

Review article

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Contact dermatitis

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Learning Objectives: Reading this article will reinforce the reader's knowledge of the definition, pathophysiology, differential diagnosis, evaluation, and management of the most common of all the "eczemas," contact dermatitis, which can have an allergic and/or an irritant pathogenesis.

Data Sources: Relevant articles and current texts on contact dermatitis were referenced and reviewed. The personal experiences of the authors in an Environmental Medicine Clinic, their private practices, and their teaching of residents and other physicians were evaluated. A MEDLINE database using subject keywords was searched from 1986 to date.

Study Selection: Book chapters, pertinent articles, data source abstracts, guidelines for the management of contact dermatitis set by the American Academy of Dermatology, and the American Contact Dermatitis Society were critiqued.

Results: The recent elucidation of the pathoimmunology of contact dermatitis is concisely reviewed, highlighting its clinical implications. The protean clinical presentations of contact dermatitis, both "allergic" and "irritant" type are cited. The signs and symptoms warranting the search for a contactant are outlined. The most likely regional contactants are listed, but the need to reference a more complete textbook is often required. That patch testing is the gold standard to identify an allergenic agent causing allergic contact dermatitis is stressed. While the "who" and "when" to patch test is amply described, a cookbook "how" to patch test has been omitted in order to emphasize the importance of "hands on" experience for such testing. The advantages and limitations of the commercially available standard patch tests (Hermal, and T.R.U.E.) are described, plus the sources for "nonstandard" patch tests is made available. Therapeutic modalities, topical and systemic, for management of the uncomfortable patient are outlined.

Conclusion: The physician who manages a patient with an "eczematous" rash must be aware of the complete differential diagnosis of that clinical presentation. Suspicion that a "contactant" is the cause must have high priority, especially when the rash is persistent, and fails to respond to "appropriate" therapy. The value of a skin biopsy is limited to confirming its eczematous (spongiotic) nature and ruling out other diseases. Appreciating the paradox of patch testing, namely the deceptive simplicity of application versus the required expertise for interpretation and recognition of clinical significance, is the key to the proper management of the patient with contact dermatitis.

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INTRODUCTION

The spectrum of contact dermatitis encompasses all adverse cutaneous reac-

tions resulting from the direct contact of an exogenous agent (a "foreign" molecule, ultraviolet light, or temper-

ature) to the surface of the skin. While the term has been most often associated with an "allergic" etiology, we are becoming more aware that the "irritant" type of contact reaction is more prevalent. The inflammatory process resulting from an allergenic substance is mediated through immunologic mechanisms, while irritant reactions result from direct tissue damage after contact with the stimulus, which initiates an alternative inflammatory reaction. Recognizing that these two types of eczematous entities constitute the most common form of skin afflictions requiring medical intervention,¹ and that they are also the leading causes of occupational disease,^{2,3} we are beckoned to better understand the relationship of percutaneous response to "contactants," and the pathologic mechanisms of the subsequent inflammatory cutaneous reaction (Tables 1 and 2).

It has been estimated that there are more than six million chemicals in the environment and that 2,800 of these have allergenic (contact-sensitizing) properties.⁴ Almost any substance, depending on its concentration, duration of contact, and the condition of the exposed skin, can induce a cutaneous reaction (or "dermatitis") (Table 3). When the agent causing the dermatitis can be identified and avoided, recovery can be anticipated. If contact persists the dermatitis may become chronic, disabling, and a serious threat to continued employment, besides being an impediment to the activities of daily living. Patch testing is the most cost-effective diagnostic procedure, especially in patients with a dermatitis of 2 to 12 months' duration.⁵ After prolonged and/or repeated episodes of

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Table 1. Irritant Versus Allergic Contact Dermatitis: Distinguishing Features*

Frequency	Irritant Contact Dermatitis 80%	Allergic Contact Dermatitis 20%
Common causes	Water Soaps Detergents "Wet work" Solvents Greases Acids and alkalis Fiberglass Particulate dusts	Cosmetics (fragrance and preservative ingredients) Metallic salts (eg, nickel, chromium, cobalt) Germicides (eg, formaldehyde, formaldehyde releasers) Plants Rubber additives (eg, latex) Plastic resins (eg, epoxy, acrylic) Rosin (eg, colophony) Topical medications
Concentration of the agent	More critical	Less critical
Mechanism/trigger	Nonimmune; sensitization not required; damage to keratinocytes	Immune; sensitization required; interaction of antigens with primed T-cells
Atopic predisposition	Increased	Decreased
Diagnostic test	None	Patch test

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contact dermatitis, some patients may never fully recover despite appropriate medical care and meticulous avoidance of the causative agent.⁶

In 1992 the Contact Dermatitis Committee of the Dermatologic Interest Section Committee of the American Academy of Allergy and Immunology surveyed its members regarding allergic contact dermatitis. The (unpublished) results from the 929 members (25% of the membership) who responded revealed that 89% treated allergic contact dermatitis; and 47% of those allergists did patch testing (prior to the availability of the TRUE test) compared with 27% of dermatologists in a recent survey by

the American Academy of Dermatology.⁷ Seventy-four percent of respondents believed they had enough experience to diagnose allergic and irritant contact dermatitis, despite having had a minimum of formal training in patch testing.

In 1995 the Task Force on Contact Dermatitis of the American Academy of Dermatology published their "Guidelines of Care for Contact Dermatitis,"⁸ and it deserves the perusal of everyone who treats patients with contact dermatitis. There are several excellent contact dermatitis textbooks⁹⁻¹¹ available, one of which should be in the library of everyone who does patch testing.

