

## REVIEW ARTICLE

# Xerosis: a Dysfunction of the Epidermal Barrier

D. Barco<sup>a</sup> and A. Giménez-Arnau<sup>b</sup>

<sup>a</sup>Servicio de Dermatología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

<sup>b</sup>Departamento de Dermatología, Hospital del Mar-IMIM, Barcelona Spain

**Abstract.** Xerosis or dry skin is a common skin disorder among the general population. It is characterized clinically by rough, scaly, and often itchy skin. This disorder is present in the course of some dermatoses such as atopic dermatitis, although it can also occur in healthy individuals if a combination of certain etiologic factors is present. It is characterized pathophysiologically by a disrupted stratum corneum, dehydration, and impaired keratinocyte differentiation. Treatment of xerosis should seek to restore physiologic lipids in the epidermis and provide substances that facilitate epidermal differentiation.

**Key words:** xerosis, dry skin, stratum corneum, ceramides, lipids.

## XEROSIS: UNA DISFUNCIÓN DE LA BARRERA EPIDÉRMICA

**Resumen.** La xerosis o piel seca es un trastorno cutáneo de alta prevalencia en la población general que se caracteriza clínicamente por una piel áspera, descamativa y habitualmente pruriginosa. Ciertas dermatosis como la dermatitis atópica cursan con este trastorno, aunque puede presentarse en individuos sanos si coinciden varios factores etiológicos. Fisiopatológicamente consiste en la modificación estructural del estrato córneo, su contenido en agua y un defecto en la diferenciación queratinocitaria. El tratamiento de la xerosis debiera buscar la recomposición de los lípidos fisiológicos de la epidermis y el aporte de sustancias que faciliten la diferenciación epidérmica.

**Palabras clave:** xerosis, piel seca, estrato córneo, ceramidas, lípidos.

## Introduction

Dry skin is a common condition in the general population and can be a symptom of certain dermatoses. It is not, however, necessarily an indication of diseased skin since the condition can also be due to predisposing environmental factors or other circumstances, such as excessive washing with water. Despite the high incidence of dry skin in the population, no consensus has emerged on a definition for this condition. It is, however, generally agreed that the basic characteristic of the disorder is the presence of rough, flaky

skin that has lost its normal mechanical properties. Skin becomes dehydrated when the stratum corneum is unable to retain water and loses moisture faster than it is replenished.

In dermatology, the term xerosis is often used to refer to the concept of dry skin. Severe xerosis can lead to the onset of a type of eczema characterized by intensely itchy, fissured, and cracked skin called xerotic eczema or eczema craquele.

Dry skin affects the patient's quality of life, and severe xerosis can interfere with work productivity, especially when the hands are affected.<sup>1</sup>

## Components of the Epidermis Involved in the Genesis of Xerosis

The epidermis is a keratinizing stratified epithelium. The apocrine and eccrine sweat glands, hair follicles, and sebaceous glands are epidermal appendages. The epidermis is the skin layer that is most affected by the processes associated with xerosis, while the dermis and hypodermis are not affected.

Correspondence:  
Ana Giménez-Arnau  
Servicio de Dermatología  
Hospital del Mar  
c/ Passeig Marítim, 25-29  
08003 Barcelona  
agimenez@imas.imim.es

## The Function of the Stratum Corneum

The epidermis is an avascular and stratified keratinized epithelium that undergoes constant renewal. The main physiologic epidermal process involved in maintaining epidermal homeostasis is keratinocyte differentiation. Disruption of the orderly and regulated stacking of corneocytes is one of the principal causes of dry skin. Barrier function and maintenance of the skin's water content depend on the stratum corneum, a cornified layer that provides physical protection in the form of a barrier that retards water loss and prevents the passage of soluble substances into the body from outside. The metabolic and enzyme activity of the stratum corneum plays a key role in maintaining this barrier function. The process involves the formation of lipids and envelope proteins (keratins, for example) and the subsequent degradation of intercellular bonds (by way of corneodesmolysis) to produce physiologic desquamation. The stratum corneum also functions as a sensor, transducing external signals to the deeper structures so that the skin can respond to external stimuli. This response takes the form of enzyme activity in the stratum corneum that promotes the synthesis of ceramides and natural moisturizing factor. Both of these elements are crucial in maintaining optimum skin hydration. Enzymes (particularly proteases, glucosidases, and phosphates) play a key role in transforming glucoceramides into ceramides, breaking down corneocyte cohesion, and protecting the skin against the entry of foreign bodies. The activity of these proteins is modulated by several factors, including pH, temperature, and hydration. A decline in lipid content gives rise to an increase in insensible water loss, which in turn destabilizes the optimum environment for epidermal enzyme activity. This change affects the process of corneocyte maturation and inhibits cell desquamation. In this way, the alterations in enzyme activity initiate a self-perpetuating cycle that gives rise to persistent dry skin.<sup>2</sup>

## Stratum Corneum Lipids

The principal acellular components of the stratum corneum are the structural proteins, intercellular lipids, natural moisturizing factor, and enzyme systems. Barrier function and skin hydration depend on the different types of lipids present in the stratum corneum and the levels of both lipids and natural moisturizing factor. A lipid deficit destabilizes stratum corneum hydration, affecting the elasticity and flexibility of healthy skin. The intercellular lipid component is arranged in bilayers between the corneocytes. These lipids, which are formed in the lamellar or Odland bodies of the stratum granulosum, migrate upwards into the stratum corneum during the process of epidermal differentiation.<sup>3,4</sup> The lipids secreted are the substrate of the enzymes—also

present in the lamellar bodies—that transform the glucosphingolipids into a mixture of nonpolar lipids, including ceramides (50%), free sterols, essential and nonessential free fatty acids (10%–20%), and cholesterol (25%).<sup>2,5</sup> Ceramides are the principal source of essential fatty acids. Linoleic acid, a structural element that plays a key role in epidermal barrier function, is the most important of these fatty acids.<sup>5</sup>

