

Technical and Ethical Problems Associated with Patch Testing

Frances J. Storrs

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

Introduction

The German dermatologist, Joseph Jadassohn, first presented the results of his innovative patch-testing technique in 1895 and published these results in 1896 (1). Thus, this is the centenary of patch testing: a diagnostic tool whose safety and efficacy has stood the test of time.

In 1994, a ready-to-use strip of patch-testing allergens which are prepared in a gel base and then affixed to a self-adhesive material became available in the United States (TRUE Test™, Glaxo Dermatology Research, Triangle Park, NC). Although this system has increased the frequency of patch testing in the United States, it has not decreased the problems that are associated with patch testing. In many instances, the result of inexperienced physicians using the TRUE Test has been misinformed or uninformed patients, and an increased number of referrals to dermatologists with patch-testing expertise. In some instances, this has represented an unnecessary duplication of effort.

This article reviews the problems that can be associated with patch testing, and it also raises some ethical issues that patch testing can present (*see* Table 1).

Should Nondermatologists Patch Test?

In the United States, 27% of the members of the American Academy of Dermatology do not perform patch testing (2). Many American dermatology residency programs do not teach patch testing in their curricula. I know of no allergy or primary care medicine programs in this country that teach patch-testing application and evaluation techniques, though there may be some.

Table 1
Possible Ethical Issues Raised by Patch Testing

Use without training
Underuse
Overuse
Deceptive testing
Clinical patch-testing experiments
Testing new allergens
Sensitization

Deciding whom to patch test requires skill in the differential diagnosis of skin disease. The misassumption that dermatomyositis, tinea manum, or psoriasis is allergic contact dermatitis can be inappropriately expensive when patients with these diseases are unnecessarily patch tested. This kind of misdiagnosis is more likely to be avoided when dermatologists are making the decision about whom they should patch test. Appreciating the subtleties of distribution in an airborne plant contact dermatitis or the possibility that a dermatitis may be photo induced, or even that it may have begun as contact urticaria which eventuated in a clinical presentation of dermatitis, all require considerable dermatologic training and experience. This is particularly the case when patch tests are interpreted, or a therapeutic regimen, which will help the patient is constructed after testing. Even dermatologists may have difficulty predicting the outcome of patch testing based on a pre-test, clinical diagnosis (3). Often the specific allergen, or even the possibility of allergic contact dermatitis is not appreciated and is incorrectly felt to be irritant dermatitis. This is, however, the reason that patch testing is done.

I appreciate that my opinion is the chauvinistic one of a dermatologist. Evidence suggests, however, that dermatologists with special training in patch testing and with focused training in the diagnosis and management of skin disease are the ones best able to do the majority of patch testing in the United States. This is an opinion that is shared by others, but of course not by everyone (4).

Problems with Patch Testing

Patch testing is the only objective means of diagnosing allergic contact dermatitis. The application methods are precise and are described in excellent current textbooks and in articles that have been written for physicians or for nurses and office assistants, who are the individuals most likely to actually apply the patch tests (5-7). The appropriate application method can be taught easily (7). The art of interpreting the results of patch testing, and of understanding the side effects and

Table 2
Side Effects of Patch Testing

Severe local reaction
Flare reaction at distant sites
"Angry back"/"excited skin" syndrome
Koebner reaction (isomorphic reaction)
Pigment changes
Persistence
Scarring and keloids
Infections
Anaphylaxis (very rare)
Sensitization

problems associated with patch testing, is a much harder skill to acquire. These skills are developed by taking courses, by reading, and by actual experience.

Patch testing, like other diagnostic tests, has potential side effects. These side effects are listed in Table 2 and can be minimized by testing with standardized allergens and using appropriate application techniques. These side effects are elaborately described in standard textbook sources (5,6). Unfortunately, the Food and Drug Administration (FDA) currently sanctions the use of only 28 allergens in the United States which has made it difficult to acquire a variety of standardized allergens, and has encouraged the use of "homemade materials." Using such nonstandardized allergens tends to increase the side effects associated with patch testing.

