

The Spectrum of Cutaneous Patch-Test Reactions in Patients with Atopic Dermatitis

Jon M. Hanifin* and Paul A. Klas

*Oregon Health Sciences University, 3181 Southwest Sam Jackson Park Road,
Portland, OR 97201-3098*

Introduction

The subject of cutaneous allergic reactions in patients with atopic dermatitis (AD) has been a source of controversy and confusion for many years. One aspect of this confusion has centered on the relationship among AD, cell-mediated immunity, delayed-type hypersensitivity, and allergic contact dermatitis (ACD) (1-4). Several studies have shown reduced contact allergy responses in subjects with AD (2,3,5,6) and early observations led to later in vitro studies which demonstrated T-cell abnormalities and formed the basis for many subsequent immunologic investigations (4,7-9). One report suggested that reduced dinitrochlorobenzene (DNCB) sensitization may be significant only in severe, active AD (10), but Rees et al. (6) demonstrated, using more sensitive methods, that reduced responsiveness was a general characteristic of AD. This is paradoxical because, although the rate of contact sensitization in subjects with AD is diminished (2,3,5), studies have shown that atopic individuals often have a contact allergy and should be patch tested (11-14).

In our long-term studies of AD we have sought control subjects with widespread dermatitis owing to proven ACD who are clearly not atopic. We have been impressed with the difficulty in finding such subjects and with the great proportion of patients in a large referral clinic for contact dermatitis who had the atopic diathesis. We carried out a study of the relationship between ACD and atopy in that population and confirmed our impressions that:

*Author to whom all correspondence and reprint requests should be addressed.

1. Over half of patients with ACD were clinically atopic;
2. A majority of patients with atopy had ACD;
3. Atopic subjects averaged significantly more positive patch tests than did nonatopics (14).

Although these results appear to conflict with other published reports showing decreased rates of contact sensitivity among patients with atopy (1–6,10), our findings were similar to those of other investigators (11,12,15), who noted a high rate of contact allergy among atopic subjects. Thus, ACD frequently coexists with atopy. How relevant is ACD to management of patients with AD? Certainly it must be considered in recalcitrant cases or in patients with suggestive localization. Additionally, corticosteroid allergic dermatitis is a concern that should always be considered in unresponsive AD as is discussed in the article by Morren in this issue (*see pp. 199–208*). Much of the confusion regarding the incidence of ACD or with any study of atopics relates to the definitions used for atopy. Some studies, especially dermatologically oriented ones, only include patients with AD while not assessing for allergic respiratory disease (ARD) (11) whereas allergist-initiated studies usually use skin-prick test positivity as an important criterion for atopy (16).

Irritant effects are also recognized as predisposing to ACD and to the clinical severity of AD. Mechanisms for these effects are unknown but may relate to multiple factors (Table 1) including the defective stratum corneum barrier, increased expression of cell adhesion molecules and altered cytokine production by the epidermal cells, and recruited inflammatory cells following irritant exposure (17–19). Atopic individuals are more sensitive to irritants and appear to be predisposed to greater inflammatory reactivity caused by cyclic adenosine monophosphate (cAMP) abnormalities in immune and inflammatory bone marrow-derived cells that infiltrate tissues (20,21). In a recent report, subjects with well-defined AD or with only ARD (individuals with no dermatitis but with well-characterized seasonal allergic rhinitis and positive immediate wheal-prick tests to relevant allergens) were compared to normal, nonatopic controls in their responses to graded concentrations of sodium lauryl sulfate (SLS) (20). The results showed a significant difference in irritant sensitivity between normal subjects and the atopic individuals, including those with inactive AD, and those with only ARD. The greatest sensitivity was clearly in the active AD group, with data showing a significantly lower irritant threshold, consistent with past studies of dermatitis in general. Clinically, non-specific irritant reactions are often seen by dermatologists, for example, as false-positive patch-test responses on the skin of patients with various types of active or flaring dermatitis. Such demonstrations of greater SLS responses in the “angry back syndrome” or “conditioned

Table 1
Factors Predisposing to Increased Cutaneous Reactivity in AD

Impaired epidermal barrier.
Decreased leukocyte cAMP (owing to increased cAMP hydrolysis by phosphodiesterase) causing increases in eicosanoid secretion and cytokine production (20,25).
Increased expression of cellular adhesion molecules.
Chronic exposure to topical skin care products and medications.

hyper-irritability" are well-known (22,23). Generally, studies have shown significantly increased irritant responses only in "active or acute AD" but not in "inactive AD" (24). Our recent study differs in showing a continuum, with significantly increased SLS reactivity even in patients with mild atopy, with or without AD, plus an even greater level of significance in active AD. The key to finding these differences was our use of small gradations in SLS concentrations and performing the readings at 48 h. Extrapolation from our data suggested that a 0.5% SLS concentration might provide an indicator of atopy in patients without other skin disease.

