

Role of Topical Emollients and Moisturizers in the Treatment of Dry Skin Barrier Disorders

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Abstract

Emollients and moisturizing creams are used to break the dry skin cycle and to maintain the smoothness of the skin. The term 'moisturizer' is often used synonymously with emollient, but moisturizers often contain humectants in order to hydrate the stratum corneum. Dryness is frequently linked to an impaired barrier function observed, for example, in atopic skin, psoriasis, ichthyosis, and contact dermatitis.

Dryness and skin barrier disorders are not a single entity, but are characterized by differences in chemistry and morphology in the epidermis. Large differences also exist between moisturizing creams. Moisturizers have

multiple functions apart from moistening the skin. Similar to other actives, the efficacy is likely to depend on the dosage, where compliance is a great challenge faced in the management of skin diseases. Strong odor from ingredients and greasy compositions may be disagreeable to the patients. Furthermore, low pH and sensory reactions, from lactic acid and urea for example, may reduce patient acceptance. Once applied to the skin, the ingredients can stay on the surface, be absorbed into the skin, be metabolized, or disappear from the surface by evaporation, sloughing off, or by contact with other materials.

In addition to substances considered as actives, e.g. fats and humectants, moisturizers contain substances conventionally considered as excipients (e.g. emulsifiers, antioxidants, preservatives). Recent findings indicate that actives and excipients may have more pronounced effects in the skin than previously considered. Some formulations may deteriorate the skin condition, whereas others improve the clinical appearance and skin barrier function. For example, emulsifiers may weaken the barrier. On the other hand, petrolatum has an immediate barrier-repairing effect in delipidized stratum corneum. Moreover, one ceramide-dominant lipid mixture improved atopic dermatitis and decreased transepidermal water loss (TEWL) in an open-label study in children. In double-blind studies moisturizers with urea have been shown to reduce TEWL in atopic and ichthyotic patients. Urea also makes normal and atopic skin less susceptible against irritation to sodium laurilsulfate. Treatments improving the barrier function may reduce the likelihood of further aggravation of the disease.

In order to have optimum effect it is conceivable that moisturizers should be tailored with respect to the epidermal abnormality. New biochemical approaches and non-invasive instruments will increase our understanding of skin barrier disorders and facilitate optimum treatments. The chemistry and function of dry skin and moisturizers is a challenging subject for the practicing dermatologist, as well as for the chemist developing these agents in the pharmaceutical/cosmetic industry.

Topical treatment is fundamental for patients with skin diseases. Corticosteroids have become a mainstay for a wide range of inflammatory and proliferative dermatoses; moisturizing creams are often added as important treatment adjuncts.^[1] However, many healthcare professionals and patients overlook the importance of moisturizers and consider them not to be 'active' treatments. Patient adherence is also a great challenge faced in the management of skin diseases and if the moisturizers are used in too small quantities they will have limited value. Moreover, moisturizers have multiple functions executed by a great variety of ingredients. Apart from moistening the skin, they affect the structure and barrier function of diseased and healthy looking skin. When moisturizers are used on so-called 'dry' skin, many distinct diseases that manifest themselves with the generally recognized symptoms of dryness are being treated.

The major functions of the skin are to protect the body against physical and chemical injury and to prevent loss of body water and other substances. The stratum corneum (SC) is composed of protein enriched corneocytes and lipid enriched intercellular domains. The SC is being continually replaced and is well adapted to its requirements for repairing damage from wear and tear. However, environmental and individual factors may interact in a complex manner to induce skin abnormalities.

Exposure to chemicals, microorganisms,^[2,3] low environmental temperature, and low humidity^[4,5] may cause symptoms of dryness and barrier abnormalities. In addition, normal aging and psycho-

logical stress have been reported to influence barrier homeostasis.^[6,7] Acute and chronic perturbations of barrier function may lead to epidermal hyperplasia^[8,9] and cutaneous inflammation by increased production and secretion of cytokines.^[10] Furthermore, symptoms of dryness and impaired barrier function to water are seen in cutaneous disorders, such as atopic dermatitis,^[11-14] psoriasis,^[15,16] and ichthyosis.^[17-20]

Atopic dermatitis has a complex pathophysiology, including interactions between genetic predisposition and exogenous provocation factors. Its prevalence is increasing and among school children in the North Europe values between 15% and 20% are reported.^[21,22] The increasing prevalence during a rather short period of time suggests factors in the environment are promoting the rise rather than genetic changes.^[23] Psoriasis is another common inflammatory disorder with a prevalence of 2-3% in the general population. The disease is characterized by an increased cell production with incomplete differentiation and parakeratotic plaques. The ichthyoses are non-inflammatory scaling disorders encompassing a wide range of keratinizing disorders with completely different pathophysiology. The skin is persistently dry and scaly as a result of abnormal formation and desquamation of the SC.

Application of moisturizers to the skin induces changes in its superficial as well as deep layers. The chemical and physical characteristics of the individual ingredients determine the performance of the formulation. In order to have optimum effect it is

conceivable that moisturizers should be tailored with respect to the many distinct diseases that contributes to the different symptoms of dryness. The biological perspective has to be further explored and transferred into the development of moisturizers.

This article reviews the role of the topical emollients and moisturizers in the treatment of dry skin barrier disorders. The chemistry and function of dry skin and moisturizers are also discussed briefly. The review is limited to conditions where moisturizers are commonly used and information on barrier function is available.

1. Structure and Function of the Epidermis

1.1 Dryness and Hydration of the Skin

The impression of dryness is formed by visible, tactile, and sensory components of changes in the skin.^[24,25] Visual changes include redness, a lack luster surface, dry white patches, flakes, cracks, and even fissures. The skin can also feel rough and uneven on touch. The frictional resistance is also reduced.^[26] The affected person may also experience a feeling of dry, uncomfortable, painful, itchy skin, and stings or tingles.

The corneocytes and their intercellular cohesive structures are prerequisites for the function of the SC as the physical/chemical barrier between interior and exterior of the body. The mechanical strength of the corneocytes is derived from the tightly packed keratin bundles and the proteins of the cornified envelopes. The protein layer covering the corneocytes is highly insoluble, due to the extensive cross-linking.^[27] The corneocyte envelope structure consists of two parts: (i) a thick layer (approximately 15nm) adjacent to the cytoplasm that is composed of structural proteins and (ii) a thin layer (approximately 5nm) on the exterior of the protein part that is composed of lipids.^[27]

Water maintains the softness and flexibility of the SC. If a piece of SC is dried out, it becomes hard and brittle, and cannot be softened by immersion in any lipid substance, such as petrolatum, lanolin, or vegetable oils.^[28] Water in the SC is associated with the hydrophilic parts of the intercellular lipids and with the keratin fibers in the corneocytes.^[29,30] Three types of water with different molecular mobilities can be found in the SC. With hydration <10% the primary water is tightly bound, presumably to the polar sites of the proteins.^[30,31] When the degree of hydration is >10%, the secondary water is hydrogen-bonded around the protein-bound water, and with hydration >40–50% the water resembles the bulk liquid.^[30,31] It is the secondary water that contributes to the plasticity of the SC.^[30,32]

The corneocytes contain a water-soluble fraction of low molecular humectants, which is termed natural moisturizing factor

