

The Allergy and Immunology Specialist

What Is the Role in the Treatment of Skin Disease?

Ernest N. Charlesworth

*Department of Allergy and Dermatology, Shannon Clinic, San Angelo, TX; Departments of Allergy/Immunology and Dermatology, University of Texas Medical School at Houston, Houston, TX;
E-mail: ECharlesworth@shannonhealth.org.*

Abstract

The practice of medicine transcends our neat borders of demarcation between the myriad of medical specialties and medical disciplines. There are no two specialties in which this clinical interface is more blurred than the clinical interface between allergy and dermatology. With a background in both dermatology and allergy, I address where the specialty of allergy/immunology is heading, as we navigate the coastal waters separating my two primary disciplines. I also discuss the tools traditionally used only in dermatology, which are now being used increasing by a vanguard of allergists to aid in the diagnosis and treatment of allergic skin disease.

Index Entries

Allergic skin disease; allergic contact dermatitis; urticaria; atopic dermatitis; eczema.

Skin Biopsy Techniques

The technique used for a skin biopsy is of paramount importance for the diagnosis of many skin disorders. There are four basic techniques used for obtaining a specimen for histopathology and they include incision, punch biopsy, shave biopsy, and curettage. For most allergists, it is the punch biopsy which is most likely to be utilized as an aid in the diagnosis of immune-mediated skin disease. The

punch biopsy usually gives an adequate tissue representation, it is simple and it requires only rudimentary surgical skills. It is important to select a proper site for biopsy. In most instances, histological examination of a fully developed lesion will give more information than examination of either an early or an involution skin lesion. The biopsy site should include subcutaneous fat. The specimen should be treated gen-

tly since "crush artifact" might occur (lymphoma and leukemic infiltrates are particularly susceptible to crush artifact).

Usually, the tissue specimen is placed in a standard formalin solution. When immunofluorescence staining is required then the specimen is placed in Michel's transport medium although an additional specimen placed in formalin (1). There are a multitude of disorders in which immunofluorescence is required to establish a diagnosis and the allergist is becoming increasingly more familiar with immunodermatology (*see* Table 1). This has traditionally been an area in which only the dermatologist was the authority; however, the allergist/immunologist is now focusing more on allergist skin diseases and it may be in the patient's best interest to develop a team approach with the dermatologist. By forming a partnership with your dermatology colleague, the allergist/immunologist can be a better patient advocate.

One hopes to obtain certain information from a skin biopsy which can be utilized to aid in the establishment of a diagnosis. There are two critical steps that are important to remember if one anticipates performing skin biopsies. One step is to make certain that the biopsy specimen is sent to a qualified dermatopathologist for processing and reading. The second step is to supply the dermatopathologist with an adequate medical history, clinical description of the skin lesions, and a comprehensive clinical differential diagnosis.

Patch Testing

Patch testing is used to document and validate a diagnosis of allergic contact dermatitis (ACD) and to identify the causative agent. ACD is mediated by CD4+ lymphocytes that have been sensitized to a specific antigenic chemical epitope which is usually encountered by either direct or indirect contact with the skin (2,3). This reaction is not antibody mediated and it falls within the Gell and Combs Type IV

Table 1
Disorders in Which a Skin Biopsy May Be Indicated

1. Vasculitis
 - a. Henonch-Scholein purpura
 - b. Urticarial vasculitis
 - c. Cryoglobulinemia
 - d. Serum sickness
 - e. Connective tissue diseases
2. Vesiculobullous diseases
 - a. Bullous pemphigoid
 - b. Pemphigus vulgaris
 - c. Dermatitis herpetiformis
 - d. Linear IgA diseases
 - e. Herpes gestationis
 - f. Epidermolysis bullosa acquisita
 - g. Paraneoplastic pemphigus
3. Connective tissue diseases
 - a. Lupus erythematosus
 - b. Lupus profundus
 - c. Scleroderma
 - d. Eosinophilic fasciitis (Schulman's syndrome)
4. Drug eruptions

reaction. The clinician should be aware that 80% of contact dermatitis is irritant and that only 20% will actually be immunologically mediated.

