6
The Dry Skin Cycle

Paul J. Matts
P&G Beauty, Rusham Park Technical Center, Egham, Surrey, U.K.

Anthony V. Rawlings
AVR Consulting Ltd., Northwich, Cheshire, U.K.

INTRODUCTION

In 1994 two key publications summarized the knowledge on the state of the art of stratum corneum biology and dry skin, namely: "Stratum corneum moisturization at the molecular level" (1) and "The correlation of water content with ultrastructure in the stratum corneum." Since then, significant advances have been made in our understanding of the pathophysiology of dry skin. This chapter will review these recent findings and from these propose a new model of a dry skin cycle (Fig. 1).

First, however, we need to consider the role of water loss through the stratum corneum (SC). Under normal circumstances, the SC must be as impermeable as possible except for a small amount of water loss to (i) hydrate the outer layers of the SC to maintain its flexibility and (ii) to provide enough water to allow enzyme reactions that facilitate SC maturation events, together with corneodesmolysis and ultimately desquamation (Fig. 2) (4–6). This inbuilt water loss is vital for the normal functioning of the SC. This does, however, generate water gradients within the tissue. Key in precipitating the condition we call "dry skin" is a perturbation of these water gradients within the SC. Scientists at Procter and Gamble were the first to demonstrate changes in SC water gradients in dry skin (7) where about one-third of the outer layers of the SC are reported to contain less than 10% water content (Fig. 3). At this level of water content the SC will be dysfunctional and brittle (8).

The SC uses three main mechanisms to hold onto water:

- the intercellular lamellar lipids whose physical conformation, predominantly an orthorhombic laterally-packed gel and 13 nm long periodicity (LPP) lamellar phase induced by linoleate containing long chain ceramides, provide a tight and semi-permeable barrier to the passage of water through the tissue
- the presence of fully matured, rigid, corneodesmosome-bound, and ceramide hydrophobed corneocytes which influence the tortuosity of the SC and thereby the diffusion path length of water

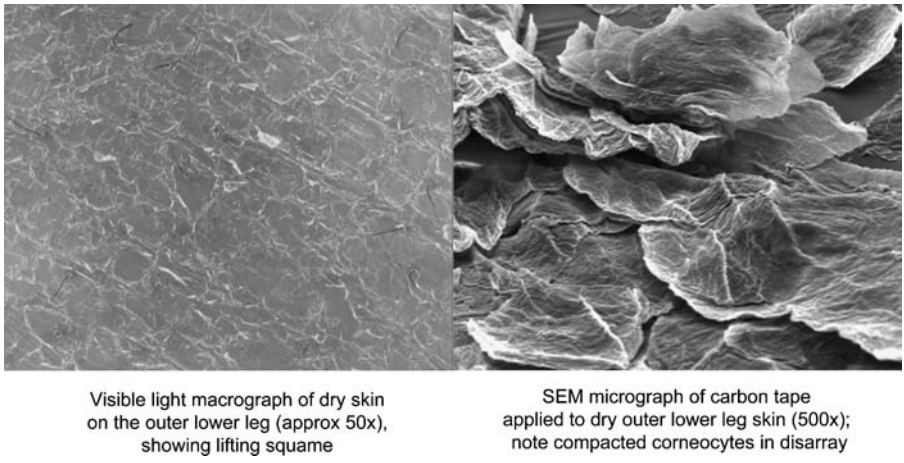

Figure 1 Typical photographs of cosmetic dry skin. *Source*: From Ref. 2.

-the presence of both intracellular and extracellular hygroscopic materials called "natural moisturizing factors" (NMF)

STRATUM CORNEUM AND EPIDERMAL STRUCTURE

Our original concept of the SC with a "basket weave" appearance at the histological level and a stratum compactum–stratum disjunctum at the electron microscope level has come under scrutiny over the last decade. For instance, Pfeiffer et al. (9) developed new high-pressure freezing followed by freeze substitution techniques for electron microscopy methods and visualized an SC that appeared more compact with smaller intercellular

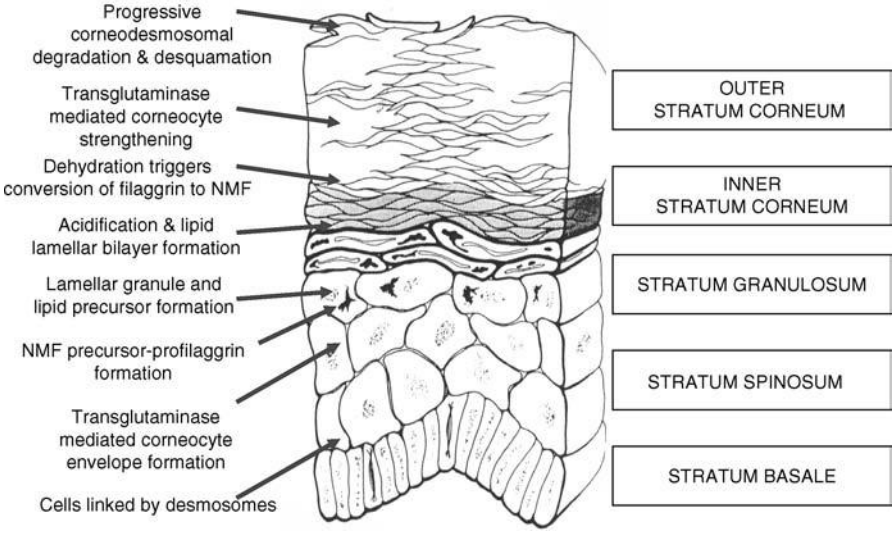

Figure 2 Typical structure of the epidermis and critical steps in formation of the stratum corneum. *Source*: From Refs. 1, 3.

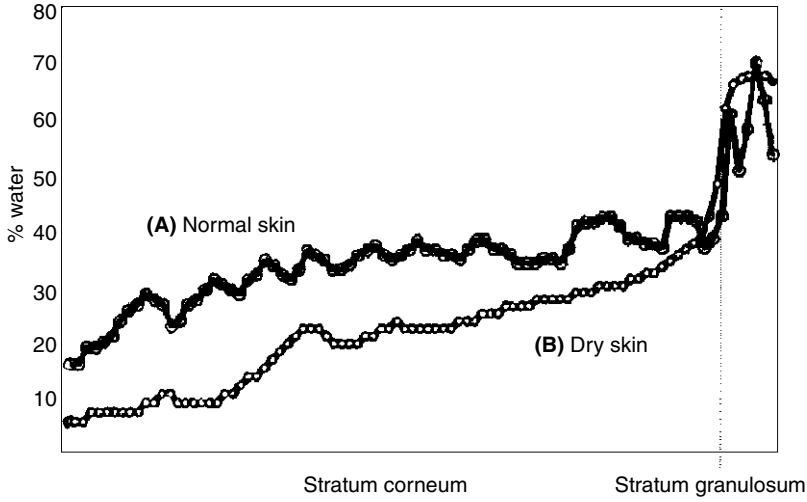

Figure 3 Water profile averaged over a single rectangular region of a cryosection obtained from an individual with (**A**) good skin, grade 0.5. The horizontal axis is distance across the SC with the SC/granulosum junction indicated by a vertical line. Water profile averaged over a single rectangular region of a cryosection obtained from an individual with (**B**) dry skin, grade 4. *Source*: From Ref. 7.

spaces and hence tighter cell-cell interactions. More controversial, however, was the lack of presence of keratohyalin granules in the epidermis. Lars Norlen (10) has also developed novel cryo-transmission electron microscopy techniques to image vitreous sections of skin without the use of cryo-protectants and, again, more densely-packed SC cells were apparent compared with conventional images and new organelles or tubular structures were observed in the epidermis. Norlen (11) has further proposed a cubic rod packing model for SC keratin structures. However, even with a more compacted SC, several SC swelling regions have been established by Bouwstra et al. (12) and Richter et al. (13) upon skin hydration which appear to be related to loss of barrier function and loss of NMF in the outer layers of the SC, hydrolysis of filaggrin to NMF, and lysis of non-peripheral corneodesmosomes, allowing greater intercorneocyte freedom and transglutaminase-mediated maturation of corneocytes towards the surface layers of the SC. As will be discussed, all of these events become aberrant in dry skin.

STRATUM CORNEUM LIPID CHEMISTRY AND BIOPHYSICS

All SC lipids are important for barrier function of the skin but due to their unique properties and structure the ceramides have been of most interest in recent years. Ceramides constitute (on a weight basis) approximately 47% of the SC lipids (14). Given this diversity, together with the identification of new ceramides, a new nomenclature based on structure, rather than the original chromatographic migration characteristics, was proposed by Motta et al. (15). In this system, ceramides are classified in general as CER FB, where F is the type of fatty acid and B indicates the type of base. When an ester linked fatty acid is present, a prefix of E is used. Normal fatty acids (saturated or unsaturated), alpha-hydroxy fatty acids, and omega-hydroxy fatty acids are N, A, O respectively, whereas sphingosines, phytosphingosines, and 6-hydroxysphingosine are indicated by S, P, and H. Sphinganine (not previously classified) is proposed to be SP in this nomenclature

system. A novel long-chain ceramide containing branched chain fatty acids is also found in vernix caseosa (16). Typical structures of human ceramides are given in Figure 4. Newly identified ceramides have also been found attached to the corneocyte envelope (CE). In addition to ceramide A (sphingosine) and ceramide B (6-hydroxysphingosine), Chopart et al. (17) recently identified covalently-bound omega hydroxyl fatty acid containing sphinganine and phytosphingosine ceramides. These covalently-bound ceramides should now be named CER OS, CER OH, CER OSP, and CER OP.

Ceramides are synthesised from either glucosylceramides, epidermosides, or sphingomyelin. Epidermosides are glycated precursors of omega, hydroxyl–containing ceramides. The studies of Hamanaka et al. (18) have demonstrated that sphingomyelin provides a proportion of CER NS and CER AS whereas the glucosylceramides are precursors to ceramides and epidermosides are precursors to the covalently bound ceramides, together with CER EOS, CER EOH, and CER EOP.

It is the packing states, however, and not only the structures of the SC lipids that are important for barrier function. Lipids in vivo appear to exist as a balance between a solid crystalline state (orthorhombic packing) and gel (hexagonal packing) or liquid crystalline states. The orthorhombically-packed lipids are the most tightly packed conformation and have optimal barrier properties. However, a greater proportion of hexagonally-packed lipid conformations are observed in the outer layers of the SC (19). This is consistent with a weakening of the barrier towards the outer layers of the SC. It is believed that short chain fatty acids from sebum contribute to the crystalline to gel transition in the upper stratum corneum layers (20).

Bouwstra et al. (21) recently proposed a new sandwich model consisting of two broad lipid layers with a crystalline structure separated by a narrow central lipid layer with

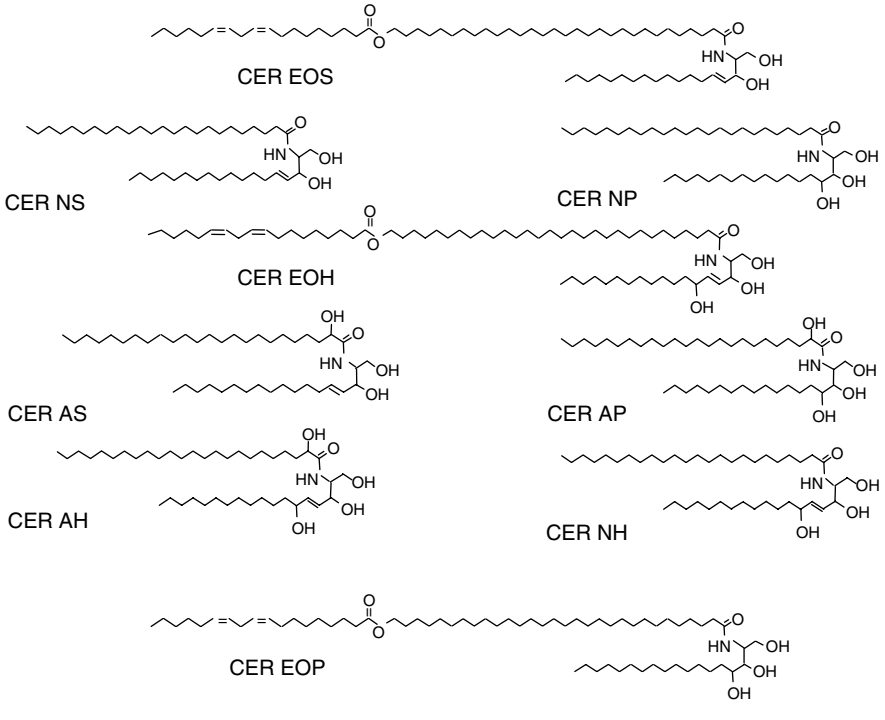

Figure 4 Structures of human stratum corneum ceramides.

fluid domains (Fig. 5). Cholesterol and ceramides are important for the formation of the lamellar phase, whereas fatty acids play a greater role in the lateral packing of the lipids. Cholesterol is proposed to be located with the fatty acid tail of CER EOS in the fluid phase. CER EOS, EOH, and EOP play an essential role in formation of the additional lamellar arrangements. The repeated distances were found to be 13 nm in dimension, composed of two units measuring approximately 5 nm each and one unit measuring approximately 3 nm in thickness. These repeat lamellar patterns were also observed by X-ray diffraction studies and were named the "LPP" and "short periodicity" (SPP) phases respectively.

Mostly hexagonal phases are also observed for total lipid mixtures in the absence of CER EOS. Equally no LPP phase is formed. Moreover, the importance of ceramide 1 or CER EOS in facilitating the formation of the LPP has been further elaborated by

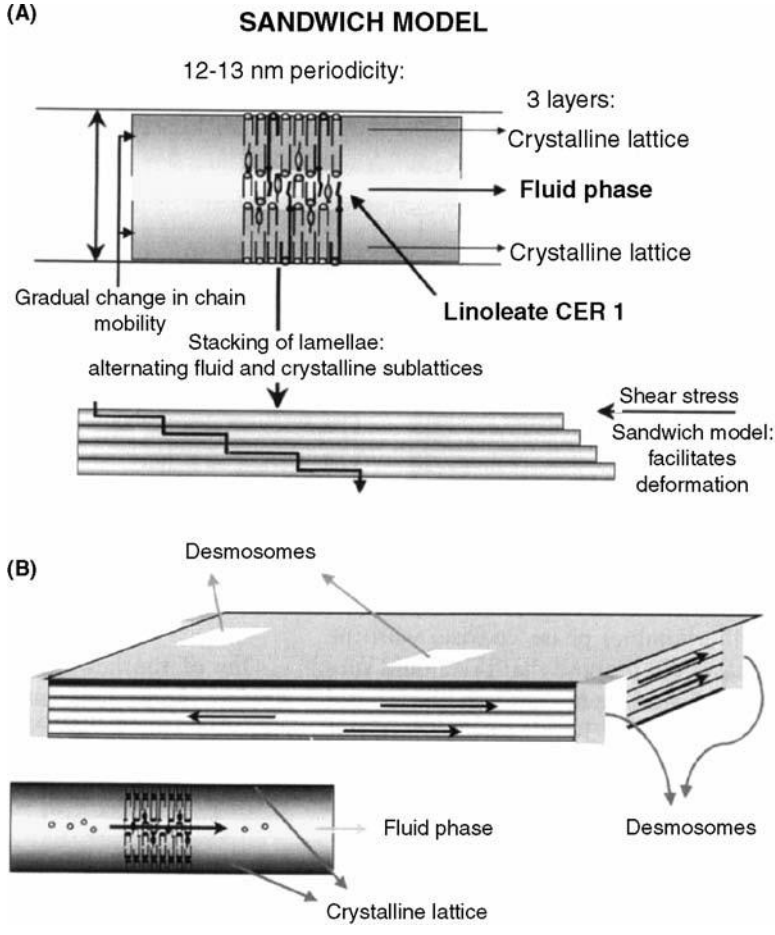

Figure 5 (**A**) "Sandwich model," the characteristics of which are: (1) the liquid sublattice is located in the central lipid layer of this phase, and in this layer mainly unsaturated linoleic acid and cholesterol are present; (2) in the sublattice adjacent to the central layer a gradual change in lipid mobility occurs due to the presence of less mobile long saturated hydrocarbon chains; (3) only a small fraction of lipids forms a fluid phase in the SC, and therefore one can assume that this central lipid layer is not a continuous phase. (**B**) The liquid phase parallel to the basal layers of the lamellae facilitates transport and therefore communication between the desmosomes. *Source*: From Ref. 21.

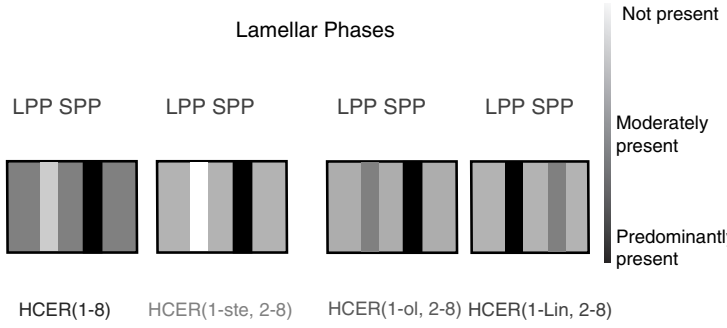

Figure 6 A summary of the lamellar phases and CER EOS in various lipid mixtures. HCER (1–8) mixtures in which HCER (EOS) is replaced with either synthetic stearate-containing CER (EOS), oleate-containing CER (EOS), or linoleate-containing CER (EOS). *Source*: From Ref. 22.

understanding the influence of the type of fatty acid esterified to the omega-hydroxyl fatty acid (Fig. 6) (22). As a consequence, the LPP is seen mainly with linoleate-containing CER EOS, less with oleate-containing CER EOS and is absent if only stearate-containing CER EOS is present in the lipid mixtures. These studies indicate that for formation of the LPP, a certain fraction of the lipids has to form a liquid phase. If the liquid phase is too high (as with the oleate-containing CER EOS) or too low (as with stearate-containing CER EOS), the levels of the SPP increase at the expense of the LPP. It is important to remember in vivo that the fatty acid composition of CER EOS is highly complex but contains a large proportion of linoleic acid.

Changes to the composition of the SC lipids could, therefore, dramatically influence the condition of the skin. In this respect, using electron microscopy of tape strippings from the outer layers of normal healthy skin, Rawlings et al. (23) reported complete loss of lamellar ordering in the outer layers of the SC (Fig. 7). These results have been confirmed by Warner et al. (24) and more recently by Berry et al. (25).

STRATUM CORNEUM CORNEODESMOSOMES AND CORNEODESMOLYSIS

The "brick and mortar" model of the SC has been known for many years. However, a more complete description of this model includes "corneodesmosomes." Corneodesmosomes (26) are macromolecular glycoprotein complexes incorporated into the CE and consist of the cadherin family of transmembrane glycoproteins, desmoglein 1 (Dsg 1) and desmocollin 1 (Dsc 1). These glycoproteins span the cornified envelope into the lipid-enriched intercellular space between the corneocytes and provide cohesion by binding homeophilically with proteins on adjacent cells. Within the corneocytes, Dsg 1 and Dsc 1are linked to keratin filaments via corneodesmosomal plaque proteins such as plakoglobin, desmoplakins, and plakophilins. The corneodesmosomal protein, corneodesmosin (Cdsn), after secretion by the lamellar bodies with the intercellular lipids and certain proteases, becomes associated with the desmosomal proteins just before transformation of desmosomes into corneodesmosomes. As these proteins are cross-linked into the complex by transglutaminase, their controlled disruption must occur by proteolysis to allow

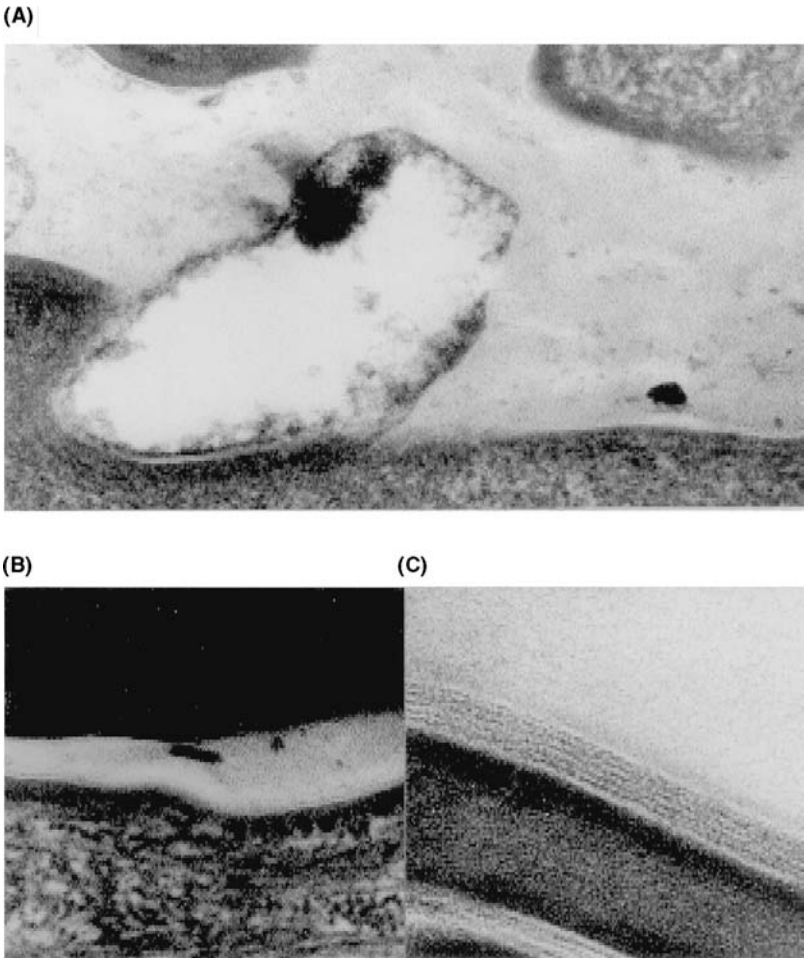

Figure 7 Organization of stratum corneum lipids in tape strippings of individuals with clinically normal skin. Transmission electron micrographs of tape strippings. Ultrastructural changes in lipid organization towards the surface of the stratum corneum: (**A**) First strip; absence of bilayers and presence of amorphous lipidic material. (**B**) Second strip; disruption of lipid lamellae. (**C**) Third strip; normal lipid lamellae. x200,000. *Source*: From Ref. 23.

desquamation to proceed. Indeed, Rawlings et al. (Fig. 8) (23) demonstrated degradation of the corneodesmosomes towards the surface of the SC in humans.

