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The diagnostic evaluation, treatment, and prevention of allergic contact dermatitis in the new millennium

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Identifying the etiology of allergic contact dermatitis is a rewarding yet challenging endeavor. Not all allergic contact reactions are eczematous in appearance. The most reliable clinical clue to the allergic nature of the dermatitis is its geographic distribution. Once a list of culprit allergens has been identified by patch testing, the practitioner must identify the relevant allergen(s) and counsel the patient in avoidance. For most individuals, allergen avoidance results in resolution of the dermatitis; however, some patients will require continuing symptomatic therapy despite avoidance. For those patients unable to avoid known allergens, immunosuppressant therapies (including phototherapy) or barriers can be beneficial. Currently, hyposensitization is not a viable alternative for the treatment of allergic contact dermatitis. (J Allergy Clin Immunol 2000;105:409-20.)

Key words: *Allergic contact dermatitis, common allergens, clinical manifestations, diagnostic evaluation, immunoregulation, treatment, prevention*

Contact dermatitis can be either allergic or irritant in etiology. The diagnosis is not usually apparent from history or physical examination alone. Without patch testing, it is impossible to delineate the cause. Thus, although it has been 105 years since Jadassohn[1] first described the use of patch tests, such testing remains vital to the appropriate diagnosis of contact dermatitis. Indeed, perhaps the only suspected allergic condition where patch testing is not indicated is that induced by exposure to plants of the *Toxicodendron* species, which can usually be recognized by the presence of the intense, often linear, papulovesicular eruption they induce (Fig 1). For most other suspected allergic reactions, patch testing is indicated and can be quite illuminating.[2] For example, it has been reported that 46% of patients who are seen with a history of apparent metal-induced dermatitis are patch test negative to nickel.[3]

Abbreviations used

ACD:	Allergic contact dermatitis
DMDM:	Dimethyoldimethyl
GPT:	Guinea pig tests
ICCVAM:	Interagency Coordinating Committee on the Validation of Alternative Methods
LCs:	Langerhans cells
LLNA:	Local lymph node assay
MCI/M:	Methylchloroisothiazolinone/methylisothiazolinone
NACDG:	North American Contact Dermatitis Group
PPD:	*para*-Phenylenediamine
PUVA:	Psoralens ultraviolet radiation
ROAT:	Repeat open application testing
TAP 2B:	Transporter associated with antigen processing 2B
UVB:	Ultraviolet B radiation

Although allergic contact dermatitis (ACD) can occur in any setting, many cases are related to exposures in the workplace. When all occupationally related illness in the United States was last estimated, ACD accounted for 7%, at an annual cost of $250 million in lost productivity, medical care, and disability payments.[4] Although the disease has probably plagued humans for millennia, the term *allergy*[5] and its clinical recognition by patch testing[1] are barely a century old. With the advent of an experimental animal model for ACD in 1926,[6] studies concerning its pathophysiologic features became possible. Despite all the clinical and scientific research since, a thorough understanding of the disease remains elusive.

THE ALLERGENS

Most environmental allergens are haptens, that is, simple chemicals that must link to proteins to form a complete antigen before they can sensitize.[7] These haptens are primarily small (<500 d) electrophilic molecules that bind to carrier proteins by covalent bonds[8] (Table I). The major exception to such covalent bonding occurs among the metallic salts (for example, nickel and cobalt), which are thought to complex with proteins in a manner analogous to the complexing of cobalt with vitamin B_{12}. Although there are more than 2800 known environmen-

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FIG 1. Acute dermatitis caused by poison ivy. Note linear arrangement of lesions typical of phytodermatitis acquired by inadvertent contact with the plant. The severe vesiculobullous reaction is typical for urushiol, the pentadecylcatechol of *Toxicodendron* spp. (Reproduced with permission of the Ronald O. Perelman Department of Dermatology, New York University School of Medicine.)

tal allergens,[10] not all electrophilic, protein-binding substances are haptens.[11] The nature of the antigenic determinants, the type of binding that the hapten undergoes with the carrier, the final 3-dimensional configuration of the conjugate, and a variety of unknown factors undoubtedly contribute to the antigenicity of a chemical.[12] However, the importance of the carrier for the hapten cannot be underestimated because potent contact sensitizers, when complexed to nonimmunogenic carriers, induce tolerance rather than sensitization.[13] HLA-DR or class II antigens on the surface of the antigen-presenting Langerhans cells (LCs) act as the binding site (carrier) for contact allergens.[14] Readers interested in current reviews of the pathophysiologic mechanisms of ACD are referred elsewhere.[15,16]

IMMUNOREGULATION

Although animal studies have clearly shown genetic restrictions on cell-mediated immunity, the evidence for a genetic influence in humans has been minimal. Skog[17] found that 5% of a defined population could not be sensitized to dinitrochlorobenzene and suggested that this was due to inheritance. In another study significant genetic association with the capacity to become sensitized to *para*-nitrosodimethylaniline was reported.[18] Nonetheless, attempts to correlate HLA haplotype with nickel sensitivity[19] or other contact allergies[20] have shown no association. However, recent studies have demonstrated increased allele and phenotype frequencies of "transporter associated with antigen processing" 2B (TAP 2B) genes in nickel-sensitive subjects.[21] Thus definitive evidence of genetic influences on ACD in humans has been meager, probably because of our diverse genetic pool and the current limitations of technology.[22] With continuing advances in molecular biology, any association(s) should become clearer in the future.

