Derm

CONTACT DERMATITIS

PAUL R. BERGSTRESSER, M.D.

Medical Grand Rounds
Parkland Memorial Hospital
November 11, 1982

I. INTRODUCTION

Two critical factors in the diagnosis of cutaneous diseases are regional distribution and individual lesion morphology. No cutaneous pathologic process exemplifies this assertion better than the collection of disorders we carry under the generic title of contact dermatitis. As the name implies, contact dermatitis requires the physical placement of an injurious substance on the skin surface - followed by a cutaneous inflammatory response. This review concerns itself with several issues: a. The capacity of contact dermatitis to produce disability in industrialized societies, b. distinctions among types of contact dermatitis, c. contributions of contact dermatitis to other cutaneous disorders, d. diagnostic techniques, e. therapeutic strategies, and f. rules concerning when to refer a patient.

I have chosen contact dermatitis as my subject today, not only because it is a subject of particular interest to me, but because recent work in laboratory studies has provided great insight into its underlying mechanisms. I shall divide my remark into several sections. First, in order to emphasize the clinical dimension I shall review the approach to patients with dermatitis. This will lead to the differential diagnosis and definition of respective clinical terms. No discussion would be complete without reviewing the underlying immunological principles involved in this area and finally, I will present to you how I manage such patients, keeping in mind that whether it is simple or difficult, spending time with such patients will provide them enormous benefit. Several resources are recommended.

CONTACT DERMATITIS RESOURCES

Adams, RM: Occupational Contact Dermatitis. J.B. Lippincott Co., Philadelphia, 1969.

Cronin E: Contact Dermatitis. Churchill Livingstone, Edinburgh, 1980.

Fisher AA: Contact Dermatitis, 2nd Edition. Lea and Febiger, Philadelphia, 1975.

Foussereau J, Benezra C, Maibach HI: Occupational Contact Dermatitis: Clinical and Chemical Aspects. W.B. Saunders Co., Philadelphia, 1982.

Fregert S: Manual of Contact Dermatitis. Munksgaard, Copenhagen, 1974.

Skin may be visualized as an interface between man and his environment. This cutaneous interface may be disrupted by a variety of insults which occur with regularity, including microbiologic, physical, ultraviolet and chemical assault. Contact dermatitis may be modeled as one type of chemical assault, a type which accounts for considerable morbidity and as a subject, is important enough for both monographs and a journal to be devoted to it exclusively. Occupational contact dermatitis constitutes the largest source of time loss disability in industry, and sixty-five percent of occupationally related diseases

are of the skin. Most occupational skin diseases result from contact with chemical substances, more than 6,000 of which are in current use in industries throughout the United States. More than 800,000 cases of skin diseases are reported to workman's compensation insurance companies yearly (Adams, 1969).

The University of Southern California's Division of Research in Medical Education undertook in the late 1970's, a sample survey of practicing physicians in more than 20 different medical and surgical specialties (Mendenhall, Girard, and Abrahamson, 1978) and as part of that effort, evaluated practice activities of dermatologists in the United States (Mendenhall, Ramsay, Girard et al., 1978). Pertinent to this discussion was their finding that contact dermatitis accounted for nearly 5% of office visits to dermatologists, representing 4,000 visits daily, in the United States. Furthermore, within the eczema group one would find additional patients with contact dermatitis, increasing that category to third highest among diseases frequently encountered by dermatologists in outpatient practice.

DISEASE	PERCENT OF OFFICE VISITS
Acne	27.4%
Warts	6.7
Eczema	4.8
Psoriasis	4.8
Actinic Keratosis	4.6
Basal cell carcinoma	4.5
Contact Dermatitis	4.3
Fungal infection	3.5

II. CUTANEOUS STRUCTURE AND FUNCTION

Cutaneous anatomical structures are relatively constant on all body surfaces although in certain areas they are highly modified to reflect the specialized functions of those areas. A cellular matrix containing three cell types constitutes the epidermis or outermost cutaneous region: kerantinocytes, melanocytes and Langerhans cells.

ANATOMIC CHARACTERISTICS OF HUMAN EPIDERMIS

1) Cellular Matrix
2) Cell Populations
   - Keratinocytes 96%
   - Melanocytes 2%
   - Langerhans cells 1-2%
   - Mononuclear Cells
3) Dimensions
   - 50 μ by 2 m^2 (100 cm^3)
   - 50,000 cells/mm^2 (1.0×10^{11} cells)

Relative populations and structural dimensions are listed in the table. The third cell type, Langerhans cell, is the least understood of cells which occur in the epidermis. By light microscopy it is not perceptible and with certain special techniques it has appeared to be similar to melanocytes. Until only

recently it was also felt to have the same origin and function. As will be seen, Langerhans cells are now postulated critical antigen processing cells for the acquisition and perhaps even the expression of delayed contact hypersensitivity.

Beneath the epidermis, a vascularized dermis provides structural and nutritive support. It is composed of a collagen and elastic tissue network through which blood vessels, lymphatics and nerves course. The bulk of this tissue consists of a mucopolysaccharide gel. In normal skin resident cellular elements include fibroblasts and mast cells. In pathologic conditions alterations in these cells and the identity of new cellular infiltrates may reflect disease processes. For this reason, skin biopsies are frequently obtained by dermatologists to assist in diagnosing skin pathology.

The primary function of skin is to form a protective interface between man and his environment. These interface functions include the regulation of heat exchange, protection from ultraviolet radiation and inhibition of molecular exchange with the environment. Heat exchange is mediated by a complex network of capillaries and by individual sweat glands. Superficial capillaries dilate and constrict in response to thermal stimuli, while sweat glands are capable of producing large quantities of sweat for evaporative cooling. The attenuation of ultraviolet light is mediated by melanin, a dark pigment which is deposited in epidermal keratinocytes by dendritic melanocytes. Of most importance for this review, is the capacity of skin to inhibit the exchange of small molecules with the environment, a function which occurs in the epidermis at the level of stratum corneum. This structure is a continuously exfoliating barrier which is replenished by maturing keratinocytes which arise from beneath. The stratum corneum has barrier properties which are similar to "Milar" plastic film and through it all chemicals, both sensitizing and irritating must pass. Consequently, barrier function is of paramount importance to a discussion of contact dermatitis.

III. CLINICAL PERSPECTIVES

The issue of contact dermatitis can only be approached with a sense of humor. First, any medical disorder which occurs largely in sites of application will on occasion lead to broad smiles as we recognize the entent to which our chemical environment assaults us and secondly, dealing with the intolerability of chronic, undiagnosable contact dermatitis as experienced by some patients, needs the relief of laughter to diminish the pain.

Dermatitis may be defined as inflammation at the skin surface. Irritant dermatitis is caused by substances which when placed on the skin surface produce inflammation by direct chemical assault. Allergic dermatitis is mediated by delayed, cell-mediated allergy. Both disorders, contact allergic and contact irritant dermtitis must be considered together because of their close clinical similarities and because of the frequent coexistence in the same patient. They also must be differentiated from other causes of dermatitis.

Clinical: The hallmark clinical symptom from the acute inflammatory response which accompanies contact dermatitis is pruritus. Although pathophysiologic mechanisms which are responsible for this sensation, more commonly know as itching, are not known, pruritus has been modeled by some investigators as subthreshold pain. One can be certain that if a patient's condition does not itch, it is not contact dermatitis. Unfortunately, the

complementary corollary is not true. Acute inflammation of the skin is not different from inflammation in other organs, therefore satisfying five cardinal signs of inflammation: Heat, Swelling, Redness, Pain, and Loss of Function. Areas of acute contact dermatitis are elevated into papules and plaques, they are red, warm, and they itch. Finally, percutaneous penetration studies demonstrate decreased barrier function in dermatitic skin, satisfying our final requirement. There is more, however, since the movement of fluid into the dermis, and more importantly the epidermis, may become so excessive that portions of the epidermis become separated into fluid-filled, small and large blisters, termed vesicles and bullae. Therefore, the clinical features of acute contact dermatitis are: itching, red color, swelling, blisters, and a distribution which is consonant with the areas of contact. In chronic contact dermatitis a different picture emerges; the skin is thickened, lichenified, crusted, and sometimes fissured. It may have increased and/or decreased pigmentation.

Histopathology: The primary inflammatory event in contact dermatitis occurs in the epidermis. This conclusion is based on the observation of cell death (necrosis) with microscopic and visible blisters (spongiosis and vesicle formation). In the dermis, one observes vasodilitation, edema, and an infiltrate of acute inflammatory cells. Lysis of necrotic cells in the epidermis may cause a loss of the entire epidermal barrier, and escaping serious fluid produces a superficial crust. In areas of less intense reactions, one observes alterations in the morphology of epidermal cells. It has been assumed that the target cell in this attack is the keratinocyte, since it is the predominant cell of the epidermis. Although this may not be correct, it is clear that in intense reactions all cells of the epidermis show alterations, but in less intense reactions it may be limited to subsets of cells.

Contact Allergic Dermatitis: Briefly, this sort of dermatitis is delayed (cell mediated) immune response to an externally applied allergen. After reaching the skin the allergen penetrates the stratum corneum barrier where processing by the immune system begins. Between five and twenty-one days after this first or primary exposure, cells of the immune system develop a permanent memory for that allergen. When it is subsequently reapplied to the skin, acute dermatitis develops. A limited number of chemical are of importance in clinical contact allergic dermatitis, and then may be divided into five broad categories.

Allergic Contact Dermatitis: Poison ivy dermatitis, the prototype: Rhus radicans, or poison ivy, and its family members, Rhus diversiloba (oakleaf poison ivy) and Rhus toxicodendrom (Western poison oak) constitute the prototype for delayed contact hypersensitivity in man. As early as 1939 Shelmire studied sufficient numbers of patients with a critical eye to report three observations:

1) The dermatitis producing oleoresin was either extractable,
2) Previous contact was necessary for the development of sensitization,
3) Attempts to demonstrate antibodies in blood serums of sensitive persons by the Prausnitz-Kustner method of passive transfer failed.

Poison ivy is a good prototype since the majority of individuals exposed become sensitized. Obviously, most adults have either observed or experienced this disorder. Secondly, both seasonal availability and sporatic exposure mean that sensitized individuals experience infrequent but clearly defined episodes.

Finally, elicitation usually occurs through normal skin so that the complicating factor of altered barrier function which occurs so often during industrial exposure is not a factor.

Photoallergic contact dermatitis is a special category of contact dermatitis in which ultraviolet radiation is necessary to create the complete antigen. A material which is otherwise not immunogenic becomes so after exposure to light this means that the disorder can be initiated or expressed only in sites of light exposure. Recently an animal model for this sensitivity has been developed. Most common among photosensitizers are phenothiazines, salicylanilides used in soaps and detergents, and para-aminobenzoates.

