

SKIN TESTS IN COMPARISON WITH OTHER DIAGNOSTIC METHODS

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What is an ideal diagnostic allergy test? Are skin tests ideal or are other tests better? Are skin tests more sensitive or merely less specific than other test methods? Are there significant differences in the performance of different tests depending upon the type of allergen evaluated?

Ideally, a diagnostic allergy test provides two different forms of information. A test first provides information about whether a specific form of allergic disease was present (e.g., if a patient has allergic or nonallergic rhinitis). A test then provides information about which allergen or allergens were responsible for the allergic disease. Compared with this ideal, current tests leave much to be desired because they are tests for immunoglobulin E (IgE)-mediated sensitization, a condition that is not invariably associated with disease. In the majority of clinical situations, the clinician must make a disease diagnosis almost totally from the patient's history and physical examination. At times, patient histories are clear and consistent, but at other times, forming a firm diagnostic opinion is difficult because of unusual or vague symptoms or because of difficulty correlating symptoms with probable allergen exposure. Ancillary tests such as spirometry and examination of nasal cytology may be helpful in many situations but are rarely diagnostic.

An advantage and disadvantage of skin tests is that they are the end result of a sequence of events from introduction of the allergen into the skin to allergen-IgE binding, mediator release, response of the end organ, and release of mediators. The advantage is that the skin test provides information on the end result of the entire sequence of events

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IMMUNOLOGY AND ALLERGY CLINICS OF NORTH AMERICA

and presumably an estimate of the potential level of reactivity of an individual to the allergen following natural exposure. The disadvantage of skin tests is that it is possible that the level of activity of individual components of the sequence may vary substantially between different organ systems in an individual. This could account for the observation of a less than perfect correlation between skin test sensitivity and clinical sensitivity. In theory, this disadvantage largely could be overcome by directly challenging the organ involved in the allergic disease with allergen, but this is inconvenient when compared with skin tests.

The advantages and disadvantages for skin tests are reversed when tests designed for the *in vitro* detection of allergen-specific IgE are considered. These tests only detect IgE antibodies and provide no estimate of the relative activity of these antibodies *in vivo*. The activity of the antibodies presumably depends on the avidity with which the antibodies bind allergen and the probability that the antibodies will be found in high density on effector cells.¹⁵

It is relatively easy to compare the value of different tests when there is an accepted standard of accuracy, commonly called the "gold standard." Unfortunately, in allergy it has been difficult to agree on a gold standard for allergic disease in part because of confusion in the literature on the difference between allergic disease and allergic sensitization. The clinical history obtained from the patient is a possible standard, but when critically examined clinical histories often do not coincide with IgE test results.^{17, 18, 25, 46} There is also the problem that many patients are not able to provide a clear and consistent history. Skin tests often are used as a gold standard, but they are not infallible. Positive skin tests are not always associated with allergic disease, and skin tests may be falsely negative even when high concentrations of allergen-specific IgE are present.^{10, 35, 42} Challenge tests involving exposure of a specific organ, other than the skin, to allergen have specific problems such as determining a realistic dose of allergen and delivering the allergen in a realistic fashion.

Given the problems inherent with selecting a standard to use for comparing the results of tests, it is easy to see why the literature is full of contradictions and inconsistencies. Though the ultimate criteria for judging a test is the amount of help the test provides in caring for patients, finding and evaluating this information can be difficult. An additional problem is that testing methods, especially *in vitro* testing, evolve more rapidly than it is possible to complete well-done comparative studies.

In addition to diagnostic value, other criteria are important when comparing tests, such as the risk of major or minor adverse reactions from the test, the convenience of the test for the patient, and the cost of the test.

SKIN TESTS IN COMPARISON WITH *IN VITRO* TESTS

The allergy literature contains many studies and reviews comparing skin tests to *in vitro* tests for allergen-specific IgE antibody.^{3, 20, 22, 31} Most

of these studies conclude that when compared with skin tests, in vitro tests are less sensitive, slower to perform, and more expensive. Though these conclusions may be valid given the data presented, many questions should be considered when reading these studies.