Table 2. Clinical Features of Allergic Versus Irritant Contact Dermatitis

Clinical Feature	Allergic	Irritant
Reaction delay after contact	Many hours to 5 to 6 days	Usually within 48 hours
Sharp demarcation	May occur	Often typical
Time for clinical resolution	Many days	Frequently diminished by 96 hours

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PRACTICAL DERMATOLOGY FOR THE ALLERGIST

Only a few millimeters thick, the skin is the body's largest organ and vulnerable to a barrage of offending insults: infectious, allergic, noxious, and traumatic. Its defense relies on its physical barrier properties which vary with its thickness and penetrability according to location and local environment, and on its ability to react immunologically. The skin must be recognized as the peripheral arm of the immune system.¹² The immunologic components of the skin are (1) the keratinocytes of the epidermis, (2) the Langerhans' cells, (3) mast cells in the dermis, (4) T-cells, (5) the dermal microvasculature, and (6) the dermal nerves (Fig 1).

Keratinocytes

These building blocks of the epidermis are the outermost sentinels of the skin, they react to the multitude of nonhappental stimuli (ultraviolet light, traumatic, and noxious) with the release of specific cytokines,^{13,14} which signal for the appropriate dermal inflammatory response.¹⁵

Langerhans' Cells

These are the "professional antigen presenting cells." While they are most commonly found suprabasally, in atopic skin they are found scattered throughout the many layers of the epidermis.¹⁶ Receptors on their surface take up substances (haptens) from the extracellular compartment. Exogenous antigens (ie, the contact dermatitis-causing chemicals, extracellular bacteria, bacterial toxins, and dermatophytes) are then broken down into peptides and delivered to the regional lymph nodes. (Atopic Langerhans' cells also have FcγE receptors, which can accept aeroallergenic haptens.) In the regional lymph nodes, the haptens are presented on MHC class II molecules, while the endogenous antigens (viral, and tumor) are preferentially presented on MHC class I molecules.¹⁷ The number of Langerhans' cells are decreased in photodamaged (tanned) skin,¹⁸ teleologically rationalizing the

Table 3. Potential Causes of Contact Dermatitis

Chemical Substances*	Metals	Other
3,350 pesticides	Chromium	Fewer than 30 allergens
3,410 cosmetics	Nickel	responsible for up to
1,815 drugs	Mercury	80% of allergic contact
8,627 food additives	Other metals	dermatitis†
48,523 commercial chemicals		

* *The Facts*. US Dept of Health and Human Services. National Research Council. 1983 Report.

† James et al. *J Am Acad Dermatol*. 1992.

decreased incidence of delayed hypersensitivity (and contact dermatitis)¹⁹ noted in sun-damaged skin.

Mast Cells

These are predominantly of the tryptase-chymase type in normal skin, but some tryptase type mast cells are found in atopic skin.²⁰ Mast cells are recognized as the protagonist of immediate-type hypersensitivity, and may

play but a "fleeting" role early in the evolution of contact dermatitis.²¹ Mast cells are present in the dermal papilla, especially in the areas of blood vessels and nerves. The numerous mast cell secretagogues induce the release of an assorted "concoction" of mediators, accounting for the different clinical manifestations of their degranulation.²² Mast cell chemotactic mediator release

summon basophils and eosinophils that then implement the "late-phase" reaction.

T-Cells

Normal skin contains relatively few T-cells. Within the skin, lymphocytes are of the T-cells rather than the B-cell type. The type of antigen presented to them by the Langerhans' cell in the regional lymph node determines the differential T-cell activation (CD4+ helper by MHC II molecules or CD8+ suppressor type by the MHC Class I molecules). Homing receptor molecules on the T-cells and reciprocal molecules (addressesins) located on the endothelial cells localize the inflammatory response to the site of original contact. CD4 cells are then typed as Th1 and Th2 cells based on their function and cytokine production. Th1 cells are predominant in allergic contact dermatitis. Their mediators produce a clinical eczematous eruption (histologically spongiotic dermatitis), and their prevailing cytokines are IL2 and IFN γ . The mediators of Th2 cells also produce a spongiotic dermatitis (seen in atopic dermatitis). Their cytokines, IL4 and IL5, induce IgE production and attract eosinophils and basophils, respectively (Fig 1).^{23,24}

Dermal Microvasculature

The bulk of the microvasculature is found in the dermal papilla. The rubor (redness) of inflammatory reactions is the result of neuropeptide-induced and histamine-induced vascular dilatation. Areas rich in this microvasculature such as the face, scalp, genitalia, and dorsa of the hands and feet are more liable to elicit an explosive, inflammatory reaction. Expression of adhesion molecules on vascular endothelium and infiltrating leukocytes recruit inflammatory cells from the circulation into the extravascular tissue. An "up-regulation" of adhesion molecules has been demonstrated in all inflammatory dermatoses.²⁵

Dermal Nerves

The "itch" associated with all allergic reactions is mediated by specific itch fibers at the dermo-epidermal junction.

