Treatment of Dry Skin Syndrome

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Editors

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The Art and Science of Moisturizers

Springer

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Preface

Our desire to apply oily materials to the skin is almost instinctive and may be as old as mankind itself. This is related to our physical and psychological functioning which is facilitated by gentle touch, particularly in terms of reducing stress, relieving pain, and in the improvement of skin characteristics. Moisturizing creams contain a great variety of ingredients that give rise to different sensory and functional effects when applied to the skin. For example, treatment of children with atopic dermatitis may feel soothing and comforting, punitive and intrusive, or functional and neutral. Treatment of normal and diseased skin also shows different effects on the epidermal biochemistry and functional characteristics, with consequences for the outbreak of inflammation, eczema and potentially asthma.

The development of moisturizers is a scientific and artistic discipline, including both formulation technology and consumer insights. This new book aims to bridge the gap between the moisturizers and the skin. The composition and development of moisturizing creams are discussed in the book, including the value of lipids, humectants, natural raw materials, and preservatives. Overviews and updates on dry skin disorders and their treatments are also covered, along with regulatory aspects and claim substantiation. In addition, the exciting sensory systems of epidermal keratinocytes are explained, and new insights into stratum corneum biomechanics, molecular organization, desquamation, and barrier function are discussed. The authors represent a cross section of the international well-known scientists from academia to industrial research.

With the use of the knowledge in this book, we anticipate that cosmetic scientists, researchers and dermatologists will go beyond the traditional thinking of skin care. The readers will have new insights that suggest the properties required for a new generation of moisturizing treatments, improving quality of life.

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Introduction

Corneobiology and Corneotherapy: A Final Chapter

A. M. Kligman

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The text obtained for this review from Professor Albert Kligman was drawn posthumously from a variety of notes that he had been planning to use to write a review on corneobiology and corneotherapy. It was a review that he had dearly hoped to complete – his final 'magnum opus' with reflections on the subject.

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Introduction

Corneobiology refers to that broad range of experimental studies that are focused on the anatomy, physiology and biology of the stratum corneum, centred particularly on the human horny layer that has features uniquely different from other mammals. Corneobiology has a very broad reach, encompassing studies that deal with immunology, endocrinology, neurobiology and psychology, comprising a network of complex interactions that have connections to the central nervous system. It has attracted the attention of a confederation of scientists from very different disciplines, including molecular biologists, anatomists, physiologists, pharmacologists, geneticists, psychologists and still others. However, it was not until the latter half of the twentieth century that the stratum corneum began to be viewed as much more than a dead, inert passive membrane, a Saran-type wrapping around the integument with the sole function of limiting the movement of substances into and out of the viable tissues, featuring the special functions of preventing diffusional water loss against a hostile, dessicating environment and limiting the penetration of exogenous toxic chemicals with antigens [1].

I have given an historical account of the evolution, one might say revolution, regarding the new appreciation of the horny layer as having multiple, dynamic functions in a previous treatise entitled 'How the dead stratum corneum became alive' [2]. Before then, the established dogma was that the principal biologic mission of the epidermis was to create the impermeable stratum corneum barrier, essentially sealing the body from the outside world, leading some authorities to label the stratum corneum as the ultimate shield against mechanical, chemical and physical external threats. For instance, in 1958, S. Rothman in his seminal text on the *Physiology and Biochemistry of Skin* depicted the stratum corneum as a loose, amorphous mass of keratin filaments, the product of the holocrine degeneration of epidermal keratinocytes, epitomized in dermatologic texts as the 'basket weave' horny layer [3]. This view of the horny layer as a loose collection of filaments separated by wide empty spaces, as seen in H&E-stained histologic specimens, posed a paradox for physiologists who universally held that the stratum corneum constituted a barrier to the penetration of exogenous substances preventing diffusional water loss to a hostile dry environment. The 'basket weave' image turned out to be an artefact of formalin fixation of H&E-stained sections.

In 1964, myself and Enno Christophers showed that the horny layer floated off as thin, tough, transparent membrane when full-thickness specimens of skin were immersed for 1 min in water at 60°C [4]. In unfixed sections swollen by 1 N NaOH, we subsequently demonstrated that the membrane was a coherent tissue composed in most body regions of 14–16 cornified cells, later called corneocytes. These findings showed unequivocally that the stratum was a cellular tissue, not an amorphous filamentous graveyard of degenerated keratinocytes. My 1964 landmark paper, entitled 'The biology of the stratum corneum', marked the inauguration of a new cutaneous discipline, 'Corneobiology', which centred on the structure and function of the horny layer [1]. This paper, however, propagated a serious misconception. The teaching of the time was that the stratum corneum was a dead, inert, passive membrane, a Saran Wrap-like impermeable shroud, encasing the body, protecting it from chemical and physical exogenous threats. In fact, this was but one of many errors regarding the structure and function of the horny layer, which has taken many years to correct, a process of deconstruction that continues to this very day.

No area of cutaneous biology has attracted more investigative attention than the stratum corneum. A multitude of studies in the last few decades have shown that the horny layer is a very complex, dynamic tissue whose formation involves many highly orchestrated metabolic enzymatic functions. The horny layer has become very much alive. It was holy doctrine in major textbooks of dermatology that the sole function of the horny layer was to provide an impermeable 'barrier' to the inward and outward diffusion of substances, especially toxic exogenous chemicals. The synonym for the stratum corneum was the 'barrier', a term which still remains popular. It is now known with certainty that the horny layer has diverse and numerous functions, indispensable for maintaining cutaneous homeostasis.

Corneobiology Enthusiasts

It is appropriate to mention briefly the academicians whose early investigations created the background for the concepts underpinning corneobiology. It was left to many scientists but most notably Professor Elias – the maestro – to articulate the concept that the epidermis had many diverse functions and that most of these localized to the stratum corneum, which in turn had many diverse functions, elevating the stratum corneum as a key player in the many biologic processes of the integument [5]. Elias, in fact, laid down the fundamental principals underlying the science of corneobiology, listing in detail ten major horny layer functions, linking each one to specific constituents, a brilliant, original, systematic exposition. For example, the linkages of each function were first to its basic principal compartment, such as the extracellular matrix or the corneocyte; then the linkage to its structural basis, such as the bilaminar membranes of the extracellular domain, corneodesmosomes, cornified envelopes and keratin filaments and cytosols; next, the chemical basis, specifically ceramides, cholesterol, antimicrobial peptides, barrier lipids, filaggrin derivatives, glycerol and proteases; and finally linkage to regulatory scientists, glucocorticosteroids, etc.

Although it may seem tedious to list individually each of Elias' ten functions, it is exceedingly informative and edifying to grasp the scope and diversity of these functions. These are as follows:

1. Permeability
2. Antimicrobial
3. Antioxidant
4. Cohesion (integrity) – desquamation (shedding)
5. Mechanical/rheological
6. Chemical, exclusion of antigens
7. Psychosensory
8. Hydration
9. Protection against electromagnetic radiation
10. Initiation of inflammation (cytokine activation)

Although the above inventory of multiple functions is impressive, it does not tell the whole story; this is a work in progress. Searching the rapidly expanding literature furnishes further examples of the diversity of functions displayed by the horny layer. To Elias' list, one may add the following:

1. A biosensor of meteorological conditions, especially humidity.
2. Regulator of innate and adaptive immunity.
3. A storage site of chemical mediators, topical drugs, cosmeceuticals, cosmetics.
4. Protection against carcinogenesis and photoageing.
5. An organ of social communication – dry, scaly, rough stratum corneum is unappealing to touch and light, engendering repulsion, inducing anxiety, anger and depression in those afflicted by ichthyotic skin.
6. Generation of natural moisturizing factors, a mixture of low molecular weight substances that are hygroscopic (urea, amino acids, glycerol).