The first question is how well were the skin tests performed? Was the extract used for the skin tests well characterized? Was there evidence that a nonirritating concentration of the extract was used for testing? How reproducible were the skin tests? (Was the device used for the skin tests capable of producing consistent results?³⁸) Were all of the skin tests done by a single person or by several persons, and if more than one person performed the tests, were the results consistent between persons? Were the skin tests evaluated in a blinded fashion, or did the person reading the skin tests know the patient's history? Were consistent and specific criteria used to evaluate the skin tests? Were other variables present that could affect the reading of the skin test results? Inadequate answers to any of these questions should raise serious questions about the validity of the study. At the present time in the United States only a few allergen extracts have been standardized: house dust mites, *Hymenoptera* venoms, cat hair/dander, a few grasses, and short ragweed pollen. The standardization of these extracts is based on defined quantities of major allergens or based on units correlated with biologic activity. The results of skin tests with nonstandardized extracts can be difficult to reproduce.

The second major element in a comparative study is the methodology and care used in testing for IgE antibodies. All in vitro tests for allergen-specific IgE involve two essential steps. The first step is the separation of the specific IgE antibodies of interest from all other antibodies in the patient's serum. The second step is to estimate the quantity of the separated, specific antibodies. Each of these steps is critical to the final result, and many variables can affect each of the steps.²² As with skin testing, the allergen used to produce the solid phase must be well characterized, and care must be taken to ensure that allergen epitopes are not lost in the preparation of the solid phase. All important allergens must be present on the solid phase in large excess to maximize the binding of IgE antibodies. If the allergens are not present in excess, there may be competition from antibodies of other isotypes. An excess of allergens also allows antibodies to bind in an affinity-independent fashion. If this is not true, it will be impossible to obtain accurate estimates of the quantity of the antibodies present.^{22, 47}

During the early development of assays for allergen-specific IgE, the quality and specificity of the antihuman IgE detecting antibody was frequently a significant problem. In modern assays the use of monoclonal or mixtures of monoclonal antibodies and polyclonal antibodies essentially has eliminated this problem, but it should be considered when reading studies prior to the 1990s. Quantitative assays for specific IgE also should have standard curves that can be traced to a well-established standard such as the World Health Organization's (WHO's) International Reference Preparation for Human IgE 75/502. It is then necessary to

demonstrate that dilutions of positive sera produce curves that are parallel to the calibration curve before quantitation is possible.⁴⁷

In the last two decades many improvements have been made in assays for specific IgE antibodies. Among the most important improvements have been the substitution of enzymes for radioactive labels on the antihuman IgE antibodies, improving the stability of this critical reagent and improving the accuracy of detection; increased automation, reducing operator variability; and the move to calibration curves based on known quantities of IgE, resulting in quantitative rather than qualitative or 'semiquantitative' assays. There also has been a major effort in the United States to improve the performance of laboratories performing all clinical tests. The Clinical Laboratory Improvement Amendments of 1998 set many new standards for laboratories performing clinical tests.

Even with all of these improvements, a study demonstrated that the results of tests for allergen-specific IgE antibodies obtained from six large commercial laboratories leave much to be desired.⁴⁴ Of the six laboratories that blindly tested multiple aliquots of the same sera, undiluted and in serial dilutions, the results of four of the laboratories were substandard in terms of poor precision and accuracy. In a number of samples and allergens the laboratories were unable to detect the difference in concentrations between twofold dilutions of the same sera. The results of two of the laboratories, however, were highly reproducible and consistently detected differences between dilutions of the sera.⁴⁴ An important question left unanswered by this study is whether the poor results were a reflection of the specific assay methods used for measuring specific IgE or a reflection of poor laboratory practices. Further studies are needed to resolve these issues.

Another important issue to consider when comparing skin tests with in vitro and other tests is the specific allergen being evaluated. Allergens often have been grouped into inhalants, foods, antibiotics, *Hymenoptera* venoms, and occupational allergens, but this classification probably leaves nearly as much diversity within groups as there is between groups. There are unique problems with skin tests, in vitro tests, and challenge tests with allergens in each of these groups. Some inhalants such as cat dander and ragweed are well characterized in terms of major allergens, and the major allergens are relatively stable in contrast to many molds in which there little is known about the major allergens or their stability. Whereas it is easy to obtain pure antibiotics for testing, relatively little is known about how most antibiotics become allergens through metabolism and binding to carrier proteins. When the results of skin and in vitro tests are compared with highly purified allergens, the results are often highly concordant. A study by Ford et al with fire ant venom and a modern in vitro assay found 100% sensitivity and 100% specificity.¹⁹ Unfortunately, there are relatively few recent studies comparing the results of skin tests, in vitro tests, and challenge tests using the best available methods.