A separate set of problems associated with patch testing relates to the skills one needs to accurately interpret the results of the testing and the consequent application of these results to a particular patient situation. The longer patch testing is done, the more humble the dermatologist becomes, and begins to realize that all he or she "knew" was true about patch testing, was not (8). Table 3 lists some of the obstacles that a patch tester can encounter. Several of these are worth elaboration.

Separating Irritant and Allergic Reactions

The separation of the irritant from the allergic reaction based on appearance can be impossible. Patch testers who maintain, with confidence, that they can make this distinction should be suspect. Alexander Fisher, the doyen of American patch testers, stated that, "There is no morphological way of distinguishing a weak irritant patch test from a weak allergic test" (5).

Even strong reactions can be difficult to distinguish and definitely deceptive. The belief that irritant reactions disappear with time, and that allergic reactions worsen with time can also lead to mistaken inter-

Table 3
Obstacles to Accurate Patch-Test Interpretation

Separating irritant and allergic reactions
Determining the optimum reading time
Reproducibility
Scoring reactions
"Angry back"/"excited skin" syndrome
Misreading reactions
False positives
False negatives
Determining relevance
Appreciating crossreactions and coreactions

pretation of results. The preparation of nonstandardized allergens is likely to make this problem even more difficult, particularly in the absence of controls. There are textbooks that suggest patch-testing concentrations for unusual allergens, and individuals doing extensive patch testing should own these books (9).

There are also methods that can be used that will help separate irritant from allergic reactions. These include such things as testing to dilutions of the allergen, doing open tests, doing use tests, and being willing to retest patients to allergens that have given confounding results (6).

In the last analysis, the separation of irritant from allergic reactions is the biggest problem that confronts patch testers, and it is done best by physicians who patch test frequently and have a clear understanding of the behavior of their own allergens, and who also are skilled in the clinical subtleties that result in a final interpretation of irritancy or allergy.

Determining the Optimum Reading Time

Although there is some controversy about the absolute best time to read patch tests after application, there is general consensus that patch tests should be read twice (10). The second reading enriches the opportunity to more accurately interpret the results by watching their evolution over a several day period. There is some evidence that, if circumstances allow only one reading, this should be done on the 4th d after patch-test application (11).

Convention dictates that patch tests are left in place for 48 h before they are read. There is some inconclusive suggestion that, at least for some patch-test allergens, 24 h of application may be sufficient.

Failure to appreciate the importance of watching the evolution of patch-test reactions over several days, particularly as it relates to the interpretation of irritancy and allergy, can be a real impediment to the accurate reading of the tests.

Reproducibility

A patch test is a bioassay, and as such is subject to the vicissitudes of the person being patch tested. Illnesses and drugs that alter immune response can have significant influence on results. It is a fact, however, that both positive and negative patch tests may not be reproducible on subsequent testing. Because of this fact, the patch tester must always be prepared to repeat both positive and negative patch tests.

The sensitivity and specificity of the patch-testing system must always be borne in mind. For any one individual, one particular allergen-testing concentration may be just high enough to produce irritation, or just low enough to produce allergy (12). Each individual has his or her own threshold for each allergen and, as a result, large panels of patients must be evaluated with allergen collections in order to get a sense of their behavior over time.

There has been a dispute in recent years as to precisely how reproducible patch testing is. The consensus suggests a reproducibility of 80–85%, though this varies from study to study (13,14).

“Angry Back”/“Excited Skin” Syndrome

When individuals with extensive dermatitis are patch tested, or when there are numerous positive allergic reactions, a phenomenon known as the “angry back” or “excited skin” syndrome may occur (15). This situation results in numerous low-grade “positive” reactions which disappear with repeat testing. Although this syndrome is somewhat controversial, there is little doubt that multiple, minimal reactions should be suspect in any given patient (16). Failure to appreciate the importance of the excited skin syndrome results in misinterpretation of “allergic” reactions in the hands of inexperienced patch testers. Such interpretations require undiagnosing when patients are reevaluated by more experienced patch testers. Most all of these misinterpretations can be avoided if the physician is willing to repeat patch tests.

