the results from 554 questionnaires among the history predictions for each 20% probability range made by the computer algorithms (5,6). The seasonal histories were predominantly clearly negative or positive. The perennial algorithm distributed the patients across the whole spectrum. This is because perennial histories are less clear-cut than seasonal ones.

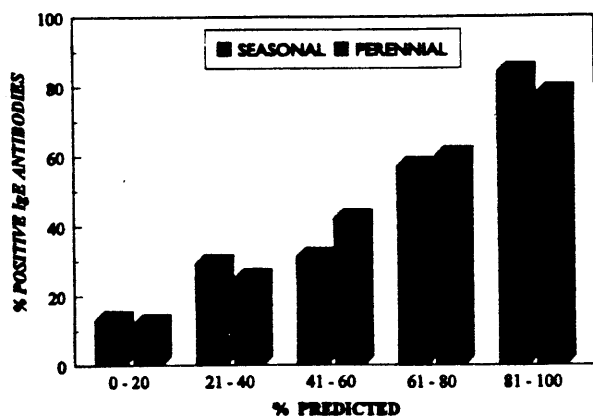


Fig. 2 Correlation between history predictions in each range of 20% probability scores and the percentage of patients with any positive IgE antibody test results. The seasonal and perennial history predictions correlate equally well with the positive RAST results to the corresponding seasonal and perennial allergens. This demonstrates that the perennial algorithm is able to cope successfully with the difficulties often encountered in trying to diagnose perennial allergies.

tine use. Normal values for nonatopic UK adults range from 1–180 kU/L with a geometric mean of 21 kU/L (10). The geometric mean for the nonatopic UK adults remains constant with age, although population surveys will show a decline after the age of 70 because of a decrease in the number of identifiable atopics (11). Yet it cannot be used as the only test to identify the atopic adult, because there is a large overlapping of the normal and atopic ranges. Thus some allergy-free patients have total IgE levels over 200 kU/L; this might be due to other diseases such as parasitoses, pemphigoid, Job-Buckley syndrome, Wiskott-Aldrich syndrome and, occasionally, Hodgkin's lymphoma. Other factors can increase circulating amounts of total IgE. Smokers have higher total IgE levels than nonsmokers (12–15), although this may be partially explained by the tendency of males to have higher total IgE levels than females (11,12,16). Similarly, race and myocardial infarctions (17) may affect total IgE levels. The reason that a small proportion of adult atopic patients have total IgE levels below 10 kU/L is unclear. Perhaps some such factor as auto-antibody is interfering in the test, or maybe most of the IgE is bound to cellular receptors.

However, there is justification for using total IgE to screen infants and young children for atopy, because it is only during these very early months that overlapping between nonatopics and atopics is minimal. IgE is synthesized in the fetus after 11 weeks (18) and although at birth levels are usually less than 1 kU/L, they rise steeply to normal nonatopic adult levels by about five years of age (19). There has been much written in the literature about the predictive

value of cord blood total IgE levels. Current opinion favors the view that the test cannot be used to predict which infants will become atopic in the future (20–22).

Nevertheless, we repeat that a knowledge of the total IgE level helps to complete the atopic picture. For example, a level over 200 kU/L is more likely to be associated with multiple atopies than is a normal level. Indeed, levels over 5,000 kU/L, which often occur in cases of severe atopic dermatitis, are a warning that artefactually high results may occur in allergen-specific IgE assays and so should be interpreted with caution. In contrast, levels less than 40 kU/L are most likely associated with nonatopics or atopics allergic to only one substance. A detailed study of 425 patients found that 212/275 atopics had a total IgE above 40 kU/L (a sensitivity of 77.1%) as did 79/150 nonatopics (a specificity of 47.3%) (23). Lowering the threshold below 40 kU/L will increase the sensitivity but reduce the specificity still further. Consequently, the total IgE test is best used in conjunction with one or more other screening tests.

Multiallergen-specific IgE antibody tests: This is a heterogeneous group and the allergenic reagents need segregating into (a) horizontal screens (e.g., grass/mite/cat) where allergens are obtained from disparate sources, and (b) vertical screens (e.g., mixed grasses or mixed animals) where the mixture is a convenient family group. We will limit the discussion to horizontal screens.