Desquamation is facilitated by the action of specific hydrolytic enzymes in the SC that degrade the corneodesmosomal linkages. Currently, several serine, cysteine, and aspartic enzymes are believed to be involved in this process, namely stratum corneum chymotryptic enzyme (SCCE), stratum corneum tryptic enzyme (SCTE), stratum corneum thiol protease (SCTP, now known as Cathepsin L-2), cathepsin E, and the aspartic protease cathepsin D. SCCE and SCTE are alkaline-optimal enzymes whereas the latter ones are acidic-optimum enzymes (27–31). Cathepsin L has also recently been implicated in Cdsn hydrolysis (32). Only SCTE and not SCCE, however, was capable of degrading Dsg 1 (33). This enzyme was also reported to be involved in the processing of pro-SCCE. Bernard et al. (34) have also identified an endoglycosidase, heparanase 1, within the SC, thought to play a role in the pre-proteolytic processing of the protecting sugar moieties on corneodesmosomal proteins.

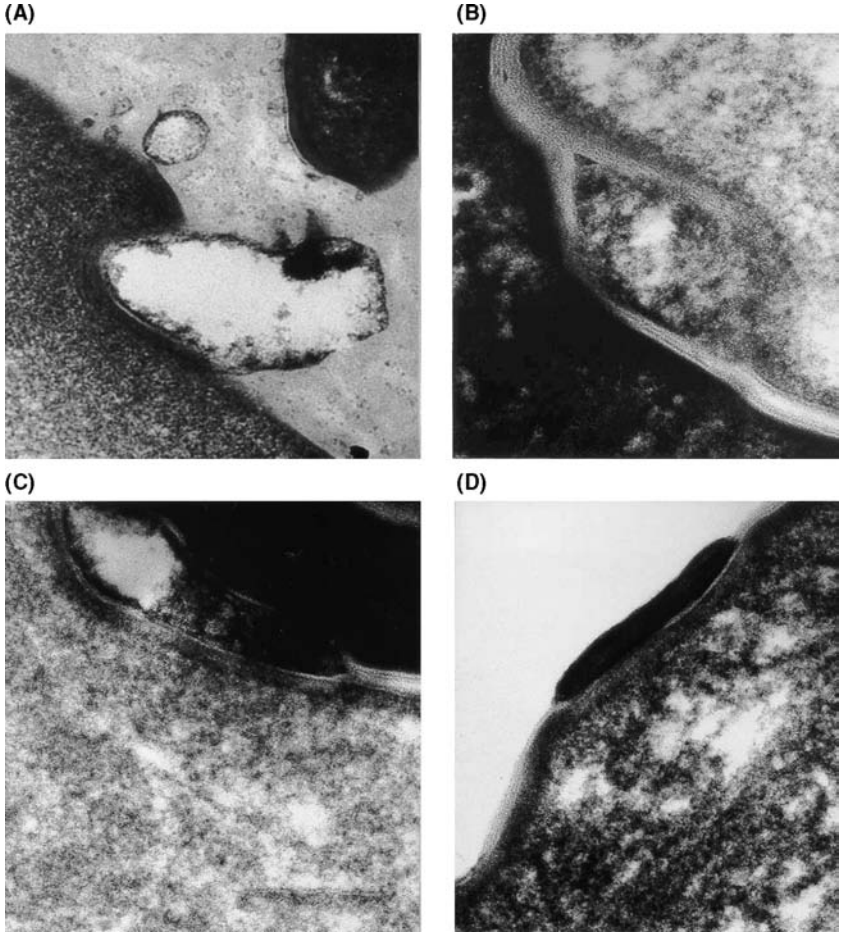

Figure 8 Electron micrographs of tape strippings of normal skin (grade 1). Degradation of corneodesmosomes (CD) toward the surface of the stratum corneum: (**A**) First strip; CD fully degraded. (**B**) Second strip; CD partially degraded and encapsulated by lipid lamellae. (**C**) Third strip; CD partially degraded, vaculation of structure. (**D**) Third strip, normal CD in contact with lamellar lipids. *Source*: From Ref. 23.

Cdsn undergoes several proteolytic steps. Cleavage of the N terminal glycine loop domain occurs first at the compactum disjunctum interface (48–46 KDa to 36–30 KDa transition), followed by cleavage of the C terminal glycine loop domain in exfoliated corneocytes (36–30KDa to 15KDa transition) (35). The last step appears to be inhibited by calcium resulting in residual intercorneocyte cohesion. Nevertheless, the presence of oligosaccharides did not protect Cdsn against proteolysis by SCCE (33). A complete list of the putuative desquamatory enzymes is given in Table 1.

These enzymes largely exist as proforms, and as they are secreted with the lamellar bodies, they have been immunolocalized to the intercorneocyte lipid lamellae. Sondell et al. (36) used antibodies that immuno-react precisely with pro-SCCE to confirm that this enzyme is transported to the SC extracellular space via lamellar bodies. In later studies, using antibodies to both pro-SCCE and SCCE, Watkinson et al. (37) demonstrated that the processed enzyme was more associated with the corneodesmosomal plaque. More recently, Igarashi et al. (38) have immunolocalized cathepsin D to the intercellular space,

Table 1 Desquamatory Enzymes

Sphingoid hydrolases	Cermidase
	Glucocerebrosidase
	Sphingomylinase
	Sphingomyelin deacylase
	Glucosylceramidedeacylase
Sulphatases	Steroid sulphatase
Glycosidases	Heparanase 1
Serine proteases	Stratum corneum chymotryptic-like enzyme (SCCE/KLK7)
	Stratum corneum tryptic-like enzyme (SCTE/KLK5)
Cysteine proteases	Stratum corneum thiol protease (SCTP/L2)
	Stratum corneum cathepsin L-like enzyme (SCCL)
Aspartic proteases	Stratum corneum cathepsin D-like enzyme (SCCDE)
	Stratum corneum cathepsin E-like enzyme (SCCEE)
	Skin aspartic protease (SASPase)
	Caspase 14

whereas cathepsin E was localized within the corneocytes. Finally, KLK8 has also been reported to be localized to the intercellular spaces of the SC (39).

As the desquamatory enzymes are present in the intercellular space, the physical properties of the SC lipids, together with the water activity in this microenvironment, will influence the activity of these enzymes. Interestingly, however, SCCE appears to have a greater tolerance to water deprivation than other proteolytic enzymes, and this may be an adaptation to maintain enzyme activity even within the water-depleted SC intercellular space (40). However, a variety of inhibitors are also present to attenuate their activities, cholesterol sulphate being one of them. Other protein and peptide inhibitors are present such as elfin, covalently bound to the CE, antileukoproteinase, alpha-1-antitrypsin, alpha-1-antichymotrypsin, and the SPINK5-derived peptides (41). Nevertheless, anti-leukoprotease is believed to be the major physiological inhibitor of SCCE; the serpins are too low in concentration to be physiologically relevant (42). Caubet et al. (33) recently speculated in a new model of desquamation that SPINK5 may also inhibit SCTE.

Currently, little is understood of the molecular activation mechanisms of SCCE or other enzymes within the SC, but Brattsand et al. (43) has proposed a model recently for the activation of the kallikreins (Fig. 9). Clearly, SC pH and water content will influence enzymic activity. As the SC pH declines towards the surface of the skin, the activity of SCTE and SCCE may be reduced and perhaps the acid optimal cathepsin enzymes mediate the final desquamatory steps. The role of the newly identified skin aspartic protease and caspase 14 in this process is still awaiting clarification.

CORNEOCYTE ENVELOPE MATURATION AND THE ROLE OF TRANSGLUTAMINASES

The CE is an extremely stable and insoluble proteinaceous layered structure. The stability of the envelope is attributed to the degree of cross-linking of envelope proteins by either disulphide, glutamyl-lysine isodipeptide bonds, or glutamyl polyamine cross-linking of glutamine residues of several CE proteins (44). The enzymes, responsible for catalysing the gamma-glutamyl-epsilon-lysine isodipeptide bond formation, are the calcium-dependent transglutaminases (TGase; glutamyl-amine aminotransferases EC 2.3.2.13),

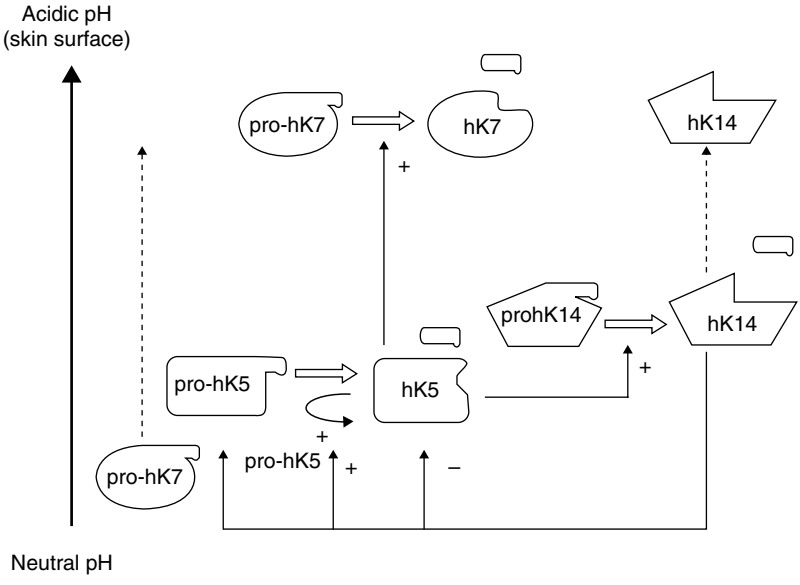

Figure 9 Proposed kallikrein activation cascade in human stratum corneum. *Source*: From Ref. 43.

of which four are expressed in the epidermis: TGase 1, 2, 3, and 5. However, only TGase 1, 3, and 5 are thought to be involved in keratinocyte differentiation.

At early time points in the keratinocyte differentiation process, envoplakin and periplakin are expressed and become associated with desmosomes in the viable epidermis. Subsequently, involucrin (the glutamyl-rich protein that covalently-bound lipids become attached to) is expressed at the same time as TGase 1 (45–47). TGase 1 then cross-links involucrin to the other early expressed proteins, such as members of the small proline-rich family of proteins. Subsequently, other plasma membrane proteins become cross-linked, and these form a scaffold for further reinforcement and maturation events (48).

By Normarski microscopy, CEs (CE's) were shown to have a crumpled surface when isolated from the lower layers of the SC and a smoother, more flattened surface when isolated from the upper SC. These two populations of CEs were named fragile (CEf) and rigid (CEr). Mils et al. (49) reported that about 80% of corneocytes from volar forearm skin were smooth and rigid, whereas 90% from foot sole were rough or fragile cells. They can also be further differentiated by their binding of tetra-methyl rhodamine isothiocyanate (TRITC), with the rigid envelopes staining to a greater extent (Fig. 10) (50). However, Hirao et al. (51) have used a more elegant method to identify CEs based upon their hydrophobicity (staining with Nile red) and antigenicity (to anti-involucrin) (Fig. 11). It is clear from these studies that immature envelopes (CEf) occur in the deeper layers of the SC (involucrin-positive and weak staining to Nile red or TRITC) and that mature envelopes occur in the surface layers of healthy skin (apparent involucrin staining lessened and increased staining with Nile red or TRITC). More recent work from Kashibuchi et al. (52) using atomic force microscopy confirmed these structural changes in corneocytes from the deeper layers of the SC.

The classification of fragile and rigid envelopes has subsequently been found to be a pertinent classification system as, mechanically, they have fragile and rigid characteristics

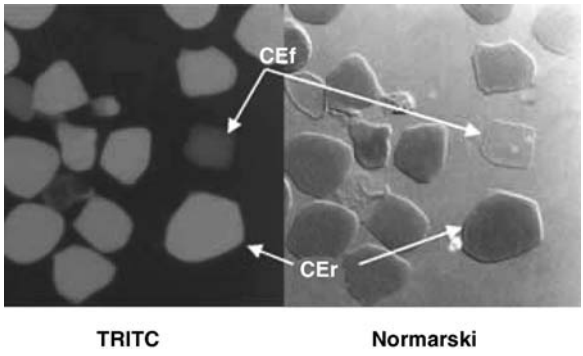

Figure 10 Fluorescence and Normaski phase contrast microscopy of TRITC stained cornified envelopes demonstrating increased fluorescence labelling of CEr compared with CEf. *Source*: From Ref. 50.

under compressional force (Fig. 12) (50). Supporting this concept of increasing CE strength, gamma glutamyl-lysine cross-links also increase in the subsequent layers of the SC, due to enhanced TGase activity. Three pools of TGase activity have been identified in the SC which have been classified based upon their solubility characteristics: a water-soluble TGase (mainly TGase 1 and 3), a detergent-soluble TGase (TGase 1), and a particulate form that cannot be liberated from the corneocyte. Whether all enzyme fractions are active in this maturation process of CEf to CEr is currently not known.

STRATUM CORNEUM NATURAL MOISTURIZING FACTORS (NMF)

A historical perspective on filaggrin biology was given by Rawlings et al. (1). Biologically, NMF allows the outermost layers of the SC to retain moisture against the

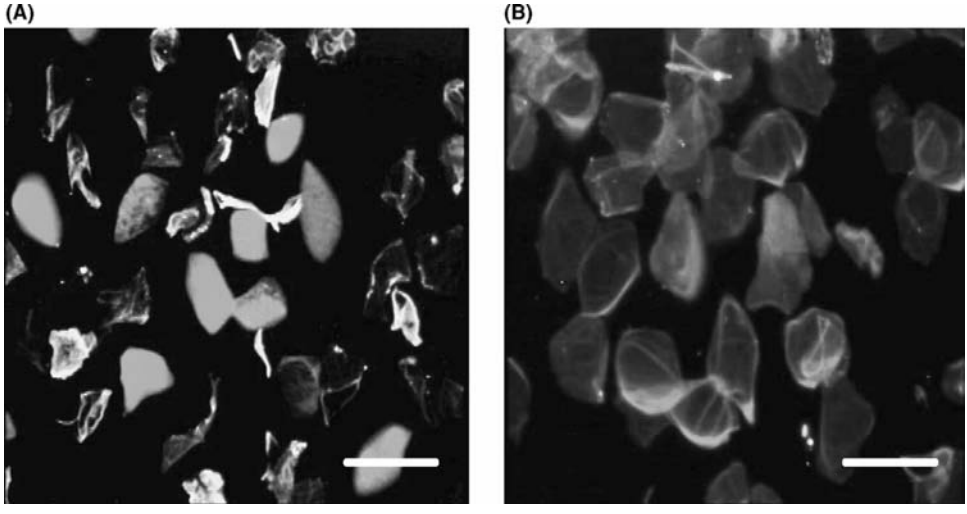

Figure 11 Double staining of CEs with Nile red and anti-involucrin (shown here in gray scale). (**A**) Face and (**B**) upper arm. *Source*: From Ref. 51.

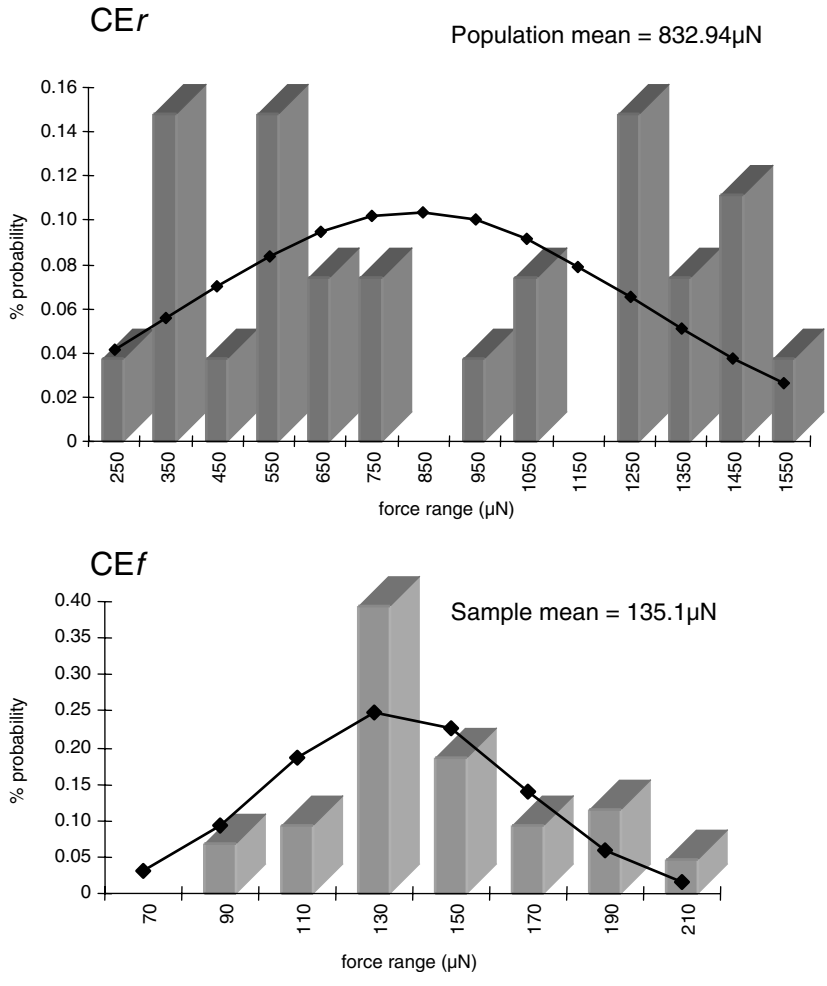

Figure 12 Distribution profile of the maximal compressional forces (uN) of individual CEs. Top panel shows the force range for CEr and the bottom for CEf. The maximal compression force was significantly different between the corneocytes. *Source*: From Ref. 50.

desiccating action of the environment. Traditionally, it was believed that this water plasticized the SC, keeping it resilient by preventing cracking and flaking which might occur due to mechanical stresses. The general mechanisms by which these NMF components influence SC functionality have been studied extensively. From a physical chemistry perspective, the specific ionic interaction between keratin and NMF, accompanied by a decreased mobility of water, leads to a reduction of intermolecular forces between the keratin fibers and increased elastic behavior. Recent studies have emphasized that it is the neutral and basic free amino acids (53), in particular, that are important for the plasticization properties of the SC. The generation of NMF is summarized by Mechin et al. (Fig. 13) (54) which also highlights the importance of peptidylarginine deminases involved in the processing of filaggrin and thereby allowing its hydrolysis to NMF.

Recently, hyaluronic acid has been shown to be present naturally in the SC (55) as has glycerol. Glycerol will also be derived from sebaceous triglyceride breakdown and

again, to emphasize the importance of this molecule, studies by Fluhr et al. (56) have indicated that topically-applied glycerol can completely restore the poor quality of SC observed in asebic mice (that are lacking sebaceous secretions) to normal. The importance of glycerol as a natural skin moisturizing molecule has also been shown by Elias et al. (57) However, typically, these two molecules have been largely ignored in descriptions of NMF composition (1). Recent data also indicates that lactate plays a critical role in influencing the physical properties of the SC. Lactate and potassium were found to be the only components of the NMF analyzed that correlated significantly with the state of hydration, stiffness, and pH in the SC (58).

The generation and maintenance of an acid pH within the SC, the so-called "acid mantle," is critical to the correct functioning of this tissue. Studies point to an essential role of free fatty acids generated through phospholipase activity as being vital for SC acidification (59), while Krein and Kermici (60) have recently proposed that urocanic acid plays a vital role in the regulation of SC pH. Although this is in dispute, it is likely that all NMF components contribute significantly to the overall maintenance of pH.

Other components of NMF are also not derived from filaggrin, and urea, like lactate, may also be derived in part from sweat. However, the presence of sugars in the SC represents primarily the activity of the enzyme beta-D-glucocerebrosidase, as it catalyzes the removal of glucose from glucosylceramides to initiate lipid lamellae organization in the deep SC (1).

New measurement tools have been developed in the last decade for the measurement of such compounds in vivo. Caspers et al. (61) have pioneered the use of confocal Raman microspectroscopy to determine the concentration of defined NMF components, non-invasively, in vivo within the SC. Typical depth-concentration profiles can be seen in Figure 14.

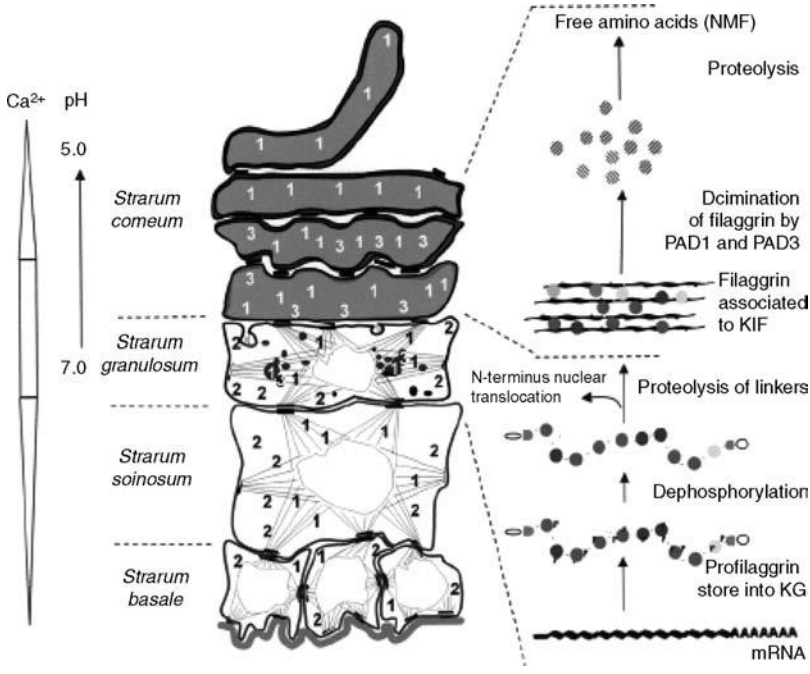

Figure 13 Schematic representation of profilaggrin catabolism and filaggrin hydrolysis to NMF and activation of peptidylarginine deiminase. *Source*: From Ref. 54.

