
Efficacy of a single diagnostic test for sensitization to common inhalant allergens

P. Brock Williams, PhD*†; Charles Siegel, MD‡; and Jay Portnoy, MD*

Background: UniCAP Phadiatop is a single laboratory test designed to determine the presence or absence of specific IgE to a variety of common inhalants. Its purpose is to aid in the differentiation of patients with symptoms attributable to allergic disease from other common causes.

Methods: Consecutive children and adolescent patients (n = 145) at two centers were examined by having their history and physical examination performed by two board certified allergists. Their conclusions along with skin prick tests and specific IgE measurements regarding seven common inhalants (mite, oak, ragweed, grass, dog, cat, *Alternaria*) were compared with UniCAP Phadiatop test results. This was done using concordance of all test results. Attempts to resolve test discrepancies, when found, included specific RAST inhibitions, total IgE values, and physicians' judgment after testing.

Results: All patients with resolved diagnoses (143 of 145, 103 positive and 40 negative) were identified correctly by the UniCAP Phadiatop test. Skin test results and specific IgE measurements correlated well, but neither correlated well with the history by itself, suggesting a minimal false-positive component of the history of 23%. UniCAP Phadiatop results demonstrated a quantitative relationship between the patient's score and the amount of IgE specific to these individual allergens.

Conclusions: The UniCAP Phadiatop test was shown to be highly sensitive and specific in differentiating individuals who are sensitized to common inhalants from those who are not. This test is recommended to all physicians as an aid in diagnostic and referral decisions for patients suspected of having an inhalant allergic diathesis.

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INTRODUCTION

Allergy symptoms, defined as clinical history compatible with an inhalant allergic diathesis, are common and can arise from a wide variety of different causes and mechanisms.¹ Defining an allergic mechanism rests with the identification of specific IgE antibodies to relevant inhalant allergens.² This can be accomplished by laboratory tests for circulating specific IgE antibodies or by the application of skin test challenge procedures which are believed to be dependent upon the presence of tis-

sue-fixed specific IgE antibodies.³ The choice of relevant test procedures is a difficult decision, particularly in a primary care setting where many of these patients are now first seen.

Individuals with symptoms upon exposure to inhalants usually produce specific IgE antibodies to at least one allergen, but more often the constitution of their disease results in the production of these antibodies to multiple inhalants.⁴ Because of this, a few select tests for specific IgE antibodies can differentiate most inhalant-sensitized individuals from those who are not.⁵ As a practical approach to the identification of sensitized individuals, one could construct a single test designed to collectively detect IgE specific to several of these common allergens simultaneously. The ideal choice of allergens for such a test would be guided by the cumulative frequency of sensi-

tizations in a large population of atopic individuals that would ideally result in 100% of them being identified.

The Phadiatop test was developed for this purpose, and numerous studies have attested to its performance.⁶ In this report, we have analyzed the ability of this test performed with a new technological format (UniCAP) to correctly identify inhalant-sensitive individuals in terms of clinical sensitivity and specificity. Parameters compared include results from serologic tests for specific IgE antibodies, individual skin prick challenge tests, total serum IgE measurements, and individual case histories performed by board certified allergists. Realizing that there is a certain subjectivity with the case history and skin testing, and that there are difficulties in identifying a true gold standard in this field, a method of categorizing patients for the determination of the UniCAP Phadiatop test's performance using concordance of the results from the different investigational tools was developed. In addition, we have also examined the quantitative aspects of the UniCAP Phadiatop test to determine whether the degree of positivity would enhance its usefulness for recommending further testing and referral options.

METHODS AND MATERIALS

Patients

One hundred fifty-two consensual consecutive children and adolescent patients seeking a board certified allergist's help from a university-based allergy training program (site I) and from a private practice (site II) were studied. Ages ranged from 6 to 18 years with an arithmetic mean of 11 (SD = 3), with 46.6% female and 53.4% male. Of the patients, 74% were Caucasian, 19% African-American,

* University of Missouri Medical School, Kansas City, MO.

† IBT Reference Laboratory, Lenexa, KS.

‡ Gladstone, MO.

