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Common skin conditions and disorders

Skin biology, xerosis, barrier repair and measurement

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The skin is a key protective barrier from the environment for terrestrial mammals and is one in a continuous state of renewal and repair. Impairment of skin barrier function is often demonstrated by an altered integrity of the stratum corneum (SC) and a consequential increase in transepidermal water loss (TEWL). Skin barrier function impairment often arises from direct damage followed by a breach in the SC and/or a decrease in or dysfunction of SC lipids. The most common dermatological disorder is dry and flaky skin. This arises from direct damage to the SC with potential mechanical failure and from an impairment in SC cell (corneocyte) maturation and its desquamation together with a decrease in the water holding capacity of the SC. Dry and flaky skin is associated with a range of pathological and physiological abnormalities and can be treated with moisturizers, especially those which enhance SC barrier function. This paper gives a brief overview of the work conducted in this area of science over the past decade.

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Introduction

The raison d'etre of the skin of our body is to protect it (Fig. 1). The outermost layer of the skin, the stratum corneum (SC) tissue, is the most crucial because it is a constantly renewable physical barrier that protects the body from excessive water loss [1]. The SC is also a biosensor that facilitates other biological protection

strategies via a signalling between the SC, epidermis and deeper skin layers as well as by SC permeability changes in response to humidity changes and perception of external stimuli [2].

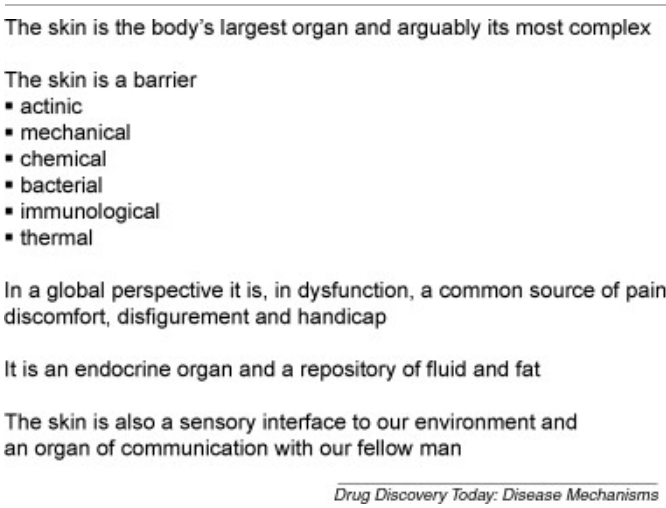

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Figure 1. The skin – a barrier and more.

A range of diseases can lead to impaired barrier function, and these are discussed in other articles within this series. Some examples of hereditary desquamatory (scaling) disorders associated with impaired barrier function include

(a) Autosomal dominant ichthyosis caused by a defect in a gene coding for profilaggrin, a protein important for producing hygroscopic amino acids in the SC [3, 4].

(b) X-linked recessive ichthyosis caused by a deficiency in steroid sulfates accumulates cholesterol sulfate thought to be involved in inhibition of SC desquamatory proteases and

(c) Nethertons Disease caused by a defect in the SPINK-5 gene, leading to aberrations [4] in the natural SC desquamatory protease inhibitors and consequent premature desquamation [4].

Heterozygosity or polymorphism at these same loci can result in more common 'forme fruste' disorders. An example is the common immune-mediated inflammatory dermatitis, atopic dermatitis through pathogenesis is more complex than the rare disorders above [5, 6]. Psoriasis is another example of an inflammatory disorder with complex genetic background in which skin barrier function is abnormal [4]. Dry scaly skin with its associated barrier and water holding capacity problems is, however, not just restricted to pathological states – it also occurs in the general population, especially the aged (Fig. 2) and in virtually all those living (and working) in low humidity climates [7, 8].

