

The Role of Food Allergy and Other Allergic Disease in Atopic Dermatitis

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Introduction

Atopic dermatitis (AD) is a complex, multifactorial disorder that was first described in the medical literature over 100 years ago. Although clinicians and researchers agree that this disorder is caused by many factors, the role of allergic disease has remained at the forefront of clinical research. In the late 19th century, Besnier provided a detailed description of a chronic, pruritic dermatitis beginning in infancy and showing associations with asthma and rhinitis (1). The term "prurigo Besnier" was subsequently used to describe these patients. In 1902, Brocq coined the term "neurodermatitis" to refer to a chronic, pruritic skin condition seen in patients with apparent nervous disorders (2). Coca was the first to denote the familial occurrence of hay fever, asthma, and eczema, and introduced the term "atopy" to describe the inherited nature of human hypersensitivity disorders (3). In 1933, Wise and Sulzberger condensed the past terminology into the descriptive term we use today—"atopic dermatitis" (4).

Several factors suggest a role for IgE-mediated hypersensitivity in the pathogenesis of AD. Most of these patients have a history of atopic disease; 50% eventually develop asthma, and 80% asthma or allergic rhinitis (5,6). In addition, approximately two-thirds of patients have a positive family history for atopy (7). Increased serum IgE concentrations are found in 80% of these children, with most having positive immediate skin test reactions to various dietary and environmental allergens (7,8). Elucidation of the late-phase IgE

response has provided further information linking abnormal production of IgE and AD (9–11).

Sampson (12,13) demonstrated that food hypersensitivity plays a pathogenic role in a significant number of children who have AD, and that appropriate identification of food hypersensitivity and subsequent exclusion diets can lead to significant improvement. Because many of these patients were specifically referred for evaluation of suspected food allergy, the true prevalence of food hypersensitivity and AD continued to be debated.

Natural History

Prevalence

Although AD is known to be a common skin disorder, the true prevalence is unknown and has been the subject of much debate among physicians and clinical investigators in many fields of medicine. The prevalence in pediatric populations has been estimated to range from 1.1 to 4.3%; however, comprehensive, longitudinal surveys have not been performed to date (14). In addition, most investigators agree that the prevalence of this condition is affected by many factors, such as geographic location and climate, thereby making prevalence studies difficult. It is well recognized that AD is more prevalent in industrialized countries compared to nonindustrialized countries or tropical regions.

Disease Course

AD is a chronic disease of infants, children, and young adults. The onset of disease is typically during early infancy. Sixty percent of affected individuals manifest characteristic lesions during the first year of life. Ninety percent of individuals will be affected by age 5 yr. The remaining individuals will typically manifest disease during late childhood or adolescence (7). It is rare for symptoms to begin during adulthood and should be a clue to question the accuracy of diagnosis.

The clinical course is variable and unpredictable. Some infants and children will have a mild course with spontaneous remission by 2–3 yr of age. Others will have more persistent disease with a chronic unremitting course throughout childhood and even into adulthood. Still others will have a waxing and waning course highlighted by unexplained remissions of varying degrees followed by equally unexplained exacerbations.

Characteristic Distribution

AD is typically divided into three clinical phases based on age of onset (7). The infantile phase is from birth to 2 yr of age. The onset in

this group is typically after 2 mo of age, but onset during the first few weeks of life may be seen. The childhood phase is between 2 and 11 yr. The adolescent and adult phase begins at age 12 yr and proceeds through adulthood. Each of these phases has a typical distribution of skin lesions that can prove useful in diagnosis.

The infantile phase is characterized by erythematous, pruritic, exudative, maculopapular lesions that contrast to the more dry, lichenified lesions seen later in childhood and adult life. In infancy, these lesions first appear on the cheeks, forehead, and scalp. Progression then occurs to involve the trunk and extensor surfaces of the extremities. As the infant grows older, the distribution of lesions may change to involve the entire extremity surface or the more typical flexural distribution of childhood.

During the childhood phase, lesions of AD are typically dry and involve a more flexural distribution of the extremities. The face, with the exception of the lips and perioral region, is less commonly affected by the age of 4–5 yr. The hands can be especially difficult areas to control in this age group. Intense pruritus and secondary scratching can produce a very anxious, hyperactive child.

The adolescent and adult phase is most commonly manifested as lichenified, pruritic macular lesions involving the face, neck, upper trunk, and flexural regions of the extremities. Many young women in their 20s experience hand involvement (i.e., hand eczema) as the first or only manifestation of AD. As previously noted, the onset of disease later in life is very uncommon and should be a clue to search for other etiologic factors or diseases.

Pathogenesis

Role of Allergens

There is a strong correlation of AD with other atopic conditions, such as asthma and allergic rhinitis. As many as 50–80% of children with AD will develop allergic respiratory disease later in life (7). In addition, many clinicians note the peculiar tendency of AD and asthma to alternate in their courses in some patients. This observation is unexplained and inconsistent with episodes of both diseases occurring simultaneously on occasion. Owing to earlier historical observations of AD associated with other atopic diseases, investigators have explored the role of various allergens as causal factors in these diseases (Table 1).

Foods

Adverse reactions to foods have been reported in the medical literature since the early 1900s when Smith reported the case of a man

Table 1
Common Allergens in AD

Aeroallergens
Pollens
Molds
Dust mite
Animal dander
Cockroach
Food allergens
Milk
Egg
Soy
Peanuts
Wheat
Shellfish
Fish
Microorganisms
Bacteria
<i>S. aureus</i>
Streptococci
Fungi/yeasts
<i>P. ovale/orbicularis</i>
<i>Trichophyton</i> species

with “buckwheat poisoning” (15). In 1918, Talbot was one of the first physicians to observe an improvement in a patient’s eczema while on a milk and egg-restriction diet (16). Tuft considered food allergy to be the most important pathogenic factor in infants and young children with AD, yielding to inhalant allergies in older children and adults (17). Since that time, many investigators have studied children with AD and food hypersensitivity. In general, they have shown that dietary manipulation has resulted in dramatic improvement in many patients with AD, especially young children.

Bock and Atkins were the first to establish the use of double-blind, placebo-controlled food challenges (DBPCFC) to assess patients with suspected food hypersensitivity (18). Because there is poor correlation between allergen-specific IgE antibodies (skin tests or radioallergosorbent tests [RAST]) and clinical symptoms related to food hypersensitivity, oral food challenges (both open and blinded) have been crucial in assisting many investigative groups in the study of food hypersensitivity and AD. Sampson first reported findings of food hypersensitivity in 26 children with AD (12). These findings were confirmed during a study in which 46 children with AD were studied with DBPCFC (19). Positive challenges were detected in 33% of patients with 91% reacting to only one or two foods. These groups

have shown a direct correlation between hypersensitivity to foods (Table 1) and the development of AD. In addition, these groups have consistently reported improvement in AD in food protein-sensitive patients while on food-elimination diets.