The upshot of these disparate observations is that the conventional view of the stratum corneum as a passive, inert, metabolically lifeless membrane is obviously archaic. The stratum corneum has obviously become very much alive. The recent publication in 2006 by Elias and Feingold, titled *The Skin Barrier*, is obligatory reading, covering every aspect of corneobiology. It is an unparalleled source of references [6].

The scientific basis of corneobiology is experimental quantification and not simply empirical observation, further strengthened by the development of non-invasive methods that allow repeated, sequential observations of the same site without damaging the tissue, as is the case of biopsies. For example, the integument is constantly being deformed by stretching by mechanical forces, about which knowledge is scanty, lacking measurable data. To fill this gap, recent studies show that using a suction device to apply strengths of 400–600 mbar to the forearms results in significant increases in transepidermal water loss (TEWL), signifying increased permeability, and marked decrease in capacitance, signifying less ability to take up and hold water, making the horny layer less resilient [7]. This is echoed by the work of Rawlings et al. [8] further demonstrating in vitro disruption of lipid bilayers with extension of the stratum corneum, resulting in increased water vapour transport rates. These results are rather surprising, considering the rheological stresses that the integument experiences in daily living, not to mention sports, and not everyone concurs with these findings.

Contributors to building the edifice, we now call corneobiology, are a motley, diverse crew of investigators, mainly situated in industry and academia from around the world. These individuals are all individually acknowledged in the delightful, historical, narrative essay by the indefatigable master of masters, Dr. Anthony Rawlings of Great Britain, entitled '50 years' of stratum corneum research and moisturization, laying out decade by decade the most innovative discoveries, starting in the 1950s [9]. Rawlings and his collaborators are best known for their exhaustive, comprehensive works on moisturization, culminating in the Rawlings magnum opus in 2004 on 'Stratum corneum moisturization at the molecular level', which is a must-read for all parvenus to the field of corneobiology, covering in exquisite detail every aspect of moisturization, including the development of an impressive assay of modern multidimensional products for effectively treating the common dry, scaling, ichthyotic conditions, a far cry from our forefathers who advocated such primitive remedies as goose grease, vegetable oils and animal fats [10].

Another distinguished name must be added to those who have made outstanding contributions to corneobiology, namely, Professor Ronald Marks of Cardiff, Wales. Dr. Marks has sponsored six international symposia, focused entirely on the stratum corneum. In 1971, he invented the cyanoacrylate skin surface biopsy technique that enables the microscopic visualization of bacteria, fungi, bacteria and demodectic mites in the superficial, desquamating portion of the stratum corneum [11]. He was also among the first to show that the impermeable dressings with no active pharmacologic agents could clear psoriatic plaques and that supposedly inert ointments, such as petrolatum, could have anti-inflammatory effects [12].

Tagami in Japan realized in 1998 that the stratum corneum was a rich reservoir of cytokines, including IL-8, IL-6, IL-10, TNF-a and others, enabling 'an

explosive inflammatory tissue' whenever fragments of the horny layer are extruded into the dermis, heralding the idea that the horny layer could start chronic inflammatory disorders [13]. Tagami immersed a sheet of normal stratum corneum in buffered saline for 2 days and found a large quantity of IL-12 in the supernatant. Marks had earlier demonstrated that a suspension of corneocytes obtained by scrubbing callus tissue initiated a severe, long-lasting, inflammatory granuloma when injected into the dermis [14]. Spontaneous examples of this response occur when epidermal cysts rupture, dumping their contents into the dermis, and also when acne comedones rupture to form papulo-pustules. Frenetic scratching can mimic this phenomenon by dislodging keratinous fragments into viable tissue. Nickoloff and Naidu had also foreseen the potential of the stratum corneum to initiate inflammatory and immune-mediated reactions [15]. They found, by immunostaining biopsied tissue, marked increases in TNF-a, IL-a, IL-16, intercellular adhesion molecules and growth factors as early as 6 h after tape stripping. They were among the first to appreciate that the epidermis vigorously participates in a multitude of homeostatic responses, well beyond producing the horny layer barrier. Nickoloff then went on to show that there was a rapid release of cytokines after topical application of irritants, as well as after application of allergens in sensitized subjects, indicating a common triggering, a pathway after injury to the stratum corneum [16].

It is appropriate to point out that the remarkable advances in our understanding of the horny layer have been made possible by the utilization of highly sophisticated, modern technology, including TEM, SEM, cryofixation, spectroscopy, staining of immunologic markers, optical coherent tomography and histochemical and other non-invasive methodologies. Some recent illuminating studies are worth mentioning.

We have been taught, since the early in vitro diffusional studies of Scheuplein and Blank, that all layers of the stratum corneum contribute to its barrier properties [17]. Now we learn, in a recent paper by Richter et al. of Beiersdorf, Hamburg, Germany, using cryofixation and scanning electron microscopy, that skin specimens immersed in 5–20% salt solutions show three distinct hydration zones within the horny layer [18]. The outermost zone where desquamation occurs shows massive swelling, whereas the innermost zone shows that the granular layer swells to more than double its normal thickness, associated with massive water inclusions between adjacent cell layers. By contrast, the middle zone remains compact, without water pools. The authors conclude that the middle zone constitutes the vaunted permeability barrier, a near heresy to conventional thinking.

An earlier paper by the same group using high-pressure cryofixation compels us to reconsider how our conventional concepts need serious revision [19]. The most surprising finding is that organelles and tonofilaments within the cytoplasm of keratinocytes are not uniformly distributed as usually depicted but instead are organized instead into 'microdomains', clusters of organelles separated by relatively empty spaces, a startling new concept of keratinocyte morphology. New knowledge is occurring so rapidly that we are no longer shocked when our conventional dogmas are overturned. The famous impermeability of the horny layer turns out to be an oversimplification, even to the point where physicists can proclaim boldly that the vaunted barrier may have porous domains.

It is now understood that permeability can be enhanced by a variety of chemical and physical techniques, including simple occlusion. The normal stratum corneum contains widely separated lacunar dilatations in the extracellular domains that can be enlarged to form continuous pore pathways, allowing for the ready penetration of both polar and non-polar molecules attesting to the new awareness of the dynamic nature of the horny layer [20].