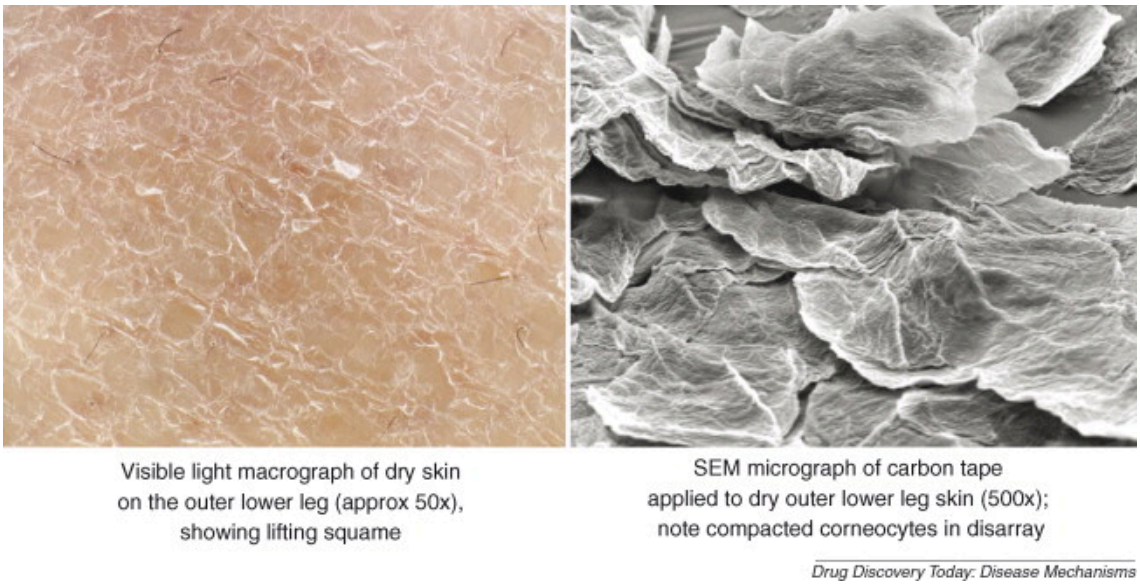

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Figure 2. Typical photographs of common dry skin.

Dry skin should be seen as not a single condition but rather as a spectrum of conditions. At one end, subclinical aberrations are only demonstrable by skin physiological techniques such as evaporimetry or capacitance. At the other end, there is physical evidence of abnormal dryness of the skin (xerosis) that might arise, for instance, from an increased blood flow (minimal erythema) due to inflammatory mediator release. Eczema, due to irritancy, erythema, oedema and more pronounced dyskeratotic features, are long-term consequences of poor barrier function [9]. The development of skin erythema can be mapped by laser Doppler flowmetry/imaging, colorimetry and polarisation spectroscopy and other methods [10].

Total failure of the SC barrier, as occurs in burns and/or in physical/chemical injury to the SC, can present a serious problem for survival, and the skin rapidly exerts its repair system to address such injuries. Such major barrier repair normally involves one or more of the wound healing stages of inflammation, proliferation/migration and maturation/remodelling. Lesser degrees of barrier perturbation are manifested by, and best, followed with evaporimetry to track changes in TEWL [10]. Excessive transepidermal water loss (TEWL) is of concern as a controlled amount TEWL through the tissue is needed so that the SC can bind water to facilitate a variety of anabolic and, especially, catabolic reactions to ensure its maturation and ultimate desquamation. Occlusion that reduces TEWL is known to exert down regulation of epidermal renewal. TEWL is increased in a variety of pathological and cosmetic conditions that have aberrant barrier function and dry scaly skin. Here, it is often the SC maturation and desquamation steps that are compromised, resulting in a loss in tissue homeostasis. Topical products used to hydrate the SC are called moisturizers, and contain emollients, humectants or occlusive agents. The development of more effective moisturisers should be based on an understanding of epidermal and SC biology, its self-repairing mechanisms, especially through barrier function and aberration of the enzyme-mediated lysis of corneodesmosomes in the SC (corneodesmolysis) and its disorders.

Stratum corneum biology

Fig. 3 shows a schematic of epidermal and SC biology. All SC lipids are important for barrier function of the skin but, owing 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 [11]. There are several types of ceramides and all are vital for the proper function of the epidermal barrier together with cholesterol and fatty acids. It is the lipid packing states, however, and not only the chemical structures of the SC lipids, that are important for barrier function [12]. 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 former represents the most tightly packed conformation, with optimal barrier properties, but a greater proportion of hexagonally packed lipid conformations is known to occur in the outer layers of the SC [12]. Electron microscopy studies have facilitated the tremendous understanding of the repeating patterns of the SC intercellular lipids. However, the repeat lamellar states can be best observed by X-ray diffraction studies where 'long periodicity' (LPP) and 'short periodicity' (SPP) phases have been identified. One particular linoleate-enriched ceramide (CER EOS) has been shown to be crucial in forming the LPP and is essential for barrier function [13]. Compositional and ultrastructual changes in 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 SC, Rawlings *et al.* [14] reported complete loss of lamellar ordering in the outer layers of the stratum corneum that have been confirmed by others [15, 16].