These findings suggested that a decreased irritancy threshold in atopic individuals was not explained solely by conditioned hyper-irritability localized to skin cells because the ARD subjects had never had skin disease. We postulate that the abnormality relates to increased amounts of mediators (e.g., cytokines and eicosanoids) (25,26) present in peripheral blood, respiratory tissues, and skin, which enhance the irritant-induced inflammatory response (Table 1). Studies of atopic blood leukocytes have demonstrated a highly active phosphodiesterase variant which lowers cAMP levels in stimulated cells (27) and causes excessive histamine release, increased prostaglandin E_2 (PGE_2) secretion, and elevated production of interleukins 4 and 10 (26,28). This lack of cAMP produces a generally permissive effect on inflammatory cells which infiltrate the skin. Evidence suggests that a subclinical inflammatory response is continuously active, even in apparently uninvolved skin of AD patients (29). The new findings suggest the same may be true of ARD patients.

Another factor which augments irritancy in AD is the derangement of the stratum corneum barrier associated with ichthyosis vulgaris or dry skin. This may predispose the atopic individual to greater ingress of irritants, thus causing dermatitis which might otherwise be subclinical (29–31). All of these factors may contribute to the general interaction among atopy, irritancy, and contact allergy in the skin (Fig. 1A).

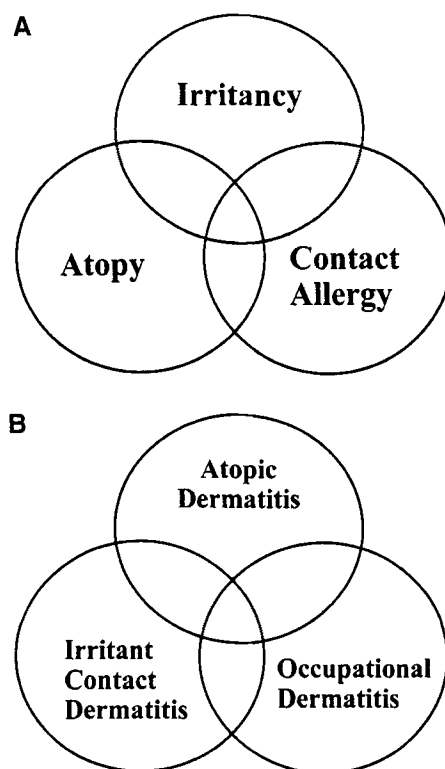


Fig. 1. Venn diagrams illustrating (A) the increased general inflammatory reactivity that predisposes to atopy, irritancy, and contact allergy and (B) the consequent overlapping relationship among AD, irritant contact dermatitis, and occupational dermatitis.

Numerous clinical observations of atopic patients have suggested that even those with no history of eczema have increased susceptibility to a variety of environmental factors which can damage the skin. Many patients with wintertime xerotic dermatitis have a personal or family history of ARD. Such patients probably represent subclinical AD which becomes manifest when they are exposed to low humidity, over-bathing, cleansing products, and often a combination of all three. This susceptibility to irritant contact dermatitis often becomes manifest when the atopic individual enters the work place. Studies have shown a striking propensity of atopics to develop occupational dermatitis (32, 33), especially when engaged in wet work jobs which alternately wet, dry, and crack the stratum corneum barrier (Fig. 1B). Similar effects of drying and irritants also cause a variety of respiratory symptoms and may well contribute to occupational asthma. All of these observations support the hypothesis that hyperreactive, cAMP-depleted inflammatory cells, whether in the skin or the respiratory mucosa, are the intrinsic

Table 2
Factors Governing Choices in Patch Testing Patients with AD

Recalcitrance
History of other contact allergies
Time to onset after exposure
Lesion distribution
Localized vs widespread
Exposed vs covered surfaces
Seasonal changes
Other allergies
Latex
Pets
Plants/pollens
Foods
Association with rhinoconjunctivitis symptoms
Other chronic, predisposing dermatitis (e.g., stasis, otitis externa)
Occupational dermatitis; relation to work exposures
Attempts at avoidance of suspect substances
Age; higher yield in adults

constitutional vectors of the atopic diathesis (21). Previous studies have shown that hyperreactivity of the respiratory tissues is intrinsic to AD, even in patients with no history of respiratory allergy (34). The new information from threshold SLS challenges show the cutaneous converse—that atopic persons with normal skin are significantly more sensitive to skin irritation (20). These considerations should reinforce the necessity of avoiding irritant factors in atopic disease generally and in AD specifically to prevent inflammation rising above the clinical threshold.

