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The Stratum Corneum Revisited: A New Understanding of Its Role in Healthy and Diseased Skin

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ORIGINAL ARTICLES

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Introduction

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The stratum corneum is arguably our most accessible anatomical structure, and yet, until 50 years ago, its structure was unstudied in any detail and its function erroneously relegated to an inert barrier (at best) or dandruff waiting to happen (at worst). In the early 1950s, Kligman likened the stratum corneum "to a tough plastic sheet which encased the body in a kind of death shroud."[1] In light of no tissue in vivo being structured with voids, it is remarkable that the "basket-weave" of keratin fibers seen with light microscopy—a histological artifact of the formalin fixation process—was so readily accepted as occurring in vivo. The difficulty of solubilizing the stratum corneum in a non-destructive manner, another technical issue in the past, further hampered the ability and enthusiasm to study the biochemical components of the stratum corneum. Indeed, Peter Elias suggested in the book he co-edited six years ago that "Perhaps no tissue is so physically maligned by processing for light/electron microscopy as is the stratum corneum … no tissue of critical importance has been so intellectually maligned as well."[2]

Over the past 50 years the "barrier function" of the stratum corneum has been refined, recognizing it to be a selective membrane and not an impermeable physical barrier. Furthermore, its barrier functions have been further expanded beyond maintaining epidermal hydration to encompass antimicrobial and innate immunity barrier activities including direct microbial killing, microbiome control, chemotaxis, modification of inflammation, angiogenesis and wound healing. Great advances have been achieved in identifying the subcellular and molecular components and genetically controlled makeup of the stratum corneum in health and disease. Correlations are being delineated between specific barrier functions of the stratum corneum and its molecular components, including anti-microbial peptides, cathelicidins, defensins, RNase 7, psoriasin, toll-like receptors, free fatty acids, sphingomyelin, ceramides, fillagrin and its breakdown "natural moisturizing factor" products, free amino acids, and proteases.

The stratum corneum may be devoid of intact viable cells capable of dividing and multiplying, but it is by no means static. It is a dynamic, crucial component of our skin in health and disease, and one worthy of our appreciation and study. The articles which follow serve to enhance our understanding of the role of the stratum corneum in skin disease and also highlight the treatments we commonly employ to combat skin disease in support of the "health" of the stratum corneum. This supplement underscores the complexity and importance of the stratum corneum and fosters the respect it so justly deserves.

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Clinical Relevance of Maintaining the Structural and Functional Integrity of the Stratum Corneum: Why Is It Important to You?

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INTRODUCTION

Prior to 1964, the stratum corneum (SC) was depicted as the end product of living epidermal cells which, after finishing their progression upward and traversing through progressive stages of squamous differentiation, disintegrate into an "amorphous mass lacking a cellular structure."[1] The perception that the SC is basically a "dead layer" devoid of any functional activity has been unknowingly perpetuated in countless new editions of pathology textbooks and in pathology reports every time the SC is described histologically as "basketweave hyperkeratosis."[1,2] In fact, this basketweave pattern, which appears to be a simple lattice of keratin fibrils, is actually an artifact of routine histologic processing. Due to the foresight of a few visionary leaders in dermatology and based on a plethora of research studies performed over five to six decades, it is now well-established that the SC is constantly involved in several active physiologic and homeostatic functions which the authors have referred to as barrier responsibilities.[3] The barrier responsibilities of the SC are depicted in Table 1, some of which will be reviewed in more detail below. Although the most unifying barrier responsibility of the SC is the permeability barrier, all of the barrier functions of the SC participate in "crosstalk," functioning as players on a team with each contributing the capabilities of their position when called upon to maintain homeostasis.[1,4-21]

Importantly, all of the SC barrier responsibilities described in Table 1 are dynamic homeostatic functions which serve to maintain healthy skin, and are unified by the natural drive of human (mammalian) integument to initiate self-repair mechanisms when the permeability barrier is compromised by external factors. Such factors include low humidity, overwashing-bathing and/or use of poorly formulated skin care products.[3,4,6,7,9,13,17,21] However, the SC is more susceptible to being overstressed and incapable of fully restoring permeability barrier integrity if it is innately impaired by an underlying genetically-programmed tendency or disease state, such as non-atopic xerosis associated with filaggrin gene mutation, atopic dermatitis, rosacea and psoriasis.[4,11,12,16,18,22-41]

The following article is not meant to be a comprehensive treatise on the formation, structure and function of the stratum corneum but was written with the goal of serving as a primer for the clinical dermatologist, with emphasis on principles that support optimal management of patients with both healthy and disease-affected skin.

Stratum Corneum Structure

Structurally, the SC has been described as bricks and mortar, with the corneocytes representing the bricks and the intercellular lipid bilayer representing the mortar.[1-4,6] Although this model provides a basic conceptual image of how corneocytes and SC lipids are organized and integrated, this description is misleading, and does not accurately represent the many physiologic roles the SC carries out simultaneously and essentially without interruption.[1-3] While a wall comprised of bricks and mortar is rigid, unyielding, impermeable, immobile and not restorative, the SC is none of these things. Instead, the SC is pliable, elastic, semi-permeable, adaptable and capable of self-restoration through a variety of mechanisms.[4,6,7,13,21,42] An overview of the progression of steps that represent the life cycle of the epidermis is outlined in Table 2. Essentially, newly-formed keratinocytes traverse upward from the basal cell layer of the epidermis. They proceed through the zone of transition (granular layer) as keratinocytes, and are subsequently converted to corneocytes. As corneocytes progress into the SC, they integrate with a carefully formed intercellular lipid bilayer phase to become an optimally functional SC. Ultimately, the journey of the epidermal cell ends with corneocyte desquamation. Within the SC, corneocytes are held together by protein structures called corneodesmosomes (CDs)—which serve as staples that provide direct intercellular cohesion—and secondarily, by interaction with the intercellular lipid bilayer.[43-45] The core structural integrity of each corneocyte is protected by a firm outer protein layer called the cornified envelope (CE), which encapsulates the corneocyte, and an outer lipid layer, the cornified-lipid envelope (CLE), composed primarily of long-chain ceramides that are covalently bound to the CE.[45]

Many structural changes occur progressively within the epidermis that directly correlate with important SC functions at different levels within the epidermis.[1-8,10,13,14,18,43-45] These structural changes include

TABLE 1.