The route of primary sensitization clearly has a regulatory effect on the subsequent immunologic response. Sulzberger[23] demonstrated that intracardiac injection of neoarsphenamine induced tolerance rather than sensitization. Tolerance induction has also been reported after primary oral ingestion of allergens[24] and after primary epicutaneous application of allergens to areas deficient in HLA-DR$^+$ LCs.[25] The exact mechanism by which tolerance ensues is controversial and may depend on the route of exposure (oral, intravenous, epicutaneous, or intraperitoneal). However, in most instances induction of hapten-specific suppressor T cells,[25] clonal deletion of the responding CD3-Ti cells,[26] or antibodies directed against the antigen recognition site of the T-cell receptor (anti-idiotypic antibodies)[27] seem to play a role. Readers interested in a better understanding of the mechanism(s) of tolerance induction are referred elsewhere.[26-28]

The aging process also modulates ACD. Clinically, aged individuals have been shown to have various defects in the induction or elicitation of ACD.[29] The precise reason for this decline in contact sensitivity is unknown, but it is likely multifactorial. Various portions of the cell-mediated response pathway are involved, including decreases in the density of antigen-presenting cells and in the production of proinflammatory cytokines.[30] Experiments in which contact-sensitized aged mice were injected with naive young T cells and subsequently

TABLE I. Thirty of the most frequent allergens in the United States, 1996 to 1998*†

Allergen	No. of patients tested	Positive reactions (%)	Reactions considered currently relevant (%)
Nickel sulfate	3429	14.2	49.1
Neomycin sulfate	3436	13.1	46.2
Balsam of Peru (Myroxylon pereirae)	3439	11.8	82.9
Fragrance mix‡	4095	11.7	86.9
Thimerosal	4087	10.9	16.8
Sodium gold thiosulfate	4101	9.5	40.6
Formaldehyde	3440	9.3	63.2
Quaternium-15	3436	9.0	88.7
Cobalt chloride	4095	9.0	55.1
Bacitracin	4103	8.7	50.4
Methyldibromo glutaronitrile/phenoxyethanol	4054	7.6	59.1
Carba mix§	3437	7.3	71.7
Ethyleneurea melamine-formaldehyde resin	4095	7.2	65.9
Thiuram mix‖	3435	6.9	79.8
p-Phenylenediamine	3441	6.0	53.1
Propylene glycol	4095	3.8	82.8
Diazolidinyl urea	4096	3.7	91.5
Lanolin	3442	3.3	78.9
Imidazolidinyl urea	4094	3.2	91.7
2-Bromo-2-nitropropane-1,3-diol	4094	3.2	68.5
MCI/MI	4083	2.9	87.2
Cinnamic aldehyde	3443	2.8	83.2
Potassium dichromate	3440	2.8	54.3
Ethylenediamine dihydrochloride	3439	2.6	23.9
DMDM hydantoin	4093	2.6	93.4
Glutaraldehyde	4094	2.6	48.1
Tixocortol-21-pivalate	4100	2.3	91.7
Benzocaine	3444	2.0	34.3
Colophony	3443	2.0	36.2
Epoxy resin	3439	1.9	55.2

Data from Marks et al.[9] *MCI/MI*, Methylchloroisothiazolinone/methylisothiazolinone; *DMDM*, dimethyoldimethyl.
*The population studied consisted of patients with suspected ACD referred for patch testing and is therefore not necessarily representative of the general population.
†Although *Toxicodendron* oleoresin in poison ivy/oak is a frequent cause of ACD, it is not listed because it was not tested in this study.
‡Cinnamic alcohol 1%, cinnamic aldehyde 1%, hydroxycitronellal 1%, amylcinnamaldehyde 1%, geraniol 1%, eugenol 1%, isoeugenol 1%, oakmoss absolute 1%.
§1,3-Diphenylguanidine 1%, zinc diethylthiocarbamate 1%, zinc dibutyl-dithiocarbamate 1%.
‖Tetramethylthiuram disulfide 0.25%, tetramethylthiuram monosulfide 0.25%, tetraethylthiuram disulfide 0.25%, dipentamethylenethiuram disulfide 0.25%.

demonstrated normal responses on antigenic challenge suggest that a failure of T-cell amplification signals or the generation of sufficient T effector cells may be the major deficiencies in aged animals.[31]

The age at which immunocompetency is fully established in infants and children remains controversial.[29] In the past it was believed that ACD rarely developed in children because of an immature immune system and that patch testing of children with standard concentrations of allergens resulted in a high percentage of irritant reactions.[32] However, recent data suggest that patch testing of children with the allergens commercially available in the United States does not result in increased, and confounding, irritant responses.[33] Nonetheless, documented allergic reactions are seen mostly in older pediatric patients and are the result of topical medications, plants, nickel, or shoe-related allergens.[34] As suggested by Strauss,[35] who was able to sensitize 35 of 48 infants (1 to 4 days old) to *Toxicodendron* oleoresin, the apparent hyporesponsiveness of children may be due to limited exposure and not to deficient immunity. Similarly, the effects of gender on the incidence of ACD seem related to the likelihood of exposure.[29,36]

Impairment of cell-mediated immunity has been reported in certain diseases. In addition to the obvious disorders associated with immunologic deficiency, such as AIDS or severe combined immunodeficiency, diseases as diverse as lymphoma, sarcoidosis, atopic dermatitis, lepromatous leprosy, and destructive conglobate acne have been associated with diminished reactivity or anergy.[37]