Tests for atopy using a horizontal mixture of different allergens: These tests will provide a YES/NO answer to the question, "Is this patient atopic?", but they do not diagnose allergy to particular allergens. The sensitivity and specificity of such tests are expected to be about 90%. These tests excel at screening an *unselected* population for atopy and so are best used in population surveys, research studies, and situations where only a very small volume of specimen is available. Note that the commercially available tests comprise only the commonly inhaled allergens—food is not included. Atopic children under three years old are more likely to produce IgE antibodies to food than to inhaled allergens, and so they are more likely to benefit from a vertical screen of mixed foods.

Originally, we reported (24) that a single multi-allergen test (the RAST atopy screen) using a mixture of timothy grass pollen, *D. pteronyssinus*, and cat epithelial extracts could identify in excess of 90% of the UK atopics. The catch-rate could have been increased by about 2% if a mold allergen had been included in the mixture (23). Selection of these allergens was based on the cluster analysis of Phadebas RAST results obtained from 267 atopic patients tested for IgE antibodies against 13 inhaled and 6 food allergens. The most significant cluster was for patients atopic only for grass pollen, while the ninth, and least significant,

cluster was for patients with positive results to all 19 allergens. The only cluster that did not include at least one of grass pollen, *D. pteronyssinus*, and cat epithelium was the mold-only one. While it was the second most significant cluster, only six patients were involved. We reasoned that to include a mixture of molds in the simple grass/mite/cat screen would have unnecessarily complicated the test for only a small gain in sensitivity. At that time, mold allergens were poorly characterized, and there was (and still is) the possibility that measurable but clinically irrelevant levels of IgE antibody to more than one allergen could accumulate into a positive result. In other words, two or three borderline results would translate into a positive one overall.

Other research groups followed this example by reporting the usefulness of a multiallergen test (25), and the first commercial test (Phadiatop®, Kabi-Pharmacia, Uppsala, Sweden) was released in 1985. Phadiatop has been subjected to a multilaboratory evaluation and shown to have both a mean sensitivity and a specificity performance of 90% (26). This means that when it is applied to a group of atopics, 90% of them will have a positive Phadiatop result (i.e., 90% sensitivity), and when applied to a population of nonatopics 90% of them will be Phadiatop-negative (i.e., 90% specificity). Unlike our original screen based on a particulate allergosorbent, Phadiatop uses paper discs and the number of allergenic sources is more than three. Although the manufacturer does not divulge how many or what allergens are attached to each paper disc, the composition is probably similar to the 12 allergens named by Diagnostic Products Corporation (Los Angeles, USA) in its multiallergen test called AlaTOP®, i.e., *D. pteronyssinus*, cat, dog, bermuda and timothy grass pollens, *Penicillium notatum*, *Alternaria tenuis*, birch and Japanese cedar tree pollens, common ragweed, English plantain and *Parietaria officinalis* pollens. We have found the Phadiatop to be a reliable, albeit expensive, atopy screening test (27), but one that is very labor-intensive, like all paper disc immunoassays. In a busy routine allergy testing laboratory, any simplification of the disc-based procedure is worthwhile; thus we have evaluated the specificity and sensitivity of the fluid-phase AlaTOP test as it can be automated and we know its component allergens. Its effectiveness as a screening test for atopy is compared with others.

Comparison of multiallergen-specific IgE antibody tests with other screening tests for atopy: clinical history scoring, determination of total serum IgE, RAST atopy screen, and skin-prick testing

Patient samples: Every month for a period of one year, serum samples from 4 men and 4 women referred

to the clinic with symptoms probably associated with atopic allergy were aliquotted and then frozen at -40°C. The cohort of 96 patients included 20 whose case history was weak but who were skin-prick test positive to at least one commonly inhaled allergen. Ages ranged from 7 to 79 years with a median of 32 for men and 34 for women. A further 4 sera from patients known to have circulating IgE antibodies only to molds were added, increasing the total number of patients investigated to 100.

Clinical history: The 100 patients completed the detailed allergy questionnaire, and their seasonal and perennial symptom scores were calculated using an "expert" computer program for evaluating and scoring clinical histories (6). A probability score of at least 50% was taken as a positive result. Any histories that produced a "Contradiction score" over 0% or "Blank" and "Don't know" scores above 15% excluded the patients from this comparison study.

