Proceedings of the 4th Georg Rajka International Symposium on Atopic Dermatitis, Arcachon, France, September 15-17, 2005

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The 4th Georg Rajka International Symposium on Atopic Dermatitis presented a comprehensive view of our current understanding and management of atopic dermatitis (AD). These proceedings highlight contributions related to the history of AD doctrines; genetic and epigenetic background; epidemiology; maturation of the immune system; infection and innate-adaptive immunity; epidermal inflammation, including neurogenic inflammation and pruritus; animal models; skin barrier; evidence-based therapy and education programs; prognostic and severity markers; and allergy testing. Several studies in animal models and human subjects point to impaired skin barrier function as a primary defect that facilitates the effect of environmental factors and immune dysregulation found in AD. The new frontier in AD therapy should, in the near future, reflect our better understanding of the skin barrier. The influence of environmental factors on the skin and other epithelial barriers in the perinatal period needs to be better understood to implement appropriate prevention programs. (J Allergy Clin Immunol 2006;117:378-90.)

Key words: *Atopic dermatitis, neonate, child, skin barrier*

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Disclosure of potential conflict of interest: A. Taïeb has consultant arrangements and has received grants from Novartis. All other authors—none disclosed.

Received for publication November 8, 2005; revised November 11, 2005; accepted for publication November 14, 2005.

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0091-6749/$32.00

doi:10.1016/j.jaci.2005.11.038

In this report we summarize the most important ideas and contributions of the 4th International Symposium on Atopic Dermatitis, as selected by the sessions' chairs and steering committee. The motto of the meeting, which had a pediatric dermatology focus, was ''Don't forget the patient!'' The abstracts of this 4th International Symposium on Atopic Dermatitis have been published in the *Journal of Investigative Dermatology*.[1]

Session 1: From history to genetics/ epidemiology, co-chaired by J. Hanifin (Portland, Ore), J. Harper (London, United Kingdom), and K. Cooper (Cleveland, Ohio)

D. Wallach from Paris gave a broad historical overview of attitudes and doctrines relating to atopic dermatitis (AD). He noted that Hippocratic humoralism, expressed by Mercurialis in the 16th century, considered cephalic oozing to be a beneficial excretory function of the skin. The necessity of oozing to clear infection and other agents thought to be transmitted through breast milk dictated a concept of not treating, which, Wallach suggested, has similarities to topical corticosteroid phobia and more recent topical calcineurin inhibitor phobia. Opposite to psoriasis, the lack of an easily recognizable primary lesion

Abbreviations used

AD: Atopic dermatitis
APT: Atopy patch test
EDC: Epidermal differentiation complex
HBD-2: Human β-defensin 2
LFC: Labial food challenge
NS: Netherton syndrome
PUFA: Polyunsaturated fatty acid
RCT: Randomized controlled trial
SA: State anxiety
SC: Stratum corneum
SCCE: Stratum corneum chymotryptic enzyme
SCTE: Stratum corneum tryptic enzyme
SCORAD: Scoring Atopic Dermatitis
SE: *Staphylococcus* enterotoxin
SOCS: Signal of cytokine suppressor
SPT: Skin prick test
TA: Trait anxiety
TEWL: Transepidermal water loss
TLR: Toll-like receptor

in AD made Willanism poorly adapted to describe the disease.[2] The 19th century was heavily focused on the concept of pruritic primacy, with itch becoming systemic to cause respiratory and enteric diseases. The focus on dietary cause and elimination also arose and was advanced in the 20th century by emphasis on immunologic reactions and allergologic doctrine.[3] This emphasis has been balanced in later years by the realization that many patients lack allergic features and that genetic and inflammatory abnormalities manifest primarily in the epidermis.[4] W. Cookson (Oxford, United Kingdom) addressed current concepts in the genetics and epigenetics of AD, particularly that for the latter, single nucleotide polymorphisms, promoter regions, CpG site methylation levels, and maternal imprinting are known as modifiers of disease expression. In addition to genome-wide scan studies, useful candidate gene approaches were emphasized. The structure of the protein (LEKTI) encoded by the SPINK5 gene[5] mutated in Netherton syndrome, which is always associated with atopic manifestations, was discussed. This serine protease inhibitor LEKTI is normally high in the epidermis, where it can inhibit inflammatory/barrier-disrupting serine proteases of microbes, such as *Staphylococcus aureus* or house dust mites (see Session 8). In Cookson's laboratory genetic mapping studies have been carried out in conjunction with *in vitro* keratinocyte gene expression studies during differentiation and inflammatory stimuli. At least 4 areas of the genome have been identified by means of genome scanning in patients with AD, generally not overlapping with asthma but overlapping with psoriasis, including areas on chromosome 1.[6] This chromosome contains the epidermal differentiation complex (EDC), which controls genes such as the S100s and cornified envelope proteins. Other candidates in the EDC include the chemokine SLC/CCL21 and the G protein–related receptor for asthma protein, which is also expressed in the airways. In a related communication, M. Moffatt and colleagues (Oxford, United Kingdom) extended observations on the EDC linkage. They identified 189 SNPs from 54 genes in the EDC and tested 111 SNPs for association in a panel of families related to severe childhood eczema (presumably AD, both pure and IgE reactive). Positional cloning identified 4 loci showing association between AD and psoriasis. One SNP showed strong association to AD and asthma.

M. Bradley (Karolinska Institute, Stockholm, Sweden) used DNA microarrays to analyze RNA expression in skin biopsy specimens taken from lesional AD skin, *Malassezia sympodialis* patch-tested skin, and control patch-tested skin. Gene expression analysis revealed a number of common features between lesional skin and patch test reactions. Immune response receptors for IL-4, IgE, and IL-6, as well a number of chemokines, were identified. Genes for epithelial cell-cell junctions and lipid metabolism, as well as antimicrobial peptides and mucin 1, were noted. Although epidermal growth factor receptor signaling proteins appeared downregulated, signal of cytokine suppressor (SOCS) 3 was upregulated. The researchers combined gene expression analysis with linkage analysis. Interestingly, SOCS3 proteins were altered, and SNPs of SOCS were genotyped. These studies indicated that an ATG haplotype conferred susceptibility, whereas a CCG haplotype was protective for disease expression. This type of analysis also confirmed the identification of overexpression of EDC 1q21 genes, such as the S100 family and SPRR. A similar approach was followed by Sugiura et al (Shiga, Japan), who concluded that abnormalities of epidermal differentiation associated with altered expression of genes located in 1q21 might be a key abnormality in AD.[7]

