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Seminars in Cutaneous Medicine and Surgery

The Epidermal Barrier in Atopic Dermatitis

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Epidermal barrier function is abnormal in individuals with atopic dermatitis (AD). It is controversial whether primary epidermal barrier abnormalities alone account for the physiological and clinical abnormalities found in those persons with AD or whether the observed barrier dysfunction is a consequence of primary immunologic abnormalities. Recent evidence is strengthening the argument for the former hypothesis. Attention to epidermal barrier care (ie, gentle skin care) has long been an important part of the therapy of AD. Advances in our understanding of the biology of the epidermal barrier and how this relates to the clinical manifestations of this disease has important consequences for new therapeutic approaches in the management of AD.
Semin Cutan Med Surg 27:108-114 © 2008 Elsevier Inc. All rights reserved.

Atopic dermatitis (AD) is a multifactorial disease with considerable clinical heterogeneity. Disease severity in affected individuals ranges from dry skin that is easily irritated to a widespread dermatitis with chronic bacterial superinfection and intractable pruritus. It has been argued that primary derangements in immunologic responses to allergens and nonspecific irritants lead to inflammation, increased skin infections, and secondary changes in the skin barrier, which further accelerate inflammatory responses and drive the disease process. This has been termed the "inside-outside" hypothesis.[1] Immunological abnormalities associated with AD have been well-studied and are reviewed elsewhere in this issue. Others have argued that primary barrier dysfunction alone is sufficient to allow antigen ingress, predispose to secondary infection, drive inflammatory responses and, in turn, further disrupt the skin barrier. This hypothesis has been termed "outside-inside."[2] Additionally, both primary epidermal barrier dysfunction *and* primary inappropriate immunologic responses may together contribute to the full expression of this disease.

In this article, the basis of the epidermal barrier will be briefly reviewed and the evidence for the relationship between primary epidermal barrier abnormalities and AD will be explored. Additionally, the relationship between exogenous barrier stresses and the clinical expression of AD will be illustrated with specific examples. Finally, implications for therapeutic intervention including newer barrier repair technologies will be discussed.

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The Permeability Barrier

The skin serves the vital function of providing multiple protective barriers between the outside world and the inside of the body. This set of defense functions localizes to the stratum corneum (SC), which has been compared with a brick wall. In this analogy, the "bricks" represent the anucleate corneocytes filled with keratin filaments, as well as filaggrin proteolytic products, surrounded by a highly cross-linked protein cell envelope. The "mortar" represents the intercellular matrix, which is largely composed of nonpolar lipids that form a hydrophobic seal. These lipids, which together account for approximately 10% of the tissue weight of the SC, are composed of approximately 50% ceramide, 25% cholesterol, and 10 to 20% long-chain free fatty acid in an equamolar (1:1:1) ratio arranged in repeating arrays of lamellar sheets.[3,4] These lipid lamellae are critical to normal permeability barrier function and their absence is devastating to barrier function.

An example of the importance of the extracellular lamellae is illustrated in Netherton's syndrome (NS), an autosomal-recessive disorder resulting from mutations in *SPINK 5*, which encodes the serine protease inhibitor lymphoepithelial Kazal-type trypsin inhibitor (LEKTI). In NS, there is unopposed serine protease activity that degrades lipid-processing enzymes, with a resulting paucity of lamellar bilayers, which results in abnormal barrier function. LEKTI deficiency causes abnormal desmosome cleavage in the upper granular layer through degradation of desmoglein 1 due to excess SC tryptic- and chymotrypic-enzyme activity. This leads to defective SC adhesion, which also contributes to skin barrier dysfunction. Additionally, excess protease activity also leads to increased profilaggrin processing, further compromising the barrier. These abnormalities lead to a near total epidermal

1085-5629/08/$-see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.sder.2008.04.005

barrier defect which manifests clinically as severe atopic-like dermatitis.[5]

In an attempt to preserve homeostasis, disturbances in the epidermal barrier regulate basal layer keratinocyte DNA synthesis and with chronic abrogation, may lead to epidermal hyperplasia. Epidermal injury also results in the accumulation of IL-1α leading to the initiation of a cytokine cascade and downstream inflammatory responses.[6]