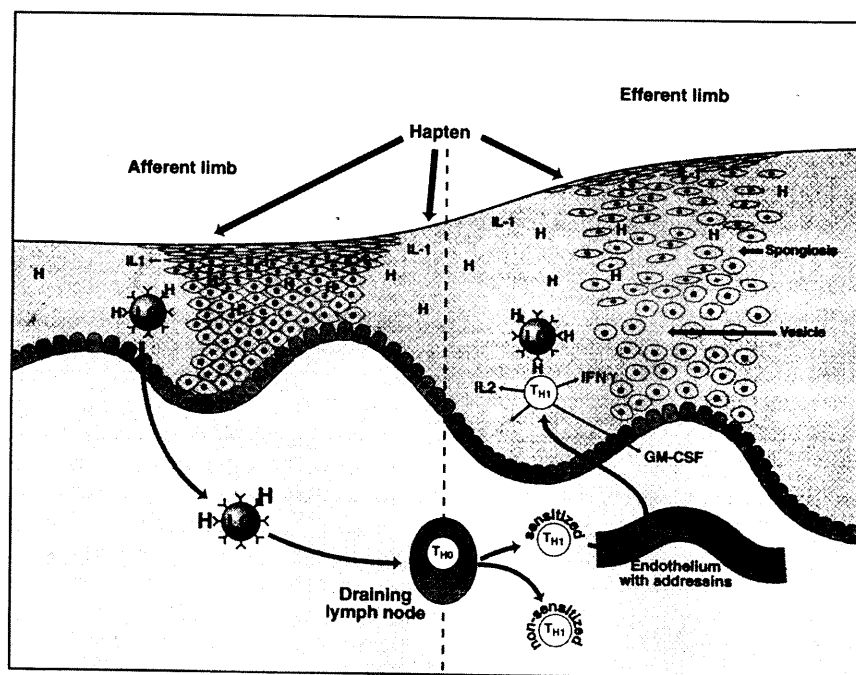


Figure 1. Immune response in allergic contact dermatitis. *Afferent limb*, A hapten gains entrance to the epidermis, activating keratinocytes to release inflammatory cytokines (IL-1, IL-6, IL-8, and GM-CSF). Haptenated (LCs) migrate to a draining lymph node (within 24 hours). Presentation of hapten to Th0-cells in the lymph nodes sensitize 1/100-500 Th1 cells as a clone of hapten-specific Th1 cells. *Efferent limb*, The sensitized Th1 cells possess skin-specific homing receptors, which are guided by endothelial cell addressesins to the hapten-provoked skin site, whereby they recognize the specific hapten presented to it by "antigen-presenting" LCs, causing them to release Th1 cytokines (IFN γ , TNF β , GM-CSF, IL-2), resulting in spongiosis (within 12-36 hours). While the afferent limb is essential in a primary or initial exposure, it plays a lesser role in secondary or subsequent exposure, which shortens the time for the appearance of spongiosis. (Special thanks to R S Kalish, MD, PhD for suggestions in creating this figure.)

tion.^{26,27} Presumably there are specific molecular receptors on the surface of itch-signaling nerve terminals to which primary pruritogenic agents (such as histamine, kallikrein, bradykinin, trypsin, papain, and substance P) have been shown to produce experimental pruritus.²⁷ These nerves also are the major source of neuropeptides (a mast cell secretagogue) in the skin. An active role of neuropeptides in allergic and nonallergic inflammation in skin reactions is assured by the anatomic proximity of mast cells to these nerves. Antidromic stimulation of peripheral nociceptive nerves releases the vasodilatory substance P, which promptly causes the area's cutaneous flare subsequently amplified by release of histamine from mast cells.

THE NATURAL HISTORY OF CONTACT DERMATITIS

The "allergic" reaction pattern expressed by the skin when it encounters exogenous substances is an eczematous dermatitis but less frequently it may be urticarial (both localized and generalized). The "nonallergic" (irritant-type) reactions can be dermatitic, acneiform, pigmentary (hyperpigmentation or hypopigmentation), and most rarely purpuric, or atrophic.²⁹ Factors to consider in the history of contact dermatitis include the following:

- the stimulus (amount and concentration),
- status of the skin in contact with stimulus,

- duration of contact,
- latency (from contact to clinical appearance of reaction), and
- evolution and resolution of clinical symptoms

Allergic Contact Dermatitis

Allergic contact dermatitis has been regarded as the prototypic example of delayed type hypersensitivity, mediated primarily by Th1 cells in response to allergens in contact with skin.³⁰ Contact allergens must be able to penetrate the stratum corneum in order to initiate the immunologic response. Clinically, the result is an eczematous eruption which histologically is a spongiotic dermatitis (the nonspecific marker of all "eczemas"). The acute stages can present as very pruritic large vesicles and bullae (Fig 2) overlying a palpable erythema. Subacutely the pruritus and erythema are less and the vesicles are more difficult to recognize macroscopically (Fig 3). The later clinical picture is minimally pruritic and is identifiable with remnants of ruptured vesicles, peeling (desquamation), some degree of postinflammatory hyperpigmentation, and variable lichenification.³¹

The stimulus must be a haptogenic antigen, which is best absorbed into the intercellular (keratinocyte) space while in solution. Sweating solubilizes the antigen and may "spread" the reaction onto skin beyond the area of application. Rarely does a "dry" substance become antigenic.²¹ Langer-

hans' cells only recognize antigens in a haptenic state.

Status of the skin. The thickness of the epidermis affects the potential for developing allergic contact dermatitis. Thinner sites, ie, eyelids, earlobe and genital skin are most vulnerable, while the thicker palms and soles are more resistant. The reactivity of the skin to contact sensitizers in early infancy, due to its immunologic immaturity, is less than it is later in life.³² Black skin, which is usually thicker than caucasian skin, confers little racial protection against contact dermatitis.³³ Humidity and warmer ambient temperature increase allergen penetration. An intact skin surface deters penetrability, while maceration by sweating, occlusion, or water immersion (as is the case for bartenders, beauticians, and food handlers), increases the accessibility of antigens and irritants. Xerotic and/or "dermatitic" skin, especially in atopic patients,⁶ presents a broken barrier and a greater vulnerability.

Duration of contact. When the antigenic exposure is episodic, eg, rhus—washing off the oleoresin within ten minutes of contact can reduce the immune response.^{34,35} (After 30 minutes, any wash is virtually useless in deterring the reaction.) A protracted exposure time, as with nickel in jewelry, is suspected by the "brand-like," more subacute/chronic appearance (Fig 4). Most challenging to identify is when exposure is part of a regular procedure such as in the work environment. The antigenicity of the hapten may be enhanced, despite a brief contact time on an abnormal barrier due to wet or xerotic skin.