The last part of this session was devoted to epidemiology. T. L. Diepgen (Heidelberg, Germany) reviewed data from the ongoing Early Prevention of Asthma in Atopic Children study, which has screened toddlers 12 to 24 months with eczema and no asthma with a positive first-degree history of atopy. In this large high-quality database, in which strong associations could be easily measured, the association between ''hygiene'' factors and sensitization, Scoring Atopic Dermatitis (SCORAD) score, or urticaria were mostly negative and weak. There was a well-documented ''dog effect'' because early exposure to dog nearly halved the risk of concomitant sensitization to cat. Commenting on the dog effect and the hygiene hypothesis, K. Yamamoto (Tokyo, Japan) mentioned that AD was rare in Mongolia, where he visited recently. In this country individuals live in close promiscuity (around 8 per tent) with no water supply and in close contact with horses and sheep but with no cats. C. Flohr (Nottingham, United Kingdom) reviewed data from an International Study of Asthma and Allergies in Childhood subsample of approximately 31,000 eight- to twelve-year-old children who were examined and photographed for evidence of flexural eczema. Atopy, as defined by skin prick test (SPT) positivity, was also assessed. The association between the 2 features was higher in affluent regions, such as Hong Kong, but negatively related in Beijing. The study

suggested the causative role of IgE in AD has been overemphasized. H. Williams (Nottingham, United Kingdom) reported in a poster on 298,080 children of the world International Study of Asthma and Allergies in Childhood database, assessing changes in prevalence over a 7-year period. The centers showing previously the highest prevalences (the United Kingdom and New Zealand) showed a plateau or decrease in prevalence when opposite trends were observed in low-prevalence centers. Measurable changes in symptoms occurring in a short time reinforce the importance of environmental factors operating through a threshold effect in genetically susceptible individuals.

Session 2: Maturation of the immune system, co-chaired by K. Thestrup-Pedersen (Aarhus, Denmark), T. Bieber (Bonn, Germany), and C. Davrinche (Toulouse, France)

P. Holt (Perth, Australia) has developed an immunoepidemiologic approach to atopic diseases, comparing high-risk versus low-risk cohorts of children monitored clinically and immunologically over the first months to years of life.[8,9] If a maximal risk for sensitization to food-inhalant allergens does exist in early life, levels of risk are highly variable and related to differences in kinetics of postnatal maturation of immune function. T_H2-dependent effector mechanisms are important in atopy pathogenesis, but other (including T_H1-dependent) mechanisms are also involved. Considering immune regulation at the feto-maternal interface (placenta), there is a generalized reduction in cytokine production capacity most marked for T_H1 cytokines. In atopic subjects, as shown by profiles of cytokine secretion, postnatal maturation of T_H1 function is delayed relative to T_H2. The peak for IFN-γ is delayed around 18 months, and the reason for this delay seems to result from epigenetic regulation limiting promoter accessibility to transcription factors caused by cytosine methylation. In children at high genetic risk of atopy, the normal developmental window of attenuated T_H1 function is exaggerated, and the timing of the window coincides with first contacts with allergens.[10] Looking at postnatal development of house dust mite–specific T-cell immunity in a birth cohort of 240 ''high-risk'' infants, high IL-13 responses to house dust mite at 12 months seem to be a good predictor of sensitization, as evidenced by SPTs. Age-dependent changes in circulating dendritic cell populations have been noted in parallel. Myeloid dendritic cells at 6 to 12 months inversely correlated with mite sensitization at 1 year. As shown with cytokine responses to tetanus toxoid, diminished T_H1 competence in atopic children is transient and nearly abolished at age 6 years. A developmental ''overshoot'' in T_H1 functional maturation might occur in atopic subjects, but its significance in terms of natural history of AD-atopic diseases remains unclear. Among populations selected for high genetic risk of atopy, early sensitization is associated with increased $CD8^+$ T-cell reactivity, in particular to *Staphylococcus* enterotoxin (SE) B. Hyperresponsiveness to SEB is a hallmark of children with active AD.

E. Isolauri (Turku, Finland) pioneered the importance of the immunoregulatory potential of gut microbiota as a key actor of the maturation of the immune system, triggering a cross-talk between the innate and adaptive system. This hypothesis, based on previous studies of gut microflora in atopic and nonatopic children, has led to interventional studies with probiotics, microbial food supplements or components of bacteria that have beneficial effects on human health. However, several questions remain partially answered: When is the critical window to intervene? Which are the protective mechanisms? Which are the best microbes to use? Probiotics stimulate gut humoral immunity (IgA) and alleviate inflammatory response, promoting overall a gut barrier effect. E. Isolauri pointed out that the interaction of several ingredients of the diet is important when considering AD as the main outcome measure of prevention. She presented a recent follow-up study from birth to 4 years indicating that increased intakes of retinol, calcium, and zinc, with perinatal administration of probiotics, reduced the risk of AD.[11] She also indicated that breast milk rich in saturated and low in n-3 fatty acids might be a risk factor for AD in the infant.[12] An interaction between probiotics and breast-feeding was further demonstrated on a number of immunoglobulin-secreting cells, suggesting that probiotics during breast-feeding might positively influence gut immunity.[13] Two studies with different strains of bacteria presented at the Symposium by Weston et al[14] (Perth, Australia) and Yim et al (Seoul, Korea), respectively, in young children (randomized controlled trial) and children and adults (open trial) with moderate-to-severe AD showed measurable but limited clinical benefit.

The other papers presented at this session covered the following. First were plasmacytoid dendritic cells, which correlate with IgE and SCORAD. These atopic plasmacytoid dendritic cells promote T_H1 or T regulatory cells with a high potential for IFN-γ and IL-5 production that protract T_H1-eosinophilic inflammation in the skin[15] (Hashizume et al, Hamamatsu, Japan). Second were recent immigrant T cells, which are measured using the marker T-cell receptor excision circles and which are related to thymic function (release of T cells). Some data suggest that thymic emigration of T cells might correlate to severity markers (Just et al, Aarhus, Denmark). Third was the role of SEB in T_H2 polarization and modulation of Toll-like receptors (TLR) 2 and 4. An interesting observation was made concerning decreased IL-12 production in response to LPS by atopic monocytes in adult AD, which was not abolished in some children, suggesting a link between T_H2 skewing and disease progression (Mandron et al, Toulouse and Bordeaux, France).

Session 3: Infection and immunity, co-chaired by J. D. Bos (Amsterdam, The Netherlands), G. Imokawa (Tokyo, Japan), and J. F. Nicolas (Lyon, France)

This session concentrated on the interaction in AD between immunology and infectious agents, mostly

S aureus. D. Y. M. Leung, (Denver, Colo) reviewed the immunologic pathways by which infectious agents play a role in the inflammation. Epicutaneous application of *S aureus* superantigens induces eczema and enhances T_H2 skin responses. Most patients with AD make specific IgE antibodies directed against staphylococcal superantigens, and these IgE antisuperantigens correlate with skin disease severity. Superantigens also induce corticosteroid resistance,[16] expand skin-homing T cells, and subvert T regulatory cell activity,[17] suggesting that several mechanisms exist by which superantigens increase AD severity. Increased binding of *S aureus* to skin is driven by underlying AD skin inflammation. This is clinically supported by studies demonstrating that treatment with topical corticosteroids or calcineurin inhibitors reduces *S aureus* counts on atopic skin. AD skin has also been found to be deficient in antimicrobial peptides (defensins and cathelicidins) needed for host defense against bacteria, fungi, and viruses.[18] Thus once *S aureus* binds to AD skin, inadequate local host defense allows bacteria to colonize and grow. The lack of skin innate immune responses predisposes these patients to infection.