## Natural Moisturizing or Natural Hydration Factor

The water content of a healthy stratum corneum under normal conditions is 15%–20%. When the water content of the cornified layer falls below 10%, visible scales form and the skin acquires a rough dry appearance.<sup>2</sup> To prevent this happening the epidermis contains a number of water retaining substances, the most important of which is natural moisturizing factor, a compound composed of a mixture of amino acids, amino acid derivatives, and salts generated by filaggrin hydrolysis.<sup>2</sup> These highly water-soluble elements are immensely hygroscopic (have great water-retention capacity). The water absorbed by natural moisturizing factor from the environment and from inside the skin acts as an intracellular plasticizer in the stratum corneum ensuring that the corneocytes retain their turgidity and preventing abnormal skin cracking and desquamation.<sup>2</sup> Decreases in moisturizing factor levels and ion content (lactate, potassium, sodium, and chlorine) in the stratum corneum are associated with decreased skin hydration and flexibility.<sup>6</sup> The cracks caused by dehydration impair the skin's capacity to keep out irritants and potentially harmful pathogens.<sup>7</sup> The stratum corneum also contains other moisturizing components—hyaluronic acid, glycerol, and lactate—that are not derived from filaggrin or urea. These components also play a role in maintaining the physical properties of the epithelial barrier.<sup>8</sup>

## Corneodesmosomes, Corneodesmolysis, and the Corneocyte Envelope

The specialized desmosomes that bind the corneocytes together (corneodesmosomes) are transmembrane glycoprotein complexes located in the corneocyte envelope.<sup>8</sup> Their basic components are desmoglein 1 and desmocollin 1, members of the cadherin family of molecules. These proteins, which span the corneocyte envelope and are embedded into the intercellular lipid cement, increase cohesion between adjacent cells by binding to keratin filaments by way of corneodesmosomal plaques composed of plakoglobin, desmoplakins, and plakophilins. The enzymes that form the links are calcium-dependent

transglutaminases (TGase); TGase 1, 3, and 5 are involved in corneocyte differentiation. The strength and flexibility of the corneocyte envelopes are ensured by the connections between several proteins (involucrin, the small proline-rich proteins, envoplakin, and periplakin).<sup>8</sup> Enzyme hydrolysis of the corneodesmosomes facilitates epithelial desquamation. The enzymes that play the most important role in this process are stratum corneum chymotryptic enzyme (SCCE), stratum corneum thiol protease (SCTP or cathepsin L2), and cathepsin D and E. Most of these enzymes are synthesized inside the lamellar bodies in the form of proenzymes that are only activated when they are secreted into the intercellular space. Their proteolytic activity is regulated by the water content, lipid content, and pH of the intercellular microenvironment.<sup>8</sup>

### Effect of Water Content on Stratum Corneum Differentiation

Certain environmental conditions influence the structure and function of the stratum corneum and can cause disturbances that give rise to xerosis. Some authors have cited decreases in ceramides and fatty acids—mainly in winter—as an example of this phenomenon. Low ambient humidity is a factor known to give rise to dry skin. This dryness triggers the mechanisms required to restore epidermal barrier function. Using animal models it has been shown that exposure to a dry environment induces an increase in ceramide synthesis, favors the excretion of lamellar bodies, and gives rise to the formation of a denser horny layer. The increase in transepidermal water loss is corrected more quickly when a person moves from a moist into a dry environment, as the abrupt change triggers increased lipid synthesis in the stratum corneum. Exposure to low humidity conditions induces synthesis of epidermal DNA and interleukin 1.<sup>8</sup> Overall, changes in the properties of the epidermal barrier can be attributed to variations in hydration. This confirms the importance of the role played by environmental conditions in maintaining the properties of the stratum corneum. It also explains how dry skin can be improved or exacerbated by certain seasonal changes in the environment.<sup>8</sup>

### Xerosis and Epidermal Barrier Function

The stratum corneum requires a water content of 10%-13% to maintain its biomechanical properties,<sup>7</sup> and xerosis and the disruption of normal skin function occurs when the water level falls below 10%.<sup>9</sup> To maintain optimum levels, water must migrate into the stratum corneum from the deep layers of the skin and be retained in the cornified layer. The stratum corneum maintains a water gradient between

its innermost layer (where the water content is the same as that of the deeper skin layers) and its outer surface, which is in direct contact with the variable ambient humidity of the atmosphere. Diffusion of water throughout the stratum corneum is a passive phenomenon governed by ambient physical conditions; external ambient temperature and relative humidity determine the steepness of the water gradient. The level of hydration is modified by the 3 factors listed in Table 1. The skin's water content is made up of transepidermal water and retained water. Transepidermal water originates from circulating blood, migrates through the dermis into the epidermis, and eventually evaporates from the surface of the skin. This movement of water plays a key role in the supply of nutrients to the epidermis, a layer devoid of blood vessels. The water retained in the stratum corneum is located between the lipid bilayers and inside the corneocytes. This static water content maintains the mechanical properties of the cornified layer, increases the plasticity of the epidermis, and enhances the hydrophilic properties of keratin.