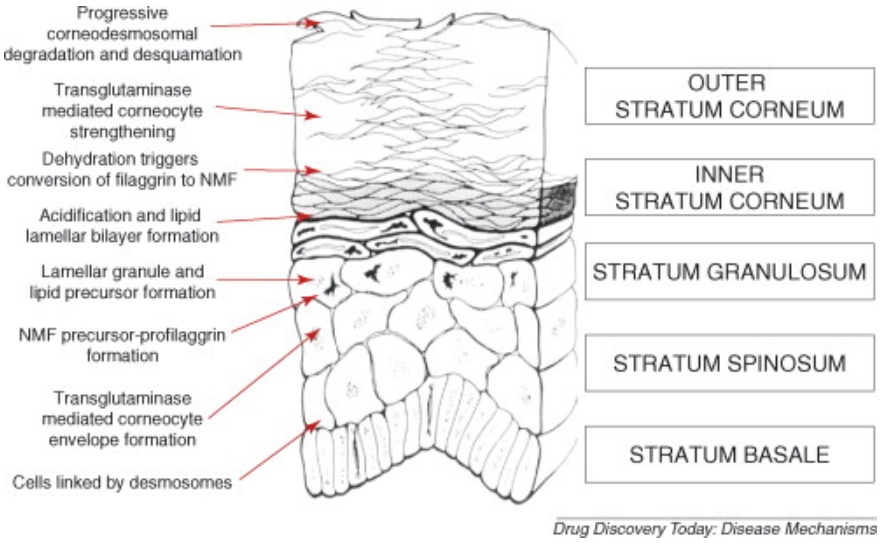

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Figure 3. Typical structure of the epidermis and crucial steps in formation of the stratum corneum. Modified from references [18].

The 'brick and mortar' model of the SC was described many years ago, but a more complete description of its structure includes the 'corneodesmosomes' (modified and specialised desmosomes [17]. These are macromolecular glycoprotein complexes consisting of the cadherin family of transmembrane glycoproteins, desmoglein 1 (Dsg 1) and desmocollin 1 (Dsc 1) together with corneodesmosin (Cdsn). Dsg 1 and Dsc 1 span the corneocyte envelope into the lipid-enriched intercellular space between the corneocytes, providing cohesion by binding homeophilically with proteins on adjacent cells. Within the corneocytes, they are linked to keratin filaments via corneodesmosomal plaque proteins such as plakoglobin, desmoplakins and plakophilins. Cdsn, after secretion by the lamellar bodies along with the

intercellular lipids and certain proteases, becomes associated with the desmosomal proteins just before transformation of desmosomes into corneodesmosomes. Importantly, because these proteins are cross-linked into the complex by the enzyme transglutaminase, their controlled disruption must occur by proteolysis to allow desquamation to proceed.

Rawlings *et al.* [14, 18] first demonstrated the degradation of the corneodesmosomes during the desquamatory process towards the surface of the SC in humans. This desquamatory process is facilitated by the action of both intracellular and extracellular SC-derived enzymes that degrade the corneodesmosomal linkages, including several kallikrein, cysteine and aspartic enzymes [19]. Cleavage of the corneodesmosomal glycoproteins occurs during desquamation, including Dsg 1, Dsc 1 and Cdsn. Deglycosylases are also involved in corneodesmosome hydrolysis [20] although glycosylation has no effect on Cdsn hydrolysis. The kallikreins especially have been studied in recent years and have been shown to be activated towards the surface layers. Many of these enzymes have been immuno-localised within the corneocytes as well as in to the intercorneocyte lipid lamellae, and the physical properties of the SC lipids together with the water activity in this micro-environment, therefore, will influence the activity of these enzymes and, ultimately, desquamation. Skin acidity also has an important impact on the quality of the SC and the desquamatory process [21]. Several anti-proteases have been observed in the SC but probably the most important are the LEKTI fragments [22, 23]. Interestingly, the association–disassociation constants between the desquamatory proteins and these inhibitors are influenced by low pH [23], that is, within the surface layers of the SC, where higher activities of the kallikreins are observed.