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Table 1. Patient Demographics

	Number	Age (Range)	Female/Male	Caucasian/Other
Site I	n = 84	10 (6–16) SD = 3	35/49 (41.7%)	51/33 (60.7%)
Site II	n = 61	11 (6–18) SD = 4	33/28 (54.1%)	58/3 (95.1%)
Total	n = 145	11 (6–18) SD = 3	68/77 (46.9%)	109/36 (75.2%)

and 6.2% other races. Site I recruited 88 patients, 53 of whom were Caucasian and 35 of other races (mostly African-American, 29). Site II recruited 64 patients, 60 of whom were Caucasian and 4 of other races (African-American, 1). The demographics are reported out by site and additively because it was probable that we were dealing with two populations differing in ethnicity and, probably, social status (Table 1). Because of incomplete skin testing data, four patients from site I and three from site II were excluded from the analysis, resulting in a total of 145 patients analyzed.

History and Physical Examination (HPE)

A careful history and physical examination (HPE) was performed on each patient. This resulted in the allergist's conclusion without the benefit of test results as to whether the subjects were sensitive (positive) or not sensitive (negative) to each of seven common inhalant allergens (*Dermatophagoides farinae*, House dust mite <d2>; *Quercus alba*, white oak <t7>; *Ambrosia elatior*, common ragweed <w1>; *Phleum pratense*, timothy grass <g6>; *Felix domesticus*, cat dander <e1>; *Canis canis*, dog dander <e5>; and *Alternaria alternata*, alternaria <m6>). If a conclusion could not be reached from the HPE, patients were judged as indeterminate by the physicians for sensitivity to a particular allergen. The allergists were again allowed to judge the allergic status of each subject to the study allergens after the review of skin test challenge results. The first conclusion is referred to as the preliminary HPE and the second as the final HPE conclusion. This was done to enable us to compare test results with clinical impressions and to judge separately their influence upon the final diagnosis.

Skin Testing Procedures

Skin prick testing (SPT) with commercial extracts of the above allergens was performed using the routine procedure for each site. Site I used allergen extracts in 50% glycerin (Bayer, Spokane WA), the Dermapik device (Greer Laboratories, Lenoir, NC), histamine base (1 mg/mL), and codeine phosphate (40, 20, 10, and 5 mg/mL) as positive controls and 50% glycerosaline for negative controls. Site II used aqueous allergen extracts (Bayer), Morrow-Brown needles (Bayer) for skin testing, histamine base (1mg/mL; Center Laboratories, Port Washington, NY) for positive controls and saline for negative controls. The allergist's judgment was used to determine whether a skin test result was positive or negative. The average wheal and erythema for tests considered positive for both sites was 11.6 mm and 29.2 mm in diameter respectively.

Laboratory Measurements of Specific IgE and Total IgE

Serologic testing (IVT) for specific IgE and total IgE was performed at IBT Reference Laboratory (Lenexa, KS) using UniCAP technology according to the manufacturer's recommendations (Pharmacia & Upjohn Diagnostics, Kalamazoo, MI). UniCAP Phadiatop tests were performed using the same technology at Pharmacia & Upjohn Diagnostics (Uppsala, Sweden). All laboratory tests were performed on serum samples obtained by venipuncture before skin testing and were blinded to the clinical impressions, skin test results, and previous serologic results. Serum samples were stored frozen at -70° until the time of assay. The cut-off for positivity for the specific IgE assays was 0.35 kU_A/L, where 1 U of IgE = 2.42 ng of the World Health Organization IgE stan-

dard 75/502. The cut-off for UniCAP Phadiatop was determined by comparison to the response of a reference serum. The published cut-off for total IgE for this age group is currently 60 kU/L.^{7,8} Samples had undergone one additional freeze-thaw cycle before performing the Phadiatop test.

Specific IgE inhibition assays were performed on relevant samples that had significant positive serologic tests and negative skin tests.⁹ This consisted of comparing the response of incubating equal aliquots of buffer or three dilutions (1/2000, 1/200, and 1/20 wt/vol) of the appropriate allergen extract with the serum 2 hours before assay. A positive inhibition result was defined as dose-response inhibition reaching > 90% inhibition with proper control values. A heterologous non-cross-reacting allergen extract was used in the same manner as a negative inhibition control in each instance.