Barrier Dysfunction in Patients With AD

There are several lines of evidence that support a primary role for epidermal barrier dysfunction in AD. Importantly, the abnormal skin barrier function found in AD parallels disease severity. Transepidermal water loss (TEWL) is greater in areas of more clinically involved disease. Even clinically uninvolved skin sites exhibit abnormal cutaneous barrier function with greater TEWL compared with individuals without AD.[7-10]

Inherited abnormalities in critical SC proteins have been associated with AD. Several loss-of-function mutations in *Filaggrin* are associated with AD in as many as 50% of European kindreds.[11-13] Filaggrin, which is discussed in detail in another article in this issue, is a critical molecule in the formation of the cornified cytosol, filament collapse and aggregation. Additionally, filaggrin's breakdown products play a key role in SC hydration as well as acidification of the SC, which are both abnormal in AD and which also parallel disease activity.[10]

Some kindreds with AD have also been shown to have an increased frequency of single nucleotide polymorphisms in *SPINK5* (when nonfunctional results in NS as discussed above) compared with case-control kindreds without AD.[14] In AD, rather than total loss of lamellar bodies, abnormal maturation and secretion have been demonstrated.[15] These abnormal lamellar body secretion results in decreased lipids and in particular, a reduction of ceramides.[16,17]

Analysis of the lipid content in AD skin has also revealed decrease in all 3 lipids and especially ceramide. The levels of ceramide types 1 and 3 were significantly lower and values of cholesterol significantly greater with respect to nonatopic subjects. The quantity of ceramide type 3 was significantly correlated with TEWL impairment.[18] The decreased ceramides may result, at least in part from increased sphingomyelin deacylase activity which degrades ceramide precursors.[19]

The antimicrobial barrier is also disturbed in AD. More than 90% of those with AD chronically carry *Staphylococcus aureus* on their skin, even in clinically uninvolved areas.[20,21] Superinfection with *S. aureus* often complicates the clinical course of those with AD, further disrupting the skin barrier and facilitating more adherence and penetration of *S. aureus*, further perpetuating the process. The ceramide metabolite, sphingosine, which has potent antimicrobial activity,[22] is decreased in AD (as a result of the aforementioned deacylase activity), favoring bacterial carriage. Additionally, *S. aureus* produces ceramidases, which may further disrupt barrier function.[23]

Antimicrobial peptides, such as cathelicidin LL-37, and the human β-defensins, produced in the skin are stored in the lamellar bodies and subsequently delivered to the SC.[24] Along with an intact SC, with its complement of antimicrobial lipids, acidic pH, and low water content, they represent important components of the innate immune system and have potent antiviral activity.[25,26] Their levels are reduced in AD, which may account for the propensity of those with AD to be susceptible not only to *S. aureus*, but also to cutaneous viral infections such as herpes simplex (ie, eczema herpeticum).

Although many pathogenic details remain unsolved, primary barrier abnormalities alone suffice to stimulate a cytokine cascade, which if prolonged, can recruit an inflammatory infiltrate.[2,4] A compromised barrier will facilitate penetration of antigens, pathogens, and nonspecific irritants, which lead to the activation of inflammatory responses, which in atopics, favor Th2 cytokines and production of IgE.[27] The ensuing downstream immunologic features that are characteristic of AD lead to further epidermal barrier compromise, creating a positive feedback loop (Fig. 1).

Clinical Examples of the Impact of Barrier Dysfunction in Patients With AD

In infants with AD, the face, scalp, and extensor surfaces are the most commonly affected sites. In older children, flexural surfaces, such as the antecubital and popliteal fossae, are more commonly involved. Eyelid and infra-auricular sites are also commonly affected sites in children with AD. Several factors may contribute to the particular areas of predilection for disease activity. The thickness of the SC has been proposed as an important factor contributing to increased vulnerability to allergens and nonspecific irritants.[28] The eyelid, flexural forearm, and posterior auricular areas are among the body sites with the thinnest epidermis,[29,30] which may contribute to persistent involvement of those sites in AD.