Multiple Physiologic and Homeostatic Barrier Responsibilities of the Stratum Corneum (SC) and/or Epidermis*

Barrier Type	Individual Components and/or Major Physiologic Functions
Permeability Barrier	Regulates transepidermal water loss (TEWL), impairs penetration of allergens, microbes, etc. Components and structure designed to sustain SC hydration needed for optimal enzyme activity Production of precursor lipids with packaging in lamellar bodies (LBs) in granular layer Release of precursor lipids from LBs into intercellular lipid phase of the SC Enzymatic conversion of precursor lipids into intercellular lipid bilayer of the SC Production on integral proteins (e.g., profillagrin, loricin, involucrin, others) Filaggrin converted to natural moisturizing factor (NMF) to sustain SC hydration NMF components collectively hygroscopic → major source of humectancy for SC Conversion to filaggrin correlated with need to maintain or repair the permeability barrier Formation of cornified envelope and the corneocyte-lipid envelope around corneocyte Maintenance of proper water flux, water gradient, calcium gradient, acidic pH of SC Biosensor sensitive to increased TEWL with initiation of cytokine cascade and self-repair Self-repair: release of stored LB lipids, increased lipid synthesis, increase in filaggrin → NMF
Antimicrobial Barrier	Acidic SC pH reduces colonization by cutaneous pathogens (e.g., *Candida albicans*) Direct antimicrobial effects of some SC lipids (e.g., free fatty acids, sphingosine) Antimicrobial peptides (AMPs) produced in epidermis (e.g., defensins, cathelicidin) AMPs delivered to SC through sebum and sweat Other diverse cutaneous molecules with antimicrobial activity as an alternative function
Antioxidant Barrier	Mitigates oxidative effects of air pollutants, ultraviolet (UV) light, some medications Counters damaging effects of reactive oxygen species (ROS) Multiple antioxidants present in epidermis (e.g., within SC, surface lipids) and dermis Hydrophilic non-enzymatic antioxidants of the epidermis, including ascorbic and uric acids Predominant lipid-soluble non-enzymatic antioxidant is alpha-tocopherol Co-antioxidants (e.g., ascorbic acid, ubiquinol) support alpha-tocopherol regeneration Antioxidant enzymes (e.g., catalase, superoxide dismutases) with interceptive function
Immune Response Barrier	Immune surveillance and antigen recognition via epidermal dendritic cells (DCs) Innate and/or acquired immune response patterns to allergenic or irritant stimuli Multiple types of dendritic cells: plasmacytoid DCs, myeloid DCs, Langerhans cells Toll-like receptors (TLRs) for recognition of microbial pathogens, other specific agonists Primary "jump start" cytokines (e.g., TNF, IL-1, IL-6) → innate response → immune cascade AMPs and some enzymatic conversion products (e.g., LL-37 antiviral properties) Balance of upregulated T cell responses with T regulatory cell system (FOXP3 cells)
Photoprotection Barrier	Optical reflectance of SC (UV protection correlated most directly with UV thickness) Epidermal melanosome and melanin barrier + SC protein barrier Epidermal antioxidants counter photooxidative stress and ROS induced by UV exposure

**Adapted from references 1-41.*

TABLE 2.

Stepwise Progression of Epidermal Differentiation and Stratum Corneum Formation: Correlation of Structural Components and Physiologic/Homeostatic Functions*

Step	Structural Formation / Conversion Steps / Functions
Formation of keratinocytes	Keratinocytes form from germinative activity of the basal layer
Upward migration of keratinocytes through spinous layer into granular layer	Formation of cornified envelope precursor protein (e.g., loricin, involucrin) Formation of precursor lipids (glucosyl ceramides, phospholipids, sphingolipids, cholesterol sulfate) and incorporation into lamellar bodies in granular layer
Conversion of keratinocytes into corneocytes at zone of transition from granular layer to stratum corneum	Flattening of keratinocytes Precursor lipids, some antimicrobial peptides and enzymes packaged in lamellar bodies Profilaggrin production in keratohyaline granules
Final conversion of keratinocytes to corneocytes	Enzymatic breakdown of packaging organelles with (1) extrusion of precursor lipids from lamellar bodies into intercellular lipid phase of stratum corneum (2) conversion of profilaggrin to filaggrin Conversion by specific enzymes of precursor lipids to ceramides, cholesterol and fatty acids (3:1:1 ratio) Integration of lipids into intercellular lipid bilayer Degradation of filaggrin into several byproducts which collectively form natural moisturizing factor (NMF) which is highly hygroscopic (provides humectancy within stratum corneum) Enzymatic cross-linking of cornified envelope proteins by transglutaminases Interdigitation of enveloped corneocytes and intercellular lipid bilayers provides limitation of transepidermal water loss, produces a semi-permeable membrane, and provides plasticity and resistance to shearing forces
Desquamation	Proteolytic enzymes cleave corneodesmosomes, allowing for shedding of individual corneocytes