Perhaps the largest body of information regarding AD and food hypersensitivity has been provided by Sampson and coworkers (12,13,20). To date, they have evaluated over 450 children with AD for food hypersensitivity by performing >1400 initial DBPCFC to suspected foods. Egg, milk, peanut, soy, and wheat accounted for 87% of positive food challenges with egg sensitivity being the most prevalent. Cutaneous symptoms were seen in 75% of positive challenges. The most common cutaneous manifestation consisted of a pruritic, erythematous morbilliform rash involving the AD predilection sites. Other symptoms noted during positive challenge included respiratory (stridor, wheezing, nasal congestion, rhinorrhea, and sneezing) and gastrointestinal (nausea, vomiting, abdominal cramping, and/or diarrhea) symptoms. All patients found to be allergic to particular foods were placed on an appropriate avoidance diet of that food. Virtually all patients reported improvement in symptoms, either noted as complete resolution or marked clearing.

In a more recent study in our institution, we sought to delineate further the role of food hypersensitivity in AD and to determine if patients with AD who had food hypersensitivity could be identified by screening prick skin tests using a limited number of food allergens (21). Patients with AD attending the Arkansas Children's Hospital Pediatric Allergy Clinic were enrolled. After a detailed medical history and physical examination, the patients underwent allergy prick skin testing to a battery of food antigens. Patients with positive prick skin tests underwent DBPCFC. One hundred sixty-five patients were enrolled and completed the study. Patients ranged in age from 4 mo to 21.9 yr (mean 48.9 mo). Ninety-eight (60%) patients had at least one positive prick skin test. A total of 266 DBPCFC were performed. Sixty-four patients (38.7% of total) were interpreted as having a positive challenge. Seven foods (milk, egg, peanut, soy, wheat, cod/catfish, cashew) accounted for 89% of the positive challenges. Utilizing screening prick skin tests for these seven foods we could identify 99% of the food allergic patients correctly. This study confirms that the majority of children with AD have food allergy that can be diagnosed by a prick skin test for the seven foods.

Sampson and colleagues have presented studies of mediator release that provide further evidence that food-specific IgE-mediated mechanisms play a role in the pathogenesis of AD (22). They have demonstrated increased plasma histamine levels in AD patients following a positive food challenge, increased spontaneous histamine

release from basophils in patients with AD and food hypersensitivity, spontaneous release of a cytokine (histamine-releasing factor) from mononuclear cells in these patients, and increased cutaneous hyperirritability to a variety of minor stimuli. These mediators and the associated cutaneous hyperirritability were all noted to be diminished to normal levels after 6–9 mo of food allergen avoidance.

In an earlier study examining the natural history of patients with AD and food hypersensitivity, Sampson reported that 26% of patients lost their clinical hypersensitivity during the first year of allergen avoidance and 11% lost reactivity during the second year (13). Therefore, Sampson and others have shown that most children tend to “outgrow” their food hypersensitivity to most foods early in life. Some of these children also show subsequent resolution of their AD, whereas others manifest aeroallergen sensitivity that seems to perpetuate the AD cycle.

Through the years, much attention has focused on the role of maternal dietary restriction during pregnancy and lactation in the prevention of AD and food hypersensitivity. The most current and comprehensive information to date comes from Zeiger and colleagues (23). This group has prospectively followed 288 American children from birth through age 4 yr and 125 of these children through age 7 yr. Some mothers and infants were randomized to a prophylactic group consisting of maternal avoidance of cow's milk, eggs, and peanuts during the third trimester of pregnancy and during lactation; use of a casein hydrolysate formula for supplementation or weaning; avoidance of all solid foods for 6 mo; and avoidance of defined allergenic foods for up to 24 mo. Others provided a control or “untreated” group in which no prophylaxis was implemented. After 7 yr, the only atopic parameters affected between groups were the prevalence of food allergy and milk sensitization prior to age 2. No difference was seen in the prevalence of AD, asthma, allergic rhinitis, food sensitization, or positive skin tests to inhalant allergens. Other studies in children have shown a direct correlation between the number of solid foods introduced before age 6 mo and the prevalence of AD at age 2 yr. These and other studies indicate the potential role of food allergens in the development of AD and the potential benefits of early allergen avoidance in some high-risk infants.

Aeroallergens

Pollens were the first aeroallergens reported in association with AD. Ragweed pollinosis has been of particular interest with clinicians citing case reports of patients with seasonal exacerbation of AD and clearing in a pollen-free environment. In the 1950s, Tuft and Heck performed intranasal challenges with ragweed pollen and noted rhinor-

rhea and itching of affected skin areas in AD patients (24). More recently, investigators have shown positive prick skin tests and patch tests to common pollens in patients with seasonal distribution of their AD. In a recent study of children, Wananukul et al. found 90% of AD children tested with epicutaneous patch testing to develop eczematous lesions in one or more AD predilection sites when tested with dust mite, cockroach, mold, and grass mix (25). Others have shown positive immediate skin tests to birch pollen in AD patients who had worsening of their disease during the birch pollen season.

Mold allergens have also been implicated as causal factors in patients with AD. Tuft and Heck induced symptoms of dermatitis in their patients following inhalation challenge with *Alternaria* when compared with talc powder or pine pollen (24).

The largest body of scientific and clinical data regarding aeroallergens and atopic diseases exist with reference to dust mite allergy. Sensitivity to dust mite was first examined in patients with asthma. Reports soon followed of improvement in AD when patients were placed in a dust-free environment and subsequent aggravation of symptoms after exposure to dust. Platts-Mills and colleagues have performed extensive studies of dust mite antigen and atopic disease association (26,27). They and others have shown positive prick skin testing and patch testing to dust mite antigen in patients with AD. In a recent epidemiologic survey, the homes of patients with moderate to severe AD showed a higher dust mite concentration than controls. Elevated serum levels of dust mite-specific antibody and increased basophil sensitivity have also been shown in AD patients when compared with controls. Several groups of investigators have also demonstrated an increased lymphocyte response and specific cytokine profile production in patients with AD and evidence of dust mite allergy. Perhaps the best clinical evidence for dust mite allergen playing a role in the AD condition of some patients comes from reports of patients showing improvement when living in a dust-free environment and having flares of disease on return to an environment of exposure to dust mites (28).

Two other types of aeroallergens are felt to play a role in the pathogenesis of AD—animal dander and cockroach allergens. Both of these allergen groups have been studied in association with asthma and allergic rhinitis and are felt to be important factors in certain susceptible individuals. Less scientific information is available with regard to AD; however, anecdotal clinical experience would support their causative roles. Of the animal danders, cat and dog dander are implicated most commonly in atopic disease states. Cat dander allergy, in particular, can manifest as severe in some atopic individuals, especially those with asthma. Cockroach allergens have been

recognized more recently in atopic disease, especially in endemic areas and climates. In Wananukul et al.'s recent study of atopic children, many of them had positive prick and intradermal skin tests to animal dander and cockroach indicating the possible relevance of these allergens in atopic disease (25). More study is needed to define further the role of animal dander and cockroach allergens in AD.