(NMF). NMF accounts for 15–20% of the total weight of the SC.^[33,34] The composition of NMF in normal skin is shown in table I. If NMF is extracted from the skin, the ability of the SC to bind water is decreased.^[34,35] A significant relationship has also been found between the moisture binding ability and the pyrrolidone carboxylic acid (PCA) content of SC.^[35] NMF not only seems to be important for the water holding capacity of skin, but it also appears to increase the elasticity of SC.^[36–38] Thus, if NMF is removed, water alone cannot restore elasticity.^[38]

Water not only affects the physical characteristics of the SC, but is also required for the metabolic processes in the epidermal layer. During their life cycle keratinocytes differentiate, gradually flatten out, extrude lipids by exocytosis, and eventually completely cornify to become corneocytes filled with keratin and amorphous matrix. Desquamation involves degradation of corneodesmosomes by enzymes dependent upon water and pH for their activity.^[39–42] In excised skin the rate of spontaneous cell dissociation is highest at neutral to weakly alkaline pH and decreases at acidic pH.^[42] In addition, divalent ions such as calcium (Ca²⁺) regulate the dissociation and chelating agents, such as edetic acid (EDTA), have been noticed to increase the rate of cell dissociation *ex vivo*.^[42] Cholesterol sulfate is also involved in the process and the observed drop in the concentration towards the outer layer of SC promotes desquamation. It inhibits proteases involved in the desquamation process.^[43] Cholesterol sulfate has been suggested to stabilize the lipid layer in the deeper layer of SC, keeping the corneocytes together.^[44] It also reduces the amount of cholesterol that is present in lipid crystalline domains.^[44] Thus, a drop in cholesterol sulfate has been suggested to induce crystallization of cholesterol and decrease the cohesion between lipid lamellae.^[44] Ca²⁺ counteracts the effects of cholesterol sulfate, indicating a proper balance of the SC components for appropriate SC lipid organization.^[44,45]

Table I. Composition of natural moisturizing factor^[33]

Constituents	(%)
Amino acids	40.0
Pyrrolidone carboxylic acid	12.0
Lactate	12.0
Urea	7.0
Sodium, calcium, potassium, and magnesium phosphates and chlorides	18.5
Ammonia, uric acid, glucosamine, creatinine	1.5
Unidentified	9.0

1.2 Permeability Barrier of the Skin

The rate of penetration of substances through the skin is inversely related to the thickness of the SC.^[46] The major route of penetration of substances through the SC is considered to be the intercellular pathway. This highly convoluted and tortuous lipid pathway around the corneocytes will give a longer distance for penetration than the actual thickness of the SC.^[47,48] In hyperproliferative diseases the projected size of the corneocytes decreases, which reduces the tortuous pathway.^[48,49] This may be one of several reasons for the greater permeability in hyperproliferative diseases.^[48]

Hyperkeratosis may be one way for the SC to compensate for a defect in barrier function, indicating a failure of epidermis to produce a competent barrier with normal thickness. This may explain normal transepidermal water loss (TEWL) in dry skin conditions.^[24] However, hyperkeratosis may also reflect an undesired inhibition of the desquamation process.

Another factor which may influence the permeability is the degree of hydration of the SC.^[50,51] Hydration allows the layer to bend and stretch more easily, avoiding cracking and fissuring. However, excessive hydration increases the permeability,^[50] and occlusion is often used to increase the bioavailability of drugs via the skin. Hydration has been suggested to create interfacial defects in the lipid bilayer.^[52,53]

The most important factor for restricting water loss is the composition and organization of the lipids within the intercellular domains.^[54] The lipid membranes contain primarily cholesterol, free fatty acids, and ceramides organized in two crystalline lamellar phases with repeat distances of approximately 6 and 13nm.^[55,56] The structural arrangement of the lipid molecules in the transverse plane is not clearly elucidated, but recent studies suggest that different lipids may segregate in the membrane and form separate fluid and solid phases within the SC.^[55,57] The bulk of the lipids has been suggested to be in crystalline/gel domain bordered by lipids in a fluid crystalline state; a 'domain mosaic model'.^[58] This model is considered an effective water barrier which allows a controlled loss of water to keep the corneocytes moistened.^[58]

1.3 Formation of Skin Barrier Lipids

The principal source of SC lipids is lamellar bodies, which contain cholesterol, phospholipids, and glucosylceramides. During barrier formation these released lipids are converted into more hydrophobic lipid products. The lamellar bodies also contain a number of hydrolytic enzymes, including proteases, glycosidases, and a family of lipases which could be involved in extracellular processing.^[54] Barrier disruption increases the activity of β -

glucocerebrosidase, the enzyme responsible for the hydrolysis of glucosylceramides to ceramides, by increasing epidermal β -glucocerebrosidase mRNA levels.^[59] Inhibition of β -glucocerebrosidase activity delays barrier repair and gives evidence of immature lamellar membranes in the intercellular spaces of the SC.^[60] A similar barrier defect and altered ultrastructure is observed in patients with severe β -glucocerebrosidase deficiency (Gaucher disease type II).^[61] Moreover, studies have shown that inhibition of secretory (type I) phospholipase A₂ (PLA₂), which converts extracellular phospholipids to free fatty acids, also inhibits barrier repair in hairless mice.^[62] Inhibition of PLA₂ results in the formation and persistence of abnormal, immature lamellar bilayers in the SC interstices. Co-application of free fatty acids allows normal barrier recovery and normal appearance of intercellular lamellar structures.^[62]

Acute and chronic perturbations of barrier function increase epidermal DNA synthesis in the basal layer of the epidermis in hairless mice.^[8] The magnitude of the increase in epidermal DNA synthesis correlates with the degree of barrier disruption. The increase is largely inhibited with an impermeable membrane, while vapor-permeable membranes permit the increase in DNA synthesis to occur in proportion to their degree of vapor permeability.^[8]

The defective barrier function stimulates the production and secretion of cytokines, which in turn may cause cutaneous inflammation,^[10,54] increased keratinocyte proliferation, and epidermal hyperplasia.^[8,9] Interferences with the processing of the extracellular lipids into normal lamellar membranes may adversely affect barrier homeostasis. For example, skin surface pH has been suggested to influence barrier recovery. Exposing barrier abrogated mice skin to neutral or alkaline pH delayed barrier recovery.^[63] The formation and secretion of lamellar bodies proceeded comparably at pH 5.5 and pH 7.4, but exposure to pH 7.4 resulted in both the persistence of immature extracellular lamellar membranes and a marked decrease in the *in situ* activity of β -glucocerebrosidase.^[63] β -Glucocerebrosidase, acid phosphatase, cholesterol acyltransferase, and one isoform of acid-sphingomyelinase are most active at acidic pH.^[64] At neutral or basic pH another form of sphingomyelinase as well as PLA₂ increase in activity.^[64,65] These results suggest that the pH gradient within the SC influences lipid processing and normal barrier homeostasis.

In addition, psychological stress has been shown experimentally to retard permeability barrier recovery in humans^[7] and low humidity increases cytokine expression in mice, suggesting induction of other inflammatory molecules.^[4]

A steep Ca²⁺ gradient exists across the nucleated layers of the epidermis, with low concentrations in the basal, proliferating layers and progressively higher concentrations as one proceeds to

the outer differentiated layers, declining again in the outer SC.^[66] Disruption of the barrier depletes Ca²⁺ from the upper epidermis and removes the gradient, which triggers secretion of lamellar bodies and barrier recovery in hairless mice.^[67-69] Application of exogenous Ca²⁺ inhibits barrier repair by maintaining the Ca²⁺ content in the upper epidermis.^[67,68] Thus, it is proposed that water loss may induce a decrease in the concentration of Ca²⁺ in the upper epidermis that in turn stimulates lamellar body secretion and barrier repair.

