The epidermis provides the primary defense against external insults to the human body, including chemical, environmental, infectious, and mechanical stressors. The largest organ of the body, it maintains fluid status, controlling the egress and ingress of water and other fluids. Maintaining the epidermal barrier is essential for the body’s well being. Understanding the structure and function of the epidermis—how the epidermal barrier is constructed and maintained and how factors alter the skin barrier—will help practitioners understand how to identify and treat various skin conditions.

This first article in a 2-part series on the epidermal skin barrier will examine the anatomy and development of the epidermis and stratum corneum, as well as homeostasis and physical stressors that affect the epidermis. The second article in the series, to be published in the November/December issue, will address the physiologic conditions that alter the skin barrier and methods that help maintain and restore epidermal functions.

ROLE OF THE EPIDERMIS AND STRATUS CORNEUM

The primary function of the epidermis is production of the stratum corneum. Research has shown that the anucleate corneocytes—the cellular component of the stratum corneum formerly believed to be metabolically inactive—are, in fact, physiologically active. The stratum corneum can be conceptualized as a brick-and-mortar complex. The corneocyte component is the brick, and the intercellular lipid complex, layered in a specific pattern between the corneocytes, is the mortar. The intercellular lipid complex comprises 15% of the stratum corneum’s total weight, with the remainder being water (15%) and protein (70%). The combination of the intercellular lipids, matured keratinocytes (corneocytes, with their protein and lipid shells), and intercellular connections between the corneocytes (desmosomes and tight junctions) are the known components of this complete barrier. The contribution of the sebaceous glands and their secretions has also recently been identified. In the presence of an abnormality in the skin barrier, insufficiencies of a component are significant, as the component functions do not overlap.

The stratum corneum helps prevent dehydration of the body, holding the average transepidermal water loss to 2 to 5 g/hour/cm². It also provides a physical and biochemical barrier against pathogens. The stratum corneum is a biosensor that communicates outside changes to the deeper layers of skin. When injured or altered, the stratum corneum sends signals to repair the breach in the barrier (Figure 1). Help is recruited to protect the body through the release of inflammatory chemicals that permeate to the deeper epidermis and dermis. These inflammatory signals send messages that stimulate epidermal repair and restore the skin barrier while simultaneously recruiting infection fighting cells into the area needing repair (see Immunology of the Stratum Corneum).

ANATOMY OF THE EPIDERMIS

The epidermis is the thinnest component of the skin, varying in thickness from 0.04 mm on the eyelids to 1.6 mm on the palms of the hand. The average thickness is 0.1 mm. Because the epidermis has no primary blood supply, it depends on capillary loops extending up into the papillary dermis from the subpapillary plexus. The epidermis starts at the basement membrane and extends up through the stratum corneum. The 4 basic zones of the epidermis are the basal/suprabasal layer, the spinous layer, the granular layer, and the stratum corneum.

Four types of cells populate the epidermis (Figure 2):

- Keratinocytes are the largest in number and ultimately form the corneocytes of the stratum corneum.
- Melanocytes synthesize and secrete melanin-containing organelles called melanosomes that are transported to the end of finger-like projections and are phagocytized by the keratinocytes; this produces the skin’s pigmentation and provides ultraviolet protection.
- Langerhans cells (leukocytes of bone marrow origin) are located in the midepidermis and send projections between the keratinocytes, spanning from the granular zone above to the...
dermal/epidermal junction. They are responsible for many immunologic activities and are classified as one of the skin’s dendritic cells. As antigen-presenting cells, Langerhans cells can initiate responses in naïve T cells and dictate the net outcome of the interaction. They are important for innate and acquired immunity.

- Merkel cells are low-threshold touch receptors that send projections into the epidermis from their position at the basement membrane. They connect with the developing keratinocytes through intercellular connections, or desmosomal junctions. The nervous system sends unmyelinated nerve endings to the area adjacent to the basement membrane and, at this junction of the dermis and epidermis, Merkel cells connect and thereby communicate with terminal nerve endings.