Determining Relevance

Once a patch test has been interpreted as being an allergic one, the most difficult task can be that of determining relevance for the allergen in the patient’s environment. There are studies which have been published that indicate both the prevalence and relevance of American patch-test reactions (17). The practical use and application of the testing results are only as good as the information base, experience, and curiosity of the individual doing the testing. The most recent textbook of contact dermatitis in the United States has 1117 pages (5). There are numerous other excellent textbooks on contact dermatitis

as well as two excellent English language journals. (*American Journal of Contact Dermatitis* [Saunders, Philadelphia] and *Contact Dermatitis* [Munksgaard, Copenhagen, Denmark]).

In the United States, the American Contact Dermatitis Society has two annual meetings in which information about new allergens is presented. This Society also has a membership directory that includes a consensus statement about patch testing and allergic contact dermatitis as well as guidelines for the evaluation of eczematous skin diseases (18).

In short, keeping abreast of the sources of allergen exposure in the United States alone can be a significant endeavor. Failure to make this effort results in patch-test evaluators who are of much less value to their patient.

Other problems that confront the novice patch tester and that require training and experience to overcome include learning how to read and score reactions, learning when to suspect false-positive and false-negative reactions, and finally learning to appreciate cross-reactions as well as predictable coreactions (e.g., neomycin and bacitracin reactions occurring simultaneously, even though they are unrelated chemically).

Failure to appreciate any of these aspects of testing renders the testing process less valuable. Fortunately, there are means of overcoming these obstacles if one is genuinely interested in learning to patch test patients with contact dermatitis.

Possible Ethical Issues Raised by Patch Testing

Helping patients with contact dermatitis is so satisfying that the effort necessary to master the techniques of patch testing is well worth it. My chauvinistic position would restrict the use of patch testing to dermatologists or to physicians with special training in this technique, as well as special training in the diagnosis and therapy of skin disease. Thus, it might be said that the paramount ethical issue that confronts the patch tester is undertaking it without proper training. This same principle could be applied to any medical procedure, of course. There are other ethical issues raised by patch testing (*see* Table 1).

Underuse of Patch Tests

A number of authors have been credited with supporting the concept that, "the greatest abuse of patch testing is the failure to use the test" (19). An appreciation of the value of diagnosing a reason for a patient's chronic dermatitis correspondingly results in great disappointment for physicians who see patients whose misery could have been abated by a much earlier use of the patch test. The decision of whom to patch test can be an important and cost-effective one. A suggested list of conditions that might benefit from patch testing is

included in Table 4, and is derived from a statement prepared by the American Contact Dermatitis Society.

Occupational skin disease is one of the most common work-related illnesses in the United States. Discovering causation, be it irritancy or allergy, for work-related skin disease, usually hand eczema, can be greatly assisted by patch testing. Failure to make these diagnoses results in patient morbidity, time loss from work, and millions of dollars in medical and work-related cost (20,21).

It was mentioned previously that, in fact, many dermatologists do not perform patch testing and are not trained in its use (2). It is also unfortunately true that even the best trained dermatologist may fail to appreciate that a chronic dermatitis has an allergic component, and additionally may be unable to predict what that allergen is (3,22). In short, even the most experienced patch testers are often surprised by what they learn from patch testing a patient with one of the conditions listed in Table 4. A dermatologist can, however, more accurately diagnose those conditions likely to benefit from patch testing.

It has been said that, if one is getting more than 60% positive patch-test reactions, they are doing too little patch testing (23). In a population of patients with suspect allergic contact dermatitis the average number of positive reactions is 53% (23).

In short, patch testing is an invaluable and essential tool in the diagnosis of allergic contact dermatitis. Failure to use it, or to ask for consultation for a patient who could benefit from its application might indeed be cited as a potential ethical misdeed.

Overuse of Patch Testing

Patch testing is a cost-efficacious procedure which is well compensated in most parts of the United States (23). Because patch tests are billed for by the unit (as much as \$11/patch in some places), a seduction can exist to apply more patch tests than are necessary. Clearly, screening trays of allergens can be helpful in patients whose histories are obscure. On occasion, however, one is seeking a specific family of chemicals, and in such instances more focused or aimed testing may be appropriate. This is possible when studies exist that allow the patch tester to use just a few, rather than many, allergens to diagnose something such as acrylate allergy to nail products, or sesquiterpene lactone allergy to compositae plant family members (24,25). If a patient's history suggests neomycin allergy as the obvious allergen, it is certainly most appropriate to begin patch testing the patient to neomycin alone and to add other allergens only if this testing fails, or if the patient worsens.