Emollients and Moisturizers: The Beginnings of Corneotherapy

It was not long ago when dermatologists were scorned and mocked for their primitive, empirical topical therapies. The therapeutic credo was: 'If it's dry, wet it. If it's wet, dry it'. The ointments followed the rule of the three S's. Their efficacy was thought to be proportionate to the degree to which they *stained, stunk or stung*. However, corneobiology, which has revealed the inner workings of the horny layer barrier, has revolutionized topical therapies, allowing striking improvements, which can be epitomized in a few sentences. They are more effective; safer, using lower concentrations of active agents, with fewer adverse side effects such as stinging, burning and irritancy; free of allergens, fragrances and preservatives; more easily and conveniently applied; more agreeable to use, being colourless and odourless, rubbing in easily and leaving no residue; more stable with a longer shelf life and compatible with other daily treatments such as sunscreens, moisturizers and cleansers. A wave of new topical drugs and cosmeceuticals has entered the market place, whose benefits are more likely to be substantiated by 'evidence-based' medicine.

The use of bland, non-medicated emollients for treating a variety of dermatologic disorders is as old as dermatology itself. Dermatologists in European centres extensively used emollients in the nineteenth and twentieth centuries to treat a variety of chronic, inflammatory disorders. The term 'emollient' (from the Greek, meaning to soften) refers to oily substances, such as ointments and creams, which are used to moderate rough, scaling, xerotic, erythematous, often pruritic conditions to make the skin flexible, soft and agreeable to the touch and sight. More recently, the term 'moisturizers', a creation of Madison Avenue merchandizers, has come into use to denote substances, usually in the form of emulsions, that 'moisten' and hydrate dry skin conditions. The two terms are now used interchangeably to encompass a huge variety of commercial formulations possessing attributes that go well beyond merely moistening and softening. It should be made clear that emollients are not drugs in the FDA sense and technically contain no pharmacologically active substances; nonetheless, they may have drug-like effects and are best classified in the category of cosmeceuticals.

The corneotherapy story begins with some prescient observations by Tree and Marks in a 1975 paper having the provocative title of 'An explanation for the 'placebo' effect of bland ointment bases' [12]. These authors were trying to explain how bland emollients, without pharmacologically active ingredients, could be effective in moderating common inflammatory disorders such

as psoriasis and atopic dermatitis. They showed that several bland agents could inhibit and prevent the increased epidermal mitotic rate, which occurred when the skin of hairless mice was tape-stripped. They found that the venerable ointment, petrolatum, exerted the greatest anti-mitotic effect among other creams and pastes. They had no explanation for this.

Penney later proffered the explanation that petrolatum might be acting as an anti-inflammatory agent [21]. He could show, at least in vitro, that petrolatum inhibits the prostaglandin-mediated formation of the pro-inflammatory arachidonic acid. In 1976, Comaish and Greener showed that petrolatum had an inhibitory effect using a quite different model [22]. Their study was based on the renowned Köbner phenomenon in which insults to the uninvolved skin of patients with active psoriasis provoke new psoriatic lesions at the traumatized sites. They provoked the Köbner reaction by making 1-cm-long deep scratches. By pretreating uninvolved skin for 3 weeks before scratching, they found that new lesions were generally inhibited.

In still another model, myself and Lorraine investigated the ability of emollients to inhibit ultraviolet-induced carcinogenesis in hairless mice [23]. The mice were irradiated thrice weekly for 20 weeks with broad-spectrum UVB. The selected emollient was applied just before each irradiation. We found that petrolatum gave almost complete protection against the formation of tumours. Another hydrophobic emollient, lanolin, was only 50% effective. By contrast, tumour formation was greatly enhanced by mineral oil in this animal model, which contains lower molecular weight hydrocarbons than petrolatum, with a potential for irradiation. USP cold cream had no protective effect. Interestingly, a modest protective effect, about 20%, was determined even when petrolatum was applied after each irradiation. It was shown that petrolatum had a negligible sunscreen effect, with an SPF of <2.

In my own studies of bland emollients for the correction of varied xerotic states with defective horny layer barriers, I have found that ancient war horse petrolatum to be highly effective. My assessment of moisturization efficacy was based on the dry skin regression method that determines the time after cessation of a 3-week treatment for skin to return to the original state [24].

The chief complaint against petrolatum, which strongly limits its acceptance, is its greasiness and disagreeable feel. After experimenting with a variety of oil-rich emollients, which are clearly superior to lotions, we have concluded that Aquaphor is second only to petrolatum for repairing defective barriers in chronic dermatoses. Patients have to be taught that once rubbed in, its perceived oiliness mostly disappears.

I proffer the following experimental example of the high efficaciousness of Aquaphor in repairing the markedly defective barrier by oral administration of 13-*cis*-retinoic acid (Accutane). I treated three men with severe acne conglobata of the face and back with 80 mg of *cis*-retinoic acid daily for 4 months with excellent therapeutic results but which resulted in marked scaling, even bruising and purpura after moderate erythema in two, associated with itching and dryness to touch and sight. One dorsal forearm, from the wrist to antecubital space, was treated with Aquaphor b.i.d. for 5 weekdays for 1 month, whereas the opposite forearm served as an untreated

control. Dryness, scaling, itching and fragility disappeared completely in 2 weeks. The following measurements were made 3 days after the end of 4 weeks of treatment, expressed in averages. Transepidermal water loss (estimated by Servomed) was 22.3 mg m^2/h on the untreated side and 5.2 mg m^2/h on the treated side, a value within the normal range of the forearm. The number of corneocyte layers determined by the alkali swelling technique on a razor slice biopsy was 6.1 on the untreated side and 10.3 on the treated side, within the normal range. Twelve Scotch tape strips induced purpura on the control side but not on the treated side. Videomicroscopy (by Hi-Scope, ×20) showed near-normal glyphic markings of primary and secondary lines on the treated side with near obliteration of glyphics on the untreated side. Despite the facial sample, the near-normal restoration of the defective barrier by b.i.d. applications of Aquaphor can scarcely be queried.

Subsequently, petrolatum in many reports has been found to be beneficial in a variety of clinical settings, for example, after chemical and laser peels, after dermabrasion, in promoting wound healing and for relieving chronic, inflammatory disorders. A noteworthy effect of petrolatum is enhanced repair of the disrupted horny layer barrier in human skin. For example, Herd and Agner examined the ability of six different moisturizers to repair the horny layer barrier damaged by a 24-h patch test of 0.5% sodium lauryl sulphate, a classic anionic detergent that makes the barrier extremely permeable, increasing TEWL to 20 times normal [25]. All six moisturizers accelerated barrier repair, measured quantitatively by a variety of bioengineering techniques, with petrolatum the best performer. The key finding in that study was that the rate of repair was directly proportioned to the respective oil content of the moisturizers. They recommended this model as a reliable way to estimate efficacy. Although still elusive, we are coming closer to understanding the mechanism by which moisturizers work.

The momentous increase in knowledge of the intricacies of stratum corneum anatomy and physiology has paid off handsomely in the way in which topical drugs are formulated to enhance penetration, thereby increasing efficacy at lower concentrations, also diminishing adverse reactions. Topical drugs can be targeted to preferentially enter follicular pathways in disorders such as acne.

Corneotherapy Is the Basis for a New Wave of Improved Topical Treatments

Corneotherapy refers to therapeutic interventions, usually topical, which are aimed at repairing stratum corneum barriers that are impaired in a wide variety of unrelated dermatologic disorders. Corneotherapy applies most often to the treatment of common chronic inflammatory disorders such as atopic dermatitis and psoriasis but also to a wide spectrum of skin diseases of very different origins, viz. occupational diseases, irritant and allergic contact dermatitis, congenital ichthyotic diseases, keloids and hypertrophic scars,

severely premature neonates, the photoaged face because of excessive solar radiation and others, which are classically manifested by dry, xerotic, scaling, often pruritic cutaneous surfaces. A variety of objective non-invasive measurements are available to characterize and quantify these diverse conditions that invariably exhibit increased TEWL and decreased capacity to maintain hydration resulting in viable dry scaly skin among other impairments of the horny layer barrier.