### Regulation of Skin Permeability

The chief function of the stratum corneum is to prevent the loss of fluids and electrolytes from the skin, and it achieves this through the structure and function of its lipids, proteins, and cells. An acute insult can suddenly deplete the lipid content of the stratum corneum. Recovery of barrier function is based on the reconstitution of the lipid-enriched intercellular substance in the interstices of the stratum corneum, a process involving 2 distinct stages: an initial rapid phase, and a second longer phase. The initial response is rapid secretion of the contents of the lamellar bodies located in the cells of the stratum granulosum. This exocytosis occurs within minutes, and the replacement of lamellar bodies in the stratum granulosum cells starts immediately and may continue for some hours.<sup>5</sup> The synthesis of new lipids (ceramides, cholesterol, and fatty acids) is a slow response that involves an increase in the

**Table 1.** Factors Affecting Skin Hydration

<i>Modifying Factor</i>	<i>Characteristic</i>
Rate of water diffusion from the dermis to the epidermis	Limits the endogenous water supply
Rate of water diffusion within the stratum corneum	Depends on the ability of the cornified layer to retain water, natural moisturizing factor, and the lipid matrix
Rate of water loss through superficial evaporation	Depends on external ambient humidity

quantity and activity of the enzymes that govern lipid formation. HMG CoA reductase and acetyl CoA carboxylase are the enzymes involved in cholesterol synthesis. Fatty acid synthase and serine palmitoyl transferase play a role in ceramide synthesis.<sup>5</sup> It has been observed experimentally that inhibition of the enzymes involved in the synthesis of cholesterol, fatty acids, ceramides, and glucosylceramides delays the recovery of barrier function by causing a decline in the production and excretion of lamellar bodies which in turn disrupts the formation of intercellular lipid bilayers.<sup>5</sup> A mixture of the required lipids in the correct proportions is essential for the reconstitution of these lipid bilayers. Topical application of only 1 or 2 of the 3 lipids required to maintain the intercellular barrier (ceramides, cholesterol, and fatty acids) may alter the correct proportions of the lipid substance to the detriment of the quality of the bilayers. However, topical application of a mixture of the 3 lipids in the correct proportions accelerates the repair of the epidermal barrier. It has been reported that lipids applied to the skin pass through the stratum corneum and are taken up by the lamellar bodies in the stratum granulosum. This implies that topical application of more physiologic lipids would contribute to the repair of the epidermal barrier, as they would not only form an occlusive layer on the skin but would also deliver the raw materials required to create new lamellar bodies.<sup>5</sup>

### The Role of Molecular Signals in the Regulation of Barrier Function

Corneocyte protein expression and the formation of the stratum corneum are regulated by nuclear hormone receptors (NHR) and their ligands. Type I NHRs, which are steroid hormones (glucocorticoids, androgens, and estrogens), regulate skin permeability in newborn infants and the homeostasis of the epidermal barrier in adults. Estrogens and glucocorticoids accelerate the formation of the epidermal barrier while androgens delay this process. Type II NHRs bind to thyroid hormone, retinoic acid, and 1,25 (OH)<sub>2</sub> vitamin D<sub>3</sub>. This group also includes another type of receptor (called lipid-sensing receptors) that binds to endogenous lipids (free fatty acids, leukotrienes, prostanoids, and oxygenated sterols) to induce development of fetal skin and keratinocyte differentiation. These lipid-sensing receptors also act on the intercellular matrix, regulating the synthesis of corneocyte proteins (involucrin, loricrin, and TGase 1) and epidermal lipids. Their function is not restricted to the regulation of the physiologic composition of the stratum corneum as they can also correct anomalies in the epidermal barrier and reduce epidermal hyperplasia and dermal inflammation. For this reason, these receptors may have a certain potential as therapeutic agents in a number of skin diseases.<sup>5</sup>

Lipid synthesis in the stratum corneum is very precisely regulated. The formation of cholesterol and fatty acid is modulated by a group of sterol regulatory element binding transcription factors. Lipid levels are detected by the binding proteins responsible for regulating the synthesis of the enzymes that govern cholesterol and fatty acid synthesis. Type 2 binding protein regulates the formation of cholesterol and fatty acids in the corneocytes, while type 1 protein regulates fatty acid synthesis.<sup>5</sup> Ceramide synthesis is mainly modulated by serine-palmitoyl transferase and by the availability of its substrate—palmitic acid—a product of fatty acid synthesis. Expression of serine-palmitoyl transferase increases in the presence of inflammatory stimuli, such as ultraviolet radiation, certain endotoxins, and cytokines (tumor necrosis factor and interleukin 1). Expression of certain cytokines, growth factors, and other inflammatory mediators also intervenes in the homeostasis of the epidermal barrier and can disrupt barrier function in some skin diseases. Certain cytokines induce the synthesis and proliferation of lipids in the keratinocytes.<sup>5</sup>

### Regulation of Desquamation

Spontaneous cyclical desquamation is one of the very specific characteristics of the epidermis and is just as important as its formation. The cells detach from the epidermis as a result of the degradation of the corneodesmosomes through the action of various proteases. The most important of these desquamatory enzymes are the stratum corneum chymotryptic and tryptic enzymes (also called kallikrein 7 and kallikrein 5, respectively). The tryptic enzyme can activate both itself and the chymotryptic enzyme and act directly on the corneodesmosomes. The activity of the chymotryptic enzyme is regulated by the tryptic enzyme, the epidermal lipids (cholesterol sulfate, and free fatty acids), and other lipids. Its activity is also regulated by certain conditions in the stratum corneum; for example an acid pH, decreased hydration, and low calcium levels all inhibit chymotryptic enzyme activity. Disruption of the epithelial barrier eliminates the inhibiting interstitial lipids, thereby increasing its water and calcium content and pH. This in turn leads to enhanced chymotryptic enzyme activity and consequently an increase in desquamation. A number of antiproteases have been identified that inhibit the activity of the proteases that facilitate epidermal desquamation (Table 2). Secretory leukocyte protease inhibitor (antileukoprotease) and skin-derived antileukocyte proteinase (elafin) are just 2 examples. The inhibitory activity of these 2 molecules is complementary. Antileukoprotease mainly inhibits chymotryptic enzyme activity, while skin-derived antileukocyte proteinase inhibits the tryptic enzyme.