1.4 Measurement of Skin Barrier Function

To evaluate effects on skin barrier function, several non-invasive bioengineering techniques can be used alone or in combination.^[70] Measuring the TEWL reveals information on the function of SC as a diffusion barrier for water and is a useful tool for monitoring the kinetics in the repair of a deteriorated barrier function. The level of TEWL has been suggested to serve as an indicator of the permeability of the skin to topically applied substances.^[71,72]

TEWL can be measured conveniently with an open chamber evaporation gradient method, used in the evaporimeter, TEWA[®]1-meter or DermaLab[®].^[73,74] In these instruments a probe applied to the skin measures the water evaporation. The probe consists of an open cylinder containing two hygrosensors coupled with two thermistors placed at different distances from the skin surface. The difference between vapor pressure at both points is directly related to the rate of the evaporative water loss through that particular skin site. The results are expressed in g • m⁻² • h. Calibration of the instruments appears critical and relative values might be more appropriate than absolute values.

Important factors to consider during TEWL measurements are room temperature and ambient humidity.^[74,75] Sweating must be avoided and a room temperature of 20–22°C is, therefore, recommended.^[74] Furthermore, air convection in the room may disturb the readings and some form of draught shield may be useful.^[73,74] The rest time before TEWL readings also has to be considered. Moreover, other volatile agents than water might influence the values if measurements are made immediately after application of moisturizers.^[76] Application of aqueous formulations results in an immediate increase in the values, whereas application of water-free petrolatum significantly reduces the values due to occlusion.^[77]

Whether change in the TEWL is predictive also for the permeability to substances other than water, depends on the mechanism underlying the detected change in the TEWL.

Evaluation of skin barrier function to other substances can be made *in vivo* by recording of a biological response following application of different substances.^[78] Substances used to assess skin permeability are those inducing vasodilatation (e.g. nico-tinates), irritation (surfactants such as sodium laurilsulfate), erosion (sodium hydroxide), whealing and flare (dimethyl sulfoxide), burning (chloroform, methanol), stinging (lactic acid), and vaso-constriction.^[78]

2. Content and General Effects of Moisturizers

2.1 Actives and Excipients in Moisturizers

The term emollient implies (from the Latin derivation) a material designed to soften the skin, and usually this implies a material that smooths the surface to the touch and makes it look smoother to the eye. The term moisturizer is often used synonymously with emollient, as in this review, but moisturizers often contain humec-tants in order to hydrate the SC.

Knowledge about the interplay between ingredients in mois-turizers is essential to get a stable and cosmetically attractive product with desired impact on the skin. The greasy and sticky properties of some creams can be a major nuisance at work and the smell of some products can be difficult to accept. Formulating elegant and yet efficient moisturizing creams is challenging for the pharmaceutical/cosmetic industry.

The concentration and type of fats, and the amount and type of emulsifiers, humectants, and preservatives have to be considered, as well as the impact of other excipients, such as chelating sub-stances, antioxidants, and fragrances. Also pH has to be consid-ered. Most formulations have pH between 3 and 8. A number of creams are stabilized by emulsifiers or contain ingredients which require pH >7 to become stable, for example emulsions with stearic acid as primary emulsifier. Moreover, skin protectants based upon zinc oxide have alkaline pH.

Topical formulations can be divided into several groups ac-cording to the European Pharmacopoeia depending on their com-positions, for example:

- Creams are multiphase preparations consisting of a lipophilic phase and an aqueous phase. In its simplest form a cream is a two-phase system (emulsion) containing two immiscible li- quids, one of which is dispersed in the other in the form of microscopic or submicroscopic droplets.
- Ointments consist of a single-phase base in which solids or liquids may be dispersed. Hydrophilic ointments are prepara- tions having bases that are miscible with water. The bases

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

usually consist of mixtures of liquid and solid polyethylene glycols. Hydrophobic ointments usually contain paraffins, vegetable oils, animal fats, waxes, and liquid polyalkylsiloxanes.

- Gels consist of liquids (hydrophilic or hydrophobic) gelled by means of suitable gelling agents.
- Pastes are semisolid preparations containing large proportions of solids finely dispersed in the base.
- Liquid preparations could be solutions, suspensions, or emulsions.

Creams are the most common types of delivery system used for emollients and moisturizers. They enable a wide variety of ingredients to be quickly and conveniently delivered to the skin. The two phases are usually oil and water, producing either an oil-in-water (O/W) or a water-in-oil (W/O) emulsion. The droplet size is usually between 1 and 100µm. To provide stability and desired rheological properties to the formulation emulsifiers are added to the cream.

2.1.1 Emulsifiers

Emulsifiers are one of the classes of compounds known as surface active agents whose unique behavior stems from the fact that they combine both hydrophilic and lipophilic components in one molecule, i.e. they have one nonpolar hydrocarbon end and one polar end. They tend not to be wholly soluble in either oil or water; thus they collect at the interface of the two phases and promote emulsification.

The emulsifiers can be classified as ionics or nonionics. The ionic types are either anionic or cationic, depending on the surface-active portion of the compound. Long-chain fatty acids are one group of commonly used anionic emulsifiers, for example, stearic acid and palmitic acid. The acids are often partially neutralized with cationic excipients in the preparation of the cream and their concentration can range from approximately 1–10%. Fatty acids with a chain length of 14–22 carbons are also found in the epidermal tissue. Cholesterol is another component of the lipid bilayer, which also can be used as an emulsifier in moisturizers. Cholesterol is a nonionic emulsifier. Nonionic emulsifiers depend chiefly upon hydroxyl groups and ether linkages (from polyhydric alcohol anhydrides and polyoxyethylene chains) to create the hydrophilic action.

The effects of emulsifiers on skin barrier properties depend on their composition. Nonionic emulsifiers are usually less irritating than ionics. Differences in skin barrier influences have been noted among nonionic emulsifiers.^[79]

2.1.2 Fats and Oils

Common fats in moisturizers are mineral oils, waxes, long-chain esters, fatty acids, lanolin and mono-, di- and triglycerides. Mineral oils are derived from petroleum; the two most important

materials are liquid paraffin and petrolatum. These are purified materials consisting of complex combinations of hydrocarbons. Depending on the distribution of the molecular weight, materials with different viscosities are obtained. During the refining process, the hydrocarbon material is hydrogenated to create oxidation-resistant molecules throughout, from the liquid to the solid waxes. This gives a long shelf life to the products. Petrolatum has been used in skin care products since its discovery by Robert A. Chesebrough in 1872 and was included in the 1880 edition of the US Pharmacopoeia.^[80]

Waxes may be classified into animal, vegetable, and mineral types. The most commonly used animal wax is lanolin. Lanolin (from the Latin *lana* for wool and *oleum* for oil) is secreted by the sebaceous glands of the sheep. Lanolin is a complex mixture of esters, di-esters, and hydroxy esters of high molecular weight lanolin alcohols and lanolin acids. Unlike human sebum, lanolin contains no triglycerides. Beeswax is a complicated mixture of hydrocarbons, esters, and fatty acids. A typical example of a vegetable-derived wax is carnauba, which is obtained from the leaves of the carnauba palm tree.