In clinical practice, an irritant contact dermatitis (ICD) and an ACD may be difficult to distinguish. Obviously, potent chemical irritants, such as acids and alkalis, may cause severe skin necrosis and the "cause and effect" may be quite obvious. Other moderately strong irritants may produce cutaneous burning and stinging, with vesicular, or even bullous lesions. The vast majority of irritants in the environment produce an eczematous dermatitis which may be difficult to distinguish from an ACD. There are clinical differences between an irritant and an allergic cutaneous response. Low-level irritants usually produce a subacute or chronic dermatitis and only very strong irritants will produce vesicles which are more likely an indication of an ACD. Early in the course of the dermatitis, irritants are more likely to produce burning and stinging, whereas aller-

gens tend to produce pruritus. Once the eruption becomes chronic, however, the two types of reaction may be impossible to distinguish and patch testing may be necessary to assist in the differentiation.

Who Should One Conduct Patch Testing On?

Any patient with a chronic eczematous dermatitis of undetermined etiology is a candidate for patch testing (4,5). Over the past two decades, dermatologists have been doing less patch testing and allergists are being called on to "take up the slack." Patients with chronic hand eczema certainly are candidates for patch testing. The differential diagnosis for chronic hand eczema includes atopic dermatitis, irritant contact dermatitis, psoriasis, dyshidrotic eczema (pompholyx), and allergic contact dermatitis. Therefore, the allergists who wish to evaluate allergic contact dermatitis should have some clinical experience in clinical dermatology. Additionally, occupationally related dermatitis is common and the clinician needs to be aware of the unique challenges in doing a work-related evaluation. Lastly, not every chronic eczematous dermatitis is irritant or allergic and one should be aware that chronic cutaneous neoplastic processes may masquerade as a pseudocontact dermatitis. For example, a cutaneous T-cell malignancy (e.g., Sezary syndrome) may fool the unsuspecting clinician who may have tunnel vision. For this reason, a detailed medical history and a complete physical examination is of paramount importance. The allergists should try to develop a good working relationship with his dermatology consultant, working together in a partnership on behalf of the patient.

The patch test is a unique in vivo test which attempts to reproduce the cutaneous disease in a diminutive manner. The patch test is easier and safer than a direct "use test" since the concentrations of allergens which are applied in standard-patch testing are in low concentra-

tions, which have been predetermined not to cause an irritant reaction in the majority of normal individuals. One should try to delay patch testing until the acute inflammation has subsided. One must be cognizant of the fact that systemic corticosteroids will result in a false negative patch test (unlike the prick or intradermal testing done for IgE mediated allergies). Fortunately, antihistamines will not interfere with the results of the patch testing. There may be situations in which one wishes to test the suspected culprit directly. Cosmetics may be applied full strength, but items of unknown irritant potential should be diluted to 1–2% in petrolatum (6–8). Before attempting direct testing with non-standardized chemicals, it is recommended that the clinician consult with a standard textbook.

The TRUE Test is a prepackaged double adhesive strip consisting of two panels of 12 allergens. Each panel has two parallel rows of six allergens in small squares of polymer attached to adhesive and this is a good general screen, identifying the cause of ACD in 60–80% of allergic patients. Clearly, the TRUE test can miss some important allergens, including newer preservative and corticosteroids. For this reason, one may wish to purchase allergens in petrolatum which are contained in preloaded syringes. For this patch testing, one uses Finn chambers which are attached to hypoallergenic Scanpor tape and the Finn chambers are loaded individually from the preloaded syringes. The testing is usually applied to the back and the order of the antigens is left to right reversed as the tape is turned over and applied to the back, thus reversed. With both the TRUE Test and the Finn chambers, the test material and the tape is removed at 48 h and read. An additional reading is recommended at 72 or 96 h for delayed reaction. Frequently, with an ACD the reaction on the skin may intensify with the delayed reading, whereas, with an irritant contact dermatitis the reaction will diminish or disappear with the delayed reading (*see Table 2*). Note that the interpretation of patch testing

Table 2
Interpretation of Patch Testing

Symbol	Interpretation
?+	Is a doubtful reaction
+	Is a weak nonvisicular reaction with erythema and possibly papules
++	Is a strong reaction with edema and/or vesicles, in addition to erythema and papules
+++	Is an extreme reaction in which there are large vesicles, bullae, and the potential for ulceration
IR	Is an irritant reaction

is very different compared to the interpretation of prick and intradermal skin testing which the allergist is familiar with.