Contact Irritant Dermatitis: The first major distinction in contact dermatitis is between irritant and allergic. Conceptually, the two are quite distinct although in some patients both may occur simultaneously, each aggrevating the other. Many substance will damage the skin when applied in high enough concentration and for sufficient time. "For sufficient time" may also mean "often enough". Obvious examples would include sulfuric acid, sodium hydroxide, and gasoline. Examples which are not so obvious would include sodium lauryl sulfate, a common emulsifier which is the major ingredient in laundry detergent or sodium hypochlorite, the active ingredient in laundry bleach. All people are susceptible to irritant dermatitis although there is wide variability in the degree of this susceptibility. It is possible to enhance reactivity by putting chemicals under an occlusive device such as a wedding ring, a rubber glove, or a piece of plastic film.

Although the major portion of scientific attention has been directed toward allergic dermatitis, contact irritant dermatitis contributes more significantly to occupational disability, particularly in industrial trades. Pathogenesis is relatively straightforward, being derived from an interruption of the major cutaneous function, barrier formation. Primary irritants may be divided according to their known actions.

PRIMARY IRRITANT DERMATITIS

1. Acids: HCl, H_2SO_4, HNO_5, Salicylic
2. Bases: NaOH, NH_4OH
3. Organic Solvents: Gasoline, Benzene, Carbon Tetrachloride
4. Detergents: Sodium Dodecyl Sulfate
5. Desiccants: CaO_2
6. Oxidizers: Bleaches, Chlorine

The six categories and items within each are not inclusive, but they save to illustrate the great variety of materials which may produce irritant dermatitis. With the exception of organic solvents they demonstrate the great dependence on concentration. In fact, sodium dodecyl sulfate and salicylic acid are used commercially in preparations which are intended for topical use:

Case: A 68 year old woman was admitted to Jackson Memorial Hospital in Miami July, 1972 for a generalized contact dermatitis covering approximately 50% of her body surface area. After admission she was treated with a regimen which included bed rest, systemic antipruritic agents, periodic wet compresses and topical applications of a steroid cream. In the course of her hospitalization she was entered, with informed consent, into a new drug protocol in which a steroid cream was applied four times daily to the moderately involved areas on

her neck and face. Four days later it was noted that while her generalized dermatitis had responded favorably to standard therapy, her face and neck had become tender and red and felt indurated to the touch as her skin surface had developed a leathery texture. The new formulation was discontinued and her face improved rapidly.

Investigation: Because of the low frequency of sensitization to active ingredients in steroid preparations, attention was paid first to the emulsifier (detergent) sodium dodecyl sulfate, which had been included in a 1% concentration. Emulsifiers are required in topical preparations to stablize the mixing of lipid and aqueous phases. Sodium docecyl sulfate is unique in several respects. First its detergent capacity makes it a favorite of the laundry industry. Secondly, it has a recognized capacity to disrupt the cutaneous barrier and enhance the penetration of simultaneously applied drugs. It may produce dermatitis, a feature obviously associated with its capacity to alter barrier function. And finally, it is occasionally a sensitizer for contact hypersensitivity. The pharmaceutical corporation had included sodium dodecyl sulface at a 1% concentration for the two-fold purpose of serving as an emulsifier and damaging the cutaneous barrier to drive in more steroid. To determine whether 1% was to high, a similar non-steroid compound was applied under occlusion on 8 trial subjects. All developed a similar primary irritant dermatitis within 5 days. When an alternative emulsifier, Brij, was tested in the same way, no dermatitis developed. The topical steroid preparation was withdrawn from testing.

This patient's facial dermatitis is instructive in several ways:

1. Irritant Dermatitis is highly concentration dependent. Materials which at low concentration may be beneficial or at least harmless produce disease when applied at higher concentrations, too frequently, or under occlusion.
2. There is considerable variation among individuals and among body regions in the susceptability to irritant dermatitis.
3. All primary irritants will affect all individuals if applied properly (improperly).

Irritant Dermatitis requires penetration of the skin barrier by relatively large amounts of the material, and several factors have been shown to be important in enhancing the rate of penetration of chemical substances into skin (Scheuplein and Blank, 1971). Data in the table was derived for drugs thought to be beneficial for man but the same factors apply to detrimental compounds. The similarities and distinctions between these two types of dermatitis are listed in two tables.

FACTORS WHICH INFLUENCE PERCUTANEOUS ABSORPTION

1. Humidity
2. Temperature
3. Vehicle
4. Dermal Circulation
5. Stratum Corneum Thickness
6. Anatomic Location
7. Disease Status

DISTINCTIONS BETWEEN CONTACT IRRITANT AND CONTACT ALLERGIC DERMATITIS

	IRRITANT	ALLERGIC
Affected Individuals:	All	Only those sensitized (0-99%)
Onset:	First Exposure	Requires prior sensitization
Chemical Concentration:	High	Low
Prototype:	Sodium dodecyl sulfate (detergent)	Rhus (poison ivy)

SIMILARITIES OF CONTACT IRRITANT
AND CONTACT ALLERGIC DERMATITIS

Extent of Disease: Limited to areas of contact
Clinical Features: Pruritis, Erythema, Induration, Blisters, Heat

IV. DIAGNOSTIC TECHNIQUES

Diagnosis of contact dermatitis requires a new set of skills, although the most important requirements are a complete history and cutaneous examination. The critical role of the history cannot be overemphasized, particularly in the day of Space Age Medicine when laboratory tests occupy so much of a physicians time. It is not uncommon for the history to require as much as 30-45 minutes.

HISTORY

Critical items in the history include:

Date of Onset: Often a new dermatitis will reflect events which may be accurately dated: a. new job duties, b. a new baby, c. new automobiles, shoes, or clothes, and d. Spring cleaning or Gardening.

Patient description of onset: Patients frequently do not understand the requirement for previous exposure to lead to sensitization, but if given time to describe the sequence of events, the identification of the source may become apparent.

Location of eruption at onset: Dermatitis will frequently begin at the site most frequently exposed but later generalizes to infrequently exposed areas, eventually blurring the relationship between exposure and dermatitis.

Effects of weekends and vacations: This is very useful in separating occupational from other categories of contact dermatitis.

Hobbies: Plastics, Glues, Rubber, Gardening.

What previous treatment has been attempted: The majority of patients will state first that none has been employed. It can safely be assumed that every patient with dermatitis has treated it despite all protests. It is frequently observed that the primary dermatologic problem has resolved and that the patient has been left with allergic contact dermatitis to an applied medication. The question "What home remedies or over the counter preparations have you applied to your skin condition?" must be asked at least three times during the course of the interview no matter what the response. Most patients try more than one

preparation and it is only after several inquires that they remember the relevant one.

Are other individuals involved as well?: Irritant dermatitis affects a majority of individuals with equivalent exposure, whereas contact hypersensitivity affects a minority.

Has there been similar dermatitis in the same site or elsewhere?: Similar eruption under jewelry, shoes or with other jobs may pinpoint the current sensitizer.

Obviously there is much more to ask, but in terms of the approach from the internist's point of view the following series are of great importance.

Questions:

1. Where did it begin?
2. When did it begin?
3. Are there new occupational or employer duties?
4. What is the effect of weekends or vacations?
5. What have you put on it already? (Ask three times)
6. Ask about hobbies, gardening and the second job.

PHYSICAL EXAMINATION

Physical examination of the skin is important to identify the extent of disease, remembering that patients with severe dermatitis will ignore moderately involved regions which may be of diagnostic importance. Furthermore, a complete examination may uncover a second cutaneous disorder which the patient is attempting to treat with a sensitizing material. Certain rules have proven to be helpful:

1. Although the hallmark of contact dermatitis is asymmetry, symmetrical dermatitis may reflect clothing dermatitis (fabric, shoes, gloves).
2. Eyelid dermatitis usually reflects materials which hands have contacted.
3. Plant dermatitis is usually linear
4. Frequently the conformation of a dermatitic area will illustrate the shape of an appliance.

PATCH TESTING

Just as scratch tests are employed for diagnostic purposes by allergists to identify IgE-mediated hypersensitivity, dermatologists who work with patients with contact allergic and contact irritant dermatitis employ epicutaneously applied patch tests to determine whether their patient has acquired delayed type hypersensitivity to a specific reactive hapten. Patch testing has a venerable history, dating to the report by Jadassohn that iodoform applied to normal skin of five previously sensitized subjects reproduced their dermatitis. (Jadassohn, 1896). Today, collections of purified antigens may be obtained commercially from a variety of sources for application to skin surfaces. In theory, a patient with suspected contact dermatitis is examined and interviewed until a list of possible sensitizers is developed. These are then placed in pure form, in appropriate vehicles, on the normal back skin under plastic occlusion. Approximately 48 hours later the patches are removed and the back inspected for

dermatitis. Patients are then examined a second time between 24 and 72 hours later. Those antigens to which a patient is sensitive will be determined. The physician then reviews the history and physical examination to determine which substances may account for the patient's dermatitis. This is particularly important for patients with obvious contact irritant dermatitis in whom an unsuspected allergic dermatitis may be a complicating factor. The patient is then instructed how to avoid such materials and he lives happily ever after.

Patch tests are simple to perform and difficult to interpret. Materials are dissolved or suspended in pure form at an appropriate concentrations in a suitable vehicle, most often petrolatum. A small amount is placed on an occlusive patch which in time is applied to a non-dermatitic normal skin site, usually the back. Available now from commercial sources are strips of patches to which a series of haptens may be applied. At the time of reading the area under the patch is inspected for acute dermatitis and graded accordingly.

Several issues are considered in the interpretation of patch tests. Both false positive and false negative results may occur.

Irritant reactions: Many sensitizers become irritants at higher concentrations and the boundary between concentrations adequate to penetrate normal skin and concentrations which produces dermatitis in a particular patient may become blurred or even overlap.

Angry back syndrome: Well recognized is a generalized cutaneous irritability state which occurs in patients with dermatitis or in patients with strong patch test reactions. Other patch tests which otherwise would be negative become positive.

False negative reactions: Patch test materials may decompose or precipitate. Furthermore, cutaneous barrier function differs among individuals, preventing appropriate penetration of the material. This rather common problem has resulted in several unsatisfactory solutions. Kligman has advocated the maximization test in which the test site is first treated with sodium dodecyl sulfate to damage the cutaneous barrier. Others have advocated the use of tests in which the material is applied repeatedly.

Excessively low concentrations of sensitizers: This is a reflection of biologic variability. Inappropriately applied patch: failure to secure the patch for complete occulsion may result in less penetration. Material is a photosensitizer: Photopatch testing is not substantially different from regular patch testing except that all patches are applied in duplicate with one series protected from ultraviolet radiation and the other exposed after 24 hours to a high intensity UVA source. Skin reactions are then read 24 or 48 hours later. Interpretation of results are similar to that for regular patch tests.

Interpretation of results: Having obtained a correctly positive or negative patch test reaction to a material, what does it mean. It means simply that the individual has or has not become sensitized to that material. It becomes the responsibility of the physician to determine whether that result relevant. Patients may have sensitivities which do not relate to the present illness. The material in question may be the true offender in the presence of a negative patch test.