Triglycerides can be divided into fats (solids) and oils (liquids) depending on their physical state. They can have animal or vegetable origin. Animal-derived materials have been used for a long time, but religious reasons and bovine spongiform encephalopathy (BSE) has increased the interest in vegetable sources. The use of tallow or other animal-derived materials have to follow strictly certified processes in order to eliminate any risk associated with BSE. Vegetable oils may also contain unwanted substances. Refining of oils, such as peanut oil, removes proteins which can elicit sensitization reactions in allergic individuals.^[81] The chemical structure of triglycerides consists of a glycerol fragment, esterified with fatty acids. There is a large variety in fatty acids, with the saturated fatty stearic acid, the monounsaturated oleic acid, and the polyunsaturated linolenic acid being the most abundant fatty acids. The fatty acid profile, which is typical for certain oil, determines to a great extent the characteristics of an oil with respect to stability, skin feel, and effects on the skin. The most important feature of a fatty acid is the number of double bonds and their distribution over the carbon chain. The degree of unsaturation has a large effect on the ease of handling. Fatty acids with a higher degree of unsaturation are oxidized more easily. Oxidation is increased by the presence of metals, heat light, and oxygen.

Oils from vegetables and fish are examples of oils containing essential fatty acids (EFAs). Fatty acids with the first double bond at the sixth carbon atom counting from the end of the carbon tail are called omega-6, whereas those with the first double bond at the third carbon atom are called omega-3 fatty acids. Omega-6 and omega-3 fatty acids are derived from linoleic and α -linolenic acid,

respectively. The essential fatty acids influence skin physiology via their effects on skin barrier function, eicosanoid production, membrane fluidity, and cell signaling.^[82] The EFAs are found predominantly within the epidermal phospholipids, but are also incorporated in ceramides where they play a critical role in barrier function. The most abundant EFA in the skin is linoleic acid and its metabolite arachidonic acid. Evening primrose oil and borage oil have γ -linoleic acid (GLA) levels over 9% and 20%, respectively. Seafood is known to contain omega-3 fatty acids, like eicosapentaenoic (EPA), docosahexaenoic, and stearidonic acid.

2.1.3 Humectants

Moisturizers often contain humectants. The majority of humectants are low molecular weight substances with water attracting properties. Some are also high molecular weight substances. Humectants differ in water binding capacity as well as in ability to penetrate and influence the degree of skin hydration.

One important group of humectants is α -hydroxy acids (AHAs), for example, lactic acid, glycolic acid, and tartaric acid. AHA is an organic carboxylic acid in which there is a hydroxy group at the two, or alpha, position of the carbon chain. Formulations containing an AHA have an acidic pH in the absence of any inorganic alkali or organic base. Lactic acid has been used in topical preparations for several decades because of its buffering properties and water binding capacity.^[37] The concentrations used for treatment of ichthyosis and dry skin have ranged up to 12%.^[83]

The sodium salt of PCA is a naturally occurring humectant in the SC at levels about 12% of the NMF^[33] corresponding to about 2% by weight in the SC.^[34] The sodium salts of PCA are among the most powerful humectants. Treatment of solvent-damaged guinea pig footpad SC with humectant solutions shows that the water held by the SC decreases in the following order: sodium PCA > sodium lactate > glycerin > sorbitol.^[37]

Urea is another physiological substance occurring in human tissues, blood, and urine. In urine the amount is of the order of 2%. Extraction of urea from urine was first accomplished by Proust in 1821 and pure urea was first synthesized by Wöhler in 1828.^[84] Urea in solution hydrolyses slowly to ammonia and carbon dioxide.^[80] Solutions containing 20% urea have been proposed to reduce experimentally-induced itching.^[85] Urea is used as a 10% cream for the treatment of ichthyosis and hyperkeratotic skin disorders,^[80,84] and in lower concentrations for the treatment of less severe dryness. Urea can also be used for avulsing dystrophic nails and a preparation with 40% urea has been shown to be slightly more effective in removing the nail than a formulation with 22% urea, but it was more irritating.^[86]

Glycerin is an important ingredient in skin care products, primarily due to its humectant and smoothing properties. In

1779, the Swedish scientist CW Scheele discovered that glycerin could be made from a hydrolysate of olive oil. The concentration in moisturizing creams can be as high as 20% without causing any significant adverse effects.^[87] Glycerin has been suggested to ameliorate dry flaky skin by facilitating the digestion of the superficial desmosomes in individuals with dry skin.^[40] Glycerin also modulates the phase behavior of SC lipids *in vitro* and prevents crystallization of their lamellar structures at low relative humidity.^[88] In dry skin the proportion of lipids in the solid state may be increased, and glycerin may then help to maintain the lipids in a liquid crystalline state at low relative humidity.^[88,89]

Propylene glycol, an alcohol, is another commonly used humectant. The substance attracts water and is widely used in cosmetics and pharmaceuticals as a solvent and vehicle especially for substances unstable or insoluble in water. Propylene glycol is also regarded as a penetration enhancer.^[80]

2.1.4 Antimicrobial Preservatives

Preservatives are included in formulations to kill or inhibit the growth of microorganisms inadvertently introduced during use or manufacturing. Contaminating organisms may be either pathogens or nonpathogens. The ideal preservative must have a broad spectrum of activity; must be safe to use; should be stable in the product; and should not affect the physical properties of the product. No single preservative meets all these requirements and usually a combination of substances is used. Parabens (methyl-, propyl-, ethyl-, and butylparaben) are among the most frequently used preservatives in creams and come closer to the ideal preservative than other substances used today.

The efficacy of the preservative is also influenced by pH and other ingredients in the formulation. Certain substances, such as ethanol and propylene glycol, may enhance the efficacy of the preservatives. In addition, alcohols may on their own prevent contamination of the product when they are used at high concentrations.^[80]

2.1.5 Antioxidants and Chelating Agents

Tocopherols, butylated hydroxytoluene (BHT) and alkyl galates are included in moisturizers to inhibit oxidation by reacting with free radicals blocking the chain reaction.^[80] Reducing agents, such as ascorbic acid, may also act by reacting with free radicals, as well as oxidize more readily than the ingredients they are intended to protect. Citric acid, tartaric acid, and EDTA and its salts usually have little antioxidant activity themselves, but enhance the antioxidant activity by reacting with heavy-metal ions. Such substances are called chelating agents. The chelated form has few of the properties of the free ion and for this reason chelating agents are often described as 'removing' ions from solution.^[80] The stability of the metal-edetate complex depends on the metal

ion involved and also on the pH. Calcium chelate is relatively weak and EDTA will preferentially chelate heavy metals, such as iron, copper, and lead.^[80]

2.2 Use of Moisturizers in Different Treatment Modalities

Moisturizers have multiple functions apart from moistening the skin. Similar to other actives, the efficacy of moisturizers is likely to depend on their composition and dosage. Ingredients can stay on the surface, be absorbed into the skin, be metabolized, or disappear from the surface by evaporation, sloughing off or by contact with other materials. Studies suggest that only 50% of applied cream remains on the surface after 8 hours.^[90] Cream and ointments seem to allow higher transfer of the actives to surrounding surfaces than lotions and tinctures.^[91]

In the case of topical treatment, it is often difficult to estimate the amount applied by the patient. This makes it difficult to compare the effectiveness of moisturizers and may also cause doubts about the compliance with the prescribed treatment. Low compliance can be a problem with topical treatments and the process of treating the skin can often itself add to the burden of having the disease.