Latency is defined as the time required for the clinical presentation of the dermatitis after contact with the allergen. Pathophysiologically it is the travel time for the Langerhans' cell to deliver the hapten to the area lymph node, where Th1 cells are activated to produce a clone of specifically sensitized cells which then "home" to the site of contact.²³ There they release their inflammatory mediators (Fig 1). Antigen-bearing Langerhans' cells remain in draining nodes for several days

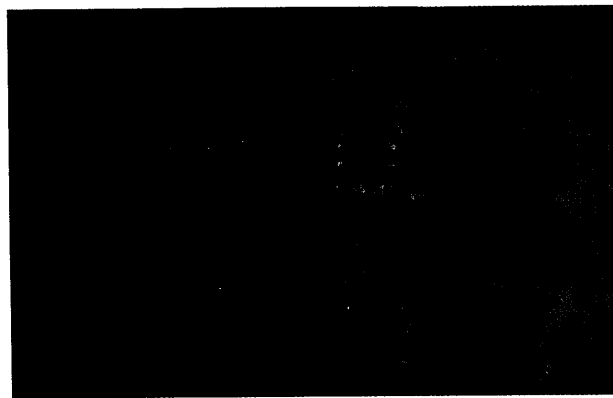


Figure 2. Acute eczematous eruption with bulla on hand of youngster 48 hours after playing in fields.

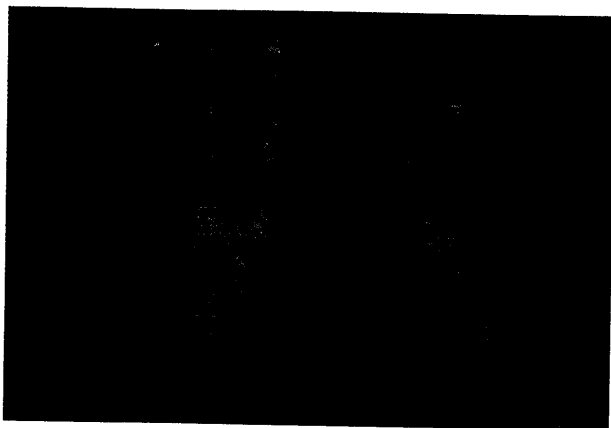


Figure 3. Chronic lichenified eczematous dermatitis on dorsum of hands of a worker in daily contact with rubber products (patch test positive to carba mix).

and then gradually disappear.³⁶ The first seasonal contact reaction with rhus requires a latency of 24 to 48 hours. Subsequent exposures in the same "season" shorten the latency to 12 to 24 hours due to an anamnestic response.³⁷

Evolution and resolution. The inflammatory mediators released by the

"homing" T cells produce the clinical picture of eczema. When the antigen is episodic such as rhus of "poison ivy," the eczema resulting from the "acute" oozing presentation to clinical resolution can last from 7 to 21 days (but may rarely persist for 40 days). Both genetic and environmental factors influence the individual course. The im-

mune response to contact allergens is the host's mechanism to eliminate foreign molecules while preserving its own integrity.³⁸ With more continual exposure to an antigen due to the failure of identifying the source, the clinical picture may persist for weeks despite its eventual removal. Spontaneous resolution occurs after the antigen is removed and the T cell mediators dissipate. (Potent topical and/or systemic steroid therapy aborts the "homing" of T cells and inhibits the release of the inflammatory mediators but does not alter the natural history of the episode. Inadequate dosage and their administration for less than the "natural" 14 to 21 days results in an incomplete clinical response.)

Irritant Contact Dermatitis

Irritant contact dermatitis cannot be defined as a single clinical entity but rather as a clinical spectrum:

- Acute
- Acute delayed
- Irritant reaction
- Cumulative
- Exsiccation eczematid
- Traumatic
- Pustular and acneiform
- Non-erythematous
- Subjective

(Modified from Eisner's Irritant Dermatitis, 1995:1-8)

Irritant contact dermatitis results from the physical exposure of an "injurious" substance to the skin surface. An appealing hypothesis for the pathogenesis of irritant dermatitis is that the "damage" results from mediators released by "nonspecifically"-activated T cells. The cutaneous response that follows may be at times indistinguishable from allergic contact dermatitis or it may present as a very different inflammatory response.⁴⁰ Instead of being predominantly pruritic, the cutaneous response of irritant contact dermatitis is a more intense, sharply demarcated redness (and at times, necrotic), with heat, swelling, and tenderness.⁴¹

Stimulus. The irritating (nonhaptenic) stimulus comes in direct contact

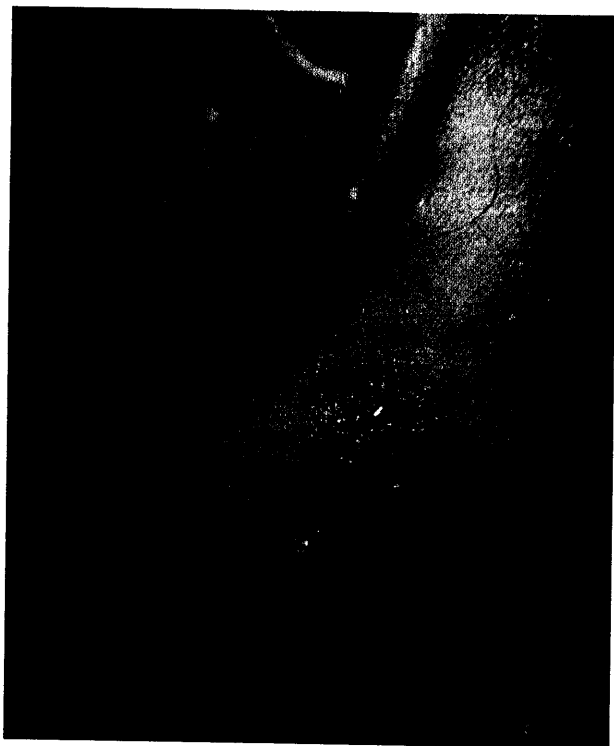


Figure 4. Chronic ulcerated eczematous eruption on earlobes and angle of jaw from contact with earrings (patch test positive to nickel).

with the target (keratinocytes of the epidermis). The resulting inflammatory response is concentration-dependent, meaning that a relatively low concentration may perturb the physiologic state, whereas a higher concentration may cause cell death. Many allergens can be irritants at "high" concentrations.⁴²

Status of skin. Individuals exposed to wet work, such as hairdressers or food handlers, etc, present with skin altered by "super-hydration." This "abnormal" barrier is then more vulnerable to chemical damage, by agents that might otherwise have been innocuous. While this condition can heal spontaneously with the avoidance of "wet-work," continued exposure may cause it to progress and become a cumulative irritant dermatitis—the result of multiple subthreshold damages to the skin. Persons with "sensitive skin" (atopics, celtics) present with a lowered threshold.³³

Duration of contact by the noxious agent resulting in damage to the skin is dependent on the "irritancy" of the substance! The less neutral the pH of the substance the less time needed to damage the skin. Traumatic irritant contact dermatitis may result from acute skin trauma, eg, burns. "Cumulative irritant contact dermatitis is a consequence of multiple subthreshold damages to the skin, and the time between insults is too brief for complete restoration of skin barrier function.