SKIN TEST IN COMPARISON WITH LOCAL ALLERGEN CHALLENGES

Many investigators have performed challenge studies involving the conjunctiva, nasal or oral mucosa, lungs and, gastrointestinal tracts.^{2, 7, 13, 29, 32} The most common rationale for these studies is to determine whether direct allergen exposure produces typical allergic symptoms. A second rationale is that challenge studies allow evaluation of local physiologic responses in terms of end-organ changes and the release of specific mediators. When physiologic responses and mediators have both been measured, it is possible to correlate symptoms with the presence of various inflammatory mediators. Finally, direct allergen challenge often provides a basis for evaluation of the effects of various therapeutic agents.

A concern about local allergen challenges is that they often employ doses of allergen that are much larger than would be expected in nonexperimental settings.³⁴ Relatively few studies have sought to address this problem directly. One study that did evaluate this question involved repeated challenges with dust mite at concentrations estimated to be similar to those encountered in a typical bedroom in nine dust mite-sensitive adults with asthma.⁴ The subjects were challenged three times per week (Monday, Wednesday, and Friday) for 4 weeks with low doses of mite extract that were insufficient to cause immediate changes in the forced expiratory volume in 1 second (FEV₁). Over the 4 weeks of the study, seven of the nine subjects had a more than twofold drop in their PC₂₀ accompanied by increased asthma symptoms and declining prechallenge FEV₁. The results of this study suggest that repeated low doses of allergen, similar to those encountered in daily life, can produce significant physiologic changes mimicking allergic disease.⁴ Unfortunately, there have been no studies comparing the results of skin or in vitro tests with the results of repeated low-dose allergen challenges.

Pulmonary challenges probably have been used more than any other forms of organ-specific challenge. Standard challenge procedures were established in the 1970s and periodically updated.^{1, 13, 43} Even with the long history of investigation there are many questions remaining concerning the relationship between allergy tests, bronchial challenges, and asthma. In 1977, Cavanaugh and coworkers published the results of 1596 allergen bronchial challenges performed between 1970 and 1974 in 276 children evaluated at National Jewish Hospital.¹² In this study, skin tests first were performed as puncture tests and if the resulting wheal was 5 mm or less in diameter, intradermal tests were performed. The results of the puncture and intradermal skin tests were compared with the results of graded bronchial challenges with the same allergens. The concentrations of the allergen extracts used for the challenges ranged from 12.5 to 10,000 protein nitrogen units (PNU)/mL. At the highest concentration of 10,000 PNU there was some nonspecific reactivity to

several of the extracts, so the correlations between skin tests and challenges were reanalyzed excluding reactions at the 10,000 PNU concentration. When this was done, puncture tests with wheals greater or equal to 5 mm in diameter were associated with positive challenges in over 90% of cases for molds, dust, and danders. With pollens the prevalence of positive challenges was only 54% with wheals greater or equal to 5 mm in diameter; however, when the puncture skin test was less than 5 mm in diameter, there were still positive challenges in 11% to 42% of the cases depending on the allergen studied. When the results of intradermal tests were considered, the results were mixed. Intradermal test with wheals less than 5 mm in diameter were never associated with a positive challenge, but there was no correlation between wheals of increasing diameter over 5 mm and an increasing probability of positive challenges. The authors concluded that a negative intradermal test result virtually rules out any response to bronchial challenge, and bronchial challenges are needed only for indeterminant cases (i.e., cases with puncture tests of <5 mm and intradermal tests of ≥ 5 mm).¹²

Whereas the study of Cavanaugh et al found a clear correlation between positive skin test responses and positive bronchial challenges, a study of 2657 individuals drawn from the general population by Burrows et al found that the risk of having asthma correlated better with age- and gender-adjusted total serum IgE concentrations than with reactivity to skin tests using a battery of common allergens.¹¹ They felt that their findings challenged the concept of "extrinsic" and "intrinsic" asthma.¹¹ Similar results were obtained in a Spanish study of 1916 adults ages 20 to 44.⁴¹ In this study individuals were evaluated with face-to-face questionnaires, spirometry, total serum IgE and specific IgE antibody tests with mite, pet, and mold allergens. The odds of having asthma in association with a total IgE level greater than 100 kU/L were 4.73, even after statistically adjusting for allergen-specific IgE, sex, age, smoking, and FEV₁. The association between total IgE and risk of asthma persisted when persons without detectable specific IgE antibodies were considered separately (odds ratio [OR], 18.0; 95% confidence interval [CI], 13.9–120). There was also an association between current wheezing and bronchial responsiveness to methacholine in persons without a history of asthma attacks (OR, 4.96; 95% CI, 2.23–10.6) that remained for persons without detectable specific IgE (OR, 5.86; 95% CI, 2.18–12.75).⁴¹ These findings raise significant questions about the role of allergic sensitivity in asthma, at least when large numbers of young adults are considered.