The corneocyte envelope is an extremely insoluble pertinacious layered structure, whose stability is attributed to the degree of cross-linking of envelope proteins by either disulfide or glutamyl-lysine isodipeptide bonds or glutamyl polyamine cross-linking of glutamine residues of several corneocyte envelope proteins [24]. The enzymes responsible for this reaction are the calcium-dependent transglutaminases (TGase). During the formation of the corneocyte envelope 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 binds to lipids) is expressed at the same time as TGase 1. TGase 1 then cross-links involucrin to the other early expressed proteins, such as members of the small proline-rich (SPRR) family and, subsequently, other plasma membrane proteins become cross-linked to form a scaffold for further reinforcement and maturation events. When viewed by Normarski microscopy, corneocyte envelopes (CEs) 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 [25]. These two populations of corneocyte envelopes were named fragile (CEf) and rigid (CEr). They can also be further differentiated by their binding of tetramethylrhodamine isothiocyanate (TRITC), with the rigid envelopes staining to a greater extent [26]. They can also be discriminated on the basis of their hydrophobicity (staining with Nile red) and antigenicity (to anti-involucrin) [27]. 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). The classification of fragile and rigid envelopes has subsequently been found to be a pertinent classification system because, mechanically, they have corresponding fragile and rigid characteristics under compressional force [26].

Natural Moisturising Factor (NMF) is derived from profilaggrin and allows the outermost layers of the SC to retain moisture against the desiccating action of the environment [28]. This bound water plays a vital role, not only for the activity of SC desquamatory enzymes, but also as plasticiser of the SC. Hyaluronic acid [29] and glycerol [30] have recently been shown to be present naturally in the SC. Glycerol can be derived from sebaceous triglyceride breakdown and again, to emphasise the importance of this molecule, studies by Fluhr *et al.* [31] have indicated that topically applied glycerol can restore to normal the quality of SC observed in asebic mice (lacking sebaceous secretions). The effect of NMF components derived from sweat on SC properties was recently described and lactate and potassium were found to be the only components of NMF that correlated significantly with the SC hydration, stiffness and pH [32]. An acid pH within the SC, the so-called 'acid mantle', is crucial to the correct functioning of this tissue. The presence of sugars in the SC is due primarily to the activity of β-D-glucocerebrosidase that catalyses the removal of glucose from glucosylceramides to initiate lipid lamellae organisation in the deep SC [33]. Studies point to the role of free fatty acids, generated through phospholipase activity, as being vital for SC acidification [34], but it is likely that all NMF components contribute significantly to the overall maintenance of pH.

The pathophysiology of winter-induced dry skin

In dry, flaky skin conditions, corneodesmosomes are not degraded efficiently and corneocytes accumulate on the SC surface. Increased levels of corneodesmosomes and their proteins in soap-induced dry skin were first reported by Rawlings *et al.* [14] and have been confirmed more recently by Simon *et al.* [35]. The lamellar lipid matrix is also perturbed dramatically in dry skin, with associated reduced levels of ceramides at the SC surface. Moreover, compositional changes in ceramides occur, with reductions in the levels of phytosphingosine-containing ceramides in dry skin, together with a shortening and lengthening of the acyl sphingoid bases sphingosine and 6-hydroxysphingosine, respectively. Linoleate also appears to be deficient in these conditions [36], as does CER EOS. These changes in lipid composition will, of course, influence the lamellar packing of the lipids. In fact, Schreiner *et al.* [37] established a reduction of CER EOS and EOH with increased concentrations of sphingosine-containing ceramides (CER NS & 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, more work is needed to ascribe this effect to a particular lipid phase. Nevertheless, as the main desquamatory enzymes are found within this lipid matrix, the physical properties of the lamellar lipids will, therefore, influence enzyme activity. Indeed, reduced desquamatory protease activities have been reported in these conditions [38, 39]. This is further compounded by reduced NMF levels and reduced maturation of corneocyte envelopes leading to the retention of immature corneocyte on the surface of the SC. High pH has been noted in xerotic skin conditions, which might indicate reduced enzyme activity [40], but the converse has been observed. However, the enhanced corneodesmolysis in non-soap induced scaly conditions might be due to elevated amounts of other inflammatory-derived proteases such as urokinase and plasmin and a recently identified SC tryptase-like enzyme [41]. See Fig. 4 for a schematic summary of the differences in SC biology in normal (A) and dry (B) skin [18, 19].

