

Continuing Medical Education

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Atopic dermatitis: The skin as a window into the pathogenesis of chronic allergic diseases

Donald Y. M. Leung, MD, PhD *Denver, Colo.*

Atopic dermatitis (AD) is a chronic inflammatory skin disease frequently seen in patients with a history of respiratory allergy.^{1,2} Population studies suggest that the prevalence of AD in children has been increasing since World War II and that 10% to 15% of the population is affected by AD at some point during childhood.³ In patients with moderate to severe AD, involvement can be lifelong, causing significant interference with school, work, and social interactions. Atopic hand dermatitis is the major cause of work-related disability caused by skin disease.⁴ At present, there are no treatments directed at the basic cause of AD. An understanding of the mechanisms that underlie chronic AD is critical for the development of newer, more effective management of this common illness.

The term, *atopic dermatitis*, was introduced in 1933 by Hill and Sulzberger⁵ in recognition of the close association between AD and respiratory allergy. However, there has been considerable debate over whether AD is primarily an allergen-induced disease or simply an inflammatory skin disorder found in association with asthma and allergic rhinitis. In part, this controversy may have been fueled by the easier accessibility of skin to histologic examination. Early studies of skin biopsy specimens from patients with AD revealed marked tissue inflammation.⁶ Because the primary patho-

Abbreviations used

AD:	Atopic dermatitis
CLA:	Cutaneous lymphocyte antigen
DBPCFC:	Double-blind placebo-controlled food challenge
DTH:	Delayed-type hypersensitivity
GM-CSF:	Granulocyte-macrophage colony-stimulating factor
ICAM-1:	Intercellular adhesion molecule-1
IFN- γ :	Interferon- γ
LPR:	Late-phase reaction
MBP:	Major basic protein
PBMCs:	Peripheral blood mononuclear cells
PGE ₂ :	Prostaglandin E ₂
SE:	Staphylococcal enterotoxin
TNF:	Tumor necrosis factor
VCAM-1:	Vascular cell adhesion molecule-1

logic process in asthma during the 1970s was thought to be "smooth muscle bronchospasm," the observation of inflammation in AD was often used as an argument against the allergic nature of this illness.

Studies of bronchial biopsy specimens from asthmatic patients have now established that airway inflammation plays a more critical role than the bronchospastic component in contributing to the chronicity of respiratory symptoms in asthma.⁷ It is therefore important to reassess our thinking about the primary mechanisms that underlie AD. Indeed, recent data strongly suggest that AD is an allergic disorder with striking parallels to asthma but involving a different regional sphere of immunologic influence, that is, the skin-associated lymphoid tissue as opposed to bronchial associated lymphoid tissue.

The genetic predisposition to develop IgE-mediated responses may be similar in patients with AD and patients with asthma. However, targeting

From the Division of Pediatric Allergy-Immunology, The National Jewish Center for Immunology and Respiratory Medicine, Department of Pediatrics, University of Colorado Health Sciences Center, Denver.

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Reprint requests: Donald Y. M. Leung, MD, PhD, Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson St., Denver, CO 80206.

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of the allergic immune response may relate to the organ in which allergen sensitization initially occurs, the capacity of immune effector cells (e.g., T lymphocytes) to home differentially to the skin versus the respiratory mucosa, and the programmed response of resident cells (e.g., epithelial cells) to injury and inflammation. This review examines the cellular and immunologic mechanisms that are believed to play an important role in the pathogenesis of chronic AD. An understanding of the immunologic basis of AD is likely to have important clinical implications in our approach to the management of this common illness. Because the skin is readily accessible for tissue analysis, lessons learned from the immunopathogenesis of AD may also provide important insights into mechanisms that may contribute to chronic tissue inflammation in other allergic diseases, such as asthma.

CLINICAL FEATURES OF AD

The diagnosis of AD is based on the constellation of clinical features summarized in Table I.^{1,2} AD usually begins during infancy. In approximately 50% of patients this illness develops by the first year of life, and in an additional 30%, between the ages of 1 and 5 years. In nearly 80% of patients with AD allergic rhinitis or asthma eventually develops later in childhood. Many of these patients outgrow their AD as respiratory allergy develops. This intriguing clinical observation is consistent with the concept that the clinical expression of allergic disease is determined in part by local tissue allergen sensitization and compartmentalization of the immune response in the skin versus the respiratory mucosa.

Skin reaction patterns in AD

Intense pruritus and cutaneous reactivity are the hallmarks of AD. In 1891, the French dermatologist Jacquet first suggested that it was not the rash that itches but the itching that was the initial event. Subsequently, in 1936, while observing children undergoing food challenges Engman noted that skin trauma inflicted by scratching played an important role in the evolution of eczema.⁸ In this regard, if the skin could be protected from scratching, the eczematoid rash could be prevented, although the patient would continue to have extreme pruritus.

Scratching may be intermittent throughout the day, but it is usually worse in the early evening and at night. Disruption of normal sleep patterns is a common problem afflicting patients with chronic

TABLE I. Diagnostic features of AD

Major features

- Pruritus and excoriations
- Typical appearance and distribution of skin lesions
 - Facial and extensor involvement in infancy and early childhood
 - Flexural involvement and lichenification by adolescence
- Chronic or frequently relapsing course (duration >6 weeks)
- Personal or family history of AD, allergic rhinoconjunctivitis, food allergy, or asthma

Minor features

- Increased susceptibility to skin infections, particularly *S. aureus*
- Xerosis (dryness of the skin)
- Early age of onset
- Multiple positive immediate prick skin test results
- Ichthyosis, keratosis pilaris, hyperlinearity of palms
- Nonspecific hand/foot dermatitis
- Scalp dermatitis (e.g., cradle cap)
- Elevated serum IgE levels

Modified from Hanifin and Rajka. *Acta Derm Venereol* 1980; 92:44-7.

AD. The pathogenesis of cutaneous pruritus is poorly understood. Experimentally, pruritus can be induced by intradermal injection of various products of inflammatory effector cells such as histamine, leukotrienes, and proteolytic enzymes. Patients with AD also have a reduced threshold for pruritus.⁹ Clinically, this is supported by the observation that allergens, reduced humidity, excessive sweating, and irritants (e.g., wool, acrylic, soaps, and detergents) can exacerbate pruritus and scratching.

A recent study by Nassif et al.¹⁰ used 48-hour Finn chamber testing with graded dilutions of sodium lauryl sulfate to determine irritation thresholds in patients with AD compared with patients with either inactive AD or allergic respiratory disease with no dermatitis and normal nonatopic subjects. Patients with active AD showed significantly greater irritant skin responses than the two control groups. Of interest, even patients with inactive AD and respiratory allergy had increased irritation compared with normal control subjects. Thus the "atopic skin" is generally associated with a lowered threshold of irritant responsiveness.

Several skin lesions are commonly seen in AD. *Acute* lesions are characterized by intensely pruritic, erythematous papules over erythematous skin. These are associated with extensive excoriations, erosions, and serous exudate. *Subacute* der-

matitis is characterized by erythematous, excoriated, scaling papules. *Chronic* dermatitis is characterized by thickened skin, accentuated skin markings (lichenification), and fibrotic papules. In chronic AD, all three stages of skin reactions frequently coexist in the same patient. At all stages of AD, patients usually manifest dry, lackluster skin. Distribution and skin reaction pattern vary according to the patient's age and disease chronicity. During infancy, AD is generally more acute and primarily involves the face, scalp, and extensor surfaces of the extremities. In older patients who have long-standing skin disease, the skin develops the chronic form of dermatitis with lichenification and localization of the rash to the flexural folds of the extremities.

Role of allergens in AD

Serum IgE levels are elevated in 80% to 85% of patients with AD. Approximately 85% of patients have positive immediate skin test or RAST results for specific IgE in response to a variety of food and inhalant allergens.^{11, 12} However, a direct relationship between immediate skin test reactivity to implicated allergens and the course of AD has been difficult to establish. In this regard, positive immediate skin test responses to specific allergens do not always indicate clinical sensitivity, and patients who outgrow AD frequently continue to have positive skin test responses. Indeed, May¹³ first made a distinction between *symptomatic* and *asymptomatic hypersensitivity* on the basis of the observation that patients with AD and positive food skin test results did not always have positive challenge responses to the foods implicated by IgE responses. These clinical observations suggest that the relationship between IgE and clinical disease is not exclusively dependent on IgE-mediated mast cell degranulation.

Well-controlled studies have, however, demonstrated that food allergens can exacerbate skin rashes in at least a subset of patients with AD. In 1978, Bock et al.¹⁴ first documented the role of foods in AD by using a double-blind, placebo-controlled food challenge (DBPCFC). They studied 68 children, mostly with asthma, who reported adverse reactions to foods. Twenty-nine children had positive DBPCFC results. Symptoms induced included eczema, wheezing, and vomiting within 2 hours of the oral challenge. Subsequently, Jones and Sampson¹⁵ studied 326 patients referred for treatment of AD and possible food allergy. In this tertiary referral group, 80% of patients had a reaction to at least one food during the DBPCFC,

and 75% of the food reactions involved the skin.¹⁵ These skin reactions developed within 2 hours of challenge and were characterized by acute pruritus, erythema, or morbilliform rashes. Although these lesions resolved within 3 hours, some patients had pruritus and macular reactions 6 to 8 hours later. Patients who experienced several such reactions during a week of DBPCFCs had eczematous skin lesions. This suggested that repeated ingestion of foods and the scratching that resulted from such exposure contributes to the development of AD skin lesions. Eggs, milk, peanuts, soy, and wheat accounted for almost 75% of positive food challenge results.

Although the data linking food allergy to AD is convincing, the majority of patients, particularly adults, do not have food allergy. Thus there has also been considerable interest in the potential role of inhalant allergens. In 1918, Walker¹⁶ first reported on several patients who had flare-ups of AD on exposure to horse dander, timothy grass, or ragweed pollen. In the 1950s, Tuft et al.¹⁷ demonstrated that in patients with AD, pruritus and eczematoid skin lesions developed after inhalation challenge with either *Alternaria* species or ragweed pollen, but not after placebo challenges.¹⁸ Further studies have examined the role of direct contact with inhalants in the development of skin lesions. In a group of patients with IgE antibodies to dust mite, Mitchell et al.¹⁹ reported that patch testing of abraded skin with mite extract resulted in an eczematous rash. Subsequently, Clark and Adinoff²⁰ reported that positive patch test results on nonabraded skin of patients with AD could be elicited in response to a variety of inhalant allergens including dust mite, weeds, animal danders, and molds. These investigators as well as Platts-Mills et al.,²¹ have reported that avoidance of aeroallergens that elicit an eczematous reaction at patch test sites or cause immediate hypersensitivity reactions results in clinical improvement of AD. Environmental rechallenge with suspected allergens resulted in exacerbations of AD.