In experimental models down-regulation of ACD has consistently been achieved with ultraviolet radiation (ultraviolet B [UVB] or psoralens ultraviolet [PUVA]), glucocorticosteroids, and cyclosporine.[38] A variety of other pharmacologic agents have been reported to interfere with the induction or elicitation of ACD in mouse models.[2] These include calcium-channel blockers, amiloride, pentoxifylline, pentamidine, clonidine, spiper-

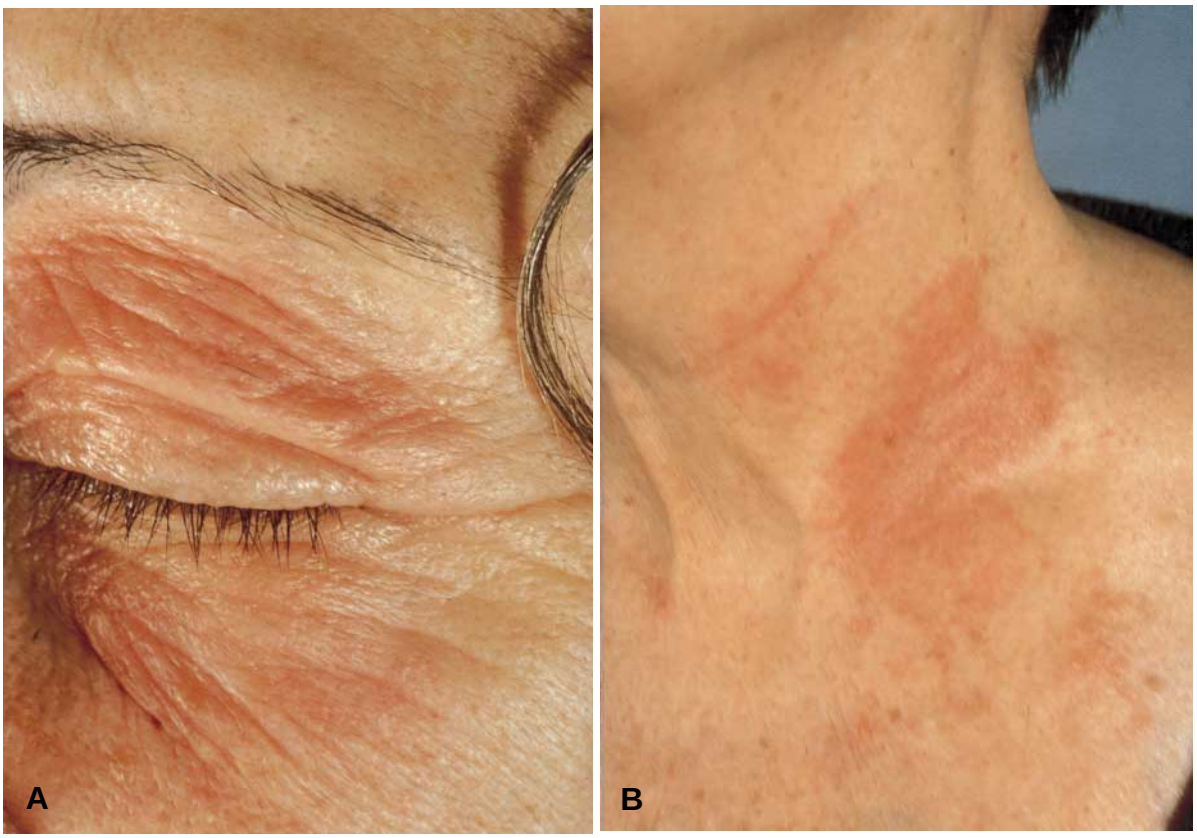

FIG 2. Chronic dermatitis of **(A)** eyelids and **(B)** neck, but not hands, from allergen in nail care products. The patient was allergic to tosylamide formaldehyde resin in her nail polish. Similar reactions from cyanoacrylate-containing nail glue and other acrylate products used about the nails can be observed. The absence of an associated dermatitis of the fingers or hands is not unusual. (Reproduced with permission of the Ronald O. Perelman Department of Dermatology, New York University School of Medicine.)

one, *N*-acetylcysteine, and flavonoids. Of these, only pentoxifylline has been evaluated in humans, where it was found to induce a slight reduction in responsiveness,[39] perhaps by an effect on TNF-α. Whether the other pharmacologic agents exert any effect on the human response remains to be determined. Of note, histamine H_1 receptor antagonists do not appear to modulate the induction or elicitation of ACD, whereas H_2 receptor antagonists enhance the induction, but not the elicitation, phase.[2,40]

CLINICAL MANIFESTATIONS

The clinical appearance of ACD varies depending on its location and duration. Acute eruptions are typically characterized by macular erythema and papules, vesicles, or bullae, depending on the intensity of the allergic response (Fig 1). However, in acute ACD in certain areas of the body (eyelids, penis, and scrotum) erythema and edema predominate, whereas vesiculation is rare. In contrast, chronic ACD of most cutaneous sites presents as a lichenified, scaling, or fissured dermatitis, with or without accompanying papulovesiculation (Fig 2, *A* and *B*). Thus neither the morphologic nor the histopathologic characteristics of ACD are necessarily distinctive. The clinicopathologic differential diagnoses include irritant contact, atopic, nummular, seborrheic, dyshidrotic, psoriasiform (especially on palms and soles), and autosensitization dermatitis.