Certainly the values that relate to too little patch testing would also suggest that, if a physician is seeing fewer than 30% positive

Table 4
Conditions Likely to Profit from Patch Testing

For diagnosis
Chronic hand eczema that worsens or changes its distribution.
Fingertip vesicular dermatitis.
Chronic stasis dermatitis.
Contact dermatitis that does not improve with avoidance of the suspected allergen or "obvious" allergen.
Dermatitis of unknown cause that prompts hospitalization for management or that limits a patient's ability to work or participate in the usual activities of daily living.
Dermatitis that recurs after treatment of systemic corticosteroids.
Any contact dermatitis where cause is unknown.
For management
Uncontrolled dermatitis even if patch tests were negative in the past.
New episodes of contact dermatitis in a patient already known to have one or more contact allergies.
Any primary skin disease that worsens with topical therapy.
For workers compensation/disability determination
Any probable workplace-related dermatitis, especially in high-risk occupations (e.g., hairdressers, machinists, health care workers).
Chronic occupational dermatitis, especially when job change is likely.
To demonstrate patch test negativity to a specific substance or persistence of positivity to another.

Adapted from ref. 18.

reactions for their patch-testing effort, they are probably doing too much testing (22).

In the United States, a vigorous effort is being made to sell a new patch-testing system (TRUE Test, Glaxo Dermatology) to both dermatologists and nondermatologists. A highly focused advertising effort is underway, and I would caution people untrained in patch-testing methods against undertaking such testing, in that it is likely to result in misdiagnoses, a need for referral and repeat patch testing (in many instances undiagnosing), and the collection of uninterpretable results. Greed is always an issue in medicine as in many other pursuits, and it is appropriate that all of us review constantly the potential for a personal conflict of interest with our patient's good (26).

Deceptive Patch Testing

Little is written on the use of patch tests to deceive patients (27). Some years ago, I was asked to evaluate a patient who had a large ulceration that involved her eye and eventually resulted in her enucleated orbital socket being covered with a large skin flap. Photographs of the early ulcer showed linear lesions that suggested factitia to most any

Table 5
Eliciting Factitial Patch-Test Reactions

Patch test in duplicate
One accessible and one inaccessible set
"Mislabel" one set of patches
Use placebo patches and arrange them blindly
Repeat confusing results
Keep patches for later confirmation
Photograph results

dermatologist that examined the pictures. In the process of evaluating her, we were able to develop a system using water as a patch-test material that would always result in the appearance of an erosion at the site of the water patch test within 24 h. Although this did not prove that the permanent waving solution that she cited as the cause of her enucleation was innocent, it did indeed cast doubt on her own credibility, particularly when irritant reactions to the suspect hairdressing materials were difficult or impossible to elicit.

The technique that we developed, we subsequently used in patients who were malingering, or who were overly concerned that their work-related claim might be rejected. This method is outlined in Table 5, and in essence consists of the use of patch tests applied in duplicate. One set of the tests is unlabeled and is applied in an inaccessible location. Another set is readily available to the patient and is labeled in a suggestive, but not necessarily accurate, fashion. For example, water, which is in fact a constituent of a hairdressing chemical, might be labeled "hairdressing chemical" instead of water. These labels are readily visible to the patient. The patch tests are arranged blindly by an assistant so that the reader is obligated to read them objectively. The results are carefully photographed, recorded, and repeated when they are doubtful.

I have found this sort of patch testing to be of great value in both identifying real malingerers, and in certifying credible patients. In my view, it is fully justified, though I accept that many readers may disagree with me. I usually do not confront my patients with the meaning of the results, but rather simply tell them what the results are. Seldom do they question me, and I indicate the results of the testing in my reports, which are invariably to other doctors, or to insurance companies or lawyers.