These clinical studies suggest that inhalation or contact with aeroallergens may play a role in the exacerbation of AD. Laboratory data supporting a role for inhalants as triggers of AD include the finding of IgE antibody to specific inhalant allergens in a large subset of patients with AD and the isolation from AD skin lesions of IL-4-secreting T cells that recognize *Dermatophagoides pteronyssinus* (Der p 1).^{22, 23} Better-controlled trials, however, are needed to examine the sensitivity and specificity of patch testing with inhalants. It is particularly important to

determine whether positive patch test reactions to inhalants are really predictive of clinical sensitivity to inhalants and whether elimination of inhalants from the environment results in clinical resolution or amelioration of skin disease.

Cutaneous infections

Patients with AD have an increased tendency to develop viral, fungal, and bacterial skin infections.²⁴ These infections are generally localized to the skin. Deep-seated infections suggest the possibility of hyperimmunoglobulinemia E syndrome or another immunodeficiency syndrome.²⁵ Viral infections include herpes simplex, vaccinia, warts, molluscum contagiosum, and papilloma virus. The most common viral infection is herpes simplex, which tends to spread locally but can become generalized. Superficial fungal infections also appear to occur more frequently in atopic individuals. Jones et al.²⁶ found a threefold increased frequency of *Trichophyton rubrum* skin infections among patients with AD compared with nonatopic control subjects. Recurrence of dermatophyte infections have occasionally been documented to coincide with exacerbation of AD. Recently, there has been considerable interest in *Pityrosporum ovale* as a pathogen in AD. *P. ovale* is a lipophilic yeast commonly present in the seborrheic areas of the skin. In one series, IgE antibodies against *P. ovale* were found in two thirds of patients with AD and were more frequent in patients with head and neck dermatitis.²⁷ The potential importance of these dermatophyte infections is suggested by the reduction of AD severity after treatment with antifungal agents, such as ketoconazole.²⁷

Perhaps the greatest attention has been focused on the contribution of *Staphylococcus aureus* colonization and infection to the severity of AD. Leyden et al.²⁸ found *S. aureus* in over 90% of AD skin lesions. In contrast, only 5% of normal subjects harbor this organism, and its localization is mainly in the nose and intertriginous areas.²⁹ The density of *S. aureus* on inflamed AD lesions without clinical superinfection can reach 10^7 colony-forming units per square centimeter on lesional skin.³⁰ Honey-colored crusting, extensive serous weeping, folliculitis, and pyoderma indicate bacterial infection usually caused by *S. aureus* in patients with AD. The importance of *S. aureus* in AD is supported by the observation that not only patients with impetiginized AD, but also patients who have AD without superinfection show clinical response to combined treatment with antistaphylococcal antibiotics and topical corticosteroids.³¹

Recent studies suggest that *S. aureus* exacerbates or maintains skin inflammation in AD by secreting a group of toxins known to act as superantigens, which stimulate marked activation of T cells and macrophages.^{32,33} Because staphylococcal enterotoxins (SEs) are globular proteins of 24 to 30 kd, the possibility that they act as allergens was investigated.³² In this regard, it has been found that nearly half of patients with AD produce IgE directed to staphylococcal toxins, particularly SEA, SEB, and toxic shock syndrome toxin-1. This is of interest because staphylococci isolated from AD skin lesions predominantly secrete one of these three exotoxins.

To study the potential functional role of IgE antistaphylococcal toxins, the capacity of SEs to induce histamine release from freshly isolated basophils of normal subjects and patients with AD was investigated. Basophils from normal subjects and patients with AD who lack IgE antitoxin failed to release any histamine on exposure to the various staphylococcal exotoxins. In contrast, basophils from patients with AD, who produce IgE antitoxin, release histamine on exposure to the relevant exotoxin but not in response to exotoxins in which there is no IgE response.³² These findings suggest the possibility that local production of SEs at the skin surface could cause IgE-mediated histamine release and thereby trigger the itch-scratch cycle, which can exacerbate AD.

THE IMMUNOLOGIC NATURE OF AD

The concept that AD has an immunologic basis is supported by the observation that patients with primary T-cell immunodeficiency disorders frequently have elevated serum IgE levels and eczematoid skin lesions that are indistinguishable from AD.³⁴ In patients with Wiskott-Aldrich syndrome, clearing of the skin rash occurs after correction of the immunologic defect by successful bone marrow transplantation.³⁵ Furthermore, nonatopic recipients of bone marrow transplants from atopic donors have been reported to have positive immediate skin test results and atopic symptoms after successful engraftment.³⁶ These data suggest that AD is not due to a constitutive skin defect but is mediated by a bone marrow-derived cell.

A number of laboratory observations suggest an underlying immunoregulatory abnormality in AD (Table II). These include studies that demonstrate that peripheral blood mononuclear cells (PBMCs) from patients with AD are decreased in CD8⁺ suppressor/cytotoxic T cell number and function.^{37,38} McCoy et al.³⁹ have also found a decrease

TABLE II. Immunologic features of AD

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- Increased IgE production
 - Immediate skin test reactivity to multiple allergens
 - Increased basophil spontaneous histamine release
 - Decreased CD8 suppressor/cytotoxic number and function
 - Increased expression of CD23 on mononuclear cells
 - Chronic macrophage activation with increased secretion of GM-CSF, PGE₂, and IL-10
 - Expansion of IL-4- and IL-5-secreting T_{H2}-like cells
 - Decreased numbers of IFN- γ -secreting T_{H2}-like cells
-

in cytotoxic CD8⁺ T cells expressing S6F1^{bright}. The latter may partially account for the increased frequency of viral infections in patients with AD. The relative lack of suppressor T-cell activity in AD is associated with evidence of concomitant cellular activation; that is, serum levels of soluble IL-2 receptor are elevated in patients with symptoms.⁴⁰

B cells and monocytes from patients with AD express increased levels of CD23 (low-affinity IgE receptor). Functional activation of these two cell types is supported by the observation that peripheral blood B cells from patients with AD spontaneously produce high levels of IgE, and AD monocytes are primed for superoxide generation.^{41, 42} Because IL-4 plays an important role in the induction of IgE synthesis, as well as CD23 expression on B cells and monocytes, these observations suggest that AD is associated with increased secretion of IL-4 *in vivo*. In this regard, it has been found that the increased spontaneous production of IgE *in vitro* by lymphocytes from patients with AD can be inhibited by the addition of anti-IL-4.^{41, 43} Furthermore, lymphocytes from patients with AD have been reported to secrete increased amounts of IL-4 and to express abnormally high levels of IL-4 receptor.^{41, 44} PBMCs from patients with AD have also been found to have a decreased capacity to produce interferon- γ (IFN- γ) in response to a number of stimuli.^{45, 46} A significant inverse correlation between IFN- γ generation *in vitro* and IgE serum concentrations *in vivo* in AD has been reported.⁴⁵

Studies of T-cell clones support the concept that activation of a subpopulation of helper cells leads to the release of cytokines important in the pathogenesis of AD. In mice, two types of CD4⁺ T-cell clones have been described on the basis of their pattern of cytokine secretion.⁴⁶ T helper type 1 (T_{H1}) cells secrete IL-2 and IFN- γ but not IL-4 or IL-5. In contrast, T_{H2} cells produce IL-4 and IL-5

but not IFN- γ . Both subpopulations of T cells produce IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). IL-4 acts as an IgE isotype-specific switch factor⁴⁷ and induces the expression of vascular cell adhesion molecule-1 (VCAM-1), an adhesion molecule involved in the migration of mononuclear cells and eosinophils into sites of tissue inflammation.⁴⁸ IL-5 promotes the differentiation, vascular endothelial adhesion, and survival of eosinophils and also enhances histamine release from basophils.⁴⁹ In contrast, IFN- γ inhibits IgE synthesis, as well as the proliferation of T_{H2} lymphocytes.^{50, 51}

The lack of IFN- γ production, as well as the concomitant activation of IL-4 and IL-5, is thought to play a critical role in the pathogenesis of AD. In support of the concept that this profile of cytokines arises from the selective activation of T_{H2} as compared with T_{H1} cells are a number of studies demonstrating increased frequency of allergen-specific T cells producing increased IL-4 and IL-5, but little IFN- γ in the peripheral blood and skin lesions of patients with AD.^{22, 23, 52, 53} IL-4 has also been demonstrated to cause marked inhibition of IFN- γ production and downregulate the differentiation of T_{H1} cells.⁵⁴ In addition, atopic monocytes have been found to have elevated cyclic adenosine monophosphate phosphodiesterase and secrete increased levels of IL-10 and prostaglandin (PG) E₂.^{53, 55} Both IL-10 and PGE₂ inhibit IFN- γ production and may therefore contribute to the decreased IFN- γ production by cultured AD PBMCs.

The activation of T_{H2} cells and monocytes may have important pathogenetic roles in the immune dysfunction that characterizes AD. Although T_{H2} cells promote IgE responses, they are less involved in T cell-mediated reactions. Furthermore, IL-10 is known to inhibit T cell-mediated reactions, and thus along with the infiltration of T_{H2} cells into AD skin, may account for the increased susceptibility to cutaneous viral infections and dermatophytosis but reduced allergic contact sensitivity reactivity.⁵⁶ In addition, IL-10 is known to inhibit cell-mediated immunity to bacterial pathogens, and along with the defective skin barrier in these patients, may account for their susceptibility to frequent bacterial skin infections.⁵⁷

IMMUNOPATHOLOGY OF AD

Histologic features of AD

The histologic features of AD depend on the acuity and therefore the duration of the skin lesion.^{58, 59} *Uninvolved* or clinically normal skin of patients with AD is histologically abnormal and

demonstrates mild hyperkeratosis, epidermal hyperplasia, and a sparse dermal cellular infiltrate consisting primarily of lymphocytes. *Acute* lesions are characterized by marked intercellular edema (spongiosis) of the epidermis and intracellular edema, noted as ballooning of the keratinocytes. A sparse epidermal infiltrate, consisting primarily of lymphocytes, is frequently observed. In the dermis there is a marked perivenular inflammatory cell infiltrate consisting predominantly of lymphocytes and occasional monocyte-macrophages. Eosinophils, basophils, and neutrophils are rarely present in the acute lesion. Mast cells, in various stages of degranulation, are present in normal numbers.