T. Werfel (Hannover, Germany) studied other aspects of the pathogenic role of *S aureus* in AD. He first noted that patients with the so-called intrinsic form of AD still have IgE-mediated sensitizations to *S aureus* superantigens and other microbial antigens.[19] He then showed a recent study of his group suggesting that superantigens amplify the allergic patch test response to house dust mites in AD. In addition to SEB, which has been studied extensively, other SEs trigger immune responses that might play a further pathogenic role. Deficiency in IgG2 antibodies against SEC1 defines a subgroup of patients with severe AD.[20] TLR-2 or TLR-4 polymorphisms are seen in 23.5% of patients with AD but only 5% of healthy control individuals, and the TLR-2 polymorphism R753Q is associated with severe AD.[21] *S aureus*–derived α-toxin activates endothelial cells and keratinocytes and $CD4^+$ T lymphocytes.[22]

M. Howell (Denver, Colo) stressed an additional role of the antimicrobial peptide cathelicidin in innate immunity against viral infection based on the clinical evidence of widespread dissemination of some viral infections in AD (eczema herpeticum and eczema vaccinatum). Using cultured keratinocytes and skin explants from AD, psoriasis, or normal skin, he demonstrated that AD skin susceptibility is due to the decreased ability of induction of cathelicidin by viral infection in AD skin compared with that in psoriasis or normal skin. Interestingly, this downregulated production in AD skin correlates with an upregulated expression of T_H2 cytokines, such as IL-4 and IL-13. The reduction of cathelicidin might potentiate vaccinia virus replication in AD skin and predispose patients with AD to adverse reactions from smallpox vaccination.[23]

S. Asano (Tokyo Women's Medical University, Japan) looked at *S aureus* colonization in the stratum corneum (SC) of AD and human β-defensin 2 (HBD-2) content. First, because of the lack of an accurate analytic method for HBD-2, she developed microanalysis of HBD-2 using the combined technique of immunoprecipitation and Western blotting, finally preparing a standard curve for its quantitation. In contrast to previously reported papers, the content of HBD-2 in the SC expressed as nanograms per microgram keratin was found to be significantly increased in AD nonlesional and lesional skin compared with that in normal skin, and this increased level was equivalent to that in psoriasis skin. Also, she found that HBD-2 increased in proportion to AD severity in both nonlesional and lesional skin and that the content of HBD-2 correlated with *S aureus* colonization in the same skin sites. Asano concluded that HBD-2 becomes inducible in response to bacteria, injury, or inflammatory stimuli and is not associated with vulnerability to *S aureus* colonization in the skin of patients with AD. D. Y. Leung commented that these data concerned only the SC and not the whole epidermis and that reduced immunostaining for antimicrobial peptides levels has been consistently observed in the basal epidermis of AD.[18]

Subsequently, N. Novak (Bonn, Germany) reviewed her most recent data on Langerhans cells and inflammatory dendritic epidermal cells, which are considered amplifiers of inflammatory skin responses in AD.[24] *In vitro* studies with tacrolimus suggest an effect mediated by TGF-β– and IL-10–producing T regulatory cells, leading to less immunogenic responses to environmental allergens.

Session 4: Epidermal inflammation, including neurogenic inflammation and pruritus, co-chaired by A. Giannetti (Modena, Italy), T. Luger (Münster, Germany), and U. Gieler (Giessen, Germany)

Pruritus is the most important symptom in AD but is, however, rarely taken as a relevant end point in pathophysiologic studies. B. Homey (Düsseldorf, Germany) reviewed chemokines associated with AD, which are key factors promoting tissue inflammation. Serum levels of CCL11, CCL17, CCL18, CCL22, CCL26, CCL27, and CX_3CL1 directly correlate with disease severity, suggesting an important role in the immunopathogenesis of AD. CCL27 is a skin-specific chemokine produced by keratinocytes that attracts $CD4^+/CLA^+$ memory T cells and binds CCR10 (GPR-2). CCL27 expression is regulated by TNF-α/IL-1β, and in a mouse model CCL27 neutralization inhibits T-cell recruitment.[25] In the vicious loop that produces-enhances pruritus, chemokines and their receptors are necessary intermediates in the cross-talk between resident and ''in-transit'' cell targets. Because mechanical trauma from scratching is at the center of the loop (Fig 1), B. Homey presented evidence that epithelial cells can trigger allergic inflammation through the thymic stromal lymphopoietin–CCL17/thymus and activation-regulated chemokine–CCL22/macrophage-derived chemokine pathway. Furthermore, allergens and superantigens induce CCL18/serum pulmonary and activation-regulated chemokine, a dendritic cell–derived chemokine.[26]

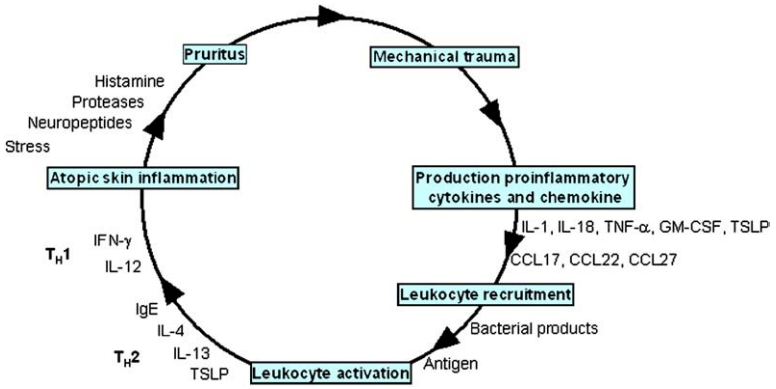

FIG 1. The amplification circle of atopic skin inflammation. Pruritus, the major symptom, induces scratching that enhances inflammation through leukocyte recruitment and activation. Among the molecules acting at each step, a key role is devoted to chemokines. Adapted from B. Homey's communication. *TSLP,* Thymic stromal lymphopoietin.

B. Homey showed evidence that the axis CCL1-CCR8 links adaptive and innate immune functions that play a role in the initiation and amplification of atopic skin inflammation,[27] including infiltration by eosinophils. In summary, CCL1, CCL17, CCL18, CCL22, and CCL27 are likely candidates to critically regulate the recruitment of memory T cells to sites of atopic skin inflammation, highlighting potential areas for therapeutic intervention by chemokine receptor antagonists.