V. DIFFERENTIAL DIAGNOSIS

In dealing with a patient whose differential includes contact dermatitis it is important to recognize that patients frequently have more than one disorder.

In fact, contact dermatitis to applied medicaments and vehicles will by definition require two disorders. This means that when one diagnosis is confirmed, the physician should not discontinue his search. In tabular form the differential diagnosis of contact dermatitis includes the following:

DIFFERENTIAL DIAGNOSIS OF CONTACT DERMATITIS

1. Allergic contact dermatitis
2. Irritant contact dermatitis
3. Dyshidrosis
4. Dyshidrotic "id" reaction (dermatophytosis)
5. Nummular eczema
6. Dermatophytosis
7. Atopic dermatitis
8. Psoriasis
9. Pustular eruption of hands and feet

The sequence of these nine diagnoses is specific, as it evolves gradually from an acute vesicular dermatitis which resembles acute contact dermatitis to chronic scaling dermatitis which resembles chronic contact dermatitis. Unfortunately, it is frequently quite difficult to distinguish many of these, probably because they do occur simultaneously.

Dyshidrosis or pompholyx are names applied to the pruritic condition in which recurrent vesiculation occurs on hands and feet (Cage et al., 1979). Frequently hyperhidrosis (excessive sweating) accompanies this disorder giving rise to the unsubstantiated notion that sweat duct blockage accounts for the blisters. There may also be an association between stress and exacerbation. Distinguishing features between this dyshidrosis and contact dermatitis are: a. the failure to observe association with applied materials; b. frequent simuntaneous eruption on hands and feet; c. involvement of the lateral aspects of fingers; and, d. negative patch tests. Obviously, the frequent use of topical medication may contribute to secondary sensitization, and both contact dermatitis and dyshidrosis may occur in the same patient.

Nummular eczema is defined by the clinical presentation of coin-shaped areas of acute and subacute dermatitis (Hellgren and Mobacken, 1969). Early primary lesions consist of minute vesicles and papules which coalesce and expand to form discrete, red, scaling, coin-shaped patches. Scaling and lichenification characterize late lesions and individual lesions tend to involve in a peripheral direction. No cutaneous disorder is less understood than nummular eczema although numerous factors may be associated with acute exacerbations including xerosis, irritant dermatitis, and bacterial infection. The distribution of this disorder does not resemble that of any percutaneously applied materials, helping to distinguish it from contact dermatitis. Care should be taken to identify secondary sensitization to treatment compounds.

Dermatophytosis: Superficial fungal infections are common. In adults they occur most often on hands and feet. Proper diagnostic techniques with microscopic exam and culture, occasionally repeatedly will identify these.

"ID" or "Trichophytid" reactions occur in patients with moderate to severe dermatophyte (superficial fungus) infections, primarily of the feet. Although theories abound as to etiology, it is not at all clear how fungal infections translate into acute vescicular eczematous eruptions. All patients with

symmetrical acute dermatitis which occurs in more than a limited site should be examined for dermatophytosis. It is believed, however, that the underlying dermatophyte infection must be symptomatic, so that occult dermatophyte infection need not be considered.

Atopic dermatitis is a chronic cutaneous disorder which resembles contact dermatitis in many ways. Frequently associated are personal or family histories of allergic rhinitis, asthma, or hay fever. The availability of many theories illustrate that its pathogenesis is not known, most attractive is the possibility that those individuals with atopic dermatitis have intrinsically altered reactivity which predisposes them toward cutaneous inflammation. Most useful among the factors which distinguish atopic dermatitis from contact dermatitis is the early age of onset for the former and the usual distribution. However, both contact allergic and contact irritant dermatitis do occur in patients with atopic dermatitis.

It is of interest that contact hypersensitivity may be more difficult to induce in patients with atopic dermatitis, a fact consistent with the notion that such patients have an intrinsic alteration in reactivity. By contrast, the frequency of positive patch tests in such patients is higher than that in normal control subjects. This apparent inconsistency is rationalized by the hypothesis that such patients experience greater frequencies of exposure. This means that patients with atopic dermatitis frequently have contact dermatitis and should be evaluated accordingly.

Primary lesions in psoriasis are red papules with or without covering scale or, an occasion, pustules. In most circumstances, it is difficult to confuse the established thickened and hyperkeratotic lesion of psoriasis with contact dermatitis. In one circumstance, however, this becomes quite difficult, that is in limited palmar-planter psoriasis and in the closely, related disorder pustular eruption of hands and feet. In both conditions, large areas of the palms and/or soles become dermatitic, but with careful examination, the primary lesions are pustules rather than vesicles. All that remains is to be certain that the patient does not have infected contact dermatitis. In this latter case, the pustules should contain bacteria.

Contact urticaria resembles contact dermatitis in that contact is required but the response is an immediate hypersensitivity response, presumably due to IgE mediated mast cell activation. Clinically one observes urticaria rather than dermatitis. For the patient it is easy to link the application of the material with the cutaneous reactivity since there is a relatively short delay in time. Contact urticaria has been reported to cinnamic aldehyde (Mathias, Chappler and Maibach, 1980).

Skin biopsy: Techniques used in the differential diagnosed cutaneous eruptions would not be complete without a skin biopsy.

VI. CLINICAL CASES

Cases will be presented to illustrate concepts of contact dermatitis, common contact sensitizers, the wide variety of sources for certain sensitizers, the wide variety of sensitizers in specific formulations.

COMMON CONTACT SENSITIZERS

Certain materials have been observed to be frequent sensitizers, that is, to be responsible for the dermatitis which leads to a physicians consultation. These are collected in the table into five major sources: metal, rubber,

topical preparations, plants, and plastic. Within each source category there are several major primary compounds.

COMMON CONTACT SENSITIZERS BY SOURCES

METAL:	Nickel, Chromium, Cobalt, Mercury
RUBBER:	Mercaptobenzothiazole, Thiuram sulfides Para-phenylenediamine
TOPICAL PREPARATIONS:	Antihistamines-Benadryl Anesthetics - Benzocaine, Procaine Lanolin Antibiotics - Neomycin, Thimerosal, Benzoyl peroxide Preservatives - Ethylene diamine, Parabens, EDTA
PLANT:	Rhus - Poison ivy, Poison oak, Ragweed
PLASTIC:	Formaldehyde resins, Epoxy resins and hardeners

COMMON SENSITIZERS

Nickel	Para-phenylenediamine
Chromium	Ethylenediamine
Neomycin	Parabens
Benzocaine	Formaldehyde
Benadryl	Colophony (rosin)
Mercaptobenzothiazole	Epoxy resins
Thiuram sulfides	Naphthyls

Unfortunately, it is not that simple because many compounds may be found in a variety of disparate materials. The cases of tetramethylthiuram and formalin are instructive.

TETRAMETHYLTHIURAM SOURCES
(Adams, 1969)

Adhesives (neoprene)	Preservatives
Crepe soles (neoprene)	Putty
Disinfectant (seeds)	Repellents (rat)
Fungicides	Rocket fuel
Insecticides	Rubber (acceleration)
Lubricating oils	Soaps and Shampoo
Paints (neoprene)	

FORMALIN SOURCES
(Adams, 1969)

Antiseptics	Inks
Adhesive	Match tips
Clothing	Mouthwash
Cosmetics	Paint
Disinfectants	Plastics
Fingerpaint	Rubber cements

Mycolog cream is an excellent example of a compound with multiple sensitizers.

MYCOLOG INGREDIENTS

CREAM	OINTMENT
Triamcinolone acetonide	Triamcinolone acetonide
Neomycin sulfate	Neomycin sulfate
Nystatin	Nystatin
Gramicidin	Gramicidin

Furthermore, it demonstrates the relative lack of sensitizers in ointments compared with creams.

MYCOLOG BASE

CREAM		OINTMENT
Polysorbate 60	Propylene glycol	Polyethylene
Alcohol	Ethylenediamine	Mineral oil
Aluminum hydroxide gel	Petrolatum	
	Cetearyl alcohol	
Titanium dioxide	Ceteareth-20	
Glyceryl monostearate	Methylparaben	
Polyethylene glycol monostearate	Propylparaben	
	Sorbitol solution	
Simethicone	Sorbic Acid	

Generalized cutaneous eruptions may follow the systemic administration of compounds to which an individual is contact sensitive. The most obvious has been to ethylenediamine which is used as a preservative in topical preparations and which is included in aminophylline suppositories (Petrozzi and Shore, 1976). The patient reported by Petrozzi and Shore had a history of contact sensitivity to Mycolog cream prior to the administration of aminophylline. Subsequent to his exfoliative dermatitis it was observed that his contact sensitivity was specific for ethylenediamine among the ingredients in Mycolog.

Penneys et al. (1976) reported an epidemic of dermatitis in a hemodialysis unit traced to thiman compounds within the dialysis equipment. Eight of 21

patients within the local dialysis facilities had sensitivity to thiuram compounds.

Contact dermatitis has been reported to occur to nitroglycerin ointment (Hendricks and Dec, 1979). Although this may not be new to some cardiologits and it should not be surpising in view of its molecular structure. The manner in which Hendricks and Dec evaluated their patients reflects the care which must be exercised before one can state conclusively that a particular molecule within a compound is solely responsible for the resulting hypersensitivity response. Their two male patients, ages 57 and 71, had severe coronary artery disease which was not amenable to bypass surgery. Each had been treated previously with pentaerythritol tetranitrate orally and with sublingual nitroglycerin, with incomplete success. Consequently, treatment was initiated with topical nitroglycerine ointment under occlusion in an attempt to obtain more uniform drug release. After several days each patient developed an acute, pruritic, erythematous, vesicular eruption which occurred only at sites of nitroglycerin application. Both were then patch tested with the following materials: two different commercial 2% nitroglycerin ointments, crushed nitroglycerine tablets in water or petrolatum, beta-lactose, lanolin, and petrolatum, plus several combinations of each. All patch tests which included nitroglycerine were positive whereas all which did not include it were negative. They concluded thereby that nitroglycerine was the offending agent. In view of the high frequency of topical nitroglycerin hypersensitivity among industrial workers (Laws, 1898; Brester, 1949) we can speculate that oral administration of nitroglycerin prior to topical application tends to induce unresponsiveness in most patients.

Topical Medicaments are Common Sensitizers: The list of topically applied pharmaceutical agents which may be responsible for contact hypersensitivity, agents which you as a physician will prescribe, was demonstrated slow evolution over time. This evolution reflects: a. Decreased utilization as sensitivities are experience, b. Changing preferences in topical treatment and c. The availability of new drugs. Early frequent offenders, penicillin, sulfonamides, and mercurials, have now been replaced by more modern drugs, neomycin, benzocaine, and ethylenediamine (Fisher, 1982). The best epidemiologic assessment of the frequency of sensitization was made by Prystowsky, Allen, Smith et al (1979). Their study is unique in that they surveyed 1,158 paid adult volunteers from a "normal" population rather than the self-selected group which presents to physicians for care. Their data concerning nickel exposure is most interesting. 5.8% of subjects were patch test positive (reactive) to nickel, a rather high frequency, suggesting that most patients make their own diagnosis and do not consult a physician. Of greater interest was the effect of stratification by previous exposure or positive reaction.