Latency. The time between exposure and eruption is usually brief, from minutes to hours, except when a delayed irritant reaction occurs as a result of "cumulative" irritant reactions. (No period for sensitization of T-cells is required as with allergic contact dermatitis.) Immediate rinsing and/or neutralization of the offending irritant can reduce the severity of the reaction.

Evolution and resolution of irritant contact dermatitis is less predictable than the natural history of allergic contact dermatitis. Tissue damage can be visible from minutes (ie, caustic burn) to weeks (ie, daily subthreshold exposure to mild "workplace" substances). Clinical presentation is more restricted to the skin directly in contact with the

offending agent ("branding sign"), not extending much beyond the site of contact. The management is predominantly aimed at symptom control. Topical and systemic steroids can suppress the nonspecific T-cell activation. Prevention of secondary complications (ie, infection) and scarring is imperative. Cicatricial scarring and/or post-inflammatory hypopigmentation or hyperpigmentation is more likely to occur following irritant contact dermatitis than allergic contact dermatitis.

DIAGNOSIS OF CONTACT DERMATITIS

Dermatologic diagnoses are based on the history and clinical appearance of the cutaneous presentation. Virtually every eczematous rash must be suspect of being a contact dermatitis. The distribution of the eruption should then be congruent with exposure to an allergen or irritant (similar to being "branded"). No doubt the more exposed areas of the skin are more open to allergen and/or irritant encounters. Thus, the hands and face are the most common body parts presenting with a contact dermatitis.⁴³ For persistent eczematous eruptions in nonexposed areas, one must suspect an applied substance such as a medication or cosmetic to be the cause. Occupational skin disease (specifically, contact dermatitis) accounts for a significant proportion of all occupational diseases. While the history can make one suspect a contactant, a recent survey by the American Academy of Dermatology negated the accuracy of relying solely on the history to diagnose contact dermatitis. They concluded that the diagnosis of allergic contact dermatitis made solely by history is undersuspected.⁴⁴ underdiagnosed, or misdiagnosed when compared with patients who were subsequently patch tested.

Skin biopsy is a diagnostic procedure that is regularly used in dermatologic practice, but for inflammatory dermatoses, results are usually nonspecific. Comparing the results of skin biopsy to patch testing in patients with inflammatory dermatoses, patch test results were more specific and most

useful in directing patient management.⁴⁵

Regional Contact Dermatitis

Eyelids. Contact dermatitis is the most common eruption of the eyelids (Fig 4) most often caused by cosmetics applied to the hair, face, or fingernails than by cosmetics applied to the eye area.^{43,46} "Poison ivy" can produce marked swelling of the eyelids with minimum dermatitis of the lids. Unfortunately the morphologic features of "allergic" and "irritant" contact dermatitis of the eyelids are not always distinguishable. Up to 25% of patients with atopic dermatitis report a more chronic type of eyelid dermatitis, and a superimposed "contact" (ie, dust mite, tobacco smoke exposure) must always be ruled out.

Hand. Eczematous eruption of the hand is a symptom, not a diagnosis. The differential diagnosis should include pompholyx (dyshidrosis), psoriasis, and atopic dermatitis. Allergic and irritant contact dermatitis can complicate any chronic eczematous process. Recognition of these complications has important management implications.⁴⁷ The prevalence of allergic contact dermatitis in patients with chronic hand dermatitis has been reported in 17% to 30% of patients. All patients with chronic hand dermatitis should be patch tested.⁴⁸

Facial Contact Dermatitis

The face is the most common and often the main site of photodermatitis. Ragweed dermatitis is most often noted on the face. A nonspecific irritation from (allergy-free) cosmetics, called "status cosmeticus," is seen in patients who experience itching, burning, or stinging following the application of any cosmetic or soap. The cause is almost always irritant and not an allergic reaction.⁴⁹

Scalp. The scalp is particularly resistant to contactants. Allergens applied to the scalp often produce reactions on the eyelids, ears, neck, and hands, and the scalp remains uninvolved.⁵⁰

Neck. The neck, like the eyelids and genitalia, is a very reactive site. Berloque (perfume) and nickel-sensitive patients frequently present with a dermatitis of the neck. "Fiddler's neck" is an area of localized lichenification of the skin on the left side of the neck, where the chin-rest of the violin is in (irritant) contact with the side of the neck.

Trunk. Nickel (under jewelry) and rubber chemical allergy frequently cause allergic contact dermatitis, especially under bras and beltline elastics.

Axilla. Deodorants will involve the entire vault of the axilla, while detergents and formaldehyde (in drip-dry clothing) spare the apex of the axilla.

Lower legs. Stasis dermatitis, a chronic varicose inflammation of the skin of the lower legs, frequently is complicated by the development of contact dermatitis. One study disclosed a 60.9% incidence of at least one significantly positive patch test reaction. Neomycin and epoxy resin were the most common culprits.⁵¹ They confirm the impression that the incidence of contact reactions to topicals in stasis dermatitis is 3 to 10 times higher than with any other dermatitis.

Vulva. Sensitizing medications (chemical contraceptives), douches, or latex condoms are well tolerated by the vaginal mucosa but will produce a vulvitis and a dermatitis of the adjacent thighs.