The percentage and severity of body surface involvement in those with AD is variable. In many affected patients, there are large cutaneous areas that are dry but nondermatitic. Indeed, even in these "uninvolved" areas, TEWL is abnormal, demonstrating that even in clinically "uninvolved" areas in patients with AD, there is impaired barrier function.[10,11] A superimposed additional "stressor" may then result in clinical manifestation of the disease. This is not conceptually different than a patient with coronary artery disease that displays normal ECG activity at rest, but demonstrates abnormal ECG activity when the heart is "stressed" on the treadmill.

An example of a "stress" leading to clinical expression of AD is the peri-oral and cheek involvement seen in infants with AD (Fig. 2). This so-called "drooling dermatitis" is due to the additional mechanical and chemical stress of saliva, breast milk, or infant formula rubbing against the skin (often under a pacifier) in this location.[31] In infants without an

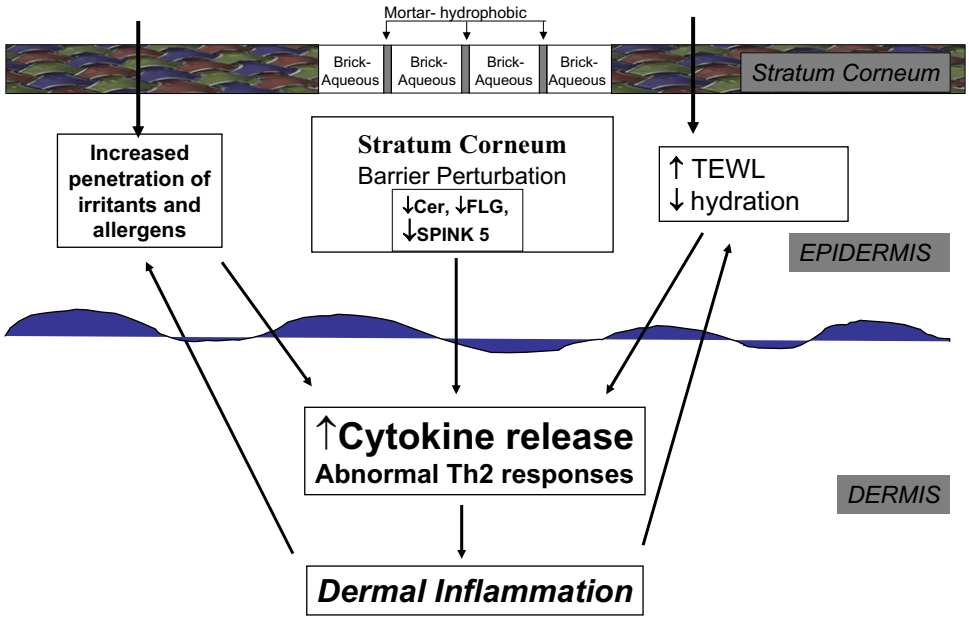

Figure 1 Epidermal barrier dysfunction and inappropriate immune responses contribute to AD. Adapted from Elias PM, Feingold KR.[5]

atopic phenotype, this mechanical stress does not result in a dermatitis, but in those with a compromised epidermal barrier, it contributes to the clinical expression of AD, manifesting as a flare in the peri-oral or cheek distribution. Affected infants almost always "grow out" of this by the time they stop nursing, stop using pacifiers, and are feeding independently with minimal mess and therefore diminished mechanical and chemical stress to this area.

Another example of mechanical stress leading to AD expression is juvenile plantar dermatosis (Fig. 3). This entity, often mistaken for tinea pedis, is seen predominantly on the plantar great toe as well as the plantar second and third toes and ball of the foot in those with both AD and hyperhidrosis of the feet.[32] In this example, the added mechanical stress is the presence of moisture on the plantar foot inside the sock and shoe; the ensuing frictional forces are significantly increased in a moist environment.[33,34] The increased coefficient of friction combined with the compromised epidermal barrier may lead to the dermatitis in those people with both AD and sweaty feet.