Decisions on the type(s) of diagnostic testing likewise depend on a wide number of variables for each individual patient (Table 2). Although much of this discussion focuses on ACD, it is very important to understand that other types of cutaneous allergy occur in AD and need to be assessed in patients who are difficult to treat. Thus, in addition to testing for ACD, we also consider indications and methods for testing for contact urticaria and for aeroallergen-induced dermatitis (Fig. 2).

Contact Urticaria Testing

Contact urticaria can result from either pharmacologic, often referred to as nonimmunologic contact urticaria (NICU) (35), or from immunologic (allergic, IgE-mediated) mast-cell release reactions (36). Usually both types of responses, because of their immediacy, are promptly connected to the causative agent by the patient who resolves the problem with avoidance. Symptoms/signs may include stinging,

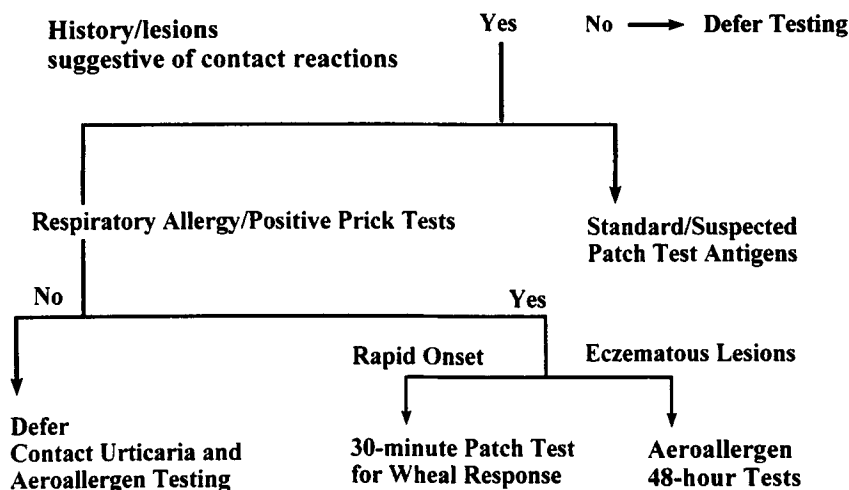


Fig. 2. Algorithm for decisions on indications for testing for ACD, contact urticaria, and aeroallergen-induced eczematous responses.

itching, erythema, papulation, edema, or discrete hives. The milder and more subtle the reaction, the less likely the patient or physician will suspect the causative agent.

The varieties of contact urticants are almost endless, and little studied. Numerous pharmacological (NICU) agents have been studied, with fragrances perhaps the most common incitants, but seldom do any of these agents cause clinically significant disease. Immunologic contact urticaria can likewise be caused by a wide variety of agents, with proteins comprising the majority of clinical problems (36–38) (Table 3). This form of contact urticaria is much more clinically relevant, especially with the increasing incidence of latex allergy. This increase appears to be the result of a combination of factors including the increased use of latex gloves and condoms since the advent of the AIDS pandemic, along with changes in the manufacturing process which left greater quantities of free latex protein. The other major factor in the development of latex allergy is the atopic diathesis, especially AD. Perhaps the largest proportion of patients with clinical latex allergy signs and symptoms are those with past or present AD and they usually have a history of associated hand dermatitis.

When latex allergy crosses the clinical threshold (Table 4), patients typically present with complaints of worsening hand dermatitis. This can be very subtle with barely perceptible erythema and papulation or mild eczematous scaling. After repeated exposure, these changes become more troublesome and begin to require treatment. This progression may be so slow that the gloves are not recognized as the source of the dermatitis; the allergen may only be recognized when sensitivity

Table 3
Materials and Products that Cause Contact Urticaria

Foods	
Eggs, seafood, meats, vegetables, fruits. Latex cross-reactants including avocados, bananas, peaches/nectarines, chestnuts, kiwi	
Animal proteins	
Saliva, urine and other fluids, epidermal materials	
Latex-containing products	
Air mattresses	Pacifiers
Baby bottle nipples	Racquet handles
Balloons	Rubber bands
Balls (rubber, tennis)	Rubber boots, raincoats
Bathing caps	Rubber cement
Cleaning/kitchen gloves	Rubber changing pads and mattress covers
Condoms	Rubber masks
Crutch arm/hand pads	Rubber toys
Diapers with elastic	Shells
Diaphragm for birth control	Sneakers
Elastic in socks, bras, briefs	Surgical drains, catheters
Erasers	Swim and scuba equipment
Finger cots	Tape (cloth adhesive, butterfly closures, moleskin, Coban)
Foam pillows	Teething toys
Goggles	Tourniquets
Latex gloves	Wheelchair tires and cushions
Milkweed plant	
Orthopedic brace linings	