Data Analysis

Diagnoses were made using all available information from the HPE, SPT, and IVT results. Patients were first placed into four categories depending upon their concordance or disagreement of test results and our ability to resolve these differences. Patients were classified as positive for atopy if they had at least one of the seven allergens determined to be positive by the preliminary HPE, SPT, and IVT and negative if all test results and the history were negative. When these parameters were in agreement, these patients were placed in category I as unambiguous positive or negative diagnoses for atopy (Table 2). When the HPE disagreed with both the SPT and IVT results that were in concordance, these patients were placed in category II (Table 2). When the preliminary HPE was judged positive and all the IVTs and SPTs were negative, a false-positive history for atopy was designated. When the preliminary HPE was judged negative and the patient had both positive SPT and IVT results, a false-negative history for atopy was designated. Patients placed in category III included those with indeterminate

Table 2. Cumulative Number of Patients by Category

	Category I (n = 96)		Category II (n = 28)		Category III (n = 12)		Category IV (n = 7)		Category V (n = 2)	
	+	-	+	-	+	-	+	-	+	-
Site I	53 (0) ^a	4 (0)	55 (2)	20 (16)	59 (4)	23 (3)	60 (1)	23 (0)	61 (1)	23 (0)
Site II	39 (0)	0 (0)	39 (0)	10 (10)	41 (2)	13 (3)	43 (2)	17 (4)	43 (0)	18 (1)
Total	92 (0)	4 (0)	94 (2)	30 (26)	100 (6)	36 (6)	103 (3)	40 (4)	104 (1)	41 (1)
UniCAP Phadiatop	92 (0)	4 (0)	94 (2)	30 (26)	100 (6)	36(6)	103 (3)	40 (4)	104 (1)	41 (1)

Category I = Unambiguous, all tests agree; Category II = History disagrees with test results which agree with each other; Category III = Indeterminate history with tests that agree; Category IV = Tests disagree but resolved; Category V = Unresolved patients.

^a Numbers in parentheses represent actual number of changed diagnoses as a result of the categorization procedure.

HPEs and were judged positive or negative for atopy if both the SPT and IVT results agreed (Table 2). Category IV and V patients were those who had test result disagreements between the SPT and IVT regardless of the HPE judgment. Some of these cases were resolved using allergen-specific inhibitions when the IVT was positive. When the SPT test was positive in lieu of a negative IVT, a decision whether to call this a positive or false-positive SPT was made according to the physician's final history with reference to total IgE values (Table 2). To be conservative, values of total IgE below 10 kU/L were considered likely to be nonatopic. Those patients whose diagnoses could not be resolved from the information available were placed in category V.

Clinical sensitivity and specificity of the UniCAP Phadiatop test were calculated using the percentage of True Positives/True Positives + False Negatives and True Negatives/True Negatives + False Positives, respectively, for each class of patient after the above decisions had been made. Overall clinical sensitivity and specificity was determined using the resolved final diagnosis. Cumulative frequencies of sensitizations in positive patients were determined by ranking the allergens in decreasing order of the frequency of IVT positives for the total population. Quantitative aspects of UniCAP Phadiatop were examined by summing the quantity of specific IgE detected in each patient to these seven allergens and comparing this to the UniCAP Phadiatop raw score.

RESULTS

The dominating symptoms in these patients were rhinitis and/or conjunctivitis (98.7%) and asthma (58.6%). The frequency of atopic dermatitis was 7.2%; 6.6% complained of urticaria; and 1.3% had gastrointestinal symptoms. A number of the patients (7.2%) reported other symptoms (such as headache), sometimes attributed to allergic causes. The most frequently reported triggering factors determined by history were grasses (15.8%), infection (12.2%), smoke (11.9%), cat (11.3%), exercise (10.4%), trees (7.7%), house dust mite (7.1%), weeds (6.3%), dog (3.9%), and perfumes (2.4%).