A last example of the effects of "stress" to the epidermal barrier contributing to the expression of AD is exposure to soaps and detergents. Soaps emulsify surface lipids, which are then washed off. Traditionally, soaps have been produced by reacting fats with sodium hydroxide (lye), which produces a very alkaline product. The skin normally has an acidic pH of 5.0 to 5.5.[35] This "acid mantle" is important for barrier function, SC adhesion, and antimicrobial activity.[36] Washing with soap disturbs barrier function by extracting

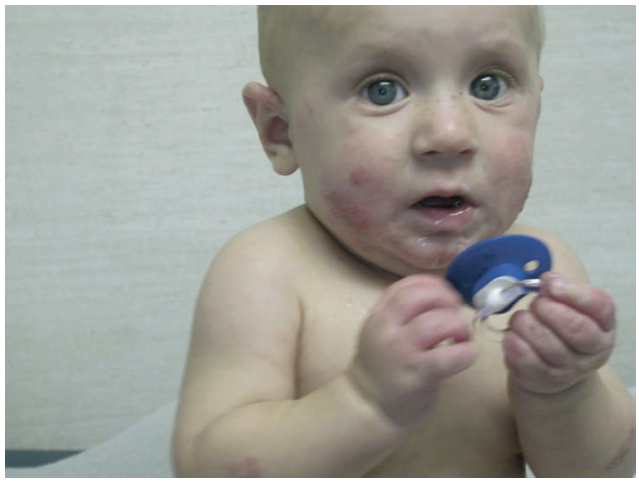

Figure 2 Drooling dermatitis caused by the additional mechanical and chemical stress of saliva, foods, and pacifiers rubbing against the skin.

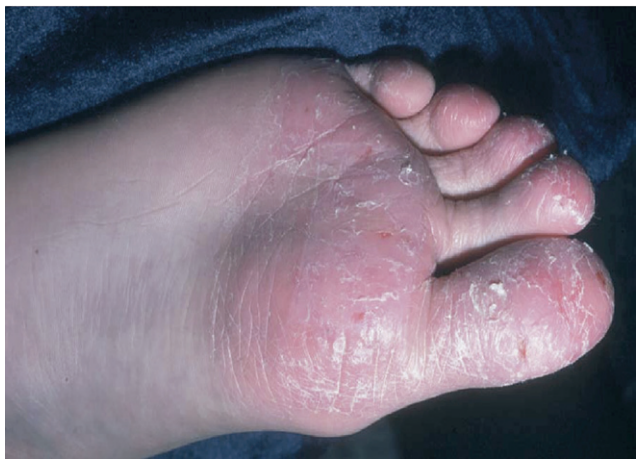

Figure 3 Juvenile plantar dermatosis (toxic/sweaty sock syndrome) caused by the increased friction in a wet sock environment combined with the compromised epidermal barrier.

lipids, thereby increasing TEWL and increasing pH.[37] Again, in those with a normal skin barrier function, harsh alkaline soaps in normal usage should not disturb the barrier enough to lead to dermatitis. However, the exposure to alkaline soaps in the setting of the diminished barrier function of atopic skin leads to further disruption of the permeability barrier and subsequent inflammation and dermatitis. For this reason, synthetic detergent (syndet) bars with a neutral pH are often advocated for patients with AD (Table 1).[38] Syndet bar use has been shown to reduce the severity of eczematous lesions, and maintain hydration in subjects with AD.[39] Even the use of syndets may increase serine protease activity and therefore should be used sparingly.