Microorganisms

The role of microorganisms in the pathogenesis of AD has received much attention in recent years. Their potential role as complicating skin pathogens has long been recognized as important, but more recently their role as "allergens" perpetuating the allergic response has been of particular interest. It is postulated that the altered skin barrier seen in patients with AD provides a portal of entry for various pathogens to gain access to the immune system, thus activating mast cells, basophils, Langerhans cells, and other immune cells. The primary classes of microorganisms involved include bacteria and yeasts.

The most extensively studied and widely recognized microorganism of importance in the disease process of AD is *Staphylococcal aureus* (*S. aureus*) (29). *Staphylococcal aureus* skin colonization of both affected and normal skin has been shown to be increased in patients with AD compared to controls. Some investigators have demonstrated colonization in over 90% of lesions in some individuals with AD. In addition, elevated IgE-specific antistaphylococcal antibodies have been demonstrated in sera of patients with AD. More recently, investigators have focused on the role of staphylococcal exotoxins in the disease cycle of AD. These studies have focused on the role of stimulating T-cell-dependent IgE production and subsequent enhancement of the allergic response. These groups and others have also suggested that these exotoxins may function as "superantigens," thereby perpetuating the immune response by stimulating T-cell proliferation independent of the usual allergic mechanisms. To emphasize further the role of *S. aureus* in the AD process, it has been clearly demonstrated that patients with AD show a better clinical response when treated with combinations of antistaphylococcal antibiotics and topical steroids than with steroids alone. Other bacteria, such as streptococcal species, may also be important, but little clinical or investigative information exists to document their role.

Various species of yeast organisms have been implicated as causal factors in the pathogenesis of AD. *Pityrosporum ovale* (*P. ovale*) and its gestational counterpart, *Pityrosporum orbiculare* (*P. orbiculare*) are lipophilic yeasts that may inhabit the skin of all individuals with predilection for the neck, face, and upper trunk. Colonization is more

commonly seen in older children and adults than in infants and younger children. Many investigators have shown a strong correlation between active AD lesions and specific antibodies to *P. ovale*. The antibodies have been demonstrated via prick skin testing and serum analysis via RAST. In addition, patients with head, neck, and upper trunk distribution of AD lesions and evidence of specific antibodies to *P. ovale* have been reported to show clinical improvement following ketoconazole therapy. Although not conclusive, these data suggest the pathogenic role of *Pityrosporum* species in some patients with AD and emphasize the need for consideration when refractory AD in the typical head and neck distribution is seen, especially in older children and adults. The possible role of other yeasts, such as *Candida albicans* and *Trichophyton*, have been implicated in the pathogenesis of AD; however, more extensive study is needed to draw firm conclusions.

Role of Environmental Factors

AD is a complex, multifactorial disease. The course of the disease is influenced by many primary and secondary factors that are often difficult to tease apart. Environmental factors frequently act as “triggers” causing exacerbations of disease, yet they are not primary causes of the underlying disease.

Climate

Several environmental factors can influence the course of disease in AD (7). One of the most important, yet often obscure factors is climate. Individuals will respond differently to various climatic influences. Most authors report disease intensification during the winter months with reports of patients having the most comfort during the months of summer. It is thought that improvement during the summer may be owing to better sebum and sweat secretion, UV rays from sun exposure, exposure to water during swim activities, reduced exposure to indoor allergens (i.e., dust mite and molds), less exposure to infection, and less psychosocial stressors during summer vacations. Some of these same influences may in fact aggravate the skin condition of others patients. It has been noted the impaired sweating mechanism in patients with AD, making excess sweating and strong heat adverse factors in those individuals. UV light exposure without appropriate skin protection can also be harmful. Although indoor allergen exposure may be minimized during summer months, outdoor allergen exposure (i.e., grass pollens) may be exacerbating in some regions. As a general rule, cold, dry weather is more aggravating to patients with AD secondary to the drying effect. Hot humid weather may also be aggravating owing to increased perspiration and

the increased potential for secondary skin infection. Extremes or sudden changes of any climatic condition (i.e., temperature and humidity) can be aggravating to patients with AD most likely secondary to an impaired ability for immediate skin adaptation. As previously stated, these factors are only secondary in the large majority of patients and vary individually.

Irritants

Factors other than primary irritants (i.e., allergens and infection) may complicate the course of AD (7). Clothing fabrics can influence the comfort level and the amount of pruritus experienced by AD patients. Wool fabrics clearly provide the most irritation and should be avoided in patients with AD. Synthetic fibers, such as nylon and polyester, may also be poorly tolerated by some individuals. Cotton is generally the fabric that provides the most comfort and least pruritic potential, and its use should be emphasized to patients.

Certain laundry detergents, bleaches, soaps, and household cleaning chemicals act as irritants for patients with AD. Mild laundry detergents without bleach are generally better tolerated. Washing clothing through a rinse cycle twice usually ensures removal of the detergent and may be beneficial in some sensitive patients. Mild skin soaps should also be used in AD patients for bathing. They are generally less drying, less irritating, and are less likely to induce pruritus. Skin should be protected from household cleaners by wearing protective gloves or clothing. The skin barrier is frequently altered in AD and will not withstand the general intrusions that normal skin can endure.

Some foods can also act as triggers of irritation and pruritus. Certain fruits and vegetables, such as tomatoes and citrus fruits, are especially irritating in some individuals. These foods are not primary allergens, but rather irritants causing pruritus secondary to their acidic composition.

Psychosocial Factors

Most clinicians agree that psychosocial factors influence the disease process of AD and further agree that these factors remain secondary and not primary in disease etiology. Emotional upset, stress, job or school tension, and unstable or unsupportive home environments all can contribute as exacerbating factors. Although not primary causes of disease, these issues must be addressed in caring for patients with AD to provide maximal symptomatic relief during periods of disease exacerbation. These issues are especially important in children and adolescents, and may occasionally require psychological, as well as medical intervention.

Genetic Associations

Like other atopic conditions, AD has a strong genetic predisposition. As many as 60–80% of patients with AD have a family history of a first-degree relative with AD, asthma, or allergic rhinitis. In studies of twins, Rajka reported a much higher concordance for atopy in monozygotic twins, whereas AD alone revealed only a 50% concordance in both monozygotic and dizygotic twins (30). Rajka's data cast doubt on the strictly hereditary influence, yet underscore the importance of the combination of hereditary and environmental factors in the disease process. Numerous reports have suggested genetic associations among families with atopic disease in general and AD specifically. These data are not definitive at present and suggest that a single set of genes is not responsible for atopic disease inheritance. Multiple patterns of disease inheritance, such as autosomal dominance, autosomal recessive, and multifactorial inheritance, have been found emphasizing the obvious complexity of genetic influence on the disease process. Throughout all these studies, however, it is maintained that individuals from atopic families are greater risk for development of atopic disease in some form.