Differences in dosing have been noted between self-application and operator-assisted application of creams.^[92] Self-application resulted in larger amount applied per unit area.^[92,93] The distribution has also been found to vary over the treated region and the real surface area. For example, the genitoanal area received >7-fold more amount of cream in comparison with its proportional surface area.^[92] In addition, distribution within the treated area differs depending on the type of vehicle.^[94] A thick ointment with only a small percentage of water was equally distributed in the center and periphery of the treated area, whereas formulations with lower viscosity and more volatile ingredients, e.g. creams, were less evenly spreaded on the skin.^[94] Moreover, jars promoted use of larger quantities than the same cream in a tube (1.7 versus 0.7 mg/cm², respectively).^[93] However, it may be expected that moisturizer treatment seldom requires the same application rate on different sites, because of different severities of the dryness in the treated areas.

2.3 Possible Roles for Moisturizers

Immediately after application of a moisturizer the surface becomes smoother as a result of the filling of spaces between partially desquamated skin flakes.^[95,96] The visual appearance of the skin changes, the surface becomes softer and the friction is changed.^[97] There is an immediate increase in the degree of hydration of the SC due to absorption of water from the product, whereas build-up of water in the SC due to the occlusive effect

from lipids is more delayed.^[77] Absorption of humectants from the emulsion also increases skin hydration and SC elasticity.

In addition, there is a growing recognition of the function of lipids in the skin as modulators of inflammation and immune response. Topically applied lipids may also enter into the skin and interfere with bilayer lipids. For example, petrolatum is absorbed into the outer layer of delipidized SC,^[98] while more physiological lipids penetrate the skin,^[99-104] and modify endogenous epidermal lipids^[100,105,106] and the rate of barrier recovery.^[105,107,108] One vegetable oil containing linoleic acid changed the ceramide levels in normal human SC and the smaller amounts of one ceramide found in the SC in winter were restored to the larger amounts found in summer months.^[106] Polyunsaturated fatty acids in oils containing omega-3 fatty acid have been suggested to be transformed enzymatically by the epidermis into 'putative' anti-inflammatory products.^[82,109] Dietary supplementation with fish oil^[110] and purified ethyl ester of eicosapentaenoic acid (20 : 5, omega-3 fatty acid) from fish oil^[111] have also shown anti-inflammatory effects on ultraviolet B-induced acute inflammation. The enzyme Δ -6-desaturase, which converts linoleic acid into GLA, which might also play a role, since it has been suggested to be impaired in atopic eczema.^[112] Lipids in ointment bases have also been found to have an antimutagenic effect on the epidermis of stripped dorsal skin of hairless mice.^[113]

2.4 Adverse Reactions of Moisturizers

Moisturizers can be considered to have a favorable safety profile compared with traditional drugs used by dermatologists. They are rarely associated with serious health hazards, even if they are used on large body areas over a long time period. However, uncomfortable skin reactions from topical preparations may be encountered. The most common adverse reactions to moisturizers are sensory reactions or subjective sensations (no signs of inflammation) immediately after application. Smarting, burning, and stinging sensations are examples of such reactions among users of dermatological preparations. Facial skin is more sensitive than other body regions.^[114,115]

Humectants such as lactic acid,^[116] urea,^[115,117] and PCA,^[118] and preservatives like benzoic acid^[118] and sorbic acid,^[115] are known to cause subjective sensations. However, formulations without known stingers may also induce subjective sensations and some individuals can be in a condition of 'status cosmeticus' in which every product applied to the face produces itching, burning, or stinging sensations.^[115]

Moisturizers are usually free from strong irritants, but repeated exposure of sensitive areas to mildly irritating preparations may cause dermatitis. For example, frequent immersion of the skin in

water is counterproductive as far as moisturization is concerned.^[28,119] In addition, a classic hydrophilic ointment contains the well-known irritant sodium laurilsulphate as co-emulsifier.^[80] Aqueous solutions of 1% sodium laurilsulphate are commonly used in experimental dermatology to induce irritation.^[120] Also fatty acids sometimes found in moisturizers as emulsifiers can influence skin barrier properties.^[79,121] Nonionic emulsifiers are the preferred stabilizers for emulsions due to their mildness, but TEWL measurements indicate that also some of them may produce invisible barrier damage in normal skin.^[79] Furthermore, nonionic polyethylene glycol emulsifiers are susceptible to oxidation, inducing formation of peroxides and aldehydes.^[122]

Very rarely humectants, emulsifiers, and oils cause contact allergy.^[123] Some dermatologists consider the lanolins to be a frequent cause of contact allergy, but this is believed to be due to inappropriate testing conditions leading to false-positive reactions.^[123] In topically applied products, fragrances and preservatives are identified as the major sensitizers. Almost all moisturizers in supermarkets contain fragrances and over 100 fragrance ingredients have been identified as allergens.^[123] However, it appears that fragrances may be used without introducing an increased rate of skin reactions.^[124,125]

Propylene glycol may cause adverse skin reactions in normal individuals at concentrations as low as 10% under occlusive conditions, and in patients with dermatitis at concentrations as low as 2%.^[126] The nature of the cutaneous response remains obscure. Skin reactions to propylene glycol have been classified into 4 categories depending upon mechanisms: (i) irritant contact dermatitis; (ii) allergic contact dermatitis; (iii) non-immunologic contact urticaria; and (iv) subjective or sensory irritation.^[116,127] Propylene glycol has also been given an acceptable daily intake value of 25 mg/kg by the Joint Food and Agriculture Organization/World Health Organization Expert Committee of Food.^[128] Poisoning has been reported after oral dosages around 100–200 mg/kg in children^[129–131] and after topical treatment with high concentrations in burn patients.^[132] Hence, repeated applications of high concentrations (>20%) of propylene glycol may not be recommended on large body areas in children with compromised skin barrier function. In addition, intoxication has been reported in children with lamellar ichthyosis due to topical treatment with salicylic acid.^[133]

3. Treatment of Skin Barrier Disorders

3.1 Environment-Induced Dermatitis and Xerosis

Dermatitis and eczema are often used synonymously to describe a polymorphic pattern of inflammation, which in the acute phase is characterized by erythema and vesiculation, and in the

chronic phase by dryness, lichenification, and fissuring. Eczema (from the Greek term *ekzein*, 'to boil over') relates to the spongiotic vesiculation of the epidermis, while dermatitis refers to the inflammation of the skin. Thus, not all forms of dermatitis are eczematous in nature. Xerosis is applicable to any condition of the skin where dryness is more than its normal dry (*xer-*) state (*-osis*).

Irritant contact dermatitis is the result of a non-specific cellular damage to the skin caused either by physical factors, such as mechanical friction or cold, or, more commonly, by chemicals.^[2–5] In clinical practice contact dermatitis can display a broad spectrum of signs and symptoms and it has been described by different clinical names. The disease can be divided into several types, for example: acute irritant contact dermatitis (following a single exposure to a noxious factor); chronic irritant contact dermatitis (following repeated exposures to noxious factors over a time period); and sensory irritancy (stinging).