PATCH TEST REACTIVITY TO NICKEL CORRELATES WITH PREVIOUS EXPOSURE
(Prystowsky et al., 1979)

	POSITIVE EXPOSURE		NEGATIVE EXPOSURE		
EXPOSURE	NUMBER	PERCENT REACTIVE	NUMBER	PERCENT REACTIVE	RELATIVE RISK
Pierced ears					
Men	38	7.9%	422	0.2%	33.
Women	470	12.0%	228	2.6%	4.6
Jewelry "rash"					
Men	59	3.4%	401	0.5%	6.8
Women	175	22.0%	523	4.6%	4.8
Earlobe "rash"					
Men	16	13.0%	444	0.5%	29.
Women	134	30.0%	564	4.1%	7.3

They selected three indicators of possible nickel exposure or dermatitis: pierced ears, jewelry "rash", and earlobe "rash". They also subdivided according to sex. In all cases and for both men and women there was a significant increase in the frequency of positivity associated with the exposure, with relative risks between 4.6 and 33. We conclude from this study that contact hypersensitivity is acquired and that the acquisition depends in a major way upon known exposure to a contactant; it is not incidental. It also demonstrates in a dramatic fashion that in all epidemiologic studies concerning contact dermatitis one may show the results in any direction by rejecting or selecting subsets of patients through history alone.

This second and important fact was illustrated well by their data on neomycin sensitivity. Twelve subjects were patch-test positive to neomycin; ten (83%) of those gave a history of using neomycin for at least one week on an inflammatory dermatosis. By contrast, only six (17%) of 36 age-, sex-, and race-matched controls reported equivalent use of the drug (X^2=14.4; P<0.001; relative risk=13). History proved to be an excellent predictor of contact sensitization. We conclude therefore that the point prevalence of patch test positivity to sensitizers such as neomycin is considerably lower than the rate at which neomycin sensitizes when used topically. These conclusions have relevance not only to governmental bodies which are charged by congress to protect individuals but also to physicians who prescribe.

VII. BENEFICIAL EFFECTS OF CONTACT HYPERSENSITIVITY

It is of interest to speculate what beneficial or protective effect might be derived from the capacity to express contact hypersensitivity in skin. Or stated more appropriately, what beneficial effect there is in hypersensitivity reactions in skin, the unfortunate accompanyment of which is contact dermatitis. Clearly this capacity is one in which foreign substances are recognized and destroyed. No matter that this foreign substance is a combination of self and non-self, carrier and hapten.

5-fluorouacil has been employed to treat actinic keratoses (Dillaha et al., 1963; Eaglstein et al., 1970) and has been used experimentally for superficial basal cell carcinomas (Klein et al., 1971). A portion of patients thus treated will develop contact sensitivity which otherwise might limit the effective use of this drug (Goette and Odom, 1977). It has been observed, however, that patients with hypersensitivity do as well if not better than others, giving rise to the concept of immunotherapy (Mansell et al., 1975). That is, the presence of a specific but unrelated immunologically mediated inflammatory reaction will help to eliminate (destroy) malignant clones of cells. This clinical observation supports in part the hypothesis that an ongoing, unrelated inflammatory process will benefit substantially the outcome of a malignant process - adjuvant therapy.

In the same way, hypersensitivity to nitrogen mustard has been associated with a more favorable outcome in patients with the cutaneous T-cell lymphoma (Mycosis Fungoides). Cutaneous T-cell lymphoma (CTCL) is T-cell malignancy in which the malignant cell exhibits epidermotropism. In late stages, malignant cells may occur in many organs, but early on there may be apparent restriction to skin. In view of the long clinical course of this disorder and a lack of compelling evidence that early aggressive therapy is beneficial to patients, many with diseases limited to skin have been treated with topical therapy for control rather than cure. One drug, nitrogen mustard has been used successfully in its treatment (Van Scott and Kalmanson, 1973). Patients treated in this way become sensitized frequently enough so that protocols for inducing unresponsiveness or for desensitizing were developed (Vonderheid et al., 1979). It was observed, however, that such patients might have a more favorable prognosis, suggesting the concept of immunotherapy (Vonderheid et al., 1981).

After considerable experimentation, contact hypersensitivity has been used in several clinical albeit experimental situation. The most novel and perhaps most controversal was the series of reports that the expression of contact hypersensitivity might initiate the regrowth of hair in alopecia areata. Reported first by Rosenberg and Drake (1976) the utility of this procedure has been debated in the literature (Daman, Rosenberg and Drake, 1978; Happle, Cebulla and Echternacht-Happle, 1978; de Prost, Paguez and Termaine, 1982). The procedure is to sensitize the patient by the application of DNCB to a remote site. Subsequently, a low level of contact hypersensitivity is elicited chronically in the site in which hair regrowth is desired by applying dilute concentrations of DNCB. Success rates in the treatment of this relatively refractory condition have been as high as 89% (80/90), reporting regrowth permanent and lasting regrowth (de Prost et al, 1982). Local complications in addition to scalp dermatitis included persistent cervical adenopathy, remote dermatitis and generalized eczematous reaction. Significantly, de Prost et al. (1982) reported that six of 42 patients (15%) acquired tolerance to DNCB during their therapeutic trial. Four of these six patients were included in the complete failure group. Believing that the expression of contact dermatitis was required for the regrowth of hair, they attempted to reverse the acquired tolerance pharmacologically with the H-1 blocker cimetadine (Damon and Rosenberg, 1977)

I present these poorly controlled studies to illustrate three ideas: First, it demonstrates the lengths to which patients will go, the symptoms they will endure, in order to return their physical appearance to normal-that is, the regrowth of hair. Secondly, it demonstrates convincingly that tolerance may be

acquired by a subset of patients undergoing chronic contact dermatitis. And finally, it illustrates that this tolerance is relative and subject to pharmacologic manipulation.

VIII. TREATMENT

Treatment of acute dermatitis is largely independent of pathogenesis. The patient must be removed from its source. Acutely dermatitic skin must be treated with wet compresses and after several days the subacute phase will be responsive to topical corticosteroids. It is at this point that one must recognize that corticosteroid creams frequently may contain lanolin, emulsifiers and antibacterial agents. Consequently, when the dermatitis results from sensitivity to such an ingredient, the patient will improve somewhat but not entirely. For this reason, suspected contact dermatitis in which allergen is not identified should be treated with steroid ointments which contain none of the above. Steroid ointments have an additional virtue of greater penetration and thus higher potency. In recent years there has been wider use of steroid gels which also are more potent and less likely to sensitize, although the inclusion of alcohol in the base makes them less suitable for acute dermatitis.

Systemic corticosteroids are requited when severe contact dermatitis involves large body areas or when occupation or schooling may be interrupted. The most common error in using systemic steroids are too little and for too short a time. The convient "dose paks" provided by many pharmaceutical companies are both too little and for too short a time. When systemic steroids are indicated they shall be used for two to three weeks, beginning with the equivalent of 50mg of prednisone per day. Schedules for the gradual reduction of steroids may be found but there is no hazzard in continuing the drug in full dose and then discontinuing abruptly. For my own patients I will generally use 60mg per day for one week, 30 mg per day for the second week and 15mg per day for the third. I discourage the use of intramuscular steroids because the physician then has no idea where the patient stands and it is impossible to discontinue the drug should a new illness develop. The second important error in the use of systemic steoids is to use them when the sensitizer has not been identified. This results in an unfortunate circumstance. As steroids are withdrawn the patient returns to his original state.

Do not wash dermatitic skin with soap or detergents and water. Once dermatitis is established only trivial amounts of material remain on the skin, and antigens are not spread by scratching. Skin washing with a defective skin barrier will increase the disability. By contrast, topical application of water alone will remove debris, cool the skin and provide what cleansing action is necessary.

It is important to identify early on whether secondary bacterial infection complicates the patients dermatitis. Obviously infected skin which is pustular or diproportionately edematous should be treated appropriately. However, the study by Feinstein et al, has demonstrated conclusively that dermatitic skin covering generous portions of the body but without obvious signs of infection will resolve more rapidly when treated with antibiotics.

CLINICAL SCORES OF 28 PATIENTS WITH SECONDARILY INFECTED DERMATITIS (Feinstein et al., 1977)

	DAY			
	0	2	4	6
Redness				
Cloxacillin	2.6	1.7	1.3	0.5
Placebo	2.4	1.8	1.3	1.4
P				<0.5
Crusting and Weeping				
Cloxacillin	2.6	1.8	0.9	0.2
Placebo	2.5	1.5	1.0	1.3
P				<0.01

Burrows and Stoughton (1976) observed that pretreating the site of DNFB application inhibited the induction of contact hypersensitivity, although all were sensitized later suggesting that unresponsiveness had not developed.

PATCH TEST RESULTS IN 20 SUBJECTS EXPOSED TO SENSITIZING REGIMEN WITH DNCB (Burrows and Stoughton, 1976)

	Control		Experimental	
SUBJECT	50µg	10µg	50µg	10µg
1	4	2	0	0
2	3	2	0	0
3	4	3	0	0
4	0	0	0	0
5	3	2	0	0
6	3	0	0	0
7	3	0	3	0
8	4	2	0	0
9	0	0	0	0
10	2	0	0	0

(Burrows and Stoughton, 1976)

IX. IMMUNOLOGIC MECHANISMS OF CONTACT HYPERSENSITIVITY (CH)

Contact hypersensitivity represents a special type of DTH in which reactive haptens first encounter the immune apparatus through the skin surface. Second exposure to the same haptens elicits an acute inflammatory response, a response which has been attributed to the generation of specifically sensitized T lymphocytes. This hypersensitivity response is divided functionally into two phases or limbs, afferent and efferent, phases during which the response is first initiated and then expressed. The expression of an immune response such as CH presupposes successful induction, but induction itself may occur in the absence

of expression. Unfortunately, studies which characterize this area of investigation are complicated by the large variety of experimental systems which have been used for its elucidation and by the capacity of subtle changes in experimental protocols to produce a wide spectrum of results.

Those materials which produce CH are first bound to skin proteins, forming complete antigens which in turn are able to stimulate, in association with accessory antigen-presenting cells, the proliferation of naive T lymphocytes. This clonal expansion of "specifically sensitized" lymphocytes gives rise to a population of long-lived cells which to recognize in skin the original complete antigen, when it reappears at a later date.