The original diagnosis by HPE without knowledge of test results judged 125 of 145 (86.2%) of these patients to be atopic, 14 of 145 (9.7%) to be indeterminate, and 6 of 145 (4.1%) to be negative. The SPT was positive in 106 of 145 (73.1%) of these patients and negative in 39 of 145 (26.9%). The IVT was positive in 103 of 145 (71%) and negative in 42 of 145 (29.0%) of these patients. UniCAP Phadiatop found 104 of 145 (71.7%) of these patients positive and 41 of 145 (28.3%) negative. For positive patients UniCAP Phadiatop agreed very closely with the IVT (99%) and SPT results (98%) but poorly with the HPE (83.2%). For negative patients UniCAP Phadiatop also agreed well with the SPT (95%) and IVT results (98%) but, again, large differences were seen between the test results and the HPE, which predicted only 4.1% (versus 27% for SPT and 29% for IVT) of the

patients to be negative for sensitivity to these allergens.

To resolve the diagnostic discrepancies, patients were placed into categories as described in the methods (Table 2). Category I patients included those patients where all parameters agreed. This included 57 patients from site I (53 positive and 4 negative) and 39 (39 positive and 0 negative) from site II for a total of 96 patients. UniCAP Phadiatop identified all 96 of these category I patients correctly (92 positive and 4 negative).

Patients in category II included those patients where the test results agreed with each other but disagreed with the HPE. This included 18 patients from site I and 10 from site II for a total of 28 patients. According to the test results, 2 of these patients represented a false-negative history whereas 26 of these 28 patients represented false-positive histories. UniCAP Phadiatop results identified all 28 of these category II patients correctly in agreement with the concordant SPT and IVT results.

There were 12 patients who fell into category III. These patients included those who had indeterminate histories but in whom the SPT and IVT test results agreed. Six of these patients were positive and six were negative. UniCAP Phadiatop results correctly identified each of these 12 patients with indeterminate histories.

There were 9 (6.2%) patients left from this analysis where the tests results differed and needed further resolution. Three of these patients had a

positive HPE and IVT and negative SPT. These patients were shown by RAST inhibition to be true positives, making it likely that the skin tests were falsely negative. On this basis, these patients were classified likely to be atopic and placed in category IV. UniCAP Phadiatop identified all three of these patients as positive.

This left 6 patients, all of whom were IVT negative and had a single SPT judged positive. Because it was impossible to verify the specificity of these SPTs, total IgE values of these patients were examined. The total IgE values of these six patients were 2.2, 8.3, 8.3, 10.8, 30, and 64 kU/L. UniCAP Phadiatop judged the first five of these patients as negative and the last one as positive. Thus, on the basis of very low total IgE values, the first four patients were placed in category IV as resolved negative diagnoses and the remaining two patients were considered to have unresolved diagnoses and placed in category V.

Of the category I, II, and III patients (100 positive and 36 negative: 93.8% of total population) in whom the diagnosis is quite certain, UniCAP Phadiatop assay demonstrated 100% sensitivity and 100% specificity. Seven patients (4.8% of total population) fell into category IV where it was possible to resolve their sensitization status by RAST inhibition³ and total IgE values.⁴ Thus, the resolved diagnosis of

143 of 145 patients agreed perfectly with the Phadiatop result (98.6%). Further study of two patients will be needed to determine the final sensitivity and specificity of the Phadiatop test.

Of the patients identified as true positives by the resolved diagnosis, 20 of 102 (19.6%) were determined to be sensitized to only one of the seven individual allergens tested whereas 82 of 102 (80.4%) were sensitized to more than one. Of these monosensitized patients, 8 were positive only to *Alternaria*, 6 were positive only to oak, 3 were positive only to house dust mite, 2 were positive only to timothy grass, and 1 patient was positive only to ragweed. UniCAP Phadiatop test identified all of these patients correctly regardless of whether they were monosensitized or polysensitized.

The frequency of sensitization to these allergens as determined by IVT results was slightly different for the two sites (Fig 1). Site I had a higher frequency of sensitization to mite and *Alternaria* allergens whereas patients from site II demonstrated higher sensitizations to grass and ragweed allergens. This coupled to the demographic data suggests that these sites recruited patients from different populations of sensitized individuals. UniCAP Phadiatop test performed equally well in both groups (Table 2).