Acute irritant contact dermatitis is considered to be less frequent than chronic irritant dermatitis. In chronic dermatitis skin recovery usually is retarded, probably due to difficulties in avoiding contacts with the relevant irritants. Repeated barrier insults may also lead to epidermal hyperplasia and inflammation. In addition, recent studies indicate that psychological stress may affect the rate of permeability barrier recovery in humans.^[7]

3.1.1 Chemical and Functional Changes

The most frequent clinical sign of environmental-induced dermatitis is dry skin (xerosis). Dryness is usually associated with impaired barrier function,^[13,134] although the clinical appearance of dryness can be confined to changes in the outermost structure of the SC with an intact permeability barrier beneath.^[135]

Substances belonging to NMF are reduced in xerotic skin in elderly patients,^[136,137] and in surfactant-induced scaly skin.^[138] The reduced level has been suggested to reflect decreased profilaggrin production.^[136]

The total amount of SC lipids is not changed due to xerosis.^[139] However, a decreased proportion of neutral lipids and increased amounts of free fatty acids are associated with the severity of dryness.^[139] The distribution of sphingolipids is also changed in surfactant-induced scaly skin.^[138]

3.1.2 Treatment

In experimental models of damaged human skin, moisturizers usually promote normalization of the skin.^[140,141] Different models for diseased skin have been used, where the barrier has been damaged, for example, by successive tape strippings, or by exposure to acetone or sodium laurilsulphate. The treated abnormality and the composition of the cream may, however, be crucial for the effect.^[105,107,108,140,142] In acetone-disrupted mice skin, mixtures with cholesterol, fatty acids, or ceramides as the dominant lipids

delayed recovery, whereas an equimolar mixture of ceramide, fatty acid and cholesterol, or pure cholesterol allowed normal barrier recovery.^[108] However, cholesterol as the dominant lipid accelerated barrier recovery in tape-stripped aged human skin.^[142] In sodium laurilsulphate-damaged human skin no acceleration of barrier recovery was monitored after treatment with ceramide-3B in different emulsions.^[143] Neither did a moisturizer consisting of ceramide-3, cholesterol, and fatty acids ('skin identical lipids') in a petrolatum-rich emulsion show superiority to pure petrolatum in human skin, damaged by sodium laurilsulphate and tape stripings.^[144] These results emphasize the importance of composition of the moisturizer in relation to the abnormality. The content of emulsifiers, lipids, chelating agents, and antioxidants may well influence the outcome of the treatment.

Clinical studies on patients with xerosis also support the beneficial effect from treatment with moisturizers (see table II). Furthermore, cleaners and kitchen workers with hand eczema showed increased dryness during a non-treatment period and normalization of the skin texture during the use of an emollient.^[145] Enhancement of the clinical effect is often found after inclusion of humectants in the moisturizer. Only a few studies have monitored TEWL, but formulations with urea show barrier-improving effects,^[146] whereas one without urea did not show any influence on TEWL.^[145]

3.2 Atopic Dermatitis

The course of atopic dermatitis is determined by environmental factors, such as psychological stress, climate (e.g. low humidity caused by cold winters and central heating), and exposure to irritants and allergens. The defective barrier function can also make atopic patients more prone to irritant contact dermatitis than a normal population, since ordinary soaps and detergents often irritate the skin. Moreover, exposure to hard water, especially to calcium in domestic water, has been found to be associated with a higher prevalence of atopic eczema in primary-school children.^[154] Whether this is related to influences of the gradient of calcium ions in the skin is not known.

Another triggering factor for atopic dermatitis might be the colonization of the skin with microorganisms, such as *Staphylococcus aureus* and *Malassezi* spp. (formerly known as *Pityrosporum ovale* and *Pityrosporum orbiculare*). *S. aureus* can release superantigenic exotoxins, which produce a massive release of cytokines.^[2] *Staphylococcus enterotoxin B* also induces eczema when applied to uninvolved atopic and normal skin.^[3] The severity of dermatitis has been reported to correlate linearly with *S. aureus* counts.^[155,156] In young adults with atopic dermatitis an exacerbation of the eczema of the head, neck and shoulders named 'head

and neck dermatitis' might be related to the presence of *Malassezi* spp.

3.2.1 Chemical and Functional Changes

The atopic skin surface shows a coarse morphology, with broad, irregularly running furrows and loss of minor furrows.^[25] The number of peaks is less and the distance between the peaks and the valleys is increased compared with normal skin.^[157] The number of SC cell layers is also increased^[137] as well as the cohesion between cells.^[14] Furthermore, in a study the turnover time in patients with atopic dermatitis was shorter than in controls and the projected size of the corneocytes was smaller.^[14,137]

The affected SC is less hydrated and less capable of binding water than normal skin.^[13,158] The content of urea in normal and dry SC is substantially reduced.^[159] In dry atopic skin higher levels of calcium are found throughout the layer, with a tendency to a steeper gradient than in normal skin.^[160] High values of zinc have also been found in atopic skin.^[166] Zinc has been suggested to bind to defensins and thus acts on the conformational status of the natural defensins harbored by the SC allowing for free action of bacteria.^[166]

In the epidermis, phospholipids and glycosphingolipids are hydrolyzed into ceramides and free fatty acids. In patients with atopic dermatitis the enzyme sphingomyelin deacylase is highly upregulated, which is suggested to cause ceramide deficiency due to competition with sphingomyelinase or β -glucocerebrosidase for sphingomyelin or glucosylceramide.^[161] Moreover, sphingomyelin acylase has been found to be upregulated, which also may cause ceramide deficiency and favor the production of fatty acids and sphingosyl-phosphorylcholine.^[162] Analyses of skin lipid composition show reduced amounts of ceramides along with a changed distribution of the different types.^[163-166] The level of cholesterol has been reported to be elevated in atopic dry skin.^[166] The changed lipid composition may account for the aberrant lipid organization in atopic skin, with an increased frequency of hexagonal packaging.^[167]

Higher TEWL is noted in dry skin in atopic patients,^[11-13,158] whereas in completely healed atopic dermatitis the barrier function is not disturbed.^[168]

3.2.2 Treatment

A range of dietary oil supplements has been suggested to be effective for treatment of atopic dermatitis. Some studies have also shown promising effects of evening primrose oil, a vegetable oil rich in GLA, when administered orally to atopic patients.^[169] However, this has not been confirmed in more recent double-blind, placebo-controlled studies, in children^[170] or adult patients.^[171,172] Antimicrobial treatment has been shown to improve

Table II. Clinical studies on the effect of moisturizers on dry skin

Condition	Active substance	Control	TEWL	Effect on dryness	Reference
Dry skin	3% and 10% urea	Untreated	Decreased	Improved	146
Dry hands, irritation	Lipocream	Untreated	No change	Improved	145
Xerosis	12% ammonium lactate	Petrolatum based cream	Not assessed	Improved more with active substance than control	83
Xerosis on legs	12% ammonium lactate	5% lactic acid + 2.5% PCA	Not assessed	Improved more with active substance than control	147
Dry heels	12% ammonium lactate	Untreated	Not assessed	Improved with active substance	148
Xerosis on legs	12% lactate	5% lactic acid/emollient lotion	Not assessed	Improved, but patients using 12% had longer remission	149
Xerosis	5% lactic acid	Eucerin lotion	Not assessed	Improved more with active substance than control	150
Xerosis	5% PCA	Placebo and 10% urea	Not assessed	Active more than placebo, and equal to urea	151
Senescent dryness on forearm	10% urea	Placebo	Not assessed	Improved	152
Asteatosis, senescent dryness on leg	4% urea + 4% sodium chloride	Placebo	Not assessed	Improved better with active substance than control	153