U. Gieler (Giessen, Germany) questioned whether AD is a neurogenic inflammatory disease. The concept of ''névrodermite'' from Brocq and Jacquet[28] was put in modern perspective, and Gieler emphasized the close connection between epidermal nerve fibers and both atopy-relevant effector cells[29] and the brain in the context of new developments in brain research and studies with neuropeptides in skin diseases.[30,31] The autonomic nervous system acts as the connector between feelings and subsequent somatic response. Lymph nodes contain sympathetic afferents; adrenergic and cholinergic fibers are found in the thymus, and the lymphocytes also have adrenergic and cholinergic receptors. Psychologic stress can be conceptualized as a social pollutant that, when ''breathed'' into the body, can disrupt biologic systems related to inflammation through mechanisms potentially overlapping with those altered by physical pollutants and toxicants.[32] Stress-induced alterations have been measured in permeability barrier homeostasis mediated by increased endogenous glucocorticoids.[33] The Kobe earthquake data on AD provide a good example of the effect of stress on the disease.[34] U. Gieler concluded that Brocq and Jacquet were correct in their 1891 concept of ''névrodermite'' (neurodermatitis) but would prefer the wording ''neurogenic dermatitis,'' with the following arguments: AD depends on nerves, AD and affective disorders interact, AD is stress dependent, AD is triggered by peripheral nerves and neuropeptides, and AD itch correlates with brain activity.

M. Takigawa (Hamamatsu, Japan) presented recent studies on AD and anxiety, with the background that stress elaborates anxiety on the one hand and affects immune functions on the other. He studied trait anxiety (TA), the anxiety felt in general, and state anxiety (SA), the anxiety felt at present, versus severity and immune parameters in AD. Serum total IgE levels were highly correlated with TA/SA ratios, indicating that those patients with AD with higher TA levels compared with SA levels had increased serum IgE levels. Anxiety did not correlate with the severity of dermatitis, itching, or eosinophil number. He suggests that persistent stress stimulates a T_H2 immune response in AD through preferential elaboration of TA. Stressors stimulate the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, releasing adrenal glucocorticosteroids and norepinephrin, respectively, and thus could tilt cutaneous inflammation toward the T_H2 response.[35]

In a related therapeutic study, M. Takigawa, noting that symptoms in patients with AD are not sufficiently relieved by antihistamines, carried out an open trial to examine the effect of tandospirone, a serotonin 1A receptor agonist exerting antianxiety effects, on relief of skin symptoms in adult patients with AD. In the patients with TA/SA ratios of greater than 1.0, the TA/SA ratio significantly decreased when treated with tandospirone compared with that without it, suggesting an attenuation of itching by successful control of mental stresses with tranquilizers. He concluded that everyday stressors might repeatedly stimulate a T_H2 immune response, resulting in protraction of inflammatory responses, and that intervention with sedatives can be a part of the management strategy in stress-associated itching in patients with AD.

C. Gelmetti (Milan, Italy) indicated the possibility of detecting by means of graphology specific deficiencies, such as physical weakness, poor memory, anxiety, stress, depression, and lack of confidence. Preliminary results indicate that the quality of handwriting can be disturbed in patients with AD and modified in the course of the disease.

Other papers presented at this session dealt with transcriptional regulation of important chemokines (CCL27 and nuclear factor κB; C. Vestergaard, Aarhus,

Denmark),[36] neurotrophin brain-derived neurotrophic factor (U. Raap, Hannover, Germany),[37] and the TNF-related apoptosis-inducing ligand (D. Simon, Bern, Switzerland)[38] and their potential implications as targets in therapy.

Session 5: Clinical research, prognostic and severity markers, co-chaired by T. J. David (Manchester, United Kingdom), J. Ring (Munich, Germany), and C. Gelmetti (Milan, Italy)

This session comprised 3 parts: a fundamental and challenging reappraisal of the whole concept and natural history of AD by Bieber linking previous hypotheses,[39,40] a series of research studies, and 3 papers that served as a sharp reminder of the striking psychosocial effect of AD.

T. Bieber (Bonn, Germany) compared ''intrinsic'' (nonallergic) and ''extrinsic'' (allergic) AD, stressing that impaired skin barrier function was common to both subsets. Curiously, in the intrinsic category, at least in adults, most affected individuals are female, an unexplained anomaly. Intrinsic eczema and extrinsic eczema are characterized by different SNPs in the IL4 and IL4RA genes, respectively.[41] In addition, the concept of an ''allergic march'' is challenged by the finding of greater similarities between the gene loci for AD and psoriasis than between the gene loci for AD and asthma. Bieber elaborated his argument by pointing out that in infants AD-like skin lesions often start in the absence of specific IgE antibodies, implying that IgE sensitization is (1) not a prerequisite for eczematous skin lesions and (2) might occur after cutaneous inflammation. To what extent this inflammatory process is driven by food allergen–specific T cells is unclear, but Bieber referred to animal models showing that repeated topical application of antigen can lead to a specific IgE response, asthma, and inflammatory skin lesions.

Bieber also made reference to the common finding (in adults with AD) of specific IgE directed against self-proteins, such as structural proteins from keratinocytes, suggesting the possibility of an autoimmune-autoinflammatory scenario evolving from mechanisms of molecular mimicry on the basis of an initial IgE response to highly conserved microbial structures. Bieber's hypothesis therefore is that AD emerges initially in the form of eczematous skin lesions and then, depending on the gene sets involved, evolves into the intrinsic or extrinsic category. The latter might be followed by ''autosensitization,'' possibly explaining why interventions, such as house dust mite allergen avoidance, might fail (Fig 2). The subsequent discussion of this presentation indicated the need to rethink what we mean by the term ''atopy'' and the need to more carefully assign or reassign patient categories in genetic linkage studies, which might have been undermined by the misallocation of patients into various disease groups and subgroups. The problem with this debate remains that the intrinsic variant is only negatively defined; what is needed is a positive marker for intrinsic (ie, nonatopic) dermatitis (Hanifin). It was also noted that skin breakage could lead to T-cell priming beyond the skin (Holt).

P. Schmid-Grendelmeier (Zurich, Switzerland) gave 2 presentations concerning the skin fungus *Malassezia sympodialis* and its relationship to AD. He found the following: (1) *M sympodialis*–specific IgE positivity was present in 24 (46%) of 52 patients but 0 of 10 healthy control subjects; (2) *M sympodialis* DNA was extracted from 36 (69%) of 52 patients and 2 (20%) of 10 control subjects; and (3) no significant correlation between SCORAD and either colonization or sensitization was present, casting some doubt on the role of *M sympodialis* in AD. In another study Schmid-Grendelmeier found that human manganese superoxide dismutase induced positive SPT results in 29 of 69 patients with AD. Interestingly, such reactivity was also found in patients with nonatopic eczema and was strongly correlated with disease severity. All patients reacting to manganese superoxide dismutase were also sensitized to *M sympodialis*, possibly representing molecular mimicry.[42]

C. O. Park (Yonsei, Korea) studied thymic stromal lymphopoietin expression in keratinocytes of patients with AD and control subjects. The finding was that thymic stromal lymphopoietin expression was greater in lesional keratinocytes than in nonlesional keratinocytes in patients and control subjects, which is consistent with previously reported findings.