Quantitative aspects of UniCAP Phadiatop test results are illustrated in

Figure 2. This demonstrates a direct relationship of the Phadiatop raw score with cumulative levels of specific IgE levels to these seven allergens in these patients ($r = .75$). This indicates that the value of the UniCAP Phadiatop raw score can be used as a gauge in making decisions for further testing and/or referral.

The importance of obtaining objective data in making decisions regarding atopic patients is illustrated in Figure 3. Here one can see from the preliminary diagnostic results by HPE alone, the number of incorrect patients was 28 of 124 (22.6%). This consisted of 26 false-positive diagnoses and 2 false-negative diagnoses. These calculations exclude the indeterminate HPEs (category III) and patients in categories IV and V that required further analysis. If we include patients from these categories (III, IV, and V), there were 45 of 145 (31.0%) changes from the preliminary diagnosis made by HPE by consideration of other test results

DISCUSSION

Clearly, one of the most frequent decisions a clinician makes is whether to order a test to diagnose a current disease. This is particularly important in the field of allergy as many of the symptoms are quite common and are difficult to differentiate from a number of other causes. These variables make it very difficult even by well-trained and experienced physicians to designate allergic disease in each patient with assurance and to sort out specific causes strictly by a largely subjective clinical history. This study points out that there is a surprisingly high rate of anticipated false-positive results predicted by the clinical history. The rate of false-positive diagnoses for atopic disease amounted to at least 28 of 124 (22.6%) of the total population studied. However, this figure does not include those patients with indeterminate histories. After resolution, approximately one half of these patients had a positive diagnosis and one half had a negative diagnosis. This rate of false-positive clinical histories is close to that observed in a recently published paper

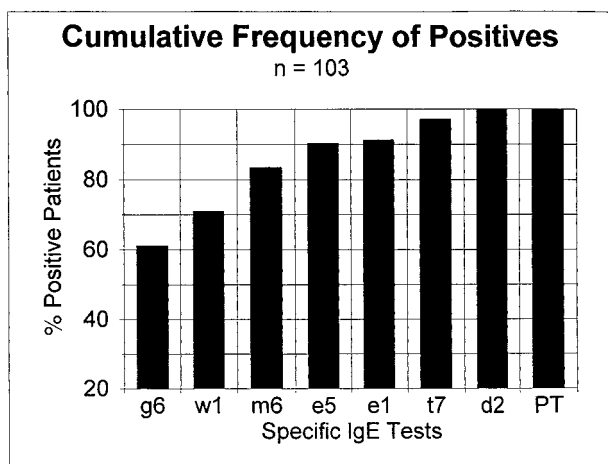


Figure 1.

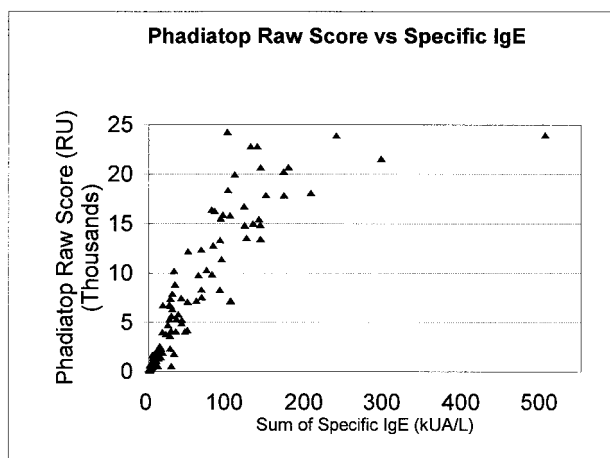


Figure 2.