ACD initially involves the cutaneous site of principal exposure. As it evolves, it may spread to other more distant sites either by inadvertent contact or, under certain circumstances, by autosensitization. Furthermore, the scalp, palms, and soles are relatively resistant to ACD and may exhibit few pathologic features despite contact with an allergen that produces significant dermatitis in adjacent areas of the skin.

Although the failure of an eczematous dermatitis to respond to standard treatments may suggest the possibility of ACD, the shape(s) and location(s) of the rash provide the most important clues, especially as to the causal allergen.[41] ACD to plants (eg, poison ivy, poison oak, *Primula obconica*, and English ivy) is often characterized by linear lesions (Fig 1). Aeroallergens such as the sesquiterpene lactones in *Compositae* involve the more exposed areas of skin with relative sparing of clothed areas. In contrast, textile-related allergens produce dermatitis of clothed areas (Fig 3).

FIG 3. Acute contact dermatitis of upper arms caused by allergic reaction to disperse blue dyes. Reactions to textile dyes, as opposed to resins, may take on a highly patterned form, as demonstrated here. Unfortunately, most cases of ACD are not this graphic. (Reproduced with permission of the Division of Dermatology, University of Kansas Medical Center.)

Not all allergic reactions are necessarily eczematous. For example, I recently evaluated a young man who had a recurrent papular eruption of the bathing suit area, which was diagnosed as "sea bather's eruption" because of the larvae of the sea anemone, *Edwardsiella lineata*. It was only when the dermatitis recurred after swimming in a pool that another cause was suspected. Patch testing revealed that he was allergic to the dyes in his bathing suit and his rash cleared when he changed to another-color suit. Noneczematous appearing variants of ACD include lichenoid contact,[42-57] the cellulitic-like appearance of dermal contact hypersensitivity,[58] contact leukoderma,[59] contact purpura,[60] erythema dyschromicum perstans,[61] and erythema multiforme,[62] among others. Of these, the lichenoid variants are most likely to be seen clinically because they have been noted to be a reaction pattern for a number of allergens, including dental amalgams[42-44] (eg, mercury, palladium, silver, and gold), tattoo pigments,[45-47] (eg, mercury, cobalt, and chromium), other metals[48] (nickel), *para*-phenylenediamine[49] (PPD) and its derivatives[50] (eg, the substituted PPD's used as antioxidants in black rubber), photographic color developers[51] (eg, CD-2 and CD-3, Fig 4), flavoring agents[52] (menthol and peppermint), Red Sea coral,[53] aminoglycoside antibiotics,[54] α-amylase,[55] fragrances[56] (especially photoallergy to musk ambrette), and plants[57] (especially *Primula* spp). In addition, many drugs may cause a lichenoid hypersensitivity, the most notorious being the quinine derivatives,[63] hydroxyurea,[64] angiotensin-converting enzyme inhibitors,[65] β-blockers,[66] and antiepileptic agents.[67]

A GEOGRAPHIC APPROACH TO IDENTIFYING ALLERGENS

As stressed by Cohen and Brancaccio,[68] a careful clinical assessment of the patient is required before any diagnostic tests to correctly identify causal allergens. Recently Krasteva et al[69] have published on the most frequently encountered causes of ACD in the major anatomic areas of the body. Summarized below is my approach to regional contact dermatitis.

ACD of the face, ears, and neck can present particular difficulties in determining the causative allergen because many substances could be responsible. The work environment must be examined in detail for potential clues: common work-related materials causing facial ACD include respirators, masks, aerosolized mists (such as those encountered by machinists), and volatile organic substances (for example, the amine hardeners in the plastic industry). Practitioners must also investigate nonoccupational exposures: the components of facial cosmetics (vehicles, preservatives, emulsifiers, fragrances), sunscreens (and other photoallergens), and grooming aids (eg, eyelash curlers [nickel, rubber] or makeup applicators [rubber]). In addition, allergy to chemicals

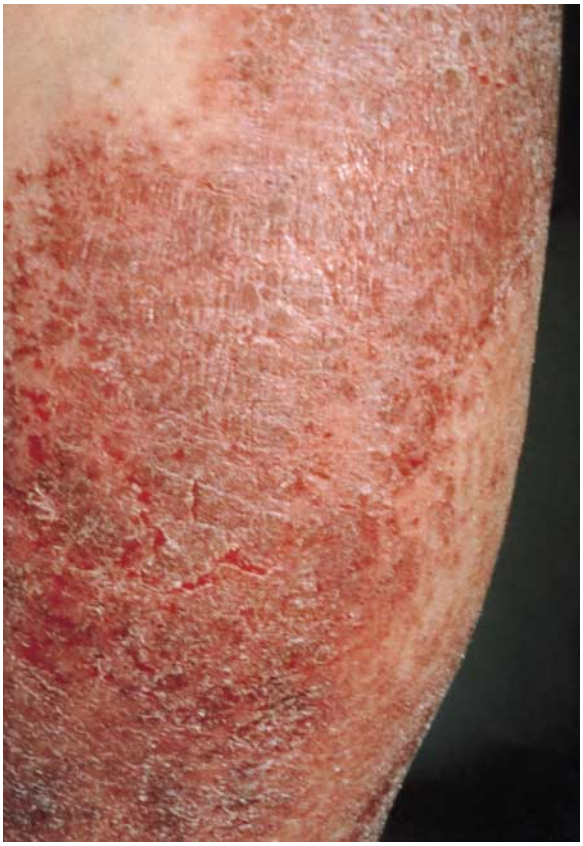

FIG 4. Lichenoid contact dermatitis caused by exposure to the photographic color developers CD-2 and CD-3. The classic lichenoid papules can be seen against a background of lichen simplex chronicus induced by chronic scratching. A number of other allergens (see text) can induce such lichenoid responses. (Reproduced with permission of the Division of Dermatology, University of Kansas Medical Center.)

applied to the scalp, which has a greater resistance to ACD, may manifest itself on the face, ears, and neck while sparing the scalp (eg, ACD from PPD in hair dyes or glyceryl thioglycolate in hair permanents).