J. S. Kim (Uijeongbu, Korea) presented data showing a significant increase in plasma macrophage migrating inhibitory factor in a sample of 265 patients with AD when compared with 116 healthy control subjects. It was speculated that this might become a useful parameter with which to distinguish between intrinsic and extrinsic AD.

N. Higashi (Tokyo, Japan) studied 47 patients aged 18 to 64 years with mild-to-severe AD and 9 healthy volunteers aged 26 to 45 years. Measurement of the serum I-309/CCL1 levels showed that the levels were significantly higher in patients (mean, 4.21 ± 4.88 pg/mL) than in control subjects (mean, 0.62 ± 0.67 pg/mL). The I-309/CCL1 levels were significantly higher in patients with severe AD than in patients with mild disease. The I-309/CCL1 levels were correlated with the eosinophil count and with the serum lactate dehydrogenase level. It was speculated that the serum I-309/CCL1 level could be used as a marker of disease severity in AD.

B. Pigozzi (Padua, Italy) measured the serum concentration of IL-16 in 34 children with AD (mean age, 6.5 years) at their first visit and then after 3 months' treatment with tacrolimus and in 10 healthy nonatopic control children. The aim of the investigation was to see whether there was any correlation between IL-16 level and skin disease severity. However, despite the finding that IL-16 levels were higher in patients than in control subjects, the important outcome was that although the dermatitis improved after treatment, the IL-16 levels were on average actually slightly higher after 3 months' treatment.

A. J. Kanwar (Chandigarh, India) compared the Hanifin and Rajka and UK Working Party diagnostic criteria in a sample of 101 children with AD and 48 control subjects.

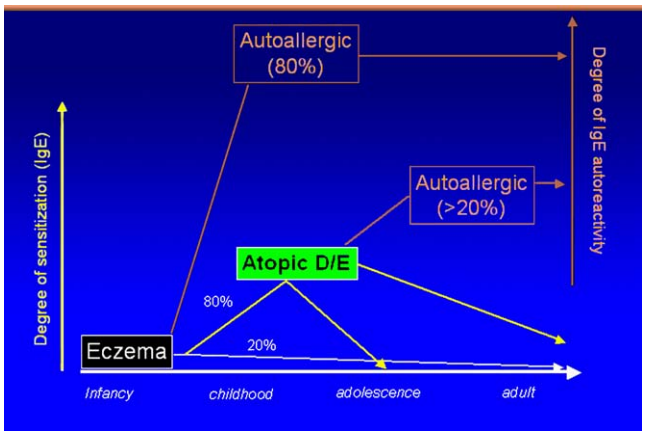

FIG 2. AD: a hypothetical lifetime scenario emphasizing relationships between IgE sensitization and IgE autoreactivity over time. Eczema corresponds in infancy to a pruritic skin inflammation without detection of markers of atopy. In these patients eczema might either vanish or persist and remain nonatopic (20%). However, for 80% of persisting cases, it is just a transient phase that precedes sensitization to common allergens. Autoallergy starts early in childhood (80% of patients are autoallergic at 6 years of age) but can begin later at adolescence. Autoreactivity is associated in adults with early-onset AD (2-6 years), marked xerosis, recurrent bacterial and viral infections, and high total IgE and specific IgE levels to *D pteronyssinus*, *Aspergillus* species, *Candida* species, and *Malassezia* species. Figures for autoallergy are derived from Mothes N, Niggemann B, Jenneck C, Hagemann T, Weidinger S, Bieber T, et al. The cradle of IgE autoreactivity in atopic eczema lies in early infancy. J Allergy Clin Immunol 2005;116:706-9.

The UK criteria are simplified for epidemiologic surveys but are not precise enough for clinical and genetic studies. Under the conditions of the study, the Hanifin and Rajka criteria performed marginally better in terms of sensitivity and specificity. As has been noted previously,[43,44] validation of research instruments must be done by independent outside groups, and epidemiologic assessments must be confirmed in various racial and ethnic groups.

F. Turk (Basel, Switzerland) reported a study of patients and parents in 8 countries (International Study of Life with Atopic Eczema [ISOLATE]). Factors that adversely affected quality of life were percentage of performance at work affected, percentage of body affected, severity of itch and eczema, and disturbance of sleep.

A. Taïeb (Bordeaux, France) presented a subset of ISOLATE data based on telephone interviews of 2002 patients (>13 years of age) with AD or the parents-caregivers of children aged 2 to 13 years. The findings were that in this large sample adolescents with AD experienced, on average, 8 flares and spent 3.5 months in relapse each year. Flares caused severe itching in 60% of adolescent patients and prevented 83% of them from participating in everyday activities. AD was shown to adversely affect mood, self-confidence, and relationships.

P. D. Arkwright (Manchester, United Kingdom) used questionnaires to compare the effects of AD with asthma on parental sleep disturbance and parental anxiety and depression scores. Mothers caring for children with AD lost a median of 39 minutes of sleep per night and fathers lost 45 minutes sleep per night compared with a median of 0 minutes sleep lost for parents of children with asthma. There was a correlation between the severity of sleep disturbance and the level of maternal depression and anxiety and the level of paternal anxiety. On the face of it, compared with looking after a child with asthma, caring for a child with AD is associated with significantly greater parental sleep disturbance. Limitations of the study include the older age of the asthmatic patients, the data on the degree of asthma control, and the rather low questionnaire response rate.

Session 6: Animal models, co-chaired by A. Kapp (Hannover, Germany) and M. Furue (Fukuoka, Japan)

There has been an increasing interest in animal models to study the induction, propagation, and persistence of the inflammatory process in AD.[45] In this session interesting models in dogs and mice were presented, investigating different aspects of inflammation and showing significant similarities with human AD.