Reactive Haptens: Materials which produce CH have certain common features. Usually of low molecular weight, less than 400 Daltons, most are lipid soluble, resulting in greater ease of passage through skin barriers, particularly through the stratum corneum. They are reactive compounds, able to bind covalently to larger molecules, most often proteins, including both structural proteins and cell surface proteins. The interchangable terms, derivatization, haptenation, and conjugation are used to describe the process by which relatively small reactive haptens bind to non-immunogenic structures, converting them to immunogenic conjugates. It is felt that protein-hapten conjugates are primarily responsible for hypersensitivity responses. The frequency with which various haptens are of clinical importance will usually reflect their availability within man's environment. Dinitrochlorobenzene (DNCB) (1-chloro-2, 4-dinitrobenzene) will sensitize the majority of individuals exposed, but it is of little clinical importance, since it is used rarely in industry. This high frequency of reactivity to DNCB has led to its widespread use as a measure of the integrity of T-cell immune reactivity in patients with suspected immune defects (Elhilali et al., 1978). In contrast, formaldehyde will sensitize only a small fraction of those exposed, but its ubiquitous presence in clothing, in certain plastic resins, and in cleaning agents makes it a significant environmental hazard. Rhus dermatitis is unique among these three disorders, since the oleoresin will sensitize a high proportion of those exposed and since the resulting morbidity constitutes a significant public health problem as well (Byers, et al., 1979).

Early Studies: Inquiry into the pathogenesis of CH received a great boost from the report by Landsteiner and Chase (1942) that they had successfully conferred CH on naive guinea pigs by the adoptive transfer of peritoneal exudate cells from previously sensitized donors. This established for the first time the transferrability of CH via cells alone, and it contrasted with previous failures to transfer hypersensitivity in humans with serum. Their observation was followed by a series of papers first by Landsteiner and Chase and then by Chase and others in which they analysed with the aid of outbred guinea pigs the immunologic characteristics of CH. Work on the cell mediated nature of CH was largely the result of these pioneering observations.

Fundamental to understanding the mechanism by which animals acquire CH was the observation by Frey and Wenk (1957) that the destruction of afferent lymphatics draining sites of immunization would prevent sensitization. Since both lymphoid cells and serum proteins pass to regional nodes through such lymphatics, this observation did not clarify whether the capacity to sensitize resided in derivatized proteins, derivatized cell membranes, derivatized viable cells, or perhaps in some combination of the three. As will be discussed, several different hypersensitivity responses may result from one immunizing process, responses which may not be distinguishable on clinical grounds.

Consequently, the possibility that CH might be elicited with both derivatized proteins or with derivatized cells does not mean that the cellular mechanisms which result in this hypersensitivity response are necessarily similar. This issue will become more clear in future studies as methods of identifying subpopulations of lymphoid cells become more refined. The work of Frey and Wenk did demonstrate, however, that the acquisition of CH does require an intact lymphatic drainage to regional lymph nodes.

Many investigators who conducted early laboratory studies in CH were equally concerned with inhibiting such hypersensitivity reactions, and considerable effort was directed at this possibility. One strategy included the oral ingestion of the reactive hapten, but Chase was unable to decrease the level of sensitization by feeding DNCB after immunization had occurred. This process of deleting the hypersensitivity response, termed desensitization, is of course the ultimate goal in human allergic contact dermatitis since patients will seek aid for their disability only after hypersensitivity has developed.

In contrast with unsuccessful attempts to desensitize immune animals, a variety of successful experimental protocols have been developed for inducing specific immunologic unresponsiveness. Chase first demonstrated in guinea pigs that immunologic unresponsiveness could be produced by oral feeding with an allergen prior to the immunization process for DTH. First attempts to establish this unresponsive state were made even earlier, however, in the era in which neoarsphenamine was the treatment of choice for syphilis. This work was prompted by the high frequency of hypersensitivity reactions which followed intramuscular injections. In an attempt to prevent this complication, Frei and Sulzberger working with humans and guinea pigs respectively, observed that if an intravenous infusion of neoarsphenamine was given first, the frequency of such hypersensitivity reactions was reduced significantly. Although the cellular events which lead to states of hypersensitivity and unresponsiveness were unknown at that time, both investigators recognized correctly that variations in routes of hapten administration might produce divergent responses. Their work introduced the concept that the route of administration would dictate both the quality and quantity of resulting immune responses, a concept which is central to an understanding of UVR effects on CH.

In an inventive series of studies Macher and Chase investigated the effect of excising sites of hapten injection within the first three days after immunization. Taking advantage of the ability to induce CH in guinea pigs with a single hapten injection into one ear, they explored this process temporally by excising ears sequentially from panels of animals. When ears treated with the hapten picryl chloride were excised twelve hours later, only one of 28 guinea pigs developed sensitization (4%). In contrast, 16 of 20 animals were sensitized normally when their ears were left undisturbed (80%). Excision of sensitization sites at 24 and 48 hours in two additional panels of animals produced intermediate frequencies of sensitization (14% and 61% respectively). One interpretation of this observation is that the acquisition of CH occurs relatively slowly, requiring sites of hapten application to remain on the respective recipients for as long as 48 hours in order for maximal sensitization to develop. A second and more plausible interpretation developed from their next set of experiments which dealt with those animals in which sensitization failed to occur. Animals not sensitized in the first study because of the premature excision of application sites were then exposed to a normal immunizing regimen in which picryl chloride was injected into their remaining ear. It was observed

that a significant percentage of the animals had become tolerant during the first procedure as they remained unresponsive after the second application of hapten. Their interpretation of these observations depended to a large extent on two independent studies. In the first, they observed that a significant percentage of applied picryl chloride will leave an injection site within minutes and reach the systemic circulation via venous outflow. And in the second, they determined that the frequency of tolerance achieved in animals subjected to early ear excision was similar to that achieved when DNCB was injected in similar amounts either intradermally or intravenously prior to the usual immunization protocol.

From these studies Macher and Chase drew three conclusions:

1. Allergen which remains in the ear after early outflow constitutes the sensitizing depot.

2. The fraction of allergen which escapes from sensitization sites soon after skin painting can induce a state of tolerance in the majority of animals from whom the sensitization sites had been removed. A similar tolerogenic effect can be obtained by the systemic injection of the sensitizer, in amounts equivalent to that which escapes during normal sensitization.

3. The eventual degree of sensitivity attained by the animals is therefore the result of two independent immunologic processes:
   a. Tolerogenic effect of escaped material.
   b. Sensitization effect of localized material.

Studies which have assessed the unique balance between hypersensitivity and suppression have also been conducted in humans. Insight with this balance of effects may be gained, from a series of papers by Lowney in which methods of inducing tolerance were explored. In the first protocol human subjects were sensitized through normal skin by the repeated application of small amounts of DNCB. Subjects treated in this manner developed lower reactivities to DNCB than did control subjects sensitized at one time with large amounts. Furthermore, among several protocols, those subjects who could never be sensitized by topical application of DNCB came preferentially from protocols which utilized repeated exposures to small amounts of DNFB. Obviously, each protocol elicited two responses reactive and suppressive, which in turn were balanced differently.

The second study of Lowney's demonstrates even more clearly the capacity of special routes of hapten administration to induce both hypersensitivity and suppression simultaneously. One cohort of 17 subjects received their first exposure to DNFB through buccal mucosa. Interestingly, eight subjects were never sensitized to DNCB, clearly demonstrating that the buccal mucosa route was more likely to induce suppression. The seven who were sensitized in this protocol were subsequently exposed to a "normal" percutaneous regimen of sensitization as were the appropriate control subjects who received two "normal" sensitizing regimens. Those who had first developed sensitivity via buccal mucosa remained significantly less responsive after this second course, indicating these subjects had acquired simultaneously both hypersensitivity and some measure of unresponsiveness.

Contact Hypersensitivity in inbred animals: Recent work in CH has been aided greatly by the availability of inbred strains of laboratory mice, hamsters, and guinea pigs. Because of genetic homogeneity which occurs with inbreeding, reactions to procedures such as immunization and elicitation are more uniform, and it is possible to transfer lymphoid cells adoptively among genetically identical (syngeneic) animals without concern for the immunologic injury of the recipient animal by transfused cells (graft vs. host reaction) or of the transfused cells by the recipient (host vs. graft reaction). Furthermore, one need not concern oneself with genetic restrictions to cellular collaboration of adoptively transfused cells, or alternatively one can identify with recombinant strains of H-2 congenic mice those genetic identities which are essential for optimal cellular collaboration.

Issues which result from genetic constraints on an immune response can be more fully appreciated in light of recent developments concerning gene products of the major histocompatability complex (MHC). To begin, major genetic influences on immune responsiveness are mediated by cell surface proteins which have been traced in a variety of species to the specialized chromosomal region, the MHC. In man this region is identified as human leukocyte antigen (HLA) region and in mice the H-2 complex. Although this close association between genetic control for immune responses and genetic control of transplantation immunity is well established, one should not confuse these disparate immune processes. In the former, such cell surface proteins control cellular recognition of an associated foreign antigen and in the latter, these same surface proteins constitute the foreign antigen. These two disciplines intersect, however, with the capacity of experiments in one to give insight into experiments in the other.

In mice the H-2 complex is organized in linear fashion into several regions. Most important among these regions are K, I, and D. Antigens which are coded in K and D occur on all nucleated cells, including cells of the immune system, and are termed Class I antigens. In contrast, proteins coded in the I region, termed Class II, occur on a limited group of lymphoreticular cells: B-lymphocytes and antigen-presenting cells, including some macrophages, dendritic cells and Langerhans cells. Obviously, the organization of the murine as well as the human MHC are much more complex than this brief statement suggests, although this is sufficient information to indicate the importance of genetic restriction on immune responses. The observation that certain aspects of an immune response are genetically restricted means that genetic identity must occur in specified regions or subregions of the MHC in order for an optimal response to occur. The implication is that these proteins or closely related proteins serve as recognition markers for the cellular collaboration which must occur for that optimal response. Furthermore, identifying differences in genetic restriction serve as a way of defining various components of an immune response. The importance of these ideas will become evident later in the review.

The utility of mice in CH was at first impeded by the failure of immune animals to develop visible skin reactions in response to epicutaneously applied haptens. This was overcome, however, by the observation of Asherson (Asherson and Zembala, 1974) that the cutaneous edema elicited by reactive haptens could be measured in ear skin with an engineer's micrometer. Subsequently, Miller and Vadas and their associates (Miller et al., 1975; Valas et al., 1975) employed a second successful assay in which the emigration of radiolabelled lymphoid cells called to elicitation sites was measured by excising the site of exposure and

measuring the number of radiolabelled cells with a scintillation counter. Because of these two developments, mice and hamsters now may be employed for studies in CH and the units of measure will, of necessity, be expressed as units of thickness or as disintegrations per unit time.