**DEVELOPMENT OF THE EPIDERMIS**

The mean turnover time of the epidermis is roughly 39 days, with 13 days for the proliferative compartment, 13 days for the maturation of the keratinocytes, and 13 days for stratum corneum transit. The balance between generation of keratinocytes and desquamation of corneocytes is tightly regulated. Orderly maturation of the epidermis is essential for a well-developed stratum corneum. With hyperproliferation of the epidermis, the time for epidermal development is shortened. This does not allow for normal development and leads to pathologic skin changes, such as those found in psoriasis and dermatoses.

Epidermal keratinocyte differentiation starts with basal keratinocytes capable of multiplying and moves through progressive stages to creation of a stratum corneum populated with fully cornified keratinocytes, or corneocytes. At the end of the maturation process, each flattened corneocyte covers an area occupied by approximately 25 basal keratinocytes. The suprabasal layer, located directly above the basal layer, is also capable of dividing and provides about one-third of the regenerative activity.

The spinous layer is located above the basal layer and contains delicate spine-like processes that cross intercellular spaces and form contacts between adjacent keratinocytes. These cellular connections are known as desmosomes and tight junctions (zonula occludens). Molecules essential to maturation of the epidermis are initially produced within the spinous layer. Lamellar granules and keratohyalin granules are the intracellular cytoplasmic products of this process. Lamellar granule contents are excreted into the extracellular space of the stratum corneum; keratohyalin granules contain key ingredients in the final production of the corneocyte protein capsule.

The granular layer is characterized by maturation of the intracellular and extracellular processes that lead to the mature skin barrier. Following extrusion of the lamellar granules, chemical processes take place that create the final barrier lipids and that organize the lipid-rich mixture into lamellae, or sheets, responsible for the skin’s hydrophobic barrier.

**ANATOMY OF THE STRATUM CORNEUM**

The stratum corneum is, on average, less than 20 µm wide and is comprised of a 2-compartment system. Corneocytes—flattened, dead cell bodies of keratinocytes—act as the bricks of the brick-and-mortar complex of the stratum corneum. Sandwiched between the corneocytes is the intercellular lipid lamellae, which acts as the biologically active mortar. The cor-
The neocyte complex has a tough, highly cross-linked protein cornified envelope, with a lipid coating outside of the envelope. In most areas of the body, the stratum corneum is comprised of about 15 tightly stacked layers of corneocytes. The exceptions are certain locations, such as the face and genitals, where the stratum corneum is extremely thin, and the palms of the hands and soles of the feet, where the stratum corneum is extremely thick.53

The presence of tightly packed sheets of intercellular lipids endows the stratum corneum with an effective barrier function.54 Primary ingredients in the lamellae are equimolar lipids of cholesterol (25% by weight), cholesterol esters (18%), ceramides (45% to 50%), and long-chain fatty acids (10% to 15%).26,46,51 Regional variations in lipid ratios exist for different parts of the body, which account for variations in the permeability barrier of the epithelium.55 For example, the palms of the hands and the soles of the feet have poorly developed intercellular lipid complexes and poor permeability barriers. They are susceptible to increased absorption of water, observed as maceration. The anterior thighs, lower legs, and forearms have more problems with dry skin, demonstrating that the skin barrier in these areas is less effective.

The intercellular connections (desmosomes of the lower cellular layers) become corneodesmosomes. Desmosomes and corneodesmosomes are responsible for cohesion of the stratum corneum. Ultimately, the breakdown of these intracellular connections allows for normal desquamation.56 Abnormal desquamation leads to scaling, which indicates abnormalities in the normal sequence of corneodesmolysis, or the breakdown of the corneodesmosomes.

The organized and proper maturation sequence of the epidermis is essential to the development of an effective skin barrier. Maintenance and repair activities are also essential for continued skin integrity.