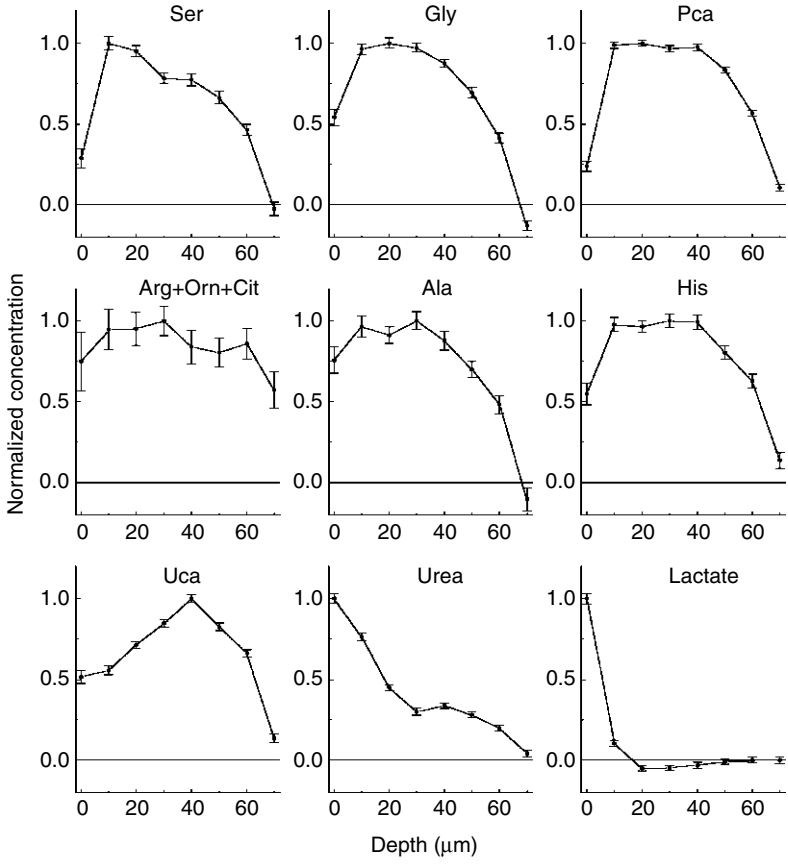

Figure 14 Semiquantitative in vivo concentration profiles of NMF and sweat constituents in the stratum corneum of the thenar as determined by Raman spectroscopy. *Source*: From Ref. 61.

THE EFFECT OF HUMIDITY ON EPIDERMAL DIFFERENTIATION AND STRATUM CORNEUM QUALITY

Before considering the biology of dry skin and the dry skin cycle, it is important to review the effect of environmental conditions on the SC, as these are the primary initiating events for the precipitation of the condition. In studies conducted in the different seasons of the year in the U.K., Rogers et al. (62) demonstrated that there was a significant reduction in the levels of SC ceramides and fatty acids, together with linoleate-containing CER EOS in subjects in winter. Similar differences in scalp lipid levels have been observed between the wet and dry seasons in Thailand (63). Nevertheless, more importantly, Declercq et al. (64) have reported an adaptive response in human barrier function, where subjects living in a dry climate such as Arizona (compared with a humid climate in New York) had much stronger barrier function and less dry skin due to increased ceramide levels and increased desquamatory enzyme levels (SCCE and SCTE).

Several animal studies have been conducted that support these findings. TEWL was reduced by approximately 30% in animals exposed to a dry ($<10\%$RH) environment due to increased lipid biosynthesis, increased lamellar body extrusion, and a slightly thicker SC layer, whereas, in animals exposed to a high humidity environment (80%RH), this induction of lipid biosynthesis was reduced (65). However, abrupt changes in environmental humidity

can also influence stratum corneum moisturization (66). After transferring animals from a humid (80%RH) to dry (<10%RH) environment, a six-fold increase in TEWL occurred. Barrier function returned to normal within seven days due to normal lipid repair processes. These changes did not occur in animals transferred from a normal to dry humidity environment. These changes in barrier function have also recently been reported in a group of Chinese workers who are exposed to very low humidity conditions. However, the changes in barrier function take longer to reach equilibrium than anticipated from the animal studies (Fig. 15) (67).

Similarly, findings were reported for the water-holding capacity and free amino acid content of the SC. Katagiri et al. (68) demonstrated that exposure of mice to a humid environment, and subsequent transfer to a dry one, reduced skin conductance and amino acid levels even after seven days following transfer; after transfer from a normal environment, however, decreased amino acid levels recovered within three days.

Exposure to low humidity conditions also increases epidermal DNA synthesis and amplifies the DNA synthetic response to barrier disruption (69). Equally, when in a dry environment epidermal IL-1 levels increased and increased levels of this cytokine were greater when the barrier was experimentally-challenged (70). More recently, the same group also reported increased numbers of mast cells and increased dermal histamine levels (but unchanged epidermal histamine levels) (71). These changes in barrier properties of the SC are attributable to changes in SC moisture content and provide evidence that changes in environmental humidities contribute to the seasonal exacerbation or amelioration of xerotic skin conditions which are characterized by a defective barrier, epidermal hyperplasia, and inflammation.

THE PATHOPHYSIOLOGY OF WINTER- AND SOAP-INDUCED DRY SKIN

The differences in SC water concentration profiles between normal and dry skin influence the enzymic reactions in the SC. In dry flaky skin conditions, corneodesmosomes are not

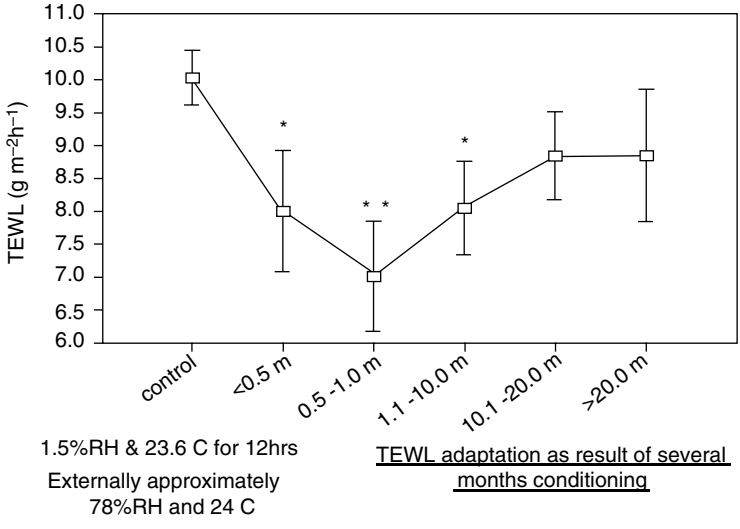

Figure 15 Time course of TEWL adaptation in humans working in an ultra-low humidity environment (1.5%RH). *Source*: From Ref. 67.

degraded efficiently and corneocytes accumulate on the skin's surface layer leading to scaling and flaking. Increased levels of corneodesmosomes in soap-induced dry skin were first reported by Rawlings et al. (23) but have been confirmed more recently by Simon et al. (72). Many corneodesmosomal proteins are now also reported to be increased in the surface layers of xerotic skin. Increased SC corneodesmosomal proteins have also been reported (23,71–73). Interestingly, however, in winter xerosis, the accumulation of the corneodemosomal proteins, Dsg 1 and plakoglobin, correlate with each. Cdsn protein levels, which were also increased, do not, however, have such an association, suggesting that different proteolytic mechanisms occur for the different corneodesmosomal components during desquamation. As suggested by Simon et al. (72), as plakoglobin is a cytoplasmic protein, this would indicate that at least the cytoplasmic domain of Dsg 1 may be cleaved. In fact, immunoreactivity to the carboxy terminal tail of the cytoplasmic portion of Dsg 1 was observed. Perhaps the intracellular portions of Dsg 1 are also degraded within the corneocyte (for example, plakoglobin by the trypsin-like activity or cathepsin E activity reported within the corneocyte matrix). Conversely, Cdsn might be degraded by SCCE, SCTE, or cathepsin D in the lamellar matrix. This is consistent with the early electron microscope images of Rawlings et al. (23) showing that corneodesmosomes become internally vacuolated, followed by complete detachment of the protein structures from the CE (Fig. 8).

The lamellar lipid matrix is also perturbed dramatically in dry skin (Fig. 16) (23). As the main desquamatory enzymes are found within this lipid matrix, the physical properties of the lamellar lipids will, therefore, influence enzyme activity.

Rawlings et al. (5) originally reported that SC SCCE levels were reduced in the outer layers of xerotic SC compared with normal skin. This has been confirmed recently in more extensive studies by Van Overloop et al. (74) who also found that the equally important SC SCTE activities were also reduced. Conversely, in SLS-induced dry skin, increased activities of these enzymes were reported (28). More recently, the over-activation of the plasminogen cascade has been associated with dry skin. Normally, only observed in the epidermal basal layers, skin plasmin is widely distributed through the epidermis in dry skin. Interestingly, a urokinase-type plasminogen activator also exists in the SC (75). Clearly these and other enzymes are potentially involved in the inflammatory and hyperproliferative aspects of dry skin.

It has been well established that, in hyperproliferative disorders such as dry skin, there is a change in SC lipid composition. In particular, the composition of the ceramide subtypes change and a predominance of sphingosine-containing ceramides (at the expense of the phytosphingosine-containing ceramides) has been observed in the SC of subjects with dry skin. Fulmer and Kramer (76) first identified these changes in SDS-induced dry skin (increased levels of ceramide 2 and 4, and reduced levels of ceramide 3). However, Saint-Leger et al. (77) could not find any changes in ceramide levels in dry skin, but found increased fatty acid levels. Rawlings et al. demonstrated the reduced levels of ceramides at the surface of the SC in winter xerosis (23). At this time, the full complexity of the different ceramide structure was not known, but, more recently, Chopart et al. (78) observed dramatic reductions in the levels of phytosphingosine-containing ceramides in dry skin (approximately 50%), together with a shortening and lengthening of the acyl sphingoid bases sphingosine and 6-hydroxysphingosine, respectively. Van Overloop et al. (74) also clearly demonstrated that the phyto-sphingosine-containing ceramides were reduced to a greater extent than other ceramides, with increasing dryness levels. Fulmer and Kramer at P&G also observed dramatic reductions in the levels of long chain fatty acids in dry skin (76). Imokawa et al. (79) did

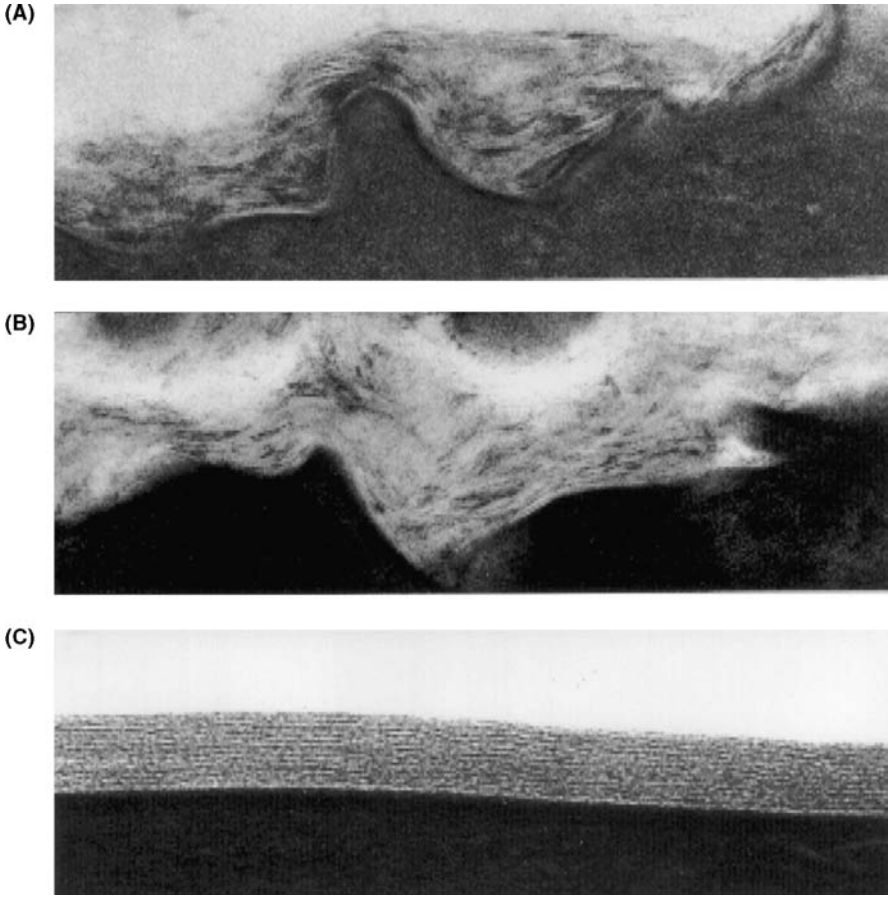

Figure 16 Organization of stratum corneum lipids in tape stripping of subjects with winter xerosis. Transmission electron micrographs of tape strippings of individuals with severe xerosis. Perturbation in lipid organization towards the surface of the stratum corneum. (**A**) First strip; disorganized lipid lamellae. (**B**) Second strip; disorganized lipid lamellae. (**C**) Third strip; normal lipid lamellae (x200,000). *Source*: From Ref. 23.

not find reduced ceramide levels in xerotic skin (but only average levels, rather than superficial levels, were measured).

These changes in lipid composition will, of course, influence the lamellar packing of the lipids. In fact, Schreiner et al. (80) established a reduction of CER EOS and EOH with increased concentrations of sphingosine-containing ceramides (CER NS and CER AS) and crystalline cholesterol in association with a loss of the LPP. However, although the lipid ultrastructure is clearly aberrant in the outer layers of dry skin (23), more work is needed to ascribe a particular lipid phase.

The proportions of the different CE phenotypes also change in subjects with dry skin (43,50). Soap washing leads to a dramatic increase in the levels of the fragile envelope phenotype at the expense of the rigid phenotype (Fig. 17). It is known that SC transglutaminase activities increase towards the surface of the SC, particularly the detergent-soluble and particulate fractions. Although the same trend of the relative increase in TGase between the inner and outer corneum is true of dry skin, TGase activities

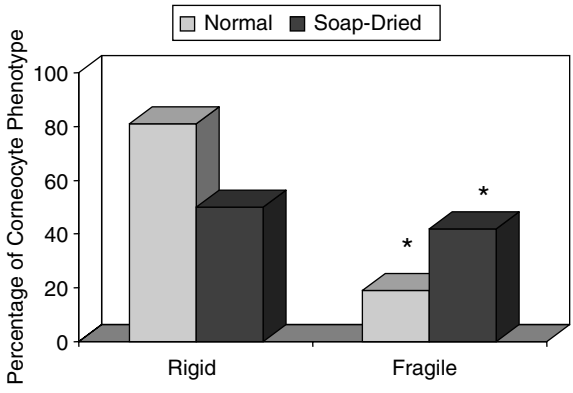

Figure 17 Percentage distribution of CEr and CEf in normal and soap-dried dry skin. *$p < 0.05$. *Source*: From Ref. 50.

are dramatically lowered in dry skin compared with healthy skin, particularly the detergent-soluble fraction, which contains mainly TGase 1.

Reduced NMF levels are also implicated in dry skin conditions. The loss of NMF generally reported with increased aging, however, is not consistent with the recent observations of Takahashi and Tezuka (81) of increased NMF in subjects with senile xerosis, and suggests that our understanding of this process is far from complete.

THE "DRY SKIN CYCLE" MODEL: A NEW WAY TO DESCRIBE INDUCTION AND PROPAGATION OF THE XEROSIS

Classically, dry skin has been described in two ways—(1) as a condition that is simply either present or not or (2) as a linear progression of sequelae, resulting in the concomitant development of clinical tools such as linear visual grading scales, etc. While not refuting the validity of these, it is proposed that the induction and propagation of dry skin conditions may be best and most intuitively expressed as a *cyclical* model, dependent on SC integrity and particularly upon barrier function and homeostasis.

A cyclical model implies a spiralling deterioration in outcome that, without intervention, would lead to a progressive worsening in model endpoints. Additionally, it is implicit that intervention at one, or preferably multiple, points within this cycle is necessary to arrest the progression of this continuing downward spiral. This is indeed the case with most dry skin conditions and, moreover, reflects extremely well consumer perception of dry skin—the seeming repetitive cycle of product usage, re-usage, disappointment with treatment outcome, and, often, a corresponding loss of compliance. The model described below describes several phases within this cycle and, therefore, possible targets against which treatments could be directed. Reference to the graphical depiction of the model below (Fig. 18) may facilitate complete understanding of the relationship of these phases, one with another.

As discussed the induction phase can be mediated by a variety of different factors:

-low environmental temperature and humidity
-abrupt changes in environmental conditions which includes the effect of modern indoor climate-controlled environments
-surfactant dissolution of SC lipid and NMF
-chronological aging and genetics

Once the skin has been provoked by one or more of these mechanisms, there is an inevitable sequence of events that may be described conveniently as a cycle.

Initially a mini-cycle of barrier deterioration is initiated and perpetuated. Blank estimated that the SC loses its flexibility once its water content falls below approximately 10% (8), the provocation for which may constitute one or a combination of the factors noted above. Without intervention, this quickly leads to a steeper SC hydration gradient, a decrease in net recondensation on the SC surface, a corresponding increase in evaporative water loss from the SC surface, a consequent further drop in SC water concentration, and so on. The inevitable rapid consequence of this series of events is a decrease in the plastic or viscous properties of the SC (commonly interpreted as skin "softness" or "suppleness"), an increase in SC fragility/brittleness, and an impairment of SC barrier function (82–85). This surface dehydration is the first step in the development of the dry skin cycle and is further exacerbated by destruction of the normal barrier lipid lamellae in the outer layers of the SC during bathing (23). The impaired barrier in the superficial layers of the SC allows leaching of NMF from the outermost skin cells, thereby reducing SC water activity. Whiteness between the dermatoglyphics (caused by backscatter from multiple tissue-air interfaces) and minor scaling due to the dehydration of individual corneocytes are the first visible steps in the cycle. Perturbation to the barrier then leads to further development of dry skin.

Due to the cyclical nature of these processes, therefore, it becomes virtually impossible to distinguish between dry skin conditions that are provoked initially by barrier disruption or by dehydration of the SC. However, once the barrier has been disrupted, even superficially, a new cascade of events is started primarily through the induction of a hyperproliferative state.

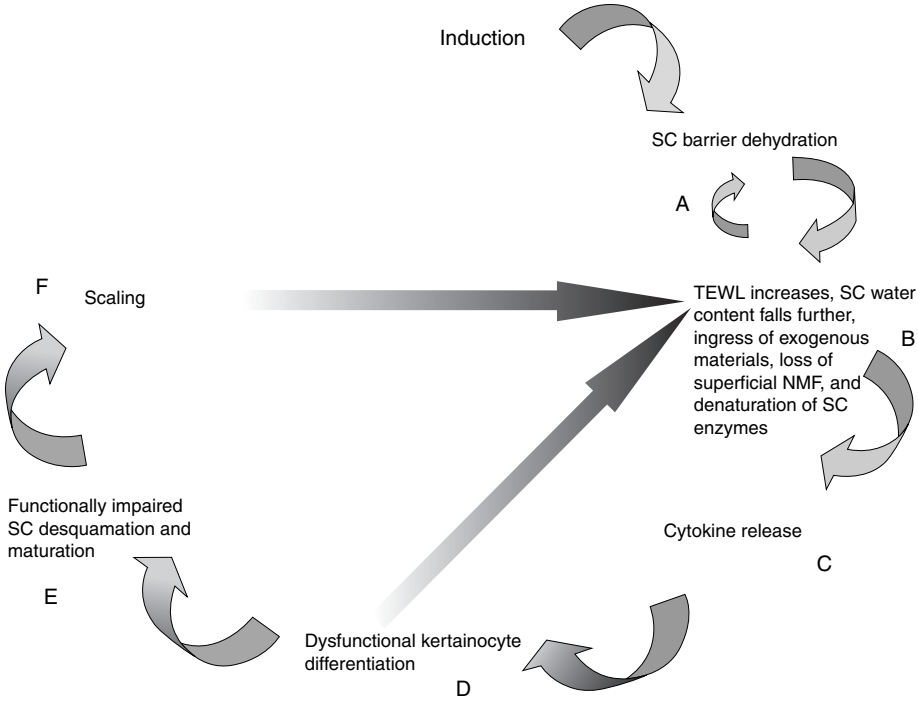

Figure 18 Schematic diagram showing pivotal events within the "dry skin cycle." *Source*: From Ref. 2.

Acute and chronic insults to the SC barrier will lead to enhanced keratinocyte proliferation, consequent hyperkeratosis, and mild inflammatory changes, one of the hallmarks of dry skin conditions, as the skin attempts to repair itself. This response is mediated via production and secretion of cytokines and growth factors, many researchers citing the ratio between interleukin 1 receptor antagonist protein and interleukin-1 alpha (IL-1 alpha) as a key marker of this process (86–89). The degree of hyperprofileration has been shown to be dependent upon the corresponding degree of barrier perturbation (90), probably reflecting both the ingress of exogenous irritants through the impaired barrier and the growing realization that the SC barrier is itself a biosensor and that corneocytes and keratinocytes themselves participating in the release of these messengers. The hyperproliferation of the epidermis probably occurs as a result of the double paracrine signaling events between the epidermis and dermis. IL-1 acts on fibroblasts which in turn secrete KGF and GMCSF inducing hyperproliferation and dysfunctional differentiation of keratinocytes (91).

The induction of this inflammatory hyperproliferative state is absolutely key in the cycle of dry skin as it fundamentally leads to aberrant differentiation and the over-hasty production of a variety of poor quality materials and structures vital to the proper functioning of the SC barrier and normal healthy skin. These include:

1. the production of smaller and immature CEs
2. changes in epidermal lipid and particular ceramide biology
3. reduced transglutaminase activity
4. reduced filaggrin synthesis and NMF levels

Finally a loss in efficiency of desquamation, due to reduced activity of desquamatory enzymes at the surface of the SC, and ensuing scaling, thickening, and loss of hygroscopicity of the SC occurs. Marked scaling is, of course, one of the obvious consumer-noticeable expressions of "dry skin." The formation of a thicker SC with impaired desquamation has, again, immense biophysical importance. The water gradient across the thicker SC becomes steeper, leading to further increases in evaporative water loss, reducing further water concentration in the outer SC, and propagating directly another round of the dry skin cycle.