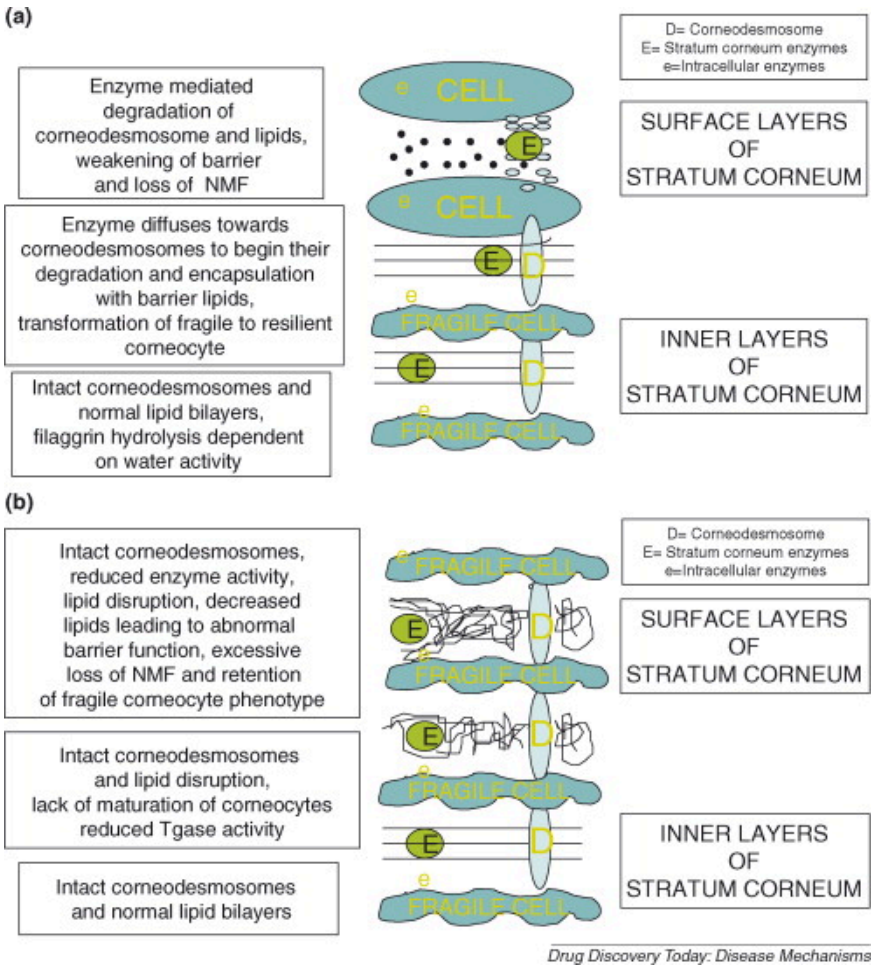

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Figure 4. Summary of stratum corneum maturation and corneodesmolysis in normal (a) and cosmetic dry scaly skin (b).

Skin barrier repair

Severe injury to the skin associated with breaching of the SC can result in the release of preformed primary cytokines and interleukins from the SC squamae. Whereas limited injury results increases lipid and DNA synthesis and facilitates barrier repair, severe or external SC injury will result in a substantial and/or continuing cytokine release and an inflammatory process – described by Elias as the 'outside–inside concept of skin pathogenesis' [2]. This inflammatory process is the first stage in skin repair after acute barrier disruption. Localised SC injury, such as associated with microdermabrasion or tape stripping of the SC leads to an increase in the transcription factors AP-1 and NF-κB that regulate inflammation and wound healing within 1 h as well as increasing the levels the primary cytokines IL-1β and TNF-α [42]. At 4 h marked increases of several matrix metalloproteinases that degrade collagen and lead to extracellular matrix remodelling were also observed [36]. As shown in Fig. 5, skin injury also leads to a change in calcium, potassium, hydrogen ion (pH) and oxygen concentrations that result in the release of inflammatory mediators such as epidermal growth factor (EGF) and transforming growth factors (TGF) that promote keratinocyte growth and migration. The changes in ionic concentrations also result in homeostatic changes in the secretion of preformed lamellar bodies and lipid synthesis and, with pH

changes, an activation of serine proteases leading to a breakdown in corneodesmosomes and easier exfoliation of SC [2].