**Adapted from references 3-12,16-19,42-45,49.*

squamous differentiation of keratinocytes, formation of specific structural proteins (e.g., involucrin and loricin of the CE) and functional proteins (e.g., profilaggrin, filaggrin conversion within the granular layer), formation of SC lipid precursors packaged into lamellar bodies (LBs) in the granular layer, co-incorporation of some antimicrobial peptides (AMPs) (e.g., cathelicidins, defensins) into LBs, conversion of lipid precursors into final SC lipids after extrusion from LBs into the SC intercellular space, formation of the intercellular lipid bilayer with an optimal relative lipid ratio, formation of the CE and CLE, and production and placement of corneodesmosomes (CDs) for intercellular adhesion. Importantly, each of these steps involve the activity of specific enzymes, all requiring a threshold level and range of necessary water content (hydration level) and pH range for optimal function.[1-8,13,18,37,42-45] Visibly imperceptible desquamation of individual corneocytes catalyzed by hydrolytic proteases requires adequate SC hydration. In individuals with otherwise normal skin, factors which enhance transepidermal water loss (TEWL) that consistently exceeds the restorative capacity of the SC creates an adverse sequence of suboptimal enzymatic activities with transition from normal-appearing skin to dry, dull-appearing, rough, fissured and scaly skin, with the scales representing clumping of corneocytes.[4,6,20,43]

Division and Correlation of SC Barrier Responsibilities

Although the SC provides and integrates many important barrier responsibilities, the primary function of the SC is formation and maintenance of the permeability barrier, including adaptive mechanisms to regulate water flux and balance.[1-4,7,13,18,21] Proper hydration of the permeability barrier—including proper water gradient—subserves all other SC functions, as semi-permeability, pliability, cohesion and resistance to shearing force provides the framework of structural and functional integrity and healthy appearance of the skin.[1-4,13,46] Each of the barrier responsibilities of the SC incorporates signaling cascades which are components of the communication network of the SC. Depending on the type and/or magnitude of exogenous "assault on the skin" (e.g., allergen, irritant, microbial), these signaling cascades when activated are capable of "cross talk" with other functions which may be needed to establish overall homeostasis of the SC. However, the permeability framework must be in place in order for the overall integration of these functions to be at peak operation.[1-4,6,47]

The intercellular lipid bilayer, also referred to as the intercellular lamellar lipid membrane, is a predominant structure which directly functions to sustain the SC permeability barrier. The SC lipids comprising the intercellular lipid bilayer are multiple ceramide subfractions (40–50%), cholesterol (25%), and fatty acids (10–15%), converted enzymatically from specific precursor lipids delivered to the SC by lamellar bodies (Table 2).[1-7,13,20-26,28] Interestingly, the relative ratio of SC lipids of the intercellular lipid bilayer is integral to its permeability barrier efficiency.[3-7,48-50] The biologic properties, relative composition and intercellular compartmentalization of the intercellular SC lipids collectively function to sustain water content

TABLE 3.

Cutaneous Disease States or Topical Therapies Associated With Innate Stratum Corneum Barrier Dysfunctions*	
Disease or Therapy	**Characteristics of Innate Stratum Corneum Barrier Impairments**
Rosacea	Signs (e.g., dryness, scaling, edema) and symptoms (e.g., pruritus, stinging, burning) common in patients with untreated papulopustular and erythematotelangiectatic rosacea; reflective of impaired permeability barrier Facial skin of females and males with rosacea innately sensitive to several skin care and personal use/body hygiene products Increase in centrofacial transepidermal water loss in patients with papulopustular rosacea and erythematotelangiectatic rosacea Lactic acid sting test positivity markedly greater in erythematotelangiectatic rosacea (5-fold increase) and papulopustular rosacea (>3-fold increase) as compared to controls
Psoriasis	Decrease in ceramide-1 from psoriatic plaques as compared to uninvolved skin and controls; direct correlation between increase in transepidermal water loss and ceramide-1 levels Defective delivery of lipids into stratum corneum in actively forming psoriatic plaques and in erythrodermic psoriasis: many lamellar bodies are entombed in the cytosol of corneocytes → impaired delivery of stratum corneum lipids into the intercellular region → less lipid accessible to form lipid bilayer as compared to chronic plaque psoriasis, where lamellar body contents are formed and secreted into the intercellular lipid phase of the stratum corneum Transepidermal water loss is highest from actively forming psoriatic plaques and erythrodermic psoriasis, intermediate in magnitude from chronic psoriatic plaques and lowest from nonlesional skin Alterations in markers of epidermal differentiation in psoriasis as compared to normal skin including an increase in keratinocyte transglutaminase type 1 (formation of cornified envelope), decrease in expression of filaggrin, increase in involucrin, increase in hyperproliferative keratins K6 and K16 and decrease in terminal differentiation keratins K1 and K10
Topical Corticosteroids	Epidermal structural and content changes including atrophy, decreased microvasculature, reduced keratinocyte size, reductions in ceramides, free fatty acids and cholesterol and increase in transepidermal water loss Epidermal structural and content changes including atrophy; decreased microvasculature; reduced keratinocyte size; reductions in ceramides, free fatty acids, and cholesterol; and increase in transepidermal water loss Short course of topical clobetasol (human and murine skin) associated with deterioration in permeability barrier homeostasis with delay in recovery, abnormal stratum corneum integrity and cohesion, and the inhibition of lipid synthesis; physiologic lipid-based emulsion shown to improve stratum corneum cohesion, integrity and permeability barrier recovery Topical calcitriol shown to restore permeability barrier impairments and alterations in antimicrobial barrier associated with topical corticosteroid application
Acne Vulgaris	Increase in transepidermal water loss, decrease in SC hydration, reduction in total ceramides and decreased percent of free sphingosine in patients with acne as compared to controls (single study, 36 patients) Controversial significance and accuracy of reported decrease in linoleic acid in sebum of patients with acne vulgaris More data needed on acne vulgaris and presence or absence of innate stratum corneum barrier abnormalities
Benzoyl peroxide	Benzoyl peroxide can increase transepidermal water loss and oxidize stratum corneum antioxidants and induce lipid peroxidation Supplementation with topical vitamin E did not alter water loss but did reduce markers of lipid peroxidation
Topical Retinoids	A barrier-enhancing moisturizer used prior to and during use of topical tretinoin facilitated adaptation to signs of cutaneous irritation ("retinoid dermatitis"), improved cutaneous hydration, and decreased transepidermal water loss

**Adapted from references 3,4,31-40,56-62.*

through water holding capacity, modulate SC water flux and modify the rate and magnitude of transepidermal water loss (TEWL), all mechanisms needed to maintain epidermal homeostasis.