Actually, corneotherapy has been practised unwittingly by dermatologists from the earliest times, encompassing different approaches and basically targeting defective horny layers ranging from traditional ancient approaches such as emollients, occlusive dressings, hydrotherapy (spas), ultraviolet light, natural and artificial, arriving at modern resurfacing strategies for correcting photoaged faces (lasers, chemical peels, dermabrasions, etc.).

Corneotherapy refers to preventive interventions that are primarily directed to the correction and restoration of the stratum corneum barrier that has been rendered defective and impaired by disease, genetics and a variety of mechanical, physical, chemical and psychological exogenous insults and stresses.

Invariable and characteristic features of defective horny layer are marked increases in diffusional TEWL to a hostile dessicating environment; a decreased capacity to take up and retain sufficient water to maintain a supple, soft, resilient, smooth horny layer and a host of structural imperfections, which degrade the ability of the horny layer to carry out its multiple and diverse protective functions.

Great advances in our knowledge of the structure and function of the stratum corneum, the science of corneobiology, have formed the background for a wave of improved, novel products that have recently entered the marketplace for the treatment of common dermatologic conditions. These products cover a wide range, including drugs, moisturizers, cleansers, sunscreens, barrier repair, enhanced wound healing, etc. Big Pharma, until recently, has essentially abandoned dermatology in favour of billion-dollar blockbuster drugs, opening up a marketing need for smaller companies that are dedicated exclusively to dermatology. The result has been a stunning variety of innovative products that have not only improved the efficacy and safety of traditional remedies but have made them more convenient, pleasant and easier to use. These innovations encompass new delivery systems to enhance penetration; new modes of application, including sprays, foams, gels and encapsulation in microspheres; stable, fixed combinations that were formerly incompatible; metered applications that reduce waste; packaging kits that provide complete treatment programs and formulations of active agents, which also reduce disagreeable adverse sensory responses such as itching, burning and stinging, enhancing compliance and even enhancing sleep patterns.

Many of these are available without prescriptions and, being produced by dermatologic companies, have passed the usual toxicity tests for allergic and irritant contact dermatitis, phototoxicity, comedogenicity, etc. The following section provides a selected few informative examples out of a number too great to review in detail.

Coal Tar

Coal tar has been a venerable treatment for plaque-type psoriasis for centuries but suffers from poor compliance because of its bad odour, messiness and dark staining of skin. These disagreeable factors have all been eliminated by its new presentation in a 2% quick-breaking foam that dries rapidly and spreads easily and is at least as effective as calcipotriol, an effective vitamin D derivative.

Region-Specific Products

Corneobiologists have demonstrated that the stratum corneum barrier varies greatly in various body regions, being very thick on the palms and soles, very thin on the eyelids and vulva, and has poor barrier properties of the face to immature corneocytes, mostly because of photoageing. Accordingly, products are now available that are specifically designed for each region; for example, keratolytics, such as salicylic acid, are included for the feet, moisturizers and sunscreens for the face.

Fixed Combinations for ACNE Therapy

Separate applications of a retinoid and benzoyl peroxide are highly effective for the treatment of acne vulgaris. These are incompatible when applied together because the retinoid becomes degraded by the oxidizing activity of benzoyl peroxide. A pharmacologic breakthrough has been released by a fixed combination of 0.1% adapalene and 2.5% benzoyl peroxide in a microsponge formulation. It should be noted that benzoyl peroxide is half the concentration of most stand-alone benzoyl peroxides. This is a synergistic combination of two drugs with different modes of action and has the highly valuable added advantage of lessening adverse sensory reactions (stinging, burning). Once-daily applications are sufficient, which greatly enhance compliance.

Azelaic Acid Gel

A 20% azelaic acid cream has been available for the treatment of rosacea for the last 20 years, often accompanied by irritancy and sensory discomforts. Modern formulations of topical drugs have come to appreciate that in addition to the usual toxicity tests to ascertain safety, also adverse sensory reactions, such as itching, burning and stinging are addressed. Patients will not use products, no matter how effective, if they cause disagreeable sensations. A new formulation (Finacea) containing 15% azelaic acid in the form of a gel is more agreeable to use, spreading easily, leaving no residue, less irritating, with minimal itching and stinging. Like most other dermatologic disorders, monotherapy is not optimal. Greater improvement is achieved by the addition of a mild cleanser and an emollient–moisturizer. The manufacturer is following a new trend, making

available Finacea Plus, a packaging kit that includes a moisturizer and cleanser, adequately tested and relieving the consumer of having to buy these separately and having to make choices among scores of competing manufacturers.

5-Fluorouracil (5-FU) for the Treatment of Actinic Keratosis

For many decades, 5% 5-FU cream has been shown to be highly effective for the treatment of actinic keratosis in a 3-week b.i.d. course. A limitation that has greatly restricted its use has been the severe, painful, erosive, crusted, irritating reactions, which all patients experience. An ingenious solution to the intolerable irritancy problem has been the development of a 0.5% 5-FU cream (Carac), which is usually well tolerated, notably because of a tenfold reduction in concentration and because it is a slow-release microsponge formulation that allows a steady release of the drug, greatly reduced toxicity, rather than a sudden burst of; moreover, once-daily application to each head and neck lesion is often sufficient to bring about complete clearing of more than 50% of AKs in 1 week. Treatment of the remaining lesions is continued until clearing in the next week or two, a flexible arrangement. This is an excellent example of employing innovative pharmaceutical knowledge to solve a dreadful problem.

The Scientific Validation of the Efficacy of Glycerine as an Effective Component of Skin Care Formulations

Glycerol is well known to the cosmetic industry as a humectant that can take up three times its weight from a water-saturated atmosphere. It has been used extensively since its discovery in 1799 to improve dry skin conditions, based on empirical observations. Now in an ingenious study, Hora and Verkman have proved conclusively that glycerol is a major determinant of stratum corneum water retention and has other beneficial effects on stratum corneum biophysical properties [26]. This study used aquaporin-deficient mice, but the results doubtless hold for human skin. In brief, the horny layer of these mice had multiple defects manifested by markedly evaluated TEWL, decreased hydration (dryness) and poor elasticity after being deformed by suction and extremely impaired barrier repair after tape stripping. After oral intraperitoneal and topical applications of glycerol, these deficiencies were completely corrected using quantitative, sophisticated and biophysical methods. Another important finding was that glycerol enhanced the biosynthesis of the physiologic lipids that are responsible for barrier function.

Interestingly, corneobiologists, but few others, are unaware that glycerine mediates still other functions beyond its spectacular humectancy, namely, in regulating orderly shedding of corneocytes at the surface, thus keeping the horny layer at a steady state of thickness during desquamation. It accomplishes this by enhancing proteolytic activity and promoting the dissolution of corneodesmosomes near the surface, which are responsible for the cohesion of corneocytes below the surface as shown by Rawlings et al. [27].