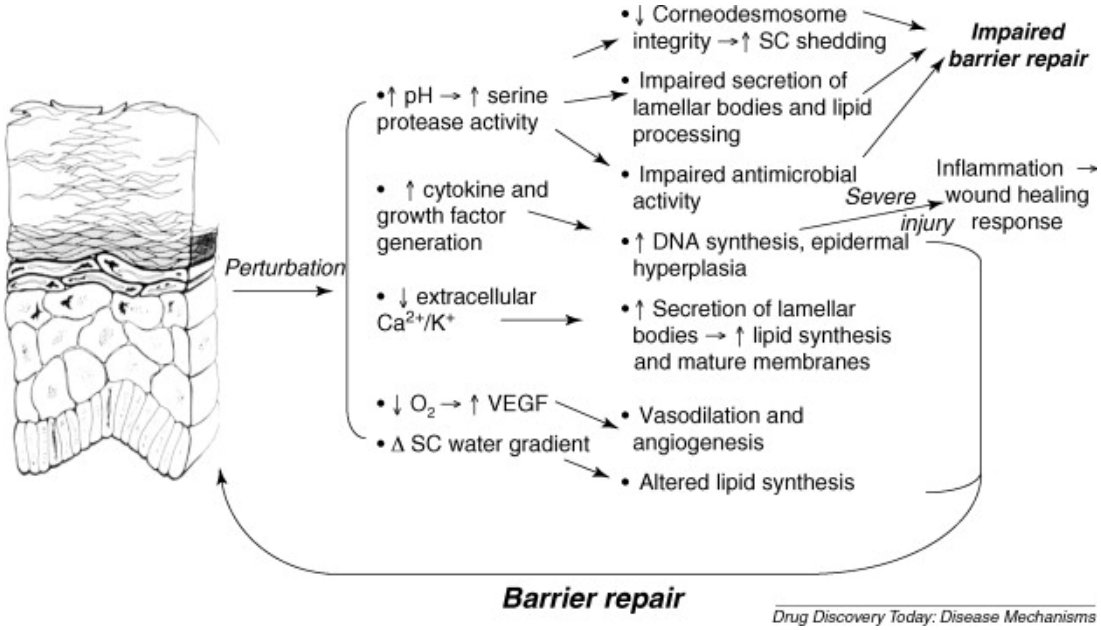

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Figure 5. Restoration of barrier function after minor and major perturbations to the SC as reflected by cytokine/growth factor release and altered ionic, oxygen and SC water gradients. Adapted from reference [2].

If damage to the skin involves dermal injury, growth factors and cytokines released during the inflammatory phase facilitate the next granulation phase involving new connective tissue synthesis, angiogenesis and epithelial wound closure. The final phase is that of scar remodelling [43]. The timings of these processes following damage (with relevant cell influx in brackets) are usually: inflammation, 1–3 days (neutrophils); 3–10 days proliferation/migration (monocytes, macrophages, T cells); 10–15 days (maturation/remodelling (mast cells) [44]. There is also an increasing appreciation that, while the large influx of leucocytes associated with the inflammatory process at damaged skin sites is essential, leucocytes can also cause fibrosis and scar tissue formation. Consistent with the model shown in Fig. 5, topical oxygen therapy has been shown to significantly enhance the rate of epithelialisation of partial-thickness excisional wounds and second-degree burns in human studies [45]. The greater the injury the greater the component of the later phases of classic wound healing. In everyday homeostasis of the skin barriers integrity and with lower degrees of damage, the process will be insensible and the healing will be complete at least from a structural point of view (a common dermatological view is that the skin will function normally first several weeks after it appears normal).

In vivo quantification of skin function

Before the explosion of non-invasive methods over the past two to three decades, the research tools available for the investigation of skin function, damage and responsiveness to therapy or intervention were limited to the following:

(a) a symptomatic report from the subject being examined;

(b) subjective description by the investigator of visible (naked eye) parameters;

(c) histological methods for estimation (also subjective or semi-quantitative) of morphological change at a microscopic level.

The situation is very different for today's scientist [10]. Many methods are available some of which have gained wider use than others. Fig. 6 shows a selection of the methods available presented according to the site within the skin that is to be studied. Choice of appropriate technique is paramount. The skin surface is very accessible for analysis and data produced can be eminently visual as in Fig. 2 or numerical and thus quantifiable in profilometry and skin friction methods [46, 47]. The measurement of skin microrelief (or skin roughness) that directly reflects the level of skin hydration can be measured [48].