A major component involved in sustaining the functional integrity of the SC is production of natural moisturizing factor (NMF), a highly hygroscopic collection of solutes (e.g., free amino acids, pyrrolidone carboxylic acid [PCA], others), principally derived from the degradation of the SC protein filaggrin.[1-4,6,7,13,18,21,23,42] Within the granular layer, intracellular keratohyaline granules contain profilaggrin, which is converted enzymatically to filaggrin. Importantly, the magnitude of conversion is dependent on SC hydration status.[1-4,6,13,18,21,42] The humectancy within corneocytes, which directly affects SC hydration status, is increased by an upregulation of filaggrin production followed by conversion into degradation products which comprise NMF.[1-7,13,21]

Biosensor Activities of the Stratum Corneum

Compromise of the SC permeability barrier initiates a signaling cascade which puts in motion a series of mechanisms which function to restore the functional integrity of the SC. Subsequent to an event insult or exposure to chronic factors that induce desiccation of the SC, several adaptive physiologic responses proceed in an organized manner, serving to restore, or self-repair, the permeability barrier. Overall, the SC functions as a biosensor, exhibiting the ability to detect early and subtle changes in TEWL, which is one of the barometers that monitor and reflect permeability barrier status.[1-7,13,42] Once increased TEWL and perturbation of hydration are detected, the SC promptly adapts via release of already stored lipids within available lamellar bodies, which partially reverses the increase in TEWL within minutes. This is immediately followed by upregulated lipid production within two to three hours to further augment formation of the major SC lipids that are integrated into the intercellular lipid bilayer, and also provide some inherent water-binding capacity.[4-6,23,28,48,49] An additional adaptive response to SC compromise that is designed to restore SC hydration and maintain homeostasis is the upregulation of filaggrin production, which leads to an increase in NMF.[4-7,13,18,21]

Exogenous Factors Which Adversely Affect the Stratum Corneum

In patients with otherwise healthy skin, or in patients with underlying disease states that innately impair the permeability barrier, there are several exogenous factors which alter SC lipids and/or proteins, increase TEWL and thus promote SC dessication.[3,4,6,20-28,31,32,34-37] In addition, certain topical medications and/or their vehicles (e.g., corticosteriods, retinoids), or oral medications (e.g., HMG-CoA reductase inhibitor cholesterol lowering agents ["statins"]) can alter specific SC components and their functions and contribute to compromise of the SC permeability barrier.[38-41] Examples of common exogenous factors that promote permeability barrier damage and precipitate SC dessication are overwashing, overbathing, use of poorly formulated cleansers and other skin care products, use of over-the-counter (OTC) skin care products which contain "therapeutic" additives which are irritants or are directly caustic to SC lipids and/or proteins (e.g., astringents, exfoliants, certain surfactants, abrasives), and climate (e.g., ambient humidity, dry indoor heating).[3,20,51-54] In many cases, the adverse effects of these skin care practices or products are unknown to patients and also sometimes to clinicians and their staff.

Endogenous Factors Which Adversely Affect the Stratum Corneum

There are several endogenous factors that are associated with innate SC permeability abnormalities and diminish the capacity of the SC to physiologically adapt to exogenous factors that disrupt the permeability barrier, as described above.[1-6,13,16,18,20-26,31-37] Some factors are not modifiable, such as genetic predispositions, age, ethnicity, underlying genetically-related disease states, and in some cases acquired disorders. Very little is known about associations between ethnicity and variations of the SC permeability barrier, however, there is some preliminary data suggesting that differences may exist.[55] Further studies are needed to determine the validity of these data and clinical relevance. Cutaneous alterations related to age may include SC lipid changes, increased fragility (e.g., at dermoepidermal junction) with lowered resistance against shearing forces, decrease in NMF, decrease in dermal matrix with less perivascular structural support (e.g., easy bruisability), and greater likelihood of underlying disease states and/or systemic medications affecting the SC permeability barrier and other SC barrier functions.[3,4,13] Importantly, many common primary skin diseases are associated with innate, endogenous, abnormalities of individual SC barrier functions, such as atopic dermatitis, rosacea, and psoriasis.

Atopic Dermatitis: The Prototype Disorder Associated With Innate Abrormalities of Stratum Corneum

The underlying medical disorder which has been studied most extensively regarding abnormalities of the SC permeability barrier and other SC functions is atopic dermatitis (AD).[22-30] In atopic dermatitis, a decrease in total SC lipid content, primarily certain ceramide subfractions, has been well-established. Specifically, the greatest magnitude of ceramide reduction is seen in lesional skin (presence of active eczema), followed by a lower reduction in SC ceramides in xerotic skin (absence of eczema) and the least reduction in normal-appearing skin (non-lesional skin) in patients with AD.[3,4,12,22,26,28]

Loss-of-function filaggrin gene mutations is the most extensively replicated genetic risk factor for development of AD, and are believed to be involved in at least 50 percent of cases of AD.[18,27] A genetically programed reduction in filaggrin results in a decrease in NMF, which causes a reduced ability to physiologically sustain SC hydration, or to increase filaggrin in response to further compromise of the permeability barrier.[3-7,13,21] Other cutaneous abnormalities inherent to AD that correlate with impairment of major epidermal and SC barrier functions include reduced levels of some antimi-

crobial peptides and some of their catabolic antiviral byproducts (e.g., cathelicidin-related LL-37), stimulation and prolongation of inflammation secondary to *S. aureus* colonization and superantigen production, an altered immune response barrier with dysregulation of both innate and acquired immune response and hypersensitivity to both cutaneous allergens and irritants.[1-4,8-12,14,22-25,29,30]