Pruritus ani and proctitis. Medicated anal cleansers, perfumed and colored toilet paper should be suspected in all cases of pruritus ani. The ingestion of spices, antibiotics, and laxatives may cause anal itching. Ingested allergens may also cause a generalized "systemic" contact dermatitis, eg, benzocaine in cough drops, cinnamic aldehyde found in spices.⁵²

Atopics

Clinical studies have shown rates of allergic contact dermatitis in atopics that are lower, the same, or higher than in the general population.^{53,54} The long-term application of medications to the "twitchy" skin of patients with atopic dermatitis subjects them to an

increased susceptibility for sensitization, and one must always suspect allergic contact dermatitis to a topical medication in any patient whose rash worsens during treatment. Irritant contact dermatitis is the most common occupationally induced skin problem, and it occurs predominantly in atopic individuals.⁵⁵ Patients with atopic dermatitis, especially those whose persistent eczema is confined to the scalp, face, neck and arms have reacted with a positive response to dust mite antigen patch testing.⁵⁶ The positive reactors did not all demonstrate serum IgE or skin test positivity to dust mites.⁵⁷ Patch testing patients with persistent eczema predominantly confined to the skin exposed to the pillows and bed linens, whether the patient is atopic or not, may be most rewarding. Beneficial results after creating a "mite-free" bedroom in those patients with positive reactions has been documented⁵⁸ (unpublished data, VS Beltrani).

Contact dermatitis to topical medications

A careful history of all treatments to the skin should be taken. The application of neosporin, a topical "caine," PABA, and/or hydrocortisone to a patient with a rash which fails to improve should indicate to the physician that each medication deserves patch testing as a possible cause.^{59,60}

Plant, Occupational, Cosmetic,⁶¹ Clothing,⁶² and Shoe⁶³

These allergens must be considered whenever the history reveals exposure, and the patient presents with a "branded" eczematous eruption. Poison ivy, oak, and sumac are the most familiar perpetrators of plant allergic contact dermatitis, but other plants and their products can also cause misery.⁶⁴

WHOM AND WHEN DO YOU PATCH TEST?

Patch testing is the gold standard for identification of a contact allergen

No test should be performed unless the information sought will be interpreted properly, and then utilized appropriately. After selecting patients for patch

testing, note the location of skin inflammation, identify morphologic nuances, and take appropriate histories.

Patch testing is performed in order to identify a specific trigger (antigen) causing a suspicious "contact" rash.⁶⁵ Objectively, a contact dermatitis is an eczematous eruption, rarely is it urticarial or morbilliform. The indications for patch testing are difficult to delineate. It is not recommended to use clinical appearance alone to decide whether to patch test. Once there is a suspicion for a contact dermatitis, patch testing is warranted. Still, it is unnecessary to test patients with single episodes of mild and/or limited eczema if empiric treatment is safe and effective, and there is no recurrence. More commonly, patch testing is reserved for patients with chronic, recurring, or unrelenting eczematous and/or lichenified dermatitis, because management is critically dependent upon isolation of an antigen.⁶⁶ It is crucial to realize that many patients are unaware of any relevant exposures, despite a careful history; then, patch testing can be surprisingly valuable. Done appropriately, patch tests always provide useful information whether the results are "positive" or "negative".⁶⁷

Patch testing should be deferred until the patient's dermatitis is no longer acute or severe. Testing a patient with flaring or severe dermatitis increases the risk of obtaining the false-positive reaction of "angry back" or "exited skin" syndrome⁶⁸ and may also significantly worsen the patient's dermatitis.⁶⁹ Systemic steroids in doses of 30 mg or less daily, probably do not inhibit a "significant" positive patch test.⁷⁰ The application of potent topical steroids to the test site for several days prior to testing may diminish or even obliterate positive results. Systemic antihistamines have no effect on eczematous patch test results.

Patch tests are considered the best method for differentiating allergic contact dermatitis from irritant contact dermatitis.⁷¹ Making this distinction is frequently very important in patient management and may have medicolegal ramifications.

HOW DO YOU PATCH TEST?

The paradox of patch testing lies in its deceptive simplicity. While the application of antigens for patch testing is rather simple, antigen selection and patch test interpretation can be difficult. It requires extensive knowledge and sufficient experience. The technical aspects of patch testing are well described in various textbooks on the subject and include the details for the purchase of antigens and materials for application, forms for record keeping, preparation of the patch test site, application of the antigens, the timing of patch test application and reading, and the interpretation of "positive" and "negative" tests.⁷²

Common Antigens Savvy

The bewildering number of potential culprits can easily alienate the novice. The basic battery of "standard" antigens (Table 4) is helpful in the great majority (80%) of cases. Using only a standard series may not suffice as some allergens will be missed because the standard series does not include all the allergens that can be sensitizing. Memorizing the trivial properties of individual antigens is less crucial than the knowledge that groups of antigens are related. Substances that commonly cause contact dermatitis include rubber, cosmetics, preservatives, fragrances, dyes, chemicals, topical medications, and nickel.

Rubber allergies are commonly evaluated with a battery of rubber mixes containing chemicals involved in rubber manufacturing, including the thiurams, mercaptothiobenzothiazole, the black rubber mix, the carba mix, paraphenylenediamine (PPD),⁷³ and more recently natural rubber latex itself.^{74,75} Most rubber-sensitive patients are usually positive to several of these antigens. Mild reactions to single rubber compounds, especially carba mix, should be interpreted cautiously.⁷⁶ In addition, patients with suspected rubber allergy may actually be reacting to additional rubber additives such as formaldehyde. Rubber allergy should be suspected in patients with hand (glove), foot (shoe), waistband, and

Table 4. Classes of Antigens in the Two Standard Panels

Class	Her-TRUE	mal Test
Rubber		
Mercaptobenzothiazole 1% pet.*	+	+
Thiuram mix 1% pet.	+	+
Black rubber mix	+	+
Mercapto mix 1% pet.	+	+
Medicaments		
Benzocaine 5% pet.	+	-
Caine mix	-	+
Thimerosal	-	+
Neomycin sulfate	+	+
Quinolone mix	-	+
Cosmetics		
Fragrances		
Cinnamic aldehyde 1% pet.	+	-
Balsam of Peru	+	+
Fragrance mix	-	+
Vehicles, preservatives, and additives		
Lanolin alcohol 30% pet.	+	-
Wool Alcohols	-	+
Imidazolidinyl Urea 2% aq.†	+	-
Quaternium-15	+	+
Formaldehyde 1% aq.	+	+
Ethylenediamine	+	+
Dihydrochloride 1% pet.		
Methylchlorisothiazolinone	-	+
Paraben Mix	-	+
Hair dyes		
p-Phenylenediamine (PPD)	+	+
Metals		
Nickel sulfate	+	+
Potassium dichromate	+	+
Cobalt dichloride	-	+
Resins		
Colophony	+	+
Epoxy resin	+	+
p-tert-Butylphenol	+	+
Formaldehyde Resin 1% pet.		