Popa failed to find a significant relationship between antiragweed IgE concentrations measured by any of four different RAST methods and the threshold response to ragweed bronchial challenge in 26 ragweed-allergic individuals.³⁰ Similar results were obtained by Crimi et al with individuals allergic to *Parietaria*.¹⁴ In contrast, Muller et al found a significant correlation between the wheal size of intradermal allergen skin tests and the PD₂₀ dose of allergen in a group of 166 individuals.²⁴ The 166 individuals included 25 subjects with asthma, 75 subjects with

allergic rhinitis, and 66 normal, nonatopic asymptomatic controls. Among persons who responded to bronchial challenges with allergen, there was no difference in the sensitivity (PD_{20}) or reactivity (slope of dose-response curve with allergen) between those subjects with rhinitis alone and those with asthma. Sensitivity and reactivity to methacholine differed significantly between asthmatics and rhinitics. In this same study, regression analysis demonstrated a stronger association between allergen and methacholine responsiveness in subjects with rhinitis than in subjects with asthma.²⁴

The complex relationship between skin test reactivity, asthma, rhinitis, and airway hyper-responsiveness to methacholine is further illustrated by the results of Sears et al in an epidemiologic study of 662, 13-year-old children.³⁷ As the wheal size for house dust mite and cat increased, the proportion of children with airway hyper-responsiveness to methacholine also increased. None of the 33 asthmatic children with methacholine PC_{20} less than 8 mg/mL were skin test negative. The relationship between skin test reactivity and methacholine airway responsiveness persisted in the 403 remaining children after excluding those with asthma or those who had ever wheezed. The relationship continued to persist in the 232 remaining children after excluding all children with any history of asthma, wheezing, or hay fever ($P < 0.001$). The results of this study led to the conclusion that there is an association between skin tests and airway responsiveness that is independent of recognized allergic symptoms.

Reddy et al compared the results of prick and intracutaneous skin tests with the results of RASTs, leukocyte histamine release, and nasal provocations in 53 individuals with perennial rhinitis and 13 health volunteers.³³ Among the 53 individuals with rhinitis there were 34 patients with totally negative prick tests to a group of 60 common allergens but a variable number of positive intracutaneous reactions when tests were performed with extracts at 1:1000 weight/volume (w/v) concentration. None of the 13 healthy, nonallergic, individuals had positive skin prick tests, RASTs, leukocyte histamine release, or nasal provocations, but three subjects had positive intracutaneous reactions of 2+ to 3+. None of the 34 positive intracutaneous tests were associated with positive RASTs, though 12 of 19 (63%) positive skin prick tests were associated with positive RASTs. Only one of the 34 patients with a negative skin prick but positive intracutaneous skin test had a positive nasal challenge, and both the RAST and histamine release were negative in this person. In contrast, 17 of the 19 persons with positive prick tests had positive nasal challenges. Among the 17 persons with a positive nasal challenge and skin prick test to an allergen, there were six individuals with negative prick but positive intracutaneous tests to other allergens. None of these six individuals reacted to a challenge with the allergen associated with the positive intracutaneous test, even though they were known to respond to nasal allergen challenge. The investigators concluded that intracutaneous tests provided no additional clinically useful information beyond what was provided by skin prick tests.³³

A similar conclusion was reached by Nelson et al in a study of 68

individuals who represented four distinct groups.²⁶ The study groups were: (1) individuals with a history of symptoms of allergic rhinitis and negative prick but positive intracutaneous test results with timothy grass, (2) individuals with a history of symptoms of allergic rhinitis and a positive skin prick test to timothy grass, (3) individuals with symptoms of allergic rhinitis and negative results of both skin prick and intracutaneous tests to timothy grass, and (4) individuals with no personal or family histories of allergic rhinitis symptoms and negative tests to a battery of 25 common allergens. The results of the skin tests were compared with the results of nasal challenges with timothy pollen and with the correlations between the patients' symptoms and the grass pollen counts during the next grass season. After analyzing the data in several different ways, the investigators concluded that intracutaneous tests provided no clinically useful information beyond what was provided by the skin prick tests.²⁶ If the investigators defined grass allergy as having a positive nasal challenge with grass pollen and an association between nasal symptoms and pollen counts during the grass season, 46% of the individuals with positive skin prick tests were grass allergic, whereas none of the individuals with only positive intracutaneous skin tests, negative intracutaneous, and none of the nonallergic control individuals were classified as grass allergic. If more liberal criteria were used for grass pollen allergy, there was no difference in the prevalence of allergy between those individuals with positive and negative intracutaneous tests.²⁶ The results of this study are consistent with the findings of an earlier epidemiologic study in which there was no correlation between allergic symptoms and intradermal skin test reactivity with a negative skin prick test.⁹