The multiple SC abnormalities associated with AD which allow for enhanced percutaneous penetration and repeated exposures to multiple antigens and irritants have collectively been suggested to be a major pathogenic cause of other atopic disorders associated with AD. These associations include subsequent development of IgE-associated hypersensitivity to aeroallergens (asthma, allergic rhinitis), and sometimes food allergens. The theorized concept that abnormalities of SC barrier function predispose to the effects of increased percutaneous penetration and antigen processing which then leads to the progressive development of atopic disorders is referred to as the outside-in theory.[29,30]

In addition to AD, other dermatologic disorders and/or some of their therapies have been associated with SC compromise, including permeability barrier disruption. Examples include rosacea, acne vulgaris and psoriasis, with details depicted in Table 3.[3,4,31-40,56-59]

Clinical Expression of Stratum Corneum Permeability Barrier Impairment

Without interruption of exogenous factors which damage the SC and, without proper therapeutic intervention, increased TEWL remains unchecked. Resultant dessication of the SC proceeds first to a subclinical stage where enzyme activities falter, then progresses to signs and symptoms of dry skin, or xerosis.[3-6,20,22,23,26,52] If the SC is "overstressed," that is if exogenous factors continue to repetitively damage the permeability barrier and exceed the restorative capacities of the SC, increased severity of SC dessication becomes more apparent clinically as xerotic changes progress and become more exaggerated.[3,52] In addition to loss of plasticity and the development of microfissures, an innate immune response sets a proinflammatory cascade into motion, resulting in the development of visibly apparent eczematous dermatitis and associated pruritus. Chronic damage to the SC permeability barrier can progress further to cause epidermal hyperplasia, sometimes with little to no associated visible inflammation, which can lead to dry, thickened, hyperkeratotic changes. In clinical practice, dry hyperkeratotic eczema commonly presents on the hands and feet, likely because the SC of palmar and plantar skin is inherently thicker than at other anatomic sites.

Management of Permeability Barrier Impairment as an Integral Component of Therapy

Regardless of whether the problem is dry skin due to climactic conditions or improper skin care, or if there is an underlying medical disorder such as AD, gentle skin cleansing, moisturization, and permeability barrier enhancement are important components of patient management. This approach has been shown to be beneficial when treating disease states where permeability barrier dysfunction is innate, treatment-related and/or precipitated by skin care practices of the patient.[3-6,22,23,39,48,51,53,54,62] Major advances have been made in gentle cleanser technology, allowing for cleansing with minimal damage to SC lipids and proteins and contribution to clinical improvement of some dermatoses, such as rosacea, acne vulgaris and "retinoid dermatitis."[51,53,54] Many different types of moisturizer and "barrier repair" formulations may reduce TEWL, increase hydration, and improve xerosis, including occlusive agents or combinations which include primarily occlusives and humectants, sometimes with additional cosmeceutical additives. More recently, research related to SC composition, integrity, and function has led to the incorporation of physiologic lipids and other permeability barrier enhancing agents. Such ingredients are included to more directly target restoration of SC function based on known SC deficiencies in xerotic and/or atopic skin.[3-6,39,48,50,62-64] Physiologic lipids that may be incorporated into the intercellular lipid bilayer through lamellar bodies appear to provide greater substantivity in permeability barrier restoration, and have also augmented barrier recovery in aged skin.[48,50]

Clinical differentiation among available moisturizer and barrier repair formulations in terms of therapeutic outcomes is difficult to achieve in studies due to the plethora of available products, the need for consensus on evaluable clinical outcomes and endpoints, the requirement that strict control of potentially confounding variables be assured, the importance of proper methodology and timing of data collection, the need for inclusion of relevant anatomic sites, the absolute necessity that standardized study protocols designed to accurately capture data on several parameters be used consistently in studies, and that results of studies are relevant clinically. In addition, regardless of excellent performance based on scientific data, a product must achieve high marks in parameters related to patient satisfaction, as one must actually be motivated to use a given product before any positive results can be achieved.

In the management of SC permeability barrier impairment, the use of formulations that can replenish lipids, augment SC hydration, and reduce potential irritation associated with topical therapies is an important adjunct to disease management. In cases associated with disease states such as atopic dermatitis and rosacea, the incorporation of therapy that restores and sustains SC hydration and reduces TEWL contributes to clinical improvement, and in AD may prolong durations of remission.[3,5,32,48,62-69]

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corneum. Two major objectives of this initiative were to explore the science and better define for the practicing dermatologist the clinical relevance of stratum corneum function and integrity to the maintenance of healthy skin and the management of disease-affected skin. Some of what was reviewed at this meeting is summarized in this article. The participants of the SCSG/SAP were: James Q. Del Rosso DO FAOCD (Chairman), Brian Berman MD, Doris Day MD, Sheila Fallon-Friedlander MD, Whitney High MD, Darrell Rigel MD, Diane Thiboutot MD, and Jacquelyn Levin DO.

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Dr. James Q. Del Rosso had served as an adviser, speaker, or consultant for Allergan, C&H Scientific, Valeant/Coria Laboratories, Galderma Laboratories, Intendis, Leo Pharma, Medicis, Graceway Pharmaceuticals, Obagi Medical Products, Ortho Dermatologics, Onset Dermatologics, Ranbaxy Laboratories, TriaBeauty, Triax Pharmaceuticals, Unilever, PharmaDerm, Promius, and Warner Chilcott. He has received grants for clinical research from Allergan, Valeant/Coria Laboratories, Galderma Laboratories, Intendis, Medicis, Graceway Pharmaceuticals, Ortho Dermatologics, Onset Dermatologics, Ranbaxy Laboratories, Triax Pharmaceuticals, Unilever, PharmaDerm, and Warner Chilcott.