Total and specific IgE antibody tests: All sera were analyzed with DPC AlaSTAT total IgE and Phadebas RAST-specific IgE tests for IgE antibodies reacting with timothy grass pollen, *D. pteronyssinus*, and cat epithelium. In addition, if the total serum IgE level exceeded 20 kU/L, RAST was performed with mixed molds, birch tree pollen, and dog dander. Other allergens suggested by the patient's clinical history were tested if the total IgE exceeded 180 kU/L. Patients were considered to be probably atopic when at least one of their RAST scores to an inhalant was classed as 2 or more (i.e., in excess of 0.7 Phadebas RAST Units (PRU)/mL). This criterion was relaxed to a score of 1 (i.e., in excess of 0.35 PRU/mL) in cases whose only positive result was for a mold.

Skin-prick testing: 96 patients were skin-prick tested with a panel of 35 inhalant and food allergenic extracts (Dome Hollister-Stier, Washington, USA). A positive result was taken as a weal diameter of at least 3 mm for inhalants and 5 mm for foods. Four patients were not tested because they were taking long-acting antihistamines; all four were positive by RAST.

Multiallergen screening tests: Sera were analyzed using the two multiallergen IgE antibody tests: AlaTOP and Phadiatop.

AlaTOP was performed in a manner similar to the AlaSTAT-specific IgE test (vide McSharry and McKay in this volume). Briefly, the biotin-labelled multiallergen reagent (200 µL) was incubated with 50 µL of test serum for 1 hour in a tube coated with biotinylated human serum albumin. Any allergen-specific antibodies of any isotype, IgG as well as IgE, complexed with multiallergen were linked to the tube by adding streptavidin (50 µL) and incubating for 1 more hour. After washing twice with buffer, any immobilized IgE antibodies were tagged with horseradish peroxidase-labelled anti-IgE (200 µL). One hour later,

after thorough washing, the peroxidase substrate was added and the endpoint absorbance determined. Results were compared with those obtained using a threshold reference serum: higher (or equal) values were interpreted as being from an atopic, lower ones as from a nonatopic. For quality control, a positive serum is included with the test kit.

The Phadiatop test was executed in a manner similar to Phadebas RAST. Briefly, the multiallergen disk was incubated with 50 μ L of test serum for 3 hours. After washing three times with RAST buffer, the disk was incubated overnight with 50 μ L of ^{125} I-anti-IgE; any radioactivity associated with it after thorough washing was measured in a gamma counter. The results were expressed, like AlaTOP, by comparing the responses with those obtained using a threshold reference serum.

Definitions

Atopy: Probable atopics were those found by Phadebas RAST to have serum IgE antibodies to either grass, *D. pteronyssinus*, cat, dog, birch, or mold. They were confirmed as definitely atopic if they also had a positive clinical history and a total IgE of at least 40 kU/L.

The *specificity* of a test refers to its performance with a disease-free (i.e., nonatopic in this context) population. For example, a specificity of 90% means that 10% of the healthy population tested as positive. Likewise, *sensitivity* is defined as the percentage of a diseased (i.e., atopic) population whose test results are positive. Specificity is a measure of the percentage of tests that are truly negative, while sensitivity measures the truly positive ones.

Results

Multiallergen tests: 86 patients were classified as probably atopic, leaving 14 probable nonatopics. Among the probably nonatopic and atopic, the specificity and sensitivity of these were calculated as 64.3%

and 97.7%, respectively, for AlaTOP and 78.6% and 95.4% for Phadiatop (Table 1). Of these 100 patients' sera, 95 (95.0%) produced AlaTOP results that were concordant with Phadiatop. Discordant results were split between four sera that were AlaTOP-positive/Phadiatop-negative and one serum with the reverse result. All of the four sera that were AlaTOP-positive but Phadiatop-negative were skin-prick test positive, two had total IgE levels above 40 kU/L, and two had positive clinical histories. The other discordant case (AlaTOP-negative/Phadiatop-positive) was also skin-prick test positive and had a total IgE level over 40 kU/L but a negative clinical history. Two of the five discordant sera were mold-only positives by RAST; both were positive by AlaTOP but negative with Phadiatop.

When applying the criteria for definite atopy, the number of atopics was reduced from 86 to 64. This increased the sensitivities for AlaTOP and Phadiatop to 100% and 98.4%, respectively (Table 2). Both of the two definitely nonatopic cases gave negative AlaTOP and Phadiatop results.