The use of patch testing in this deceptive fashion is an excellent example of the kind of ethical issue that one can confront. I have chosen to use some deception in evaluating this special group of patients, and do believe that it is justified.

Clinical Patch-Testing Experiments

On occasion, individuals interested in contact dermatitis may wish to report a new allergen whose performance in patch tests is uncertain. In order to validate eczematous allergic responses to this chemical, the allergen should be applied to many control patients. Although this may involve the application of these new allergens in low doses and as part of panels of allergens to patients who have other kinds of contact dermatitis, it is generally accepted by patch-testing experts that this is appropriate and necessary. In some centers, informed consent is obtained for even the application of standard allergens. In many others, it is not.

Another example of a clinical patch-testing experiment would include the evaluation of irritants in patients with an underlying skin disease such as atopy. In instances such as this, the patch testing is not being done for control development, nor is it of any necessary value to the patient. In such instances, it is most appropriate that informed consent be obtained from the patient, and that appropriate approval be obtained from an institutional review board.

In order to understand new allergens, on occasion patients with one allergy will be patch tested to numerous other related substances in an effort to determine the magnitude of crossreactions. Again, although the individual patient may not benefit greatly from such an evaluation, it is generally agreed that with the informed consent of the patient, this sort of experimental patch testing is justified (24,28).

Recently, the FDA in the United States has requested extensive patch testing of previously sensitized individuals in order to verify that allergens being marketed could indeed identify individuals known to be allergic to them (13). This sort of requisite testing has delayed, dramatically, the reintroduction of allergens previously readily available in the United States, and long available in Europe. It has additionally caused discomfort through the repeat patch testing to the paid patient volunteers who agree to participate in these studies, and has shown the same problems with reproducibility that all patch-test studies have. The costs of this testing have been great, and this has been reflected in the increased cost of patch testing allergens in America. Whether such testing is ethically justified may be a moot point, but it is clearly a subject that might be vigorously debated.

Sensitization

Sensitization by patch testing was cited in Table 2 as a potential side effect. Sensitization does occur, but it is a rare event. One would suspect sensitization to an allergen if the reactions were read as nega-

tive at a 2, 4, and 7-d session, but the site of the allergen application flared after 10–20 d and then a positive reaction resulted after a 2- and/or 4-d reading on retesting. It is known that if the concentration of a patch test is too great, the likelihood of sensitization is markedly increased (29–31). This risk is greater when nonstandardized allergens are used for patch testing and must be borne in mind when one is evaluating new allergens (32). Despite the fact that sensitization can occur, it is an unusually rare event, and even when it does occur, it is probably not clinically significant. A number of follow-up patch testing studies have demonstrated that as patients gain and lose allergens, their clinical disease remains static (33,34).

A slight variation on this theme includes the risk associated with repetitive patch testing. In clinical patch-test studies, patch tests are often applied several times: One substance may be applied at several points on the back, one substance may be applied every week or so in combination with related substances, and so on. Although one might think that such studies might worsen the underlying dermatitis or could increase even further the risk of sensitization, the data shows that this is not the case.

In a classical study performed by Kligman (35), volunteer patients who were repetitively patch tested to poison oak actually became less reactive to the allergen over time. This has also been shown in clinical situations. Hairdressers who knew they were allergic to glyceryl thioglycolate found in permanent wave solutions refused to stop administering permanent waves, and rather than worsening their hand eczema, many of them actually improved (36). Such interesting responses have also been seen in brake-lining factories where many workers became allergic to the catechols in the cashew nuts that were used to manufacture the brake linings. Over time they recovered from this allergy and were able to work with the previously allergenic substances (37).

Sensitization is certainly a theoretical concern, but in actuality it is seldom, if ever, of practical significance. The standard trays of allergens available in the United States and Europe have been developed to exclude chemicals that have a record of sensitization, such as salicylanilides and some dyes. Concentrations are low enough to identify most allergic patients and to minimize sensitization (12,31).