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Managing Epidermal Barrier Function in the Treatment of Dermatoses

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INTRODUCTION

Recently, the importance of epidermal barrier function has been demonstrated in the evolution and treatment of various skin diseases.[1-7] The epidermal barrier protects the skin from transcutaneous water loss as well as a variety of potentially harmful environmental factors including bacteria, viruses, fungi and chemicals.[2,3,8,9] Mounting evidence suggests that disruption of this barrier is directly involved in the pathophysiology of eczema.[5-7]

The barrier resides primarily in the stratum corneum and is synthesized as keratinocytes convert to corneocytes during transition through the layer of cells located just inferior to the corneal layer (i.e., the stratum granulosum).[1,2] It relies on both proteins and lipids including ceramides, cholesterol and free fatty acids to maintain functional barrier activities.[1,2] Disruption of the lipids has been shown to increase the permeability of the barrier, exposing the epidermis, and ultimately the dermis, to potential irritants and bacterial invasion.[3,10,11]

Non-steroidal medical device products designed to protect and replenish the barrier have recently been used in treating eczema.[12,13] Such products are used as both primary therapy and as an adjunct to other topical agents. When used as a primary therapy, those medical device products containing ceramides and lipids may confer epidermal repair properties through lipid restoration to reduce transepidermal water loss (TEWL).[12,14] Products formulated with hyaluronic acid contribute to barrier repair and homeostasis through restoration of humectancy in the stratum corneum via water binding activity.[15] As an adjunctive therapy, these products also work to prime the epidermis resulting in more efficient penetration of topically applied medications.[1] In other words, moist skin allows for better penetration of topically applied medications than does dry skin. Think of the epidermis as a sponge: a dry sponge, when exposed to a puddle of water, will simply push the water, absorbing little (if any). Conversely, a pre-moistened sponge is much more effective in absorbing water.

Barrier replenishing products can be used effectively in the treatment of a variety of skin diseases, including atopic dermatitis, acne, rosacea and psoriasis.[1] These medications serve two functions—one is to protect the skin from topical agents such as topical corticosteroids, retinoids and benzoyl-peroxide products, which can be both drying and irritating.[16,17] The second function is to essentially prime the skin by trapping moisture and allowing more efficient penetration of topically applied medications resulting in improved skin barrier function.[18,19] Protecting and replenishing the barrier allows for decreased exposure of patients to medications which carry potentially harmful side effects (such as topical steroids) when used for extended periods of time. The following case studies provide examples of treatment regimens and outcomes when using a non-steroidal medical device product to address skin barrier dysfunction as an adjunct to topical corticosteroid therapy. In both cases, it was possible to reduce or discontinue the application of topical steroids once effective barrier restoration therapy was introduced.

Case 1

This patient is an eight-year-old male who presented with eczematous patches involving his legs, neck, and trunk. The patient reported a history of the eczematous signs and symptoms for several weeks and was under the care of his pediatrician. He was undergoing treatment with topical steroids. Examination revealed eczematous patches involving the medial aspect of both ankles (Figure 1), the abdomen (Figure 2) and the mid posterior neck. Clinically, the condition was consistent with atopic dermatitis versus nummular dermatitis. The patient was started on a combination of Hylatopic Plus™ foam, applied to towel dried skin immediately after bathing, and Elocon® cream applied twice daily.

Follow-up examination after two weeks of treatment revealed complete resolution of the eczematous patches involving the medial aspect of both ankles (Figure 3) and the abdomen (Figure 4). A marked decrease in scaling and erythema was seen on the mid posterior neck. The patient was instructed to continue applying HylatopicPlus foam daily after bathing. Elocon cream was decreased to daily on Monday, Wednesday, and Friday.

Case 2

This patient is a nine-year-old male who presented with severe dermatitis involving his right lower leg (Figure 5). The patient had received dermatologic care for several weeks prior to being seen in the author's office. During that time, he was treated with topical steroids.

Examination revealed large eczematous patches involving the right lower leg. The patient was started on a combination of Cipro® 200 mg twice daily by mouth for five days, HylatopicPlus foam applied daily to towel dried skin after showering and Elocon cream to affected areas once daily.

FIGURE 1. Eczematous patches involving the medial aspect of both ankles, before treatment.

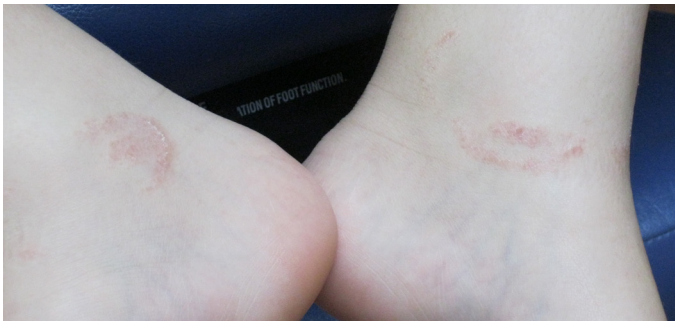


FIGURE 2. Eczematous patches involving the abdomen, before treatment.

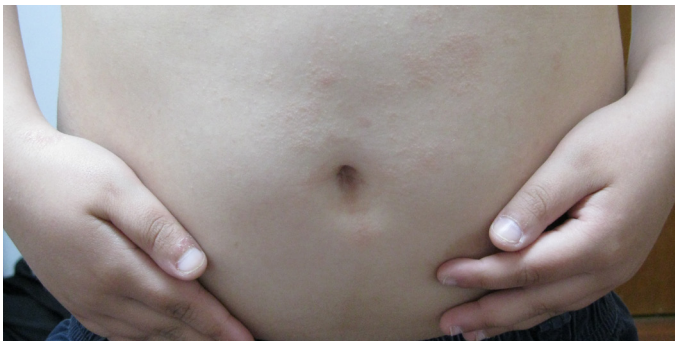


FIGURE 3. Eczematous patches involving the medial aspect of both ankles, after treatment.