When a facial dermatitis is particularly severe about the eyelids, the components of ophthalmic medicaments, eyelid/eyelash cosmetics, or airborne ACD must be considered. In many parts of the United States the most common airborne allergen is ragweed. However, it is also necessary to be concerned about other materials, such as volatile organic substances, fragrances, and chemicals contained in smoke. Other causes of a facial dermatitis with accentuation about the eyelids, especially the upper lids, are products that are applied to the hands and are unwittingly transmitted to the face. In women these chemicals are frequently found in nail enamels applied to the fingernails. Previously, tosylamide formaldehyde resin was the common culprit but, today, numerous acrylics are being used in nail polishes and topcoats and are becoming almost as common a cause of allergic eyelid dermatitis as the formaldehyde resins (Fig 2, *A* and *B*).

Although ACD of the neck is often associated with a facial dermatitis, patients can also have an isolated dermatitis of the neck. In these cases there are 3 groups of chemicals likely to have caused the reaction. Cosmetic allergens, especially fragrances and nail care chemicals, typically induce dermatitis on the lateral neck. A linearly distributed dermatitis of the lower neck frequently results from reactions to metals and occasionally to exotic woods, present in necklaces. The third common cause for a nuchal dermatitis, again one that wraps linearly about the lower part of the neck, is textile dermatitis to either the dyes or the formaldehyde resins in clothing. Periaxillary involvement sparing the vault of the axillae should lead to the strong suspicion of allergy to textiles.

Dermatitis overlying the torso is frequently textile related. Typically, textile dermatitis is accentuated about the posterior neck, upper back, lateral thorax, waistband, and flexor surfaces of the extremities, with relative sparing of the axillary vault and undergarment areas. The usual textile allergens are the azo-aniline (disperse) dyes used to color clothing and/or the urea formaldehyde resins used to finish the clothing, especially clothing resistant to wrinkling. Other causes of textile dermatitis include the rubber-related allergens found in elasticized garments and the metal allergens found in the metallic components of clothing.

Generalized reactions of the torso and extremities can be due to allergens other than those present in textiles. For example, patients can react to fragrances, preservatives, vehicles, and other constituents of moisturizing lotions. Although the product may be applied to the entire body, the rash often takes on a textile-like distribution. Such a reaction pattern points out the role of such nonimmunologic factors as friction, pressure, heat, and perspiration in accentuating the allergic response.[15]

Dermatitis of the hands and forearms that ends at the midupper arms, particularly when associated with a facial dermatitis, suggests a photosensitive process. When the face is not involved and when the patient has made no attempt to protect the facial skin from sun exposure, look for occupational allergens and for potential allergens in soaps and moisturizing creams used only for the hand and arms.

Isolated hand dermatitis is one of the most challenging problems for physicians. When seeking an allergic cause for hand dermatitis, pay particular attention to those chemicals listed in standard texts[70] that are handled in the occupation(s) and hobbies of the patient. In addition, the many household and cosmetic products the patient uses must be identified. In general, when an allergen is applied to the entire hand, the thinner dorsal skin is more severely involved than the thicker palmar skin, where the density of antigen-presenting LCs is decreased.[71] Although the palmar aspects of the hands are relatively resistant to the induction of allergy and typically are less involved than the dorsal aspects, if the patient is handling a solid object that contacts only the palmar aspects the dermatitis will occur only in this area.

Together with the feet, the popliteal fossa and inner thigh are the most common areas of the lower extremity

to be affected by ACD. The most frequently encountered allergens are those in textiles. In women, dyes in pantyhose (especially blue disperse dyes in darker-colored hose and disperse yellow No. 3 in flesh-colored hose) are the usual offenders. Other nontextile causes of ACD of the legs include the fragrances, preservatives, and vehicles present in moisturizers and other cosmetic preparations.

ACD of the feet is seen much less commonly than that of the hands; however, as with the hands, the dermatitis is usually most severe over the dorsal aspect of the feet. ACD of the feet is often accentuated over the joints and spares the lateral aspects of the toes and thicker skinned heel area. The allergic nature of this condition is suggested by the sparing of the arch of the foot and of the creases of the toe. Like the palmar hand, if the plantar foot is the only portion contacting the allergen, the dermatitis will be restricted to this area. The most common allergens are *para*-tertiary butylphenol formaldehyde resin (a component of shoe glues), rubber components, and chromate (used to tan leather). Shoe dyes are very uncommon causes of allergy.[72]

Allergens applied to mucosal surfaces very often do not induce significant mucosal pathologic features. Most patients allergic to allergens applied intraorally have cheilitis but not stomatitis. The unusual individual who reacts to nickel, mercury, palladium, or gold in dental amalgams presents with a systemic contact dermatitis, with or without a localized, often lichenoid, stomatitis.[73] Given the widespread exposure of the oral mucosa to allergens, the limited number of reports of mucosal ACD makes it obvious that patients rarely react to allergens intraorally. The reason for this is unclear.