Corneocytes that should be in a mature fully hydrophobed format are now replaced by fragile corneocytes. The resulting barrier protecting these corneocytes and their contents is now weaker due to changes in barrier lipid profiles and surface hydrophobicity. Equally, the hygroscopic (though highly water-labile) NMF present within corneocytes of normal SC, are depleted gradually through normal everyday activities such as cleansing and/or occupational duties (1,61). The corneocytes of dry SC are, therefore, subject to exaggerated insult such due to their changed biochemical and biophysical properties. The dry skin cycle, thus, is propagated further by an increased loss of NMF relative to normal skin and a corresponding loss in SC hygroscopicity.

Finally and most importantly, the development of an increasingly thick, dry SC results in a layer characterized, from a biomechanical viewpoint, by a dramatic increase in hardness and brittleness. The consumer perceives this as tightness. These properties create an SC barrier inherently susceptible to mechanical stress and fracture, another factor driving the impairment in barrier function cyclical nature of the dry skin cycle.

The clinical endpoint of "dry skin" cannot be regarded as static but rather is most fully described as a cycle that, without intervention, tends to perpetuate itself. Pivotal to every stage of this cycle and its propagation is a compromised SC barrier. Interventions that truly break the dry skin cycle, therefore, by definition need not only to treat symptomatic manifestations, but repair and augment SC barrier function. This will yield a

skin that is inherently better able to cope with the constantly changing external environment of the modern world.

MANAGEMENT OF DRY SKIN

Although a major analysis of dry skin treatments are outside of the scope of this review it is worth mentioning just briefly the biology that needs to be corrected in cosmetic dry skin conditions and some key examples of suitable treatments.

Traditionally, humectants, occlusives, and emollients have been, and will continue to be, the mainstay of cosmetic treatments (92):

Arguably, the most widely used and effective humectant used in cosmetic treatments for xerotic skin is glycerol, due to its excellent safety profile, cost, and simply outstanding water-retaining (humectant) and hygroscopic properties. There is now much evidence, however, that glycerol is not only a "mere" humectant, but also (i) is a lipid fluidizer (93), modulating the temperature-dependent rheology of SC lipid, thus preventing a loss of fluidity of their lamellar structure at low relative humidities and (ii) has corneodesmolytic activity, facilitating the proteolytic digestion of superficial corneodesmosomes in dry skin (94). Humectants are also an essential requirement for most of the additional approaches. In O/W creams occlusives and bilayers-forming lipids (described below) also require glycerol to alleviate dry skin. Moreover, humectants are required for the transglutaminase-mediated CE maturation that is required for a healthy SC (95). In this respect, combinations of humectants including glycerol have been shown to be more effective than just using glycerol alone. Glycerol has also been shown to enhance the barrier function of the SC (96).

Like glycerol, urea is a natural component of the SC NMF and has been used as a humectant in creams since 1943 (97). Ten-percent urea has been shown to be more efficacious than salicylic acid and petroleum jelly. Urea-containing moisturizers have been reported to improve barrier function and reduce TEWL, increase skin capacitance, and reduce irritation reactions (98–101).

As a principal component of NMF, considerable interest has been paid to the ability of PCA and its derivatives to moisturise the SC. Creams and lotions containing the sodium salt of PCA are widely reported to help hydrate the SC and improve dry flaky skin conditions (102–106).

Petroleum jelly acts primarly as an occlusive agent having been shown to reduce TEWL by over 98%, whereas other oils only manage a 20–30% reduction. Yet this agent does not simply act as an occlusive film over the surface of the skin; it has been shown to diffuse into the SC intercellular domains which may add to its efficacy. On penetrating the epidermis it was also shown to accelerate lipid biosynthesis, thereby aiding barrier repair (107).

Recent years, however, have seen a dramatic increase in the development and inclusion of novel technologies that complement these mainstays of moisturization.

Bilayer-Forming Lipid

From the current understanding of the compositional changes in dry skin five aspects of stratum corneum lipid biochemistry need to be corrected:

The lowered levels of ceramides generally.

The phytosphingosine-containing ceramide insufficiency.

The ceramide one linoleate (CEOS) insufficiency.
The lowered covalently bound ceramides.
The precise chain length of the ceramide sphingoid bases and free fatty acids.

Overall, however, the lipid lamellar architecture in the outer layers of the stratum corneum needs to be normalized in dry flaky skin conditions. Evidence also indicates that a reduction in long chain fatty acids also occurs in SLS-induced dry skin. As these lipids are important for inducing an orthorhombic lateral packing state, these will also need to be supplied to the skin to more effectively correct barrier function. Moreover correction of the reduction of SC NMF levels, correction of the aberration of CE maturation, and the impaired corneodesmolysis are needed for dry skin treatments.

Several clinical studies evaluating the effects of ceramides have been conducted recently. However, it is important to remember that to derive the full benefits of ceramide technology formulation into heavy emulsions where other emollients dominant the formulation will be difficult to discern unless the ceramides are at a high enough concentration. Nevertheless, two studies investigating the properties of Locobase Repair cream have found opposite effects on barrier recovery. Barany et al. (108) could not find any improvements to placebo whereas Kucharekova et al. (109) found that the CER NP-containing cream significantly reduced TEWL, erythema, and epidermal proliferation compared with placebo cream. Nevertheless, further improvements in function are observed with complete lipid mixtures. De Paepe et al. (110) have demonstrated improvements in barrier functionality and SC hydration from a lipid mixture of CER NP (0.2%), CER AS (0.1%), and CER UP (0.2%) together with cholesterol (0.25%), linoleic acid (0.25%), and phytosphingosine (0.5%) compared with placebo lotions and a lotion containing only CER NP (0.6%) and CER UP (0.4%). The percentage increases in TEWL and SC hydration are shown in Figure 15. Berardesca et al. (111) have also established that balanced lipid mixtures containing CER NP are effective in improving the barrier properties and clinical condition of skin in subjects with contact dermatitis. Equally convincing are the studies of Chamlin et al. (112) showing that a ceramide dominant barrier repair lipid cream alleviates childhood atopic dermatitis. Over the six-week treatment period TEWL values decreased by 50% and the number of D-squame tape strippings required to break the barrier increased from approximately 12 to 22 strippings, indicating a stronger SC barrier function.

In addition to ceramides, which have been introduced to supplement the SC barrier, (113) phospholipids are also bilayers-forming lipids and when combined with glycerol have been demonstrated to be clinically superior to petroleum jelly in relieving dry skin (114).

Hydroxy Acids

Hydroxy acids are being used to facilitate desquamation and improve lipid biosynthesis together with barrier function. The influence of alpha-and beta-hydroxy acids (115) on desquamation is now well established, but new lipophillic variants of salicylic acid appear to influence corneodesmolysis differently. Whereas lactic and salicylic acid act on all corneodesmosomes, LSA only acted in the stratum disjunctum corneodesmosomes. These lipophillic variants appear to act on the whole structure of the corneodesmosomes whereas the "ordinary" acids fractionate the corneodesmosomes. Fartarsch et al. (116) also demonstrated that the action of glycolic acid on corneodesmolysis was restricted to the stratum disjunctum suggesting a targeted action without compromising barrier function. Medium chain fatty acids have also been reported to not only improve SC flexibility but

also assist in the relief of dry skin in combination with barrier lipids. Further enhanced dry skin relief was observed in the presence of barrier lipids (117), and the L isomer, in particular, increased SC extensibility and keratinocyte proliferation as reported by Rawlings et al. (118). Rawlings et al. also reported that longer chain hydroxy acids were more effective than short chain fatty acids at facilitating corneocyte cell release in the presence of several calcium chelators. This may be due to a fluidizing effect of these longer chain fatty acids on the lamellar lipids as in SC extensibility studies using extensions where only lipids are believed to being extended longer chain alpha-hydroxy acids plasticize the corneum (119).

SC turnover time measured by dansyl chloride (a measure of epidermal proliferation matched by desquamation) increased by 15% by applying a moisturizing cream at pH 3.8. However, further increases were observed with increasing concentration of the free acid of glycolic acid or by decreasing the pH of the base. At 8% glycolic acid concentration (4% free acid) Johnson (120) reported approximately 30% increase in SC turnover time. The increased turnover time needs to be matched by increased desquamation; otherwise, retention hyperkeratosis would occur, which clearly it does not. In fact, the opposite occurs. So desquamation must also be enhanced by further activating acidic optimum enzymes or by also chelating calcium, which is known to reduce the final processing steps involved in Cdsn degradation.

Nevertheless, not all hydroxy acids perform equally, and, in fact, some appear to enhance the skin's sensitivity to UV irradiation, especially glycolic acid. However, glucanolactone and tartaric acid have been shown to be not only superior to glycolic acid and lactic acid in improving barrier function but have been shown to not increase in sunburn cell formation (121).

SC Barrier Augmentation by Inducing Epidermal Differentiation

Ligands for nuclear receptors such as the peroxisomal proliferator activated receptor have been shown to improve epidermal differentiation, increasing ceramide and filaggrin levels (122). This superfamily of nuclear transcription receptors includes the retinoic acid receptors, the steroid receptors, the thyroid receptors, and the vitamin D receptors and also the peroxisome proliferator activated receptor (PPAR), together with farnesol activated receptor (FXR) and the liver activated receptor (LXR). These transcription factors bind their respective ligands and regulate many of the aspects of cellular proliferation and differentiation. Fatty acids are important ligands for the PPAR receptor, farnesol for the FXR, and hydroxylated cholesterol derivatives or cholestenoic acid for the LXR. All of these pathways stimulated epidermal differentiation and increased the synthesis of involucrin, filaggrin, and enzymes of the ceramide synthesis pathway.

The transcription factor most intensively investigated is the PPAR. There are three main PPAR isoforms: alpha, beta/delta, and gamma. Nevertheless, PPAR delta was recently observed to be the predominant PPAR subtype in human keratinocytes, whereas PPAR alpha and gamma were only induced during epidermal differentiation, suggesting non-redundant functions during differentiation (123). Respective ligands for all of these isoforms increased epidermal differentiation. Pharmaceutical ligands for the PPAR receptors increase ceramide synthesis in vitro by increasing the expression of SPT, glucosyl ceramide synthase, and glucocerebrosidase but not sphingomyelinase (124). More recently PPAR delta ligands were found to be the most potent in inducing epidermal differentiation (tetrathioacetic acid) by increasing involucrin and transglutaminase while decreasing proliferation.

Petroselinic acid (125) and conjugated linoleic acid (126) have been identified as potent PPAR alpha activators improving epidermal differentiation, reducing inflammation, increasing extracellular matrix components, and eliciting skin lightening. In vitro increased levels of transglutaminase, involucrin, filaggrin, and CE formation were observed in keratinocytes after treatment with petroselinic acid. These effects were confirmed in vivo by short-term patch testing studies over three weeks and increases in involucrin and filaggrin were also observed. Using this technology, improvements in the signs of photodamage, skin tone and dry skin were observed in a 12-week clinical study on forearm skin (127). Octadecenedioic acid has also recently been identified as a pan-PPAR agonist (with a preference for PPAR gamma) and has been shown to reduce skin hyperpigmentation, but with its PPAR agonist activities it is also expected to improve epidermal differentiation (128).

SC Barrier Augmentation by Inducing Epidermal Lipogenesis

Changes in lipid levels and types can be corrected by topically applying agents to manipulate the lipid synthesis process within the viable epidermis. However, as described above, in dry skin conditions the epidermis makes less phytosphingosine-containing ceramides, changes the carbon chain lengths of other sphingoid bases and synthesis less long chain fatty acids. These results suggest that changes in the levels or activities of the different fatty acid synthetases, as well as the enzymes involved in phytosphingosine synthesis, occur in dry skin. The biology of these enzymes is yet to be described in these conditions.

Elias et al. (129), however, has used lipid mixtures to aid barrier recovery in acetone damaged barrier studies. Cholesterol itself was shown to aid barrier recovery in a tape stripping model in aged skin but not young skin. In fact any incomplete mixture of one or two of the three major lipid species slows barrier recovery in this model. The equimolar mixture of the three dominant SC lipids allows normal rates of barrier recovery in normal skin, whereas its further adjustment to a 3:1:1 molar ratio accelerates barrier recovery. As expected the requirements for optimal barrier recovery in aged skin is different, and it has been shown that a cholesterol dominant lipid mixture accelerates barrier recovery in aged skin whereas a fatty acid dominant mixture delays barrier recovery. In young skin any of the lipid species can be the dominant lipid and the barrier will recover more quickly with one exception, and that is in atopic dermatitis where a ceramide dominant mixture is required (130). Further studies on the use of long chain fatty acids are recommended. Exploiting these facts it has been shown that (131) mevalonic acid, the product of the rate limiting enzyme HMGCoA reductase, increases cholesterol biosynthesis.

Several other routes have been shown to increase ceramide synthesis in vivo and improve barrier function. As described above alpha-hydroxy acids well known for their desquamatory properties also stimulate lipid biosynthesis. Lactic acid, and especially the L isomer, increases ceramide biosynthesis in vitro and in vivo. Presumably lactic acid achieves this by acting as a general lipid precursor by providing acetate and providing more reducing power in the form of NADH or NADPH (132). Corresponding improvements in barrier function were reported. Interestingly, lactic acid also increased the levels of linoleate-containing CER EOS which may be contributing to these improvements in skin functionality.

The pleotropic skin benefits of niacinamide have been the subject of intense study by Procter & Gamble and have been excellently reviewed by Matts et al. (133). Niacinamide has been reported to stimulate the synthesis of glucosylceramides, sphingomeylin, cholesterol, and fatty acids by keratinocytes in vitro (127). The increases in ceramide synthesis were achieved by enhancing the activity of SPT together with the expression of

Table 2 Agents That Increase Ceramide Biosynthesis

Lipids	Optimized mixtures of ceramides, cholerterol & fatty acids
Lipid precursors	Phytosphingosine, tetra-acetylphytosphingosine, omega-hydrosy-fatty acides, linoleic acid
Alpha-hydroxy acids	L-Lactic acid
Humectants	Glycerol, urea
Vitamins	Niacinamide, lipoic acid, ascorbic acid
Protease inhibitors	Aminocyclohexanecarboxylic acid, egg white lysozyme
Monerals	Magnesium, calcium
Histamine receptor	H1 receptor antagonist
Antagonists	H2 receptor antagonist
PPAR	PPAR alpha agonists
Electrical potential	Negative potential
Triterpenoids	Ursolic acid
GABA agonists	GABA type A agonists (musimol, isoguvacine)
Purinergic receptor	P2Y antagonists
Fragrances	Fragrances
GC receptor	Glucocorticoid receptor antagonists

LCB 1 and 2. In vivo, however, increased levels of stratum corneum fatty acid (67%) and ceramide (34%) levels were observed. Similar to studies with lactic acid, increases in the levels of stratum corneum cholesterol seem to be refractory to change. In their further studies Tanno et al. (134) at Kanebo have also been researching the changes in skin functionality with presence of sensitive skin. In their most recent studies topical application of niacinamide improved the barrier of the most severely affected subject with

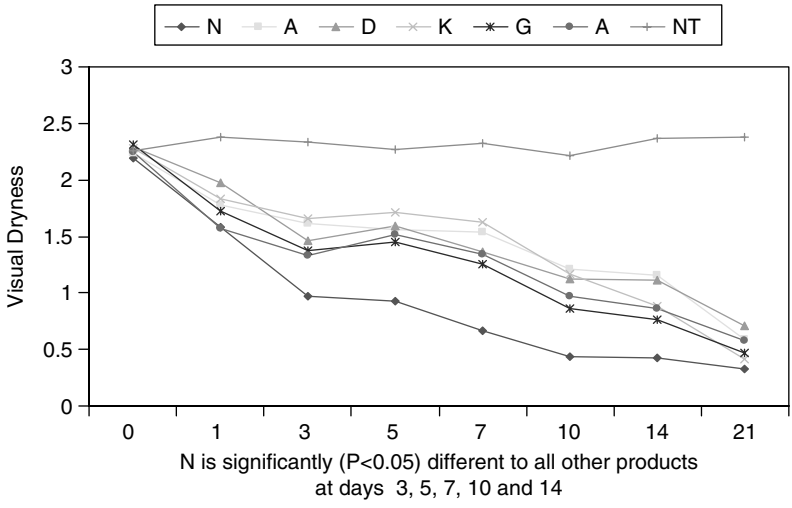

Figure 19 Results from the treatment phase of a Kligman-type regression study (products applied twice-daily at 2 mg/cm^2 to randomized sites on the outer, lower leg of female subjects [n = 36] with inclusion of a no-treament control). Products represented high-efficacy commercial moisturizers with ingredients of differing dry skin relief mechanism. *Abbreviations*: NT, no treatment control; N, niacinamide-containing lotion; A, lactic acid-containing moisturizer; other product codes represent commercial products with high loadings of traditional humectants and emollients (including glycerin and petrolatum). *Source*: From Ref. 2.

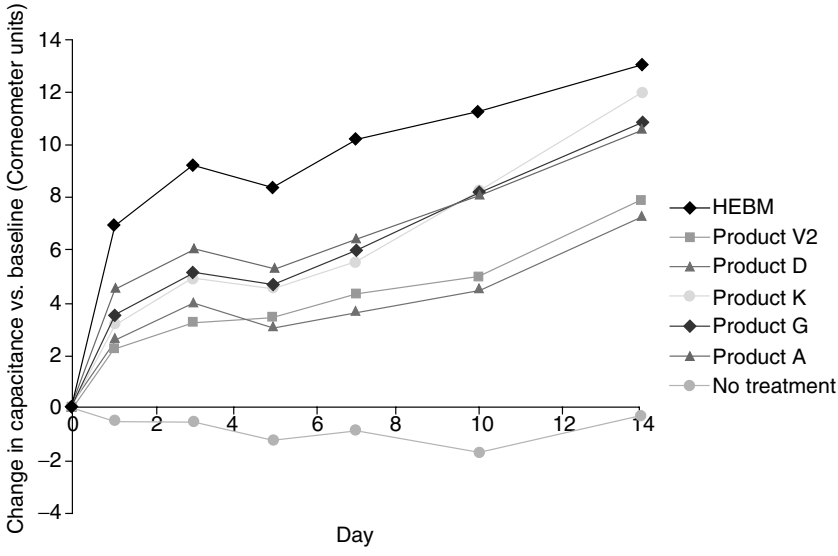

Figure 20 Change in capacitance during treatment with several moisturizers expressed as difference from baseline. *Source*: From Ref. 144.

sensitive skin with a concomitant improvement in stinging score. Ertel et al. (135) observed similar improvements in barrier functionality together with an increased SC turnover rate using a 2% niacinamide cream. Draelos et al. (136) similarly observed a significant improvement in SC barrier function and improvement in global skin condition in subjects with stage 1/11 Rosacea.

Topical application of phytosphingosine and its derivatives have also been shown to increase SC ceramide levels and barrier function (137). This is especially important as the phytosphingosine-containing ceramides are deficient in dry skin. Although increases in the total levels of ceramides were observed, greater increases in CER EOS and CER AS were found when combined with juniperic acid and linoleic acid. Linoleic acid on its own has

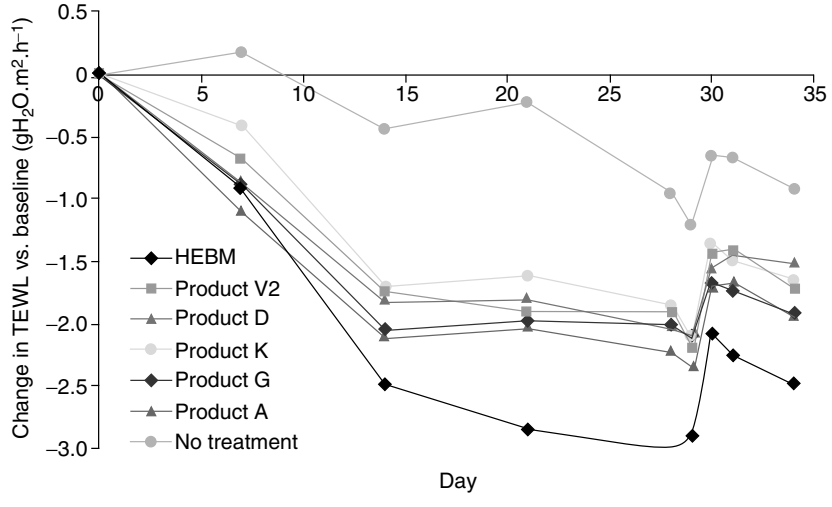

Figure 21 Change in TEWL during treatment and regression phases expressed as difference from pre-treatment baseline. Regression starts at day 28. *Source*: From Ref. 144.