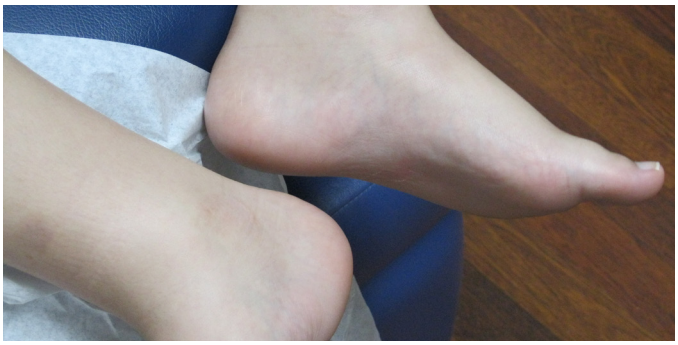
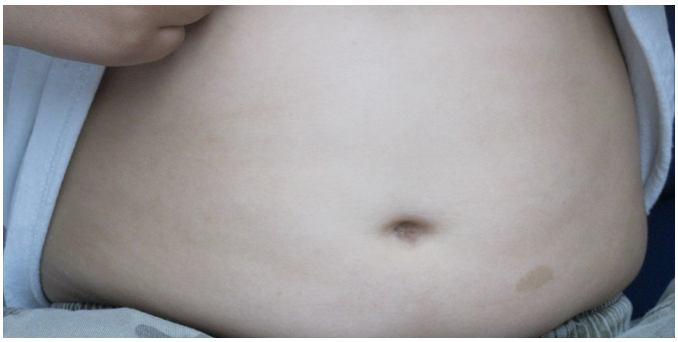


FIGURE 4. Eczematous patches involving the abdomen, after treatment.



The patient returned for follow up one week later. Examination at that time revealed a marked decrease in scaling and erythema at the affected site (Figure 6). Cipro was discontinued. The patient continued to use a combination of HylatopicPlus foam applied daily after showering and Elocon cream once daily.

DISCUSSION

Conventional therapies in the treatment of dermatitis include systemic steroids, nonsteriodal anti-inflammatory medications, ultraviolet therapy, oral and topical antibiotics and immunosuppressive agents. Each of these therapies offers potential benefits as well as significant risks. The advantage of using systemic steroids is rapid onset of relief from inflammation and pruritus. The disadvantages of these medications are that they carry considerable risks of side effects, including atrophy of the skin, bone damage, increased blood sugar, weight gain, acne and gastric upset or bleeding.[20] Topical steroids also deliver rapid relief from inflammation and pruritus. However, they have been associated with the development of striae, telangiectasia and tachyphylaxis.[21]

Ultraviolet therapy has been effective in treating a specific population of patients, usually those unresponsive to standard therapies. However, some patients fail to respond to this type of therapy and patient adherence to treatment schedules may be unsatisfactory. In addition, exposure to ultraviolet radiation carries the risk of severe burning of the skin, future skin cancer, and rebound eczema upon termination of treatment.[21]

The advantages of oral and topical antibiotics include the eradication of secondary skin infections often associated with atopic dermatitis. In addition, oral and topical antibiotics are generally well-tolerated. However, oral antibiotics can cause severe reactions in patients who are allergic to these medications. Importantly, if used indiscriminately or over an extended period of time, antibiotic use contributes to the growing problem of microbial resistance.[22]

The use of barrier restoration therapy is safe, effective and can be used for long-term management of chronic dermatitis. In practice, this has reduced and/or eliminated the need for the use of other medications which may have serious side effects when used over an extended period of time. This is particularly important in the management of chronic dermatitis in young children, where steroid use should be minimized if possible. Reported side effects of barrier repair therapies are few and have been limited to burning, stinging, or tingling at the application site.

In conclusion, conventional therapies, when used either alone or in combination, can be safe and effective. However, neither steroids nor antibiotics address the underlying problem of skin barrier dysfunction that is common to acute and chronic dermatoses. Addressing the barrier defect in the treatment of acute and chronic dermatitis is both safe and effective. In addition, non-

FIGURE 5. Severe dermatitis involving right lower leg, before treatment.

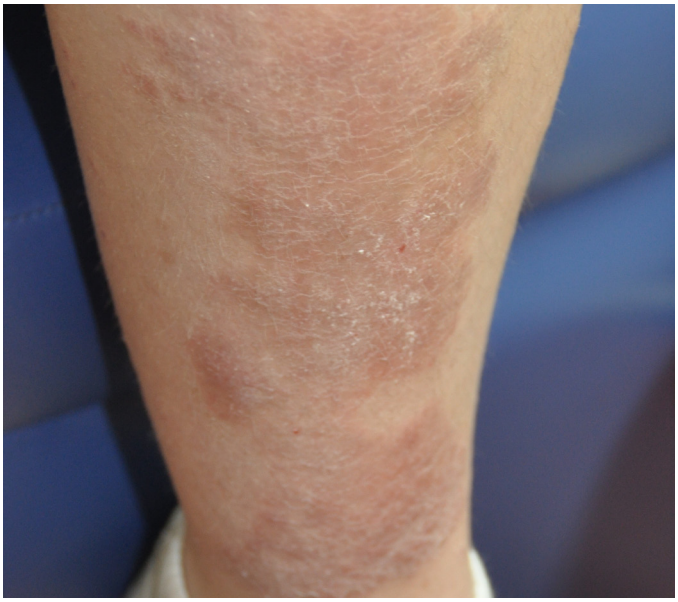
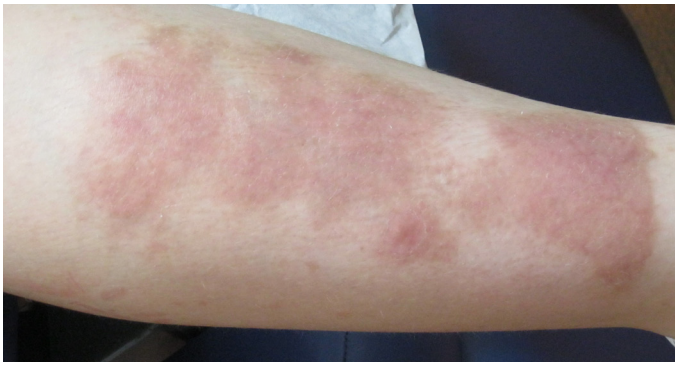


FIGURE 6. Severe dermatitis involving right lower leg, after treatment.



steroidal medical device products containing ceramides, lipids and hyaluronic acid can help to mitigate or eliminate the drying effects of topically applied medications without reducing the efficacy of those medications.