Skin-prick testing: Four patients could not be skin-tested because of the risk of aggravating their symptoms, but the remaining 96 were tested with a panel of 35 allergens and 87 gave at least one positive result. Of these 87 patients, 82 were classified as probably and 60 as definitely atopic. All the patients classified as probably and definitely atopic were positive by skin testing. Among the probably and definitely nonatopics there were no positive skin tests. Had we chosen a positive skin test to be the criterion of atopy, the sensitivity of AlaTOP and Phadiatop would have been 97.9% and 95.8%, respectively, while the specificities would have been 100% for both tests. Again using this criterion, the Phadebas RAST screen was actually less sensitive (94.3%) than the multiallergen tests.

Total serum IgE: Among the 86 probable atopics, 79 sera were found to have total IgE levels of at least

TABLE 1 Specificity and sensitivity performance determined for two multiallergen tests (AlaTOP and Phadiatop), a total IgE test, and a computer-assisted clinical history test on 100 patients categorized after testing with 6 Phadebas RAST allergens as either probably atopic ($N = 86$) or probably nonatopic. Probably atopic patients all had RAST scores of at least "2" versus any of timothy grass pollen, *D. pteronyssinus*, cat epithelium, dog dander, birch tree pollen, or at least "1" versus a mold mixture (*Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, and *Alternaria tenuis*). The probably nonatopics had RAST scores of "0" or "1" versus all allergens except the mold mix for which they had a "0" score. By definition the RAST panel test has a specificity and sensitivity of 100%

Test	Nonatopics ($N = 14$)		Atopics ($N = 86$)	
	Number of false positives	% Specificity	Number of false negatives	% Sensitivity
AlaTOP	5	64.3	2	97.7
Phadiatop	3	78.6	4	95.4
Total IgE	11	21.4	7	91.9
History	6	57.1	17	80.2

TABLE 2 Specificity and sensitivity performance determined for two multiallergen tests (AlaTOP and Phadiatop) on 66 patients categorized as definitely atopic ($N = 64$) or definitely nonatopic after testing with 6 Phadebas RAST allergens, a total IgE estimation, and clinical history scoring. Definitely atopic patients all had a total IgE of at least 40 kU/L, a clinical history probability score of at least 50%, and RAST scores of "2" or more versus any of timothy grass pollen, *D. pteronyssinus*, cat epithelium, dog dander, birch tree pollen, or at least "1" versus a mold mixture (*Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, and *Alternaria tenuis*). The definitely nonatopics had total IgE levels below 40 kU/L, clinical history probability scores below 50%, and RAST scores of "0" or "1" versus all allergens except the mold mix, for which they had a "0" score

Test	Nonatopics ($N = 2$)		Atopics ($N = 64$)	
	Number of false positives	% Specificity	Number of true positives	% Sensitivity
AlaTOP	0	100	64	100
Phadiatop	0	100	63	98.4

40 kU/L and so total IgE produced a sensitivity of 91.9%. Among the 14 probable nonatopics, the specificity was 21.4%. By definition, the specificity and sensitivity values for the 64 definite atopics and the 2 definite nonatopics was of course 100%. The test procedure was controlled using high (200 kU/L), medium (80 kU/L), and normal (24 kU/L) control sera, and the between-assay coefficients of variation were 6.3, 4.3, and 5.8%, respectively.

Clinical history: The clinical history predicted a better than 50% probability of seasonal or perennial atopic allergy in 69/86 probably atopic cases—a sensitivity of 80.2%. Specificity was determined to be 57.1%.

Testing AlaTOP performance with monospecific sera: Several patients' sera were monospecific for timothy grass pollen ($n = 10$) and *D. pteronyssinus* ($n = 20$) by Phadebas RAST. Four sera were RAST-positive only to mixed molds. AlaTOP was positive to all the timothy grass-only atopics, as was Phadiatop (100% sensitivity for both tests). Among the *D. pteronyssinus*-only atopics, 20 were AlaTOP-positive (sensitivity = 100%) and 18 were also Phadiatop-positive (sensitivity = 90%). Taking all 4 mold-only atopics, 3 (75%) were positive by AlaTOP and 1 (25%) by Phadiatop.