Both antileukoprotease and antileukocyte proteinase have a low baseline expression, which increases in psoriasis,

**Table 2.** Substrates and Inhibitors of the Proteases Involved in Epidermal Desquamation

<i>Protease</i>	<i>Substrate</i>	<i>Antiprotease</i>
SCTE	Desmoglein 1, pro-SCCE	LEKTI-1
SCCE	Desmocollin 1, corneodesmosin	SDALP, SLPI, LEKTI-1
Stratum corneum cysteine protease	Desmocollin 1, corneodesmosin	Cystatin E/M, cystatin a, SLPI
Cathepsin G	Desmocollin 1, corneodesmosin	SLPI

Abbreviations: LEKTI-1, serine proteinase inhibitors; SCCE, stratum corneum chymotryptic enzyme; SCTE, stratum corneum tryptic enzyme; SDALP, skin-derived antileukocyte proteinase; SLPI, secretory leukocyte protease inhibitor.

during tissue scar formation, and when the epidermis is damaged. A defect in protease inhibitor function can give rise to structural anomalies in the lamellar membrane similar to those found in Netherton syndrome.<sup>5</sup>

### Factors Involved in the Onset of Dry Skin

Xerosis is observed in the context of various skin diseases and in patients whose skin has been exposed to external insults, such as solar radiation, changes in ambient humidity, or low temperatures. Dry skin or xerosis can occur in any individual in the presence of 1 or more of these etiologic factors (Table 3).<sup>8</sup> The specific mechanisms that can impair or disrupt stratum corneum barrier function include defective ceramide synthesis and reduced natural moisturizing factor levels. Deterioration of ceramide synthesis in the stratum corneum tends to perpetuate the dry skin cycle by disrupting lipid bilayer structure, inducing dysfunctional keratinocyte differentiation, and amplifying the inflammatory response.<sup>10</sup> A number of authors have observed ceramide deficiencies in the healthy skin of patients with atopic diathesis, a finding that suggests that this population may have a predisposing factor for constitutional xerosis.<sup>10</sup> In both xerosis and atopic dermatitis, besides alterations in lipid levels, changes also occur in the composition of natural moisturizing factor and in the free amino acid content of the stratum corneum. A relationship between certain genetic abnormalities and atopic dermatitis has recently been reported, and a mutation of the gene that encodes filaggrin has been identified in atopic patients from a number of different geographical areas.<sup>11</sup> The presence of low levels of filaggrin in aged skin is another finding that supports the importance of the role played by this protein in the genesis of dry skin.<sup>12</sup> The filaggrin mutations alone do not explain the disrupted barrier function observed in the skin of patients with atopic dermatitis. Environmental factors also influence the composition of natural moisturizing factor. For example, a decrease in ambient humidity has been shown to reduce the generation of free amino acids in the stratum corneum

**Table 3.** Factors Affecting Dry Skin

<i>Facilitating factors</i>
Inherited Predisposition
<i>Precipitating Factors</i>
Age
Comorbid diseases
Atopic dermatitis
Psoriasis
Hypothyroidism
Intestinal malabsorption
<i>Triggering factors</i>
Related to environmental conditions:
Temperature
Humidity
Exposure to sunlight
Air conditioning
Heating
Related to chemical agents:
Soaps and bath gels
Lotions and perfumes
Detergents
Pharmacotherapy
Related to physical insult:
Friction
Abrasion
Radiation

and increase skin dryness.<sup>13</sup> The reduction in intercellular lipid content and natural moisturizing factor that characterizes xerosis is both a cause and a consequence of

abnormal epidermal differentiation. In fact, disruption of epidermal differentiation perpetuates the phenomenon of dry skin. As mentioned above, disruption of the epidermal barrier activates a metabolic response directed towards recovering epithelial homeostasis and reestablishing normal corneocyte differentiation. The main response is an increase in the biosynthesis of lipids, such as cholesterol, ceramides, and fatty acids. Slight disturbances of barrier function usually only affect the superficial epidermis, but repeated or severe damage gives rise to an inflammatory response that involves the deeper epidermal layers and even the endothelium.<sup>14,15</sup> These phenomena give rise to abnormal keratinization and close the cycle that perpetuates the lesions. Table 3 summarizes the factors that precipitate xerosis.

### Skin Diseases and Conditions Characterized by Xerosis or Dry Skin

Dry skin is often the result of a combination of etiologic factors, in particular genetic abnormalities, but also metabolic and environmental triggers. The following are the most important skin diseases in which dry skin may be a symptom.

#### Winter Xerosis

Cold weather and low ambient humidity during winter months are associated with decreased cutaneous hydration.<sup>16,17</sup> Winter xerosis is aggravated by the warm dry air produced by modern central heating systems.<sup>2</sup>

#### Aged Skin

It is estimated that generalized or diffuse xerosis affects 75% of individuals over 75 years of age and is the most common cause of itching in this age group. While dry skin in older people is usually first noted on the lower limbs, the disorder may spread to other areas of the body. Itching is often more intense at night after a hot bath because of changes in temperature, a drop in ambient humidity, or exposure to products containing strong detergents. While there are many possible causes of dry skin in older people, the common factor is a lower rate of epidermal proliferation than that of normal skin.<sup>18</sup> Skin aging is associated with a number of physiologic changes that may contribute to the onset of xerosis. Age-related changes in collagen content give rise to a decrease in skin elasticity that heightens the sensation of dryness. A decline in gonadal and adrenal androgens is associated with decreased synthesis of sebum and cutaneous ceramides.