Insight has been gained into the balance between unresponsiveness and hypersensitivity by methods which interrupt specifically one aspect on the other. Working from the observation that delivering reactive haptens via a stomach tube could produce specific immunologic unresponsiveness, Polak et al (1975) demonstrated that this unresponsiveness was prevented by pre-treatment of mice with cyclophosphamide an inhibitor of cell division, suggesting that the suppression which normally results is an active process which requires cell division. Subsequently, Asherson et al (1977) demonstrated that the administration of either of the two sensitizers oxazolone or picryl chloride would result in the generation of at least two different generic populations of suppressor cells, one a B-cell population, and the other a T-cell population. These observations demonstrate clearly the complexity of cellular interactions which result from such immunization procedures. More recently, Green, Dorf, Benacerraf and their collaborators as well as Miller, Claman, Moorhead and associates have produced evidence that as many as three distinct subpopulations of T lymphocytes participate in suppression and regulation of CH responses to haptens in mice.

In sum, the interpretations of in vivo experimental immune responses are complicated by the realization that such responses are summations of a family of responses, some of which are antagonistic and some of which are synergistic. Furthermore, each may have differing latencies for onset and for peak responses.

Antigen presenting cells in contact dermatitis: The development of CH after exposure to a contact allergen is dependent upon cellular collaboration among lymphoid cells. In the acquisition of CH, as in numerous other immune responses, antigens must be presented to T-lymphocytes. This collaborative process is genetically restricted, that is, with genetic identity at the MHC for optimal antigen presentation will occur. Likewise, the elicitation of an immune response may under certain circumstances require both antigen presentation and genetic restriction, although for in vivo CH these requirements have not been fully established.

Recent evidence indicates an essential role for an antigen presenting accessory cell for lymphocyte activation and proliferation (Thomas, et al., 1977). Much of the work in this review depends upon such cells. The elegant work of Rosenthal, Shevach, Green, and collaborators during the mid and late 1970s firmly established that macrophages, usually identified by virtue of their capacity to adhere to plastic surfaces and to phagocytize particulate material, were essential to the process of antigen recognition by immunocompetent lymphocytes. While the precise form of the immunogenic antigen moiety presented by macrophages has yet to be elucidated, an important aspect requires participation of cell surface molecules encoded by genes within the H-2 chromosomal segment. As the dogma began to build that macrophages represent the true antigen presenting cells, a minority population of adherent cells that fail to undertake phagocytosis was reported to fulfill antigen presenting functions.

Recent work by Steinman and his associates (Steinman et al., 1979) has documented a subpopulation of splenic cells, termed dendritic cells, to be extraordinarily efficient at antigen presentation. These cells account for about 1% of splenic cells; they bear on their surfaces gene products of the MHC, and

their antigen presenting function exhibits genetic restriction. They are also unusual in that they lack critical differentiation markers of B-cells (surface immunoglobulin), T-cells (Thy-1 antigen) and of Macrophages (Fc receptors). In terms of function, dendritic cells were first described to stimulate the allogeneic (Steinman et al., 1978) and the syngeneic (Nussenzweig and Steinman, 1980) mixed leukocyte reaction at exceedingly low densities. Secondly, they are able to perform accessory cell function in in vitro secondary immune responses. Most significant in the context of contact hypersensitivity was the recent observation that dendritic cells could function as the critical accessory cell to present antigen in vitro in the development of anti-trinitrophenol (TNP) cytotoxic T lymphocytes (Nussenzweig, et al., 1980). This observation suggests strongly that dendritic cells may act in vivo in this same capacity.

Langerhans cells: Simultaneously with the work on splenic dendritic cells, immunologists and dermatologists examined carefully the dendritic epidermal Langerhans cell while assessing the hypothesis that it might account for certain immunologic attributes of mammalian skin. Epidermis, the structure in which Langerhans cells chiefly reside, is a multilayered, cellular tissue, comprised mainly of keratinocytes which contribute to protective interface between an animal and its environment. Differentiated keratinocytes arise from a proliferating epidermal subpopulation and after a series of maturational steps, flatten into hexagonal leaflets which are bound together into a semipermeable surface membrane. Since keratinocytes constitute approximately 95% of all epidermal cells, these processes of proliferation and barrier formation are major epidermal functions. About two percent of cells within this epidermal matrix are Langerhans cells, distributed across the skin surface in a regular gridlike network. Each Langerhans cell possesses a central body with lobulated nucleus and several long dendritic processes which extend outward from the central body to pass between keratinocytes in radial fashion. This dendritic morphology is similar to that of melanocytes, the third major resident epidermal cell, but on the basis of histochemistry, immunochemistry, or electron microscopy they may be distinguished.

The hypothesis that Langerhans cells perform immunologic function is based on several lines of evidence, some of which is circumstantial and some of which is functional. Langerhans cells exclusively among epidermal cells bear unique surface proteins and surface receptors usually found on cells of macrophage/monocyte lineage. They bear cell surface Fc and C3b receptors (Stingl et al., 1977; Berman and Gigli, 1980). Murine Langerhans cells bear Ia antigens (Rowden et al., 1979) and in guinea pigs and humans they bear B-cell alloantigens (Stingl et al., 1978). It is clearly established that epidermal Langerhans cells do possess these features and that they possess them in common with macrophages.

In terms of Langerhans cell function, disaggregated epidermal cells which are enriched for Langerhans cells on the basis of their cell surface receptors may substitute for macrophages in in vivo functional tests (Stingl et al., 1978). In that study, suspensions of epidermal cells which were enriched for Langerhans cells induced a marked proliferative response in syngeneic primed T lymphocytes exposed to the appropriate antigens. This response was genetically restricted and it was abrogated by pretreatment of the cell suspensions with anti-Ia antisera and complement, thus linking the function of Langerhans cells with that of macrophages.

Work employing special cutaneous sites has supported the hypothesis that Langerhans cells play a significant role in contact hypersensitivity. Although

Langerhans cells are evenly distributed over most skin surfaces, in sites such as the cornea, hamster cheek pouch and murine tail, unusual distributions and decreased densities of cells are associated with unique immunologic features (Bergstresser et al., 1980).

In a series of studies Toews, Bergstresser and Streilein and Streilein and Bergstresser assessed the relationship between surface densities and distributions of Langerhans in special cutaneous surfaces and the capacity of each to promote the induction of contact hypersensitivity to DNFB. In mice, surface densities of Langerhans cells in tail skin are significantly lower than in body wall skin, with the C57BL/6 strain having by far the lowest density, less than 20% of body wall skin. When a normal immunizing regimen was carried out through tail skin, C57BL/6 mice failed to become sensitized. Moreover, when C57BL/6 mice treated in this way were subsequently exposed to a normal immunizing regimen through body wall skin, the animals were specifically unresponsive to DNFB, suggesting that an overriding suppressive reponse resulted from the skin painting of a site deficient in Langerhans cells. In a subsequent unpublished study this unresponsiveness was adoptively transferred with lymphoid cells to naive recipients, suggesting that an active suppression process was operative.

Similar observations were made in studies conducted with Syrian hamsters, animals which also serve as useful models for contact hypersensitivity (Streilein et al., 1980). Streilein and Bergstresser demonstrated that painting of the intact hamster cheek pouch epithelium resulted in the induction of a state of specific unresponsiveness. When the cheek pouch epithelium was grafted heterotopically to a body wall site, similar unresponsiveness resulted from painting of that site, making the oral ingestion of the hapten considerably less likely. Furthermore, viable lymphoid cells from unresponsive hamsters could transfer that unresponsiveness to naive hamsters suggesting that active suppression was at least partly responsible for this response. Although the cheek pouch is unique not only for its exceedingly low density of Langerhans cells but also for the absence of a lymphatic drainage, these studies form a background on which the effect of ultraviolet light on the induction of contact hypersensitivity might be placed.

Additional circumstantial evidence links Langerhans cells to contact hypersensitivity. Sensitizing materials which may serve as haptens in vivo were reported by Shelly to accumulate preferentially within the dendritic Langerhans cells of epidermal whole mounts, and Wolff and Schreiner have demonstrated that Langerhans cells take up and process exogeneously applied proteins. In a series of electron microscopic studies, Silberberg and her associates have demonstrated in sites of delayed hypersensitivity reactions, lymphocytes in direct contact with epidermal Langerhans cells in sites of delayed hypersensitivity reaction and a sequential appearance of antigen-bearing Langerhans cells in the dermis, dermal lymphatics and draining lymph nodes after thoratrast is injected into the dermis.

Most recently, studies with radiation chimeras have demonstrated that Langerhans cells are not epithelial in origin, but are, in fact, derived from bone marrow precursors (Frelinger et al., 1974; Katz et al., 1979).

The question of which lymphoid cells might be capable of initiating contact hypersensitivity has been of concern to many investigators. Ptak et al assessed the capacities of cells from several sources to induce contact hypersensitivity after derivatization in vitro, followed by readministration into

recipient animals by a variety of routes. Their significant finding with respect to skin and more specifically to Langerhans cells was that derivatized epidermal cells were the only cells which, when given intravenously, could induce CH. This hypersensitivity response was genetically restricted, and partial purification of epidermal cells for those which possessed cell surface Fc receptors (Langerhans cells) provided a cell population which when haptenated and infused intravenously was the most efficient in inducing contact hypersensitivity. Furthermore, the resulting hypersensitivity was long-lasting, its time course being similar to that obtained in skin-painted animals. They interpreted these results as meaning that epidermal Langerhans cells as derivatized cells were better at inducing contact sensitivity than were cells from any other source, suggesting that they may perform antigen presenting function for the induction of contact hypersensitivity in vivo.

The results of Ptak et al (1980) were partially confirmed by Tamaki, Fujiwara and Katz (1981). These investigators derivatized cells from two sources, spleen and epidermis, with trinitrobenzene sulfonate (TNBS) and introduced them into syngeneic recipient mice by various routes. Contact hypersensitivity was assessed by the application of TNCV to ear skin followed gy micrometer measurements of ear swelling. As observed by Ptak, hypersensitivity regularly resulted from the subcutaneous injection of TNP-conjugated cells from either source, and it was always stronger and longer lasting when derivatized epidermal cells rather than spleen cells were used. In contrast, with the observation of Ptak et al., derivatized cells from both sources did not induce contact hypersensitivity when introduced intravenously. Moreover, both cell sources induced hyporesponsiveness or no response at all. Importantly, the most significant difference between routes of administration occurred with intraperitoneal administration of derivatized cells. Derivatized epidermal cells induced hypersensitivity while derivatized spleen cells induced unresponsiveness.

Toews, Bergstresser and Streilein (1980), working with C57BL/6 mice, assessed the impact of relatively low doses of UVB on the integrity of Langerhans cells as judged by cell surface ATPase activity and on the induction of CH as judged by DNFB sensitization. Ultraviolet radiation was administered by unfiltered FS-20 "Sun Lamp" fluorescent tubes, which emit a continuous ultraviolet spectrum with a peak at 313nm and high output in the sunburn or erythema spectrum. Shaved, one inch square abdominal wall skin received 100 J/m^2 on each of four days prior to skin painting with a standard immunizing regiment of dinitrofluorobenzene (DNFB). This radiation schedule produced modest changes in the visual and histopathologic appearance of the irradiated skin, including some epidermal thickening, but no significant cellular infiltrate. Changes which were seen were confined to the epidermis.