In his presentation, ''Canine AD: a natural model to study the human disease,'' T. Olivry (Raleigh, NC) clearly demonstrated that dogs are the only other species with naturally occurring AD. Moreover, AD represents a common canine disease in which clinical signs resemble those of the human disease. Treatments with good evidence of efficacy are glucocorticoids and calcineurin inhibitors, like in human subjects. Actual immunologic studies of canine AD suggest homology with the human disease. Taken together, canine AD is probably the closest animal model to human AD.[46]

L. Nagelkerken (Leiden, The Netherlands) presented a novel model of AD that develops spontaneously in human apolipoprotein C1 (APOC1) transgenic mice, which were developed to study the role of APOC1 in lipid metabolism. These mice display a disturbed skin barrier function evident from increased transepidermal water loss (TEWL). From the age of 9 weeks onward, they experience

symptoms of dermatitis, such as scaling, discoloration, lichenification, excoriations, and increased pruritus. Affected skin shows increased numbers of inflammatory cells in the dermis and epidermal hyperplasia. Increased levels of IgE are found in serum and in association with the mast cells in the dermis. All of these aspects appear sensitive to suppression by topical application of 0.1% triamcinolone acetonide.[47]

A. Hennino (Lyon, France) reported the establishment of a mouse model for AD in normal C57Bl6 mice by using *Dermatophagoides farinae* as the eliciting allergen for epicutaneous application. It was shown in this study that repeated topical application of protein allergens in normal mice is responsible for the induction of AD-like lesions. $CD8^+$ T cells appeared to be the major effector cells in this model. Development of eczematous lesions was increased in CD4-depleted mice, suggesting a regulatory role for $CD4^+$ T cells in this model. Moreover, the development of an AD phenotype was not associated with detectable IgE production.

S. Takeuchi and colleagues (Fukuoka, Japan) reported a mouse model to assess the effects of scratching. They used plastic collars that were placed around the neck to prevent the mice from scratching (or grooming) their ears during cutaneous hypersensitivity. After elicitation, the ear swelling of collared mice was significantly decreased by 41% to 51% compared with that seen in control mice in which collars were not used. The authors concluded that scratching contributes considerably to the increase in ear thickness that is seen in cutaneous hypersensitivity in mice. This model thus enables them to assess itching as a part of the cutaneous hypersensitivity skin reaction and might be suitable to assess or screen antipruritic agents or new drugs.

H. Mizutani (Mie, Japan) presented a new system for rapid and specific acoustic analysis of the itch in an AD mouse model. For this purpose, a novel counting system for scratching has been developed by using a computer-based acoustic analysis system. This system clearly evaluated invisibly rapid scratching of the mice as accurate as slow-motion video–based systems within a few minutes and revealed effects of an antihistamine to itching in mice models.

Session 7: Skin barrier, co-chaired by J. F. Stalder (Nantes, France), C. Turjanmaa (Tampere, Finland), and M. Takigawa (Hamamatsu, Japan)

This session provided the newest insights into the abnormalities of the skin barrier. Particular emphasis was put on the recent rediscovery of a metabolic view of the skin barrier, with an imbalanced protease/antiprotease ratio leading to allergen-irritant penetration and to innate-acquired immunity disturbances. In particular, the penetration in the skin of the most common allergens, large molecules which have a proteolytic activity, is now better understood.

A. Hovnanian (Toulouse, France) has identified mutations in the SPINK5 gene encoding the serine protease inhibitor LEKTI as causative of Netherton syndrome (NS).[48] This discovery, based on the strong association of NS with atopy and especially AD, has generated a new view on the barrier defect in AD. In his laboratory he has generated SPINK5-null mice, which faithfully replicate key features of NS, including abnormal desquamation, impaired keratinization, hair malformation, and a skin barrier defect.[49] LEKTI deficiency in mice causes SC tryptic enzyme (SCTE) and SC chymotryptic enzyme (SCCE)–like hyperactivity, resulting in desmoglein 1 degradation and abnormal desmosome cleavage in the upper granular layer. This leads to defective SC adhesion and resultant loss of skin barrier function, from which the animals die within a few hours of birth. Profilaggrin processing is increased, and loricrin and involucrin are overexpressed, implicating LEKTI in the cornification process. Intercellular adhesion is lost in the inner root sheath, and hair shafts are irregular and shrunken. Transplantation experiments of whole skin from SPINK5 knockout mice reproduce major histologic changes similar to those seen in patients with NS. In a related poster P. Descargues and colleagues (Toulouse, France) analyzed the expression of desmosomal proteins and terminal differentiation markers by means of immunohistochemistry in the skin of 12 patients with NS and showed anomalies of desmosomal protein expression, with altered desmosome ultrastructure in the upper living layers of epidermis and a redistribution of SCTE immunostaining in 3 patients with NS in the same cellular layers where the expression of desmosomal components was reduced. SC protease activities were increased in the epidermis of patients with NS in comparison with that seen in the epidermis of control subjects, as shown by means of *in situ* zymography. Hovnanian concluded that LEKTI is a key regulator of epidermal protease activity, with profound effects on epidermal desquamation, the cornification process, and hair formation.

J.-P. Hachem (Brussels, Belgium) defined the primary function of the SC as limiting excess transcutaneous water loss from the aqueous interior. Whereas the acidic surface mantle of the skin was first described more than a century ago, its functions, other than antimicrobial, remain largely unknown. At least 3 endogenous mechanisms exist: (1) free fatty acid generation from phospholipid hydrolysis, (2) a sodium-proton antiporter (NHE1), and (3) histidine metabolism to urocanic acid, acidify either whole SC, inner versus outer SC, or specific membrane microdomains. Acidification regulates the key SC function: permeability barrier homeostasis, integrity-cohesion, and antimicrobial activity.[50] In collaboration with P. Elias (San Francisco, Calif), he has recently shown that permeability barrier recovery is delayed by even short application of superbases, compounds that are 10 times more basic than in 1N sodium hydroxide.[51] In contrast to transient pH alterations, sustained SC neutralization alters not only barrier recovery kinetics but also basal barrier function because of serine protease–mediated enzyme degradation and causes accelerated corneodesmosome degradation (Fig 3). Sustained increases in SC pH are an appropriate model for neonatal skin, which displays

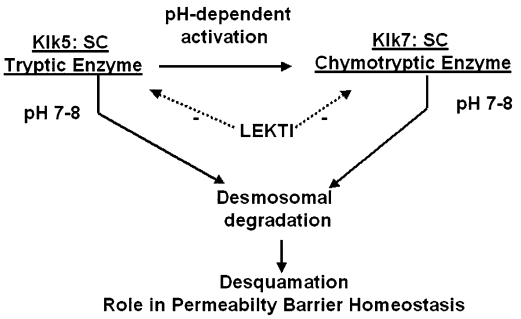

FIG 3. pH-Dependent roles for serine proteases and serine protease inhibitors, such as LEKTI. Several types of protease activity have been identified in the SC, with a convincing link to desquamation for 2 serine proteases, SCCE/Klk7and SCTE/Klk5, based on *in vitro* inhibitor studies. Because both of these serine proteases are most active at a neutral pH, the normal acidic environment of the SC would reduce the catalytic activity of these enzymes, and conversely, an increase in SC pH would increase serine protease activity, a factor of barrier disruption that could be further aggravated if inhibitors are poorly functional or defective (eg, absence of LEKTI in NS). Adapted from J. P. Hachem's communication. *Klk,* Kallikrein.

normal basal barrier function but abnormalities in both barrier recovery and SC integrity-cohesion. Hachem et al[52] emphasized that a sustained increase in SC pH could either trigger, exacerbate, or prolong the manifestations of AD and other inflammatory skin disorders.