Clinical Manifestations

History

AD typically begins early in life, most commonly with skin lesions developing in the first 6 mo. Although this pattern is typical, alterations in presentation frequently occur. A careful history can therefore be useful in making the diagnosis of AD. As noted previously, a family history of atopic disease may provide a clue to the etiology of a patient's skin disease. As many as 80% of patients with AD have a positive family history of atopy (7). A comprehensive history with regard to possible exacerbating triggers can also be helpful. These triggers may include foods, seasonal allergens, environmental conditions, irritants, emotional distress, and occupational exposures. A careful history will often uncover an exacerbating factor that is unapparent to the patient or the physician. The most prominent and persistent feature detected by historical evaluation is intense pruritus associated with a chronically relapsing course of skin disease.

Physical Findings

Although typical distribution of lesions can be detected during various stages of development, no firm diagnostic pattern is seen among all patients. The diagnosis of AD therefore relies on informa-

Table 2
Guidelines for the Diagnosis of AD^a

Must have three or more basic features
Pruritus
Typical morphology and distribution
Flexural lichenification or linearity in adults
Facial and extensor involvement in infants and children
Chronic or chronically relapsing dermatitis
Personal or family history of atopy (asthma, allergic rhinitis, AD)
Plus three or more minor features
Xerosis
Ichthyosis/palmar hyperlinearity/keratosis pilaris
Immediate (type I) skin test reactivity
Elevated serum IgE
Early age of onset
Tendency toward cutaneous infections (especially <i>S. aureus</i> and herpes simplex)/impaired cell-mediated immunity
Tendency toward nonspecific hand or foot dermatitis
Nipple eczema
Cheilitis
Recurrent conjunctivitis
Dennie-Morgan infraorbital fold
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor/facial erythema
Pityriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Perifollicular accentuation
Food intolerance
Course influenced by environmental/emotional factors
White dermographism/delayed blanch

^aFrom ref. (31).

tion compiled from all aspects of the clinical history, physical examination, and laboratory data. Hanafin and Rajka have provided useful guidelines to assist in diagnosing AD (Table 2) (31).

The rash of AD typically begins as an erythematous, papulovesicular eruption, which progresses to a scaly, lichenified maculopapular dermatitis with time. Weeping, crusting lesions of the head, neck, and extensor surfaces of the extremities are common in infancy. These lesions may involve the entire body surface, yet the diaper area may be spared. The scalp is often affected in infants with some having features of a concomitant scalp seborrhea. Because of

intense pruritus and scratching, traumatic injury occurs over time providing a portal of entry for secondary bacterial infection. The early erythematous lesions will frequently discolor over time and become dry, hyperpigmented lesions as seen in chronic dermatitis of the older child. Older children and adults have a more flexural distribution of lesions. Lesions are typically dry, lichenified maculopapular lesions. These lesions commonly remain intensely pruritic with resultant scratching, traumatic skin injury, and secondary infection. Hyperpigmentation of chronic lesions is seen with areas of hypopigmentation from older, healed AD lesions. Dry skin, ichthyosis, hand eczema, and chronic cheilitis may also be prominent features of the disease. Skin lichenification may be persistent long after "active" dermatitis lesions resolve.

Clinicians have long recognized that patients with AD have a generalized "pallor" to their skin. This has been attributed to an abnormal vascular response that can be demonstrated by the abnormal "blanching" response seen in these patients. This delayed blanching response can be seen in both affected and normal skin of AD patients as demonstrated by application of pressure or cold on the skin. In addition these patients will frequently demonstrate "white dermographism." When the skin of an AD patient is stroked with a blunt object, a red line will form, which will then be rapidly replaced by a white line without an associated wheal. Under the same conditions, normal skin will develop a red line owing to capillary dilatation, an erythematous flare caused by arteriolar dilatation, followed by a wheal secondary to the leaky, dilated capillaries. These abnormal vascular responses of AD have also been implicated in the temperature instability and poor regulatory responses seen in some patients.

Another prominent physical finding in patients with AD is an impaired sweating mechanism. Several investigators have documented this phenomenon with patients demonstrating less sweating under periods of stimulation. In addition, patients frequently complain of increased pruritus during periods of sweating. An increased transepidermal water loss has also been noted in patients with AD. This has been attributed to fewer sebaceous glands and less total lipid content of AD skin. All of these findings contribute to the clinical manifestations of dry skin and increased pruritus.

Laboratory Findings

Laboratory tests provide few clues to the diagnosis of AD. Several parameters can be helpful in eliciting triggering agents and underlying causes of disease, but none are diagnostic.

Hematologic Findings

Peripheral blood eosinophilia is commonly seen in patients with AD. Eosinophils usually comprise 5–10% of the total white blood cell count in AD patients. The degree of eosinophilia typically does not correlate with the degree of disease severity and is generally not a useful parameter to follow disease activity. Eosinophil mediators, such as major basic protein and eosinophil cationic protein, have been found in the circulation and biopsy specimens of patients with AD (29). Eosinophil cationic protein has been found in increased amounts in the circulation of AD patients with disease activation compared to AD patients with inactive disease or normal controls. This parameter has therefore been proposed as a useful marker for disease activity. More information is needed to determine if this parameter is actually a valid means of following the disease status in AD.

Serum IgE Antibody

Many investigators have found a correlation between elevated serum IgE concentrations and the presence of AD. Juhlin et al. reported that 82% of AD patients evaluated had elevated serum IgE levels (32). In two subsequent surveys, Johnson and O'Loughlin reported the incidence of elevated IgE in AD to be 43 and 76%, respectively (8,33). Both noted that increased levels were seen more commonly in patients suffering from more severe disease and in those with concomitant atopic respiratory disease. In addition, these investigators report a significant number of patients with typical AD and normal IgE concentrations. Other groups have also found elevated IgE levels in nonatopic individuals. At present, most investigators agree that the finding of an elevated serum IgE concentration is a secondary, not a primary phenomenon. Serum IgE determinations in patients with AD provide little practical benefit in the diagnosis or management of patients with AD.