It is not unusual for a patient with ACD to have a "scattered, generalized" dermatitis. These reactions are usually the result of allergens that are ubiquitous in the environment, such as formaldehyde, formaldehyde-releasing preservatives, rubber-related chemicals, nickel, fragrances, and balsam of Peru. However, individuals can also have a widespread cutaneous eruption after internal absorption of chemicals to which they were previously sensitized topically.

Although uncommon, reactions to internally absorbed chemicals, referred to as "systemic contact dermatitis," occur in individuals who have been sensitized topically to an allergen and are subsequently re-exposed systemically. Such re-exposure can be in the form of a drug or chemical introduced intramuscularly, intravenously, orally, rectally, or vaginally. Other sources of exposure include foods and medical or dental devices that contact mucosal surfaces or that have been implanted surgically into the body. Although the clinical reaction is typically a dermatitis limited to the site(s) of the original sensitization, more pronounced reactions ranging from an extensive, bizarre-appearing dermatitis to erythroderma also occur. Agents such as cinnamic aldehyde and balsam of Peru (which can be used as flavorings) or parabens (which are common food preservatives) must be highly suspect in such cases. In addition, contaminants in foodstuffs, such as nickel,[74,75] can also cause systemic ACD. Systemic contact dermatitis highlights one of the poorly understood aspects of ACD: the potential for long-lasting immunologic memory in previously sensitized areas of skin.

Finally, iatrogenic ACD must always be suspected when the primary dermatitis does not respond to usual therapies. A secondary ACD of the hands can develop in a patient with nonallergic hand dermatitis who uses rubber gloves to protect the hands. Iatrogenic contact dermatitis can also develop from the various topical preparations, including prescriptions, that patients apply. In the United States the principal offending allergens are topical antibiotics (neomycin and bacitracin)[76] and topical glucocorticosteroids.[77] It can be particularly difficult to identify the allergic nature of iatrogenic ACD because the eczematous quality can be muted by the underlying dermatosis-dermatitis for which the topical preparation was used.

DIAGNOSIS

The only useful and reliable method for the diagnosis of ACD remains the patch test. Only 23 commercially prepared allergens are currently available in the United States (Table II). A comparison of Table I with Table II makes it apparent that most, but not all, of the common allergens in the environment are contained on these trays. However, given the fact that there are greater than 2800 potential environmental allergens,[10] physicians interested in fully evaluating patients with ACD must be prepared to perform tests with other materials. For individuals compounding their own allergens, texts detailing appropriate concentrations and vehicles are available.[10]

Like any in vivo assay, patch testing is subject to pitfalls.[78] A primary concern is that even when a chemical is found to be allergenic for a given patient, it cannot be assumed that it is the cause of the dermatitis. As Table I illustrates, the relevance of presumably true-positive reactions to current episodes of ACD ranges from as low as 16.8% for thimerosal to as high as 93.4% for DMDM hydantoin. To determine whether an allergen is likely to be the culprit, the results of a positive patch test must always be correlated with materials encountered by involved areas of skin. Furthermore, even when patients are allergic to chemicals in products they are using, the allergen may be present in only minimal amounts and may not be responsible for the dermatitis. In this regard, repeat open application testing (ROAT), in which the patient applies the commercial product to normal skin several times daily for 1 to 2 weeks, can be helpful.[79] With use of such provocative tests, members of the North American Contact Dermatitis Group (NACDG) found that 5 of 10 individuals who tested positive to MCI/MI at 100 ppm in water did not react to a generic skin care lotion preserved with 15 ppm MCI/MI.[80]

When performing patch tests, the clinician must always be alert to the possibility of false-positive and false-negative reactions. False-positive reactions can result from the use of allergens at irritant concentrations

TABLE II. T.R.U.E. TEST Allergen Patch Test Panel*

Allergens	Principal contactants
Nickel	Metals, foods
Lanolin (wool) alcohol	Vehicle for creams and lotions
Neomycin sulfate	Antibiotics, vaccines
Potassium dichromate	Leather, spackling compounds, detergents
Caine mix	Anesthetics
Fragrance mix	Fragrances, flavorings
Colophony (rosin)	Adhesives, waxes, rosin
Paraben mix	Preservative in creams, lotions, foods
Negative control	
Balsam of Peru	Fragrances, flavorings
Ethylenediamine dihydrochloride	Stabilizers in creams, lotions, and intravenous solutions, certain antihistamines
Cobalt	Metals, blue pigments, vitamin B_{12}
Para-tertiary-butylphenol formaldehyde resin	Adhesives, shoe glues
Epoxy resin	Glues, plastics
Carba mix	Rubber products, fungicides
Black rubber mix	Rubber products
MCI/MI	Preservative in creams and lotions
Quaternium-15	Preservative in creams and lotions
Mercaptobenzothiazole	Rubber products
Para-phenylenediamine	Hair dyes (poor screen for textile dyes)
Formaldehyde	Preservative in many materials
Mercapto mix	Rubber products
Thimerosal	Preservatives in medications and vaccines
Thiuram mix	Rubber products, fungicides

*Manufactured by Kabi Pharmacia Service A/S, Hillerød, Denmark, and marketed in the United States by Glaxo Dermatology, Research Triangle Park, NC 27709.

or from the excited skin syndrome.[81] The false nature of these reactions can usually be resolved by repeating the patch tests individually or in lower concentrations. In contrast, false-negative reactions are more difficult to detect and require high levels of suspicion and diligence to uncover.