When the usual immunizing procedure was conducted on abdominal wall skin treated in this way with UVB, normal immunization did not occur. Moreover, there was a direct correlation between the number of Langerhans cells and the capacity of such skin to permit intermediate levels of sensitization during the time period during which Langerhans cells returned to the irradiated skin after UVL treatment had been discontinued. In a subsequent study, mice which had received their first exposure to DNFB through UVR-treated skin then received a normal immunizing regiment through untreated dorsal body wall skin. These animals had become unresponsive to this attempt at conventional immunization, an unresponsiveness which was specific for the DNP moiety. Most importantly, however, this capacity to induce specific unresponsiveness through UVB-treated

skin was local and limited to the site of irradiation, since irradiation of abdominal wall skin did not alter the capacity of dorsal body wall skin to sustain contact hypersensitivity. This local effect of UVB was presumed to be related to the inability of perturbed Langerhans cells to function normally.

Lynch, Gurish and Daynes (1981) have confirmed these observations, although they employed an ultraviolet light dose which was approximately 30-fold greater than what was used previously. Significantly, they also observed that skin painting of murine abdominal wall skin, this time in the C3H strain, which had been irradiated daily for six previous days resulted, not in hypersensitivity but in unresponsiveness as judged by subsequent sensitization through an unirradiated site. Evidently, skin painting of unirradiated skin in a similar cohort of animals resulted in hypersensitivity, indicating that the unresponsiveness was not a general phenomenon.

In view of the classical study by Macher and Chase (1969), the local effect of UVB on the induction of contact hypersensitivity becomes more clear. Macher and Chase concluded from their study and from contemporary studies that hapten injected into the skin is dealt with in at least two ways, with a major portion of administered hapten escaping rapidly via venous ourflow during the first 24 hours. This early outflow via venous drainage tends to tolerize as demonstrated by the fact that intravenous injection of similar amounts also induce tolerance. In contrast, hapten remaining in the ear skin after early outflow constitutes the sensitizing depot. Specific tolerance could be secured by early excision of the sensitizing depot, just as intrveous injection of a sensitizing material does, with the skin depot being bypassed. They concluded that the eventual degree of sensitivity attained by the animals was the result of two immunologic processes which occurred relatively independently. There was the tolerogenic effect of the escaped material and the sensitizing effect of the localized material.

Extending this work to the observations on the effect of low doses of ultraviolet light on the capacity of skin to sustain the induction of contact hypersensitivity, the data are consistent with the hypothesis that ultraviolet light does not interrupt those processes which tend toward tolerance such as the passage directly into the venous circulation or perhaps oral ingestion of derivatized stratum corneum, while, in contrast, it interrupts the processes that depend upon a cutaneous depot and tend to induce sensitivity. Much circumstantial evidence implicates in a strong way the pivotal role Langerhans cells may have in this processes.

An important question, one which will provide additional contrast with experimental protocols employing large doses of UVB, concerns the effect of low doses on other hypersensitivity responses. In unpublished work, Freeman, Bergstresser and Streilein exposed several panels C3H mice to low UVB from FS-20 fluorescent tubes (200 J/m^2 per day for four days). Those animals which were painted with DNFB in the site of irradiation displayed no CH as assayed by ear swelling while those which received painting through irradiated skin developed normal CH respones. Furthermore, a third panel of animals which was immunized with DNFB derivitized cells. These observations complete the evidence which demonstrates the clear separation between local effects of low dose UVB and systemic effects of high doses.

In an attempt to study directly the relationship between the UVR-induced alterations in Langerhans cells and the UVR-induced suppression of CH, Sauder et al. (1981) drew on the capacity of derivatized epidermal cells to induce contact hypersensitivity when introduced subcutaneously. Employing FS-20 sunlamps, they

observed that 192 J/m^2 of combined UVA and UVB irradiation, delivered to the cells in vitro prior to derivatization with TNBS, would prevent optimal sensitization. Moreover, animals receiving such cells were suppressed significantly in their capacity to develop CH to normal skin painting six days later. Suppression in this circumstance was as much as 70% when compared with normal immunizing procedures. In a subsequent study this suppression could be adoptively transferred to naive recipients, a transfer which could be abrogated by pretreatment of the transferred cells with anti-theta antisera and complement. These observations suggest strongly that the suppression is an active process and that it is mediated by theta-positive T lymphocytes. It is of interest that in these studies a dose response for this process in terms of irradiated cells infused and in terms of UVL exposure could be seen. Furthermore, it was demonstrated that the UVL had no significant effect on epidermal cell survival as judged by survival of the entire cell suspension and as judged by the survival of Ia-positive subfraction of cells within the suspension (Langerhans cells). This work strongly supports the hypothesis that UVL is capable of interrupting directly the antigen-presenting capacity of antigen-presenting cells (LCs) within the epidermis.

Recent work by Stingl et al (1981) sheds considerable light on the mechanism by which UVB might interrupt directly the induction of contact hypersensitivity. These studies were designed to look at antigen presentation in a secondary delayed-type hypersensitivity (DTH) response rather than contact hypersensitivity but they took advantage of the capacity of epidermal cells (and most likely only the Langerhans cell subpopulation) to serve as antigen presenting cells in such secondary immune responses (Stingl et al, 1978). In this study they employed T-lymphocytes immune to purified protein derivitive of tuberculin (PPD) and to dinitrophenylated ovalbumen (DNP_6-OVA) from either BALB/c or C3H/He mice. Lymphocyte proliferation was induced by coculturing the immune lymphocytes with primed syngeneic, semiallogeneic or allogeneic antigen presenting cells, which consisted of either peritoneal exudate cells (macrophages) or unpurifed epidermal cells (consisting of about 2-4% Langerhans cells). In the absence of UVB, they observed that both sources of primed stimulator cells could, in a genetically restricted way, induce a vigorous proliferative response. This response could be abolished by pretreating stimulator cells with a monoclonal anti-Ia reagent and complement without, in the case of epidermal cells, killing significant numbers, suggesting strongly that Langerhans cells were solely responsible for antigen presentation by the epidermal cells.

When epidermal cells were exposed, either before or after priming, to UVB delivered from FS-20 fluorescent tubes, there was a dose dependent inhibition of the proliferative response seen after four days in culture. This inhibition was about 20% at 25 J/m^2 and rose to greater than 95% at 200 J/m^2, dosages which correspond directly to the skin surface dosages employed by Toews et al (40) (100 J/m^2 daily for four days). Control mixing studies demonstrated this effect to be the result of killing of antigen presenting cells rather than an inibition attributable to the release of toxic epidermal cell products.

These studies clearly demonstrate the capacity of UVB to interrupt directly antigen presentation by epidermal Langerhans cells and give direct insight into the in vivo studies employing similar amounts and quantities of ultraviolet radiation. It is quite likely that sensitization through a UV-irradiated site results in an alteration in the presentation of the antigen by Langerhans cells, and that this alteration is responsible for the resulting suppression. What is

not clear is whether the induction of suppression in vivo is passive and results from bypassing the Langerhans cell because of UV-induced damage, or whether the UV-irradiated Langerhans cell actively stimulates the suppressor cell pathway. It is also not yet clear whether the depressed elicitation of CH in UVR-exposed skin is due to an effect of UV on LC, or whether the alteration of Langerhans cells by UVR plays a role in the transient systemic suppression of CH following high doses of UVR.

Summary: Contact hypersensitivity represents a DTH response in which reactive haptens encounter the immune system via percutaneous routes. Elements which are essential for the induction of CH include antigen presenting cells and functioning lymphatic vessels which drain to regional lymph nodes. The induction of CH results in a clonal expansion of specifically sensitized T-lymphocytes which are able to mediate an acute inflammatory response after reapplication of the same hapten. Recent evidence demonstrates that the induction of CH results in not one, but a family of immune responses, some of which contribute to the intensity of the hypersensitivity reaction and some of which tend to inhibit or suppress it, and that the route of hapten administration tends to influence greatly which responses will predominate. In general, oral and intravenous routes tend to tolerize and percutaneous routes tend to result in hypersensitivity. Because of the simultaneous development of several responses, in vivo elicitation responses represent a sum or integration process to which several individual responses contribute.

Since 1975, a growing literature has documented epidermal Langerhans cells to play a pivotal role in the acquisition of CH. These antigen-presenting cells cover most skin surfaces as a regularly distributed network, residing entirely within the epidermis. Although the sequence of cellular interactions which occur during the acquisition of CH are not known, Langerhans cells may contribute, through antigen-presentation, to the proliferation and clonal expansion of the sensitized T-lymphocytes which mediate the reaction. Important to an assessment of Langerhans cell function has been the observation that relatively low doses of UVB irradiation will perturb them in selective ways, deleting both cell surface ATPase activity and Ia antigens. Furthermore, similar doses of UVB delivered in vivo to sites of hapten application will interrupt the acquisition of CH so that profound unresponsiveness rather than hypersensitivity develops. This unresponsiveness has been transferred adoptively with T-lymphocytes from UVB and hapten-exposed donors into naive genetically identical recipients. By contrast, UVB-treated animals are able to develop CH in unirradiated sites and DTH to subcutaneous immunization with haptenated cells. This capacity of low doses of UVB to interrupt the acquisition of CH only in sites of irradiation suggest strongly that Langerhans cell function has been altered in such areas, a result which contrasts with parallel studies demonstrating that higher doses of UVB will inhibit systemically the function of antigen-presenting cells from both skin and the spleen. Future studies of UVB induced changes in Langerhans cell function will define more carefully their role in CH and will test possibilities that defective immunologic recognition within the epidermis may contribute not only to perturbations in the acquisition of CH but to ultraviolet carcinogenesis as well.

X. SUMMARY OF CONTACT DERMATITIS

1. Contact dermatitis is either allergic or irritant in origin although both may occur simultaneously.
2. Contact dermatitis is confined largely to sites of application on skin surfaces.
3. Acute contact dermatitis is an acute inflammatory process which includes pruritus, redness, vesiculation, and induration; after this acute phase, subacute and chronic expressions develop as lesions become scaly and crusted.
4. Common antigen source for allergic contact dermatitis include topical skin preparation, clothing, metal, rubber, plastics and plants.
5. Diagnostic techniques are available to identify precisely the molecular species responsible for the sensitivity.
6. Many sensitizers are found in a widely disparate variety of compounds and materials.
7. Contact dermatitis frequently accompanies other cutaneous disorders.
8. Contact deramtitis may exacerbate with the administration of systemic medication.
9. Although topical and systemic corticosteroids have been used to treat contact dermatitis, only prophylaxis by separating the patient from the source is ultimately successful.