M. Brattsand (Umea, Sweden), who works in T. Egelrud's laboratory, noted that to keep the skin barrier intact, it is very important to have a well-regulated proteolysis at the skin surface balanced with *de novo* differentiation of keratinocytes starting from the basal cell layer. This balance is disturbed in AD. She reported on 3 different serine proteases present in the active form from the outermost parts of the SC. All 3 enzymes, SC tryptic enzyme (kallikrein 5), SC chymotryptic enzyme (kallikrein 7), and kallikrein 14, belong to the same gene family, the tissue kallikreins. Both kallikreins 5 and 7 are thought to be involved in the degradation of desmosomes at physiologic pH.[53] If all 3 proteins can be detected on the outermost surface of the SC, kallikrein 14 is different compared with the other 2 proteins because immunohistochemistry shows predominant staining of the sweat glands. All 3 enzymes are produced as inactive preproenzymes that are exported to the outside of the cells. To become active, a proteolytic cleavage by an enzyme with tryptic cleavage specificity of the propeptide is required. Kallikrein 5 can activate itself, as well as kallikreins 7 and 14, in a pH-dependent manner that might have physiologic implications.[54]

A prospective study on infantile AD was presented by F. Boralevi et al (Bordeaux, France), investigating possible correlations between TEWL and aeroallergen sensitization and showing that 89% of infants with AD had positive atopy patch test (APT) responses to common aeroallergens and a significantly higher TEWL than control subjects. TEWL correlated with the number of APT sensitizations and increased with AD severity. No correlation was found between positive APT responses and exposure to house dust mite, cat, and dog at home. Boralevi suggested an early and provocative role of a constitutive epidermal barrier impairment for atopic sensitization in infantile AD.

H. Matsuki (Osaka, Japan) presented 2 papers from Imogawa's group. The first investigated barrier function and water content of nonlesional forearm AD skin compared with AD global severity and intensity of dryness-scaling-itchiness at the same skin sites. It was suggested that the abnormal barrier functions of nonlesional skin in patients with AD predominantly reflect the severity of AD but are also associated with the intensity of the local skin dryness caused by decreased water content. Matsuki then reported on a topically applied synthetic ceramide- or hirudoid-containing cream to the nonlesional skin of patients with AD for 4 weeks. Treatment for 4 weeks with the ceramide-based cream provided a better recovery in barrier function, which suggests that the barrier-replenishing effect is a more important factor for treatment of AD nonlesional skin than just restoring water losses.

Session 8: Evidence-based therapy, education, and quality of life, co-chaired by Y. de Prost (Paris, France), P. Schmid-Grendelmeier (Zürich, Switzerland), and T. L. Diepgen (Heidelberg, Germany)

In his lecture H. Williams (Nottingham, United Kingdom) reviewed the 80 randomized controlled trials (RCTs) published since the UK National Health Science–sponsored Heath technology assessment systematic review.[55] He reviewed RCTs validating the concept of weekend therapy for topical steroids, which improves the time to relapse with good safety,[56,57] as well as RCTs concerning topical tacrolimus and pimecrolimus,[58] probiotics, cetirizine (Early Treatment of the Atopic Child [ETAC] study), and gammalinolenic acid. He introduced in the future hot topics the education programs that have been developed using an RCT method.

T. Werfel (Hannover, Germany) and U. Gieler (Giessen, Germany) presented the German multicenter trial of education in AD, the German Atopic Dermatitis Intervention Study,[59] showing the benefit of educational programs of patients or caregivers in this chronic affliction. Standardized AD group intervention programs were developed to educate parents of children with AD 3 months to 7 years of age (group 1, n = 274), parents and their children with AD aged 8 to 12 years (group 2, n = 102), and adolescents with AD aged 13 to 18 years (group 3, n = 70). All patients had a severity of AD of at least 20 points on the SCORAD scale. Parents, children, or both in the interaction group took part in 6 weekly group sessions of 2 hours each. In all age groups, significant improvements in SCORAD severity and subjective severity of AD were seen in the intervention groups compared with the control groups. An improvement of the quality-of-life subscales was also noted in all the intervention groups.

K. B. Suhr (Daejeon, Korea) also determined the effect of a parental training program in 257 families attending weekly educational programs for 1 month. Significant effects were shown regarding regular bathing and use of topical steroids and a significant reduction in the use of alternative therapy.

H. Wang and T. L. Diepgen (Heidelberg, Germany) reviewed the association between AD and cancer risk. Pooled quantitative data extracted from 23 published studies tend to support a lower risk of cancer among persons with a history of AD. This background information might be helpful to interpret the risk of long-term treatments with topical immunomodulators.[60]

C. Goujon et al (Lyon, France) presented an open retrospective study that showed that a low dose of methotrexate (weekly dose of 7.5-25 mg) was effective in patients with severe AD unresponsive to routine therapies. Controlled studies comparing methotrexate and placebo and methotrexate and cyclosporine are ongoing.

Session 9: European Task Force on AD (ETFAD) Workshop on allergy testing in AD, co-chaired by U. Darsow (Munich, Germany), F. Rancé (Toulouse, France), and T. Werfel (Hannover, Germany)