In *chronic* lichenified lesions, the epidermis is hyperplastic with elongation of the rete ridges, prominent hyperkeratosis, and minimal spongiosis. There is an increased number of Langerhans' cells in the epidermis, and macrophages dominate the dermal mononuclear cell infiltrate. Mast cells are increased in number but are generally fully granulated. Endothelial cells of the superficial venular plexus and deep venules are hypertrophied with enlarged nuclei and prominent nucleoli. A prominent finding in the lichenified plaque is fibrosis of the upper dermis.

Immunophenotype of cells in AD skin

T cells. Immunohistochemical staining of acute and chronic skin lesions of patients with AD with monoclonal antibodies has demonstrated that the lymphocytic infiltrate consists predominantly of memory T cells bearing CD3, CD4, and CD45 RO (suggesting a previous encounter with antigen).^{59, 60} This subset of helper T cells appears to have undergone intralesional activation because these helper T cells express CD25 and HLA-DR on their surfaces. Essentially all T cells infiltrating the skin lesion express high levels of cutaneous lymphocyte antigen (CLA), which functions as a skin homing receptor for T lymphocytes.^{61, 62} CLA is thought to comprise a sialylated carbohydrate structure, probably a sialylated form of Lewis x (sLe^x) that is closely related to the major neutrophil oligosaccharides representing the sLe^x ligand for E-selectin.

Endothelial cells. Vascular endothelial cells in AD skin lesions express abnormally high levels of E-selectin, VCAM-1, and intercellular adhesion molecule (ICAM-1).⁶³ The induction of E-selectin by IL-1 and tumor necrosis factor (TNF)- α on vascular endothelium is thought to play the primary role in targeting skin-homing T cells expressing the CLA to cutaneous sites of inflammation, such as AD skin lesions.⁶⁴ Subsequent transmigration

of memory CLA⁺ T cells into inflamed skin is likely modulated by leukocyte function associated antigen-1/ICAM-1 and very late antigen-4/VCAM-1 interactions.⁶⁵ VCAM-1, which is induced by IL-4 and IL-13,⁶⁶ is also involved in the migration of eosinophils and mononuclear cells into sites of allergic inflammation.

Langerhans' cells. Increased numbers of Langerhans' cells expressing CD1b, CD36, and HLA-DR surface antigens are present in the dermis and epidermis of chronic AD as compared with acute AD skin lesions.^{59, 67} Epidermal Langerhans' cells do not express CD1b and CD36 in normal skin. Functional evidence that Langerhans' cells from AD skin express an activated phenotype is suggested by the observation that AD lesional epidermal cells induce an accelerated autologous T-lymphocyte reaction.⁶⁷ Langerhans' cells, as well as macrophages infiltrating the AD skin lesion, have also been found to have surface-bound IgE molecules.^{68, 69}

Keratinocytes. In AD skin lesions, keratinocytes show evidence of cytokine-induced activation. In this regard, increased levels of ICAM-1 are expressed on keratinocytes from AD lesions.⁷⁰ CD36 and CD1a have also been observed on AD epidermal keratinocytes.⁷¹ In contrast to allergic contact dermatitis, however, epidermal keratinocytes in AD lesions do not express HLA-DR.⁷²

Eosinophils. Increased numbers of eosinophils are observed in chronic but not acute AD skin lesions.⁷³ In support of a functional role of eosinophils in chronic AD lesions, Leiferman et al.⁷⁴ have found that eosinophil-derived extracellular major basic protein (MBP) can be detected by immunofluorescence in a fibrillar pattern associated with the distribution of elastic fibers throughout the upper dermis. In more than half of AD specimens examined, they also found MBP deposition in a granular pattern deeper in the dermis. Extracellular MBP deposition was much more extensive in the involved areas than in the uninvolved areas of skin. Although the role of MBP in the pathogenesis of AD is not completely understood, it is thought to contribute to tissue injury in AD through its cytotoxic properties and its capacity to induce basophil and mast cell degranulation. Its capacity to produce profibrogenic cytokines, such as transforming growth factors, may also contribute to dermal fibrosis.⁵⁰ Eosinophil cationic protein is elevated in sera of patients with AD and correlates with disease severity, providing further evidence for eosinophil activation and involvement in AD.⁷⁵

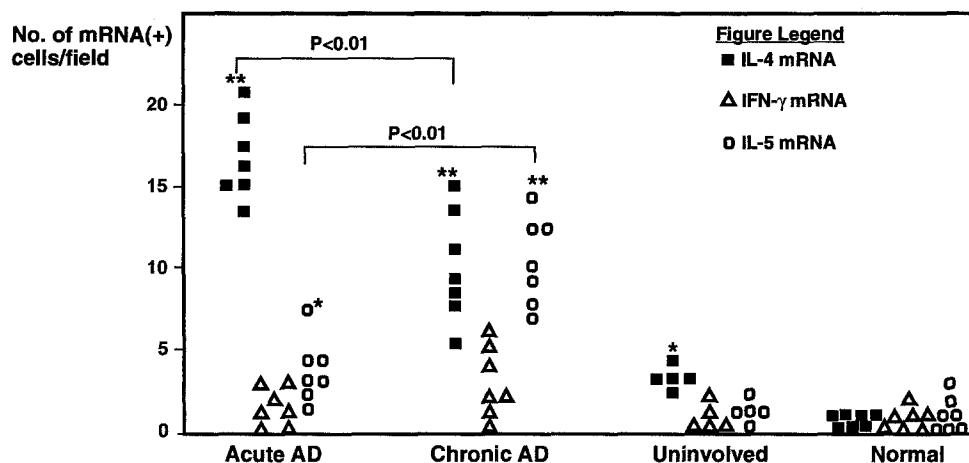


FIG. 1. In situ cytokine mRNA expression in AD skin lesions versus normal skin. Reproduced with permission from Hamid et al. *J Clin Invest* 1994;94:870-6.

Patterns of cytokine expression in AD skin lesions

The pattern of cytokines, expressed locally, plays a critical role in modulating the nature of tissue inflammation. Therefore an analysis of cytokine expression in AD is critically dependent on the acuity or duration of the skin lesion. In a recent study, Hamid, et al.⁷³ used in situ hybridization to investigate the expression of IL-4, IL-5, and IFN- γ messenger RNA in skin biopsy specimens from clinically normal (uninvolved), acute (erythematous AD lesions of <3 days' duration) and chronic (>2 weeks' duration) skin lesions of patients with AD (Fig. 1). As compared with normal control skin, uninvolved skin of patients with AD had a significant increase in number of cells expressing IL-4 but not IL-5 or IFN- γ mRNA. Acute and chronic skin lesions, when compared with normal skin or uninvolved skin of patients with AD, had significantly greater numbers of cells that were positive for mRNA for IL-4 and IL-5. However, neither acute AD nor uninvolved AD skin contained significant numbers of IFN- γ mRNA-expressing cells.

As compared with acute AD lesions, chronic AD skin lesions had significantly fewer IL-4 mRNA-expressing cells but significantly more IL-5 mRNA-expressing cells. T cells constituted the majority of IL-5-expressing cells in acute and chronic AD lesions. Chronic lesions also expressed significantly greater numbers of activated IL-5 mRNA-expressing eosinophils than acute lesions. These data indicate that although cells in acute and chronic AD lesions are associated with increased activation of IL-4 and IL-5 genes, acute skin inflammation in AD is associated with a

predominance of IL-4 expression, whereas maintenance of chronic inflammation is predominantly associated with increased IL-5 expression and eosinophil infiltration. In addition, recent studies have demonstrated overexpression of GM-CSF and IL-10 expression in chronic AD lesions.^{55, 76}

AD SKIN INFLAMMATION: A MULTIFUNCTIONAL ROLE FOR IgE

Although routine histologic examination of the skin lesion in AD shows a close resemblance to a type IV delayed-type hypersensitivity (DTH) reaction, several lines of evidence indicate that AD is not a conventional DTH reaction and also that IgE-mediated mechanisms play a role in the pathogenesis of AD. T cells that infiltrate into conventional DTH skin reactions (e.g., tuberculin skin reactions) secrete IFN- γ and therefore induce the expression of HLA-DR on skin keratinocytes.⁷⁷ In contrast, keratinocytes in the AD skin lesion do not express HLA-DR.⁷² More direct evidence that the T cells in skin lesions of AD differ from the T_{H1} cells in conventional DTH reactions has come from studies demonstrating that allergen-specific T_{H2} -type lymphocytes can be cloned from skin lesions of patients with AD^{22, 23} and from in situ hybridization studies demonstrating increased IL-4 and IL-5 but not IFN- γ mRNA expression in acute AD skin lesions.⁷³ Furthermore, studies by Müller et al.⁷⁸ have demonstrated that T_{H2} cells are just as effective in inducing skin inflammation as T_{H1} cells. However, the mediation of skin inflammation by T_{H2} cells is IL-4- but not IFN- γ -dependent. Taken together, these data suggest that two histologically indistinguishable cutaneous DTH reactions exist. The first is mediated by IFN- γ -secret-

ing T_{H1} cells found in conventional DTH reactions. The second is mediated by IL-4- and IL-5-secreting T_{H2} cells and involves allergen-induced cell-mediated reactions.

IgE molecules can contribute to the induction of a mononuclear cell infiltrate by several mechanisms. In this regard, clinically significant allergen-induced reactions are associated with an IgE-dependent biphasic response.⁷⁹ In such reactions, after exposure to allergen, mast cells bearing IgE directed to the relevant allergen release various mediators, cytokines, and leukocyte chemotactic factors into local tissue within 15 to 60 minutes of allergen challenge. This immediate reaction likely contributes to the acute pruritus and erythema observed after exposure of patients with AD to relevant food and inhalant allergens.