Asherson GL and Zembala M (1974): Suppression of contact sensitivity by T cells in the mouse. I. Demonstration that suppressor cells act on the effector stage of contact sensitivity; and their induction following in vivo exposure to antigen, Proc R Soc B, 187:329.

Asherson GL, Zembala M, Perera MACC, Mayhew B and Thomas WR, (1977): Production of immunity and unresponsiveness in the mouse by feeding contact sensitizing agents and the role of suppressor cells in the Peyer's patches, mesenteric lymph nodes and other lymphoid tissues, Cell Immunol, 33:145.

Bergstresser PR and Eaglstein WH (1973): Irritation by hydrophilic ointment under occlusion. Arch Dermatol 108:218-219.

Bergstresser PR, Fletcher CR and Streilein JW, (1980): Surface densities of Langerhans cells in relation to rodent epidermal sites with special immunologicl properties, J Invest Dermatol, 74:77.

Berman B and Gigli I (1980): Complement receptors on guinea pigs epidermal Langerhans cells, J Immunol, 124:685.

Burrows WM and Stoughton RB (1976): Inhibition of induction of human contact sensitivization by topical glucocorticosteroids. Arch Dermatol 112:175-178.

Bresler RR (1949): Nitroglycerine reactions among pharmaceutical workers. Ind Med Surg 18:519-523.

Byers VS, Epstein WL, Castagnoli N and Baer H (1979): In vitro studies of poison oak immunity. I. In vitro reaction of human lymphocytes to urushial, J Clin Invest, 64:1437.

Cage GW, Shwachman H, Sato K (1979): Eccrine glands in Fitzpatrick TB et al. Eds. Dermatology in General Medicince, McGraw Hill, New York.

Chase MW (1946): Inhibition of experimental drug allergy by prior feeding of the sensitizing agent, Proc Soc Exp Biol Med, 61:257.

Damon AL, Rosenberg EW, Drake L (1978): Treatment of alopecia areata with dinitrochlorobenzene. Arch Dermatol 114:1046-1038.

Daman AL, Rosenberg EW (1977): Acquired tolerance to dinitrochlorobenzene by cimetadine. Lancet 1:726.

de Prost Y, Pagnez F, Touraine R (1982): Dinitrochlorobenzene treatment of alopecia areata. Arch Dermatol 118:542-545.

Dillaha CJ, et al. (1963): Selective cytotoxic effect of topical 5-fluorouracil. Arch Dermatol 88:247-256.

Eaglstein WH, Weinstein GD and Frost P (1970): Fluoronuracil: mechanism of action in human skin and actinic keratoses. Arch Dermatol 101:132-137.

Elhilali MM, Brosman SA, Vescera C, Paul JG and Fahey JL (1978): The effects of treatment on delayed cutaneous hypersensitivity responses (DNCB, croton oil, and recall antigen) in patients with genitourinary cancer, Cancer, 41:1765.

Fisher AA (1982): Topical medicaments which are common sensitizers. Ann Allergy 49:47-100.

Frelinger JG, Hood L, Hill S and Frelinger JA (1979): Mouse epidermal Ia molecules have a bone marrow origin, Nature, 282:321.

Frey JR and Wenk P (1957): Experimental studies on the pathogeneis of contact eczema in guinea pigs, Int Arch Allergy Appl Immunol, 11:81.

Giovinazzo VJ, Harber LC, Bickers DR, et al. (1979): Photoallergic contact dermatitis to musk ambrette.

Goette DK and Odom RB (1977): Allergic contact dermatitis to topical fluoromacil. Arch Dermatol 113:1058-1061.

Guill MA and Odom RB (1979): Evans blu dermatitis. Arch Dermatol 115:1071-1073.

Happle R, Cebulla K, Echternacht-Happle K (1978): Dinitrochlorobenzene therapy for alopecia areata. Arch Dermatol 114:1629-1631.

Hellgren L, Mobacken H (1969): Nummular eczema: clinical and statistical data. Acta Derm Venerol 49:189-196.

Hendricks AA, Dec GW, Jr, (1979): Contact dermatitis due to nitroglycerine ointment. Arch Dermatol 115:853-855.

Katz SI, Tamaki K and Sachs DH (1979): Epidermal Langerhans cells are derived from cells originating in the bone marrow, Nature, 282:324.

Klein E, Stoll HL and Milgrom, et al. (1971): Tumors of the skin XLI. Topical 5-fluoromacil for epidermal neoplasms. J Surg Oncol 3:331-349.

Landsteiner K and Chase MW (1942): Experiments on transfer of cutaneous sensitivity to simple compounds, Proc Soc Exp Biol Med, 49:688.

Laws GC (1898): The effects of nitroglycerine upon those who manufacture it. JAMA 31:793-794.

Lynch DH, Gurish MF and Daynes RA (1981): Relationship between epidermal Langerhans density ATPase activity and the induction of contact hypersensitivity, J Immunol, 126:1892.

Macher E and Chase MW (1969): Studies on sensitization of animals with simple chemical compounds. XII. The influence of excision of allogenic depots on onset of delayed hypersensitivity and tolerance, J Exp Med, 129:103.

Mansell PW, Litwin MS and Ichinose H, et al.(1975): Delayed hypersensitivity to 5-fluoromacil following topical chemotherapy of cutaneous cancers. Cancer Res 35:1288-1294.

Mathias CGT, Chappler RR and Maibach HI (1980): Contact urticaria from cinnamic aldehyde. Arch Dermatol 116:74-76.

Mendenhall RC, Ramsay DL and Girard RA, et al. (1978): A study of the practice of dermatology in the United States. Arch Dermatol 114:1456-1462.

Mendenhall RC, Girard RA and Abrahamson S (1978): A national survey of medical and surgical specialties: Background, purpose and methodology. JAMA 240:848-852.

Miller JFAP, Vadas MA, Whitelaw A and Gamble J (1975): A radioisotopic method to measure delayed type hypersensitivity in the mouse. II. Cell transfer studies, in Arch Allergy Appl Immuunol, 49:693.

Mitchell JC (1975): The angry back syndrome. Eczema creates eczema. Contact Deramtitis 1:193-194.

Nussenzweig MC and Steinman RM (1980): Contribution of dendritic cells to stimulation of the murine syngeneic mixed leukocyte reaction, J Exp Med, 151:1196.

Nussenzweig MC, Steinman RM, Gutchinov B and Cohn ZA (1980): Dendritic cells are accessory cells for the development of anti TNP, cytotoxic T lymphocytes, J Exp Med, 152:1070.

Rosenberg EW and Drake L (1976): Alopecia areata. Arch Dermatol 112:256.

Petrozzi JW and Shore RN (1976): Generalized exfoliative dermatitis from ethylene diamine. Arch Dermatol 112:525-526.

Penneys NS, Edwards LS and Katsikas JL (1976): Allergic contact sensitivity to thiman compounds in a hemodialysis unit. Arch Dermatol 112:811-813.

Polak L, Geleick H and Turk JL (1975): Reversal by cyclophosphamide of tolerance in contact sensitization. Tolerance induced by prior feeding with DNCB, Immunology, 28:939.

Prystowsky SD, Allen AM, Smith RW, Nonomura JH, Odom RB, AKers WA (1974): Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine. Arch Dermatol 115:959-962.

Ptak W, Rozycka D, Askenase PW and Gershon PK (1980): Role of antigen-presenting cells in the development and persistence of contact hypersensitivity, J Exp Med, 151:362.

Rowden G, Phillips TM and Delovitch TL (1978): Expression of Ia antigens by murine keratinizing epithelial Langerhans cells, Immunogenetics, 7:465.

Sauder CN, Tamaki K, Moshell AN, Fujiwara H and Katz SI (1981): Induction of tolerance to topically applied TNCB using TNP-conjugated ultraviolet light-irradiated epidermal cells, J Immunol, 127:261.

Schenplein RJ and Blank IH (1971): Permeability of the skin. Physiol Rev 51:702-747.

Steinman RM, Kaplan G, Witmer M and Cohn ZA (1979): Identification of a novel cell-type in peripheral lymphoid organs of mice. V. Purification of spleen dendritic cells, new surface markers, and maintenance in vitro, J Exp Med, 149:1.

Steinman RM and Witmer M (1978): Lymphoid dendritic cells are potent stimulators of the primary mixed leukocyte reaction in mice, Proc Nat Acad Sci USA, 75:5132.

Stingl G, Wolff-Schreiner EC, Pichler WJ, Gschnait F, Knapp F and Wolff K (1977): Epidermal Langerhans cells bear Fc and C3 receptors, Nature, 268:245.

Stingl G, Katz SI, Shevach EM, Wolff-Schreiner E and Green I (1978): Detection of Ia antigens on Lasngerhans cells in guinea pig skin, J Immunol, 120:570.

Stingl G, Katz SI, Clement L, Green I and Shevach EM (1978): Immunologic functions of Ia-bearing epidermal Langerhans cells, J Immunol, 121:2005.

Streilein JW and Bergstresser PR (1981): Langerhans cell function dictates induction of contact hypersensitivity or unresponsiveness to DNFB in Syrian hamsters, J Invest Dermatol, 77:272.

Streilein JW, Sullivan S and Thompson S (1980): Contact hypersensitivity, humoral immunity, and specific unresponsiveness can be induced in Syrian hamsters with simple haptens, J Immunol, 124:577.

Tamaki K, Fujiwara H and Katz SI (1981): The role of epidermal cells in the induction and suppression of contact sensitivity, J Invest Dermatol, 76:275.

Thomas DW, Forni G, Shevach EM and Green I (1977): The role of the macrophage as the stimulator cell in contact sensitivity, J Immunol, 118:1677.

Toews GB, Bergstresser PR and Streilein JW (1980): Epidermal Langerhans cell density determines whether contact hypersensitivity on unresponsiveness follows skin painting with DNFB, J Immunol, 124:445.

Vadas MA, Miller JFAP, Gamble J and Whitelaw A (1975): A radioisotopic method to measure delayed type hypersensitivity in the mouse. I. Studies in sensitized and normal mice, Int Archs Allergy Appl Immunol, 49:670.

Valsecchi R, Bontempelli M, Vicari O, Scudeller G, Cainelli T (1982): HLA Antigens and contact sensitivity. Arch Dermatol 118:553-554.

Van Scott EJ and Kalmanson JD (1973): Complete remission of mycosis fungoides lymphoma induced by topical nitrogen mustard: Control of delayed hypersensitivity to HN_2 by desensitization and by induction of specific immune tolerance. Cancer 32:18-30.

Vonderheid EC, Van Scott EJ and Wallner PE, et al. (1979): A 10-year experience with topical mechlormethamine for mycosis fungoides. Comparison with patients treated by total skin electron beam irradiation therapy. Cancer Treat Rep 63:681-689.

Vonderheid EC, Dellatorre DL and Van Scott EJ (1981): Prolonged remission of tumor-stage mycosis fungoides by topical immunotherapy. Arch Dermatol 117:586-589.