In a study using a current *in vitro* test method and a standardized cat extract, Wood and coworkers also compared the results of skin prick tests, intradermal skin tests, and radioallergosorbent tests (RASTs) for the diagnosis of cat allergy.⁴⁶ The standard for the diagnosis of cat allergy in this study was the response of the person when placed in a small room in which two cats resided for 1 hour. Of the 128 adults between the ages of 18 and 65 years who were evaluated, 81 had positive skin prick tests to a standardized cat extract, 26 had negative prick but positive intradermal skin tests, and 13 had negative prick and intradermal skin tests. Strong associations were found between positive skin prick test results and the onset of significant upper and lower respiratory symptoms during the challenge in the cat room. Some individuals had negative skin prick tests and developed symptoms during the cat exposure challenge, but these individuals could not be distinguished by the results of the intradermal skin tests done with either 100 or 1000 BAU/mL concentrations of standardized cat extract. The results of the RASTs were very similar to the results of the skin prick tests and correlated equally well with the results of the cat exposure challenges. The authors concluded that "major therapeutic decisions, such as environmental control or immunotherapy, should never be based on a positive intradermal skin test result alone."⁴⁶

Several studies designed primarily for evaluating physiologic responses to allergen challenges provide further insight into the relative value of skin tests and *in vitro* tests. Pelikan and Pelikan-Filipek evaluated changes in maxillary sinus radiographs after nasal challenges with allergens selected based on skin test or RAST results.²⁸ In the 41 instances in which there was a positive response to the nasal challenge, maxillary sinus radiographs changed 32 times. Both positive skin tests and RAST results were associated with positive nasal challenges, but skin tests were more sensitive and were positive in 27 of the 41 positive challenges compared with positive RASTs in only 11 of the positive challenges.²⁸ In a nasal challenge study reported by Ackerman et al, there was a significant relationship between IgE antibody concentrations to timothy grass and ragweed and the dose of allergen required to produce rhinitis symptoms and eustachian tube obstruction. All of these patients had strongly positive skin tests to the two allergens.²

In contrast to the studies of asthma, several large epidemiologic studies have shown clear associations between the results of skin tests and rhinitis symptoms.^{11, 17} In the previously mentioned study of Burrows et al, there was a stronger association between positive skin prick tests to common inhalant allergens and nasal symptoms than between total serum IgE and nasal symptoms.¹¹ In another large study of 2167 individuals in the Netherlands, positive skin test results were associated highly with nasal symptoms.¹⁷ In this study the combination of skin tests and *in vitro* test results was somewhat better at predicting nasal symptoms than either one alone. When used individually there was little, if any, difference in the value of skin tests and *in vitro* tests.¹⁷ In a different study from the Netherlands that evaluated skin and *in vitro* tests in relationship to asthma and chronic obstructive pulmonary disease, skin test results were better predictors of clinical allergy.⁸

Crimi and coworkers evaluated a new method for obtaining improved correlation between the results of tests of specific IgE antibodies and the results of allergen challenges.¹⁵ They reasoned that an estimate of the density of IgE on effector cells correlates better with the results of challenges than estimates of the concentration of specific IgE antibodies in serum. To estimate the density of IgE, they divided the quantity of allergen-specific IgE by the total serum IgE concentration. They then compared the concentration of specific IgE in the patients' serum and the density of IgE with the results of bronchial and nasal allergen challenges. They found that the estimates of IgE density correlated with the nasal challenge scores, bronchial challenge scores, and late asthmatic response better than the concentration measurements.¹⁵ If the results of this study are confirmed, *in vitro* tests of IgE density may provide better diagnostic information than standard *in vitro* or skin tests.