DISCLOSURES

Dr. Contard is a speaker for Allergan, GlaxoSmithKline, and Quinnova.

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FOR TOPICAL DERMATOLOGICAL

AND EXTERNAL USE ONLY.

Rx Only

HylatopicPlus™

INDICATIONS FOR USE

Under the supervision of a healthcare professional, HylatopicPlus™ is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including atopic dermatitis, allergic contact dermatitis and radiation dermatitis. HylatopicPlus™ also helps to relieve dry, waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.

CONTRAINDICATIONS

HylatopicPlus™ is contraindicated in persons with a known hypersensitivity to any of the components of the formulation.

WARNINGS

Use only as directed. **Keep out of the reach of children.** Avoid contact with eyes. For topical use only. Not for ophthalmic use. Do not apply within four hours prior to a radiation session. *HylatopicPlus™ Emollient Foam: Contents under pressure. Do not puncture or incinerate container. Do not expose to temperatures above 120ºF (49ºC).*

PRECAUTIONS AND OBSERVATIONS

- HylatopicPlus™ does not contain a sunscreen and should not be used prior to extended exposure to the sun.
- If clinical signs of infection are present, appropriate treatment should be initiated; use of HylatopicPlus™ may be continued during the anti-infective therapy.
- If the condition does not improve within 10–14 days, consult a physician.
- HylatopicPlus™ may dissolve fuchsin when this dye is used to define the margins of the radiation fields to be treated.

INSTRUCTIONS FOR USE - CREAM

Dispense HylatopicPlus™ Cream into palm of hand and apply to affected area 3 times per day, or as directed by a physician. Massage gently into the skin until completely absorbed. If the skin is broken, cover with appropriate dressing.

INSTRUCTIONS FOR USE - FOAM

Important: Prime Can Before Initial Use.

To Prime Can: Gently push up on front of actuator with thumb until tab breaks. Grasp can in one hand. Shake can vigorously (until product moves inside can). Firmly strike bottom of can onto palm of other hand or a hard surface at least 3 times. Hold can upright and direct initial spray to a non-skin surface. **Until foam dispenses, DO NOT spray directly on the skin as the initial spray may expel cold liquid propellant.** Press down on actuator for 1-3 seconds until foam begins to dispense. If foam does not dispense within 3 seconds, prime can again.

Before Each Use: Shake can vigorously. Firmly strike bottom of can onto palm of other hand or a hard surface at least three times.

During Use: Holding can upright, dispense HylatopicPlus™ Emollient Foam into palm of hand and apply to affected area 3 times per day, or as directed by a physician. Massage gently into the skin until completely absorbed. If the skin is broken, cover with appropriate dressing. Wipe off any excess foam from actuator after use.

INGREDIENTS

Water, Glycerin, Ethylhexyl Palmitate, Cetearyl Alcohol, Propylene Glycol, Dicetyl Phosphate, Theobroma Grandiflorum Seed Butter, Petrolatum, Dimethicone, Steareth-10, Ceteareth-10 Phosphate, Hydroxypropyl Bispalmitamide MEA (Ceramide), Tocopheryl Acetate, Methylparaben, Disodium EDTA, Propylparaben, Sodium Hyaluronate and Sodium Hydroxide. *HylatopicPlus™ Emollient Foam also contains Hydrofluorocarbon 134a (propellant).*

HOW SUPPLIED

HylatopicPlus™ Cream is available in 3g professional sample tubes (NDC 16781-216-04) and 100g commercial tubes (16781-216-96). HylatopicPlus™ Emollient Foam is available in 5g professional sample aluminum cans (NDC 16781-197-06) and 100g (NDC 16781-197-96) and 150g (NDC 16781-197-97) commercial aluminum cans.

Caution: Federal law restricts this device to sale by or on the order of a physician or other licensed health care practitioner.

Store between 59°F - 86°F
(15°C - 30°C).

Protect from freezing.

HylatopicPlus™
Emollient Foam:
Store upright.
Patent Pending
P/N 2626 Rev. 1

Manufactured for:
Onset Dermatologics
Cumberland, RI 02864
(888) 713-8154
www.onsetdermatologics.com

Onset DERMATOLOGICS

IN THE TREATMENT
OF ATOPIC DERMATITIS

Simple Addition Equals Clinical Success

- 3 critical factors impede the healing process in atopic dermatitis (structural barrier damage, heightened immune response, and poor adherence to therapy)
- Addressing all 3 factors simultaneously with HylatopicPlus™ and a topical steroid may help provide optimal results
- HylatopicPlus™ is the patient-pleasing barrier therapy that *repairs* and *prepares* the skin while *sparing* the excessive use of steroids[1,2]

HylatopicPlus™

PROOF POSITIVE IN DERMATITIS

NOW AVAILABLE
IN CREAM AND
EMOLLIENT FOAM

IMPORTANT SAFETY INFORMATION:
HylatopicPlus™ is contraindicated in persons with a known hypersensitivity to any component of the formulation.

References: 1. Frankel A, Sohn A, Patel RV, Lebwohl M. Bilateral comparison study of pimecrolimus cream 1% and a ceramide-hyaluronic acid emollient foam in the treatment of patients with atopic dermatitis. *J Drugs Dermatol.* 2011;10(6):666-672. **2.** Lucky AW, Leach AD, Laskarzewski P, Wenck H. Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children. *Pediatr Dermatol.* 1997;14(4):321-324.

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