Skin Test Reactions

Prick and intradermal skin tests to various aeroallergens and food allergens are commonly used in the assessment of AD and provide the most sensitive test for allergen detection. Controversy exists among allergists and dermatologists with regard to the clinical relevance of positive tests. Some investigators have reported that as many as 80% of individuals with AD will have positive specific IgE to a variety of allergens (7). This finding has been explained by some groups to be nonspecific and only an indicator of a generalized atopic state. Others report the clinical significance of specific IgE antibody

and skin test reactivity in some patients with AD, and report the observation of clinical improvement while instituting specific allergen avoidance. Knowledge of the allergens eliciting positive skin test reactions can be used as a clinical guide for the management of disease and detection of exacerbating conditions. These tests must be interpreted with caution. The presence of a positive skin test to an aeroallergen or a food allergen may not have strict clinical relevance and must be analyzed in light of the clinical history. For aeroallergen sensitivity, findings of seasonal distribution of other associated disease, such as allergic rhinitis and asthma, may provide additional clues for interpreting positive skin tests and instituting appropriate avoidance procedures. In the case of food allergen sensitivity, Sampson found prick skin tests to have an excellent negative predictive accuracy of 82–100% but a poor, highly variable, positive predictive accuracy of 25–75% when compared to blinded food challenge (28). Positive results must be correlated with the clinical history and dietary assessment then confirmed with a trial of an allergen elimination diet and subsequent food challenge.

Radioallergosorbent Test (RAST)

RAST provide another less sensitive method of evaluating a patient for the presence of IgE antibody to specific allergens in the serum. RAST can be performed on patients with AD in whom the extent of body surface involvement and severity of the dermatitis prohibits skin testing. These tests are less reliable than skin testing, especially when assessing for food allergen sensitivity. Like prick skin tests, Sampson found that RAST had an excellent negative predictive accuracy approaching 100%, but a poor positive predictive accuracy of 0–57% when compared to blinded food challenge (34). These findings limit their usefulness, but may still provide clinical clues, especially when negative results are found. The CAP-RAST™ has been studied and found in a preliminary study to have better predictive values for at least some of the major food allergens, including milk, eggs, and peanuts (35). The study indicated that if the patient had CAP-RAST™ value above a certain point, then there was either a 90% or 95% likelihood that the patient would have a positive food challenge. The cutoff value was different for each of the food allergens.

Role of IgE in AD

Support for an IgE-mediated mechanism in AD is suggested by the following findings typical of AD: elevated serum IgE concentration, positive immediate skin tests and RAST to a variety of food and aeroallergens, association with other atopic diseases (i.e., asthma and

allergic rhinitis), and a positive family history for atopy in 80–90% of patients (7). In addition, bone marrow transplant data have documented the ability to transfer IgE antibody, specific allergen sensitivity, and AD to previously nonatopic bone marrow recipients. Although the histologic appearance of AD lesions suggest a Type IV, cell-mediated hypersensitivity reaction owing to the cellular infiltrative pattern, recent information on the allergic “late-phase reaction” (LPR) has shown a distinctive cellular infiltrate that is consistent with that seen in AD. Following allergen challenge, IgE-bearing mast cells bind allergen and become activated, releasing cytokines and mediators that perpetuate the allergic response. This “immediate or early” reaction occurs within 15–60 min of allergen challenge and is characterized by erythema, pruritus, and increased capillary permeability. Approximately 4–8 h after the initial allergen challenge, the LPR begins with infiltration of eosinophils, neutrophils, lymphocytes, and monocytes into the site of inflammation. At 24–48 h, lymphocytes and monocytes predominate the cellular infiltrate. This infiltrate seen during the LPR following antigen challenge is similar to the infiltrate noted in the lesions of AD (29).

Clinical and laboratory correlates have been made in numerous studies in patients with food hypersensitivity and AD. Following positive food challenge, Sampson and colleagues (13,22) have shown a rise in plasma histamine, without a change in complement activity, basophil number, or total basophil histamine content. Skin biopsy specimens obtained 4 and 14 h after challenge revealed eosinophil infiltrate and deposition of major basic protein. They concluded that food allergen-induced mast cell activation was shown to trigger both an “early” phase reaction and an LPR in the skin of patients with AD.

IgE molecules have also been found to participate in the inflammatory response via mechanisms other than direct mast cell activation. Sampson et al. have shown that children with AD and food hypersensitivity have high spontaneous basophil histamine release *in vitro* when compared with normal controls or AD patients without food hypersensitivity (22). Mononuclear cells from these patients also secreted high levels of histamine-releasing factor (HRF). These levels were associated with cutaneous hyperreactivity to a variety of minor stimuli. After an appropriate food-elimination diet was implemented for approx 1 yr, spontaneous basophil histamine releasability and production of HRF fell to baseline levels and correlated clinically to less cutaneous hyperreactivity. In addition, passive transfer of this releasing factor could be demonstrated in nonatopic controls. Basophils from nonatopic individuals were stripped of all IgE molecules and sensitized with IgE from food allergic patients. This rendered the “normal” basophils capable of secreting histamine in response to HRF.

The observation that Langerhans cells and macrophages infiltrating into the dermis of AD skin lesions bear IgE surface molecules provides an important link to understanding the immunopathology of AD (36–38). These IgE-bearing cells also express the low-affinity receptor for IgE (CD23) and presumably function in antigen processing and presentation. Mudde and coworkers demonstrated that in vitro, IgE-bearing Langerhans cells from dust mite allergic patients were capable of capturing house dust mite allergen for antigen presentation, whereas IgE-negative cells from normal controls or atopic controls who were not dust mite-allergic were unable to capture the allergen (39). Once activated, these cells have been shown to produce cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF), that are important in lymphocyte attraction and activation at the inflammatory site. In Mudde et al.'s (39) study, IgE-positive cells were shown to activate lymphocytes after specific allergen challenge, whereas IgE-negative cells did not result in lymphocyte activation. In addition to mast cells, these cells likely function as a bridge between initial allergen contact and processing and subsequent lymphocyte activation and perpetuation of the immune response.

Role of T-Cells in AD

The role of T-lymphocytes in the pathogenesis of AD has been the subject of many investigative studies during the last 15–20 yr (29). The concept that T-cells play a critical role in IgE regulation has been elegantly demonstrated in the murine model. Recently, evidence for this same type of interaction has been found in human studies. Cytokines produced by activated lymphocyte clones regulate the immune response. In the murine model, T helper (T_H) cells are divided into two distinct subpopulations based on the cytokine profile secreted. T helper type 1 (T_H1) cells produce IL-2, IL-3, IL-10, and interferon- γ (IFN- γ) and function in cell-mediated immunity responses (i.e., infection and delayed-type hypersensitivity). T helper type 2 (T_H2) cells produce IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and granulocyte-macrophage colony forming unit (GM-CSF), and function in hypersensitivity responses. These same profiles have been seen in human studies, but with some degree of overlap.