Levels of filaggrin, the protein from which the components of natural moisturizing factor are derived, are also lower in aged skin.<sup>2</sup>

#### Atopic Dermatitis

Atopic dermatitis is a chronic inflammatory skin disorder characterized by recurrent outbreaks of symmetrical and bilateral eczema on the flexural surfaces of the body accompanied by severe pruritus. It is a multifactorial condition associated with genetic abnormalities that give rise, among other things, to immunological imbalance. Initial symptoms include dry skin and intense pruritus. The isolated genetic component alone is not sufficient to cause the characteristic symptoms, and genetically predisposed individuals must be exposed to certain environmental antigens that promote disruption of the epidermal barrier and the manifestation of the disease.<sup>19</sup> These patients usually have a personal or family history of immunological processes related to immunoglobulin E. The skin of patients with atopic eczema is characterized by low ceramide levels,<sup>2</sup> increased transepidermal water loss,<sup>20</sup> and decreased water-binding capacity.<sup>21</sup> The unaffected skin of patients with atopic dermatitis has also been reported to have abnormally low levels of ceramides 1 and 3, molecules rich in polyunsaturated fatty acids, and particularly linoleic acid. It has recently been shown that the genetic predisposition to atopy also favors overexpression of stratum corneum chymotryptic enzyme and consequent disruption of the epidermal barrier as a result of premature corneodesmolysis. The use of detergents and the application of topical corticosteroids increases the expression of this protease and contributes to the chronicity of the disease.<sup>19</sup>

#### Ichthyosis

Ichthyosis is a family of genetic skin disorders all characterized by xerosis caused by defects in the formation and function of the epithelial barrier. Ichthyosis vulgaris is characterized by abnormalities in the formation of keratohyalin granules and consequently in filaggrin. This abnormality leads to the formation of a stratum corneum deficient in many of the components of natural moisturizing factor. Impaired corneodesmolysis caused by defective water-binding in the stratum corneum and alterations in skin pH give rise to visibly abnormal desquamation. X-linked recessive ichthyosis is characterized by the presence of large scales. This condition is caused by a steroid sulfatase deficiency that leads to an accumulation of cholesterol sulfate and a reduction in cholesterol levels in the stratum corneum.<sup>22</sup> These

anomalies give rise to an abnormal intercellular lipid profile that increases intercellular cohesion. The accumulated cholesterol sulfate inhibits some of the proteases involved in desquamation<sup>23</sup> and contributes to the abnormal retention of corneodesmosomes.

## Irritant Hand Eczema

Dermatitis of the hands is caused by contact with exogenous substances that irritate the skin. Although this type of eczema can occur in any person, it is most often found in individuals with impaired barrier function, such as patients with an atopic constitution and those constantly exposed to moisture in the workplace. Xerosis, desquamation, and cracked or fissured skin are usually found on the palms of these patients.<sup>24</sup> Irritant hand eczema is very difficult to treat, and exposure to the irritant substances must be avoided during treatment. Constant hydration of the hands with appropriate emollient creams is also essential.

## Topical Treatment of Dry Skin

The basis of the treatment of xerosis or dry skin is epidermal rehydration—repairing barrier function by applying lipids similar in composition and in similar concentrations to the physiologic lipids present in the skin.

## General Care

There are a number of recommendations that should be followed to ensure appropriate care of the skin. In addition to proper hygiene, the condition of the skin is also related to nutrition and physical exercise. A balanced and varied diet is recommended as this guarantees the nutritional intake required to maintain epidermal homeostasis. In fact, even slight nutritional deficiencies can give rise to xerosis (for example, the syndrome caused by a lack of essential fatty acids). Physical exercise stimulates blood circulation, thereby increasing the transfer of nutrients and oxygen to the keratinocytes. It also favors epithelial regeneration, strengthens connective tissue, and increases collagen production. The increase in sweating that accompanies exercise favors the elimination of skin waste substances. The skin barrier is susceptible to the damaging effects of agents that accelerate skin aging, such as tobacco,<sup>2</sup> alcohol, and solar radiation. Nicotine triggers capillary constriction, reducing blood flow and favoring the accumulation of harmful substances in the skin. Patients should be advised to stop smoking and minimize exposure to sunlight. Table 4 shows general skin care guidelines.

**Table 4.** General Recommendations for Skin Care and Hydration

Drink sufficient water
Eat a varied and balanced diet including plenty of fruit and vegetables
Avoid smoking, alcohol consumption, and direct exposure to sunlight
Take regular moderate exercise
For daily hygiene use soaps that have an acid pH and contain humectants

## Specific Skin Care Regimens

In the care of dry skin we must also bear in mind additional measures that can enhance the efficacy of topical treatments. Patients should take short lukewarm baths and avoid rubbing or sponging the skin. Irritating soaps should also be avoided. After bathing, oil or hydrating cream should be applied immediately as this prevents transdermal water loss, a result of the temperature contrast. Many moisturizing lotions should be applied to wet skin and this means that towels should not be used to dry the body. Toweling the skin dry increases intercellular lipid loss and hampers the reconstitution of skin balance. Perfumed colognes, creams, and lotions should not be used (particularly if they contain alcohol) because these products tend to dry the stratum corneum. Patients should wear soft fabrics, preferable natural materials such as cotton to minimize friction that could exacerbate the xerosis. Any detergents or fabric softeners used in laundry should be products specifically designed to be gentle on the skin and preferably those guaranteed to be suitable for sensitive skin.<sup>2</sup> Tight clothing may aggravate dry skin through a combination of physical aggression (rubbing) and constriction that could limit blood circulation and interfere with the proper delivery of oxygen and nutrients to the skin. Table 5 lists specific recommendations for the management of xerosis.