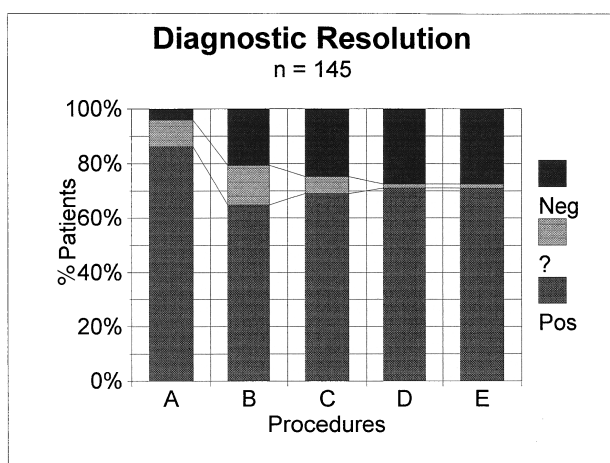


Figure 3.

dealing with the diagnosis of allergy to latex in which a rate of 15% false-positive clinical histories was observed.¹⁰

Unfortunately, the clinical history in this field has been used almost exclusively as the standard upon which the various tests used to make these decisions are evaluated. This practice has lead to several aberrations in this field. The most onerous of these is that it has encouraged the use and development of tests that are also likely to yield false-positive results because they agree better with the history. For example, often allergists employ intradermal skin tests or potent allergen extracts to verify suspicions raised by the history. Recent publications indi-

cate that this adds little to the accuracy of the diagnosis.^{11,12} Alternatively, questionably small skin test reactions may be counted as positive.^{13,14} In addition, some serologic tests for specific IgE, formerly criticized for their lack of sensitivity, have been constructed to agree better with the history by lowering the cut-off for positivity of the assay. This also has the drawback of increasing the incidence of false-positive results.¹⁵ Although these practices might result in better agreement with the clinical history used as the gold standard, this apparent agreement is tantamount to a self-fulfilling prophecy, and, as such, has been misleading.

For these reasons we were obligated to place patients into categories based

upon concordance of test results and other available information. This resulted in the definition of patients with false-positive histories, false-negative histories, and the resolution of those patients with indeterminate histories and those with test results that were at variance. This process enabled us to more correctly judge the performance of the UniCAP Phadiatop test results in the patients in this study. As a result, UniCAP Phadiatop identified correctly all the unambiguous patients from category I (66% of total), all the patients with false-positive and false-negative histories from category II (19% of total), all the patients with indeterminate histories from category III (8% of total), and all the patients with a resolved diagnosis in category IV (5% of total). This represents a calculated clinical sensitivity and specificity of this test in 98% of the patients of 100%. These results are in close agreement with Hamilton¹⁶ who studied Phadiatop assay performance with an earlier format.

If the history had been used as the standard upon which all other tests are compared, in this study, the SPT, IVT, and UniCAP Phadiatop would have shown sensitivities of 77.6%, 76.8%, and 77.6% respectively. These calculations required omitting 16 patients (11%) who were indeterminate to these allergens by the HPE. By using all available information to resolve these diagnoses, we prevented this error and achieved accurate data reflecting actual clinical sensitivity and specificity data. It should be realized that the false-positive component of the history might be inflated in this and other studies as compared with actual practice where evolving disease is observed over time. Nevertheless, the history in study protocols has repeatedly been used to determine and judge assay performances and this practice continues today. For licensing purposes, the FDA demands performance characteristics of tests be judged using the clinical history as the standard.¹⁷ To ensure accurate test results, it is obvious that this policy should undergo serious revision.

The SPT results, although exhibiting individual differences with the IVT results, agreed well with the IVT when used to define atopic patients. In this study we identified only three patients in whom instances of false-negative skin tests were likely. UniCAP Phadiatop results identified as positive all three of these patients. These patients could have been under the influence of one of the many drugs that inhibit skin tests¹⁸ or procedural problems may have been encountered.¹⁹ In contrast, the specific IgE identified may have been incapable of causing mediator release, which would also result in negative skin tests. Regardless, the specific IgE in these patients was real, as demonstrated by specific inhibitions, and would only be present in atopic patients. Thus, even if the specific IgE identified in these patients was non-functional or at a preclinical level, the patient must still be considered atopic, and the positive test result, at the very least, may be possibly prognostic of future problems.²⁰

It is possible that specific IgE may be present and detected by both the SPT and IVT, which is not clinically relevant.²¹ This would be unlikely to occur with seven different allergens simultaneously, but could partially explain the conclusion of a false-negative history with positive test results. Because there were only two false-negative and six indeterminate histories with both positive IVT and SPT results, this would not be likely to significantly affect our conclusions.