This session provided evidence that skin testing in AD is useful in pathophysiology but might also help in addressing aggravating factors, whatever the age group. A. Scheynius (Stockholm, Sweden) studied *Malassezia* species as a model for host-microbe interactions in AD. Thirty percent to 60% of all patients with AD have specific IgE, skin test reactivity, or both to *Malassezia* species. Interestingly, 50% of all patients having the so-called intrinsic type of AD are sensitized through IgE to *Malassezia* species. Dr Scheynius presented new data indicating that the release of *M sympodialis* allergens is significantly higher at pH 6, reflecting the higher pH in the skin of patients with AD. Her group cloned, sequenced, and characterized 9*M sympodialis* –derived allergens, designated Mala s 1 and Mala s 5 through 12. Four of their identified *M sympodialis* allergens are without homology to known proteins, whereas the others have potential cross-reactivity to human homologues, like stress-induced heat shock proteins and manganese superoxide dismutase.[61] U. Darsow (Munich, Germany) reported on results from a recent European multicenter study on APTs in 324 patients and control subjects.[62] Positive aeroallergen APT reactions were seen in 10% to 39% (mostly to *D pteronyssinus*) of patients and in none of the control subjects. Positive SPT responses (44% to 57%) and increased specific IgE levels (46% to 59%) were more frequent. Depending on the allergen, 20% to 34% of patients had a predictive history. Seven percent to 17% of patients had a clear-cut positive APT response without a positive SPT response or increased specific IgE level. Two of these patients with a corresponding history of atopic eczema triggered by house dust contact and with a positive APT response to *D pteronyssinus* showed sIgG4 against Der p 3. With regard to an aeroallergen-specific history, APT specificity ranged from 64% to 91%. Studies using the APT as an inflammation model showed that APT reactions can be enhanced in volunteers after exposure to volatile organic compounds and might be modulated by pretreatment with pimecrolimus. A. Giannetti (Modena, Italy) discussed data on food allergy in AD. He pointed out that for provocation of eczematous reactions, the oral food provocation on consecutive days is necessary. The Modena group observed a high rate of late eczematous skin reactions using their provocation scheme. In their large series of patients, the sensitivity of the APT was higher than the sensitivity of the SPT with foods, whereas the specificity was comparable. A. P. Oranje (Rotterdam, the Netherlands) reviewed the diagnostic method of the skin application food test[63] for children until the age of 3 years. This test is based on the short application of food allergens onto the skin (10-30 minutes) and a contact urticaria mechanism. The skin application food test corresponds well with the outcome of oral food challenges. The APT adds an additional 10% to 20% positive reactions to patients with food allergy with AD. K. Turjanmaa (Tampere, Finland) reported on the current activity of a task force of the European Academy of Allergology and Clinical Immunology on the APT with food and aeroallergens.[64] She showed data from a meta-analysis of different aspects of this diagnostic tool. A 48-hour occlusion time with readings at 48 and 72 hours seems convincing, the skin of the back is the best place for applying APT, and the APT seems to be fairly reproducible. She pointed out that further well-planned multicenter studies are needed to calculate the predictive values of this test for different foods. In her opinion the food challenge test still remains the gold standard for diagnosing food allergy. In a related poster the same author explored the outcome of individually tailored elimination diets by following 92 infants (<1 year old) after extensive skin and food provocation testing. After 1 and 2 years, 50% of patients were totally free of symptoms, often without further steroid or emollient use. J. Lübbe and A. M. Calza (Geneva, Switzerland) reported on the role of ''classical'' (chemical) patch testing in children with AD. In their retrospective analysis a total of 56 children were identified who had presented with 1 or several positive reactions to epicutaneous patch tests with both standard and preservative series. Forty-three children were atopic, and 13 were nonatopic. Twenty-seven of 43 atopic patients were sensitized to 1 or several preservatives compared with only 1 of 13 nonatopic patients. They concluded that children with atopic diathesis are more often sensitized to preservatives than nonatopic children. This might reflect higher exposure because of intensive use of emollients or because of the defective skin barrier. The problem of the selection bias of such studies was addressed. Labial food challenge (LFC)[65] in children with AD was the main topic of F. Rancé (Toulouse, France). This technique can use both commercial extracts and crushed fresh food resuspended in physiologic salt solution. A drop is placed

on the lower lip and left for 2 minutes, with the mouth slightly opened and with a cotton swab between the lip and gum. The relatively poor sensitivity of the method requires oral food challenge after negative LFC results. Dr Rancé commented also on the varying decision points for SPT and specific IgE to food, depending on author, age, allergen, and disease. A related poster presentation of F. Boralevi (Bordeaux, France) also dealt with the LFC. In 426 children with AD (mean age, 4 years; range 1-12 years), 110 had a positive LFC result, and 136 had positive oral food challenge results. Compared with the food challenge, the positive predictive value was 0.55 and the negative predictive value was 0.77, without influence of the food tested. Thus this study again advocated for the food challenge as the gold standard. Another related poster by K.-B. Suhr (Daejeon, Korea) compared a large food allergen panel in APTs with SPT results in Korean patients with AD. Egg white, cow's milk, beef, chicken, and soybean elicited the most (in 23% to 39%) positive APT reactions. The authors noted an age-dependent decrease in SPT and APT reactivity. Compared with a repeated open food challenge test, APT sensitivity was higher than SPT sensitivity (55% vs 30%; food, egg white). However, combined sensitivity reached 75%.

Session 10: New frontiers in therapy, co-chaired by D. Atherton (London, United Kingdom) and A. P. Oranje (Rotterdam, The Netherlands)

Pointing out that up to 66% of children with clinically typical AD do not have increased IgE levels,[66] M. Cork (Sheffield, United Kingdom) suggested that this might reflect a primary skin barrier defect,[67] which results in a transitory intrinsic form of the disease.[68] M. Cork explained that corneodesmosomes are essential for the protective barrier function of the SC and are cleaved by proteolysis, leading to corneocyte shedding. A strong genetic association has been demonstrated in children with intrinsic AD and an AACC insertion in the 3′UTR of the SCCE gene.[69] Theoretically this would lead to increased SCCE activity in the skin and accelerated proteolytic barrier breakdown, which would allow irritant and allergen penetration and dermatitis. Active dermatitis is associated with high levels of secondary and exogenous proteases, further enhancing barrier breakdown. Increasing skin pH as a result of soap and detergent is also associated with increased SCCE activity.[70] Topical corticosteroids can cause a thinning of the SC as a result of corneodesmosome damage.[71,72]

S. Langan and H. C. Williams (Nottingham, United Kingdom) systematically searched and appraised 234 articles (of which 26 were relevant) in Medline from 1966 through 2005 for evidence to support roles of individual flare factors in atopic eczema. Experimental and provocation studies suggest that diet and house dust mite might have a significant role in subgroups. Dr Langan also highlighted a recent observational study that suggested that there might be winter and summer types of eczema, the former flaring in cold weather and the latter when pollen counts are high.[73] Dr Langan concluded that the relationships between stress, bacterial infections, irritants, and climate and atopic eczema remain unclear and that no definite conclusion can yet be drawn regarding other putative flare factors.

I. Jakasa (Amsterdam, The Netherlands) described an interesting model to study the penetration of chemicals and drugs in the skin.[74] Jakasa investigated the differences in percutaneous penetration of polyethylene glycol in subjects with normal skin barrier and subjects with a history of AD in relation to the molecular weight. The results suggested that even noninvolved skin in patients with AD has a compromised barrier function.

H. Kobayashi et al (Osaka, Japan) studied the effect of diets balancing n-3/n-6 polyunsaturated fatty acid (PUFA) in subjects with recalcitrant AD. They found an indication that excess intake of n-6 PUFAs and decrease in n-3 PUFAs ingestion might be an aggravating factor. According to the authors, a balanced traditional Japanese diet in addition to conventional treatment might be successful in cases of severe AD.[75]

Conclusions

In conclusion, according to this final session and most of the information gathered at this symposium, the new frontier in AD therapy is a better understanding of the skin barrier. Several studies point to impaired skin barrier function as a primary defect that facilitates the effect of environmental factors and immune dysregulation found in AD.

This report was written by Alain Taïeb, with the help of J. Hanifin and K. Cooper (Session 1); J. D. Bos and G. Imokawa (Session 3); T. J. David, J. Ring, and C. Gelmetti (Session 5); A. Kapp and M. Furue (Session 6); Y. de Prost (Session 8); U. Darsow and T. Werfel (Session 9); and D. Atherton and A. P. Oranje (Session 10). We thank D. Y. Leung for editing the manuscript.

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