Three to four hours after this immediate reaction begins to subside, onset of an IgE-dependent late-phase reaction (LPR), characterized initially by expression of leukocyte adhesion molecules on postcapillary venular endothelium, occurs and is followed by the infiltration of eosinophils, neutrophils, and mononuclear cells into the inflamed area.⁸⁰ Granulocytes reach their maximum cell accumulation at 6 to 8 hours, and by 24 to 48 hours after onset of the reaction, the cellular infiltrate consists predominantly of mononuclear cells. Using *in situ* hybridization, Kay et al.⁷ have reported that the cellular infiltrate in allergen-induced late-phase skin reactions expresses increased mRNA for IL-3, IL-4, IL-5, and GM-CSF, but no mRNA for IFN- γ . These results suggest that the T cells infiltrating the allergen-induced LPR, similar to allergen-specific T cells grown from AD skin lesions, are T_{H2} -like cells.

It has also been demonstrated that LPRs are associated with the release of cytokines, such as IL-1 and TNF.⁸¹ These cytokines, along with IL-4, play an important role in the induction of leukocyte adhesion molecules.⁸² Of note, the AD skin lesion, as well as the cutaneous LPR, is associated with the expression of leukocyte adhesion molecules such as endothelial leukocyte adhesion molecule-1 (E-selectin), VCAM-1, and ICAM-1.⁶³ More importantly, the induction of adhesion molecules, such as E-selectin, in allergen-stimulated atopic skin can be blocked by neutralizing antibodies to IL-1 and TNF.⁸⁰ Thus the release of these cytokines likely represents an important initiating event in the local accumulation of inflammatory cells at the site of allergic reactions.

Additional evidence of the importance of IgE-mediated mechanisms in AD can be derived from

studies by Sampson et al.⁸³ of patients with AD and food hypersensitivity. These investigators have demonstrated that plasma histamine levels rise in children after positive oral food challenges but not after placebo challenges. Sampson et al.⁸⁴ also reported higher rates of spontaneous histamine release from basophils in patients with AD and food hypersensitivity compared with control subjects. The increased spontaneous basophil histamine release was dependent on continued ingestion of offending food allergens. More importantly, elimination of implicated food allergens from these patients' diets resulted in amelioration of skin disease and reduction of spontaneous basophil histamine release. Mononuclear cells from patients with food allergy produced an IgE-dependent histamine-releasing factor *in vitro*, which provoked histamine release from basophils of other food-sensitive patients, but not from normal control subjects. Furthermore, patients with severe AD and food allergy were found to have increased basophil releasability of histamine compared with patients with mild AD.⁸⁵

Langerhans' cells and macrophages infiltrating the AD skin lesion bear IgE antibody on their surfaces.^{68, 69} Binding of IgE to Langerhans' cells occurs through both high-affinity and low-affinity IgE receptors.^{86, 87} Macrophages can express low-affinity IgE receptors (CD23) in response to IL-4 or GM-CSF.^{87, 88} Allergens have been demonstrated to activate IgE-bearing macrophages in an IgE-dependent manner with the formation of leukotrienes, platelet activating factor, IL-1, and TNF.^{89, 90} Patients with AD also have circulating autoantibodies to IgE, which can also activate macrophages bearing IgE.⁹¹ The activation of IgE-bearing Langerhans' cells and macrophages by allergens and autoantibodies to IgE could thus contribute to the skin inflammation associated with AD. Although IgE-bearing Langerhans' cells and macrophages have been found in other inflammatory skin diseases such as psoriasis, these other skin conditions are not associated with the production of allergen-specific IgE. Thus the expression of IgE-bearing Langerhans' cells in these inflammatory skin conditions may not have the same immunologic consequences as in AD.

In addition, there is mounting evidence that IgE-bearing Langerhans' cells in AD skin play an important role in cutaneous allergen presentation to T_{H2} cells. Of note, IgE-bearing Langerhans' cells from AD skin lesions, but not Langerhans' cells lacking surface IgE, are capable of presenting house dust mite allergen to T cells.⁹² These results suggest that

cell-bound IgE on Langerhans' cells facilitates binding of allergens to Langerhans' cells before processing and antigen presentation. Furthermore, CD4⁺ T cells, repeatedly stimulated with Langerhans' cells, appear to preferentially differentiate into T_{H2} cells.⁹³

Although allergen challenges and experimental models suggest the participation of specific mechanisms of inflammation, it should be emphasized that an analysis of the AD skin lesion does not allow simple classification discretely into an IgE-mediated LPR or a T cell-mediated immune reaction. Thus in all likelihood, the mononuclear cell infiltrate in the AD skin lesion reflects a combination of both IgE-dependent mast cell or basophil degranulation and T_{H2} cell-mediated responses elicited during acute exposures to allergen and other antigens or superantigens.

Finally, although the release of a variety of mediators (e.g., histamine) and proteases into the skin after challenge with allergens triggers acute pruritus in patients with AD, clinical studies have clearly demonstrated that the actual development of eczematoid skin rashes is dependent on the skin trauma inflicted by scratching.⁸ Once the itch-scratch cycle is triggered, the mechanisms by which scratching promotes inflammation of the skin are suggested by a number of recent observations, which demonstrate that the keratinocyte is an important epidermal source of cytokines including IL-1, IL-6, IL-8, GM-CSF, and TNF- α .⁹⁴ In this regard, any injury, including mechanical trauma to the keratinocyte, will result in the release of cytokines, which can induce inflammation through a number of actions.⁹⁵ This includes the release of IL-1, TNF- α , and IL-4, which are critical cytokines in the induction of adhesion molecules (such as ELAM-1, ICAM-1, and VCAM-1) that attract lymphocytes, macrophages, and eosinophils to cutaneous sites of inflammation.^{49, 82} At this stage many different resident and infiltrating cells are then capable of secreting cytokines and mediators that sustain the inflammation. AD therefore results from a combination of different specific and nonspecific cellular mechanisms, which serve to trigger and maintain skin inflammation.

AD AS A SKIN-DIRECTED T_{H2}-LIKE CELL RESPONSE

Taken together, these data suggest that AD is an allergic disorder with important parallels to asthma. Both diseases have in common the local infiltration of T_{H2}-like cells in response to allergen, IgE responses to specific allergens, the development of chronic local tissue inflammation, and the

presence of organ-specific (cutaneous vs bronchial) hyperreactivity that is likely related to underlying tissue inflammation. Recent paradigms of the pathogenesis of allergic diseases have suggested that memory T_{H2}-like cells producing IL-4 and IL-5 play a critical role in the induction of local IgE responses and the recruitment of eosinophils into the bronchial airways of patients with asthma or into the skin lesions of patients with AD.^{73, 96}

The potential mechanisms that determine tissue specificity of T-cell responses in different allergic diseases are therefore of particular interest. In this regard, studies in animal models have demonstrated clear heterogeneity in the ability of memory T lymphocytes to migrate to mucosal versus nonmucosal tissues.⁶² This tissue-selective homing is regulated in large part at the level of T-lymphocyte recognition of vascular endothelial cells through the interaction of differentially expressed T-lymphocyte homing receptors and their endothelial cell ligands. In human beings lymphocyte/endothelial cell adhesion molecule pairs believed to participate in "tissue-selective" lymphocyte homing include the skin-selective homing receptor called CLA and the peripheral lymph node homing receptor, L-selectin.^{62, 97, 98}

It has been found that T cells migrating into the skin are highly enriched for the CLA-expressing memory/effector T-cell subset, whereas memory/effector T cells isolated from the airways of patients with asthma are predominantly CLA-negative.⁹⁹ Thus the propensity of a given individual to have AD, as opposed to asthma, may depend on differences in the skin- versus lung-seeking behavior of their memory/effector T cells. Children with food-induced AD provide a unique opportunity for determining whether there is a relationship between the tissue specificity of a clinical reaction to an allergen and the expression of homing receptors on T cells activated in vitro by the relevant allergen. To this end, we recently assessed the expression of CLA and L-selectin on peripheral blood T cells from patients with AD and milk-induced eczema and compared their homing receptor expression, at baseline and after stimulation with casein, with T cells collected from patients who had allergic eosinophilic gastroenteritis or milk-induced enterocolitis or with nonatopic healthy control subjects.¹⁰⁰ We found that the casein-reactive T cells from patients with milk-induced eczema displayed significantly higher levels of CLA than *Candida albicans*-reactive T cells from the same patients and either casein- or *C. albicans*-

reactive T cells from nonatopic control subjects or atopic patients without eczema. We postulate that in patients with AD and milk-induced eczema, the high CLA expression of casein-reactive cells may facilitate the localization of these T cells in skin, thereby playing a key role in determining the predominantly cutaneous manifestation of their atopic disease.

Further evidence for the relationship between CLA and cutaneous T-cell responses in atopic disease has been recently provided by Babi et al.¹⁰¹ These investigators analyzed the CLA phenotype of circulating memory T cells in patients with AD compared with asthmatic patients who were sensitized to house dust mite. When peripheral blood CLA⁺CD3⁺CD45RO⁺ T cells were separated from CLA⁻CD3⁺CD45RO⁺ T cells, the mite-specific T-cell proliferation response in patients with AD sensitized to dust mite was localized to the CLA⁺ T-cell subset. In contrast, mite-sensitive patients with asthma had a strong mite-dependent proliferation response in their CLA⁻ T-cell subsets. The link between CLA expression and skin disease-associated T-cell effector function in AD was demonstrated by the observation that freshly isolated circulating CLA⁺ T cells in patients with AD, but not in normal control subjects, selectively demonstrated both evidence of activation (HLA-DR expression) and spontaneous production of IL-4 but not IFN- γ .

These observations strongly support the concept that in human allergic diseases, immunologic mechanisms exist to selectively target memory T_{H2} cells with a particular allergen reactivity to specific organs. In the case of skin-seeking T cells, as compared with lung-seeking T cells, there is selective expression of the CLA homing receptor. In allergic patients it remains to be determined whether this preferential CLA induction on allergen-specific T cells is due to allergen preferentially entering the body via cutaneous routes or to other regulatory influences promoting CLA induction in non-skin-associated microenvironments, such as the gut-associated lymphoid tissue, which could tie the increased prevalence of abnormal gut permeability with eczema in patients with food allergy.