Food Challenges

Double-blind, placebo-controlled food challenges (DBPCFC) have become the standard for the diagnosis of food allergy.⁷ Though DBPCFCs

may be difficult to perform in routine clinical settings, they offer the advantage of reproducing symptoms with a dose and route of allergen exposure that is essentially identical to the normal exposure to the allergen. When skin tests and *in vitro* tests for food-specific IgE antibodies are compared with DBPCFCs, neither method is clearly superior at predicting positive challenge results.¹⁰ Depending on the patient population, both skin and *in vitro* tests typically have sensitivities of 50% to 90% and specificities of about 90%. This finding means that negative prick skin or *in vitro* test results make a positive DBPCFC unlikely, but positive tests may or may not be associated with a positive challenge.¹⁰ As in testing with other allergens, skin testing or *in vitro* testing for foods is highly dependent on having the relevant allergens present in the extracts. Some food allergens are highly labile, making commercial extracts of these foods inadequate for diagnosis. In these cases the prick-by-prick method of skin testing is useful. With this method the device used for the test first pricks the food of interest and then pricks the patient's skin.^{10, 27}

At least one study has suggested that there may be some advantage to *in vitro* test results done with an assay system that provides results in terms of mass units of IgE for food allergens.³⁶ For a number of common food allergens (e.g., milk, egg, peanut, fish), it was possible to define a serum concentration of IgE above which positive DBPCFCs occurred with 95% certainty.³⁶ Given this degree of certainty concerning the probable results of a challenge, many physicians would consider a DBPCFC unnecessary given a test result above the predictive value. Though these results are intriguing, it should be remembered that all of the children in this study had atopic dermatitis and many had other forms of allergic disease such as rhinitis or asthma.³⁶ It would be valuable to have other studies examining relationships between concentrations of food-specific IgE antibodies and the results of DBPCFCs in children with less severe manifestations of food allergy to confirm the predictive values. It also seems that specific IgE values may be of benefit for predicting which latex-sensitive individuals with spina bifida will have symptoms following latex exposure.⁶

IN VITRO VERSUS SKIN TESTING DATA

A few studies have suggested that allergen-specific IgE measurements can provide information that is difficult or impossible to obtain by skin testing. Most of these studies are based on detecting 'locally produced' IgE or on correlating the quantity of IgE to a specific disease process. Several studies have suggested that allergen-specific IgE can be detected in the tears of some skin test-negative individuals.^{5, 21, 23} These studies suggest that this specific IgE is locally produced and is capable of causing local allergic symptoms. Limited local production in the conjunctiva explains why there is insufficient IgE to sensitize the skin.^{5, 21, 23}

Local production of IgE also has been suggested in the nose and vagina.^{23, 40, 45}

Another use for the quantitative information obtainable from modern assays for specific IgE antibodies is to estimate ongoing allergen exposure.¹⁶ After studying 40 mite-allergic individuals, De Lovinfosse et al found that there was a significant association between RAST scores and the quantity of house dust mite allergenic individuals were exposed to ($P < 0.001$).¹⁶ When antimitite IgE concentrations were less than 2 kU_A/L there was a 77% probability that the individual was exposed to less than 10- μ g/g dust of mite allergen, and when antimitite IgE was greater than 2 kU_A/L there was a 77% probability that the individual was exposed to greater than 10 μ g/g of mite allergen in mattress dust.¹⁶ If this association can be verified by other investigators, specific IgE measurements could be used to monitor the adequacy of dust-mite avoidance measures or avoidance of exposure to an occupational allergen. Studies also have shown that when mite-allergic children are taken from their homes (where mites are endemic) to alpine schools that are essentially mite free, there is a fall in their serum concentrations of mite-specific IgE antibodies.³⁹

SUMMARY

In general there are high correlations between positive results to properly performed epicutaneous skin tests and the results of eye, nose, or lung challenges with the homologous allergen. The results of epicutaneous skin tests are also highly correlated with the results of in vitro tests and clinical histories. These correlations between the tests and challenges are highest when potent, well-characterized allergen extracts are used. For most common allergens, the results of intracutaneous skin testing add little if anything to correlations between skin test results and the results of challenges or to predicting clinical histories. The extra sensitivity of intracutaneous skin tests may be valuable when high potency extracts are not available or when the risk of a falsely negative test is high, as with drug or insect venom allergies; however, this commonly stated assumption rarely has been examined critically. All physicians caring for patients with histories suggestive of allergic disorders must be keenly aware of the strengths and limitations of all available testing methods.

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