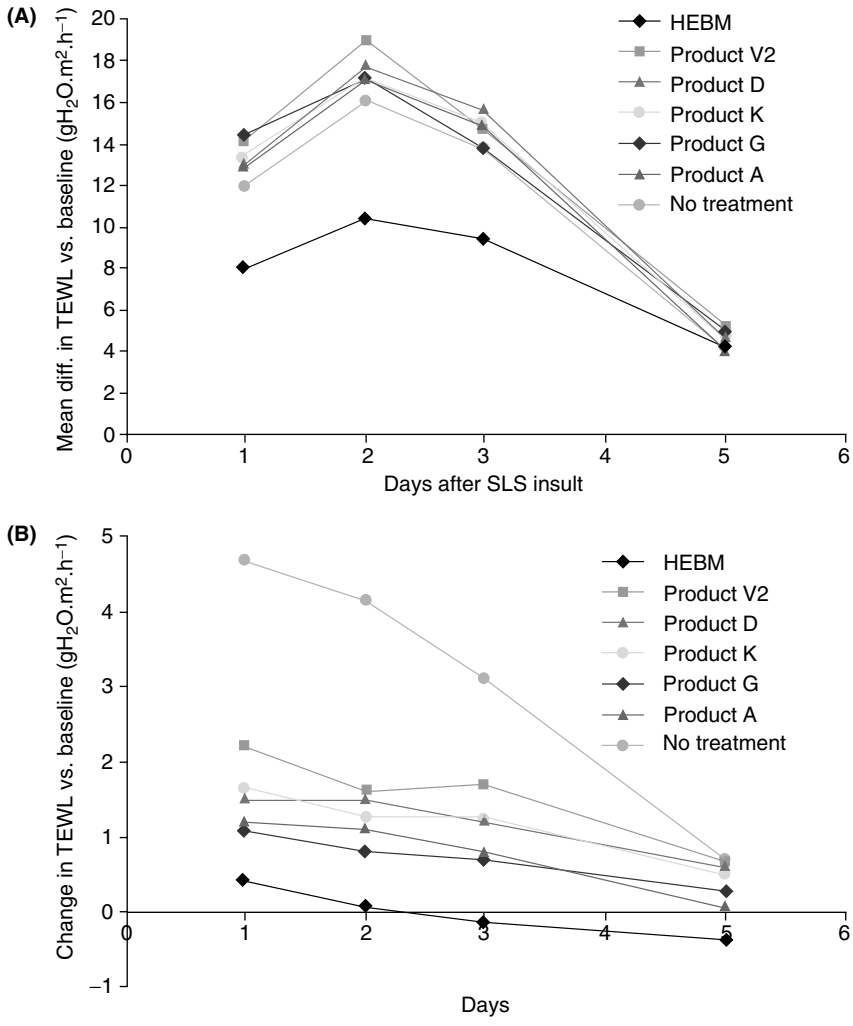

Figure 22 (**A**) Change in TEWL in post-treatment phase after SLS patch chemical insult expressed as difference from pre-treatment baseline. (**B**) Change in TEWL in post-treatment phase after tape stripping mechanical insult expressed as difference from pre-treatment baseline. *Source*: From Ref. 144.

also been proven to be incorporated into CER EOS in vivo (138) which is obviously important for the lipid phase behavior and skin properties. Lipid fractions from unsaponifiable fractions of avocado (furanyl-8-11- cis heptadecadiene) and sunflower oleodistillates (mainly linoleic and oleic acids) also increase ceramide and cholesterol biosynthesis ex vivo (139).

The effects of increasing SC lipid levels by stimulating ceramide biosynthesis have been investigated extensively by Denda et al. (140). Histamine antagonists and certain fragrances stimulate lipid biosynthesis. Mixtures of magnesium and calcium salts have also been shown to accelerate skin barrier recovery and improve surfactant-induced or tape stripping-induced dry skin. Although these studies indicate the importance of these ions for epidermal homeostasis, more work is needed with cosmetic formulations. More recently, it has been demonstrated that gamma-aminobutyric acid (GABA) type A

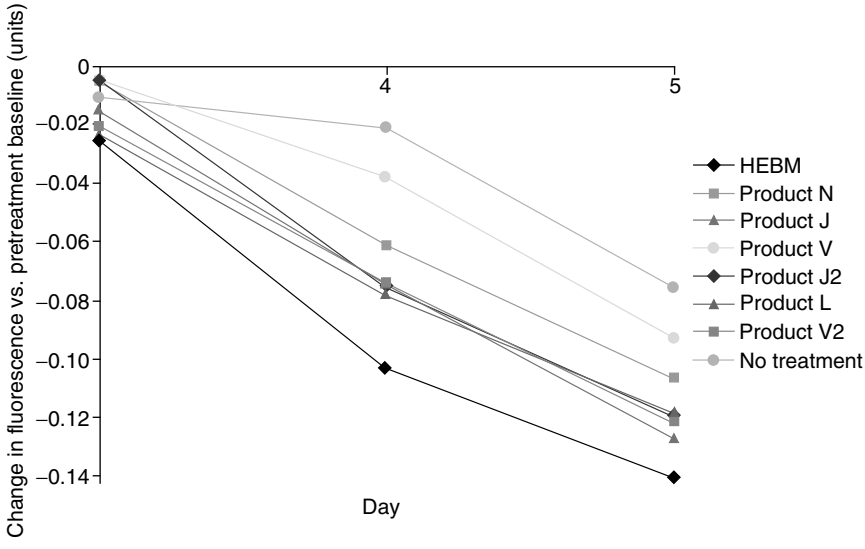

Figure 23 Change in absolute dansyl chloride fluorescence over five days following staining. *Source*: From Ref. 144.

receptor agonists, musimol, and isoguvacine accelerate barrier recovery following barrier disruption. Conversely, ATP (purinergic) receptor (P2X) agonists delay barrier recovery whereas P2Y antagonists accelerate it. These also reduced the epidermal hyperproliferative response induced by acetone treatment under low environmental humidity (Table 2).

Other agents have been shown to stimulate ceramide synthesis in vitro. Lipoic acid and N-acetylcysteine were also reported to increase ceramide synthesis in vitro (141). Recently vitamin C has been shown to activate PKC and increase ceramide synthesis and improve the ceramide subspecies profile in epidermal skin equivalents (142). Yarosh and Brown (143) also demonstrated that Ursolic acid increased ceramides in human skin. For a complete analysis of agents that stimulate lipid biosynthesis see Table 2.

Very recently, exploiting its lipogenesis and differentiation enhancing effects, niacinamide has been introduced into lotions, together with glycerol and other NMF components, that effectively alleviate dry skin and provide a significant improvement in SC barrier function (144). These lotions have been shown to be more effective than traditional emollient and lactic acid-containing moisturisers in relieving dry skin in the treatment phase of a typical Kligman-type regression study (Fig. 19), together with the changes in moisturization (Fig. 20) and barrier function (Fig. 21) as well as improving resistance to SLS and tape stripping-induced barrier perturbation (Fig. 22) (101). The improvement in desquamation was also proven with a dansylchloride exfoliation test (Fig. 23).

SUMMARY AND CONCLUSIONS

New and exciting discoveries have been made in SC biology over the last decade, but more importantly the understanding of the aberration of the normal functioning of the SC in dry, flaky skin conditions has become clearer and a new model of dry skin has been described. On perturbation of SC barrier function, a futile cycle of events begins first with the superficial dehydration of the SC and subsequent release of inflammatory mediators, induction of hyperproliferation of epidermal keratinocytes, and disruption of epidermal

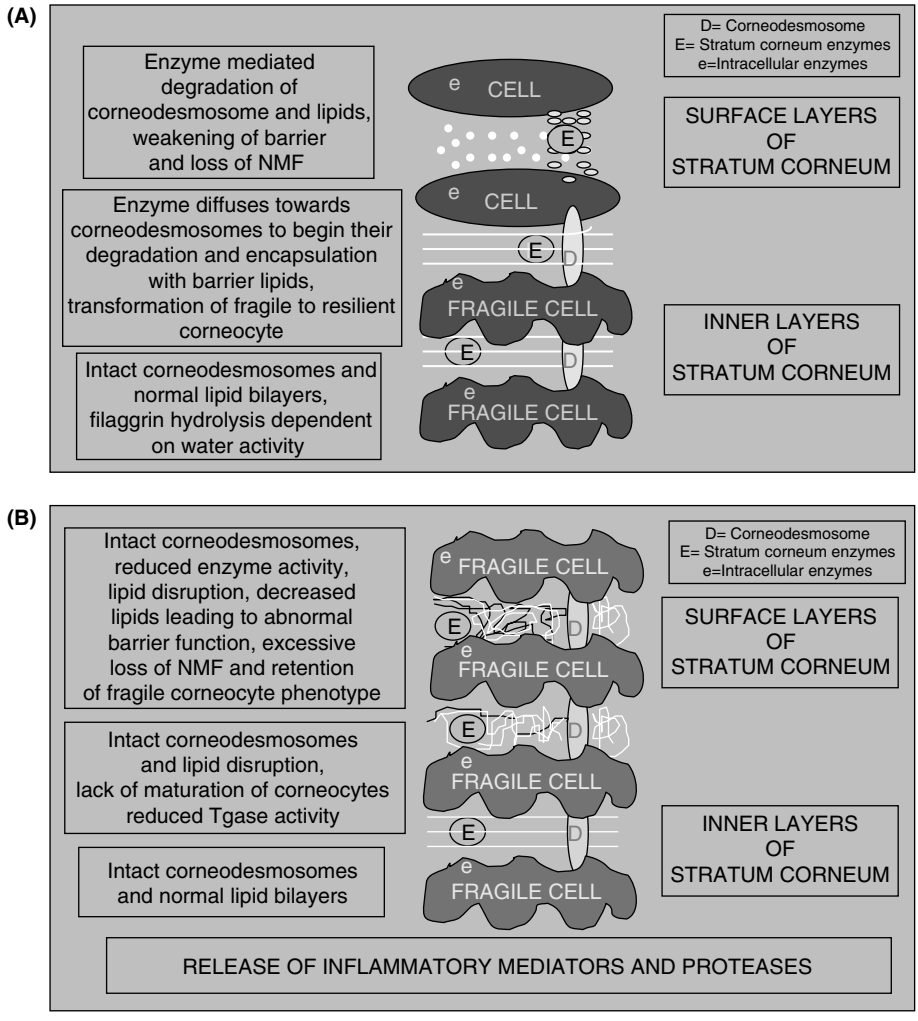

Figure 24 Summary of stratum corneum maturation and corneodesmolysis in (**A**) normal and (**B**) dry skin. *Source*: From Ref. 2.

differentiation, leading to an inferior SC. As has become apparent, reductions in SC water and NMF levels, changes in lipid ultrastructure, and reductions in enzyme activities contribute to the reduced corneodesmolysis known to occur in these conditions. See Figure 24 for a schematic summary of the differences in SC biology in normal and dry skin. As a result, new therapies for the treatment of dry skin have been developed that target all aspects of the aberrant biology described by the "dry skin cycle."

REFERENCES

1. Rawlings 0AV, Scott IR, Harding CR, Bowser PA. Stratum corneum moisturization at the molecular level. J Invest Dermatol 1994; 103:731–740.
2. Rawlings AV, Matts PJ. Stratum corneum at the molecular level: an update in relation to the dry skin cycle. J Invest Dermatol 2005; 124:1099–1110.

3. Rawlings AV, Harding CR. Moisturization and skin barrier function. Dermatol Ther 2004; 17:43–48.
4. Rawlings AV. Skin waxes: their composition, properties, structures and biological significance. In: Hamilton RJ, ed. Waxes: Chemistry, Molecular Biology and Functions. New York: The Oily Press, 1994:221–256. Chapter 6.
5. Harding CR, Watkinson A, Rawlings AV. Dry skin, moisturization and corneodesmolysis. Int J Cosmet Sci 2000; 22:21–52.
6. Rawlings AV, Harding CR, Watkinson, Scott IR. Dry and xerotic skin conditions. In: Leyden JJ, Rawlings AV, eds. Skin Moisturization. New York NY: Marcel Dekker 2002:119–143.
7. Warner RR, Lilly NA. Correlation of water content with ultrastructure in the stratum corneum. In: Elsner P, Berardesca E, Maibach HI, eds. Bioengineering of the Skin: Water and the Stratum Corneum. Boca Raton: CRC Press Inc, 1994:3–12.
8. Blank IH. Factors which influence the water content of the stratum corneum. J Invest Dermatol 1952; 18:433–440.
9. Pfeiffer S, Vielhaber G, Vietzke JP, Wittern KP, Hintze U, Wepf R. High-pressure freezing provides new information on human epidermis: simultaneous protein antigen and lamellar lipid structure preservation. Study on human epidermis by cryoimmobilization. J Invest Dermatol 2000; 114:1030–1038.
10. Norlen L. Skin barrier structure and function: the single gel phase model. J Invest Dermatol 2001; 117:830–836.
11. Norlen L, Al-Amoudi A. Stratum corneum keratin structure, function, and formation: the cubic rod-packing and membrane templating model. J Invest Dermatol 2004; 123:715–732.
12. Bouwstra JA, de Graaff A, Gooris GS, Nijsse J, Wiechers JW, van Aelst AC. Water distribution and related morphology in human stratum corneum at different hydration levels. J Invest Dermatol 2003; 120:750–758.
13. Richter T, Peuckert C, Sattler M, et al. Dead but highly dynamic—the stratum corneum is divided into three hydration zones. Skin Pharmacol Physiol 2004; 17:246–257.
14. Downing DT, Stewart ME. Epidermal composition. In: Loden M, Maibach HI, eds. Dry Skin and Moisturizers Chemistry and Function, 2000:13–26.
15. Motta SM, Monti M, Sesana S, et al. Ceramide composition of psoriatic scale. Biochem Biophys Acta 1993; 1182:147–151.
16. Oku H, Mimura K, Tokitsu Y, Onaga K, Iwasaki H, Chinen I. Biased distribution of the branched-chain fatty acids in ceramides of vernix caseosa. Lipids 2000; 35:373–381.
17. Chopart M, Castiel-Higounenc I, Arbey E, Schmidt R. A new type of covalently bound ceramide in human epithelium. Stratum Corneum 2001; III.
18. Hamanaka S, Hara M, Nishio H, Otsuk F, Suzuki A, Uchida Y. Human epidermal glucosylceramides are major precursors of stratum corneum ceramides. J Invest Dermatol 2002; 119:416–423.
19. Pilgram GSK, Engelsma-van Pelt AM, Bouwstra JA, Koerten HK. Electron diffraction provides new information on human stratum corneum lipid organisation studied in relation to depth and temperature. J Invest Dermatol 1999; 113:403–409.
20. Brancaleon L, Bamberg MP, Sakamaki T, Kollias N. Attenuated total reflection-fourier transform infrared spectroscopy as a possible method to investigate biophysical parameters of stratum corneum in vivo. J Invest Dermatol 2001; 116:380–386.
21. Bouwstra J, Pilgram G, Gooris G, Koerten H, Ponec M. New aspects of the skin barrier organization. Skin Pharm Appl Skin Physiol 2001; 14:52–62.
22. Bouwstra J, Gooris GS, Dubbelaar FER, Ponec M. Phase behavior of stratum corneum lipid mixtures based on human ceramides: the role of natural and synthetic ceramide 1. J Invest Dermatol 2002; 118:606–617.
23. Rawlings AV, Watkinson A, Rogers J, et al. Abnormalities in stratum corneum structure lipid composition and desmosome degradation in soap-induced winter xerosis. J Soc Cosmet Chem 1994; 45:203–220.

24. Warner RR, Boissy YL. Effect of moisturizing products on the structure of lipids in the outer stratum corneum of humans. In: Loden M, Maibach HI, eds. Dry Skin and Moisturisers. Boca Raton: CRC Press Inc, 2000:349–372.
25. Berry N, Charmeil C, Gouion C, et al. A clinical, biometrological and ultrastructural study of xerotic skin. Int J Cosmet Sci 1999; 21:241–249.
26. Serre G, Mils V, Haftek M, et al. Identification of late differentiation antigens of human cornified epithelia, expressed in re-organized desmosomes and bound to cross-linked envelope. J Invest Dermatol 1991; 97:1061–1072.
27. Lundstorm A, Egelud T. Cell shedding from human plantar skin in vitro: evidence that two different types of protein structures are degraded by a chymotrypsin-like enzyme. Arch Dermatol Res 1990; 282:237–243.
28. Suzuki Y, Nomura J, Koyama J, Horii T. The role of proteases in stratum corneum: involvement in stratum corneum desquamation. Arch Dermatol Res 1994; 286:249–253.
29. Horikoshi T, Igarashi S, Uchiwa H, Brysk H, Brysk MM. Role of endogenous cathepsin D-like and chymotrypsin-like proteolysis in human epidermal desquamation. Br J Dermatol 1999; 141:453–459.
30. Horikoshi T, Arany I, Rajaraman S, et al. Isoforms of cathepsin D human epidermal differentiation. Biochimie 1998; 80:605–612.
31. Watkinson A. Stratum corneum thiol protease (SCTP): a novel cysteine protease of late epidermal differentiation. Arch Dermatol Res 1999; 291:260–268.
32. Bernard D, et al. Analysis of proteins with caseinolytic activity in a human SC extract revealed a yet unidentified cysteine protease and identified the so called 'SC thiol protease' as Cathepsin L2. J Invest Dermatol 2003; 120:592–600.
33. Caubet C, et al. Degradation of corneodesmosome proteins by two serine proteases of the kallikrein family. J Invest Dermatol 2004; 122:1235–1244.
34. Bernard D, Mehul B, Delattre C, Simonetti L, Thomas-Collignon A, Schmidt R. Purification and characterization of the endoglycosidase heparanase 1 from human plantar stratum corneum: a key enzyme in epidermal physiology. J Invest Dermatol 2001; 117:1266–1273.
35. Simon M, Jonca N, Guerrin M, et al. Refined characterization of corneodesmosin proteolysis during terminal differentiation of human epidermis and its relationship to desquamation. J Bio Chem 2001; 276:20292–20299.
36. Sondell B, Thornell LE, Stigbrand T, Egelrud T. Immunolocalization of SCCE in human skin. Histo Cytom 1994; 42:459–465.
37. Watkinson A, Smith C, Coan P, Wiedow O. The role of Pro-SCCE and SCCE in desquamation. 21st IFSCC Congress 2000; 16–25.
38. Igarashi S, Takizawa T, Yasuda Y, et al. Cathepsin D, degrades desmosomes during epidermal desquamation. Brit J Dermatol 2004;151:355.
39. Ishida-Yamamoto A, Simon M, Kishibe M, et al. Epidermal lamellar granules transport different cargoes as distinct aggregates. J Invest Dermatol 2004; 122:1145–1153.
40. Watkinson A, Harding C, Moore A, Coan P. Water modulation of stratum corneum chymotryptic enzyme activity and desquamation. Arch Dermatol Res 2001; 293:470–476.
41. Komatsu N, Takata M, Otsuki N, et al. Elevated stratum corneum hydrolytic activity in netherton syndrome suggests an inhibitory regulation of desquamation by SPINK5-derived peptides. J Invest Dermatol 2002; 118:436–443.
42. Franzke CW, Baici A, Bartels J, Christophers E, Wiedow O. Antileukoprotease inhibits stratum corneum chymotryptic enzyme. J Biol Chem 1996; 271:21886–21890.
43. Brattsand M, Stefansson K, Lundh C, Haasum Y, Egelrud T. A proteolytic cascade of kallikreins in the stratum corneum. J Invest Dermatol 2005; 124:198–203.
44. Watkinson A, Harding CR, Rawlings AV. The cornified envelope: its role on stratum corneum structure and maturation. In: Leyden JJ, Rawlings AV, eds. Skin Moisturization. New York NY: Marcel Dekker 2002:95–117.

45. Candi E, et al. Transglutaminase cross linking properties of the small proline rich 1 family of cornified envelope proteins. J Biol Chem 1999; 274:7226–7237.
46. Kim IG, Gorman JJ, Park SC, Chung SI, Steinert PM. The deduced sequence of the novel protransglutaminase-E (TGase 3) of human and mouse. J Biol Chem 1993; 268:12682–12690.
47. Nemes Z, Marekov LN, Steinert PM. Involucrin cross linking by transglutaminase 1. J Biol Chem 1999; 274:11013–11021.
48. Cabral A, Voskamp P, Cleton-Jansen M, et al. Structural organisation and regulation of the small proline rich family of cornified envelope precursors suggest a role in adaptive barrier function. J Biol Chem 1923; 26:19231–19237.
49. Mils V, Vincent C, Croute F, Serre G. The expression of desmosomal and corneodesmosomal antigens shows specific variations during the terminal differentiation of epidermis and hair follicle epithelia. J Histochem Cytochem 1992; 40:1329–1337.
50. Harding CR, Long S, Richardson J, et al. The cornified cell envelope: an important marker of stratum corneum maturation in healthy and dry skin. Int J Cosmet Sci 2003; 25:1–11.
51. Hirao T, Denda M, Takahashi M. Identification of immature cornfield envelopes in the barrier-impaired epidermis by characterization of their hydrophobicity and antigenicities of the components. Exp Dermatol 2001; 10:35–44.
52. Kashibuchi N, Hirai Y, O'Goshi K, Tagami H. Three-dimensional analyses of individual corneocytes with atomic force microscope: morphological changes related to age, location and to the pathologic skin conditions. Skin Res Technol 2002; 8:203–211.
53. Jokura Y, Ishikawa S, Tokuda H, et al. Molecular analysis of elastic properties of the stratum corneum by solid-state C-13-nuclear magnetic resonance spectroscopy. J Invest Dermatol 1995; 104:806.
54. Mechin MC, Enji M, Nachat R, et al. The peptidylarginine deiminases expressed in human epidermis differ in their substrate specificities & subcellular locations. CMLS DO1 2005;1–12.
55. Sakai S, Yasuda R, Sayo T, et al. Hyaluronan exists in the normal stratum corneum. J Invest Dermatol 2000; 114:1184.
56. Fluhr JW, Mao-Qiang M, Brown BE, et al. Glycerol regulates stratum corneum hydration in sebaceous gland deficient (Asebia) mice. J Invest Dermatol 2003; 120:728.
57. Choi EH, Man MQ, Wang F, et al. Is endogenous glycerol a determinant of stratum corneum hydration in humans. J Invest Dermatol 2005;1–6.
58. Nakagawa N, et al. Relationship between NMF (potassium and lactate) content and the physical properties of the stratum corneum in healthy subjects. J Invest Dermatol 2004; 122:755.
59. Fluhr JW, et al. Generation of free fatty acids from phospholipids regulates stratum corneum acidification and integrity. J Invest Dermatol 2001; 117:44.
60. Krein PM, Kermici M. Evidence for the existence of a self-regulated enzymatic process within the human stratum corneum- an unexpected role for urocanic acid. J Invest Dermatol 2000; 115:414.
61. Caspers PJ, Lucassen GW, Carter EA, Bruining HA, Puppels GJ. In vivo confocal raman microspectroscopy of the skin: non-invasive determination of molecular concentration profiles. J Invest Dermatol 2001; 116:434–442.
62. Rogers J, Harding CR, Mayo A, Banks J, Rawlings AV. Stratum corneums lipids: the effect of ageing and the seasons. Arch Dermatol Res 1996; 288:765–770.
63. Meldrum H. The characteristic decrease in scalp stratum corneum lipids in dandruff is reversed by use of a ZnPTO containing shampoo. IFSCC Mag 2003; 6:3–6.
64. Declercq L, Muizzuddin N, Hellemans L, et al. Adaptation response in human skin barrier to a hot and dry environment. J Invest Dermatol 2002; 119:716.
65. Denda M, Sato J, Masuda Y, et al. Exposure to a dry environment enhances epidermal permeability barrier function. J Invest Dermatol 1998; 111:858–863.
66. Sato J, Denda M, Chang S, et al. Abrupt decreases in environmental humidity induce abnormalities in permeability barrier homeostasis. J Invest Dermatol 2002; 119:900–904.