Psychological stress also impacts the expression of AD by impacting permeability barrier function.[40] In animal models and in humans, psychological stress leads to increased secretion of endogenous glucocorticoids, which in turn disturb permeability barrier homeostasis.[41] Oral and topically administered steroids are also detrimental for the epidermal barrier due to multiple mechanisms including decreased lipid synthesis, decreased epidermal proliferation and differentiation, and decreased production of antimicrobial peptides.[42,43]

Implications for Therapy

The application of topical corticosteroids (CS) for the treatment of AD is considered standard treatment and is highly effective for acute flares. However, application of topical CS for as little as 3 weeks leads to disturbed barrier function with significant increases in TEWL.[44] Superpotent topical CS (0.05% clobetasol propionate) applied to intact nonatopic skin has no effect on basal TEWL, but TEWL from tape-stripped skin (a proxy for endogenous skin barrier disruption) treated with clobetasol was much higher than non-steroid-treated controls. Additionally, clobetasol treated skin showed decreased SC adhesion. Electron micrographs have revealed a significant reduction in lamellar bodies and corneodesmosomes within the SC in the clobetasol-treated group, suggesting that clobetasol allowed more corneocytes to be removed with tape-stripping, which resulted in increased TEWL and decreased barrier function.[45] Topical CS have also been shown to upregulate mRNA of proteases (SC chymotryptic enzyme) potentially further compromising corneodesmosome function and SC adhesion.[43] Discontinuation of both topical and oral CS, especially after long term use, often results in rebound flare which is consistent with their ability to compromise the epidermal barrier.[46,47] The overall anti-inflammatory effects of topical steroids surely outweigh their negative effects on skin barrier function during an acute flare, consistent with their observed clinical benefit. However, the use of topical CS for maintenance in AD, as has been advocated by some,[48,49] may not be the optimal long term approach.

Table 1 Cleansers Used in Skin Care

Cleanser	Type	pH
Aveeno	Syndet	6.9
Burt's Bees	Soap	10
Basis	Soap	10.6
Camay Soap	Soap	9.5
Cetaphil cleanser	Syndet	6.7–7.7
Dermalogica The Bar	Syndet	5.5
Dial Soap (liquid and bar)	Soap	9.5
Dove Bar, Baby Dove Bar	Syndet	7.0
Dr. Bonner Liquid Soaps	Soap	8.0
Irish Spring Soap	Soap	9.5
Ivory Soap	Soap	9.5
Johnson & Johnson Baby Wash	Syndet	6.5–7.0
Lever 2000	Soap	9
Neutrogena Extra Gentle Cleansing Bar	Syndet	6.0–7.57
Olay Foaming Face Wash	Syndet	6.85–7.36
Palmolive soap	Soap	10
Purpose Facial Cleanser	Syndet	6.5–7.0
Zest	Soap	10

Adapted from Baranda et al.[40]

The use of moistarizers in addition to anti-inflammatory therapy with topical CS have been mainstays in the management for AD for decades. Emollients have been shown to enhance the benefits of topical CS therapy in children with AD in a randomized comparison study.[50] Additionally, the encouragement of emollients leads to reduced topical steroid usage.[51] Moisturizers often contain occlusives such as petrolatum, lanolin, mineral oil, and silicone. Petrolatum (eg, petroleum jelly) is a mixture of very long chain, straight chain, saturated hydrocarbons.[52] Traditionally, occlusives have been thought to moisturize by forming a hydrophobic shield on the surface of the skin, under which water is trapped. Petrolatum has been shown to penetrate into the SC, where it may displace preformed lamellar bilayers. It does not however, permeate past the SC into the nucleated layers of the epidermis.[53] Applications of petrolatum in damaged skin partially restore barrier function in acute injury models, but this benefit is fairly short.[54] Petrolatum is even efficacious even in concentrations as low as 2% to 4%.[55] Humectants (glycerin, propylene glycol, urea), which are also common ingredients in moisturizers, instead draw water from the surrounding milieu into the stratum corneum.

Recent advances in our appreciation and understanding of the pathophysiology of the epidermal barrier and its relation to disease expression on AD had led to renewed interest in barrier repair therapy in the treatment of AD. A quick trip to the drug store identifies many over-the-counter (OTC) products with the words "barrier repair" or "skin repair" printed on the boxes. Additionally, there are several new prescription products making the same claims. But what do we mean by "barrier repair therapy"? In a strict sense, emollients that claim to have barrier repair properties should normalize epidermal barrier function by reducing TEWL and improving SC hydration. Ideally, these products would also be shown to modify AD disease severity in a controlled clinical trial.