TEWL = transepidermal water loss; **PCA** = pyrrolidone carboxylic acid.

atopic dermatitis in patients who were colonized with *S. aureus*.^[156]

Addition of moisturizers to the treatment arsenal of atopic dermatitis reduces the need for frequent application of corticosteroids.^[1] Moisturizers may reduce pruritus that characterizes atopic dermatitis. Furthermore, it is conceivable that moisturizers which improve abnormal barrier function will reduce the prevalence of atopic dermatitis.^[23,173] The mechanism for the barrier improving effects is far from elucidated and not all moisturizers appear to have this effect. For example, in one study on dry skin in atopic and non-atopic individuals, a moisturizer containing ammonium lactate as humectant had no effect on TEWL, although there was an improvement in clinical appearance.^[174] However, one ceramide-dominant lipid mixture improved childhood atopic dermatitis in an open-label study, with lower clinical scoring of disease severity and decreased TEWL.^[175] In addition, one moisturizer with 5% urea reduced TEWL in atopic dermatitis patients^[176] and made skin less susceptible against irritation to sodium lauryl-sulphate.^[177] A moisturizer with 4% urea was also superior to 20% glycerin in lowering TEWL in a recent double-blind study in patients with atopic dermatitis.^[87] However, 4% urea cream did not reduce TEWL in another study in patients with atopic dermatitis.^[178]

3.3 Psoriasis

Psoriasis is seen in men and women of all ages, but the most common ages of onset are in the ranges of 15–25 years and 40–50 years. The disease is most prevalent among Caucasians.^[179] The cause of psoriasis is not fully understood, but there is a strong genetic component. However, a number of environmental risk factors have also been identified, including injury, stress, throat infection, and certain drugs.

3.3.1 Chemical and Functional Changes

Psoriatic epidermis demonstrates a defective program of growth and differentiation, including an abnormal permeability barrier.^[15,16] There is a virtual absence of NMF^[180] and the composition of ceramides is changed in the SC.^[181] The normal calcium gradient is lost in psoriatic plaques and substantial amounts of Ca²⁺ are present in superficial layers of the SC.^[182] Patients with erythroderma and active plaque phenotypes show elevated TEWL and increased number of epidermal lamellar bodies, while patients with chronic plaque psoriasis display a lower increase in TEWL, a normal number of lamellar bodies, and abundant extracellular lamellar material.^[15,183] This is consistent with the proposed hypothesis that the initial appearance of psoriasis and changes in disease phenotype are driven by alterations in barrier function.^[15]

3.3.2 Treatment

Studies suggest that oral or topical supplements of EPA and/or omega-3 fatty acid derivatives can decrease the severity of psoria-

sis.^[101,102] Clinical improvement of scaling and plaque thickness was reported from treatment with fish oil compared with the placebo-treated site, but erythema was not affected.^[102] However, oral and topical treatments in randomized and double-blind studies could not support the effect in patients with moderate psoriasis.^[184,185] Topical treatment with sunflower seed oil (rich in linoleic acid) increased the level of linoleic acid of the epidermal phospholipids, but did not improve the disease or change TEWL.^[183] Treatment with clobetasol healed the skin and reduced TEWL.^[183]

Artificial restoration of the permeability barrier by occlusion results in regression of lesions in psoriasis. Plastic occlusive dressings decrease the mitotic rate and the granular layer reappears.^[186] In addition, a near-normal epidermal calcium gradient is re-established and the intercellular multilamellar structures show an almost mature pattern.^[187] Inhibition of enzyme activity and establishing an artificial water barrier have been postulated as potential mechanisms for the improvement.^[188,189]

Emollients and moisturizing agents are an important adjuvant therapy of classical psoriasis treatment modalities and used as supportive treatment in relapse-free phases.^[190,191] Mild forms of psoriasis can be treated with compounds with good skin compatibility and low cosmetic problems. W/O emollients have been reported to be as effective as steroid-sparing agents in plaque psoriasis.^[191] The replacement of one application of twice daily betamethasone treatment by a W/O emollient did not adversely affect the treatment results.^[190,191] Finlay also reported an effective cream therapy adjunct to dithranol for the treatment of chronic plaque psoriasis.^[192] In an early study, it was shown that white soft paraffin may inhibit the development of Koebner response in psoriasis.^[193]

Keratolytics, such as salicylic acid and urea, are typically used on areas with thick scaling. In an open-label study on five psoriatic patients with chronic therapy-resistant lesions, a 10% urea cream made the skin soft and pliable, but had no effect on erythema.^[194] In a randomized, double-blind study, three psoriatic lesions on the extremities were treated three times a day for 2 weeks with an ointment containing 10% urea, with a vehicle (without urea), or were left untreated. All patients showed clinical improvement on the urea-treated areas. The epidermal proliferation decreased significantly, measured as an altered expression of involucrin and cytokeratin.^[195] No significant decrease in TEWL was observed, but higher values of skin capacitance (suggested to reflect skin hydration) were noted on urea-treated areas.^[195] *In vitro* and *in vivo* data showed a lowered DNA-synthesis index with a thinning of the epidermis and a reduction of the epidermal cells in the cell cycle.^[196] Topical treatment with 10% urea ointment improved the water content and hygroscopicity, and reduced TEWL, in patients

with psoriasis vulgaris.^[197] In addition, 15% glycolic acid, with and without occlusion, lowered TEWL and erythema.^[198]

3.4 Ichthyosis

The two most common forms of ichthyosis, autosomal dominant ichthyosis vulgaris (IV) and X-linked recessive ichthyosis (XRI), occur at frequencies of about 1/300 and 1/2500 in most populations, respectively.^[199] Lamellar ichthyosis (non-bullous ichthyosiform erythroderma) and epidermolytic hyperkeratosis (bullous ichthyosis) are more rare with incidences in most populations around 1/100 000 and 1/300 000, respectively.^[199] The word ichthyosis is derived from Greek word elements and means literally a fishy (*ichthy-*) condition (*-osis*). The disease resembles vaguely the scales or other surface characteristics of fish.

3.4.1 Chemical and Functional Changes

IV is a retention hyperkeratosis with normal rates of epidermal proliferation. The stratum granulosum is thin or missing due to a defect in the processing of profilaggrin, which also is noticed as tiny and crumbly keratohyalin granules.^[199] This defect results in a deficiency of NMF, the osmotically active molecules within corneocytes.^[200] Skin surface pH is slightly higher than in normal skin.^[41] Furthermore, a neutral pH is observed already halfway through the SC, possibly reflecting a congenital lack of acidic breakdown products from keratohyaline.^[41] The disease displays a relatively mild clinical spectrum and in a humid climate the disease is usually not a major problem to the patient, whereas in a dry and cold climate xerosis and hyperkeratosis may become severe. Scaling usually does not appear until late infancy or early childhood.