* pet = petrolatum.

† aq = aqueous.

chest (bra strap) rashes. Knee braces, elbow braces and other prostheses are also common culprits. Shoes present a particular challenge in these patients as virtually every commercially available shoe contains some rubber. Options include hand sewn leather moccasins, wooden clogs, or custom stitched leather shoes. Rubber glove allergy can be addressed by using one of sev-

eral rubber free products (generally vinyl or neoprene).

Sensitivity to natural rubber latex antigens is more recently appreciated as a significant cause of type I immediate hypersensitivity, especially among health care workers⁷⁷ and patients frequently exposed to rubber medical supplies.⁷⁸⁻⁸⁰ The rubber precursor molecule cis-1,4-polyisoprene is extracted from the rubber tree *Hevea brasiliensis* in association with antigenic proteins.⁸¹ Sensitized patients are at risk for acute localized reactions as well as anaphylaxis.⁸² Deaths have been reported, many occurring during surgical procedures.

Interestingly, many latex-sensitive patients have been found to have similar sensitivities to avocado, bananas, celery, chestnuts, fig, papaya, passion fruit, and peach,⁸³ although the specific cross reacting protein has yet to be defined. RAST testing and skin prick testing are available for evaluation of suspected patients.⁸⁴

Cosmetic preservatives are ubiquitous antibacterials used in the industry to prevent contamination. As a rule, products with more water (lotions) require the most preservatives, and pure ointments (petroleum jelly) can be preservative free. Formaldehyde, quaternium-15, imidazolidinyl urea, dimethyloldimethyl, hydantoin, methylchlorisothiazolinone, and parabens are the most common preservatives in use today, and all but the parabens are common sensitizers.⁸⁵ Quaternium-15, imidazolidinyl urea, and dimethyloldimethyl hydantoin are potential "formaldehyde releasers" and may therefore be positive in formaldehyde-sensitive patients. Either the preservative itself or the formaldehyde released may be responsible for the allergic dermatitis; therefore, patch tests must be interpreted as a group and not individually. To add to the confusion, each preservative can be identified by a vast number of synonyms and the clinician must be familiar with these when reading product labeling.⁸⁶

Formaldehyde is probably the most ubiquitous chemical in industry today and its avoidance is almost impossible.

Table 5. Source for Patch Testing Materials

Sources of allergens	Finn Chambers & Scanpor Tape
TRUE Test Information: Glaxo Dermatology Division of Glaxo, Inc. Five More Drive Research Triangle Park North Carolina 27709 Tel. (919)248-2100	Finn Chambers on Scanpor Product Code 1446 Hermal Pharmaceutical Laboratories, Inc. Delmar, NY 12054 Tel. 1-(800)-HERMAL-1
Allergen Patch Test Kit Hermal Pharmaceutical Laboratories, Inc. 163 Delaware Avenue Delmar, NY 12504 Tel. 1(800)-HERMAL-1 FAX (518)475-0180	
Dormer Laboratories, Inc. Chemotechnique Allergens 91 Kelfield Street (Unit #5) Rexdale, Ontario M9W5A3 Canada Tel. (416)242-6167 FAX (416)242-9487	
OmniDerm Inc. Trolab Allergens 8400 Darnley Road Montreal, Quebec Canada H4T 1M4 Tel. (514)340-1114 or 1-800-363-8805 Ext. 3038	
To Order National Specialty Services 556 Metroplex Drive Nashville, TN 37211 Tel. 1(800)878-3837	

Fortunately, even sensitive patients are rarely clinically affected with dermatitis due to low concentration, brief duration of exposure, and other variables. The relative rarity of formaldehyde dermatitis is striking when one considers its use in textiles (clothing), glues, paper (newspaper), cosmetics, disinfectants, cleaners and polishes, medications, food preservatives, rubber products, paints, and smoke. Clearly, an exhaustive review⁸⁷ of the subject is beyond the scope of the overview. It is essential to interpret mild positive reactions with caution, however, as it is frequently an irritant rather than a true allergen.

Nickel is a ubiquitous metal and a common sensitizer.⁸⁸ Nickel dermatitis⁸⁹ can be so obvious that testing is usually unnecessary (Fig 4). On the other hand, nickel exposure can be so

obscure that it may never be considered a culprit unless patch testing is performed. While the investigation of contact to metallic objects may be straightforward, the role of ingested dietary metals (especially nickel) in various eczemas (dyshidrosis) is far more challenging to determine.⁹⁰

While common, plant dermatitis is not evaluated with the standard patch testing, as the pertinent antigens are not included. The most common plant dermatitis is caused by poison ivy and/or poison oak. Their allergenicity is due to the antigen urushiol.⁹¹ It must be emphasized that the serum exuding from the blisters of any contact dermatitis is NOT allergenic, ie, one does not spread or get poison ivy by touching the rash! Linear streaks and plaques of papulovesicles are pathognomonic for this eruption, and the diagnosis is

rarely a problem. More important is the cross reactivity to other related plants such as cashew, mango skin, and ginko (tree leaves). Patients with acute perioral dermatitis due to these foods are usually unaware of the cross-relationship.