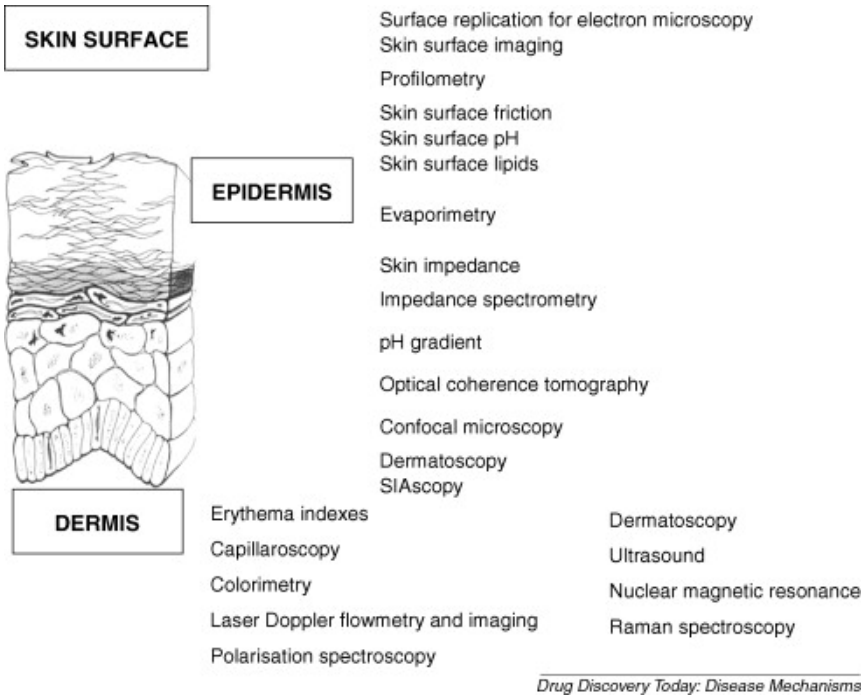

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Figure 6. Bioengineering methods for the assessment of skin function at a surface, epidermal and dermal level.

In the measurement of epidermal attributes, TEWL open chamber evaporimetry, though preceded by skin conductivity, epitomises the advent of the new bioengineering device era emphasising acquisition of objective chronological data defining skin function and reactivity [49, 50]. Evaporimetry provides the most reliable assessment of the range of functional aberration in dry skin as well as a useful measure of the SC barrier competence in a resting state or after provocation or intervention/treatment [51, 52]. Closed chamber systems are more recent developments [53, 54].

Epidermal water content can be measured by many different methods of which most rely on measurement of impedance that in turn depends on two components resistance and capacitance. *In vitro* and *in vivo* measurements constitute different scenarios [55, 56]. Multifrequency measurement of impedance in skin

can be processed to handle the large amount of information to enable presentation relevant to tissue structure [57, 58]. *In vivo* confocal microscopy, which has two formats, reflectance of fluorescent (demanding the use of an applied photophore) can produce images of epidermal structures including individual corneocytes and keratinocytes [59, 60]. Optical coherence tomography is another of the new alternatives for imaging [61] as are nuclear magnetic resonance, *in vivo* Raman spectroscopy and several other techniques [10]. Dermatoscopy, which optimises the presentation of skin morphology to the eye of the observer has become a very useful research and clinical tool of relevance both for the epidermis and dermis including adnexal organs [62].

The dermis contains the anatomical pre-requisites for blood flow and measurement of the amount of blood and its flow (speed) have been a dominant issue in cutaneous bioengineering development. Erythema indexes (and melanin indexes) are derived from reflectance data from the skin at specific wavelengths [63, 64]. Colorimetry uses tristimulus computer-controlled colour analysis according to colour space values [65, 66]. Laser Doppler flowmetry and imaging, is another landmark in bioengineering, enabling redness or erythema due to an increase in skin blood flow to be quantified [67, 68, 69, 70]. Spectrophotometric intracutaneous imaging 'SIAscopy' quantitates parameters including erythema from reference [71]. Polarisation spectroscopy is an emerging method for the quantification of erythema [72].

The taking of a tissue biopsy gives information, which though limited to the point in time that the biopsy was taken, gives much information on gene activation and protein production [73, 74]. This can be related to the chronological information that bioengineering data are up to the point of the biopsy. *In vivo* confocal and multiphoton techniques are newer techniques under development [59, 60, 75].

Moisturizers and the treatment of dry skin

Traditionally, humectants, occlusives and emollients have been, and will continue to be, the mainstay of the medical and cosmetic treatments [76] for xerotic skin. Arguably, the most widely used and effective humectant is glycerol, owing to its excellent hygroscopicity, lipid-modulating and corneodesmolytic activity together with its effect on transglutaminase-mediated corneocyte envelope maturation. Other humectants include urea and NMF components, whereas other corneodesmolytic agents include the hydroxyacids. The lipid lamellar architecture in the outer layers of the SC needs to be normalised directly or through renewal of the SC in dry, flaky skin conditions. Topically applied ceramides and other bilayer-forming lipids are, therefore, an option. An equimolar mixture of the three dominant SC lipids (ceramide, cholesterol and fatty acids) has been shown to allow normal rates of barrier recovery, whereas adjustment to a 3:1:1 molar ratio accelerates barrier recovery (For review see reference [77]). As expected, the requirements for optimal barrier recovery in aged skin are 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 lipid species can be dominant and the barrier will recover quickly, whereas in atopic dermatitis, a ceramide-dominant mixture is required. In addition to ceramides to supplement the SC barrier, phospholipids are also bilayer-forming lipids and, when combined with glycerol, have been shown to be clinically superior to petroleum jelly in relieving dry skin [78]. There are several other means to increase ceramide synthesis *in vivo* and improve barrier function. As described above, α-hydroxy acids, well known for their desquamatory properties, stimulate lipid biosynthesis especially the L-isomer of lactic acid. Interestingly, lactic acid also increases the levels of linoleate-