One way to avoid false-negative reactions is to perform a second reading of the test sites after the initial 48-hour inspection. This second reading, sometime between 4 and 7 days after application of the patches, is particularly important for elderly patients, who take longer to mount an allergic reaction.[82] A second reading is also important in detecting positive reactions to allergens such as neomycin, more than half of which are not evident until 96 hours after application of the patch test.[83] Geier et al[84] have identified PPD and cobalt as other allergens that are "slow" to develop. In their exhaustive study of 3475 patients, it was found that readings at days 3 and 5 after placement of the patch tests yielded the greatest number of positive results.

False-negative reactions can also occur when the allergen is used at too low of a concentration for patch testing, as can happen when cosmetic products are tested as is. False-negative reactions in these circumstances are a result of threshold and vehicle phenomena, which are only now being studied. It has been reasoned that both quantitative (eg, the degree to which hapten is conjugated and the intensity of signals for LC migration and maturation) and qualitative (eg, the type of immune response elicited) factors are involved in false-negative reactions.[85] In this regard, it has been shown that sensitization (and presumably elicitation) is dependent on the dose of chemical per unit area of skin, as opposed to the total dose delivered, down to a limit of <0.1 cm^2 of skin.[86] Rees et al[87] reported that when an allergen was applied to an area of 0.08 cm^2, little sensitization ensued, suggesting that a minimal number of epidermal LCs must be activated to elicit a response. In addition, the vehicle for the chemical can have a significant impact on the response by affecting such processes as skin penetration, cytokine production, LC migration, and other variables.[88-90] Therefore, if clinical suspicion warrants, and despite a negative patch test, additional testing such as ROAT with the suspect product can unmask the cause of ACD.

With more than 2800 potential allergens,[10] negative reactions may simply indicate that the responsible chemical has not been tested. Although it has been widely quoted that 70% to 80% of patients with ACD can be diagnosed with use of screening trays such as the T.R.U.E. TEST (Kabi Pharmacia Service A/S, Hillerød, Denmark),[91] these numbers have recently been questioned. In an analysis of the 1994-1996 NACDG data on 3120 patients,[92] it was found that 62% of these individuals had at least one positive reaction to an allergen present on the T.R.U.E. TEST, of which 45% were relevant to the current dermatitis. However, by expanding the panel from 23 to 50 allergens, additional allergens of potential relevance were identified in 31% of these patients.[92] In their study of 732 patients over 5.5 years,

Cohen et al[93] found that only 23% of patients reacted exclusively to allergen(s) on a similar (but not identical) standard series, 37% reacted to allergens on both their standard series and other supplementary tests, and 40% reacted only to supplementary allergens. Thus, to maximally benefit patients, practitioners of patch testing must use allergens beyond those deemed appropriate for commercial sale by the Food and Drug Administration. In the case of fragrance allergens, Larsen et al[94] found that the addition of a "natural mix" of 2% jasmine absolute, 2% ylang-ylang oil, 2% narcissus absolute, 2% sandalwood oil, and 2% spearmint oil increased the sensitivity of detecting fragrance allergy to 95% from the 81% detected with the standard allergens, fragrance mix and balsam of Peru.

In vitro tests for the diagnosis of ACD have received much attention in the last decade of the 20th century. Laboratory studies such as lymphocyte transformation or macrophage migration inhibition have been evaluated as measurements of ACD in both humans and animals.[95] One of the major problems in developing in vitro systems is the lack of knowledge about what constitutes the antigenic moiety of a particular chemical. Nonetheless, these assays are now being extensively studied and reliably standardized.[96] In data submitted by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the local lymph node assay (LLNA, a test of lymphocyte transformation) did not accurately predict all weak sensitizers (false-negative) and some strong irritants (false-positive).[97] However, when the LLNA was compared with currently accepted methods (ie, guinea pig methods), the LLNA performed equivalently in the prediction of the risk for human ACD. In a review of 209 chemicals, of which both LLNA and guinea pig data were available for 126 chemicals and both LLNA and human data were provided for 74 chemicals, the accuracy of the LLNA versus all guinea pig tests (GPTs) was 86% and versus human data was 72%, whereas that of all GPTs versus human tests was 73%.[98] In terms of accuracy, sensitivity, specificity, and positive/negative predictability, the ICCVAM found the performance of the LLNA to be similar to that of GPTs. Equally important, the performance of the LLNA and the GPT was similar when each was compared with human data. Thus, although in vivo patch testing in which the skin can process the allergen for presentation remains the "gold standard" for the near future, the new millennium brings exciting prospects for in vitro testing.

TREATMENT AND PREVENTION

The treatment of ACD lies in correctly identifying its cause and in instructing the patient to avoid the responsible allergen(s). Because many allergens may share common antigenic moieties, the practitioner must also instruct the patient about possible cross-reacting allergens. For example, the patient allergic to benzocaine must potentially avoid many cross-reacting substances, which include agents as diverse as other anesthetics (eg, procaine), certain medications (eg, sulfonamides), hair dyes (eg, *para*-phenylenediamine), textile dyes (eg, aniline dyes), some sunscreens (eg, *para*-aminobenzoic acid), and other products. Because cross-reactions are not always evident to the nonchemist (eg, benzoyl peroxide with cocaine), practitioners must consult standard texts[99,100] when instructing their patients.