Sesquiterpene lactones are chemicals found in plants of the Compositae family, the significance of which is related to the vast number of related compounds and the intricate puzzle of potential cross reactivity.⁹² Sesquiterpene lactones are found not only in members of the Compositae family (chrysanthemum, ragweed, artichoke, chamomile, daisy, dandelion, etc) but also in unrelated plants. In addition, balsam of Peru and turpentine contain similar terpenes and they themselves cross react with countless other antigens. A "positive" reaction to balsam of Peru on routine patch testing may lead rather circuitously to a Compositae contactant.

Other antigens included in standard series are more limited in scope, but the clinician should be familiar with them due to the frequency of related contact allergy. Additionally, hundreds of antigens are available (Tables 5 and 6) for more specific testing and some familiarity with these will allow more selection when appropriate. Obviously negative patch testing does not necessarily rule out contact allergy and the experienced clinician should be able to choose the pertinent antigens for further testing.

INTERPRETING PATCH TESTS⁹³

Correct interpretation of patch tests is as crucial as correct antigen selection and requires experience and skill.⁹⁴ The American Contact Dermatitis Society has created a standard grading system (Table 7) to describe reactions. It defines reactions from absence of any physical findings through vesicles and bullae spreading beyond the patch site. A 1+ is used for uniform palpable erythema (Fig 5) and a 2+ is appropriate for infiltrated erythema with papules and early vesicles (Fig 6). A 3+ implies an intense vesicobullous

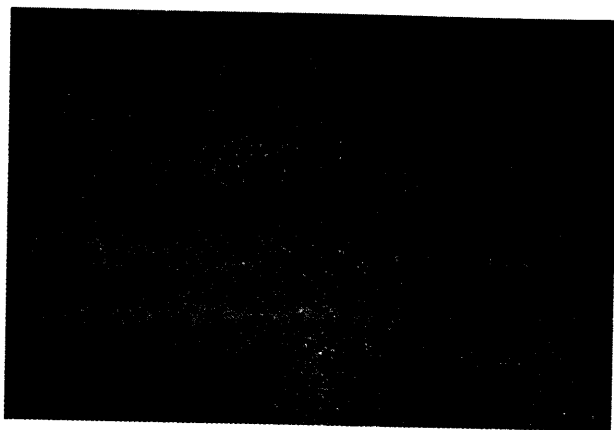


Figure 5. 1+ positive patch test.

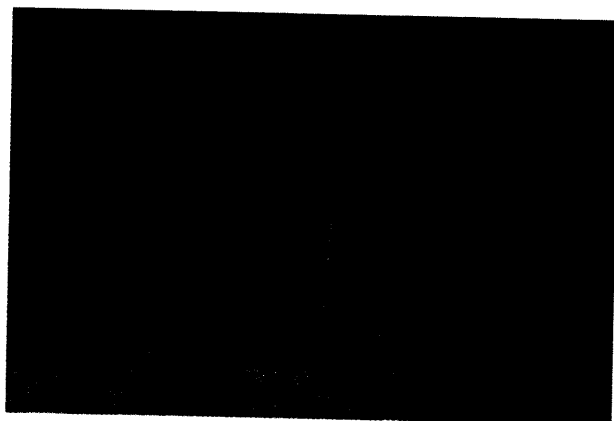


Figure 6. 3+ positive patch test.

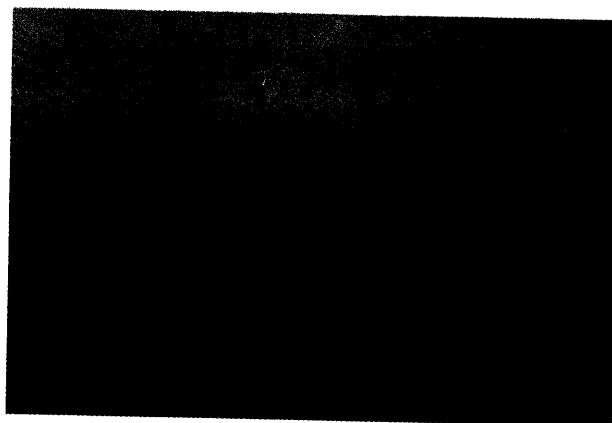


Figure 7. Irritant response to applied patch.

mg/kg/d, given as a single AM dose) and duration of therapy (generally 14 to 21 days, without the "daily" taper of the commercial Dospak, but by a 50% abrupt reduction in five to seven days, to zero, five to seven days later!)

should be prescribed for each patient. Obviously, careful patient selection is mandatory before placing any patient on oral steroids.

Antihistamines are of little to no value in the management of any de-

layed hypersensitivity reaction (contact dermatitis).

PUVA photochemotherapy is a rather complicated, but generally effective treatment for eczematous dermatitis¹⁰⁰ that should be considered only by physicians trained in its use. It is attractive in that patients improve without incurring the systemic toxicities of oral steroids or other immunosuppressants. Unfortunately, office-based treatments two to three times per week can be cumbersome and many patients find it difficult to comply. Side effects are basically UVA induced and include acute phototoxicity (sunburn and suntan), and when used for a long-term (months to years) chronic photodamage (wrinkles, changes in skin texture, freckling, dyspigmentation), skin cancer (usually keratoacanthomas and squamous cell carcinomas), and cataracts. In addition, some patients experience significant nausea from the ingestion of the photosensitizing psoralen.

CONCLUSIONS

Contact dermatitis is common. The greater the level of suspicion, the more frequently the diagnosis will be made. The greatest abuse of patch testing is in its lack of utilization. It is important to remember an axiom of the patch test pioneer Dr. Albert Kligman. "Anyone can do a patch test. Few do it well. Fewer still can properly interpret patch tests!"

In this review we have set down guidelines and emphasized some pitfalls. The need for hands-on experience cannot be overly stressed. Attendance at workshops will provide the basic science, but attending a "patch test" facility supervised by experts and their technicians is essential to gain the confidence and expertise required for the proper care of patients with contact dermatitis.

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