Table 4
Clinical Presentations of Contact Urticaria

Hand eczema
Facial dermatitis
Perioral inflammation in children
Eyelid dermatitis
Vulvar itching/dermatitis
Erythematous papulation
Immediate urtication
Mucosal edema
Angioedema

progresses to the point of rapid onset itching, wheals, or edema. Alternatively, the allergy is noted when latex contacts mucosal surfaces; for example, during dental or surgical procedures. These episodes may range from mild swelling and urtication to anaphylactic shock. Other presentations include eyelid dermatitis, edema, and eczematous changes over the face.

Table 5
Diagnostic Testing for Allergic Contact Urticaria

Demonstrable reaction when a material is applied to the skin or mucosal surface including itching, papulation, wheal formation, or edema within 30 min

OR

Relevant history of reproducible symptoms with exposure to a substance

PLUS

RAST or immediate skin-test reactivity to that substance

Contact urticaria should be considered in all cases of hand and/or facial dermatitis and especially when AD is in the background. Patients should be closely questioned regarding sensitivity induced by food handling or during glove or animal exposure. In children, AD localized to the cheeks and perioral areas may be caused by food-induced contact urticaria, even when ingestion of the food causes no problems. Diagnosis is made most directly by observing urtication when allergen is rubbed on the skin or applied for 5–30 min under patch tests (Table 5). There may be many false negatives with this test procedure, however, depending on the intactness of the stratum corneum barrier and the degree of sensitivity. Conversely, skin-prick tests and intradermal tests may be overly sensitive, causing false-positive responses. The same is true for radioallergosorbent test (RAST) determinations. Positive RAST and/or immediate skin test reactions must be accompanied by a response to skin or mucosal application of a suspected, historically, and clinically relevant product. Because of rare reports of anaphylaxis with latex skin-prick testing (39), it is advisable to first determine whether RAST reactivity exists before skin testing patients, especially if there is any suggestion of rapid or marked skin/mucosal sensitivity to a suspected contact urticant. With low or negative RAST binding, it should be safe to advance to patch testing to verify contact urticaria or to detect ACD to rubber chemicals (Fig. 2), which not infrequently accompanies latex contact urticaria (40). Alternatively, if RAST binding is high and a history of skin or respiratory reactivity exists, a presumed diagnosis of contact urticaria can be made and it may be reasonable to forego patch testing unless there is a strong need to document the contact urticaria; e.g., if workers compensation deliberations require verification.

Testing for ACD in Patients with AD

As discussed, ACD patch testing has widely different perspectives depending on whether one is trying to detect ACD in suspect patients

referred to a contact dermatitis clinic, or trying to find an antigen which may account for therapeutically recalcitrant AD. Although these two groups of patients have similar nuances, especially with regard to irritancy (14), this article focuses entirely on rationale, problems, and interpretation of ACD patch testing in patients with AD.

Rationale

The rationale is similar to that when testing for aeroallergens (described in the next section), the AD is severe and unresponsive to therapy, often widespread and even disabling. Frequently these are corticosteroid-dependent patients referred by increasing concerns about steroid toxicity. Some case reports illustrate the problems and solutions.

Case 1

A 47-yr-old professional photographer had typical AD from infancy. The severity waned during adulthood but worsened 20 yr previously and became unresponsive to topical therapy. The dermatologist began treating the patient with systemic corticosteroids, eventually electing a regimen of alternate-day oral betamethasone therapy which continued during many years. The patient eventually questioned this therapy when he developed premature cataracts and evidence of osteopenia. On referral, the patient suggested that his work with photography chemicals could be contributory. Corticosteroid therapy was discontinued to allow for patch testing which revealed unequivocal 48- and 96-h eczematous reactions to color developer (CD3) and chromate, both relevant to his work. Avoidance of the chemicals allowed resolution of the dermatitis within a month and not even residual AD was evident. We can conclude that this patient's well-documented AD had been replaced with occupational ACD and any patient severe enough to require repeated courses of systemic corticosteroids should be considered for patch testing to exclude the possibility of allergen-induced dermatitis.