Although occlusive moisturizers provide effective ancillary therapy,[51] they do not correct the underlying lipid biochemical abnormality in AD. The lipid abnormality in AD (eg, global reduction in all 3 key barrier lipids, cholesterol, free

fatty acids, and ceramide),[16,56] provides the rationale for lipid-replacement therapy. Physiologic lipid-based products behave differently than nonphysiologic occlusive products (eg, petrolatum). They are taken up by keratinocytes, packaged into lamellar bodies, and then re-secreted to form lamellar bilayers. The correct molar ratio of 1:1:1 (ceramide, cholesterol, FFA) permit normal barrier recovery in acute injury models. Incorrect molar ratios may actually delay barrier recovery after injury.[54]

Several OTC lipid-replacement moisturizers have been marketed recently (CeraVe and CeraTopic). CeraVe contains ceramides, 1,3,6-11 cholesterol, phytosphingosine (a ceramide precursor), as well as the occlusives petrolatum and glycerin. CeraTopic contains all 3 key lipids (ceramide, cholesterol, FFA). These products seem appropriately designed and contain "barrier repair" ingredients but the lipid ratios and final concentrations are not known and, most importantly, there is no published data demonstrating the efficacy of these products in restoring SC function or in improving AD. In contrast, (TriCeram®), a barrier repair formulation with a predominance of Ceramides (3:1:1), has been shown to improve SCORAD and TEWL in children with AD.[57] Additionally, a ceramide analog has been shown to selectively recover perturbed human skin barrier in an ex vivo study.[58]

A placebo-controlled, double-blind, randomized, prospective study of a 20% glycerol-based emollient was studied in 24 patients with AD. After 4 weeks, SC hydration was significantly improved, and epidermal barrier function was restored under treatment with glycerol-containing cream compared with the glycerol-free placebo. However, no significant differences were detectable for SCORAD and local severity between the glycerol-containing cream and placebo.[59] This product is not currently available in the United States.

There are at least 3 prescription products currently approved in the United States that make barrier repair claims (Mimyx, Atopiclair, and Epiceram). They are approved by the Food and Drug Administration as medical devices. Devices are marketed like prescription drugs and positioned as topical dermatology medications although they are technically prescription devices. Devices with new technology and indications can be developed and rapidly approved via the 510k pathway by the Center for Devices at the Food and Drug Administration. The preclinical and clinical testing requirements for these medical devices are much less rigorous than for a traditional pharmaceutical product. Some feel that this is a loophole and that these products are really cosmetics and that none of them actually contain a drug. In contrast to pharmaceuticals, medical devices are evaluated using a risk-based classification system that determines their regulatory pathway. The barrier repair products mentioned previously are actually classified as wound dressings (ie, "Dressing, Wound & Burn, Hydrogel With a Drug or Biologic").

Mimyx contains the fatty acid *N*-palmitamoyl ethanolamine (instead of ceramides) and the nonphysiologic lipid squalane, which may aid in barrier repair. It contains natural moisturizers (olive and vegetable oils), pentylene glycol, and glycerin. Unfortunately, like the OTC barrier repair creams described herein, there is no published data on its efficacy in restoring SC function or in improving AD. However, in an observational study, authors administered Physiogel® A.I. Cream (distributed by Stiefel Laboratories, which also makes Mimyx), which contains *N*-palmitamoyl ethanolamine, and demonstrated relief of objective and subjective symptoms of patients with AD after regular skin care.[60] Unfortunately, this study is limited by the absence of a control group.