There were six patients with negative IVT results and positive SPTs. All of these patients had positive skin tests to only one of the study allergens. Because the specificity of the SPT reaction is practically impossible to establish, the total IgE values of these six patients were used to resolve the diagnoses. Four of these patients had very low total IgE values. In these patients, the Phadiatop results were negative. A final resolved diagnosis was not possible in the other two patients. One was Phadiatop-positive and one was Phadiatop-negative. These patients were relegated to category V patients, in

whom further data would be needed to make a certain diagnostic decision.

The frequency of having patients positive to different allergens differed for the two sites used. The most common sensitization for site I was *Alternaria*, followed by house dust mite. These were largely inner-city patients. For site II, ragweed and grass were the most frequent sensitizations observed, and most of these patients were from suburbs. There were also differences in ethnicity between these two populations and probable differences in social status as well. Significantly, UniCAP Phadiatop performed equally well in both populations.

Of relevance to the determination of a patient's atopic status, it should be noted that three individual specific IgE tests identified 88% of the atopic individuals in the total population studied. This number was 95% for four individual specific IgE tests and 98% for five individual specific IgE tests. These numbers verify the logic behind the design of the UniCAP Phadiatop test, indicating that a singular test for multiple common inhalants can identify the majority of atopic patients.⁵

UniCAP Phadiatop is indicated for screening purposes, and it is recommended that it be reported as either positive or negative. We demonstrated that the total quantitative amount of specific IgE to only seven common allergens correlated well with the raw Phadiatop score. A better correlation would be expected if specific IgE were measured to more allergens. This finding indicates that a measurement of the extent of an individual's atopic disease can be estimated using the raw score with the caveat that, in an individual patient, one can never know whether a single allergen or several allergens are contributing to the serologic result observed. This is an important consideration for referral because a low UniCAP Phadiatop result would indicate a different treatment or, perhaps, referral level from a high score.²² It also indicates that an elevated score very likely indicates a complex allergic patient whose interests would best be served by referral to a trained allergist.

Limitations of this study include the fact that although these were consecutive patients, a very high number were positive. Thus, the observed test efficiency may be different if a population with a lower frequency of atopy were studied. Each site also used different skin test extracts, devices, and procedures for skin testing. Despite these differences, the correlation with SPT and UniCAP Phadiatop for determining atopic status was very favorable.

It should be clearly pointed out that UniCAP Phadiatop is a measure of atopy and does not inform one as to which allergens a patient has a sensitivity. This raises the possibility that rare inhalant allergies in monosensitized individuals may be missed. It should also be mentioned that the presence of food allergies is not evaluated by this procedure and that a positive Phadiatop UniCAP result will require further testing to identify which allergens are involved in each patient.

CONCLUSION

A new method to characterize patients using concordance of results from different diagnostic tools was used in this analysis. Previous studies have arbitrarily chosen one of these tools as the standard to which the others are compared. Our results demonstrate the possibility that this could (and most likely has) lead to false impressions regarding the diagnostic efficiency of various tests in this field. On the positive side, we have shown that for screening purposes, the skin prick testing and serologic testing results agree closely. Whether this occurs in everyday practice remains to be studied.

Our results do indicate that UniCAP Phadiatop is a single test that performs admirably to determine the sensitization status of a patient. It also can give one an estimation of the extent of a patient's sensitization.^{22,23} Given the complexity of the symptoms of allergy and the many possible confounding factors, it represents a relatively simple and accurate procedure to rule in or out common inhalant allergic problems. With the finding that the history and physical examination tends to overes-

timate allergic sensitization, it seems that this test would also be useful to allergists.

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Request for reprints should be addressed to:
P. Brock Williams, PhD
IBT Reference Laboratory
10453 W. 84th Terrace
Lenexa, Kansas 66214
E-mail: pbrockwil@aol.com