Case 2

A 23-yr-old male with lifelong typical flexural AD had become resistant to all attempts at therapy and was referred from another state. He presented with total body erythroderma and was hospitalized in order to institute intensive topical therapy to clear the skin and maintain control of the AD during the 48-h patch-test application. Patch tests demonstrated that this patient had delayed, eczematous reactivity to Kathon CG, a preservative in his long-used moisturizer cream. This patient had ACD to a relevant, frequently used allergen which was causing exacerbation of his AD.

Problems

Patients with AD are without doubt the most difficult group in which to successfully carry out diagnostic 48-h patch testing (Table 6). Problems associated with this testing are daunting:

1. It may be impossible to find an adequate area on the back for patch testing. The requirements include:
 - a. Uninflamed skin: If there is more than very mild erythema, angry back syndrome is likely and the whole process must be repeated. Sometimes application of topical steroids may reduce the inflammation enough to make patch testing feasible.
 - b. Nonimmunosuppressed skin: Systemic corticosteroids should ideally be discontinued at least 1 wk prior to testing and topical steroids must not be used on these sites for at least 48 h before applying patches.
 - c. Up to 50% of the back may be needed for patch-test application. Patients with extensive dermatitis involving the back, which does not respond to topical therapy, must be hospitalized because the only other way to clear the skin is with systemic corticosteroids or other immunosuppressives. If that is done, they cannot be reliably patch tested because the immune reaction will be suppressed. For these reasons, with severely affected patients, hospitalization (for 5–7d) is required to accomplish adequate testing.
2. Wide range of antigen exposures: Patients with AD are chronically treated, often with a myriad of different agents. In some instances, one or a few highly suspect antigens may be tested. Usually a large number must be screened. The most important of these would include:
 - a. Skin care products used by the patient or partner.
 - b. Topical medications including corticosteroids.
 - c. Occupational materials.
 - d. Rubber, especially in gloves and shoes.
 - e. Chemicals to which the patient may be exposed from hobbies or other leisure pursuits.

Generally it is best also to test patients with a series of common chemical allergens such as that prepared by the North American Contact Dermatitis Group (41) or a standard set available commercially from the American Academy of Dermatology (42). A new commercial product is marketed as TRUE Test but its reliability in testing patients with AD has not been established.

3. Keeping patch tests on: These patients have very scaly skin and tape almost never sticks well. An additional problem is that their skin is often saturated with lipid moisturizers. Generally the back should be tested 1 h after bathing it with generous use of mild soap or cleanser. Patch-test tapes are then multiply reinforced by apply-

Table 6
Problems Encountered in Patch Testing of Patients with AD

Finding an uninflamed adequate area on the back for testing
Deciding which antigens to test
Keeping patch tests in place for sufficient time to allow early (2-d) readings
Keeping test sites marked for 2–5-d late readings
Hyper-irritability, angry back syndrome
Ambiguous reactions
Irritant
Rapid onset, usually within 24 h
Well-demarcated
Confined to exact test site
Smooth, glazed, or cracked surface with slight erythema
Develops in most subjects
Allergic
Delayed onset, 48–96 h
Indistinct margins
Spreading reaction beyond test site
Induration, papulation, and vesiculation
Affects only a few, sensitized subjects
Establishing relevancy of positive ACD responses
Educating patients in avoidance of proven allergens

ing to skin prepared with tincture of benzoin or Mastisol® to increase adhesion.

4. Test sites must be indelibly marked when patches are removed at 48 h so that the late reading can be accomplished 2–5 d later. Patients must be advised before starting the patch-test process that the area cannot be bathed for at least 4 d.
5. Skin hyper-irritability: This is intrinsic to AD and the concern about the angry back syndrome (23) requires that the general level of dermatitis be stable and well-controlled throughout the patch-test process. As noted, it is best if patients are controlled in hospital during at least the 2-d period of patch application. Even in the best controlled situations, some patients will have complete or partial flaring over the test area and patches will have to be reapplied at a later date.
6. Distinguishing between irritant and allergic responses: The characteristics of these responses are listed in Table 6. Even with extensive experience, ambiguous reactions are encountered, especially on AD skin. If there is any doubt of allergic positivity or relevancy, a given test or group of tests should be repeated. Whenever multiple irritant reactions are noted, it is a firm policy to repeat those reactions at a later date (14).
7. Establishing relevancy: When a patch-test site has all the characteristics of ACD (Table 6), persisting at least 72–96 h, it can be

considered indicative of allergy to that chemical. It should not be considered clinically relevant unless the patient has had exposure to that antigen in proximity to the clinical dermatitis. Also, clinical relevancy cannot be considered conclusive unless avoidance of the chemical leads to clearing (*see* Cases 1 and 2) and re-exposure reproduces the clinical disease. Obviously, not all of these requirements can be met for every case, but it is a disservice to label as allergy an irritant reaction or an isolated sensitivity to which the patient has had no recent exposure.