IMMUNE BASIS FOR CHRONIC ALLERGIC SKIN INFLAMMATION

Although there is considerable information on the basis of allergen-induced acute and late-phase reactions, relatively little is known about the mechanisms regulating persistence of local tissue T-cell activation and inflammation in chronic allergic

TABLE III. Mechanisms of chronic allergic skin inflammation

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- Persistent exposure to allergens or superantigens
 - Antagonistic effects of established T_{H2} cell response
 - Chronic inflammatory cell activation caused by "escape from apoptosis"
 - Altered steroid responsiveness caused by inflammation-induced glucocorticoid receptor-binding abnormalities
-

diseases. Several factors are likely to play a role (Table III). First, patients with chronic AD are frequently being exposed to food, inhalant, and microbial allergens that are repeatedly triggering allergic responses and T_{H2} cell expansion. In the case of food and inhalant allergens, repeated or long-term exposure to allergens can contribute to the severity of skin disease. Elimination of allergens has been reported to result in the amelioration or clearing of AD.^{15, 21}

It is also known that treatment of patients with chronic AD with antistaphylococcal antibiotics can markedly reduce the severity of their skin disease.³¹ This clinical effect may be due to the capacity of antibiotics to reduce toxin (superantigen) production by *S. aureus*. Staphylococcal superantigens have recently been demonstrated to induce T-cell expression of the skin homing receptor (CLA) through stimulation of IL-12 production.¹⁰² In the case of AD, we have proposed that staphylococcal superantigens secreted at the skin surface could penetrate inflamed skin and stimulate epidermal macrophages or Langerhans' cells to produce IL-1, TNF, and IL-12. Local production of IL-1 and TNF induces the expression of E-selectin on vascular endothelium, allowing an initial influx of CLA⁺ memory/effector cells.^{80, 82} Local secretion of IL-12 could increase CLA expression on those T cells activated by allergen or superantigen and thereby increase the efficiency of T-cell recirculation to the skin, perhaps including areas with only low levels of vascular E-selectin and minimal inflammatory activity. IL-12 secreted by toxin-stimulated Langerhans' cells,¹⁰³ which migrate to skin-associated lymph nodes (and serve as antigen-presenting cells therein) could upregulate the expression of CLA and influence the functional profile of virgin T cells activated by the toxins, thereby creating additional skin-homing memory-effector T cells. Together, these mechanisms would tend to markedly amplify the initial cutaneous inflammation in AD and perhaps also create conditions favoring staphylococcal skin colonization.

Second, once a T_{H2} cell response is established, it antagonizes the function and activation of T_{H1} cells. Of note, T_{H2} cells produce IL-4 and IL-10. Both of these cytokines reduce cytokine production (e.g., IFN- γ secretion) by T_{H1} cells.⁵⁶ Skin-infiltrating T cells from patients with chronic AD are predominantly T_{H2} cells and therefore, after exposure to allergen, secrete cytokines (i.e., IL-3, IL-4, IL-5, IL-6, and GM-CSF), which promote the migration, differentiation, and survival of two major inflammatory components of AD: IgE and eosinophils. In addition, allergen-stimulated mast cells can produce IL-4 and monocyte/macrophages in the chronic AD lesion overexpressing IL-10 and PGE₂, both of which inhibit IFN- γ and further amplify the T_{H2} -like response in AD skin lesions.^{54, 55, 104} IFN- γ inhibits IgE synthesis and the differentiation of IL-4-producing T_{H2} cells.^{46, 51} The inability to produce IFN- γ may therefore contribute to the increased IgE synthesis and sustained T-cell activation observed in AD.

Third, apoptosis, or programmed death of effector cells, is thought to contribute to the control or resolution of tissue inflammation. Enhanced survival of inflammatory cells in inflamed tissues may therefore be a factor in the establishment of chronic inflammation. Recent data have demonstrated that IL-4 enhances apoptosis of normal human monocytes after stimulation and may therefore play an important role in control or resolution of inflammation.¹⁰⁵ Because chronic AD is associated with activation of circulating and infiltrating monocytes,^{42, 54, 55, 76} as well as with increased production of IL-4,^{41, 43, 44, 46} it has been suggested that monocytes from patients with AD may have a paradoxical response to IL-4 with regard to survival. In this regard, Bratton et al.⁷⁶ found that cultures of peripheral blood monocytes from patients with AD had a lower incidence of spontaneous apoptosis and were unresponsive to IL-4-induced apoptosis after stimulation, in marked contrast to the responses of monocytes from normal donors. Furthermore, their data demonstrated that the likely cause of this inhibition of apoptosis and nonresponsiveness to IL-4 was the increased production of GM-CSF by circulating monocytes of patients with AD. Finally, the demonstration of increased levels of GM-CSF mRNA in the inflamed tissues of AD suggests a role for this cytokine in contributing to the increased numbers of macrophages and eosinophils in the chronic lesion of this skin disease.

An analysis of cytokine gene expression in AD has also demonstrated that in the transition from

acute to chronic skin lesions, there is a significant decrease in IL-4 expression but a significant increase in IL-5 expression.⁷³ This shift in cytokine gene expression was accompanied by an increase in the number of activated IL-5-expressing eosinophils and T cells in the chronic AD skin lesion. Thus enhanced survival and infiltration of eosinophils in the chronic AD lesions may occur through IL-5- and GM-CSF-dependent autocrine and paracrine pathways.

Finally, recent studies on mononuclear cells from patients with atopic asthma indicate that allergen-induced immune activation can alter T-cell response to glucocorticoids by inducing cytokine-dependent abnormalities in glucocorticoid receptor binding affinity.¹⁰⁶ Of interest, we have found that PBMCs from patients with chronic AD also have reduced glucocorticoid receptor-binding affinity, which can be sustained with the combination of IL-2 and IL-4.¹⁰⁷ Endogenous cortisol levels have been found to control the magnitude of cutaneous allergic inflammatory responses, suggesting that impaired response to steroids could contribute to chronic AD.¹⁰⁸

Taken together, long-term allergen and microbial antigen or superantigen exposure, T_{H2} cell stimulation, allergen-specific IgE production, mast cell degranulation, eosinophil infiltration, and inflammation amplified by keratinocyte injury caused by scratching contribute to the chronic skin inflammation in AD (Fig. 2). Just as airway inflammation contributes to the non-antigen-specific bronchial hyperreactivity seen in asthma, cutaneous inflammation undoubtedly plays an important role in the pathogenesis of cutaneous hyperreactivity seen in AD.

IMPLICATIONS FOR MANAGEMENT OF AD

Current treatment of AD is directed toward symptom relief and reduction of cutaneous inflammation.² Characterization of each patient's skin disease reaction pattern and reduction of exacerbating factors are critical for effective management. Factors that must be considered and eliminated include irritants, allergens, and emotional stresses. Maintenance of daily skin care with hydration of the skin and appropriate use of topical steroids to reduce skin inflammation is critical. Systemic antimicrobial therapy, in particular anti-staphylococcal antibiotics, is often necessary because AD skin has enhanced binding properties for *S. aureus* and because sites of frequent scratching become secondarily infected. Therapy must be individualized and is dependent on whether the patient is experiencing an acute

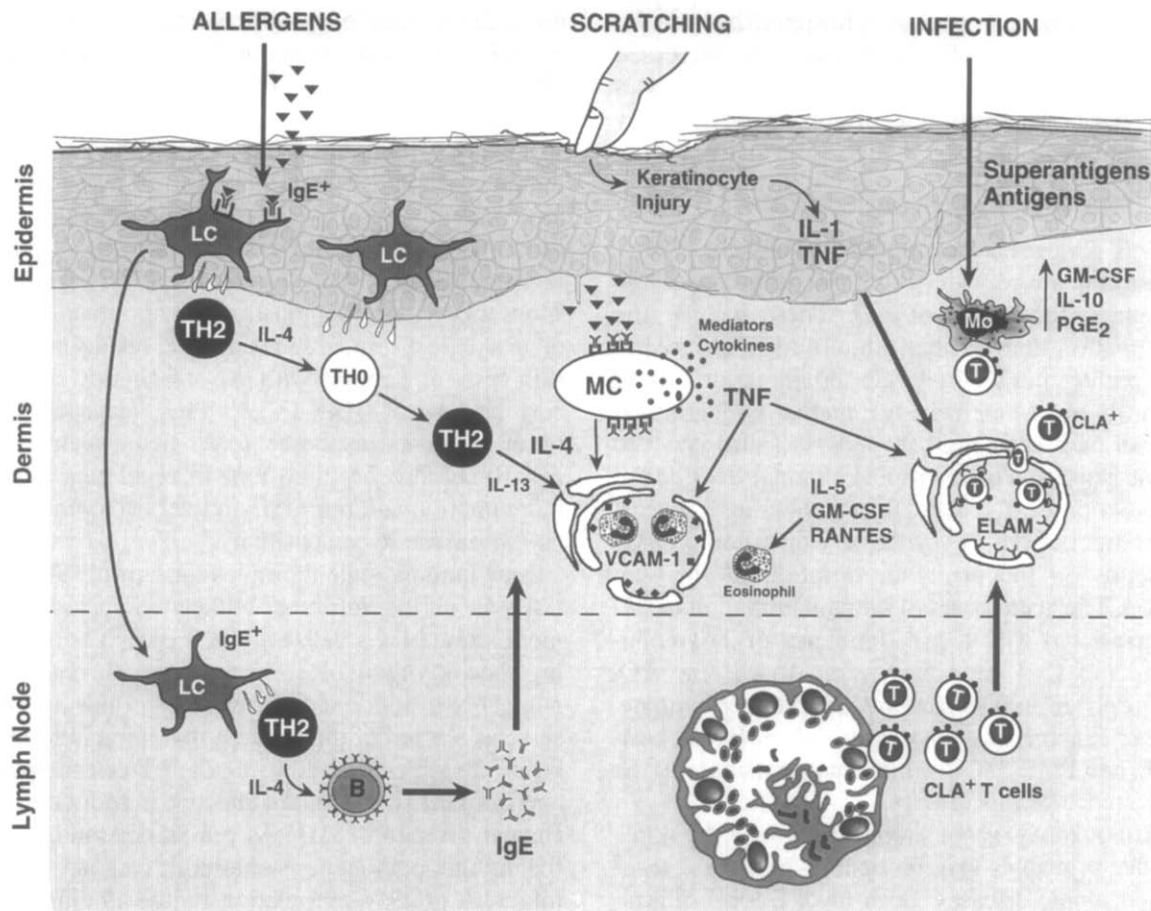


FIG. 2. Cellular and cytokine interactions involved in the pathogenesis of AD. LC, Langerhans' cell; MC, mast cell; Mo, monocyte.

exacerbation or dealing with the management of chronic AD.