Equally, glycerol also has effects on cornified envelopes, a previously unrecognized structural component of the horny layer that provides a new target for cutaneous therapeutics. The famous brick and mortar mould of the structural architecture of the horny layer failed to appreciate the presence of rigid, insoluble structures that surrounded the horny cells (corneocytes) and were composed of a mixture of proteins assembled during differentiation. Hirao et al. in Japan have now demonstrated that cornified envelopes are critical elements in the construction of the barrier and in mediating its functions [28]. These workers collected corneocytes by tape stripping the outermost layers of the stratum corneum and then stained these to determine the degree of maturation of cornified envelopes using Nile red to assay their acquiring hydrophobicity during maturation and anti-involucrin antibodies to evaluate loss of antigenicity during maturation. This ingenious method enabled them to differentiate immature corneocytes, which are fragile and in varying sizes and shapes, from mature ones which are rigid, flat and sturdy.

The findings of this elaborate and ingenious study are groundbreaking and very illuminating. The story begins with the discovery of the common disorders that are characterized by dysfunctional, impaired barriers, such as psoriasis and atopic dermatitis, and immature cornified envelopes were abundant in the outermost stratum corneum in contrast to the normal body areas such as the trunk and extremities where the envelopes were fully mature, whether the subjects were Caucasians, Japanese or Afro-Americans. On the other hand, immature cornified envelopes were frequently found on the face, especially in winter, explained by the fact that the facial horny layer is a poor barrier, thinner and more permeable, qualifying as dysfunctional, an unpractical area exposed to environmental stresses, such as arsenic damage. It is now firmly established that immature fragile corneocytes inevitably signify an impaired barrier [29].

Next, ex vivo incubation of corneocytes from the face in a humidified environment for a few days resulted in a rapid maturation of the corneocyte envelopes. Interestingly, exposure to facial corneocytes to commercial moisturizers accomplished the same degree of maturation, attributable simply to increased water content. To complete this picture, in vivo treatment of the face with a moisturizer had the beneficial effect of eliminating immature corneocyte envelopes, associated with improved barrier functions, such as decreased TEWL [30]. These findings are consistent with those of Rawlings and collaborators who showed that fragile corneocyte envelopes, which are increased in dry skin conditions, are converted into mature, rigid corneocytes by the application of moisturizers to the face [31].

The practical clinical message of this innovative investigation is that corneocyte envelopes should become a target for evaluating the efficacy of moisturizers in promoting the function of the horny layer barrier.

Effect of Emollients on Very Premature Infants

In no other skin disorder is the beneficial effect of an oil-rich, non-medicated emollient so striking on the general parameters of well-being as in very

premature infants. Premature infants with an estimated gestational age of less than 33 weeks are born with an extremely impaired horny layer barrier. Transepidermal water loss may be 15 times greater than in the full-term infant, with drastic immediate consequences relating to dehydration, electrolyte imbalance and thermal instability. Topically applied drugs may penetrate the highly permeable stratum corneum so easily as to produce toxic systemic reactions [32]. Monitoring devices such as transcutaneous intravascular lines, urine catheters, chest tubes, etc., lead to nosocomial infection, as high as 30% [33]. Increases in the density of bacterial and fungal microflora may lead to bacteraemia and sepsis.

In a model systematic study, Nupper et al. [34] applied Aquaphor (Beiersdorf) ointment twice daily for 2 weeks to 30 very premature infants while monitoring a matched untreated control group of 30 premature infants. Aquaphor is a hydrophobic ointment that contains no preservatives and is water miscible, whose ingredients consist entirely of petrolatum, lanolin mineral oil and lanolin alcohols. They found that TEWL decreased 67% 30 min after application, greatly enhancing repair of the severely defective barrier throughout the 2-week study in relation to untreated skin. Bacterial cultures of the skin revealed significantly decreased colonization by the resident microflora, chiefly *S. epidermidis*. Positive blood and cerebrospinal cultures were 33% in the treated group and 20.7% in the untreated group. Clinical evaluation of the general condition of the skin showed increased scaling in the control group and no xerosis in the treated group. Mild dermatitis (not defined) was less apparent in the treated group.

My own group has previously conducted a pilot study on eight children with comparable lesions of severe, itchy atopic dermatitis on opposite antecubital spaces, comparing once-daily applications of the vehicle, which was not oil rich, on one side, to Eucerin Cream on the opposite side. At the end of 3 weeks, there were no differences between the two sides in any clinical criteria of improvement. However, there was a marked difference in the time to first relapse when treatment was discontinued. In three of the eight subjects, the relapse time was the same, approximately 2–3 weeks. For the other five, the vehicle-treated side showed a relapse time that was 2 weeks greater on the Eucerin side in three subjects and 3–4 weeks greater in the remaining two. The message here is that relapse times are relevant in comparing efficacy.

Treatments for Atopic Dermatitis

Awareness of the primary role of the stratum corneum in the pathogenesis of chronic inflammatory diseases, of which atopic dermatitis is the best example, has opened up new therapeutic options. Depletion of physiologic lipid, especially ceramides, is a fundamental biochemical marker that accounts for increased TEWL, decreased hydration and the signs of xerotic dry skin [35]. Old-fashioned, traditional moisturizers, such as lanolin and petrolatum, are helpful but remain trapped in the horny layer and do not reach the viable epidermis. The newest formulations by contrast contain physiologic ceramide-dominant lipids that penetrate the viable epidermis,

are taken up by keratinocytes and then secreted into the intercellular lipid domains of the stratum corneum, repairing the defective, leaky barrier [36]. 'Barrier repair' creams are now very popular moisturizers, on full display on the shelves of pharmacies [12]. One of these physiologic lipid creams, EpiCeram, containing the correct molar 1:1:1 ratio of ceramides, cholesterol and fatty acids, employed as monotherapy for atopic dermatitis, has been shown to be as effective as a mid-potency corticosteroid fluticortisone (Cuterate) [37]. Another very welcome advantage of these ceramide-dominant creams is their preparation in the form of foams that leave no residue and are pleasant to use, completely avoiding the messiness of ointments.

The historical origins of corneotherapy for this application derive from the numerous, innovative works of Elias and co-workers in San Diego, California. They first laid out this approach in a 2001 paper with this interesting title, 'Does the tail wag the dog?', in which they introduced the concept of 'outside-in therapy', a novel and radical notion in the current age of immunology which holds that in common chronic inflammatory disorders, such as psoriasis, the abnormal T cells in the circulation become trapped in the dermis, which causes derangements in the overlying epidermis and stratum corneum [38]. Which Elias et al. have dubbed the 'inside-out' concept of pathogenesis, the stratum corneum alterations are secondary downstream events [39, 40]. Accordingly, the rational therapeutic approach is the use of anti-inflammatory agents, notably corticosteroids and immunosuppressives, such as calcineurin inhibitors, to suppress the dermal inflammatory reaction that in turn leads to the normalization of the impaired horny layer barrier. By contrast, outside-in therapy assumes that the abnormal horny layer is the primary pathologic event, the correction that mitigates the underlying dermal inflammatory reaction. This turns the conventional anti-inflammatory approach upside down; clinical clearing occurs as a downstream event secondary to restoration of the affected horny layer barrier. Incidentally, this highlights an unusual feature of corneotherapy, which in its form does not require the use of pharmacologically active drugs, a case in point being bland emollients and occlusive dressings. In this sense, corneotherapy is more benign as it avoids atrophogenic events such as atrophy and striae. It should be noted that the inside-out and outside-in approaches are not actually exclusive but are often complimentary in the real world.