One should be aware of potential causes for false-negative reactions, in addition to potential causes of false-positive reactions. Some of the causes for false-negative reactions include the following: low concentration or insufficient amount of antigen, improper testing technique, depressed reactivity because of systemic steroids, or a failure to reproduce concomitant conditions such as heat, friction, or trauma to the skin. False-positive reactions may be secondary to the following: primary irritant reaction, reaction to the tape or pressure effect, reaction because of the effect of occlusion on the skin, and the presence of impurities in the test material. Lastly, there is a condition which is referred to as the "angry back syndrome" or "excited skin syndrome." This is a situation in which multiple concomitant positive patch tests may result in a rather diffuse non-specific reaction.

The standard allergy tray consists of medications, preservatives, rubber compounds, vehicles, and metals. The reader is referred to reference sources for the exact ingredients and for ordering information (*see* Table 3). Clearly, the diagnosis and treatment of allergic contact dermatitis is being done more as well as cosmetic dermatology and dermatologic surgery. This trend behooves the allergist/immunologist to learn more about dermatology and to become familiar with a more comprehensive differential diagnosis of eczematous skin lesions.

Atopic Dermatitis

Atopic dermatitis (AD) is the prototype of allergic skin disease with this disorder representing the clinical interface between immunology and dermatology. Allergists are uniquely positioned to understand this disease and to treat this disease. AD is a chronic relapsing dermatitis associated with intense pruritus and it can typically be divided into three stages: infantile, childhood, and adult AD. Not uncommonly, there are periods of quiescence and exacerbation between infantile/childhood AD and adult AD. Acute inflammation with involvement of the extensors and the face is characteristic of the infantile form, whereas, chronic inflammation appears to increase with age and is associated with lichenification and involvement of the flexures. The skin manifestations of AD are very pleomorphic and range from dry erythematous patches to hypopigmented macules to exudative plaques and even generalized erythroderma of the skin.

The incidence of AD, like that of asthma, has been increasing over the past several decades (9–10). Depending on the study, the incidence of AD appears to be between 7% and 17% of the general population. Because 90% of the cases of AD have their onset before the age of 5 yr old, much of the prevalence data is derived from young school children. AD is felt to be the result of a dynamic interface between one's environment and one's genetic predisposition for allergic disease. More recent studies have suggested that regional geographic differences,

Table 3
Resources Helpful in Ordering
Patch-Testing Material

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1. Allerderm Laboratories, Inc.
PO Box 2070
Petaluma, CA 94953-2070
Telephone: 1-800-365-6868
Fax: 707-664-0666
Website: www.allerderm.com
 2. Dormer Laboratories, Inc.
91 Kelfield Street, #5
Rexdale, Ontario M9W5A3
Telephone: 416-242-6167
Fax: 877-430-7637
E-mail: info@dormer.com
Website: www.dormer.com
 3. Hermal Kurt Herrmann
Scholtzstrasse 3
D-2057 Reinbek
Hamburg, Germany
Telephone: 0049/40-72704 0
Fax: 0049/40-722 92 96
 4. Chemotechnique Diagnostics AF
PO Box 80, Edvard Ols vag 2
Sweden
Telephone: 46-40 46 60 77
Fax: 46 40 46 67 00
E-mail: info@chemotechnique.se
 5. Pharmascience, Inc.
8400ch Darnley Rd
CND-Montreal, Quebec H4T 1M4
Telephone: 0450 458 0158
Fax: 0450 458 1477
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including the degree of urbanization, may be a contributing factor. This has led to the proposal of the "hygiene hypothesis" in which early exposure to exogenous bacteria and endotoxins may result in a decreased probability of developing clinical AD (11). If this hypothesis is validated, then it may explain why there appears to be an increased prevalence of this disease in highly industrialized societies and in higher socioeconomic classes.