Discussion

It is estimated that about 30% of the populations in industrialized countries suffers from symptoms associated with atopic allergy. Furthermore, the incidence appears to be increasing, although whether this is a worldwide phenomenon or merely due to better diagnoses is not entirely clear. In this type of study, it is necessary to have a clear understanding of what is meant by atopic allergy. Allergens are antigens that can be so deposited in the upper airways as to provoke an immediate hypersensitivity reaction. The atopic state is characterized by the ready ability to mount an IgE response against minute quantities of these allergens, and symptoms may be initiated after allergens

interact with specific IgE antibodies strongly bound to mucosal mast cells. However, these symptoms can have nonallergic counterparts, and it is desirable to differentiate one form from the other. For example, the ear, nose and throat surgeon needs to know whether to treat or operate on the patient who is suffering with atopic or nonatopic rhinitis. Unfortunately, there is no single test that can be used as a "gold standard" for atopic allergy. Even bronchial challenge with allergen, regarded by some as the ultimate test for allergic asthma, does not strictly mimic natural exposure, because of the relatively larger doses of allergen administered in the clinic. Furthermore, other allergens normally encountered at home may be missing from the clinic.

For these reasons, we have concentrated on the immunological definition of atopy by identifying serum IgE antibodies using either Phadebas RAST alone to identify the "probable atopics," or together with raised total serum IgE levels and case histories to classify the "definite atopics." Both sets of criteria have been used to evaluate the usefulness of two commercial multiallergen tests—AlaTOP and Phadiatop—in identifying the atopic individual. These tests employ mixtures of commonly inhaled allergens to identify the atopic state, not the specific allergy. They aim to provide all clinicians with a "Yes" or "No" answer to the question, "Is this an atopic patient?" Neither test will, nor claims to, identify those subjects who are allergic only to (a) foods, (b) uncommonly inhaled allergens (e.g., anhydrides, isocyanates), or (c) allergens administered parenterally (e.g., drugs, venoms).

It is straightforward to screen 100 sera in 4 hours with AlaTOP, but technical expertise is required. This means that both AlaTOP and Phadiatop tests are more suited to the laboratory than the doctor's office. Phadiatop requires an overnight incubation and its paper disc allergosorbent requires very careful washing at two separate stages in the assay procedure. Both tests can be semiautomated, but it is more difficult for a robot to handle a solid-phase than a liquid-phase aller-

gosorbent. It seems likely that the simplicity of the AlaTOP fluid-phase procedure will render it more acceptable in the routine laboratory than the more cumbersome solid-phase procedures.

Sera were obtained from 100 patients over a 12-month period so there is unlikely to be any dominance of one particular seasonal allergen. Most patients were adults, but four children aged less than 10 years were included. All these children were classified as "definite atopics" and gave positive AlaTOP and Phadiatop results. The sensitivities found for both tests were virtually identical no matter whether they were calculated for the "probable atopics" or "definite atopics." AlaTOP and Phadiatop had similar specificities (100% and 98.4%) for the "definite atopics," and AlaTOP also classified a few more of the "probable atopics" as atopic—a specificity of 97.7% versus 95.4%. Perhaps surprisingly, AlaTOP scored more of the probable atopics as positive than did Phadiatop. We had anticipated the reverse because the allergenic material manufactured for Phadebas RAST was also likely to be used in Phadiatop. This may reflect the difficulty of ensuring that a representative sample of allergens is attached to the Phadiatop solid phase. This is an inevitable consideration that has to be given to any formulation of a multiallergen reagent. Attaching a mixture of allergens to an insoluble support is technically demanding, because once the linking reaction has been performed there is no chance to bolster the mixture with an underrepresented component. This is not a problem with a liquid reagent because each individual allergen can be titrated before preparing the final mixture. Another concern is whether an accumulation of IgE antibodies will produce a positive result, even though individually each would have been classified as negative. From our results, and others (27), it is evident that both AlaTOP and Phadiatop are multiallergen tests that can be used to screen the UK population. AlaTOP performed marginally better than Phadiatop, and because we know it contains the common allergens found in lands with climates different from that prevalent in the UK, it is reasonable to expect that it will perform just as well in those countries. Phadiatop is also marketed worldwide, but we believe it is a mistake for the manufacturer not to divulge the composition of this product.