DEVELOPMENT OF THE STRATUM CORNEUM
The origin of the stratum corneum intercellular lamellar membrane—the tightly stacked sheets of lipids that are responsible for the skin barrier—is the lamellar granules.57 The lamellar granules are small organelles formed within the keratinocytes that grow in number as the cells mature; they are most prominent in the granular cell layer of the epidermis. These complex organelles are the source of the precursors of the final lipid content of the stratum corneum barrier. Enzymes contained in the lamellar granules are responsible for lipid transformation, corneodesmolysis, antimicrobial functions, and other normal activities.17,50,58 Recent evidence supports distinct timing of the synthesis of these products and separate transport of the different cargo types within the lamellar granules from the trans-Golgi network.59 The lamellar granule organelle is similar to the lysosomes and Golgi apparatus. Lipid precursors include phospholipids, cholesterol, and glucosylceremide.60 The essential fatty acid linoleic acid is also included in the intercellular lipid complex. Because it is an essential fatty acid, linoleic acid is not made de novo in the developing epidermis, but must come from the circulation. It is also recycled within the skin. Deficiency of linoleic acid will lead to an altered barrier, due to the resulting abnormal intercellular lipid complex.61,62

The lamellar granules also house proteases needed to break down the corneodesmosomes, which allows for timely shedding in the lamellar granules from the trans-Golgi network.59
IMMUNOLOGY OF THE STRATUM CORNEUM

Inflammatory cutaneous reactions are often a byproduct of the dual reaction to permeability barrier disruption. Barrier disruption leads to an increase in transepidermal water loss and stimulates both reparative and protective responses of the stratum corneum (Figure 3). The inflammatory cytokines that are secreted with barrier disruption can recruit and trap inflammatory cells in the dermis and epidermis. These preformed cytokines—interleukin-1α (IL-1α), IL-1β, and tumor necrosis factor-α (TNFα)—are released from the corneocytes and granular cells in response to minimal external perturbations. IL-6 is present in small amounts in cells of the epidermis, but levels quickly increase after barrier disruption. Simultaneously, changes leading to repair are aided by these cytokines, triggering proliferation and rebuilding of the epidermis.

Byproducts of the inflammatory reaction can induce problems that further disrupt the barrier and slow recovery if elevated levels persist. The primary stratum corneum-initiated inflammation cascade can lead to changes that infiltrate the epidermis, dermis, and dermal capillaries with inflammatory chemicals and cells. This can then trigger the systemic immune system. The inflammatory process can sustain the abnormal skin condition initiated by the primary barrier disruption. Treatment of the inflammation and barrier repair is needed to disrupt the cycle.

Acute and chronic disruption of the cutaneous permeability barrier increase messenger ribonucleic acid (mRNA) levels for TNF, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1α, IL-1β, and IL-6 in the epidermis. IL-1ra (an inhibitor of IL-1α) mRNA levels are also increased in a coordinated manner. The net result provides a regulatory mechanism for controlling the biologic effects of increased IL-1 production. An excess of 10 to 100 times the amount of IL-1ra is needed to modify the IL-1-induced biological response by 50%.

Persistence of an abnormal skin barrier is a significant problem in many pathogenic skin conditions and is believed to be the pathogenic pathway to the abnormal healing patterns of scars and keloids. Treating the abnormality in the skin barrier is a key factor in reducing the inflammatory process.

Active immune and defensive functions beyond the physical barrier of the skin are numerous. The cells in the stratum corneum, including keratinocytes, Langerhans cells, NK-T cells, and conventional T cells, process antigens to stimulate the immune processes. The epidermis expresses antimicrobial peptides, including alpha and beta defensins and a human cationic antimicrobial protein (hCAP-18), with its C-terminal antimicrobial peptide LL-37. These have antiviral, antifungal, and antibacterial activity. The lipids and fatty acids of the intercellular lipid complex also have antimicrobial activity. Each of the cell types of the epidermis have unique toll-like receptors that recognize and respond to many infectious insults. These receptors enhance both innate and acquired immunity.

The epidermal skin barrier is impaired in many pathogenic skin conditions and is believed to be the pathogenic pathway to abnormal healing patterns of scars and keloids. Treating the abnormality in the skin barrier is a key factor in reducing the inflammatory process.

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of the aged corneocytes. Lamellar granules are discharged from the keratinocytes into the extracellular space in the upper granular zone. The lipids are transformed into the final lipid products of the intracellular matrix, yielding fatty acids, cholesterol, and ceramides. Organization of the intercellular lipid matrix and proper bonding to the corneocytes depends on integrated function with the developing corneocytes.