8. Educating for avoidance: When a relevant ACD is diagnosed, it can provide a cure of the disease, if the patient discontinues exposure to the allergen. Ideally, that person would be informed of all possible sources of that chemical in the environment and could freely substitute nonallergenic materials. This ideal is seldom met but we can provide lists of common allergen sources and can access standard reference books that will inform about the more unusual sensitizers (43–45). Once informed, it behooves patients to consistently read chemical constituents of products they use. This is especially true if patients develop allergy to constituents of skin care products; they are well-advised to use the simplest, least chemically adorned preparations possible.

Interpretation

This crucial element to diagnosis is dealt with in items 5–7 in the previous section. By far the greatest source of misinterpretation is the overreading of patch-test site reactions, diagnosing allergy when it is not conclusive. There is always a desire to find something positive—in essence, producing a “reward” for both patient and physician—but this can have a continuing negative impact on the patient. It often also propounds misinformation that may be transmitted to other physicians and cause diagnostic confusion for many years.

Aeroallergen Patch Testing

This is the most primitive type of allergy testing for patients with AD. It has received irregular but considerable attention from investigators during the past decade. The hope is that this type of testing will bridge the uncertain gap between the immediate skin-test wheal response, which is easily elicited, present in 80% of AD patients, but not at all representative of AD lesions, and the eczematous response which characterizes AD. If this dichotomy could be resolved, it might provide better evidence for allergen causation of AD.

Unfortunately this testing method has not yet provided reliable answers because of the wide variation in techniques that create an almost infinite number of confounding variables (Table 7). These vari-

Table 7
Confounding Variables in Aeroallergen Patch Testing

Frequency of positive tests (25–100%)
Varied antigens—pure protein to fresh-ground mites
High vs low antigen concentrations
Site preparation—intact, abraded, scratched, or stripped
Patch test materials and methods
Uncertain relationship to prick-test reactivity
Presence/absence of basophils
Duration of response (48 h or 7 d)
Reaction frequency in atopic controls (irritancy)

ables include widely different antigens both qualitatively and quantitatively, skin-test site preparations, patch-test chamber types, and many other methodologic inconsistencies. Reflecting this, the frequency of positive aeroallergen patch test results have varied from the most usual 20–30% range to extremes of approaching 100% (46–54, and *see* Table 1 in Taïeb and Ducombs article in this issue). Irritant controls have not been stringently included in most studies, causing considerable uncertainty in trying to interpret results. Consistency and reproducibility of positive patch tests are unknown in aeroallergen patch-test studies.

In spite of all these doubts, however, there appear to be some conditions and some patients with AD who develop eczematous allergic responses to preparations such as house dust mite, birch, grass, and animal allergens (55). Darsow et al. (56) recently attempted to improve aeroallergen patch testing, what they call the “atopy patch test,” toward a more standardized approach. They recommended large (12 mm) Finn Chambers on untraumatized skin sites over the back for 48-h test durations using relatively high allergen protein nitrogen unit (PNU) concentrations. With these methods, they observed positive eczematous reactions in nearly 50% of patients with AD, particularly in those with a history suggestive of aeroallergen worsening of their dermatitis. This latter point relates to relevancy but unfortunately for this important proof factor, history is notoriously imprecise and there are no good challenge methods (Table 8). Thus, although there is reasonable evidence for aeroallergen-induced lesions in a proportion of patients with AD, we are far from ascertaining the size of that proportion. Many physicians assume, based largely on faith, that the proportion is high; critical scrutiny finds most studies based more on opinion than hard data.

At present, there is no way to prove aeroallergen causation, but a positive, properly controlled eczematous patch-test reaction in a clinically relevant setting would provide better support for allergy prevention. Immediate wheal responses alone rarely correlate clinically with

Table 8
Evidence Needed for Proof of Allergen Causation of AD

Maintenance/worsening of disease when environment contains suspect allergen
Clearing/improvement in allergen-free environment
Morphologically and histologically similar lesion consistently reproduced by epicutaneous skin-test application of purified antigen
Disease extent and distribution reproduced by challenge (cutaneous, respiratory, or gastrointestinal) with purified antigen

allergen triggering of AD, thus providing little support for such allergen avoidance measures.