It has been demonstrated that IL-4 acts as an isotype switch factor that commits B-cells to produce IgE (29). Furthermore, B-cells from patients with AD have been shown to produce spontaneously higher levels of IgE than normal controls. These B-cells also have increased expression of the low-affinity IgE receptor (CD23) on their surface. In vitro data have also shown that IL-4 not only increases IgE production, but upregulates the expression of CD23. Numerous investigators

have shown an imbalance in cytokine profiles in patients with AD. These patients typically have a T_H2 -like cytokine profile with increased secretion of IL-4, IL-5, and IL-13, in particular. Human T-cell clones from such patients demonstrate a decreased production of IFN- γ and increased production of IL-4, resulting in an ability to induce IgE synthesis. This reciprocal relationship between IFN- γ and IL-4 and subsequent induction of IgE synthesis have been documented by several groups. Many have shown that production of IFN- γ or its addition to cell culture will inhibit IgE production and will downregulate the expression of CD23. Van der Heijden and coworkers (39a) have also demonstrated a high frequency of IL-4-producing allergen-specific T-cells in lesional skin from AD patients. Van Reijsen noted the same allergen-specific clones from lesional skin with 70% demonstrating a T_H2 phenotype (40). Both groups suggested that percutaneous sensitization to aeroallergens (e.g., dust mite) may occur and that activation of T_H2 -type allergen-specific T cells may be responsible for the high levels of specific IgE found in 80% of AD patients. These data suggests that atopic patients, and those with AD in particular, have an inability to produce IFN- γ and therefore have a predominance of T_H2 -type cells, resulting in increased IL-4 production, increased IgE synthesis, and continuation of the allergic immune response. Of further interest is the apparent differential expression of IL-13 and IL-12 in acute vs chronic AD skin lesions, respectively. These data provide further evidence for a T_H2 phenotype in acute lesions leading to inflammation. In contrast, the increase in IL-12 in chronic lesions suggests a possible role for IL-12-producing cells in modulating chronic inflammation (41).

Differential Diagnosis

Many types of primary skin disorders, metabolic disorders, and immunologic diseases have associated skin conditions that resemble AD (Table 3). Certain characteristics of these conditions help to distinguish them from AD.

Skin Diseases

Seborrheic dermatitis is the most common skin disorder confused with AD. It is characterized by a greasy yellow or salmon-colored scaly dermatitis that begins within the first few weeks of life, usually before the typical age of onset of AD. Lesions are primarily distributed on the scalp, cheeks, and postauricular areas but may also occur on the trunk, perineum, and intertriginous regions of the hands and feet. In contrast to AD, significant pruritus is generally not a feature of seborrhea.

Table 3
Treatment for AD

Environmental control
Climatic control
Nonabrasive clothing and bedding (cotton)
Minimization of emotional stress
Avoidance of irritants
Avoidance of aeroallergens
Dietary control
Food allergen restriction
Skin care
Minimize trauma
Avoidance of harsh soaps/detergents
Hydration
Lubrication
Antipruritics
Hydroxyzine
Diphenhydramine
Corticosteroids
Topical
1% Hydrocortisone ointment to facial lesions
Medium potency ointment to body lesions
Systemic (rare use only)
Tar preparations
Antibiotics
Antistaphylococcal/antistreptococcal
Antifungal (rare use only)

Nummular eczema is a disorder characterized by well-circumscribed, circular lesions occurring primarily on the extensor surfaces of the extremities in areas of dry skin. Lesions begin as vesicles and papules that coalesce to form the discrete nonexudative, coin-shaped lesions. Lesions are only mildly pruritic. This disorder is not typically associated with atopy or elevated serum IgE.

Contact dermatitis, both irritant and allergic, can be seen in infants and young children. The skin eruption of irritant dermatitis varies with etiologic agent, but is commonly seen on the cheeks, chin, extensor surfaces of the extremities, and the diaper area. Irritant dermatitis is typically less pruritic than AD and improves with removal of the irritant, i.e., soaps, detergents, or abrasive bedding. Allergic contact dermatitis is characterized by a pruritic, erythematous papulovesicular eruption that involves exposed areas of contact. This dermatitis is uncommon during the first few months of life and can frequently be delineated by a careful history.

Psoriasis is a primary skin disorder that is most commonly seen in older children and adults, but may be seen on occasion in younger children. Fully developed lesions are distinctively different in

appearance from those of AD. Lesions are usually erythematous and covered by a silvery scale. Distribution is primarily on the scalp, extensor surfaces of the extremities, and the genital region. Nail involvement is commonly seen with pitting or punctate deformities of the nail surface.

Metabolic Disorders

Phenylketonuria is an inherited disorder caused by an inability to metabolize phenylalanine secondary to a defect in the enzyme phenylalanine hydroxylase. Affected individuals have fair complexion and blond hair. If untreated, seizures and mental retardation result. Approximately 25% of these individuals have an eczematous-like rash associated with their disease.

Acrodermatitis enteropathica is a lethal autosomal-recessive disorder with clinical symptomatology resulting from profound zinc deficiency secondary to an undefined defect in zinc absorption. The condition is characterized by dermatitis, failure to thrive, diarrhea, alopecia, nail dystrophy, severe gastrointestinal disturbances, and frequent infections. Dermatitis lesions are vesiculobullous and are distributed in a symmetric pattern in the acral and periorificial regions. Treatment of choice is elemental zinc replacement.

Celiac disease is a malabsorption disorder secondary to sensitivity to gliadin, the alcohol-soluble portion of gluten found in cereal grains. An eczematous dermatitis, dermatitis herpetiformis, has been reported to occur in some patients. Dermatitis herpetiformis is a highly pruritic skin rash that is characterized by a chronic papulovesicular eruption on the extensor surfaces and buttocks. This disorder is associated with celiac disease in up to 85% of patients. Treatment for celiac disease is lifelong dietary avoidance of gluten-containing foods.

Immunologic Diseases

Wiskott-Aldrich syndrome is an X-linked disorder characterized by the triad of thrombocytopenia, recurrent infections, and eczema. Patients have impairment of both humoral and cellular immune function. Elevated serum IgE is frequently found. The distribution of the eczematous rash is different from that typically seen in AD and is less responsive to usual medical management.

Nezelof and DiGeorge syndromes are disorders of T-cell immunity. Both have been associated with eczematous rashes and elevated serum IgE concentrations in some patients. The cause of the rash is unknown, but likely associated with the underlying immune dysfunction.

Severe combined immune deficiency (SCID) is a disorder of profound humoral and cellular immune deficiency. Infants frequently

present in the first 6 mo of life with failure to thrive, recurrent infections, diarrhea, and dermatitis. Like other immune deficiency syndromes, the eczematous appearing rash is in an atypical distribution and less responsive to conventional therapy.

Selective IgA deficiency is the most common immune deficiency disorder affecting approx 1 in 400 individuals. It is characterized by decreased mucosal immunity resulting in recurrent sinopulmonary, gastrointestinal, and genitoureteral infections. Some patients remain asymptomatic, whereas others manifest evidence of disease. IgA deficiency may be seen in association with atopic disease in some patients. These patients may develop asthma, allergic rhinitis, or AD. The dermatitis is more typical of AD, both in character and distribution.

Hyper IgE syndrome is an immune deficiency disorder characterized by markedly elevated serum IgE concentrations in association with recurrent, severe staphylococcal abscesses of the skin and lungs primarily. A chronic, pruritic dermatitis is commonly seen, but does not occur in the same distribution or have the same course as AD. Immunologic abnormalities have been found in both humoral and cellular function.