In addition to avoidance of the allergen and its cross-reactants, treatment of ACD should be directed to its symptoms. This is particularly true because, as is evident from numerous studies, patients with ACD will not always improve with avoidance of allergens and job changes.[101] Pryce et al[102] showed that more than 70% of machinists continued to have symptoms of contact dermatitis 2 years after diagnosis, regardless of whether they changed jobs. Halbert et al[103] showed that almost 70% of their patients continued to have a dermatitis for years after the diagnosis of chromate allergy, despite avoidance. They further showed that the chronicity of the dermatitis increased when the diagnosis was delayed longer than 12 months, thus stressing the need for early diagnostic intervention. As demonstrated by Lips et al,[104] if the disorder is diagnosed early, if strict allergen avoidance is enforced by authorities, and if financial support exists for job retraining, the prognosis is often good. However, in the United States and other countries where the social safety net is more porous, persons with chronic contact dermatitis may well retain it in some form despite continuing therapy, a finding that has serious implications for Worker's Compensation.

Acute weeping eruptions benefit from drying agents such as topical aluminum sulfate–calcium acetate; chronic lichenified eruptions are best treated with emollients. Pruritus can be controlled with topical antipruritics or oral antihistamines; topical antihistamines or anesthetics should be avoided because of the risk of inducing a secondary allergy in already dermatitic skin. Treatment with physicochemical agents that down-regulate responsiveness may also be required; glucocorticoids and UV radiation are the clinical agents most widely used. Although topical glucocorticosteroids usually suffice for most patients with ACD, individuals with involvement of greater than 25% of their body surface area or those exposed to certain allergens (such as *Toxicodendron* oleoresin, which appears to persist locally in the skin for weeks after exposure) may require systemic glucocorticosteroids. In some of these patients phototherapy with UVB or PUVA can be beneficial, especially for those individuals with occupational ACD who are economically unable to discontinue working with the offending allergen and who are also unable to work with gloves or effective barrier creams. In these cases, long-term maintenance therapy with UVB[105] or PUVA[106] may obviate clinical manifestations of the allergy despite persistent contact. In this millennium potential therapeutic modalities include new classes of immunosuppressants (topical FK 506, ascomycin), inhibitors of cellular metabolic activity, inhibitors of cell adhesion molecules, targeted skin application of regulatory cytokines, and neutralization of proinflammatory cytokines with antisense

oligonucleotides, anticytokine antibodies, or soluble cytokine receptors.[107-109]

Although prevention of ACD rests with avoidance of the allergen, for various reasons, principally economic, this is not always possible. The hairdresser allergic to glyceryl thioglycolate (in acid permanent solutions), which can persist in hair for months[110] and can penetrate vinyl and latex gloves,[99] may be unable to avoid daily contact with the allergen. A plastic glove made of proprietary laminate has been introduced (4H, available from Safety 4, Lenexa, Kan; URL, http://www.safety4.com). In clinical trials the 4H glove, which is only 0.07 mm thick, was impervious to more than 90% of all randomly selected organic chemicals for 4 hours at 35°C.[111] However, this glove is not form fitting and is thought by many professionals to impede the fine dexterity needed in their work. In the future, barrier creams may be available to help such patients. Now, however, barrier creams are available for only a limited number of allergens (principally poison ivy and poison oak), are effective only if the protected area is washed within several hours of contact with the allergen, and are objectionable to many patients because of their thick tack and greasy consistency. Thus the search for suitable alternatives continues. A recent article has touted the benefit of ginkgo biloba in a sodium carboxy-methyl-β-1,3-glucan formulation as a protectant against ACD induced by nickel, fragrance, balsam of Peru, and MCI/MI.[112]

Although the possibility of hyposensitization for ACD has intrigued researchers for decades, it currently is not a viable alternative. Despite the early encouraging work of Schamberg[113] and Strickler[114] with oral or intramuscular *Toxicodendron* antigen to desensitize the Rhus-allergic individual, such therapy has never been clearly found to be effective. In his exhaustive study, Kligman[115] concluded that complete desensitization of the highly sensitive subject by oral or intramuscular administration is impossible. In these studies, months of treatment with *Toxicodendron* oleoresin resulted in a temporary lessening of the intensity of the allergic response but not an ablation of it. In another study in which the active ingredients of Rhus oleoresin (pentadecylcatechol and heptadecylcatechol) were fed to 44 patients, no effect was seen.[116]

One theoretic possibility for prevention of occupational ACD is the induction of tolerance to the known occupational allergens before employment. When an antigen to which an individual has not yet been sensitized is administered either systemically[24] or topically to areas deficient in functional LCs,[25] long-lived tolerance ensues. However, because allergic reactions to apparently innocuous materials, such as nickel, persist in the human genotype, it must be questioned whether there is a selective advantage to the trait. It cannot be assumed that simple chemical allergens do not cross-react with viral or tumor-related antigens. In the absence of information concerning how the antigenic moieties of many simple chemicals might relate to antigenically more complex viruses and malignancies, it would seem unethical to induce tolerance to even the most problematic environmental allergens given the theoretic risk of enhancing susceptibility to potentially more life-threatening diseases. Hopefully, the solution to this and other dilemmas surrounding ACD will be found early in this millennium.

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