Very rarely, paraphenylenediamine will sensitize a patient undergoing standard patch testing, but in large, multicenter patch-test trials of standard batteries of allergens, sensitization has been a virtual nonoccurrence (14). When nonstandard allergens are used, and particularly when they are used in inappropriately high concentrations, sensitization is indeed a risk, and consequently must be considered from an ethical viewpoint when using “homemade” allergens.

Summary

When relevant allergens are identified by patch testing, and patients can avoid them in their environment, improvement of dermatitis is the rule. Some forms of chronic dermatitis may not clear completely, but patients are usually satisfied with modification of their previously more severe problem. In 1981 when asked what he felt were the five most important advances in clinical dermatology during the 20th century, Dr. Marion B. Sulzburger, an icon in American dermatology, said that, "The increased use and usefulness of the patch test and the international standardization of test concentrations and methods" was number one. Those of us who are enthusiastic patch testers and fascinated by the evaluation of patients with irritant and allergic contact dermatitis would agree.

It is a thrilling clinical experience to be able to tell a machinist that he need not stop his lifelong occupation, but instead will do fine if he will simply avoid the waterless hand cleanser he has been using which is preserved with glutaraldehyde. The woman whose facial dermatitis has embarrassed her for years and clears when she stops using the Quaternium-15 preserved moisturizer that you have identified in your patch testing is grateful to you forever, and again happy in her own life.

In 1991, my research assistants, Patricia Norris and Mary Lou Belozar, and I studied 30 university hospital workers who answered our advertisement asking for individuals who believed they were troubled by their rubber gloves (unreported study). By evaluating these people through history, physical examination, and patch testing, we were able to prove glove relatedness in 14 of them. Nine of the 14 had contact urticaria to latex, and only 5 had allergic contact dermatitis to rubber glove ingredients. Fifteen of our patients had irritant dermatitis. In this study, none of the patients with allergic contact dermatitis to glove ingredients had contact urticaria. However, since that time, we have observed a number of patients who had both forms of allergic reaction.

Three of our patients who presented with nummular (patchy) hand dermatitis also had contact urticaria to latex, but no positive patch tests. With latex glove avoidance, their dermatitis resolved; an example of how scratching urticaria can eventuate in longer lasting dermatitis in some people ("the itch that rashes"). The patients presented to their dermatologist with dermatitis, but their true initiating event was urticaria which lasted only hours.

The gratifying part of this study was that patch testing and contact urticaria testing allowed us to discover the 5 patients with allergic contact dermatitis and the 9 patients with contact urticaria who could benefit from glove alternatives. We were also able to assure patients in the

remainder of the group that their hand eczema was not glove induced, but rather was related to their wet work. In most instances, therapeutic intervention helped, but in several cases job changes were required.

Patch testing, when done properly, produces exciting results. When done improperly, it confuses and misleads patients and results in embarrassment to physicians who cannot properly interpret their results. Should a physician choose to include patch testing in his or her evaluation of patients with contact dermatitis it is essential, in my view, that he or she have highly developed skills in the diagnosis and treatment of skin diseases, and that these physicians be elaborately trained in the techniques of application and the methods of interpretation of patch tests.