Other Disorders

Leiner's disease (erythroderma desquamativum) is a disorder that usually begins during the first few months of life and is characterized by severe generalized seborrheic dermatitis, intractable diarrhea, recurrent infections (usually Gram-negative organisms), and marked wasting and dystrophy. The dermatitis involves an intense erythema of the entire body, and extensive large, yellow, greasy scales affecting large portions of the body surface. These scales are desquamative, and large skin areas may slough. IgE levels are typically normal, and eosinophils are not present. The exact etiology of this disease is unknown, but a familial form exists and has been associated with dysfunction of the fifth component of complement (C5).

Langerhans cell histiocytosis disease is a lethal disorder that is a spectrum of diseases affecting the reticuloendothelial system. A subset of that spectrum, previously known as Letter-Siwe disease, involves a dermatitis that displays features of both seborrhea and AD. The eruption usually begins on the scalp and postauricular areas as a scaly, erythematous rash resembling seborrhea. The rash progresses to involve the trunk with dark, crusted papules that may be associated with petechiae or purpuric papules.

Treatment

At present there are no known cures for AD, and current therapy is largely symptomatic (7). Certain therapeutic measures can be

instituted that will dramatically reduce symptoms and control the overall skin condition (Table 3).

Environmental Control

Environmental control measures, both in the form of minimizing allergen exposure and pruritic stimuli, should be instituted in all patients with AD. Minimization of extreme fluctuations of temperature and humidity results in less pruritus. Sweating will induce pruritus in many patients with AD; therefore, a moderate temperature environment should be maintained. Clothing should be loose and free of wool. Cotton fabrics are generally the best tolerated. Coarse fabrics in clothing and bedding should be avoided. Complete rinsing of detergents, soaps, and bleach from clothing and bedding will also minimize their irritant potential. Occupational avoidance of aggravating agents, such as chemicals, irritants, and solvents, should be performed by older patients with AD. Minimization of emotional stress will also lessen the potential for pruritus.

Avoidance of known aeroallergens should be instituted when possible. The most easily avoided allergens are dust mites and animal danders. Dust mite-sensitive patients should institute full dust mite-avoidance procedures consisting of the following: plastic or hypoallergenic covers encasing mattresses and pillows, removal of all feather pillows and stuffed animals from the patient's room, frequent high-temperature washing of the bedding, and removal of carpeting and draperies from the patient's room when practical. Animals (especially cats and dogs) should be removed from the home, and contact should be minimized. Practical avoidance of other aeroallergens (e.g., avoidance of cut grass) should be attempted.

Dietary Restriction

In patients with food hypersensitivity, food allergen avoidance results in improvement of AD. Sampson and McCaskill have shown that by following a strict avoidance diet of relevant food allergens, patients experienced symptomatic relief of pruritus and clearing of skin rash (13). Owing to the high false-positive rate of prick skin testing and RAST for food allergens, an elimination diet followed by a blinded (single- or double-blind) or open food challenge should be performed to confirm clinical reactivity to a particular food, unless a convincing history of anaphylaxis is obtained. Extensive elimination diets should not be prescribed on the basis of skin test positivity alone owing to the obvious nutritional complications. The period of dietary restriction is allergen-dependent, but generally should occur for 1–2 yr before reintroduction or rechallenge with the implicated food.

Skin Care

General measures to reduce skin trauma owing to scratching should be instituted. Appropriate bedding and clothing can help minimize itching. In infants and children, gloves and socks can be used to reduce scratching, especially during sleep. Fingernails should be trimmed to minimize skin trauma from scratching.

Skin hydration is an extremely important measure in controlling the rash and pruritus associated with AD. Although some clinicians feel that frequent or routine bathing is contraindicated in AD, many others institute frequent bathing as part of the treatment protocol. Bathing hydrates the chronically dry skin of AD and may reduce the likelihood of bacterial superinfection, both of which will reduce pruritus and activation of lesions. In addition, swimming has long been recognized by patients with AD as a soothing therapy. Patients should bath in lukewarm water for 30 min once or twice a day (depending on the severity of disease). Burrow's solution, oatmeal, or oils (i.e., Alpha-Keri) may be added to the bath water to reduce pruritus further. Hydrating body wraps with water-soaked towels may be used in addition to bathing to maximize hydration of severely affected areas. Showers are inadequate in the management of AD owing to the lack of hydration obtained. Mild soaps (i.e., Dove or Basis) should be used for cleansing. Harsh soaps may be drying and serve to increase pruritus.

Lubricants should be applied to the skin immediately following bathing and other times during the day with a minimal application of twice daily. Lubricants will counteract dryness and "seal in" the hydration obtained from the prolonged bathing experience. Lubricants should be free of alcohols and perfumes, both of which can be irritating and drying. Effective lubricants include Vaseline, Unibase (oil in water preparation), Eucerin, or Aquaphor (water in oil preparations) plus others.

Antipruritics

Of major importance in the successful treatment of AD is interruption of the itch-scratch cycle. In addition to the methods mentioned previously, antihistamines and occasionally sedatives provide valuable relief of symptoms. Hydroxyzine (2 mg/kg/d divided every 6 h or given at bedtime; maximum adult dose 600 mg/d) and diphenhydramine (5 mg/kg/d divided every 6 h or given at bedtime; maximum adult dose 400 mg/d) have been shown to reduce drastically itching and sleep disturbance in patients with AD. In young children with severe disease, short-term sedation with chloral hydrate (50 mg/kg/d given at bedtime) may be needed until control of symptoms can be obtained. Topical application of Doxepin cream also pro-

vides relief of pruritus, but poses a greater risk for side effects owing to its systemic absorption. Doxepin should be used with close observation in all patients, especially children and patients with large skin surface areas affected.

Corticosteroids

Corticosteroids are used in AD to control inflammation. These preparations are very effective in controlling skin lesions of AD, but should be used wisely. There is little role for systemic corticosteroids in the management of AD, except in the most severe cases. When used, oral corticosteroids should be prescribed for only a limited time period and should be tapered judiciously. Patients will typically clear quickly with the use of oral corticosteroids, but frequently relapse once their use is discontinued. In addition, the side effects associated with use of systemic corticosteroids are well known and generally preclude their use.