## Topical Treatment

In addition to these measures aimed at maintaining the skin in optimum condition, dry skin will also benefit from the topical application of the components required by the epidermis to reestablish normal keratinocyte differentiation. Specialists currently advocate the usefulness of applying topical treatments containing active ingredients that rapidly penetrate the epidermis to stimulate the production pathways of intercellular lipids. This “inside out” approach, compared

**Table 5.** Specific Recommendations for the Management of Dry Skin

After bathing in lukewarm water, immediately apply a preparation that prevents the evaporation of water from the surface of the skin
Avoid friction caused by rubbing with sponges or bath gloves
Use soaps specifically designed not to irritate the skin
Do not use lotions, colognes, perfumes, or similar products that contain alcohol
Wear soft fabrics, preferably cotton, in contact with the skin
Avoid tight clothing

to the traditional “outside in” approach, appears to produce more effective therapeutic outcomes.<sup>2</sup> The topical preparations designed to treat dry skin are emollient or hydrating substances in preparations such as lotions or creams, that is, oil-in-water (O/W) emulsions (higher concentration of oil than water) or W/O emulsions (higher concentration of water than oil). Topical treatment has a number of objectives, which are discussed below.

### Repair of the Lipid Barrier

Lipids are the essential ingredient in formulations used to treat dry skin. The delivery of water alone will not repair the lipid barrier, natural physiologic lipids (cholesterol, ceramides, and fatty acids) must also be supplied.<sup>2</sup> Nonphysiologic lipids are not recommended because they do not contribute to the reconstitution of the fatty bilayers.<sup>2,25</sup> The principal lipid components found in the epidermis are ceramides (50%) and cholesterol derivatives (25%). The physiologic lipids have several advantages over nonphysiologic molecules: they are not occlusive, they penetrate the stratum corneum more easily, they gain better acceptance from patients because they are natural, and they restore proper epidermal differentiation. In short, physiologic lipids, such as the ceramides, function as structural elements in the epidermal barrier and mediate the stimuli that trigger epidermal repair.<sup>2</sup>

### Supply and Retention of Water in the Stratum Corneum

We should differentiate between “humectant” and “hydrating” molecules. Humectants are substances that

attract and retain water<sup>2</sup>; they play a passive role from the outside. A hydrating substance, however, is one that plays an active role in supplying and restoring water to the skin. Humectants are generally hygroscopic substances, such as glycerin or propylene glycol, while hydrating agents or moisturizers are complex mixtures of active ingredients or special combinations of amino acids. The inclusion of a humectant, such as glycerol or urea, as an active ingredient in a topical treatment for dry skin is based on the scientific evidence that indicates that humectants are capable of correcting defects in skin elasticity and barrier function when these deficiencies are not related to lipid loss.<sup>2,26</sup> Glycerol plays a crucial role in keeping the stratum corneum hydrated: changes in aquaporin-3, an epidermal water/glycerol transporter, lead to decreased hydration and loss of skin elasticity that can only be corrected by the topical application of glycerol.<sup>2</sup> It is therefore recommended that topical moisturizers should include this substance.

### Alleviation of Pruritus

The sensation of itching makes a patient want to scratch, and scratching represents a physical aggression that damages the skin’s epithelial lipid layer. When the patient stops scratching, the epidermal lesion is reduced and epidermal differentiation is restored.<sup>2</sup> Topical application of certain natural agents, such as glycine, blocks the release of histamine from the mast cells, thereby breaking the self-perpetuating cycle of itching-scratching-epidermal lesion.<sup>2</sup> Glycine blocks the release of histamine by the mast cells,<sup>27</sup> thereby interfering with the release of the mediators of the inflammation-itch phenomenon. Other products, in particular corticosteroids, are used to treat itching. Topical corticosteroid preparations have an indirect effect on itching as they improve the condition of the skin, particularly if exacerbated by a comorbid inflammatory process, such as eczema. It should be noted, however, that prolonged use of topical corticosteroids can cause undesirable side effects, such as dermal atrophy.<sup>8</sup>

### Repair of the Stratum Corneum

As the skin and its different layers are structures that undergo continual renewal, dry skin can be treated by delivering components, such as dexpanthenol, that stimulate and accelerate the process of epidermal regeneration. Dexpanthenol promotes fibroblast proliferation and migration and stimulates intracellular protein synthesis,<sup>2</sup> while hydroxyacids facilitate desquamation and improve lipid biosynthesis.<sup>8</sup>

## Active Ingredients for the Topical Treatment of Xerosis

Topical preparations for the treatment of dry skin should contain molecules that activate the epidermal regeneration process and restore the lipid content of the horny layer. Table 6 shows the active ingredients that should be included in any formulation for a topical moisturizing preparation and lists the principal action of each one.<sup>2</sup> It is essential to choose the most suitable excipient for the area of the skin to be treated (Table 7).<sup>2</sup> The ideal formulation would contain physiologic lipids (ceramides, cholesterol), a physiologic humectant (glycerol), an anti-itching agent (glycerol), and a component that enhances epidermal differentiation (dexpanthenol).<sup>2</sup>

### Humectants

Humectants are natural oily substances that do not intervene in the metabolic processes of the skin but rather act passively by preventing excessive water loss. They can be classified according to general chemical categories: hydrocarbons, oils and fatty alcohols, colloid substances, and silicones (Table 8).