The mature corneocyte has a unique structure. A tough protein envelope surrounds the inner perimeter of the cell. This protein envelope is linked to the bundles of keratin filaments in the interior of the cell. Around the outer surface of the cell is a lipid envelope made of omega-hydroxyceramides. This lipid coat is chemically bonded to the protein envelope inside the cell and also connects to the intercellular lipid lamellae. This highly developed structure gives skin its strength and provides support for the lipid lamellar matrix. The tight junctions and corneodesmosomes linking the corneocytes provide additional strength, structure, and barrier function.

Several natural moisturizing factors are found within the corneocytes, including amino acids and their derivatives, lactic acid,
urea, and glycosaminoglycans. These natural moisturizing factors are chemicals that help retain water within the stratum corneum. They also help maintain the acidic pH of the skin. Intracellular fluids maintain the flexibility of the stratum corneum.

**HOMEOSTASIS**

The epidermis has several essential features: its pH gradient, its specific mixture of lipids in the extracellular space, and its gradient of calcium, magnesium, and other ions from the basement membrane to the surface. In addition, proper epidermal development depends on adequate hydration of the corneocytes and adequate time for complete maturation of the stratum corneum, among other elements.

Dysfunction in any of these processes leads to abnormal development of the stratum corneum barrier. Proper conditions produce the timely breakdown of the corneodesmosomes so that the stratum corneum is not too thick, which would cause abnormal scaling, or too thin, which would leave an inadequate barrier. The granular layer of the epidermal cells extrudes well-equipped lamellar bodies into the intracellular space. Post-extrusion chemical processing of the lipids yields well-organized, adequate lipid lamellae. The corneocyte matures with production of natural moisturizing factors and connects to the intercellular lipid complex. Development of the mature skin barrier depends on specific enzymes being present, adequate hydration, normal electrolyte balance, normal balance of enzyme inhibitors, and a normal pH.

Disruption of the skin barrier by any mechanism produces changes in the epidermis that lead to restoration. Recovery occurs as a result of immediate secretion of preformed lamellar bodies into the extracellular space, followed by synthesis and processing of new proteins and lipids necessary for the production of additional lamellar bodies.

Hydration of the stratum corneum is essential, and it correlates with the feeling of skin softness. Each maturation step, including corneocyte strengthening, lipid processing, the generation of natural moisturizing factors, and corneodesmosomal synthesis, is influenced by the hydration of the stratum corneum.

Transsepidermal water loss is the most important factor in controlling loss of water in an intact intercellular lipid barrier. Other sources of water loss and variables affecting transepidermal water loss include sweating, skin temperature, corneocyte surface area, and variations in microcirculation. Normal hydration of the epidermis is 10% to 30%. The presence of lipid layers impedes evaporation. Intracellular water content produces changes in the corneocytes that give flexibility, allowing free movement without cracking or fissuring. Lack of hydration leads to a slowdown in barrier recovery, reduced enzyme activity, and a shift in the pH of the stratum corneum. Lack of hydration also triggers the release of inflammatory chemicals from the corneocytes. Epidermal hyperplasia follows, due to the secondary effects of these inflammatory chemicals to stimulate more rapid proliferation of the basal keratinocytes. The epidermis accelerates and interferes with the normal maturation of the epidermis, causing a poorly formed stratum corneum. The primary water supply for the stratum corneum is the underlying tissue, provided its water-holding capacity is intact. Within the corneocytes, the presence of natural moisturizing factors depend on production of the protein filaggrin by the corneocytes and intracellular postprocessing of filaggrin, which is associated with orderly maturation. The active transport of glycerol into the epidermis and the production of glycerol from breakdown of triglycerides in the sebaceous glands by lipases have recently been found to be an additional source of significant hydration.

The gradient of extracellular calcium is another key component of the epidermis, with its highest concentration in the granular layer and decreasing concentrations toward the basal layer. Elevating levels of calcium reduce the proliferation of cells and induce maturation of the keratinocytes to corneocytes. The epidermal calcium gradient depends on an intact skin barrier. Magnesium is also important. The stratum corneum surface has a negative potential, which affects the levels of ions in the stratum corneum.