In XRI, the level of cholesterol sulfate is greatly increased due to deficiency in steroid sulfatase, which hydrolyzes cholesterol sulfate.^[201,202] The accumulation of the ester is supposed to alter the organization of the lamellar membranes impairing barrier function.^[203] In addition, cholesterol sulfate inhibits proteases which delays dissolution of corneodesmosomes, thereby preventing desquamation.^[43] Desquamation has been shown to correlate with conversion of cholesterol sulfate to free cholesterol.^[204] The pH gradient in the SC is more shallow and reaches a plateau at 6.2–6.6 instead of about 7 in normal skin.^[41] Patients display both an abnormal barrier function under basal conditions, and a delay in barrier recovery after acute perturbation, which correlate with minor abnormalities in membrane structure and extensive lamellar-phase separation.^[203]

Lamellar ichthyosis is caused by mutations in the gene that encodes the enzyme transglutaminase 1, which is responsible for assembly of the cornified envelope. TEWL is increased in patients with lamellar ichthyosis.^[19] The impaired barrier function is relat-

ed to discontinuities in the extracellular membrane structure.^[17] The hexagonal packing of the lipids is predominantly present, whereas the less permeable orthorhombic packing is observed only occasionally.^[167] Crystalline cholesterol has been proposed to be present in the SC.^[19]

3.4.2 Treatment

The treatment of ichthyosis encompasses oral retinoids and a wide variety of emollients containing hydrating and keratolytic agents, such as salicylic acid, urea, and lactic acid. Keratolytics which are too potent will often aggravate the condition by disrupting the barrier and increase the risk for painful wounds. The treatment of bullous ichthyosis has to be tailored to different body areas. Blisters and erosions should be protected from breakage and allowed to heal, while the hyperkeratosis should be reduced to minimize the disfiguring scales.

In 1974, van Scott and Yu reported that AHAs were therapeutically beneficial for topical treatment of ichthyosis. This pioneering study on keratolytic substances was conducted on 14 patients with various forms of ichthyosiform dermatoses.^[205] More than 60 test materials, including a number of AHAs at 5%, were incorporated into a hydrophilic ointment or plain petrolatum, and applied twice daily to the appropriate test site for 2 weeks. AHAs and closely related compounds were the most effective, causing disappearance of scales from lesions or restoring the skin to healthy-looking skin in all patients, except one with epidermolytic hyperkeratosis. Testing of the comparative effectiveness in one patient with lamellar ichthyosis showed glycolic and lactic acid resulting in substantial improvement after 2 days and 1 day, respectively, and restoration to normal-looking skin after 3 days in one patient.^[205] Histology revealed distinct changes suggesting that AHA may affect the epidermis primarily, and that this effect mediates a prompt influence on the keratinization process. There was an abrupt loss of the entire abnormal SC, and not a gradual loss of successive outer layers. It has been suggested that this may be due to a diminished cellular cohesion between the corneocytes at the lowermost and newly forming levels of the SC, at its junction with the stratum granulosum.^[206,207] The researchers also found that the epidermal thickness was greatly diminished by treatment with 5% glycolic acid and 5% lactic acid.^[205] A reduced number of SC layers was also found in six of 11 patients with ichthyosis after treatment with 10% urea in combination with 5% lactic acid.^[208] Furthermore, a soft and pliable skin was obtained in seven patients with severe ichthyosis after treatment with a 10% urea formulation.^[194]

Randomized and controlled studies have also been performed on ichthyotic skin. In a double-blind, controlled trial 84 outpatients with either IV or XRI were treated with four topical preparations.^[209] The preparations (two creams without any humectants,

one cream with 10% urea plus 5% lactic acid, and one ointment with 2% salicylic acid) were applied twice daily to the affected area on one leg and one arm for 2 weeks. At the end of the 2-week treatment period the clinicians assessed the urea cream to be better in controlling the ichthyosis than the other three preparations. Patients with XRI have also been treated with topical cholesterol and some improvement in the functional and the structural abnormalities was found.^[203,210]

In two randomized, double-blind comparison studies two preparations containing 10% urea but with different base properties were compared in 30 patients with ichthyosis associated with atopic dermatitis.^[211] Only patients with bilateral dry, scaling skin were included. After 4 weeks of treatment the investigator and patients rated the creams on the basis of efficacy. Both investigators and patients expressed preference for the urea cream containing multisterols, phospholipids and, fatty diols with a pH of about 6. The other urea cream also contained lactic acid and had a pH of about 3. Several patients reported burning sensations with the low pH cream, whereas no adverse effects were noted with the other urea preparation. In a recent double-blind study in 60 children it was also shown that 10% urea was superior to placebo in reducing the severity of generalized ichthyosis.^[212]

Outstanding improvement in lamellar ichthyosis was recently reported after treatment of one patient with 10% N-acetylcysteine in a moisturizing cream.^[213] N-acetylcysteine was found to have antiproliferative effect on a culture of human keratinocytes.^[213] Promising effects in reducing the signs of scaling, hyperkeratosis, and xerosis have also been reported after treatment of 10 patients with lamellar ichthyosis with 5% lactic acid combined with 20% propylene glycol.^[214] The investigators suggested that the ingredients acted synergistically in reverting hyperkeratosis. However, higher TEWL was found after the treatment.^[20] Reduced TEWL was found in another study in 14 patients with ichthyosis.^[215] The patients applied 10% urea cream to one limb and the base (without urea, betaine, and lactic acid) to the opposite limb. After 3 weeks, significant clinical improvement had occurred at sites treated with urea cream compared with those treated with the base. Besides reduction in TEWL, the water-holding capacity of the ichthyotic scales was increased.^[215]

3.5 Infantile Seborrheic Dermatitis

Dermatitis of the seborrheic areas may occur in infants. The relation of the dermatitis to sebum production is not known. Usually the disease starts during the first month of life and if left untreated lasts 3 or 4 months before clearing. Infantile seborrheic dermatitis is usually nonpruritic and the parents are more often disturbed by the disease than the infants are.

3.5.1 Treatment

The prognosis of infantile seborrheic dermatitis is excellent and calm reassurance to anxious parents is recommended. Excessive application of soap to the skin or other aggressive attempts to remove sebum should be avoided. Topical application of borage oil is claimed to have good effect against infantile seborrheic dermatitis by virtue of its high content of GLA.^[103,104] The eruption clears not only in the treated diaper area but in distant sites as well, indicating that borage oil seems to be readily absorbed through the skin and exerts its beneficial action at locations distant to the site of application. TEWL on the forearm returns to normal after borage oil treatment.^[104] The biochemical mechanism of the possible therapeutic effect is unclear, but circumventing an immaturity of the enzyme (Δ -6-desaturase) has been proposed to be linked to the improvement.^[103,112]

4. Conclusion

Skin barrier disorders are not a single entity, but are characterized by differences in chemistry and morphology in the epidermis. Large differences also exist between moisturizing creams. They contain substances considered as actives (for example, humectants) and substances conventionally considered as excipients (for example, emulsifiers, antioxidants, preservatives). However, recent findings indicate that actives and excipients may have more pronounced effects in the skin than previously considered. Advanced biophysical and biochemical techniques allow a closer examination of the functional impact of moisturizing creams on diseased skin. The role of SC as a biosensor regulating the metabolic response to a variety of exogenous stimuli appears essential.^[173] New methods will enhance tailoring of moisturizers, which will be of benefit in the treatment and prevention of skin barrier disorders.

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