### Moisturizers

Hydrating agents play an active role in the process of maintaining the water balance of the stratum corneum and are listed in Table 8.

### Active Relipidating Agents

Active relipidating agents supply the components the skin needs to balance the composition of the interlamellar lipid bilayers. In dry skin, the fatty acid content of these layers is low and ceramide content is disproportionately high (Table 8).

### Promoters of Epidermal Differentiation

Some topical formulations for dry skin include an active ingredient that stimulates cell proliferation and lipid synthesis. One example of this type of component is dexpanthenol, a precursor of pantothenic acid and a constituent of coenzyme A.<sup>2</sup> It has been observed that pantothenic acid increases the proliferation and migration of fibroblasts<sup>28</sup> and stimulates intracellular protein synthesis.<sup>29</sup> Dexpanthenol has been used for some time to enhance skin barrier function in a number of different situations including

**Table 6.** Action of the Principal Active Ingredients Used in a Topical Preparation for the Treatment of Dry Skin

<i>Active Ingredient</i>	<i>Action</i>
Lipids	Replaces the lost natural skin lipids
Physiologic lipids	Epidermal differentiation and repair of the structural elements in the stratum corneum. Signal for epidermal reconstruction
Hydrating agents and humectants	Balance the water content of the stratum corneum and reestablish barrier function
Antipruritic agents	Break the itch-scratch cycle
Others (for example dexpanthenol)	Fibroblast proliferation and migration, intracellular protein synthesis, epidermal differentiation

**Table 7.** Characteristics of the Hydrating Preparation Depending on the Specific Requirements of the Case

<i>Circumstances</i>	<i>Recommended Preparation</i>
Facial area	Water-rich cream
Limbs and folds	Lipid-rich ointment
Acute eczema	Water-rich cream, solutions
Chronic eczema	Lipid-rich ointments and unguents
Summer	Water-rich cream
Winter	Lipid-rich ointment

dermal regeneration following skin graft extraction and after x-ray irradiation.<sup>30</sup>

### Other Active Ingredients

Table 8 lists other active ingredients that play a role in the recomposition of the xerotic stratum corneum.

## Conclusion

Dry skin or xerosis is a very common disorder in the general population. Although certain diseases such as atopic dermatitis are predisposing factors, xerosis can occur in healthy individuals when several predisposing factors coincide, especially in older patients. While the pathophysiology of this process is complex, disruption of

**Table 8.** Substances Included in Topical Preparations for the Treatment of Xerosis

<i>Type</i>	<i>Compound</i>	<i>Characteristic</i>
Humectants	Hydrocarbons	Mineral oils, such as paraffin and Vaseline
	Fatty oils and alcohols	
	Colloid substances	Some are hygroscopic, such as the cellulose derivatives (ethyl cellulose), natural polymers (xanthan gum), and synthetic polymers (carbopol)
	Silicones	No strong smell
		Not comedogenic
		Excellent tolerance
		Nongreasy formulations
Hydrating agents	Polyols	Highly hydrating
		Restore the flexibility of the cornified layer
		Prevent crystallization of lipids
		Promote corneodesmolysis
		Examples: glycerol, sorbitol, propylene glycol
	Urea	A component of natural moisturizing factor
		Highly hygroscopic and good exfoliating qualities
	Reconstituted natural moisturizing factor	Mixture of amino acids, sodium lactate, lactate acid, citrate, and others
		Repairs the upper layers of the stratum corneum with a hydrating action similar to that of natural moisturizing factor
		Hyaluronic acid
		High capacity to hydrate the stratum corneum
		Restores the flexibility and elasticity of the skin
		Well tolerated by skin
Relipidating active ingredients	Ceramides	Facilitate epidermal differentiation by reestablishing the cellular lipids
	Cholesterol	Ensures the availability of this natural lipid in the stratum corneum to facilitate regeneration and epidermal differentiation
	Essential fatty acids	Provides consistency and cohesion in the stratum corneum
		Anti-inflammatory, immunogenic, and antimicrobial activity
		Principal fatty acids: linoleic, g-linoleic, and arachidonic acid
	Fatty acids are found in vegetable oils, such as evening primrose, shea, jojoba, borage, olive, wheat germ, and sun flower.	
Other active ingredients	Oats	Complex composition: very rich in water, proteins, glucides, lipids, mineral salts, and vitamins
		Hydrating, restructuring, antipruritic, and anti-inflammatory
		Improves the compatibility between the components in the preparation
	Allantoin	Conditioning, hydrating, and keratoplastic
	a-bisabolol	Anti-inflammatory, emollient, and bactericidal
	Aloe vera	Soothing and emollient
	Glycyrrhetic acid	Anti-inflammatory and emollient

normal epidermal differentiation is one of the principal etiologic factors. This disturbance gives rise to an imbalance in water content in the stratum corneum and impaired barrier function. The epidermal lesion causes itching, which provokes scratching. This in turn further aggravates the disturbance of the stratum corneum and completes the self-perpetuating skin damage cycle. Recent advances in our understanding of the function and metabolism of the skin allow us to advocate an “inside out” approach to the treatment of xerosis that contrasts with the classic therapeutic approach. This new approach is based on the concept that the skin is an active organ that requires the nutrients needed to ensure epidermal differentiation. It has allowed us to reevaluate the essential aspects of topical treatment for xerosis, and has led us to modify some aspects of the composition of the preparations used. For the treatment of dry skin, in addition to general care measures, the topical application of preparations containing the elements necessary for the repair of the epidermal barrier is considered to be a priority. The most recommended moisturizing preparations contain physiologic lipids and other substances that contribute to the repair of the intercellular lipid bilayers and the reestablishment of normal keratinocyte differentiation.