67. Chou TC, Lin KH, Wang SM, et al. Transepidermal water loss & skin capacitance alterations among workers in an u;tra-low humidity environment. Arch Dermatol Res 2005; 296:489–495.
68. Katagiri C, Sato J, Nomura J, et al. Changes in environmental humidity affect the water-holding capacity of the stratum corneum and its free amino acid content, and the expression of filaggrin in the epidermis of hairless mice. J Dermatol Sci 2003; 31:29–35.
69. Denda M, Sato J, Tsuchiya T, Elias PM, Feingold KR. Low humidity stimulates epidermal DNA synthesis and amplifies the hyperproliferative response to barrier disruption: implication for seasonal exacerbation of inflammatory dermatoses. J Invest Dermatol 1988; 111:873–878.
70. Ashida Y, Ogo M, Denda M. Epidermal interleukin-1 generation is amplified at low humidity: implications for the pathogenesis of inflammatory dermatoses. Br J Dermatol 2001; 144:238–243.
71. Ashida Y, Denda M. Dry environment increases mast cell number and histamine content in dermis in hairless mice. Br J Dermatol 2003; 149:240–247.
72. Simon M, Bernard D, Minondo AM, et al. Persistence of both peripheral and non-peripheral corneodesmosomes in the upper stratum corneum of winter xerosis skin versus only peripheral in normal skin. J Invest Dermatol 2001; 116:23–30.
73. Long S, Banks J, Watkinson A, Harding C, Rawlings AV. Desmocollins: a key marker for desmosome processing in stratum corneum. J Invest Dermatol 1996; 106:872.
74. Van Overloop L, Declercq L, Maes D. Visual scaling of human skin correlates to decreased ceramide levels and decreased stratum corneum protease activity. J Invest Dermatol 2001; 117:811.
75. Kawai E, Kohno Y, Ogawa K, et al. Can inorganic powders provide any biological benefit in stratum corneum while residing on the skin surface. 22nd IFSCC Congress Edinburgh P10, 2002.
76. Fulmer AW, Kramer GJ. Stratum corneum lipid abnormalities in surfactant-induced scaly skin. J Invest Dermatol 1986; 86:598–602.
77. Saint-Leger D, Francois AM, Leveque JL, Stoudemayer TJ, Kligman AM, Grove G. Stratum corneum lipids in skin xerosis. Dermatologica 1989; 178:151–155.
78. Chopart M, Castiel-Higounenc C, Arbey E. Quantitative analysis of ceramides in stratum corneum of normal and dry skin. Stratum Corneum 2001; III.
79. Imokawa G. Ceramides as natural moisturizing factors and their efficacy in dry skin. In: Leyden JJ, ed. Skin Moisturization. New York NY: Marcel Dekker 2002:267–302.
80. Schreiner V, Gooris GS, Pfeiffer S, et al. Barrier characteristics of different human skin types investigated with x-ray diffraction, lipid analysis and electron microscopy imaging. J Invest Dermatol 2000; 114:600–654.
81. Tezuka T. Electron microscopical changes in xerotic senilis epidermis. Its abnormal membrane coating granule formation. Dermatologica 1983; 166:57.
82. Matts PJ, Goodyer E. A new instrument to measure the mechanical properties of human skin in vivo. J Cosmet Sci 1998; 49:321–333.
83. Matts PJ. In: Elsner P, Beradesca E, Wilhem KP, Maibach HI, eds. Hardware and Measurement Principles: the Gas-Bearing Electrodynamometer and Linear Skin Rheometer, in Bioengineering of the Skin: Skin Biomechanics. Boca Raton: CRC Press, 2002.
84. Cooper ER, Missel PJ, Hannon DP, Albright GB. Mechanical properties of dry, normal and glycerol-treated skin as measured by the gas-bearing electrodynamometer. J Cosmet Sci 1985; 36:335–348.
85. Christensen MS, Hargens CW, III, Nacht S, Gans EH. Viscoelastic properties of intact human skin: instrumentation, hydration effects, and the contribution of the stratum corneum. J Invest Dermatol 1977; 69:282–286.
86. Denda M, Wood LC, Emami S, et al. The epidermal hyperplasia associated with repeated barrier disruption by acetone treatment or tape stripping cannot be attributed to increased water loss. Arch Dermatol Res 1996; 288:230–238.
87. Kikuchi K, Kobayashi H, Hirao T, Ito A, Takahashi H, Tagami H. Improvement of mild inflammatory changes of the facial skin induced by winter environment with daily

applications of a moisturizing cream. A half-side test of biophysical skin parameters, cytokine expression pattern and the formation of cornified envelope. Dermatology 2003; 207:269–275.
88. Terui T, Hirao T, Sato Y, et al. A increased ration of interleukin-1 receptor antagonist to interleukin-1 in inflammatory skin diseases. Exp Dermatol 1998; 7:327–334.
89. Proksch E, Jensen J, Elias PM. Skin lipids and epidermal differentiation in atopic dermatitis. Clin Dermatol 2003; 21:134–144.
90. Proksch E, Feingold KR, Man MQ, Elias PM. Barrier function regulates epidermal DNA synthesis. J Clin Invest 1991; 87:1668–1673.
91. Angel P, Szabowski A. Function of AP-1 target genes in mesenchymal-epithelial cross-talk in skin. Biochem Pharmacol 2002; 64:949–956.
92. Rawlings AV, Canestrari DA, Dobkowski B. Moisturizer technology versus clinical performance. Dermatol Ther 2004; 17:49–56.
93. Mattai J, Froebe CL, Rhein LD, et al. Prevention of model stratum corneum lipid phase transitions in vitro bu cosmetic additives. J Soc Cosmet Chem 1993; 44:89–100.
94. Rawlings AV, Watkinson A, Hope J, Sabin C, Harding R. The effect of glycerol and humidity on desmosome degradation in stratum corneum. Arch Dermatol Res 1995; 287:457–464.
95. Hirao T, Takahashi M, Kikuchi K, et al. A novel non-invasive evaluation method of cornified envelope maturation in the stratum corneum provides new insight for skincare cosmetics. 22nd IFSCC Congress, Edinburgh. P51, (2002).
96. Fluhr JW, Gloor M, Lehmann L, et al. Glycerol accelerates recovery of barrier function in vivo. Acta Derm Venereol 1999; 79:418–421.
97. Rattner H. Dermatologic uses of urea. Acta Derm Venereol 1943; 37:155–165.
98. Fredrikkson T, Gip L. Urea creams in the treatment of dry skin & hand dermatitis. Int J Dermatol 1990; 14:442–444.
99. McCallion R, Po AL. Modelling TEWL under steady state conditions & relative humidities. Int J Pharm 1994; 105:103–112.
100. Loden M. Urea containing moisturisers influence barrier properties of normal skin. Arch Dermatol Res 1996; 288:103–107.
101. Pigatto PD, Bigardi AS, Cannistraci C, et al. 10% urea cream for atopic dermatitis. J Dermatol Treat 1996; 7:171–175.
102. Scott IR, Harding CR. A filasggrin analogue to increase natural moisturising factor synthesis in skin. Dermatology 2000; 773:1993.
103. Kwoyo Hakko Kogyo. Pyrroliodone carboxylic acid esters compositions to prevent loss of moisture from the skin. Patent JA 4882046, 1982.
104. Org Santerre. Pyrolidone carboxylic acid sugar compounds as rehydrating ingredients in cosmetics. Patent FR 2277823, 1977.
105. Clar EJ, Foutanier A. L'acide pyrrolidone carboxylique et la peau. J Cosmet Sci 1981; 3:101–113.
106. Middelton JD, Roberts ME. Effects of a skin cream containing the sodium salts of pyrrolidone carboxylic acid on dry & flaky skin. J Soc Cosmet Chem 1978; 29:201–205.
107. Ghadially R, Halkiersorenson L, Elias PM. Effects of petrolatum on stratum corneum structure & function. J Am Acad Dermatol 1992; 26:387–396.
108. Barany E, Lindberg M, Loden M. Unexpected skin barrier influence from non-ionic emulsifiers. Int J Pharm 2000; 195:189–195.
109. Kucharekova M, Schalkwijk J, Van De Kerkhof PC, Van De Valk PG. Effect of a lipid-rich emollient. Contact Dermatitis 2002; 46:331–338.
110. De Paepe K, Roseeuw D, Rogiers V. Repair of acetone- and sodium lauryl sulphate-damaged human skin barrier function using topically applied emulsions containing barrier lipids. JEADV 2002; 16:587–594.
111. Berardesca E, Barbareschi M, Veraldi S, Pimpinelli N. Evaluation of efficacy of a skin lipid mixture in patients with irritant contact dermatitis, allergic contact dermatitis or atopic dermatitis: a multicenter study. Contact Dermatitis 2001; 45:280–285.

112. Chamlin SL, Kao J, Frieden IJ, 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.
113. Wollenweber U, Korevaar K, Rawlings AV, Schick. Application of a skin-identical lipid concentrate for enhanced skin moisturization and protection. SOFW-J 2004; 130:9.
114. Summers RS, Summers B, Chandar P, Feinberg C, Gurskey R, Rawlings AV. The effect of lipids with and without humectant on skin xerosis. J Soc Cosmet Chem 1996; 47:27–39.
115. Leveque JL, Saint-Leger D. Salicylic acid and derivatives. In: Leyden JJ, Rawlings AV, eds. Skin Moisturization. New York NY: Marcel Dekker 2002:353–364.
116. Fartasch M, Teal J, Menon GK. Mode of action of glycolic acid on human stratum corneum: ultrastructural and functional evaluation of the epidermal barrier. Arch Dermatol Res 1997; 289:404–409.
117. Bowser P, Evenson A, Rawlings AV. Cosmetic composition containing a lipid and a hydroxyl or ketcarboxylic acid. EP0587288B1.
118. Rawlings AV, Davies A, Carlomusto M, et al. Effect of lactic acid isomers on keratinocyte ceramide synthesis, stratum corneum lipid levels and stratum corneum barrier function. Arch Derm Res 1996; 288:383–390.
119. Rawlings AV, Hope J, Ackerman C, Banks J. Hydroxycaprylic acid improves stratum corneum extensibility at low relative humidity and protects desmosomes against mechanical damage. IFSCC Congress, Yokohama, 1992: P1.
120. Johnson AW. Hydroxyacids. In: Leyden AV, Rawlings JJ, eds. Skin Moisturization, 2002:323–352.
121. Berardesca E, et al. Alpha hydroxy acids modulate stratum corneum barrier function. Br J Dermatol 1997; 137:934.
122. Hanley K, Jiang Y, He SS, et al. Keratinocyte differentiation is stimulated by activators of the nuclear receptor PPAR alpha. J Invest Dermatol 1998; 110:368–375.
123. Westergaard M, Henningsen J, Svendsen ML, et al. Maodulators of keratinocyte gene expression and differentiation by PPAR selective ligand tetradecylthioacetic acid. J Invest Dermatol 2001; 116:702–712.
124. River M, Castiel I, Safonova I, Ailhaud G, Michel S. Peroxisome proliferator-activated receptor-alpha enhances lipid metabolism in a skin equivalent model. J Invest Dermatol 2000; 114:687–691.
125. Alaluf S, Barrett KE, Green MR, Ottey A, Rawlings AV. A cosmetic composition for treating aged wrinkled skin through topical application of a composition containing petroselenic acid. US6042841.
126. Alaluf S, Rawlings AV. A topical composition comprising from petroselenic acid and conjugated linoleic acid. US6423325.
127. Lee R, Paterson S, Marti V, Ginger R, Watkinson A, Rawlings AV. Peroxisome proliferator activated receptor alpha activators: Petroselenic acid as a novel skin benefit agent for antiperspirants. 22nd IFSCC Congress, Edinburgh P11 (2002).
128. Wiechers JW, Rawlings AV, Garcia C, et al. A new mechanism of action for skin whitening agents: binding to the peroxisome proliferator activated receptor. Int J Cosmet Sci 2005; 27:123–132.
129. Mao-Qiang M, Feingold KR, Elias PM. Exogenous lipids influence permeability barrier function. Arch Dermatol 1993; 129:729–738.
130. Chamlin SL, Frieden IJ, Fowler A, et al. Optimization of physiological lipid mixtures for barrier repair. J Invest Dermatol 1996; 106:1096–1101.
131. Haratake A, Ikenaga K, Katoh N, Uchiwa H, Hirano S, Yasuho H. Topical mevalonic acid stimulates de novo cholesterol biosynthesis and epidermal permeability barrier homeostasis in aged mice. J Invest Dermatol 2000; 114:247–252.
132. Rawlings AV, Davies A, Carlomusto M, et al. Effect of lactic acid isomers on keratinocyte ceramide synthesis, stratum corneum lipid levels and stratum corneum barrier function. Arch Derm Res 1996; 288:383–390.

133. Matts PJ, Oblong JE, Bissett DL. A review of the range of effects of niacinamide in human skin. IFSCC Mag 2002; 5:285–290.
134. Tanno O, Ota Y, Hikima R, Matsumoto M, Ota, M, Inoue S. An increase in Endogenous Epidermal Lipids Improves Skin Barrier Function. 20th IFSCC International Congress. P 347–358 (2000).
135. Ertel KD, Berge CA, Mercurio MG, et al. New facial moistuizer technology increase exfoliation without compromising barrier function. 58th Annual meeting of the American Academy Of Dermatology, San Francisco (2000).
136. Draelos ZD, Ertel E, Berge C, et al. A facial moisturizing product as an adjunct in the treatment of rosacea. 59th Annual meeting of the American Academy Of Dermatology, San Francisco (2001).
137. Davies A, Verdejo P, Feinberg C, Rawlings AV. Increased stratum corneum ceramide levels and improved barrier function following treatment with tetraacetylphytosphingosine. J Invest Dermatol 1996; 106:918.
138. Conti A, Rogers P, Verdejo P, Harding CR, Rawlings AV. Seasonal influences on stratum corneum ceramide 1 fatty acids and the influence of topical essential fatty acids. Int J Cos Sci 1996; 18:1–12.
139. Msika P, Piccirilli A, Chesne C. Effects of two specific lipidic ingredients on the synthesis of epidermal lipids in human skin explants in culture. 21st IFSCC Congress, Berlin. P1-5 (2000).
140. Denda M. New stategies to improve skin barrier homeostasis. Ad Drug Del Rev 2002; 54:123–130.
141. The effect of thiols on epidermal lipid biosynthesis. Zhang K, Kosturko K, Rawlings AV. Annual Meeting Of Society For Investigative Dermatology, Chicago, USA, 1995. J Invest Dermatol 1995; 104:687.
142. Uchida Y, Behne M, Quice D, et al. Vitamin C stimulates sphingolipid production and markers of barrier formation in submerged human keratinocyte cultures. J Invest Dermatol 2001; 117:1307–1313.
143. Yarosh DB, Both D, Brown D. Liposomal ursolic acid (merotaine) increases ceramides and collagen in human skin. Horm Res 2000; 54:318–321.
144. Matts PJ, Gray J, Rawlings AV. In: The 'Dryskin Cycle'-A New Model of Dry Skin & Mechanisms for Intervention, Vol. 256. London: The Royal Society Of Medicine Press International congress & symposium series, 2005:1–38.

7
Factors Influencing Optimal Skin Care and Product Selection

James Q. Del Rosso
Department of Dermatology, University of Nevada School of Medicine, Las Vegas, Nevada, U.S.A.

Due to consistent marketing influences promoting multiple products that claim "removal of fine lines, wrinkles, and age spots," consumer demand for products that provide a "fresh look and a more youthful appearance," television and written advertising media campaigns promoting individual product lines, and the myriad of products available for the consumer to choose from, it is not surprising that patients are confused about which products to use for their skin and how to use them. Despite the high level of confusing "white noise" created by media and advertising promotions, optimal skin care is not rocket science! Based on a few basic principles and knowledge of appropriate product formulation, the dermatologist or designated skin care professional is trained to match a sound skin care regimen with the needs of the individual patient.

Prior to product selection, skin type characteristics, history of previous skin sensitivities or allergies, presence of underlying skin disorders, current skin care regimen, and medication history need to be evaluated. A thorough understanding of skin care product formulations and their differentiating features affords the clinician greater knowledge, confidence, and flexibility when recommending products and designing a skin care regimen for patients.

Unfortunately, the value of basic skin care practices such as cleansing and moisturizer use as a component of the management of dermatologic disorders has taken a back seat due to the strong emphasis on management with pharmacologic agents. Greater attention to basic skin care products and procedures, and maintenance of epidermal barrier function, may provide additive therapeutic benefit for patients. The following chapter emphasizes the core significance of maintaining epidermal barrier integrity. The basic fundamentals of optimal skin care, gentle cleansing and moisturization, and their intimate correlation with product formulation and selection are discussed.

BASIC SKIN CARE PROCESSES

Proper skin cleansing and moisturization are the two basic processes that must work in harmony to maintain overall skin health and epidermal barrier integrity (1,2). The role of

skin cleansing is to remove external debris, cutaneous secretions, and microorganisms. In addition, the integrity of the epidermal barrier must be consistently maintained to allow for cutaneous homeostasis as the presence of proper skin water content is mandatory for enzymatic functions required for lipid synthesis and barrier restoration. Therefore, moisturization is a vital component of "routine maintenance" of the outer skin barrier. This is especially true in conditions where epidermal barrier dysfunction and reduced epidermal water content are present. Examples of such conditions include low ambient humidity, xerotic skin disorders such as atopic dermatitis, genedermatoses such as ichthyosis vulgaris, underlying systemic disease states such as hypothyroidism and diabetes mellitus, use of skin care products that produce significant epidermal barrier damage such as harsh soaps and cleansers or astringents, and some topical medications such as topical retinoids (3–5).

The plethora of cleanser and moisturizer products available make it difficult for both professionals and consumers when faced with the question, "Which products should be used?" The bottom line is to maintain a "simplest is best approach," especially as many product claims, special ingredients, and heavily promoted "designer" products are substantiated by little to no scientific evidence supporting their purported benefits and high expense (1,2,5,6).

THE EPIDERMAL BARRIER AND WATER CONTENT

Normal skin appearance, water balance, and continued barrier integrity necessitate an intact epidermal barrier with maintenance of the proper water content required for physiologic and enzymatic functions. As the epidermis is a living dynamic unit, several physiologic functions continue as an ongoing process, with perturbations of barrier integrity requiring necessary adjustments and repairs before the epidermal barrier can return to its normally functioning physiologic state. The epidermal barrier is comprised of two components which work in concert to assure barrier integrity through functions such as maintenance of proper epidermal water balance, physiologic stratum corneum water content (20–35%), optimal lipid synthesis, limitation of transepidermal water loss (TEWL), and orderly corneocyte desquamation (1–4). The first component of the epidermal barrier, the *cellular matrix,* is comprised of a staggered and layered lattice of keratinocytes, referred to as the "bricks." In its uppermost layer, the flattened stratum corneum cells are referred to as corneocytes. The second component of the epidermal barrier, the *intercellular lipid bilayer matrix,* surrounds the keratinocytes, and is referred to as the "mortar" (1–3). Disturbances of these epidermal barrier components, associated with a variety of causes such as use of harsh soaps or underlying "sensitive skin" disorders such as atopic dermatitis or rosacea, enhance TEWL, which can lead to xerotic skin changes. When increased TEWL produces a reduction in stratum corneum water content to below 10%, this marked loss of epidermal barrier integrity is visibly expressed as dryness, scaling, roughness, and fine fissuring, the clinical features of xerosis (2,3,6–8).

The epidermis is in constant flux as keratinocytes traverse from the basal layer, later flattening as they pass upward into the stratum corneum, leading ultimately to surface shedding, or corneocyte desquamation. As referred to above, under normal circumstances, adequate water content allows for enzymatic degradation of the attachments between corneocytes (corneodesmosomes), allowing for the physiologic separation and shedding of superficial corneocytes. Corneocyte moisture content is maintained by a collection of diverse intracellular hygroscopic compounds which have been collectively termed "natural moisturizing factor" (NMF). The components of NMF include filaggrin-derived

amino acids, pyrrolidone carboxylic acid, lactate, sugars, and several electrolytes (1–3,5). Under abnormal conditions associated with xerosis, corneodesmosomes are not readily deagraded, leading to clumping of corneocytes. The visible expressions of clumped corneocytes with impaired desquamation are flaking and scaling (1–3,5,8,9).

EPIDERMAL BARRIER INTEGRITY, FUNCTION, AND REPAIR

A pivotal component of epidermal barrier formation is the synthesis within nucleated keratinocytes of the intercellular lipid bilayer, a functional permeability barrier composed of specific lipids present in proper ratio. Epidermal barrier lipids are autonomous from lipids circulating in the bloodstream and are composed predominantly of equimolar concentrations of free fatty acids, cholesterol, and ceramides (1–3,5,10–12). Within lamellar bodies (Odland bodies) located within keratinocytes of the upper epidermis, precursor epidermal lipids are used to create newly synthesized lipids which are organized into a lipid bilayer referred to as the lamellar unit membrane structure (1,10–17). Ultimately, as cornification occurs in the upper epidermis, a phospholipid-enriched plasma membrane is converted to a ceramide-rich bilayered membrane by weight (1,8,17).

The intercellular lipid bilayer matrix ("the mortar") functions to control intercellular water movement, maintain intracellular water content, and limit TEWL. The major homeostatic signal stimulating epidermal lipid synthesis is an adverse change in epidermal barrier status, sensed as an increase in TEWL. In the presence of exogenous (i.e., use of a harsh soap) or endogenous (i.e., underlying dermatologic disease) insults that cause a loss in barrier lipids which comprise the intercellular matrix, an increased TEWL of as little as 1% produces a physiologic signal that upregulates lipid synthesis (1–3,5). Depending upon the degree of barrier insult and several other factors, normalization of barrier function may occur over a period of hours to days (1,15,17).