Elevation of the stratum corneum’s pH alters multiple functions. Ideal acidity for the stratum corneum is a pH of approximately 5.4. Factors that alter the pH of the stratum corneum will also alter the enzyme systems in the epidermis. Elevated pH reduces the stratum corneum’s ability to produce the proteins and lipids that are essential to the skin. Elevated pH also alters the skin’s antibacterial capacity and hydration, weaken-
ing the skin barrier and increasing inflammatory reactions. The pH directly regulates the epidermal permeability barrier homeostasis and stratum corneum integrity and cohesiveness.\textsuperscript{71,76} If the pH of the stratum corneum is elevated, both lipid processing and desquamation are abnormal.\textsuperscript{71,77,78} Enzymes that break down the corneocyte connections in the stratum corneum are sensitive to pH, requiring the acidic pH for normal activity.

Changes in pH associated with chronic inflammation likely play a role in the abnormal scaling observed in many skin conditions. Inflamed skin shows an increased pH, either as a primary or secondary effect. The skin in the intertriginous areas also has a higher pH, making these areas more susceptible to infections.\textsuperscript{79}

**ENVIRONMENTAL CONDITIONS AND AGE-RELATED CHANGES ALTERING THE SKIN BARRIER**

**Humidity**

When sensed by the stratum corneum, variations in humidity lead to changes in the intercellular lipid complex and the corneocytes. The stratum corneum’s biosensor feature induces changes, depending on the humidity, in the deeper layers of the nucleated stratum corneum that alter lamellar granule secretion and intracellular protein production.\textsuperscript{51,22,80} Decreased relative humidity reduces water in the stratum corneum by increasing evaporation, thereby increasing transepidermal water loss. The increase in transepidermal water loss is a signal that leads to changes that enhance barrier structure and function, which helps to prevent more rapid dehydration in a low-humidity environment.\textsuperscript{81} The intercellular lipid layer primarily controls transepidermal water loss and becomes more effective in a dry environment.

Humidity greater than 80\% is associated with a decrease in natural moisturizing factors and corneocyte hydration.\textsuperscript{82} Prolonged exposure to high humidity leads to a gradual deterioration in the barrier; less than 20\% humidity enhances barrier function.\textsuperscript{83} The epidermis adapts to alterations in the barrier, depending on environmental requirements. Changes in the humidity, especially going from high to low humidity, will cause a definite, but transient decline in barrier function.\textsuperscript{84}

Low humidity has been correlated with an increased number of mast cells in the dermis.\textsuperscript{85} Skin sensitivity to physical or chemical stimulation in low humidity is increased but does not correlate with transepidermal water loss or barrier adequacy.\textsuperscript{86} Low humidity amplifies the hyperproliferative and inflammatory response to barrier disruption.\textsuperscript{22} Release of interleukin-1\textalpha\ (IL-1\textalpha) is also augmented when low humidity causes barrier stress.\textsuperscript{87} The overall effects of humidity are significant and create a need for barrier repair.

**Aging**

Cellular and structural changes of the epidermis occur with aging. The number of melanocytes, Merkel cells, and Langerhans cells decrease, and the dermal-epidermal junction flattens. A reduction in melanocytes predisposes the skin to easier burning. A decreased Merkel cell level leads to reduced sensation, and a decline in Langerhans cells decreases the immune response. Flattening of the dermal-epidermal junction leads to a reduction in the nutrients delivered to the epidermis. A weakening of the connection between the epidermis and dermis also reduces shearing and blistering thresholds, decreases communication between the dermis and epidermis, and reduces microcirculation to the epidermis.

With aging, the proliferation of the keratinocytes and turnover of the epidermis is slowed.\textsuperscript{88} The main source of skin hydration—moisture diffusing from the vasculature of underlying tissues—is also reduced. Transepidermal water loss is normal or decreased in aging skin, suggesting a normal skin barrier. If the stratum corneum is injured, however, barrier recovery is abnormal; in fact, the degree of injury necessary to induce an abnormal barrier is reduced with age.