Perturbations of the permeability barrier regardless of type, solvents, tape stripping, detergents, burns and mechanical, physical and chemical injuries all result in the stimulation of metabolic responses in the underlying epidermis aimed at normalizing the stratum corneum. The most notable response is the initiation of the cytokine and chemokine cascade, referring to the release of preformed pools of IL-Ia and TNF-b adhesion molecules, including Langerhans cell activation, inducing further downstream effects leading to trapping of circulating inflammatory cells in the dermis, angiogenesis and fibroplasia.

The cytokine cascade can provoke and sustain several important chronic inflammatory dermatoses accompanied by the accumulation of abnormal T cells in psoriasis and atopic dermatitis.

These changes are followed by barrier repair mechanisms, which these workers divide into three types:

1. Dressings containing no active pharmacologic ingredients
2. Non-physiologic lipids such as petrolatum and hydrophobic emulsions (Aquaphor)
3. Physiologic lipids comprising cholesterol, ceramides and free fatty acids in proper proportions

Non-physiologic lipids, for example, hydrophobic emulsions, such as Eucerin or Aquaphor, are indicated in extremely low-birth weight, premature infants, as they entirely lack a lamellar body secretory system and have no way to process physiologic lipids. On the other hand, physiologic lipids are indicated in atopic dermatitis and photoaged skin where depletion of ceramides has been demonstrated. In these cases and other disorders, a deficiency of lipids, application of ceramide-dominant physiologic lipids is the preferred strategy for barrier repair as the mechanism for exocytic processing of lamellar bodies into intercorneocytic bilamellar membranes is already in place.

Defective barriers can arise in a wide range of dermatologic disorders; for example, in bullous diseases, chronologic ageing and phototoxic reactions. Barrier defects associated with immunologic or pathophysiologic changes are common and familiar examples, including psoriasis, irritant and allergic contact dermatitis, hypertrophic scars and keloids, occupational dermatitis and congenital ichthyosis, and, of course, atopic dermatitis has yielded new insights regarding pathogenesis and has suggested novel approaches to treatment.

Originally it was thought that abnormalities of the adaptive immune functions were key features in pathogenesis involving Th1/Th2 cell dysregulation, increased IgE production, dendritic cell (Langerhans) signalling and production of mast cell mediators, resulting in the intense pruritus and chronic inflammatory changes that characterize this disorder. These clinical manifestations have been widely assumed to reflect downstream consequences of the immunologic abnormalities, the basis for the historical ‘inside–outside’ concept, promoting the use of anti-inflammatory agents to effect clinical clearing [38–40]. This traditional view has been challenged, indeed completely reoriented as a primary disorder of the structure and function of the stratum corneum. Accordingly, the well-known permeability barrier abnormality in AD is not merely an epiphenomenon, a downstream consequence of inflammation, but is in fact the very revision, the driver of disease activity, the newly constructed outside–inside view of pathogenesis. This revision is strengthened by the observation that the barrier abnormality persists years after clinical clearing, both in involved and uninvolved skin, and that specific replacement of the depleted physiologic lipids that are a hallmark feature not only corrects the barrier deficiency but comprises effective anti-inflammatory activities, replacing the use of atrophogenic corticosteroids. Furthermore, the characteristic increase in surface pH, increased serum protease activity, exposure to low environmental relative humidity, increased use of detergents for washing and barrier impairment by psychologic stress all point to weakening of the barrier as a primary factor in pathogenesis. The ascending view is that atopic dermatitis represents a genetically determined broad barrier failure.

These convergent pathologic features create a strong rationale for the deployment of specific strategy to restore barrier function, ranging from a simple reduction in pH (acidification), application of well-described effective moisturizers that have been shown to steroid-sparing application of serine protease inhibitors, culminating in the recent commercial development of ceramide-rich, triple lipid, barrier repair creams, notably EpiCeram (Ceragenix Pharmaceuticals, Denver, Colorado), which has been shown to be therapeutically equivalent to a high-potency corticosteroid, fluticasone [41]. For a more complete discussion of the genetic factors underlying atopic dermatitis, the essay by Michael Cork entitled 'Epidermal barrier dysfunction in atopic dermatitis', is a splendid, highly informative review of current knowledge [42].

Finally, the paper by Voegeli, Rawlings and collaborators on increased stratum corneum protease actively provides a detailed account of recent developments and novel therapeutic options [43]. These investigators demonstrated increased protease activity in atopic dermatitis, including tryptase-like enzyme, plasmin, urokinase and leucocyte elastase, associated with impaired barrier function, irritation and reduced capacitance (hydration). These findings suggest that serine protease inhibitors present a new option for the effective treatment of atopic dermatitis.

The Steroid-Sparing Effects of Emollients

Physicians, including dermatologists, have fallen into the habit, long sanctioned by tradition, of prescribing topical drugs to be applied twice and even three times daily. This is almost a reflex decision, not validated by evidence-based medicine. In no instance is this practice less rational and potentially more harmful than in the case of topical corticosteroids, which are first-line treatments for chronic inflammatory disorders. Recent studies have made it abundantly clear that once-daily applications of corticosteroids alternating with an emollient, usually the vehicle, are therapeutically equivalent to twice-daily applications of the corticosteroid.

Once-daily applications are salutary for two obvious reasons: the savings in cost are considerable, especially for the most potent steroids that are outrageously expensive; additionally, once-daily applications reduce the threat of adverse reactions such as atrophy, striae, rebound flares and inhibition of the pituitary–adrenal axis, especially when long-term use is required. Convincing examples of the benefits of once-daily applications abound, especially for atopic dermatitis.

In 25 children with atopic dermatitis, Lucky et al. compared the efficacy of twice-daily applications of 2.5% hydrocortisone cream to once-daily applications of the steroid alternating with an oil-rich emollient once daily (Eucerin Cream, Beiersdorf) [44]. There were no differences between the two groups at the end of 3 weeks of treatment. Both were equally effective. A high degree of satisfaction was registered by the parents and the investigators for the alternating regimen. Note that the emollient was Eucerin, not the vehicle base of the hydrocortisone cream. The vehicle is generally inferior to a time-tested oil-rich emollient.

In a similar large, multi-centred study in the United Kingdom, Bleehen et al. [45] treated 275 patients with moderate to severe atopic dermatitis, comparing twice-daily applications of 0.05% fluticasone propionate cream to once-daily application of the steroid alternating with the vehicle base. No differences were noted in therapeutic efficacy.

Kanzler treated 24 patients with plaque-type psoriasis, comparing twice-daily applications of 0.1% triamcinolone acetonide cream, a mid-potency corticosteroid, to once-daily application of the steroid alternating with its vehicle base, as in the earlier studies [46]. At the end of 4 weeks and all intervals in between, no differences in efficacy could be discerned. He also made the important observation that emollients alone can improve psoriatic plaques by as much as 25%. He urged, as we and others concur, to break the habit of twice-daily applications of corticosteroids, especially when using high-potency steroids.