Atopiclair contains hyaluronic acid and glycerin as humectants. It also contains many botanicals, such as grape vine extract, allantoin, glycerratinic acid (licorice root derivative with antiinflammatory properties), and Shea butter. There are several clinical studies demonstrating the benefits of Atopiclair. In a small randomized double-blind, vehicle-controlled study in adults, it showed benefit in mild-to-moderate AD.[61] In a subsequent multicenter, randomized, vehicle-controlled clinical study of Atopiclair for mild-to-moderate atopic dermatitis in 218 adults, Atopiclair was statistically ($P < 0.0001$) more effective than vehicle in all outcomes at all time points.[62] Finally, a double-blind, randomized, vehicle-controlled clinical study showed improvement of pediatric AD by investigator global assessment.[63]

EpiCeram® Skin Barrier Emulsion is a derivative of Triceram which, as mentioned previously, has been shown to improve AD and restore SC function by improving TEWL and SC hydration.[57] Epiceram® contains a mixture of the 3 SC lipids, with free fatty acids, cholesterol, and a synthetic pseudoceramide as the dominant, Cer-equivalent lipid species. EpiCeram™ was evaluated in a multicenter, investigator-blinded trial as monotherapy in 113 children with moderate-to-severe AD. EpiCeram® was effective as monotherapy, reducing clinical disease severity, assessed by changes in SCORAD scores, reducing pruritus, and improving sleep habits at both 14 and 28 days. Epiceram® was also compared with fluticasone (Cutivate®) cream. Although fluticasone was better at improving AD than Epiceram® at 28 days, this difference was not statistically significant.[64]

Conclusions

There are many lines of evidence that support the hypothesis that primary skin barrier dysfunction plays an essential role in AD. It is important to remind ourselves and our patients and families that AD is a chronic disease which currently we cannot cure. Flares of disease are common and often mysterious but can usually be reduced to the balance between genetic predisposition and environmental factors (Fig. 4). Therapy therefore requires long-term multi-modal management which must seek to minimize disease exacerbation by reducing the "stress" to the epidermal barrier, controlling itch, and promoting regular use of topical emollient products with a proven record of efficacy in AD, as well as managing acute flares with judicious use of topical antiinflammatory medications (CS and calcinurin inhibitors) and controlling infection with antibacterial medicines as indicated. As our understanding of the biology of the epidermal barrier and its role in AD becomes better understood, the relationship be-

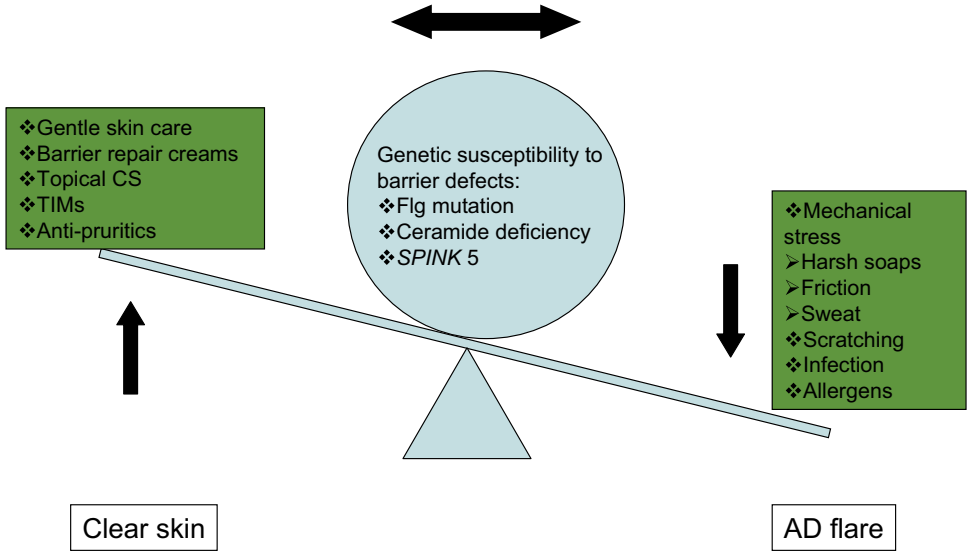

Figure 4 The relationship between genetic and environmental factors tip the balance from clear skin to AD flare.

tween epidermal barrier dysfunction and immune dysregulation in this disease will become elucidated. This will surely lead to more efficacious and safer topical treatments for this common and chronic skin disease.

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