### Conflicts of Interest

The authors declare no conflicts of interest.

## REFERENCES

- Burdette-Taylor SR. Eczema, ichthyosis, psoriasis: conditions of cornification. *Ostomy Wound Manage* 1995;41: 36-8.
- Proksch E, Lachapelle JM. The management of dry skin with topical emollients—recent perspectives. *J Dtsch Dermatol Ges*. 2005;3:768-74.
- Feingold KR, Mao-Quian M, Menon GK, Cho SS, Brown BE, Elias PM. Cholesterol synthesis is required for cutaneous barrier function in mice. *J Clin Invest*. 1990;86: 1738-45.
- Grubauer G, Feingold KR, Harris RM, Elias PM. Lipid content and lipid type as determinants of the epidermal permeability barrier. *J Lipid Res*. 1989;30:89-96.
- Elias PM. Stratum corneum defensive functions: an integrated view. *J Invest Dermatol*. 2005;125:183-200.
- Nakagawa N, Sakai S, Matsumoto M, Yamada K, Nagano M, Yuki T, et al. Relationship between NMF (lactate and potassium) content and the physical properties of the stratum corneum in healthy subjects. *J Invest Dermatol*. 2004;122: 755-63.
- Clark C. How to choose a suitable emollient. *Pharm J*. 2004; 273:351-3.
- Rawlings AV, Matts PJ. Stratum corneum moisturization at the molecular level: an update in relation to the dry skin cycle. *J Invest Dermatol*. 2005;124:1099-110.
- Rycroft RJG. Low humidity and microtrauma. *Am J Ind Med*. 1985;8:371-3.
- Di Nardo A, Werz P, Giannetti A, Deidenari S. Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. *Acta Dermatol Venereol*. 1998;78:27-30.
- Morar N, Cookson WO, Harper JI, Moffatt MF. Filaggrin mutations in children with severe atopic dermatitis. *J Invest Dermatol*. 2007;127:1667-72.
- Takahashi M, Tezuka T. The content of free amino acids in the stratum corneum is increased in senile xerosis. *Arch Dermatol Res*. 2004;295:448-52.
- Katagiri C, Sato J, Nomura J, Denda M. Changes in environmental humidity affect the water-holding property of the stratum corneum and its free amino acid content, and the expression of the filaggrin in the epidermis of hairless mice. *J Dermatol Sci*. 2003;31:29-35.
- Elias PM, Ansel JC, Woods LD, Feingold KR. Signaling networks in barrier homeostasis: the mystery widens. *Arch Dermatol*. 1996;132:1505-6.
- Elias PM, Woods LD, Feingold KR. Epidermal pathogenesis of inflammatory dermatoses. *Am J Contact Dermat*. 1999;10:119-26.
- Rycroft PJG, Smith WDL. Low humidity occupational dermatoses. *Contact Dermatitis*. 1980;6:488-92.
- Agner T, Serup J. Seasonal variation of skin resistance to irritants. *Br J Dermatol*. 1989;121:323-8.
- Engelke M, Jensen JM, Ekanayake-Mudiyanselage S, Proksch E. Effects of xerosis and ageing on epidermal proliferation and differentiation. *Br J Dermatol*. 1997;137: 219-25.
- Cork MJ, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowan A, et al. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. *J Allergy Clin Immunol*. 2006; 118:3-21.
- Werner Y, Lindberg M. Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. *Acta Derm Venereol*. 1985;65:102-5.
- Thune P. Evaluation of the hydration and water binding capacity in atopic skin and so-called dry skin. *Acta Derm Venereol*. 1989;144 Suppl:133-5.
- Shapiro LJ, Weiss R, Webster, Frances JT. X-linked ichthyosis due to steroid sulphatase deficiency. *Lancet*. 1978;1:70-2.
- Sato J, Denda M, Nakinishi J, Nomura J, Koyama J. Cholesterol sulphate inhibits proteases that are involved in desquamation of stratum corneum. *J Invest Dermatol*. 1998;111:189-94.
- Ramírez C, Jacob SE. Dermatitis de manos. *Actas Dermosifiliogr*. 2006;97:363-73.
- Chamlin SL, Kao J, Freiden IJ, Sheu MY, Fowler AJ, Fluhr JW, et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol*. 2002;47:198-208.
- Hara M, Verkman AS. Glycerol replacement corrects defective skin hydration, elasticity and barrier function in aquaporin-3-deficient mice. *PNAS*. 2003;100:7360-5.
- Paubert-Braquet M, Lefrançois G, Picquot S. Etude in vitro du pouvoir antiprurigineux du glyco-colle: effet sur la dégranulation des mastocytes. *Thérapeutique*. 1992;95:2-3.
- Weimann BI, Hermann D. Studies on wound healing: effects of calcium pantothenate on the migration, proliferation and

- protein synthesis of human dermal fibroblasts in culture. *Int J Vitam Nutr Res.* 1999;69:113-9.
29. Lacroix B, Didier E, Grenier JF. Effects of pantothenic acid on fibroblastic cell cultures. *Res Exp Med.* 1988;188:391-6.
30. Girard P, Beraud A, Goujon C. Effect of bepantthen ointment on the graft-donor site wound-healing model: double-blind biometrological and clinical study, with assessment by the patient versus the vehicle. *Nouv Dermatol.* 1998;17: 559-70.