IMPACT OF EXOGENOUS MOISTURIZATION ON BARRIER REPAIR

In a state of epidermal barrier disruption characterized by increased TEWL and reduced epidermal water content, a properly formulated moisturizer can act in a manner similar to endogenous epidermal lipids in promoting and restoring epidermal barrier function (1–3,13–24). Lipids applied externally in moisturizer formulations intercalate between corneocytes and have been shown to reduce surfactant-induced skin irritation (15–18). The use of nonphysiologic lipids such as petrolatum initially restores barrier function by producing a diffuse hydrophobic interstitium. Importantly, physiologic lipids applied in moisturizers can be directly incorporated into barrier lipids and lamellar units and do not appear to downregulate physiologic lipid production in skin (16–18). However, it is vital that all three lipid components (ceramide, cholesterol, free fatty acids) be incorporated in moisturizer formulations in optimized concentrations in order to avoid impairment of barrier recovery (16,17).

CLINICAL IMPLICATIONS OF EXOGENOUS MOISTURIZATION

In a clinical study of adult and pediatric patients treated for atopic dermatitis twice daily over a three-week period with a low-potency topical steroid lotion, with or without a moisturizer cream, both regimens exhibited consistent reductions in signs and symptoms

of disease, although greater improvement was noted at treated sites where moisturizer was also used (25). Importantly, patients recognized the therapeutic benefit of moisturizer use as a component of the combination regimen with preference for the combination reported by 96% of patients.

The significance of repeated application of externally applied moisturizers should not be underemphasized. Factors such as the inherent limitations of product substantivity related to formulation characteristics, superficial loss of applied product due to external "wear and tear" effects prior to thorough skin penetration, and the natural consequence of continual corneocyte shedding mandate that repetitive moisturizer application on a daily basis is required for maintenance of barrier function and repair (3,19). In addition, individual moisturizers may vary in the persistence of their moisturizing properties after discontinuation of application based on regression phase analysis studies (20,24).

COMPONENTS OF MOISTURIZER FORMULATIONS

Whether or not a moisturizer formulation "makes it in the real world" is ultimately dependent on recognizable efficacy, cosmetic acceptability, and patient preference. It is important to recognize that the term *moisturizer* does not imply that moisture (water) is being added to the skin. A properly formulated moisturizer contains *occlusive*, *humectant*, and *emollient* ingredients that are ultimately formulated to produce an effective product that is also cosmetically elegant (1–5,8,17,26). Occlusive and humectant ingredients work in a complimentary fashion to maintain epidermal water content and barrier function. Occlusive agents retard water loss via evaporation by forming a hydrophobic film on the skin surface and within the stratum corneum interstitum. Humectant compounds attract water "from the inside out," that is, from the dermis with passage into the upper epidermis (3–5,8,17). Emollients include a wide spectrum of compounds ranging from esters to long-chain alcohols which function to fill "the fine cracks and crevices" between corneocytes in the upper stratum corneum; specific emollients are often incorporated into formulations to enhance efficacy and improve cosmetic elegance by providing a smooth, soft texture to the cutaneous surface (2–5).

BALANCING EFFECTS AND COSMETIC ELEGANCE OF PRODUCT COMPONENTS

The greasiness of occlusive agents such as petrolatum and lanolin can limit their clinical usefulness due to lack of cosmetic elegance (2–5). For example, odor and potential allergenicity may limit the use of lanolin. Although mineral oil demonstrates less capability to reduce TEWL as compared to some other occlusive agents, it is a popular formulation component due to its favorable texture and easy spreadability (5). Silicone derivatives are also popular formulation ingredients as they may serve both occlusive and emollient functions, do not impart a greasy feel to the skin, exhibit a barrier protectant effect that is often incorporated into "hand creams," and are used in combination with petrolatum to achieve greater cosmetic acceptability by reducing the greasiness of the overall product texture (2,5).

Most effective formulations which enhance skin moisturization include humectant agents, such as glycerin, hyaluronic acid, urea, ammonium lactate, and panthenol, which serve to attract water from the dermis into the epidermis, with some humectants also imparting emolliency (1–5). In order to prevent exacerbation of TEWL, a humectant agent

should always be combined with an occlusive ingredient. For example, skin application of glycerin alone without an accompanying occlusive agent results in a significant increase in TEWL (29%) (2,3,5). As referred to above, although emollients may vary in their inherent moisturization and barrier maintenance properties, the elegant characteristics they impart to the overall product may be appreciated by the user after product application and often relate directly to consumer product preference (5).

FORMULATION CHARACTERISTICS

Most moisturizers are formulated as creams (water-in-oil emulsion) or lotions (oil-in-water emulsion) (1,2,8,13). The "heaviness" of the final formulation correlates with the inclusion and relative concentration of heavier occlusive agents such as petrolatum and lanolin derivatives, the inherent qualities of individual emollients and humectants that may be included in some products, and the oil-water ratio (5). Night creams are examples of products that are specifically designed to be heavier formulations. Specific ingredients are often combined in formulations to correlate with use for individual "skin types" such as dry, normal, or oily complexions. This is achieved by altering the heaviness characteristic of the occlusive agent used through selection of specific emollients that may be either protective, fatting, dry, or astringent in their inherent quality, and through adjustment of oil-water ratios. Examples of ingredient adjustments designed to correlate with use in specific skin types include dimethicone, a non-greasy, noncomedogenic emollient agent used in "oil free" facial moisturizers marketed for individuals with "oily skin" or inclusion of oil-absorbent compounds such as kaolin or talc, added to formulations to reduce "facial shine" by absorbing excess sebum (5).

SPECIAL ADDITIVES AND INGREDIENTS

Special ingredients may be added to basic moisturizer formulations to create "targeted moisturizer products" (1–3). Alpha-hydroxy acids, such as glycolic acid and lactic acid, have been added to many formulations to create exfoliant moisturizers, often marketed as anti-aging preparations (2,3,5). In order to reduce associated irritation, reduction in concentration or use of neutralizing additives (buffering) is common. However, as clinical efficacy correlates with availability of free acid, neutralization to a $pH > 4.8$ results in loss of efficacy (2,3,5). Retinol (vitamin A) and retinyl palmitate are added to some anti-aging moisturizer preparations to improve photodamage by decreasing fine wrinkling and tactile roughness. Both are inactive "precursor retinoids," requiring enzymatic conversions to produce retinoic acid from retinol; it is believed that the extent of retinol conversion to retinoic acid in skin is limited (2,3,5). Niacinamide (nicotinamide) is stable and compatible in moisturizer preparations due to its high water solubility, appears to produce an exfoliant effect, and may have anti-aging characteristics (5). The role of niacinamide in prevention of photocarcinogenesis and promotion of antineoplastic changes in keratinocytes in murine skin models is of considerable interest and is currently a focus of additional research (5,27,28). The addition of effective sunblock or sunscreen agents to moisturizer formulations is significant as photoprotection is important in the maintainance of epidermal integrity, dermal infrastructure and support, avoidance of small vessel damage and formation of telangiectasia, prevention of photocarcinogenesis, and reduction in pigmentation irregularities. Combination moisturizer-sunscreen formulations may

enhance compliance as both are applied together, usually early in the day, in a "one step" process.

THE SIGNIFICANCE OF GENTLE SKIN CLEANSING

The goal of an effective cleanser is to encompass, loosen, and promote easy removal of accumulated surface cutaneous debris, inclusive of natural skin secretions (i.e., sebum, desquamating corneocytes), dirt, microorganisms, and externally applied products (i.e., cosmetics, skin care products, medication residue) (6,29,30). As cleansing is a regular "daily ritual" for many cultures, the choice of an effective and nonirritating cleanser is significant. Cleansers containing irritant or abrasive components may enhance loss of epidermal integrity and barrier function. Improper or aggressve cleansing and overbathing are common causes of epidermal insult, irritation, and xerosis (4,6,29–31).

BASIC CLEANSER FORMULATIONS

Soap is created by a heating process called saponification; an alkali and a long-chain fat compound are combined, producing a fatty acid salt which exhibits detergent properties (6). A surfactant effect from usage of a soap reduces surface tension between water and surface debris, allowing for separation and removal by a lathering effect. A major difficulty with basic soap formulation is a pH of >7 (usually pH 9–10); the normal pH of skin ranges between 4.5–6.5 (6). The use of true soaps commonly leads to unacceptable dryness and irritation.

The development of soap-free synthetic detergent ("syndet") bars and non-lipid liquid cleansers has significantly improved the cosmetic acceptability and tolerability of skin cleanser formulations (6,29). Syndet bars are efficacious cleansers formulations, effectively limit damage to the epidermal barrier, and are widely accepted and very popular in the marketplace (6,30). These formulations are comprised of $<10\%$ soap and sustain an adjusted pH of 5.5–7 by utilizing synthetic detergents ("syndets") and filler substances that are associated with effective cleansing and little to no irritation (6). Lipid-free liquid formulations are also effective cleansers which may create a thin moisturizing film and produce little to no irritation in patients with normal, sensitive, photoaged, or diseased skin (6). They are also effective in the removal of cosmetics and makeup. Major components of non-lipid liquid cleansers include water, cetyl alcohol, stearyl alcohol, and glycerin (6).

The terms *gentle* or *mild* do imply that irritation is significantly minimized or absent due to the combination of ingredients and adjusted pH of the formulation, and do not imply a lack of efficacy. Several studies support the efficacy, high degree of patient preference, and lack of irritation associated with use of syndet bars and non-lipid liquid cleansers (6,31). Some combination bars ("combars") utilize additives to improve the "feel" of the formulation and reduce dryness through creation of a superfatted soap or by addition of humectants (i.e., glycerin). However, these formulations usually sustain an alkaline pH >9, and some tend to dissolve rapidly during usage (6).

CONCLUSION

The primary goals of skin cleansing and moisturization are to sustain overall skin health and appearance by maintaining epidermal barrier integrity. This is achieved by selecting

products that are formulated to preserve retention of water content, limit damage to epidermal lipids and proteins, minimize TEWL, and contribute to barrier repair during episodes of compromise. Optimal product selection is based primarily upon the inherent qualities of the formulation, correlated with the needs and skin type characteristics of the individual patient. Ultimately, effective products are well designed with regard to their fundamental skin care characteristics and not dependent on multiple special additives that are included based on marketing trends rather than scientific validity.

REFERENCES

1. Johnson AW. The skin moisturizer marketplace. In: Leyden JJ, Rawlings AV, eds. Skin Moisturization. New York: Marcel Dekker, 2002:1–30.
2. Draelos ZD. Therapeutic moisturizers. Dermatol Clin 2000; 18:597–607.
3. Flynn TC, Petros J, Clark RE, et al. Dry skin and moisturizers. Clin Dermatol 2001; 19:387–392.
4. Rawlings AV, Harding CR, Watkinson A, Scott IR. Dry and xerotic skin conditions. In: Leyden JJ, Rawlings AV, eds. Skin Moisturization. New York: Marcel Dekker, 2002:119–144.
5. Draelos ZD. Moisturizers. In: Draelos ZD, ed. Cosmetics in dermatology. 2nd ed. New York: Churchill-Livingstone, 1995:83–95.
6. Draelos ZD. Skin cleansers. In: Draelos ZD, ed. Cosmetics in Dermatology. 2nd ed. New York: Churchill-Livingstone, 1995:207–214.
7. Kirsner RS, Froehlich CW. Soaps and detergents: understanding their composition and effect. Ostomy/Wound Manage 1998; 44:62S–69S.
8. Wehr RF, Krochmal L. Considerations in selecting a moisturizer. Cutis 1987; 39:512–515.
9. Proksch E, Elias PM. Epidermal barrier in atopic dermatitis. In: Bieber T, Leung DYM, eds. Atopic Dermatitis. New York: Marcel Dekker, 2002:123–143.
10. Shurer NY, Plewig G, Elias PM. Stratum corneum lipid function. Dermatological 1991; 183:77–94.
11. Grubauer G, Feingold KR, Elias PM. The relationship of epidermal lipogenesis to cutaneous barrier function. J Lipid Res 1987; 28:746–752.
12. Yamamoto A, Serizawa S, Ito M, et al. Stratum corneum lipid abnormalities in atopic dermatitis. Arch Dermatol Res 1991; 283:219–223.
13. Jackson EM. Moisturizers: adjunct therapy and advising patients. Am J Contact Derm 1996; 7:247–251.
14. Imokawa G, Abe A, Jin Y, et al. Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? J Invest Dermatol 1991; 96:523–526.
15. Menon GK, Feingold KR, Elias PM. Lamellar body secretory response to barrier disruption. J Invest Dermatol 1992; 98:279–289.
16. Zettersten EM, Ghadially R, Feingold KR, et al. Optimal ratios of topical stratum corneum lipids improve barrier recovery in chronically aged skin. J Am Acad Dermatol 1997; 37:403–408.
17. Fluhr J, Holleran WM, Berardesca E. Clinical effects of emollients on skin. In: Leyden JJ, Rawlings AV, eds. Skin moisturization. New York: Marcel Dekker, 2002:223–243.
18. Mao-Qiang M, Brown BE, Wu-Pong S, et al. Exogenous non-physiologic vs physiologic lipids. Divergent mechanisms for correction of permeability barrier dysfunction. Arch Dermatol 1995; 131:809–816.
19. Tabata N, O'Goshi K, Zhen XY, et al. Biophysical assessment of persistent effects of moisturizers after daily applications: evaluation of corneotherapy. Dermatology 2000; 200:308–313.
20. Kligman A. Regression method for assessing the efficacy of moisturizers. Cosmet Toil 1978; 93:27–32.
21. Lazar AP, Lazar P. Skin, water, and lubrication. Dermatol Clinics 1991; 9:45–51.

22. Salka BA. Emollients. Cosmet Toil 1997; 112:101–106.
23. Loden M. Barrier recovery and influence of irritant stimuli in skin treated with a moisturizing cream. Contact Dermatitis 1997; 36:256–260.
24. Loden M, Andersson A-C, Lindberg M. Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizer cream. Br J Dermatol 1999; 140:264–267.
25. Hanifin JM, Hebert AA, Mays SR, et al. Effects of a low-potency corticosteroid lotion plus a moisturizing regimen in the treatment of atopic dermatitis. Curr Ther Res 1998; 59:227–233.
26. Presland RB, Jurevic RJ. Making sense of the epithelial barrier: what molecular biology and genetics tell us about the functions of oral mucosal and epidermal tissues. J Dental Ed 2002; 66:564–574.
27. Ludwig A, Dietel M, Schafer G, et al. Nicotinamide and nicotinamide analogues as antitumor promoters in mouse skin. Cancer Res 1990; 50:2470–2475.
28. Gensler HL. Prevention of photoimmunosuppression and photocarcinogenesis by topical niacinamide. Nutr Cancer 1997; 29:157–162.
29. Rawlings AV, Harding CR. Moisturization and skin barrier function. Dermatol Ther 2004; 17:43–48.
30. Rawlings AV, Canestrari DA, Dobkowski B. Moisturizer technology versus clinical performance. Dermatol Ther 2004; 17:49–56.
31. Del Rosso JQ. Understanding skin cleansers and moisturizers: the correlation of formulation science with the art of clinical use. Cosmet Dermatol 2003; 16:19–31.

8
Antiperspirants

John E. Wild
Hill Top Research, Miamiville, Ohio, U.S.A.

A. C. Lanzalaco and D. F. Swaile
P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

INTRODUCTION

Personal care has been a concern of both men and especially women since the beginning of recorded history and most likely prior to those times as well. The ancient Egyptians used perfumes while bathing and for their hair and clothing (1).

The art of making the body smell better was evident in the early civilizations of Babylon, Assyria, Persia, China, Greece, and Rome (2). Although this chapter topic is related to antiperspirants it is difficult to separate the fact that the antiperspirant market has grown to its sales level in the market place because an antiperspirant delivers not only wetness control but, as a secondary benefit, imparts deodorant efficacy as well.

History

While deodorizing or masking of unpleasant body odor has been in practice for much of recorded history, controlling underarm wetness has only become a personal care practice in the past 100 or so years. Underarm products began to appear in the market place in the United States in the late 19th century with the introduction of a product called MUM in 1888. At the dawn of the 20th century the first brand name antiperspirant appeared on the U.S. market as EverDry. It was followed in a few years by a product called Odo-RO-No (3). These early products lacked the aesthetic qualities of today's brands. Aluminum chloride solutions were wet and runny and had very little cosmetic appeal but managed to sell at a reasonable rate and therefore had enough potential for their manufacturers to keep them in the market. The greatest shortcomings of these products were their irritating effects on the skin and the damage they caused to clothing materials (3).

During the early part of the 20th century the antiperspirant market progressed slowly. Following World War II the antiperspirant market expanded very rapidly. The

technology advancements that occurred because of the war could now be applied to non-war related applications. The ball point pen led to the idea for roll-on applicators. Aerosolized packaging led to aerosol antiperspirants and deodorants.

Radio and, the most impactful communication system of our time, television provided a medium for commercial advertising that captured the attention of millions of consumers with both verbal and visual displays.

Manufacturers of antiperspirants and deodorants were quick to buy into TV advertising to extol the virtues of their new products. TV watchers were provided a daily barrage of how to control offensive body odor and underarm wetness. The fact that people themselves can experience their own odor and wetness, as well as notice these attributes in others, reinforced the commercial appeal of these products.

Antiperspirants and deodorants, which in earlier days had been formulated as creams and solutions, now became available in all types of product forms. There were pads, daubers, pump sprays, squeeze bottles, powders, stick creams, solids, roll-ons, and aerosols.

The aerosol market grew rapidly and created "family use" products that were an aesthetically as well as hygienically pleasing way of delivering the product. The aerosol market captured the greatest market share until late in the 1970s when the use of aerosols became severely impacted by the concerns for the atmospheric ozone layer depletion and the ultimate ban on chloroflurocarbon propellants for aerosols. New propellant technology has preserved the aerosol but the solid cream and gel sticks came to the forefront of the United States market in the 1980s and remain as a large market share of the current formulation market place.

ANTIPERSPIRANTS

Definition

An antiperspirant, as defined by the Department of Health and Human Services in the final antiperspirant monograph published in 2003, reads as follows:

"A drug product applied topically that reduces the production of perspiration (sweat) at that site" (4).

There has always been some confusion in the industry that consumers do not always relate to the basic difference between antiperspirant and deodorant products. Antiperspirants, because of their ability to reduce perspiration and thus diminish the medium that is a factor in the development of axillary odor, can also claim to be a deodorant. However, because a deodorant product only reduces the body odor and does not reduce perspiration it can only be labeled as a deodorant.

Delivering that message to the consumer has been difficult because of that dual capability of the antiperspirant product. This problem may have been more prevalent during the earlier history of these products than now. In the European market the problem continues as labeling allows products containing antiperspirant actives to be labeled as deodorants. More recently some manufacturers have begun marketing these products as antiperspirants within Europe and these have started to reduce deodorant market share. The United Kingdom was the only one of the European markets that was always open to the use of antiperspirants and now the remaining countries in the common market are showing greater market share with antiperspirants. Japan seems to categorize antiperspirants with deodorants and suggests that their mode of action is the reduction of body odor by way of suppression of perspiration.

Regulatory Status

The regulatory status of antiperspirants is somewhat different in various regions of the world market place.

United States

In the United States an antiperspirant is categorized as an over-the-counter (OTC) drug product and therefore subject to regulations by the Food and Drug Administration (FDA). In 1972 the FDA announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by an independent advisory panel. In 1978 the FDA announced the establishment of a monograph and notice of proposed rulemaking that would establish conditions under which OTC antiperspirants are generally recognized as safe and effective and not misbranded.

In 1982 the FDA issued a tentative final monograph for antiperspirants. In 1990 the FDA issued a rule that certain active ingredients which were used in antiperspirants are not generally recognized as safe and effective and are misbranded. Then in 2003 the FDA issued the final monograph for antiperspirant products. The final antiperspirant monograph became effective in December of 2004 and did not address foot antiperspirancy claims. In addition the monograph did not identify any OTC antiperspirant products to be effective in reducing problem or especially troublesome perspiration. However, there was no data submitted to support those claims. The agency remains open to those potential claims if data are submitted with individuals who perceive themselves to have problem perspiration (4).

European Union

In the European Common Market antiperspirants are considered to be cosmetic products and are therefore subject to the European Cosmetic Directive. The definition of a cosmetic product is "any substance or preparation intended to come in contact with the various surface areas of the body (epidermis, hair, and capillaries, nails, lips, and external genital organs) or with the teeth and buccal mucosae, solely or principally for cleansing, perfuming, or protective purposes in order to maintain them in good condition, modify their appearance, and/or improve body odor, and/or protect or maintain them in good order" (5).

The European Cosmetic Directive has three essential objectives: (i) to ensure consumer safety, (ii) to harmonize legislation between the different Member States of the European Union, and (iii) to respond to the consumer's need for information (5).

The overall impact of the Cosmetics Directive is to deliver safe products to the consumer. There is also the implication that the manufacturers should possess data that supports the product's efficacy. However, unlike the OTC monograph for antiperspirants which sets a minimum standard of 20% reduction in axillary perspiration for an antiperspirant, there is no minimum level of efficacy stipulated.

Japan

In Japan antiperspirant products are controlled under the system of the Ministry of Health and Welfare (MHW). The regulation governing them is Japan's Pharmaceutical Affairs Law (PAL). Antiperspirant products in Japan are regulated and classified as quasi-drugs. A quasi-drug is an article used only for certain purposes that are specifically designated by the MHW. Antiperspirants are categorized under body deodorant quasi-drugs based upon their indication of effects against body odor, perspiration odor, and suppression of

Table 1 Data Required in Applications for Approval of Cosmetics and Quasi-Drugs

Data required	Scope	Quasi-drug	Cosmetic
Origin, background of discovery; use in foreign countries	Origin and details of discovery	X	X
	Use in foreign countries	X	X
	Characteristics and comparison with other quasi-drugs or cosmetics	X	X
Physical and chemical properties, specifications, testing methods, etc.	Determination of structure	X	X
	Physical and chemical properties	X	X
	Specification and testing methods	X	X
Stability	Long term storage	X	
	Severe test	X	X
	Acceleration test	X	
Safety	Acute toxicity	X	X
	Subacute toxicity	X	[a]
	Chronic toxicity	[a]	NA
	Reproductive effects	[a]	NA
	Skin sensitization, photosensitization, etc.	X	X
	Mutagenicity	X	X
	Carcinogenicity	[a]	NA
	Skin irritation, mucosa irritation, etc.	X	X
	Absorption, distribution, metabolism, and excretion	X	X
Indications or effects	Laboratory tests supporting indications or effects	X	NA
	Use test in humans	X	NA

[a] May not be required under certain conditions.
Abbreviations: X, required; NA, not applicable.

perspiration (6). Quasi-drugs and cosmetics are clearly stipulated to be articles whose biological activities are gentle and mild. Table 1 presents a tabular summary of the data required in an application for approval of cosmetics and quasi-drugs.