For patients with AD that is resistant to therapy, alternative treatments should be considered.¹⁰⁹ Ultraviolet light (UVB or PUVA) therapy may be a useful adjunctive modality in the treatment of chronic recalcitrant AD. Under professional supervision UVB can be effective and has been found to have antiinflammatory effects resulting in part from its ability to inhibit lymphocyte trafficking and antigen-processing. Photochemotherapy with oral psoralen therapy, followed by UVA (PUVA), may also be helpful for patients with severe disease. However, PUVA is reserved for patients with more recalcitrant disease because of the expense and the potential increased risk of skin cancer.

Because patients with AD manifest abnormalities in immune regulation, therapy directed toward correction of their immune dysfunction represents an alternative approach. In this regard, therapeutic trials with several experimental immunomodulators have been reported. Thymopentin, a synthetic

pentapeptide, which promotes differentiation of thymocytes and suppressor/cytotoxic T-cell function, has been found to provide significant relief of pruritus and erythema caused by AD.¹¹⁰ IFN- γ , a cytokine that downregulates T_{H2} cell function, has also been found in placebo-controlled trials to reduce clinical severity associated with AD and decrease total circulating eosinophil counts.^{111, 112} Finally, cyclosporine, a drug that downregulates cytokine production, has also been reported in double-blind, placebo-controlled trials to cause a significant improvement in AD.¹¹³ Cyclosporine therapy did, however, lead to mild renal and liver toxicity. Thus the side effects associated with prolonged systemic cyclosporine therapy make it an unlikely candidate for long-term treatment of AD. Nevertheless, these observations suggest that modulation of the immune system with approaches that inhibit IgE responses or interfere with the action of IL-4 and IL-5 may represent exciting future alternatives to be used in patients with AD that is resistant to currently available therapy. In addi-

tion, the new high-potency phosphodiesterase inhibitors may be useful in targeting the increased phosphodiesterase activity in atopic monocytes and have demonstrated promising preliminary clinical results.¹¹⁴

SUMMARY AND CONCLUSIONS

This review has attempted to highlight several important advances in our understanding of the immunopathogenesis of AD. These include the observation that IgE has a multifunctional role in the pathogenesis of allergic inflammation. Aside from its involvement in IgE-mediated degranulation of mast cells and basophils, it is also involved in the activation of macrophage/monocytes and the stimulation of T_{H2} cells. Recent data also suggest that the pattern of cytokine expression in AD depends on the acuity or duration of the skin lesion. The acute onset of skin inflammation in AD is associated with a predominance of T lymphocytes and IL-4 gene expression. In chronic AD, macrophage and eosinophil activation dominate. These effector cells overexpress IL-5, IL-10, GM-CSF, and PGE₂, all of which may contribute to the persistence of this disease.

Although AD is not simply "asthma of the skin," similar principles may be operative in these associated atopic diseases. Both involve local infiltration of IL-4- and IL-5-secreting T_{H2}-like cells, and both show pathologic evidence of epithelial damage, which likely serves to amplify tissue inflammation. In the case of AD, keratinocyte damage caused by scratching or microbial agents (e.g., *S. aureus*) is accompanied by the release of proinflammatory cytokines. In the case of asthma, bronchial epithelial damage (e.g., damage caused by viruses or eosinophil cationic proteins) and cytokine release from airway epithelium are believed to play an important role in the pathogenesis of airway inflammation.¹¹⁵ The observation that chronic AD is associated with lichenification and dermal fibrosis, which are only slowly responsive to topical corticosteroids, is somewhat analogous to the recent concerns over airway remodeling (e.g., subepithelial airway fibrosis) in asthma¹¹⁶ and the finding that early intervention with inhaled corticosteroids is needed for optimal responses.¹¹⁷

Differences in the clinical manifestations of disease in these important target organs are likely to lie in their distinct resident cells, environment exposures that occur in the skin but not the lung, and the immune response to allergen sensitization of specialized lymphoid systems. Although the major focus of research in allergy to date has been

on understanding of generic mechanisms underlying IgE regulation and action, it is well known that although IgE responses are necessary, they are not sufficient to account for the chronicity or tissue specificity of different allergic diseases. Indeed, a number of studies have demonstrated that even after patients outgrow their allergic disease (e.g., food or inhalant allergy), either naturally or after immunotherapy, their allergen-specific IgE responses persist, as demonstrated by positive immediate skin test results. Furthermore, results of food skin tests in patients with AD frequently do not correlate with DBPCFCs.¹³ This suggests that other immune responses (e.g., tissue-seeking T cells) may also be important in regulating tissue inflammation and therefore in the development of "symptomatic hypersensitivity."

New immunologic therapies for chronic allergic diseases in the future are likely to include the modulation of T_{H2} cells and their cytokines targeting specific organs. Recent studies with recombinant IFN- γ and cyclosporine are promising and serve as a proof of the concept that immunomodulatory therapies that downregulate T-cell function and cytokine secretion are effective in reducing the clinical severity of AD. As our understanding of the immunopathogenesis of allergic responses continues to grow, manipulation of the immune response in AD and other allergic diseases is likely to take an exciting new direction in the treatment of this common group of illnesses.

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REFERENCES

1. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980;92:44-7.
2. Leung DYM, Rhodes AR, Geha RS, Schneider L, Ring J. Atopic dermatitis. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freeberg IM, Austen KF, eds. *Dermatology in general medicine*. New York: McGraw-Hill, 1993:1543-64.
3. Schultz-Larsen F, Holm K, Henningsen K. Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1986;15:487-94.
4. Schmunes E, Keil JE. Occupational dermatoses in South Carolina: a descriptive analysis of cost variables. *J Am Acad Dermatol* 1983;9:861-6.
5. Hill LW, Sulzberger MB. *Yearbook of dermatology and syphilology*. Chicago: Year Book Medical Publishers, 1933:1-70.

6. Leung DYM. Immunopathology of atopic dermatitis. *Springer Semin Immunopathol* 1992;13:427-40.
7. Kay AM, Ying S, Varney V, et al. Messenger RNA expression of cytokine gene cluster, interleukin 3 (IL-3), IL-5, and granulocyte/macrophage colony-stimulating factor, in allergen-induced late-phase cutaneous reactions in atopic subjects. *J Exp Med* 1991;173:775-8.
8. Engman MF, Weiss RS, Engman ME Jr. Eczema and environment. *Med Clin North Am* 1936;20:651-63.
9. Rajka G. Itch duration of the uninvolved skin of atopic dermatitis (prurigo Besnier). *Acta Derm Venereol* 1968;48:320-1.
10. Nassif A, Chan SC, Storrs FJ, Hanifin JM. Abnormal skin irritancy in atopic dermatitis and in atopy without dermatitis. *Arch Dermatol* 1994;130:1402-7.
11. Hoffman DR, Yamamoto FY, Geller B, Haddad Z. Specific IgE antibodies in atopic eczema. *J ALLERGY CLIN IMMUNOL* 1975;55:256-67.
12. Sampson HA, Albergo R. Comparison of results of prick skin tests, RAST, and double-blind placebo-controlled food challenges in children with atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 1984;74:26-33.
13. May CE. Objective clinical laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J ALLERGY CLIN IMMUNOL* 1976;58:500-15.
14. Bock SA, Lee WY, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. *J ALLERGY CLIN IMMUNOL* 1978;62:327-34.
15. Jones SM, Sampson HA. The role of allergens in atopic dermatitis. *Clin Rev Allergy* 1993;11:471-90.
16. Walker IC. Causation of eczema, urticaria, and angioneurotic edema by proteins other than those derived from foods. *JAMA* 1918;70:897-900.
17. Tuft L, Tuft HS, Heck VM. Atopic dermatitis. I. An experimental clinical study of the role of inhalant allergens. *J Allergy* 1950;21:181-6.
18. Tuft L, Heck VM. Studies in atopic dermatitis. IV. Importance of seasonal inhalant allergens, especially ragweed. *J Allergy* 1952;23:528-40.
19. Mitchell EB, Crow J, Chapman MD, Jouhal SS, Pope FM, Platts-Mills TAE. Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet* 1982;1:127-30.
20. Clark RA, Adinoff AD. The relationship between positive aeroallergen patch test reactions and aeroallergen exacerbations of atopic dermatitis. *Clin Immunol Immunopathol* 1989;53:S132-40.
21. Platts-Mills TAE, Chapman MD, Michell B, Heymann PW, Deuell B. Role of inhalant allergens in atopic eczema. In: Ruzicka T, Ring J, Przybilla B, eds. *Handbook of allergens in atopic eczema*. Heidelberg: Springer-Verlag, 1991:192-203.
22. Van der Heijden F, Wierenga EA, Bos JD, Kapsenberg JL. High frequency of IL-4 producing CD4⁺ allergen-specific T lymphocytes in atopic dermatitis lesional skin. *J Invest Dermatol* 1991;97:389-94.
23. Van Reijssen FC, Bruijnzeel-Koomen CA, Kalthoff FS, et al. Skin-derived aeroallergen-specific T-cell clones of the T_{H2} phenotype in patients with atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 1992;90:184-93.
24. Lacour M, Hauser C. The role of microorganisms in atopic dermatitis. *Clin Rev Allergy* 1993;11:491-522.
25. Leung DYM, Geha RS. Clinical and immunologic aspects of the hyper IgE syndrome. In: Curnette J, ed. *Hematology and oncology clinics of North America*. Philadelphia: W.B. Saunders, 1988:81-100.
26. Jones HE, Reinhardt JH, Rinaldi MG. A clinical, mycological and immunological survey for dermatophytosis. *Arch Dermatol* 1973;107:217-22.
27. Kieffer M, Bergbrant I-M, Faergemann J, et al. Immune reactions to *Pityrosporum ovale* in adult patients with atopic and seborrheic dermatitis. *J Am Acad Dermatol* 1990;22:739-42.
28. Leyden JE, Marples RR, Kligman AM. *Staphylococcus aureus* in the lesions of atopic dermatitis. *Br J Dermatol* 1974;90:525-30.
29. Noble W. Skin carriage of the *Micrococcaceae*. *J Clin Pathol* 1969;22:249-52.
30. Hauser C, Wuethrich B, Matter L, Wilhelm JA, Sonnabend W, Schopfer K. *Staphylococcus aureus* skin colonization in atopic dermatitis patients. *Dermatologica* 1985;170:35-9.
31. Lever R, Hadley K, Downey D, Mackie R. Staphylococcal colonization in atopic dermatitis and the effect of topical mupirocin therapy. *Br J Dermatol* 1988;119:189-98.
32. Leung DYM, Harbeck R, Bina P, Hanifin JM, Reiser RF, Sampson HA. Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis: evidence for a new group of allergens. *J Clin Invest* 1993;92:1374-80.
33. Kotzin BL, Leung DYM, Kappler J, Marrack P. Superantigens and human disease. *Adv Immunol* 1993;54:99-166.
34. Buckley RH, Fiscus SA. Serum IgD and IgE concentrations in immunodeficiency diseases. *J Clin Invest* 1975;55:157-65.
35. Saurat J-H. Eczema in primary immune-deficiencies: clues to the pathogenesis of atopic dermatitis with special reference to the Wiskott-Aldrich syndrome. *Acta Derm Venereol* 1985;114:125-8.
36. Agosti JM, Sprenger JD, Lum LG, et al. Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *N Engl J Med* 1988;319:1623-8.
37. Leung DYM, Rhodes AR, Geha RS. Enumeration of T cell subsets in atopic dermatitis using monoclonal antibodies. *J ALLERGY CLIN IMMUNOL* 1981;67:450-55.
38. Leung DYM, Wood N, Dubey D, Rhodes AR, Geha RS. Cellular basis of defective cell-mediated lympholysis in atopic dermatitis. *J Immunol* 1983;130:1678-82.
39. McCoy JP, Hanley-Yanez K, McCaslin D, Tharp MD. Detection of decreased cytotoxic effector CD8⁺ T lymphocytes in atopic dermatitis by flow cytometry. *J ALLERGY CLIN IMMUNOL* 1992;89:688-90.
40. Colver GB, Symons JA, Duff GW. Soluble IL-2 receptor in atopic eczema. *Br Med J* 1989;298:1426-8.
41. Rousset F, Robert J, Andary M, et al. Shifts in interleukin-4 and interferon- γ production by T cells of patients with elevated serum IgE levels and the modulatory effects of these lymphokines on spontaneous IgE synthesis. *J ALLERGY CLIN IMMUNOL* 1991;87:58-69.
42. Polla BS, Ezekowitz RAB, Leung DYM. Monocytes from patients with severe atopic dermatitis are primed for superoxide production. *J ALLERGY CLIN IMMUNOL* 1992;89:545-51.
43. Vollenweider S, Saurat J-H, Röcken M, Hauser C. Evidence suggesting involvement of interleukin-4 (IL-4) production in spontaneous *in vitro* IgE synthesis in patients with atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 1991;87:1088-95.