Watsky et al. [47], continuing in the same vein, treated 56 male and 40 female psoriatic patients with twice-daily application of a high-potency steroid, betamethasone dipropionate, in comparison with once-daily application of the steroid alternating with once-daily application of an oil-rich emollient (Eucerin Cream; Beiersdorf, Hamburg, Germany) for 4 weeks.

Again, at all intervals, the two regimens gave identical results in respect of all clinical signs and symptoms of plaque-type psoriasis as well as clinical grading. It is noteworthy that the subjects themselves uniformly expressed satisfaction with the alternating regimen. These investigators also showed that the alternating regimen was superior to once-daily betamethasone dipropionate.

Finally, application of a potent steroid under a hydrocolloid dressing (DuoDERM) was determined to be a steroid-sparing strategy par excellence. Volden treated 48 patients with therapy-resistant atopic dermatitis including hand eczema, nummular eczema, prurigenous lichenoid papules and lichenifications, with once-weekly applications of clobetasol propionate cream, under occlusive DuoDERM hydrocolloid patches [48]. Complete clearing was obtained in 44 of the 48 patients, generally by 2 weeks. Volden estimated that the amount of steroid required to obtain these impressive results was one-twentieth to one-hundredth of the amount used in daily unocclusive applications.

The Stratum Corneum as a Depot for Topically Applied Drugs

In 1955, Malkinson and Ferguson, studying the penetration of radiolabelled hydrocortisone in humans, proposed that the stratum corneum might serve as a depot for topical drugs [49]. They suggested, wrongly as it turned out, that the open spaces within the airy ‘basket weave’ stratum corneum might allow the accumulation of drugs. It was Vickers in 1963 who unequivocally showed, in a series of simple but elegant studies, that the horny layer was a reservoir for topical drugs [50]. He applied the corticosteroids, fluocinoline acetonide and triamcinolone acetonide, under Saran Wrap, an impermeable plastic film, which in

less than a day produced visible vasoconstriction, lasting for 10–12 h after removing the film. He then showed that vasoconstriction (blanching) could be recalled for up to 2 weeks by simply reapplying Saran Wrap. This manoeuvre released the steroid stored from within the interstices of the horny layer.

Since then, many examples of the depot effect have been reported using a variety of lipid-soluble drugs. Roberts, Gross and Anissimov have developed rigorous pharmacokinetic models of the various factors, such as partition coefficients and diffusivity, which predict deposition of the drug [51].

One of the earliest examples of the depot effect, not understood at the time, relates to systemic toxicity, including death of newborn babies by using a hexachlorophene-containing detergent to wash the diaper area. Hexachlorophene had been used for decades with no hint of adverse events, having achieved an excellent safety record. It turned out that while single washings were innocuous, repeated washings led to a build-up of hexachlorophene in the stratum corneum. Wetness of the diaper area increased permeability, as is now well known [52].

Unawareness of the depot effect can be harmful. For example, shower and bath oils are now very popular for their convenience in treating dry skin over the whole body. Consumers of these bath oils have been led to believe that these products are unusually safe and are in addition an effective way to deliver oils to combat xerosis. Loden and co-workers, however, have called attention to an unexpected adverse effect especially when used by people with sensitive skin. They applied 10% solutions of eight popular bath oils in Finn chambers for 24 h, followed by rinsing. Surprisingly, four of the oils produced a clear-cut irritant reaction, verified by increased TEWL and increased blood flow by laser Doppler velocimetry. Three other oils had negligible effects similar to a negative water control. They then rubbed some of each undiluted bath oil for 5 s over each rinsed site, followed by another 5 s rinsing with tap water. The sites were then covered with empty Finn chambers for 24 h with the intent of hydrating the skin by preventing TEWL. One of the oils, containing MIPA-laureth sulphate, showed an irritant reaction under the empty chambers. Thus, so-called protective oil films may increase the risk of an irritant by inducing a subclinical, invisible injury [53].

The depot effect may turn up unexpectedly under rather surprising circumstances. For example, the application of 10% lactic acid to the nasalar cheek for 10 min, followed by rinsing, is often used to identify persons with ‘sensitive skin’, who typically experience stinging, peaking in about 8 min, as originally described by Frosch and Kligman in 1977 [54]. The site was rinsed with tap water at the end of the test to remove the residue. We studied many factors that influence the stinging reaction but did not anticipate one feature that was brought to our attention by some subjects, namely that taking a shower hours after the application of 10% lactic acid resulted in recall of stinging to the original level.

We examined the recall phenomenon more closely in five women who were moderate lactic acid ‘stingers’. Recall was provoked at various intervals by covering the site with a 2 square of non-woven cloth (Webril) saturated with water, sealed under impermeable tape for 10 min, thoroughly wetting the site. After a 1-h interval, wet Webril fully restored stinging to the original degree. After 3 h, the stinging was slightly less. By 6 h, stinging was

barely perceptible in three of five subjects and was no longer evident by 24 h. In another study of the same five subjects, the lactic acid site was not rinsed off after the 10-min application. In that case, moderate stinging was recalled in four of the five subjects after a 48-h interval but was no longer perceptible after 72 h. Our interpretation is that lactic acid established a depot in the horny layer of the face, known to be more permeable than other body areas. Wetting the site swelled the horny layer, releasing the stored lactic acid.

Knowledge of the storage effect, presently underappreciated, may impact clinical practices. A good example is the use of topical anaesthetics to reduce pain from minor surgical procedures or exposure to lasers. Friedman et al. [55] compared the efficacy of four topical anaesthetics applied for 1 h under occlusion and tested for the degree of induced anaesthesia by pulses from a Q-switched Nd:Yag laser.

Two of the four yielded more anaesthesia at the end of 60 min. The most interesting finding, however, was that the anaesthesia increased with all four when tested 30 min after the 60-min exposure. The authors correctly surmised that a reservoir had been stored in the 'upper skin layers', doubtless the horny layer, supporting the practical suggestion of Arends–Nielson and Bjerring that patients should apply the anaesthetic under occlusion for 1 h at home before going to the office for painful laser treatment [56].

The Effect of Dressings on Disorders in Which the Human Barrier Layer Is Defective

In 1985, R. Shore, a practising dermatologist, made the serendipitous observation that a Band-Aid left in place over a psoriatic plaque for 3 weeks resulted in clinical clearing of the plaque, surprising enough to warrant publication in the *New England Journal of Medicine* [57]. One year later, he looked at various factors that might enable impermeable dressing to resolve psoriatic plaques. He found that:

1. It was best to leave the tapes in place continuously for at least 1 week.
2. Two- to 3-week continuous applications were necessary for complete clearing.
3. Occlusive tapes were more effective than semipermeable ones.
4. Application of a moderately potent corticosteroid under the tapes enhanced efficacy.
5. The occluded sites stayed clear for at least 2 weeks and sometimes as long as 1 year.

Shore could offer no plausible explanation for the effects of occlusion, a mystery that remains mostly unsolved to this very day. Earlier in 1970, Fry et al. [58] had made some preliminary observations that occlusive dressings might cause clearing of psoriatic plaques, but the findings were inconclusive and did not stimulate further work. It is worth noting, for historical accuracy, that Tree and Marks in 1975 had noted incidentally, while trying to explain the placebo effect of bland ointments, that occlusion alone inhibited the increased mitotic rate induced by tape stripping of hairless mice [12].