References

1. Jadassohn, J. (1896), *Arch Dermatol. Forsch.* **34**, 103.
2. James, W. D., Rosenthal, L. E., Brancaccio, R. R., and Marks, J. G. (1992), *J. Am. Acad. Dermatol.* **126**, 991-994.
3. Podmore, P., Burrows, D., and Bingham, E. A. (1984), *Contact Dermatitis* **11**, 283,284.
4. Aberer, W., Andersen, K. E., and White, I. R. (1993), *Contact Dermatitis* **28**, 12.
5. Rietschel, R. L. and Fowler, J. R., Jr., eds. (1995), *Fisher's Contact Dermatitis*, 4th ed., Williams & Wilkins, Baltimore, MD.
6. Rycroft, R. J. G., Menne, T., Frosch, P. J., eds. (1995), *Textbook of Contact Dermatitis*, 2nd ed., Springer-Verlag, New York.
7. Corey, G. (1993), *Am. J. Contact Dermatitis* **4**, 175-181.
8. Storrs, F. J. (1993), *Cutis* **52**, 301-306.
9. DeGroot, A. C. (1994), *Patch Testing: Test Concentrations and Vehicles for 3700 Chemicals*, 2nd ed., Elsevier, Amsterdam.
10. Rietschel, R. L., Adams, R. M., Maibach, H. I., Storrs, F. J., and Rosenthal, L. E. (1988), *J. Am. Acad. Dermatol.* **18**, 42-45.
11. MacFarlane, A. W., Curley, R. K., Graham, R. M., Lewis-Jones, M. S., and King, C. M. (1989), *Contact Dermatitis* **20**, 127-132.
12. Nethercott, J. R. (1994), *Am. J. Contact Dermatitis* **5**, 136-142.
13. Belsito, D. V., Storrs, F. J., Taylor, J. S., Marks, J. G., Adams, R. M., Rietschel, R. L., Jordan, W. P., and Emmett, E. A. (1992), *Am. J. Contact Dermatitis* **3**, 193-200.
14. TRUE Test Study Group (1989), *J. Am. Acad. Dermatol.* **21**, 846-849.
15. Bruynzeel, D. P. and Maibach, H. I. (1986), *Arch. Dermatol.* **122**, 323-328.
16. Kligman, A. and Gollhausen, R. (1986), *Br. J. Dermatol.* **115**(Suppl. 31), 93-100.
17. Storrs, F. J., Rosenthal, L. E., Adams, R. M., Clendenning, W., Emmett, E. A., Fisher, A. A., Larsen, W. G., Maibach, H. I., Rietschel, R. L., Schorr, W. F., and Taylor, J. S. (1989), *J. Am. Acad. Dermatol.* **20**, 1038-1045.
18. American Contact Dermatitis Society (1995), *Evaluation of Eczematous Skin Disease: When to Use Patch Testing*, American Contact Dermatitis Society, 930 North Meacham Road, Schaumburg, IL 60173-6016.
19. Calnan, C. D. (1987), in *Occupational and Industrial Dermatology*, Maibach H. I. and Gellin, G. A., eds., Year Book Publishers, New York, pp. 28-31.
20. Mathias, C. G. T. (1985), *Arch. Dermatol.* **121**, 332-334.
21. Adams, R., ed. (1990), *Occupational Skin Disease*, 2nd ed., Saunders, Philadelphia, PA.

22. Cronin, E. (1972), *Trans. St. John's Hospital Dis. Skin* **58**, 153–162.
23. Rietschel, R. L. (1989), *J. Am. Acad. Dermatol.* **21**, 885–887.
24. Koppula, S. V., Fellman, J. H., and Storrs, F. J. (1995), *Am. J. Contact Dermatitis* **6**, 78–85.
25. Paulsen, E., Andersen, K. E., and Hausen, B. M. (1993), *Contact Dermatitis* **29**, 6–10.
26. Crawshaw, R.L. (1994), *Arch. Dermatol.* **30**, 170–172.
27. Maurice, P. D. L., Rivers, J. K., Jones, C., and Cronin, E. (1987), *Clin. Exp. Dermatol.* **12**, 204–206.
28. Storrs, F. J. (1984), *J. Am. Acad. Dermatol.* **11**, 74–85.
29. Skog, E. (1965), *Arch. Dermatol.* **92**, 274–280.
30. Witten, V. H. and Shair, H. M. (1949), *Ann. Allergy* **7**, 32–45.
31. Bjorkner, B., Bruze, M., Dahlquist, I., et al. (1986), *Contact Dermatitis* **14**, 85–90.
32. Fregert, S. (1985), *Contact Dermatitis* **12**, 123–134.
33. Meneghini, C. L. and Angelini, G. (1977), *Contact Dermatitis* **3**, 138–142.
34. Agrup, G. (1968), *Br. J. Dermatol.* **80**, 631–634.
35. Kligman, A. M. (1958), *Arch. Dermatol.* **77**, 149–180.
36. McClain, D. C. and Storrs, F. J. (1992), *Am. J. Contact Dermatol.* **3**, 201–205.
37. Reginella, R. F., Fairfield, J. C., and Marks, J. (1989), *Contact Dermatitis* **20**, 275–279.