Although the total lipid content in aging skin is decreased, it is normal in distribution.\textsuperscript{89} The intercellular lipid layers are normal in structure but focally reduced, leaving random channels of inadequate barrier. A global reduction in stratum corneum lipids and a profound abnormality in cholesterol synthesis can be found.\textsuperscript{90} The thickness of the stratum corneum is normal to increased, and the corneocytes are larger in size, possibly reflecting the slower turnover rate. Sebaceous gland secretion is also decreased\textsuperscript{91} and the amino acid content of the corneocytes is reduced, leading to decreased natural moisturizing factors and decreased water binding of the corneocytes.\textsuperscript{65}

The pH of aging skin is increased and has a reduced buffering capacity, making it difficult for the skin to counteract the effects of alkaline products and to maintain the essential acid mantle.\textsuperscript{92} Reduced signaling in the epidermis of the IL-1 family of cytokines may be a basic problem in aging skin, causing sluggish skin barrier recovery. The IL-1 family of cytokines signals proliferation of the keratinocytes and reparative processes. However, tumor necrosis factor-\textalpha\ (TNF-\textalpha) signaling appears to be unchanged with age.\textsuperscript{93} These conditions lead to reduced hydration, abnormal scaling, fissuring, cracking, and itching.

The elderly are more susceptible to humidity changes, especially low humidity. A relative humidity of 40\% is recommended to reduce transepidermal water loss. Dryness is the most common cause of pruritus; scratching the skin leads to further damage, worsening the condition.\textsuperscript{94} Inflammation and susceptibility to irri-
tants and contact allergens also increase with age. Furthermore, transdermal drug permeability of lipid-soluble drugs is decreased and water-permeable drug absorption is increased.95,96

Water
Immersion of the stratum corneum in water for a prolonged period of time induces disintegration of the stratum corneum, which is observed as maceration.97 With excessive hydration, the intercellular lipid complex is disrupted and results in the stratum corneum being more permeable to water, polar molecules, and topically applied drugs.98 Natural moisturizing factors decline with excessive hydration, as well as with repeated hydration and evaporation cycles. Too much water deteriorates the stratum corneum pH47 and the balance of ions such as calcium. In addition, too much water increases bacterial counts and promotes scaling, due to water’s effect on cornodesmosylation.88

Other Physical Stressors
Tape stripping causes physical removal of the corneocytes, which decreases the skin barrier. Any lipid-extracting solvent, such as acetone or detergents that leech the lipids and proteins from the stratum corneum, will also lead to barrier disruption. However, these solvents create problems in the stratum corneum that are more disruptive than tape stripping.99 Friction, shear, blistering, and other mechanisms leading to mechanical damage also disrupt the stratum corneum.

Although the stratum corneum is generally resistant to injury, the cellular components of the epidermis and dermis are not. Injuries that initially occur in these lower levels can later manifest as a disrupted, poorly formed stratum corneum, as the damage and proliferation of the lower levels comes to the surface. Examples of this include ultraviolet A and ultraviolet B damage, radiation injury, and freezing.99 In these cases, transepidermal water loss is initially normal, then increases approximately 10 days later, immediately preceding the presence of abnormal skin. Even when appearance of the skin later normalizes, transepidermal water loss remains abnormal. The intercellular lipid complex and corneocyte maturation remain abnormal because of the sustained effects of the injury. Addressing the deficiencies of the abnormal barrier will aid the disturbed skin and will reduce the associated inflammatory reaction.100

The effects of stool and urine on the skin barrier are likely multifactorial. Urine and stool are alkaline when compared with the skin. This combined with digestive enzymes, acids, and the heavy bacterial burden of stool damage the skin. Minimizing excessive hydration and gently cleansing with pH-balanced products helps to maintain a normal pH reduce skin irritation.

Oclusive Dressings
The degree of skin occlusion has an effect on barrier recovery. Oclusive products suppress barrier recovery and reduce the epidermal proliferative response to an abnormal stratum corneum barrier. Although reducing transepidermal water loss, semipermeable treatments do not slow barrier recovery. This concept is helpful when choosing a dressing for recently healed skin. A fully oclusive dressing will prevent transepidermal water loss and will slow the epidermal maturation and barrier repair. A semiocclusive dressing will not suppress epidermal proliferation and barrier repair, but will slow transepidermal water loss, helping to maintain moisture in an immature epithelium. Oclusion of the skin increases the infectious organisms, potentially raising the skin’s pH. Occlusion will also directly increase the pH of the skin.101 This effect of occlusion, with its antiproliferative activity on the epidermis, may be responsible for the benefits noted with oclusive dressings in the management of keloids and scars.

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