Unlike allergic rhinitis and extrinsic asthma, the immunopathology of AD is punctuated by a biphasic cytokine profile. In the subclinical acute phase of AD, there is spongiosis (epidermal cell swelling) of the epidermis. This is fol-

lowed by marked perivascular inflammation with infiltrates of CD3+, CD4+ T-cells which express CD25+ and HLA-DR+ markers indicating that these cells are activated (12). These Th2 helper T-cells are unique in that they express a lectin homing receptor for E-selectin, which is referred to as the cutaneous lymphocytes antigen (CLA+). The endothelial cells in the dermis are enlarged and are activated with E-selectin, VCAM-1, and ICAM-1 expression. Epidermal thickening is the predominant finding in chronic lesions of AD with the presence of Langerhans cells (LC) and monocytes/macrophages playing a role in both early and late cutaneous pathology. Additionally, it has been shown that mast cells and eosinophils degranulate with the release of histamine and cationic proteins, respectively.

Cutaneous cytokine expression in lesions of AD appears to mirror the underlying immunopathologic process. Early, it appears that Th2 cell cytokines (IL-4, IL-5, IL-10) are predominant, whereas the Th1 CD4+ helper cells may play a more dominant role in the orchestration between a Th2 and a Th1 cytokine response which explains the difficult challenge facing the treating clinician.

Despite all of the recent knowledge regarding the immunopathology of AD, the diagnosis rests on a constellation of clinical features and not laboratory features. According to diagnostic guidelines defined by Hanifin and Rajka in 1980, one must have 3 out of 4 major features and 3 out of 23 minor features (13). The major features consist of pruritus, typical morphology, and distribution of skin lesions, a chronic and relapsing dermatitis, and a personal or family history of atopy. Nevertheless, the astute clinician should remember that there is a differential diagnosis for AD. Any adult who presents with an AD-like dermatitis who has no prior history of atopic disease or family history of atopic disease should not be assumed to be AD. Many patients who have a cutaneous T-cell lymphoma may present with an AD-like clinical picture.

Treatment of AD represents a challenge in which new treatment modalities merge with the "art of medicine." Each patient is unique and there are indeed triggers which may be unique to a particular patient. These triggers may include identification of specific allergens such as dust mite or animal dander. Infections are a common trigger and we know that greater than 90% of AD patients are colonized with *Staphylococcus aureus* and many of these isolates may induce skin inflammation through a super-antigen mediate mechanism (14,15). The endotoxin from these organisms is capable of triggering a wide spectrum of T-cells to become activated and produce pro-inflammatory cytokines. Other triggers include emotional stress, environmental factors such as heat, humidity, and dryness in the winter months of the years and the self-perpetuating effects of the ever present "itch-scratch" cycle.

Laboratory Evaluation of AD

One must remember that the diagnosis is clinical and not laboratory. It may be prudent to obtain a CBC with manual eosinophil count and a total serum IgE level to assess the global atopic state (16,17). Not uncommonly, the eosinophil count may correlate with disease severity. Allergy testing (either prick/intradermal or RAST) may be helpful in order to identify and anticipate seasonal flare, exacerbation by dust mite or animal exposure or to identify specific food triggers. In regard to foods, it is important to realize that most children with AD will have a positive skin-prick test to several foods, but only one third of positive skin tests correlated with a positive food challenge. Fortunately, only a small number of foods (e.g., cow's milk, egg, peanut, soy, wheat, tree nuts, fish, and shellfish) account for more than 90% of clinical reactions.