Topical corticosteroid use in AD is the mainstay of therapy. The potency of topical steroids used is dependent on the severity of skin disease and the location of skin lesions. In general topical steroid potency is related to the vehicle and the chemical preparation. Gel preparations penetrate more effectively, but are drying and therefore not of great benefit in AD. Ointments penetrate well and enhance hydration, but feel occlusive and may be poorly tolerated during periods of high temperature (i.e., summer). Creams and lotions are less potent and penetrate less effectively than gels or ointments, but are more comfortable to some patients. Except in mild cases, ointments should be used owing to their higher penetrance and potency. The lowest strength that give adequate results should be used. Halogenated corticosteroid preparations, such as 0.1% betamethasone (Valisone), 0.025% flucinolone (Synalar), and 0.1 or 0.025% triamcinolone (Aristocort, Kenalog), have potent anti-inflammatory properties and can be used sparingly on affected body lesions. These preparations should not be used on the face. 1% Hydrocortisone cream or ointment can be sparingly used on the face, but the use of stronger preparations should be avoided. Topical steroids should be applied twice daily after application of lubricating creams or ointments as discussed. These preparations will penetrate the lubricant and reach the affected skin. Although generally safe from systemic absorption, diffuse application of topical steroids over long periods of time can have the adverse effects of striae, atrophic thinning of skin, ulcerations, hirsutism, acne, and telangiectasia. In addition, cases of adrenal suppression secondary to topical steroids have been reported. Although these complications are rare with prolonged use of low-potency topical steroids, their use in children and adults with severe disease should be monitored.

Tar Preparations

Coal tar preparations have been used for many years in the management of AD. Although topical corticosteroids have generally replaced the routine use of these keratolytic agents, they are still effective in the management of chronic, lichenified skin lesions that respond poorly to corticosteroids. The mechanism by which coal tar preparations work is unknown, but clinical evidence has shown that they have both anti-inflammatory and antipruritic effects. These preparations are well tolerated, but prolonged use may lead to folliculitis and photosensitivity. Shampoos containing tars are especially useful in the patient with scalp involvement, i.e., as in both AD and seborrhea.

Antibiotics

As previously stressed, patients with AD have a high degree of bacterial colonization of both affected and unaffected skin. The risk and occurrence of bacterial superinfection of the AD skin is therefore high, most commonly with *S. aureus* and streptococcal organisms. In addition, Leung and others (41a) have shown that some patients with AD produce specific IgE antibodies to various exotoxins produced from *S. aureus*. Because of these factors, antistaphylococcal and antistreptococcal antibiotics should be used liberally in the AD patient with documented or suspected bacterial superinfection. Skin cultures can be helpful in documenting the type of organism present and the antibiotic sensitivities of the organism. From a clinical standpoint, all patients with exudative, crusted, or excoriated lesions should raise the clinical index of suspicion for secondary bacterial infection. Appropriate antibiotic therapy should be instituted for 10–14 d. In cases of limited distribution of infected skin lesions, topical antibiotic therapy with preparations, such as Bactroban ointment, may be adequate. For most cases, systemic antibiotics will be required to eradicate the infection. Increased skin care regimen with more frequent bathing may also help to reduce the bacterial load.

A few reports have addressed the issue of secondary infection caused by fungal infections, such as *P. ovale*. These investigators have advocated the use of topical agents to fight fungal growth, such as use of Sebulex or Selsun shampoo. Others have recommended the use of oral antifungal agents when fungal organisms are documented or highly suspected. Experience to date is relatively empiric and not well established.

Phototherapy

UV light therapy with UV-A rays has been offered to some AD patients for control of lesions. Favorable results have been reported in

a small series of AD patients when phototherapy was provided to eczematous skin lesions and maintenance therapy was sustained. This method of therapy has been proposed for the patient who is poorly responsive to conventional therapy or in whom severe AD is present. Some have noted that phototherapy may be beneficial in children with severe disease requiring systemic steroids to reduce the potential side effects of long-term corticosteroids. Most commonly, UV therapy must be given at least weekly and sustained over long periods of time to prevent relapse. This regimen raises the issue of adverse effects of long-term UV light exposure, such as induction of malignancy and chronic skin changes. Most clinicians feel that the risk/benefit ratio is too high to encourage this form of therapy for the average AD patient. Phototherapy should therefore be reserved for the complicated patient that is poorly responsive to other forms of therapy.

Immunotherapy

Although allergen immunotherapy has been useful in some atopic conditions (i.e., allergic rhinitis), its role in the treatment of AD has been limited. In clinical practice, immunotherapy will frequently exacerbate the condition of AD rather than provide relief. Some clinicians advocate the use of immunotherapy, especially in older patients with significant aeroallergen hypersensitivity, but recommend initiating therapy with a much smaller dilution of allergen extract than would be performed in standard therapy for allergic rhinitis. The dose of extract needed to induce tolerance is often greater than the dose tolerated by the patient with AD, thereby precluding its use in most patients.

Immunomodulatory Therapy

As previously discussed, AD is associated with abnormalities of the immune system, especially with regard to cytokine production and IgE regulation. In particular, many investigators have shown a predominance of T_H2 -type lymphocytes, which produce excess amounts of IL-4 and therefore upregulate IgE production. These patients are noted to have little IFN- γ production in comparison. Some of these same investigators have also shown that IFN- γ suppresses IgE production in vitro and has effects on immune effector cell function. A recent, double-blind, placebo-controlled, multicenter trial was conducted to examine the effects of recombinant IFN- γ (rIFN- γ) administration to patients with chronic AD. Patients treated with IFN- γ had a significant reduction in symptoms and a mean reduction in circulating eosinophils when compared to the placebo-treated group. A previous trial of 23 patients also showed a significant fall in IgE synthesis in rIFN- γ -treated patients. These studies provide examples

of potential immune modulatory therapy that will likely become of more importance in the future as our understanding of the immunopathogenesis of AD expands.

Psychotherapy

AD is a very aggravating chronic disease that can be emotionally challenging for patients and families alike. Emotional distress and problems can trigger episodes of pruritus and worsen the AD condition. In addition young patients and their families may have difficulty understanding and coping with this chronic condition and may need help to establish parameters for discipline without adding to the emotional tension of an already aggravated child. Older children and adolescents may also experience body image problems related to the obvious skin abnormalities. For all of these reasons, some patients and their families will benefit from social service support and/or psychological counseling to address these issues. This is particularly important in the severe, chronic patient.

Prognosis

Currently there are no prospective, longitudinal studies evaluating the prognosis and disease remission of AD. Vickers retrospectively evaluated 2000 children with AD after 20 yr and noted an overall clearance rate of 84% (42). Vowles et al. likewise evaluated 84 patients after 13 yr and found only 45% resolution of disease (43). These and other studies reflect the difficulty in assessing prognosis with reports of disease resolution ranging from 37 to 84% in various retrospective surveys. In addition, no specific disease factors are predictive of the disease severity or course. Some patients are noted to have spontaneous resolution of their disease during infancy and early childhood. Improvement may also be seen during puberty in some patients, but exacerbations noted in others. Adults will often resolve or significantly improve after the second decade of life. As is common with atopic diseases, some patients resolve their AD, but develop other forms of atopy, such as allergic rhinitis and asthma. Until a well-designed, prospective, longitudinal survey of AD is conducted, predictions of disease outcome will remain purely speculative and based on clinical experience. These factors reiterate the need for consistent long-term follow-up and management to best serve the needs of patients with AD.

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