containing CER EOS, which might contribute to the observed improvements in skin functionality [79]. Unsaturated fatty acids (ligands for nuclear receptors such as the peroxisomal proliferator activated receptor) have been shown to improve epidermal differentiation and increase ceramide and filaggrin levels [80]. Improvements in the signs of dry skin were also observed in a 12-week clinical study on forearm skin. Niacinamide has also been reported to stimulate the lipid synthesis and recently, niacinamide has been formulated in lotions, together with glycerol and other NMF components, which effectively alleviate dry skin (Fig. 7) and provide significant improvement in SC barrier function and hydration compared with other non-barrier enhancing moisturizers [81].

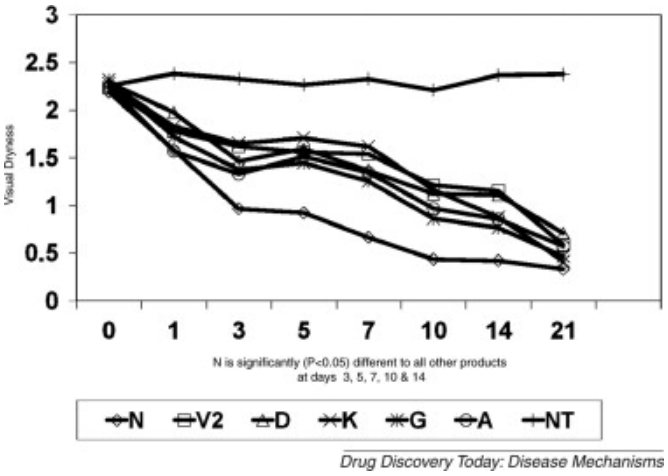

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Figure 7. Results from the treatment phase of a Kligman-type regression study (products applied twice-daily at 2mg/cm^2 to randomised sites on the outer, lower leg of female subjects [n=36] with inclusion of a no-treatment control). Products represented high-efficacy commercial moisturisers with ingredients of differing dry skin relief mechanism. Key: NT, no treatment control; N, niacinamide-containing lotion; A, lactic acid-containing moisturiser; other product codes represent commercial products with high loadings of traditional humectants and emollients (including glycerin and petrolatum).

Perception of dry skin

The topography of dry, flaky skin is considerably rougher than normal skin, with a corresponding increase in friction and consequent negative haptic perception [82] as well as change in skin microrelief [48]. The tribology of rough skin can be modified acutely by the use of emollient oils that lubricate the SC surface, reducing friction. In the long-term application of moisturisers (days to weeks), the need for these effects becomes gradually less because corrected desquamation leads to a natural smoothing of the SC surface.

Although the skin is described as a ‘barrier’ it is also a sensory interface with the environment and an organ of social (and sexual) interaction with our fellow human. An individual's psychosocial well-being, her perception of herself and others perception of her are intimately related with each other. Recent combined research by biologists and evolutionary psychologists has underlined the importance of the physical characteristics of the skin in driving a negative perception of age, health and attractiveness [83, 84]. Owing to the dramatic increased scattering of light by the loose sheets pf squamae associated with xerosis and their reduced light transmission, the visible ‘contrast’ of dry skin is high, leading inevitably to

an unsatisfactory appearance, with consequent negative judgements of age, health and attractiveness. Agents such as glycerol and mineral oils, which approximate the refractive index of the SC (1.55), are effective in providing an immediate reduction in the flaky, powdery appearance of dry skin [85]. Once again, long-term usage of effective moisturisers will also lead to improved optics and perception, owing to the removal of optically compromised excess squame sheet.

Conclusion

A modern understanding of the SC presents a picture of a dynamic barrier, regulating the fundamental interaction of our bodies with the often-hostile environment. Dry skin can be a prelude to disease in the form of, for example, eczema. We have the skin physiological, chemical and histological tools to quantitate skin barrier function both in health and disease. We also now understand more fully the psychosocial role of this outer layer in perception and, therefore, how it impinges on personal well-being and social interaction. The importance of skin care cannot be over-estimated, therefore, placing hitherto humble moisturisers in a new preventive light. A rapid increase in cosmetic technology development, combined with a wealth of new understanding of SC biology and its individual variability, means that we can look forward to many fascinating years ahead in this unique and rewarding branch of science.

Acknowledgement

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