The practical result of the U.S., EU, and Japanese regulatory control of antiperspirants is that to be in a global market place, such products require a high level of formulation and manufacturing expertise to ensure safety and efficacy.

ANTIPERSPIRANT EFFICACY

In the U.S. the FDA has included in the OTC Antiperspirant Final Monograph guidelines that the manufacturer may use in testing for effectiveness. The agency does not require that these guidelines be used but requests that alternate methods and statistical evaluations are subject to FDA approval (4).

The FDA has established in the monograph the minimum standard for effectiveness at 20% sweat reduction to allow a product to be labeled as an antiperspirant. There are no guidelines suggested in the European Cosmetics Directive, however, because there are

many publications on this topic concerning antiperspirant efficacy, and techniques for proving efficacy are well known and readily available in the testing market place.

In Japan, Tagami indicates that the MHW does not specify in the PAL any specific standard test methodology for evaluating the clinical effects of quasi-drugs. It only makes reference to the use of a clinical use test in humans, under conditions simulating actual daily usage, for supplying data to assess the effects and safety of such products (6).

Recommended and Approved Uses

The antiperspirant monograph provides very specific labeling requirements for an antiperspirant drug product as follows:

1. A statement that the product be identified as an antiperspirant and that the product contains a drug identified by its established name, if a drug is present.
2. Under a heading titled "uses" the following language may be used by selecting one of the following phrases: "decreases," "lessens," or reduces underarm: "dampness," "perspiration," "sweat," "sweating," or "wetness." Other language can be appended to the phrase if it is truthful and not a misleading statement describing an established use as follows: "decreases, lessens or reduces" underarm "dampness, perspiration, sweat, sweating or wetness due to stress." For products that demonstrate the minimum standard of 20% sweat reduction over a 24-hour period the label may state either "all day protection," "lasts all day," "lasts 24 hours," or "24-hour protection."

For products that demonstrate extra effectiveness of 30% sweat reduction the label may state "extra effective." In addition for products that demonstrate the extra effective reduction over a 24-hour period the language for the standard reduction may be used or combined with any one of these statements: "24-hour extra effective protection," "all day extra effective protection," "extra effective protection lasts 24 hours," or "extra effective protection lasts all day."

The product label must also contain the following items listed under "Warnings:"

"Do not use on broken skin."

"Stop use if rash or irritation occurs."

"Ask a doctor before use if you have kidney disease."

If the product is aerosolized:

"When using this product keep away from face and mouth to avoid breathing it."

The label must also contain the following under the heading of "Directions:"

"Apply to underarms only" (4).

The regulatory agencies in other countries have not been as specific in as many details as the FDA.

Function of Antiperspirants

Antiperspirant products are relatively unusual drug formulations. Unlike most drugs, their mechanism of action is physical rather than pharmacological. Figure 1 illustrates how the antiperspirant actives form a shallow plug near the opening of an eccrine sweat duct on the skin surface (7). These blockages prevent the eccrine excretion from reaching the skin surface in the axilla without creating a significant systemic effect on the thermal regulatory system. These blockages can remain within the sweat duct for seven to 14 days depending on the rate of skin desquamation, consumer's hygiene regime, activity type, and quality.

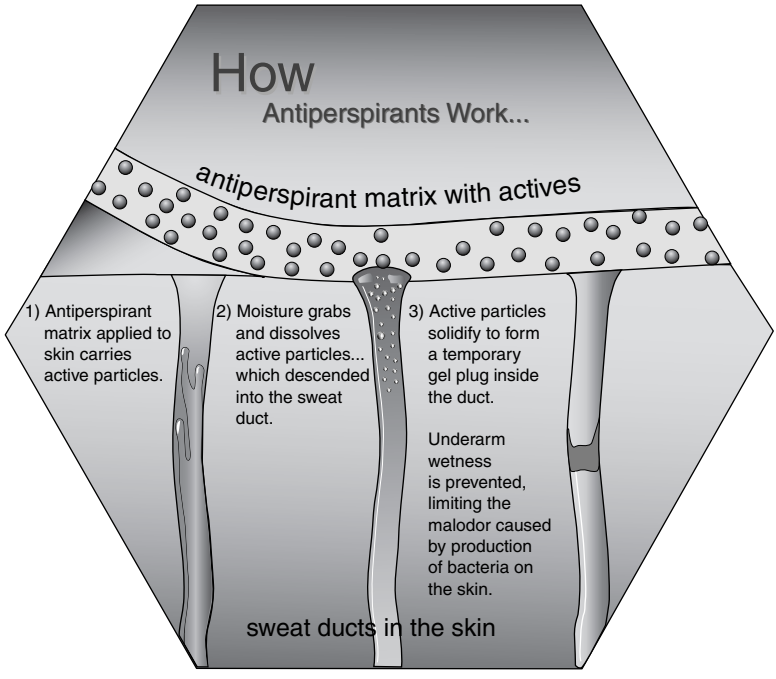

Figure 1 Graphic showing the formation of the shallow plug in the sweat duct demonstrating the mechanism of action for current antiperspirant products.

Function of Deodorants

Historically, there has been some confusion among the public when distinguishing between the benefits provided by commercial antiperspirant and deodorant products (8). While antiperspirants are designed to reduce both axillary sweating and malodor, deodorants provide only malodor control. The most effective deodorants are typically glycol-based products containing odor-masking fragrances. The use of a glycol base is especially effective as it augments the masking fragrance by providing microbial control of the odor causing bacteria (9). However, these products do not impact axillary sweating in any way.

In contrast, OTC antiperspirant products provide the dual benefits of axillary wetness and malodor control. Antiperspirants reduce malodor through a combinatorial effect that includes the microbial inhibition of the aluminum and zirconium salts; the deleterious effect on the odor causing bacterial ecosystem of a drier axillary vault and the ability of skin substantive antiperspirant products to extend the residence time of masking fragrances (10). For perspective, in a head-to-head clinical comparison, a fragrance-free aluminum zirconium tetrachlorohydrex glycine-containing antiperspirant was shown to be superior to a fragrance-free glycol-based deodorant at reducing axillary malodor (11).

FORMULATION

Approved Active Ingredients

The final OTC antiperspirant monograph itemized the 18 active ingredients that are approved for use in antiperspirant products in the U.S. Table 2 shows each of the approved

Table 2 Antiperspirant Active Ingredients

Active ingredient	Concentration	Dosage form
Aluminum chloride	Up to 15% (calculated on hexahydrate form)	Only aqueous solution (must be nonaerosol)
Aluminum chlorohydrate	Up to 25%	Aerosol or nonaerosol
Aluminum chlorohydrex polyethylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum chlorohydrex propylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum dichlorohydrate	Up to 25%	Aerosol or nonaerosol
Aluminum dichlorohydrex polyethylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum dichlorohydrex propylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum sesquichlorohydrate	Up to 25%	Aerosol or nonaerosol
Aluminum sesquichlorohydrex polyethylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum sesquichlorohydrex propylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum zirconium octachlorohydrate	Up to 20%	Nonaerosol
Aluminum zirconium octachlorohydrex gly	Up to 20%	Nonaerosol
Aluminum zirconium pentachlorohydrate	Up to 20%	Nonaerosol
Aluminum zirconium pentachlorohydrex gly	Up to 20%	Nonaerosol
Aluminum zirconium tetrachlorohydrate	Up to 20%	Nonaerosol
Aluminum zirconium tetrachlorohydrex gly	Up to 20%	Nonaerosol
Aluminum zirconium trichlorohydrate	Up to 20%	Nonaerosol
Aluminum zirconium trichlorohydrex gly	Up to 20%	Nonaerosol

ingredients, concentration limits, and dosage forms/types in which the approved active can be formulated.

There are no specific active ingredient lists specified by the EU or Japan.

Formulation Variations

As with all treatment programs, the key to achieving maximum benefit is compliance. Antiperspirant products can require up to 10 consecutive days to reach maximum efficacy and benefits can be completely eliminated within 14 days of treatment termination. Barriers to compliance are typically associated with products' aesthetics rather than skin irritation. Refer to Table 3 for details on formulation and compliance. Erythema and

Table 3 Formulation and Compliance

Product types	Active types	Carrier system	Barriers to compliance	Comments
Water-based roll-on	Aluminum chloride Aluminum chlorohydrate Aluminum zirconium tetrachlorohydrate gly	Water Oil in water Emulsion	Skin irritation (aluminum chloride) Wet sticky skin feel	Only form available with aluminum chloride in mass market
Powder-based roll-on	Aluminum zirconium tetrachlorohydrate gly	Anhydrous emollients	Wet skin feel at application	
Gels	Aluminum zirconium tetrachlorohydrate gly	Water in silicone emollient emulsion	Sticky skin feel	
Stick	Aluminum chlorohydrate Aluminum zirconium trichlorohydrate gly Aluminum zirconium tetrachlorohydrate gly	Silicone emollient system solidified with wax	White residue on skin and clothes	Most common product form in mass market
Creams	Aluminum zirconium trichlorohydrate gly Aluminum zirconium tetrachlorohydrate gly	Silicone emollient system thickened with wax	Skin feel at application	Generally the most efficacious form in mass market

stinging can still be common for products containing Aluminum Chloride and/or high levels of glycol or fragrance but are not common on most commercial antiperspirants. Unscented products based on the emollients cyclopentasiloxane and dimethicone have very good skin compatibility.

Most common barriers to compliance are associated with the skin feel of product, product appearance on skin, product transfer to clothes, and fragrance. Typically, consumers view antiperspirant application as part of their total grooming process and often create application behaviors that reduce product efficacy. Behaviors such as removing the product shortly after application, not applying the dose of product recommended by the manufacturer, or only applying it to a portion of the axilla will reduce efficacy. Encouraging consumers to identify a product form that allows them to comply with a daily application routine will maximize their observed benefit. Efficacy can further be improved by placing the user on a nighttime application to remove issues with the user's morning grooming routine. Night time application allows the active to enter the duct during a time of low sweating rates and allows for more efficient plug formation.

FORMULATING FOR THE CONSUMER

The approach taken by manufacturers to encourage compliance has been to offer a wide choice in product form and aesthetics. Today's consumers are accustomed to a variety of choices in their antiperspirant selection. It is clear, from even a cursory glance at the antiperspirant/deodorant shelves in any supermarket or pharmacy, that there is a wide range of aesthetic experiences acceptable to people. The desired experiences are delivered through a multitude of packaging presentations, both in size variation and product type. These include aerosol sprays, silicone/wax sticks, aqueous clear gels, and lotion-like creams. In addition, most antiperspirant brands provide a variety of fragrance options for their consumers. All of these variations cater to the consumer's demands for both gender and ethnic preferences. Manufacturers long ago discovered that people tend to gravitate to the form that they are most comfortable with, which in turn ensures compliance leading to effective axillary wetness control. Importantly, the drive to meet the consumer's demand for aesthetically appealing products applies globally to the antiperspirant market place.

INTRODUCING NEW ANTIPERSPIRANT ACTIVE FORMULATIONS

In the U.S. the introduction of any new antiperspirant actives into the market will require a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA). These procedures will no doubt inhibit bringing new actives into the market place unless there is a strong inclination by the manufacturer to believe their new active will bring a large return from the market place. The submission of an NDA or ANDA requires a major commitment of time and capital by the manufacturer. When consumers demand new and more effective products, industry will usually respond as long as there will be the hope for a return on its investment.

MEDICAL APPROACHES TO HYPERHIDROSIS

Hyperhidrosis is defined as excessive sweating. The profusion of sweat may be in the axillae, the palms, the feet, the face, on the trunk, or a combination of any or all of the above body parts. The excessive sweat is beyond the person's physiological requirement to regulate the body's temperature and is largely under emotional control (12).

In a culture where the personal hygiene and social standards are established to not emit unpleasant odors and/or exhibit underarm wetness, clammy skin, etc., a hyperhidrodic condition can be devastating in social environments. The condition can adversely affect the person's ability to attain a normal and healthy quality of life. Persons suffering with hyperhidrosis have reported both physical and emotional impairment and difficulty in their professional and social lives. Approximately 0.5% of the U.S. population suffers from axillary hyperhidrosis and report that their excessive sweating is barely tolerable to intolerable and interferes in some way with their daily activity (12,13).

Treatment

Antiperspirants

The treatment of hyperhidrosis with OTC antiperspirant products is usually the first method employed by those who suffer with this condition. There are no currently marketed

antiperspirants that are explicitly designed or claim to have a beneficial effect on excessive sweating. As stated earlier the FDA has not approved any marketed OTC antiperspirant product for an excessive sweating condition. In addition, all the currently marketed OTC antiperspirant products are explicitly labeled to be used only in the axilla and are not approved for any other body location. The FDA has, however, remained open to a claim for the treatment of excessive sweating if data are submitted for their review for this claim (12).

The currently marketed OTC antiperspirant products most likely offer only marginal effectiveness to those who suffer from hyperhidrosis. Because this condition is so socially devastating, a large number of those who suffer with hyperhidrosis seek the advice of a health professional (12,14).

There are prescription drug solutions available for those who seek medical treatment for their condition. These prescription products usually contain aluminum chloride concentrations greater than those which have been established as safe and effective in the final OTC antiperspirant monograph. These higher concentration products are usually recommended to be used at bedtime to allow for maximum absorption at a time when sweating may be at a minimum for the day. They are typically applied nightly for three nights under the occlusion of plastic wrap. The plastic wrap occlusion traps perspiration in the armpit and hydrates the skin enhancing penetration of the aluminum chloride solution, which increases efficacy. After this initial treatment period, the plastic wrap occlusion is discontinued and the aluminum chloride solution is only applied every other night for a week and then twice weekly for a week. Patients are advised to keep decreasing the frequency of aluminum chloride application until the minimum application frequency to maintain sweating control has been determined. Applications at this frequency are continued indefinitely as the aluminum chloride only decreases axillary sweating temporarily.

The higher concentrations of aluminum chloride can be more irritating to the skin than OTC antiperspirant products. These higher concentrations have also been known to be harmful to fabrics, and therefore caution should be used about clothing worn during treatment (12).

Other treatment options are also available to those who suffer with hyperhidrosis. These treatments include some of the following.

Iontophoresis

This procedure employs the use of weak electric current to slow down sweat production. It requires the purchase of a battery-operated device with a removal pad. The pad is soaked either with tap water or a dilute solution of aluminum chloride in tap water. The device is placed in the armpit and turned on for approximately 20–30 minutes. During this time, the low voltage electric current is used to drive the tap water with or without aluminum chloride into the duct of the eccrine sweat gland to create a plug. This plug prevents the release of the sweat into the armpit. Devices are also available for the palms of the hands and the soles of the feet.

The primary drawback to this technique is the time required to administer the treatments. With continued use, it is possible to cut back on the frequency or sessions from daily, to twice weekly, to once weekly. It is key to maintain the plug in the sweat duct for efficacy. Once the plug is gone, the previous rate of sweating will return. Unfortunately, iontophoresis can only decrease the amount of sweating, not stop it completely (12).

Endoscopic Thoracic Sympathectomy Surgery

Early surgical techniques that were used to treat hyperhidrosis were invasive, risky, scarring, and sometimes unsuccessful. Endoscopic thoracic sympathectomy (ETS) surgery

is less invasive, since it is performed with the aid of a small endoscope that is introduced into the body. This surgery is designed to interrupt the transmission of nerve signals to the sweat glands. This procedure carries with it the usual risks that can be encountered during surgery, such as nerve damage, as well as other side effects, such as chronic pain syndrome. The most notable of these side effects may be compensatory sweating, that is, increased sweating may occur at a new body location. In addition, the cut nerves may reconnect, rendering the procedure completely unsuccessful (12).

Prescription Medications

Anticholinergic drugs, such as Robinal, may help prevent the stimulation of the sweat glands and thus inhibit sweat output. The FDA has not approved any drug for the treatment of hyperhidrosis. Although these drugs may be effective in inhibiting excessive sweat, there are significant side effect risks with these medications. These include such effects as dry mouth, blurred vision, urine retention, constipation, impaired swallowing, taste, etc. Medications such as these are usually taken only for special occasions when sweat control is important. Most persons cannot tolerate the side effects on a daily basis (12).

Botulinum Toxin A Injections (Contributed by Zoe Diana Draelos, M.D.)

Botulinum toxin A (Botox, Allergan) is the most effective method of reducing axillary hyperhidrosis. It is classified as a method of chemodenervation, since it interrupts the nerve signal to sweat. As mentioned previously, axillary hyperhidrosis is largely under central control. The brain must send a signal to the nerves in the armpit to initiate sweating. If the nerve signal is never received by the sweat gland, sweating does not occur. This is how botulinum toxin works. Unfortunately, it cannot be applied to the skin surface, but must be injected with a small insulin syringe just beneath the skin surface where the sweat glands lie.

Botulinum toxin A treatment for hyperhidrosis is typically administered as a medical procedure in the office of a dermatologist. The armpit is first cleaned thoroughly to remove all sweat and antiperspirants. It is then painted with an iodine solution and dusted with cornstarch. The reaction between the sweat and iodine will turn the cornstarch black once perspiration has begun. An indelible marker is then used to draw a line around the area of maximum sweating. This is the location for the botulinum toxin A injections.

Once the area of maximum sweating has been determined, the botulinum toxin A is removed from the freezer, where it must be keep until just before use. The freeze-dried botulinum toxin bottle containing 100 units is then reconstituted with 2 cc of unpreserved sterile saline. Approximately 10 units are drawn up into 20 insulin syringes for injection with 10 syringes used in each armpit. The injections are made just under the skin surface to raise a tiny wheal at 2 cm intervals in a whirl configuration from the central armpit outward until the entire area outlined by the indelible marker has been injected. As might be imagined, this is a painful and tedious procedure.

Fortunately, the sweat reduction induced by the botulinum toxin A lasts for approximately six months, or longer in some individuals. The treatment does not completely eradicate axillary sweating, but significantly diminishes its amount. Any remaining sweating can usually be controlled with traditional nonprescription antiperspirants. Botulinum toxin A can also be injected into the hands and feet for purposes of sweat reduction.

Other Surgical Treatment Options

There are a variety of other treatment options that have been tried with limited documented success. These treatments include such surgeries as excision of sweat glands

and liposuction. It is very difficult to excise the sweat glands without creating movement problems in the armpit. The hair bearing skin typically denotes the location of the sweat glands in the armpit, but removal of this quantity of skin is both scarring and restrictive. A better alternative is liposuction. Liposuction can be performed under a form of local lidocaine anesthesia known as tumescent anesthesia. Here a dilute solution of water and lidocaine is introduced into the fat just below the armpit skin. The lidocaine provides pain relief and raises the armpit skin away from the underlying nerves and vessels that must not be damaged during surgery. A 2 mm opening is made in the armpit and a metal tube, known as a cannula, is inserted. The cannula has a cutting edge just below the tip and is vigorously pulled against the undersurface of the skin to intentionally damage and scar the sweat glands. The cannula is attached to a negative pressure vacuum suction device that collects the removed tissue and anesthesia. Tumescent liposuction of sweat glands is effective at reducing axillary sweat in some individuals.

REFERENCES

1. Miller J. The H & R Book of Perfume. London: Johnson, 1984.
2. Parisee AJ. Antiperspirants. In: Waggoner WC, ed. Clinical Safety and Efficacy Testing of Cosmetics. New York: Marcel Dekker, 1990:163–223.
3. Laken K. Introduction and History of Antiperspirants and Deodorants. In: Laden K, Felger CB, eds. Antiperspirants and Deodorants. New York: Marcel Dekker, 1988:1–13.
4. Federal Register, Antiperspirant Drug Products for Over-the-Counter Human Use. Final Monograph, Food and Drug Administration 21 CFR Parts 310, 350 and 369, U.S. Vol. 68. Rockville, Md: Department of Health and Human Services, 2003:34273–34293.
5. Masson, Ph. The Contribution of the European Cosmetic Directive Towards International Harmonization: Impact on the Evaluation of Safety and Efficacy. In: Elsner P, Merk HF, Maibach HI, eds. Cosmetics: Controlled Efficacy Studies and Regulations. Berlin: Springer, 1999:20–35.
6. Tagami H. Claim Support in Japan: Legal Aspects. In: Elsner P, Merk HF, Maibach HI, eds. Cosmetics: Controlled Efficacy Studies and Regulations. Berlin: Springer, 1999:36–49.
7. Swaile DF. Variation in efficacy of commercial antiperspirant products based on differences in active composition and manufacturing method. In: 61st Annual Meeting of the American Academy of Dermatology. San Francisco, CA: American Academy of Dermatology, March 21–26, 2003:P337.
8. Laden K. Preface. In antiperspirants and deodorants. 2nd ed. Revised and Expanded. New York: Marcel Dekker Inc, 1999: preface.
9. Karabit MS, Juneskans OT, Lundgren P. Studies on the evaluation of preservative efficacy. In the determination of antimicrobial characteristics of some pharmaceutical compounds in aqueous solutions. Int J Pharm 1989; 54:51–56.
10. Benohamian A. Antiperspirants and deodorants. Clin Dermatol 2001; 19:398–405.
11. Lanzalaco AC, Rocchetta M, Snyder M, Chabi G. In the absence of fragrance, both deodorants and antiperspirants show effective control of underarm odor. J Am Acad Dermatol 2005; 52:91.
12. Accessed May 2005 at http://sweathelp.org.
13. Lowe NJ, Glaser DA. Botulinum toxin type A in primary axillary hyperhidrosis. In: A 52-week, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Trial; 62nd Annual Meeting of the American Academy of Dermatology, Feb. 6–11, 2004:P195.
14. Kowalski JW, Eadie N, Dagget S, et al. Validity and reliability of the Hyperhidrosis Disease Severity Scale (HDSS). In: 62nd Annual Meeting of the American Academy of Dermatology. Washington, DC: American Academy of Dermatology, Feb. 6–11, 2004:P195.