Management of AD

The management of AD is complex and it varies from one patient to the next. Certainly, a complete discussion of management of this

single disease is beyond the scope of this review. However, management of this disease can be divided into the following:

1. Allergen and irritant avoidance.
2. Restore the skin barrier.
3. Topical immunomodulators.
4. Anti-allergic strategies.
5. Systemic therapies.
6. Fungal therapies.

The identification and avoidance of allergens is alluded to in the above discussion. Irritant avoidance is equally important and it is just as ubiquitous. Patients are asked to avoid chlorine in hot tubs and pools and to avoid irritating garment fabrics such as wool. The restoration of the skin barrier is extremely important since the skin of AD patients has been shown to be dysfunctional resulting in an increased loss of water from the skin and an increased opportunity for penetration of exogenous irritants and allergens. Daily lukewarm baths or showers with a mild soap followed by the immediate application of an unscented moisturizing cream are an integral part of any treatment plan.

The mainstay of therapy for almost 50 yr has been the use of topical steroids. The anti-inflammatory effects must be balanced with short-term and long-term side effects including skin thinning, hypopigmentation, easy bruisability, striae, cataract formation, and adrenal suppression. The introduction of topical macrolides which have an anti-inflammatory effect different from topical corticosteroids has interjected a degree of excitement in the treatment of AD. Tacrolimus ointment and Pimecrolimus cream are thought to work by inhibiting T-cell activation and cytokine production.

Chronic Urticaria

There is no condition known to medicine which is more frustrating for both the clinician and patient than chronic idiopathic urticaria

(CIU) (18–19). Fifteen percent of the general population will experience urticaria at one time or another in their life and many of these may go on to develop CIU. These patients frequently go from one physician to another in hopes of finding the elusive cause. These patients are in constant hope of finding that extraordinary physician who might be able to identify the cause, eliminate the culprit and thereby cure their hives. There has been a considerable amount of exciting research relevant to urticaria that has focused on defining a subpopulation of patients in whom an IgG antibody is directed against the high affinity IgE receptor on mast cells and basophils (20). This urticarial population may develop lesions which last 12–24 h, although they do not leave cutaneous bruising as urticarial vasculitis does.

As physicians, we must broaden our perspective regarding the pathogenesis of urticaria and understand that an urticarial lesion represents a cutaneous reaction pattern in which the skin may be responding intrinsically or may be responding to a multiplicity of potential exogenous triggers. Therefore, urticaria should be regarded as symptoms, much as a febrile response is a symptom that might be triggered by several disease states, ranging from infectious diseases to malignancy. If the urticaria involves primarily the dermis, then circumscribed erythematous pruritic plaques of subcutaneous edema develop. These urticarial plaques are often fleeting, lasting a few minutes to several hours. In one-half of the urticaria patients, involvement of the deeper subcutaneous tissues results in angioedema. When urticaria and angioedema coexist, this appears to define a subpopulation of urticaria patients who have a worse prognosis than the majority of urticaria patients, and this unfortunate subgroup may suffer recurrent episodes for longer than 5 yr. Approaching urticaria as a cutaneous symptom complex rather than a disease entity alone allows the physician to make a more complete global assessment.

Because urticaria represents a clinical spectrum, it should not be surprising that there are several dermatological disorders that may have urticarial lesions as part of their clinical presentation. Erythema multiforme (EM) patients frequently have urticarial lesions and, likewise, chronic urticaria may at times have “targatoid” lesions that are similar to those typically seen with EM. Like urticaria, EM is a cutaneous reaction pattern of the skin and is associated with a plethora of potential causes, including infections, drugs, and underlying malignancy. Although some lesions of EM may have an urticarial component, the lesions remain relatively fixed and are not in a constant state of waxing and waning. Bullous pemphigoid (BP) is an autoimmune bullous eruption in which immune complexes are directed toward an antigen at the dermoepidermal junction, resulting in a generalized bullous eruption. In BP, early lesions are frequently pruritic and may have a clear urticarial component. In patients with BP in whom the disease is limited, it is possible that the urticarial plaque may not blister. In such a situation, a skin biopsy from perilesional skin submitted for immunofluorescent staining should be diagnostic. Dermatitis herpetiformis (DH) is another skin disease in which early lesions may present with urticaria. DH is usually symmetrically located on the trunk, buttocks, and upper extremities. Like other autoimmune bullous skin diseases, a skin biopsy of a perilesional area may be diagnostic showing the presence of IgA immune complex with the dermal papillae.