A proportion of our sera were monospecific for grass pollen and for *D. pteronyssinus*, and these allowed us to show that allergens from these sources were adequately represented on the allergosorbent used in both tests. However, AlaTOP was better than Phadiatop at identifying those rare patients atopic only for molds. We think that if mold atopy alone is suspected, it would be better to use a more sensitive test than Phadiatop to identify this relatively rare cluster of patients. In the small number of mold-only patients

tested, three of the four were positive by AlaTOP compared with only one of the four by Phadiatop. Both multiallergen tests, AlaTOP and Phadiatop, function better than the grass/mite/cat screen because they have the possibility to detect atopics in the mold cluster group, whose members by definition have no IgE antibodies to grass, mite, or cat antigens.

Both AlaTOP and Phadiatop tests were better discriminators of the atopic state than case history alone. We expect case history to be relatively nonspecific because atopics and nonatopics express similar symptoms (28). Again, history was less sensitive (80.2%) than AlaTOP (97.7%). Clearly, not every atopic is symptomatic, probably because some people had long outgrown their symptoms or have yet to experience them.

In our clinic population, the total IgE was more sensitive (91.2%) than it would be in a less highly selected group. However, it was also much less specific. This was expected as total IgE can be elevated in parasitoses and any other disease where there is an immune dysfunction. It is interesting to note that when we investigated 85 cases of unexplained high total serum IgE levels, 15 showed evidence of sensitization to the dog parasite *Toxocara canis* (unpublished data from our laboratory). Additionally, several authors have reported an elevation of total IgE in nonatopic smokers, and there may even be a disturbance of the IgE regulation after viral or bacterial infections. Consequently, the total IgE, except for infants, will not identify the atopic as well as a multiallergen IgE test. However, it is still very helpful in "filling in" the picture, interpreting specific IgE results, and gauging the number of specific IgE tests that may be required.

The atopic person can produce both positive RAST and skin-prick test results as evidence of sensitization. However, these need not be associated with current symptoms, so it is essential that multiallergen test results be interpreted together with clinical histories. For example, the clinical history may strongly indicate some source of allergen not represented by the multiallergen test; that could be a food (especially important in infants and young children), venom, drug, or an allergen only encountered in a factory. On the other hand, the history could be so complex as to indicate that many different allergens are relevant and a significantly raised total serum IgE would support this indication. The total serum IgE is a test whose main use is still as an aid to determine the scale on which a search for IgE antibodies should be mounted—the more elevated the value, the greater is likely to be the variety of IgE antibodies encountered. Consequently, we believe that the multiallergen test should be substituted for the grass/mite/cat-RAST in the screening system, rather than as a replacement for both this and the total IgE and history tests.

Conclusions

A key feature of any allergy investigation is taking the clinical history. This is usually very time-consuming. Most doctors' offices are now equipped with computer systems, and the possibility exists of using them to take and to score a clinical history. There are examples, including allergy, where "expert programs" based on a set of rules and invoking probability theory are utilized (6). We recognize that this is worthy of further investigation and believe that a simple questionnaire should be completed whenever blood is taken for analysis.

There is often a need to screen patients efficiently for atopic allergy when these patients are not consulting an allergy specialist. Such instances might include visits to a general practitioner, occupational health officer, ear, nose and throat surgeon, or a dermatologist specializing in contact allergies. Other examples might include those cases when only a small sample specimen is available, as often happens in infants or tear, nasal and bronchial secretions, or even the blood stains processed by forensic laboratories. On occasion, an allergy specialist may prefer to use an atopy screening test because there is usually no point in conducting an extensive allergy investigation when the patient is a nonatopic.

The multiallergen screening tests produce reliable results. AlaTOP was simpler to perform than Phadi-atop and so is easier to automate. When compared to the more conventional RAST atopy screening test for grass, mite, and IgE antibodies, the multiallergen tests produced similar results, except in those rare instances of patients who were RAST-positive only for molds, where the multiallergen tests were decidedly superior. The multiallergen tests contain only inhalant allergens and thus cannot be used for screening infants and very young children whose IgE response, if any, is probably limited to foods. However, they should prove much less costly than screening with a large panel of allergens by RAST, a procedure already shown to be most unrewarding (29), but in countries where there is a small number of screening allergens, e.g., grass, mite, and cat in the UK, testing for these only is likely to be more cost-effective if marginally less efficient. When used in conjunction with a clinical history and a total IgE estimation, the multiallergen test involving a horizontal spread of allergens can provide sufficient information for the nonspecialist to decide whether to refer the patient to an allergist. Should a referral be made, this spread of basic information will save the allergist considerable time and effort in deciding upon the correct course of treatment.

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