Summary

We have outlined rationale and problems associated with three types of patch tests that may provide diagnostic help in patients with difficult-to-manage AD. Each of these methods is imperfect and in need of greater study using a critical approach, better techniques, more attention to irritant controls, and better definition of atopic populations. Proof of validity for aeroallergen patch testing will necessarily require large quantities of purified antigens. In spite of all these problems, patch testing can be useful and sometimes essential for the diagnosis and management of difficult AD.

References

1. Lobitz, W. C., Jr., Honeyman, J. F., and Winkler, M. W. (1972), *Br. J. Dermatol.* **86**, 317–328.
2. Rostenberg, A., Jr. and Sulzberger, M. B. (1937), *Arch. Dermatol.* **35**, 433–454.
3. Jones, H. E., Lewis, C., and McMarlin, S. L. (1973), *Arch. Dermatol.* **107**, 117.
4. Hanifin, J. M. and Lobitz, W. C. (1977), *Arch. Dermatol.* **113**, 663–670.
5. Palacios, J., Fuller, E. W., and Blaylock, W. K. (1966), *J. Invest. Dermatol.* **47**, 484.
6. Rees, J., Friedmann, P. S., and Matthews, J. N. S. (1990), *Arch. Dermatol.* **126**, 1173–1175.
7. Byrom, N. A. and Timlin, D. M. (1979), *Br. J. Dermatol.* **100**, 491–498.
8. Elliott, S. T. and Hanifin, J. M. (1979), *Arch. Dermatol.* **115**, 36–39.
9. Elliott, S. T. and Hanifin, J. M. (1979), *Arch. Dermatol.* **115**, 1424–1426.
10. Uehara, M. and Sawai, T. (1989), *Arch. Dermatol.* **125**, 366–363.
11. Cronin, E. and McFadden, J. P. (1993), *Contact Dermatitis* **28**, 225–228.
12. Lever, R. and Forsyth, A. (1992), *Acta. Derm. Venereol. (Stockh.)* **176(Suppl.)**, 95–98.
13. Whitmore, S. E. (1994), *Dermatologic Clinics* **12**, 491–499.
14. Klas, P. A., Corey, G., Storrs, F. J., Chan, S. C., and Hanifin, J. M. (1996), *Contact Dermatitis* **34**, 121–124.
15. Lammintausta, K., Kalimo, K., and Fagerlund, V.-L. (1992), *Contact Dermatitis* **26**, 234–240.
16. De Groot, A. C. (1990), *Contact Dermatitis* **22**, 273–277.
17. Goebeler M., Meinardus-Hager, G., Roth, J., Goerdts, S., and Sorg, C. (1993), *J. Invest. Dermatol.* **100**, 759–765.