44. Renz H, Jujo K, Bradley KL, Domenico J, Gelfand EW, Leung DYM. Enhanced IL-4 production and IL-4 receptor expression in atopic dermatitis and IL-4 receptor expression in atopic dermatitis and their modulation by interferon-gamma. *J Invest Dermatol* 1992;99:403-8.
45. Reinhold U, Pawelec G, Wehrmann W, Herold M, Wernet P, Kreysel HW. Immunoglobulin E and immunoglobulin G subclass distribution *in vivo* and relationship to *in vitro* generation of interferon-gamma and neopterin in patients with severe atopic dermatitis. *Int Arch Allergy Appl Immunol* 1988;87:120-6.
46. Mosmann TR, Cherwinski H, Bond MW, Giedlin MH, Coffman R. Two types of murine helper T cell clones. I. Definition according to profiles of lymphokine activities and secretory proteins. *J Immunol* 1986;136:2348-57.
47. Vercelli D, Geha RS. Regulation of IgE synthesis: from membrane to the genes. *Springer Semin Immunopathol* 1993;15:5-16.
48. Schleimer RP, Sterbinsky SA, Kaiser J, et al. Interleukin-4 induces adherence of human eosinophils and basophils but not neutrophils to endothelium: association with expression of VCAM-1. *J Immunol* 1992;148:1086-92.
49. Weller PF. Role of eosinophils in allergy. *Curr Opin Immunol* 1992;4:782-7.
50. Jujo K, Renz H, Abe J, Gelfand EW, Leung DYM. Decreased gamma interferon and increased interleukin-4 production promote IgE synthesis in atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 1992;90:323-30.
51. Gajewski TF, Fitch FW. Anti-proliferative effect of IFN- γ in murine regulation. *J Immunol* 1988;140:4245-52.
52. Wierenga EA, Snoek M, Bos JD, Jansen HM, Kapsenberg ML. Comparison of diversity and function of house dust mite-specific T-lymphocyte clones from atopic and nonatopic donors. *J Immunol* 1990;190:4651-6.
53. Chan SC, Kim JW, Henderson WR, Hanifin JM. Altered prostaglandin E₂ regulation of cytokine production in atopic dermatitis. *J Immunol* 1993;151:3345-52.
54. Vercelli D, Jabara HH, Lauener RP, Geha RS. IL-4 inhibits the synthesis of IFN- γ and induces the synthesis of IgE in human mixed lymphocyte cultures. *J Immunol* 1990;144:570-3.
55. Ohman JD, Hanifin JM, Nickoloff BJ, et al. Overexpression of IL-10 in atopic dermatitis: contrasting cytokine patterns with delayed-type hypersensitivity reactions. *J Immunol* 1995;154:1956-63.
56. Rees J, Friedmann PS, Matthews JNS. Contact sensitivity to dinitrochlorobenzene is impaired in atopic subjects. *Arch Dermatol* 1990;126:1173-5.
57. Sieling PA, Abrams JS, Yamamura M, et al. Immunosuppressive roles for interleukin-10 and interleukin-4 in human infection: *in vitro* modulation of T cell responses in leprosy. *J Immunol* 1993;150:5501-10.
58. Mihm MC, Soter NA, Dvorak HF, Austen KJ. The structure of normal skin and the morphology of atopic eczema. *J Invest Dermatol* 1976;67:305-12.
59. Leung DYM, Bhan AK, Schneeberger EE, Geha RS. Characterization of the mononuclear cell infiltrate in atopic dermatitis using monoclonal antibodies. *J ALLERGY CLIN IMMUNOL* 1983;71:47-56.
60. Bos JD, Hagenara C, Das PK, Krieg SR, Voorn WJ, Kapsenberg ML. Predominance of "memory T cells (CD4+, CDw29+) over "naive" T cells (CD4+, CD45R+) in both normal and diseased human skin. *Arch Dermatol Res* 1989;81:24-30.
61. Berg EL, Yoshin T, Rott LS, et al. The cutaneous lymphocyte antigen is a skin lymphocyte homing receptor for the vascular lectin endothelial cell-leukocyte adhesion molecule 1. *J Exp Med* 1991;174:1461-6.
62. Picker LJ, Butcher EC. Physiological and molecular mechanisms of lymphocyte homing. *Annu Rev Immunol* 1992;10:561-91.
63. Wakita H, Sakamoto T, Tokura Y, Takigawa M. E-selectin and vascular cell adhesion molecule-1 as critical adhesion molecules for infiltration of T lymphocytes and eosinophils in atopic dermatitis. *J Cutan Pathol* 1994;21:33-9.
64. Rossiter H, van Reijssen F, Mudde G. Skin disease-related T cells bind to endothelial selectins: expression of cutaneous lymphocyte antigen (CLA) predicts E-selectin but not P-selectin binding. *Eur J Immunol* 1994;24:205-10.
65. Babi LFS, Moser R, Soler MTP, Picker LJ, Blaser K, Hauser C. Migration of skin-homing T cells across cytokine-activated human endothelial cell layers involves interaction of the cutaneous lymphocyte-associated antigen (CLA), the very late antigen-4 (VLA-4), and the cutaneous lymphocyte-associated antigen-1 (LFA-1). *J Immunol* 1995;154:1543-50.
66. Bochner BS, Klunk DA, Sterbinsky SA, Coffman RL, Schleimer RP. IL-13 selectively induces vascular cell adhesion molecule-1 expression in human endothelial cells. *J Immunol* 1995;154:799-803.
67. Taylor RS, Baadsgaard O, Hammerberg C, Cooper KD. Hyperstimulatory CD1a+CD1b+CD36+ Langerhans cells are responsible for increased autologous T lymphocyte reactivity to lesional epidermal cells of patients with atopic dermatitis. *J Immunol* 1991;147:3794-802.
68. Leung DYM, Schneeberger EE, Siraganian RP, Geha RS, Bhan AK. The presence of IgE on monocytes/macrophages infiltrating into the skin lesion of atopic dermatitis. *Clin Immunol Immunopathol* 1987;42:328-37.
69. Bruijnzeel-Koomen C, van Wichen DF, Toonstra J, Berrens L, Bruijnzeel PLB. The presence of IgE molecules on epidermal Langerhans cells in patients with atopic dermatitis. *Arch Derm Res* 1986;287:199-205.
70. Singer KH, Tuck DT, Sampson HA, Hall RP. Epidermal keratinocytes express the adhesion molecule intercellular adhesion molecule-1 in inflammatory dermatoses. *J Invest Dermatol* 1989;92:746-50.
71. Bieber T, Dannenberg B, Ring J, Braun-Falco O. Keratinocytes in lesional skin of atopic eczema bear HLA-DR CD1a and IgE molecules. *Clin Exp Dermatol* 1989;14:35-9.
72. Barker JNSN, MacDonald DM. Epidermal class II human lymphocyte antigen expression in atopic dermatitis: a comparison with experimental allergic contact dermatitis. *J Am Acad Dermatol* 1987;16:1175-9.
73. Hamid Q, Boguniewicz M, Leung DYM. Differential *in situ* cytokine gene expression in acute vs. chronic atopic dermatitis. *J Clin Invest* 1994;94:870-6.
74. Leiferman KM, Ackerman SJ, Sampson HA, Haugen HS, Venecie PY, Gleich GJ. Dermal deposition of eosinophil granule major basic protein in atopic dermatitis: comparison with onchocerciasis. *N Engl J Med* 1985;313:282-5.
75. Kagi MK, Joller-Jemelka H, Wuthrich B. Correlation of eosinophils, eosinophil cationic protein, soluble interleukin-2 receptor with the clinical activity of atopic dermatitis. *Dermatology* 1992;185:88-92.