Pathogenic Mechanisms Involved in Urticaria

Because the approach to urticaria in this discussion is one in which urticaria is considered a symptom that is part of a clinical spectrum, it should not be surprising that several pathogenic mechanisms may be operative in patients presenting with urticaria, albeit many patients will not be defined by a specific

Table 4
Mechanisms Involved With Urticaria

1.	Immune-mediated urticaria Specific antigen: drug, food, insect venom Atopic diathesis Autoimmune (IgG autoantibody directed against the high-affinity IgE receptor)
2.	Complement-mediated urticaria Hereditary angioedema Acquired angioedema Serum sickness (type III) Necrotizing vasculitis
3.	Nonimmunological-mediated urticaria Direct mast cell-releasing agents: opiates, certain antibiotics, radiocontrast dye Intolerance reactions: aspirin, nonsteroidal anti-inflammatory drugs Histamine-releasing factors

etiology. Urticaria can be divided into three general mechanisms: immune-mediated urticaria, complement-mediated urticaria, and nonimmunologic mediated urticaria (*see* Table 4). This classification may be helpful in organizing one's approach to this disease (21).

IgE antibodies directed against ingested drugs and foods are certainly potential causes of urticaria. The patient's medical history remains the single most important aid in sorting out the potential role of an ingested allergen in recurring urticaria, and keeping a food diary may be helpful for some patients. Allergic reactions to foods as a cause of urticaria are much more common in children than in adults. Champion et al. (21) showed that the incidence of food allergy as a cause of urticaria was less than 2%. In reality, the incidence of IgE-mediated food allergy as a cause for urticaria is probably rare and over diagnosed as a cause of urticaria. Patients with a personal or family history of asthma, allergic rhinitis, or atopic dermatitis do not have an increased incidence of CIU; however, atopic patients may be more likely to have acute urticaria.

Complement mediated urticaria/angioedema is exemplified by hereditary angioedema, acquired angioedema, serum sickness,

and urticarial vasculitis (22). Because the anaphylatoxins C5a, C3a, and C4a are all capable of triggering mast-cell histamine release, it is possible that the generation of complement products may play a pivotal role in other types of urticaria as well. An increased incidence of urticaria in patients with systemic lupus erythematosus would suggest the possibility of immune-mediated complement as etiological factor.

Workup of Urticaria

There is considerable difference of opinion regarding the extent of laboratory workup for patients with CIU, however, the underwriter of the cost of the workup should have a realistic expectation that the workup will be directed by the patient's medical history and that it will not simply be a survey of laboratory tests. The medical history should be directed toward sinusitis, systemic constitutional symptoms, arthritis, peptic ulcer disease, cutaneous fungal infection, thyroid disease, food allergies, and infections (hepatitis, parasites, etc.).

It is probably cost effective to obtain a complete blood count with a differential analysis, erythrocyte sedimentation rate, and a urinalysis on most patients with CIU (21). In selected patients with urticaria, other tests to consider depend on the directed history and physical examination and may include those listed in Table 5.

There is little role for routine screening by skin testing in CIU unless the history gives one a clue that a food may be a possible culprit. Inhalant aeroallergens are an uncommon cause of urticaria and there is no reason to routinely do pollen skin testing, although animal dander and saliva may be a cause for contact urticaria.