18. Lindberg, M., Farm, G., and Scheynius, A. (1990), *Acta. Derm. Venereol.* **71**, 384–388.
19. Nickoloff, B. J., Griffiths, C. E. M., and Barker, J. N. W. N. (1990), *J. Invest. Dermatol.* **94**, 151S–157S.
20. Nassif, A., Chan, S. C., Storrs, F. J., and Hanifin, J. M. (1994), *Arch. Dermatol.* **130**, 1402–1407.
21. Hanifin, J. M. and Chan, S. C. (1995), *J. Invest. Dermatol.* **105(Suppl.)**, 84S–88S.
22. Bruynzeel, D., Van Ketel, W., Von Blomberg van der Flier, M., and Scheper, R. (1983), *J. Am. Acad. Dermatol.* **8**, 392–397.
23. Roper, S. and Jones, H. (1982), *J. Am. Acad. Dermatol.* **7**, 643–650.
24. Agner, T. (1991), *Br. J. Dermatol.* **125**, 140–146.
25. Chan, S. C., Kim, J.-W., Henderson, W. R., and Hanifin, J. M. (1993), *J. Immunol.* **151**, 3345–3352.
26. Ohmen, J. D., Hanifin, J. M., Nickoloff, E. N. J., Rea, T. H., Wyzykowski, R., Kim, J., et al. (1995), *J. Immunol.* **154**, 1956–1963.
27. Butler, J. M., Chan, S. C., Stevens, S. R., and Hanifin, J. M. (1983), *J. Allergy Clin. Immunol.* **71**, 490–497.
28. Chan, S. C., Li, S.-H., and Hanifin, J. M. (1993), *J. Invest. Dermatol.* **100**, 681–684.
29. Uehara, M. and Miyauchi, H. (1984), *Arch. Dermatol.* **120**, 1186–1190.
30. Finlay, A. Y., Nicholls, S., King, C. S., and Marks, R. (1980), *Br. J. Dermatol.* **102**, 249–256.
31. Traupe, H. (1991) *Ann. Dermatol. Venereol.* **118**, 487–496.
32. Shmunes, E. and Keil, J. E. (1983), *J. Am. Acad. Dermatol.* **9**, 861–866.
33. Rystedt, I. (1985), *Contact Dermatitis* **12**, 164–171.
34. Barker, A. F., Hirshman, C. A., D'Silva, F., and Hanifin, J. M. (1991), *J. Allergy Clin. Immunol.* **87**, 780–783.
35. Lahti, A. (1980), *Acta. Dermatol. Venereol.* **60(Suppl. 91)**, 1–46.
36. Hjorth, N. and Roed-Petersen, (1976), *Contact Dermatitis* **2**, 28–42.
37. von Krogh, G. and Maibach, H. I. (1981), *J. Am. Acad. Dermatol.* **5**, 328–342.
38. von Krogh, G. and Maibach, H. I. (1982), *Semin. Dermatol.* **1**, 59–66.
39. Task Force on Allergic Reactions to Latex (1992), *J. Allergy Clin. Immunol.* **92**, 16–18.
40. Rich, P., Belozzer, M., Norris, P., and Storrs, I. F. (1991), *J. Am. Acad. Dermatol.* **24**, 37–43.
41. Marks, J. G., Jr., Belsito, D. V., DeLeo, V. A., Fowler, J. F., Jr., Fransway, A. F., Maibach, H. I., Mathias, C. G. T., Nethercott, J. R., Rietschel, R. L., Rosenthal, L. E., Sheretz, E. F., Storrs, F. J., and Taylor, J. S. (1995), *Am. J. Contact Dermatitis*, **6**, 160–165.
42. Storrs, F. J. and Bell, D. E. (1983), *J. Am. Acad. Dermatol.* **8**, 157–170.
43. Rietschel, R. L. and Fowler, J. F., Jr., eds., (1995), *Fisher's Contact Dermatology*, 4th ed., Williams and Wilkins, Baltimore.
44. Adams, R. M., ed. (1990), *Occupational Skin Disease*, 2nd ed., Saunders, Philadelphia.
45. Estrin, N. F., Crosley, P. A., and Haynes, C. R., eds. (1982), *CTFA Cosmetic Ingredient Dictionary*, 3rd ed., The Cosmetic, Toiletry and Fragrance Association, Inc., Washington DC.
46. Reitamo, S., Visa, K., Kaehonen, K., Kayhko, K., Lauerman, A. I., Stubb, S., and Salo, O. P. (1989), *Acta. Derm. Venereol. Suppl. (Stockh.)* **144**, 119–121.
47. Adinoff, A. D., Telez, P., and Clark, R. A. F. (1988), *J. Allergy Clin. Immunol.* **81**, 736–742.
48. Bruynzeel-Koomen, C. A. F. M., van Wichen, D. F., Spry, C. J. F., Venge, P., and Bruynzeel, P. L. B. (1988), *Br. J. Dermatol.* **118**, 229–238.
49. Gondo, A., Saeki, N., and Tokuda, Y. (1986), *Br. J. Dermatol.* **115**, 485–493.
50. Imayama, S., Hashizume, T., Miyahara, H., Tanahashi, T., Takeishi, M., Kubota, Y., Koga, T., Hori, Y., and Fukuda, H. (1992), *J. Am. Acad. Dermatol.* **27**, 531–538.

51. Seidenari, S., Manzini, B. M., Danese, P., and Giannetti, A. (1992), *Ann. Allergy* **69**, 201–206.
52. Mitchell, E. B., Crow, J., Chapman, M. D., Jouhal, S. S., Pope, F. M., and Platts-Mills, T. A. E. (1982), *Lancet* **1**, 127–130.
53. Castelain, M., Birnbaum, J., Castelain, P. Y., Ducombs, G., Grosshans, E., Jelen, G., et al. (1993), *Contact Dermatitis* **29**, 246–250.
54. Cabon, N., Ducombs, G., Mortueux, P., Perromat, M., and Taïeb, A. (1996), *Contact Dermatitis*, in press.
55. Norris, P. G., Schofield, O., and Camp, R. D. R. (1988), *Br. J. Dermatol.* **118**, 435–440.
56. Darsow, U., Vieluf, D., and Ring, J. (1995), *J. Allergy Clin. Immunol.* **95**, 677–684.