76. Bratton DL, Hamid Q, Boguniewicz M, Doherty DE, Kailey JM, Leung DYM. Granulocyte macrophage-colony stimulating factor inhibition of monocyte apoptosis contributes to the chronic monocyte activation in atopic dermatitis. *J Clin Invest* 1995;95:211-8.
77. Tscipoulous A, Hamid Q, Varney V, et al. Preferential messenger RNA expression of Th1-type cells (IFN- γ +, IL-2+) in classical delayed-type (tuberculin) hypersensitivity reactions in human skin. *J Immunol* 1992;148:2058-61.
78. Müller KM, Jaunin F, Masouye I, Saurat J-H, Hauser C. Th2 cells mediate IL-4 dependent local tissue inflammation. *J Immunol* 1993;150:5576-84.
79. Solley GO, Gleich GJ, Jordan RE, Schroeter AL. The late phase of the immediate wheal and flare skin reaction: its dependence upon IgE antibodies. *J Clin Invest* 1976;58:408-16.
80. Leung DYM, Cotran RS, Pober JS. Expression of an endothelial leukocyte adhesion molecule (ELAM-1) in elicited late phase allergic skin reactions. *J Clin Invest* 1991;87:1805-10.
81. Bochner B, Charlesworth E, Lichtenstein L, et al. Interleukin-1 is released at sites of human cutaneous allergic reactions. *J ALLERGY CLIN IMMUNOL* 1990;86:830-9.
82. Cotran RS, Pober JS. Endothelial activation: its role in inflammatory and immune reactions. In: Simionescu N, Simionescu M, eds. *Endothelial cell biology*. New York: Plenum, 1988:335-47.
83. Sampson HA, Jolic PL. Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N Engl J Med* 1984;311:372-6.
84. Sampson H, Broadbent KR, Bernhisel-Broadbent J. Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity. *N Engl J Med* 1989;321:228-32.
85. James JM, Kagey-Sobotka A, Sampson HA. Patients with severe atopic dermatitis have activated circulating basophils. *JACI* 1993;91:1155-62.
86. Bieber T, de la Salle H, Wollenberg A, et al. Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin E (Fc ϵ RI). *J Exp Med* 1992;175:1285-90.
87. Vercelli D, Jabara HH, Lee B, Woodland N, Geha RS, Leung DYM. Human recombinant interleukin-4 induces Fc ϵ R $_2$ /CD23 on normal human monocytes. *J Exp Med* 1988;167:1406-16.
88. Williams J, Johnson S, Mascali JJ, Smith H, Rosenwasser LJ, Borish L. Regulation of low affinity IgE receptor (CD23) expression on mononuclear phagocytes in normal and asthmatic subjects. *J Immunol* 1992;149:2823-9.
89. Borish L, Mascali J, Rosenwasser L. IgE-dependent cytokine production by human peripheral blood mononuclear phagocytes. *J Immunol* 1991;146:63-7.
90. Rouzer CA, Scott WA, Hamill AL, Liu F-T, Katz DH, Cohn ZA. Secretion of leukotriene C and other arachidonic acid metabolites by macrophages challenged with immunoglobulin E immune complexes. *J Exp Med* 1982;156:1077-86.
91. Quinti I, Brozek C, Geha RS, Leung DYM. Circulating IgG antibodies to IgE in atopic syndromes. *J ALLERGY CLIN IMMUNOL* 1986;77:586-94.
92. Mudde GC, Van Reijnsen FC, Boland GJ, DeGast GC, Bruijnzeel PLB, Bruijnzeel-Koomen CAFM. Allergen presentation by epidermal Langerhans cells from patients with atopic dermatitis is mediated by IgE. *Immunology* 1990;69:335-41.
93. Hauser C, Snapper CM, Ohara J, Paul WE, Katz SI. T helper cells grown with hapten-modified cultured Langerhans cells produce interleukin 4 and stimulate IgE production by B cells. *Eur J Immunol* 1989;19:2435-51.
94. Kupper TS. Interleukin-1 and other human keratinocyte cytokines: molecular and functional characterization. In: Callen JP, Dahl MV, Schachner LA, Stegman S, eds. *Advances in dermatology*. Chicago: Year Book Medical Publishers, 1988:293-307.
95. Nickoloff BJ, Naidu Y. Perturbation of epidermal barrier function correlates with initiation of cytokine cascade in human skin. *J Am Acad Dermatol* 1994;30:535-46.
96. Robinson DS, Hamid Q, Ying S, et al. Predominant T $_{H2}$ -like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992;326:298-304.
97. Shimizu Y, Newman W, Tanaka Y, Shaw S. Lymphocyte interactions with endothelial cells. *Immunol Today* 1992;13:106-12.
98. Picker LJ, Treer JR, Ferguson-Darnell B, Collins PA, Bergstresser PR, Terstappen LWM. Control of lymphocyte recirculation in man. II. Differential regulation of the cutaneous lymphocyte-associated antigen, a tissue-selective homing receptor for skin-homing T cells. *J Immunol* 1993;150:1122-36.
99. Picker LJ, Martin RJ, Trumble AE, et al. Control of lymphocyte recirculation in man: differential expression of homing-associated adhesion molecules by memory/effector T cells in pulmonary vs. cutaneous effector sites. *Eur J Immunol* 1994;24:1269-77.
100. Abernathy-Carver KJ, Sampson HA, Picker LJ, Leung DYM. Milk-induced eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. *J Clin Invest* 1995;95:913-8.
101. Babi LFS, Picker LJ, Soler MTP. Circulating allergen-reactive T cells from patients with atopic dermatitis and allergic contact dermatitis express the skin-selective homing receptor the cutaneous lymphocyte-associated antigen (CLA). *J Exp Med* 1995;181:1935-40.
102. Leung DYM, Gately M, Trumble A, Ferguson-Darnell B, Schlievert PM, Picker LJ. Bacterial superantigens induce T cell expression of the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen (CLA). *J Exp Med* 1995;181:747-53.
103. Rook AH, Kang K, Kubin M, et al. Interleukin-12 mRNA and protein production by epidermal Langerhans' cells [Abstract]. *Clin Res* 1994;42:231A.
104. Plaut M, Pierce JH, Watson CJ, Hanley-Hyde J, Nordan RP, Paul WE. Mast cell lines produce lymphokines in response to cross-linkage of Fc ϵ RI to calcium ionophores. *Nature* 1989;229:64-7.
105. Mangan DF, Robertson B, Wahl SM. IL-4 enhances programmed cell death (apoptosis) in stimulated human monocytes. *J Immunol* 1992;148:1812-6.
106. Nimmigadda SR, Leung DYM, Spahn JD, Surs W, Szeffler SJ. Mechanisms underlying allergen induced glucocorticoid receptor binding abnormalities [Abstract]. *J ALLERGY CLIN IMMUNOL* 1995;95:256.
107. Clayton MH, Leung DYM, Surs W, Szeffler SJ. Altered glucocorticoid receptor binding in atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 1995;96:421-3.
108. Herrscher RF, Kasper C, Sullivan TJ. Endogenous corti-

- sol regulates immunoglobulin E-dependent late phase reaction. *J Clin Invest* 1992;90:596-603.
109. Cooper KD. New therapeutic approaches in atopic dermatitis. *Clin Rev Allergy* 1993;11:543-60.
110. Leung DYM, Hirsch RL, Schneider L, et al. Thymopentin therapy reduces the clinical severity of atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 1990;85:927-34.
111. Boguniewicz M, Jaffe HS, Izu A, et al. Recombinant gamma interferon in treatment of patients with atopic dermatitis and elevated IgE levels. *Am J Med* 1990;88:365-70.
112. Hanifin J, Schneider L, Leung D, et al. Recombinant interferon gamma therapy for atopic dermatitis. *J Am Acad Dermatol* 1993;28:189-97.
113. Sowden JM, Berth-Jones J, Ross JS, et al. Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. *Lancet* 1991;338:137-40.
114. Chan SC, Hanifin JM. Immunopharmacologic aspects of atopic dermatitis. *Clin Rev Allergy* 1993;11:523-42.
115. Montefort S, Herbert CA, Robinson C, Holgate ST. The bronchial epithelium as a target for inflammatory attack. *Clin Exp Allergy* 1992;22:511-20.
116. Roche WR, Beasley R, Williams JH, Holgate ST. Subepithelial fibrosis in the bronchi of asthmatics. *Lancet* 1989;1:520-4.
117. Haahtela T, Jarvinen M, Kava T. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.

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CME examination

Identification No. 009559

Leung DYM. Atopic dermatitis: The skin as a window into the pathogenesis of chronic allergic diseases.

J ALLERGY CLIN IMMUNOL 1995;96:302-18.

Questions 1-6

Choose the correct answer:

1. In AD skin lesions, the following cell types express the high-affinity IgE receptor:
 - a. B cells
 - b. Monocytes
 - c. Keratinocytes
 - d. Langerhans' cells
 - e. T cells
2. The following are complications of AD:
 - a. Striae
 - b. Skin atrophy
 - c. Xerosis
 - d. Psychosis
 - e. All of the above
3. Patients with AD have a tendency to have skin infections with:
 - a. *Klebsiella* species
 - b. Staphylococci
 - c. Pneumococci
 - d. *Fusobacterium* species
4. The most effective medication for AD is:
 - a. Oral antihistamines
 - b. Oral antibiotics
 - c. Topical glucocorticoids
 - d. Topical cromolyn
 - e. Topical antifungal therapy
5. The acute skin lesion in AD has T cells expressing:
 - a. IL-4
 - b. IL-5
 - c. CD4
 - d. HLA-DR
 - e. All of the above
6. The chronic, as compared with the acute, AD skin lesion is associated with:
 - a. Decreased IL-5 expression
 - b. Increased IL-4 expression
 - c. Decreased IL-10 expression
 - d. Increased GM-CSF expression
 - e. Decreased interferon- γ expression

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