There is currently no routine laboratory test for the detection of histamine-releasing autoantibodies. In experienced hands, one may consider doing intradermal skin testing with autologous serum. The test is positive when a pink wheal that is at least 1.5 mm greater in diameter than that caused by a control injec-

Table 5
Selected Medical History
Directed Testing in Urticaria

Stool examination for ova and parasites
Blood chemistry profile
Antinuclear antibody titer
Hepatitis B and C screen
Skin tests for IgE-mediated reactions
CAP-RAST for specific IgE
CH ₅₀
Thyroid function and antibody screen
Cryoproteins and cryoglobulins
Serum immunofixation for monoclonal antibodies

tion with saline. When routine serum testing for the anti-Fc epsilon R1 autoantibody becomes more available than it is currently, then this may be very helpful in the classification of CIU. Recent studies have been able to classify urticaria into the following five subsets according to the presence of antibodies (23):

1. Immunoreactive histamine-releasing anti-Fc epsilon R1 autoantibodies (26%).
2. Immunoreactive anti-FcεR1 auto-antibodies without histamine release (15%).
3. Anti-IgE-like autoantibodies (9%).
4. Mast cell histamine-releasing factor (9%).
5. Serum with no factor (41%).

In the above studies, patients with serum histamine-releasing activity had more severe urticaria than patients without such activity and it is this subset of patients which poses the greatest challenge to the practicing allergist. Additionally, positive skin tests to autologous sera were associated with histamine-releasing antibodies and the skin testing did not detect those individuals who had nonhistamine releasing autoantibodies. So much has been learned about the mechanisms involved with CIU but there remains much more to learn before we can effectively translate our knowledge into treatment at the bedside.

In addition to the above diagnostic tests, a simple 4-mm punch biopsy should be consid-

Table 6
Histological Groups of Urticaria Based
on Skin Biopsy

Group 1: Neutrophilic vasculitis
Group 2: Polymorphous perivascular infiltrate
Group 3: Sparse perivascular lymphocytic infiltrate

ered in all patients in which the urticarial lesions remains in the same location for 24 h or in urticarial lesions that have a pigmented or purpuric component to them. A skin biopsy is an easy minor procedure and every well-trained allergist should be capable of accomplishing this. There are three basic histological groupings of skin biopsies from patients with CIU (see Table 6) (21):

- Group 1: Neutrophilic vasculitis;
- Group 2: Polymorphous perivascular infiltrate; and
- Group 3: Sparse perivascular lymphocytic infiltrate.

This classification can be very useful clinically because it is the group 3 urticaria patients with only a sparse lymphocytic infiltrate who respond best to H1 antihistamines. Group 1 urticaria patients represent the urticarial vasculitis group that may require more aggressive treatment. Finally, group 2 may be more likely to represent the autoimmune type of urticaria in which the presence of an IgG anti-IgE antibody results in a histological picture which is similar to the cutaneous late-phase to antigen. When doing skin biopsies of patients with urticaria it is important to biopsy a mature urticarial lesion that is at least 8–12 h old.

Miscellaneous Allergic Skin Disorders

The allergist is expected to be expert in the diagnosis and treatment of a plethora of disorders that cross that interface between allergy/immunology and dermatology. We have discussed allergic contact dermatitis, atopic der-

matitis, and urticaria; however, there are many other skin conditions that cannot be reviewed owing to space constraints. Autoimmune bullous skin diseases have been alluded to here but the allergist/immunologist should be familiar with the immunopathology of pemphigus vulgaris, bullous pemphigoid, dermatitis herpetiformis, bullous linear IgA disease, and bullous SLE. Photoinduced skin lesions pose a particular challenge and include solar urticaria, polymorphorphic light eruptions, and connective tissue disease.

The Future of the Allergist in the Diagnosis and Treatment of Immune-Mediated Skin Disease

The human organism is a complex interactive orchestration of multiple organ systems working in concert and harmony. There is no artificial division between the immune system contained within the integument wrapping which we refer to as "skin." It is entirely appropriate for the allergist/immunologist to broaden his or her horizon to include the skin as an integrated immune organ. The allergist/immunologist should become expert in doing simple skin biopsy for routine histology, for immunofluorescent staining, and for immunophenotype markings of the cellular influx. As a specialty, we must shed our confinement to view the immunology of our specialty as simply an IgE-mediated mechanism and we must open the integument door to broaden our clinical utility as immunologists.

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