Interestingly, India-rubber (gutta-percha) dressing, which is occlusive, had been intensively used in the latter half of the nineteenth century in Hebra's clinic in Vienna to treat various dermatologic disorders, apparently with successful outcomes in many cases. India-rubber was eventually abandoned when it was determined that it often induced allergic contact dermatitis.

Actually, it was Winter's classical observations in 1962 that scabs would not form over wounds that were kept moist under semipermeable dressings, warning that complete occlusion might be harmful by inducing maceration [59]. In any case, it is relevant to the thesis of corneotherapy, which we are proposing, that the horny layer barrier is invariably defective in all chronic inflammatory dermatoses, such as atopic dermatitis and psoriasis, and that repair of the barrier by whatever means, pharmacologically or by dressings, is a prerequisite for healing. Furthermore, a great variety of dressing devices have flooded the marketplace, whose efficacy in correcting barrier-impaired dermatoses can no longer be questioned.

My intent in this section is to review the results of various experimenters, including my own group, to exploit the dressing technologies to promote repair of impaired barrier in various disease states. A good place to begin is the extensive studies by Visscher et al. [60] on the effect of semipermeable dressings in superficial, non-ablative wounds, inflicted on forearm skin by partial tape stripping of the stratum corneum. They found that semipermeable dressings provided the optimal water gradient for repair of the defective horny layer, while complete occlusion actually retarded healing as measured by several bioengineering techniques. I strongly recommend close reading of this paper for the insights it provides, especially for bringing forward and elaborating the new concept of 'comfort science'. In this view, the stratum corneum functions as a 'biological smart material important for imparting the visual and tactile sensory signal processing', which determines fabrics that are most comfortable to wear. I have also identified the stratum corneum as a 'smart tissue' that acts as a biosensor of external environmental changes, reacting adaptively to restore homeostatic equilibrium. I note that this is the first paper to use the term 'corneotherapy', borrowed from me, which in this case is an illustration of the practical application of comfort science. The most complete scientific analysis of 'comfort science' is to be found in the publication by Hoath et al. titled 'Sensory transduction and the mammalian epidermis' [61].

The area that has received the greatest amount of experimental attention regarding dressings and which has provided the most information and insights regarding mechanisms relates to the treatment of psoriatic plaques following the footsteps of Shore's Band-Aid discoveries [57]. The 1995 paper by Christophers et al. [62] is perhaps the most informative and revealing regarding problems encountered. They begin at the outset with the frank statement that the mechanisms are unknown. Their focus was on the diverse immunologic events in psoriatic plaques under occlusion therapy for 1 week. They compared occlusion alone, fluocinomide alone for 3 weeks and the combination of the two, finding by global clinical estimation that occlusion alone was just as effective as fluocinomide alone, whereas, of course, the combination of the two was the most effective compared to the untreated control. They

used a battery of immunohistologic techniques in a quest to explain the beneficial effects of a 1-week course of occlusive dressings now that it is understood that psoriasis is an activated T-cell dependent, immunologic-mediated disorder. The epidermal immunologic tests included CD4-T cells, CT8-T cells, Langerhans cells, keratinocyte ICAM-I, IL-8 and others. The dermal tests added endothelial E-selections. The startling finding was that none of these tests were effective by any of the three treatment groups, proffering not even a clue to the mode of action.

These findings were mostly an agreement with Gottlieb et al. [63] who after 2 weeks of occlusion could detect no reduction in immunological markers. Likewise, van Vlijmen-Willems et al. [64] found no reduction along epidermal keratinocytes after 3 weeks of occlusion. The startling disparity between clinical clearing and total lack of immunologic changes is a paradox yet to be resolved. In a way, the absence of immunologic changes is consistent with my earlier findings in my thesis of 'Invisible dermatology' that the characteristic histologic changes of psoriasis, acanthosis and lymphocytic infiltrates were still present many months after clearing of psoriatic plaques by potent corticosteroids [65].

The later report by Hwang et al. [66] in 2001 was fortunately more enlightening than the previous negative reports. These workers focused on the effects of prolonged occlusion in calcium gradients that are known to be disturbed in psoriasis, along with histologic changes revealed by electron microscopy. After 7 days of occlusion, they observed dramatic changes in the parameters under study. They found by light microscopy that 7 days of occlusion resulted in markedly decreased parakeratosis, hyperkeratosis and neutrophilic infiltrates. By electron microscopy, utilizing ruthenium staining of the intercellular spaces, they were able to show striking changes, viz. decreased epidermal thickness and decreased lipid droplets in the stratum corneum, and normalization of intercorneocyte lipid layers, which are scanty and dressed in untreated prose. Increased secretion of lamellar bodies was also noted; in short, almost complete restoration of the abnormal TEM changes. Moreover, the markedly distorted loss of the normal calcium gradient was completely restored to the normal gradient in which Ca deposition is very low in the basal cell layer, reaching a peak level in the outer stratum corneum. Thus, normalization of the epidermal calcium gradient appears to be responsible for the correction of the proliferation and differentiation defects in psoriatic plaques. Although immunologic markers may not be altered by occlusive dressings, it has been shown that for 3 weeks of occlusion therapy with hydrocolloid dressings in psoriasis, expression of differentiating markers such as filaggrin and involucrin was normalized. This has important implications in that these two markers are important for the generation of natural moisturizing factors (NMF) that keep the stratum corneum hydrated even in a dry environment.

Occlusive therapy has become a field unto itself and has resulted in the industrial manufacture of a variety of devices, notable among which are hydrocolloid dressings that are not only occlusive but have the special feature of providing hydration.

Effect of Occlusive Dressing on Keloids and Hypertrophic Scars

In studies of the pathogenesis of keloids and hypertrophic scars, investigators have focused almost exclusively on the prominent changes of the dermal matrix, viz. increased deposition of collagen resulting in elevated indurated lesions, increased production of glycosaminoglycans (GAGs) and increased density of mast cells throughout the upper and lower dermis. Mast cells have received particular attention because they secrete a variety of chemical mediators that could explain the symptoms of itching, pain and inflammation associated with these scars. Little thought has been given to the possible role of the epidermis and stratum corneum when the pathologic changes are considered downstream, events secondary to alterations of the dermal matrix.

An alternative view was proposed by Suetake and co-workers in Japan who undertook an analysis of the functional changes of the stratum corneum overlying hypertrophic scars and keloids reported in 1996 [67]. Clinically, the surface seemed rather dry but they found by non-invasive hygrometric measurements that the surface was actually more hydrated than the surrounding skin. They determined that the horny layer was markedly defective as shown by a great increase in TEWL, indicating a leaky, permeable barrier. Moreover, the turnover time of the horny layer was decreased at least twofold, reflecting increased proliferative activity in the basal layer of the epidermis. Unlike other proliferative disorders, such as atopic dermatitis and psoriasis, they found that the water-holding capacity of the horny layer was increased, not decreased, as is usually the case.

Four years later, this same group, intrigued by the observation of a number of researchers that silicone gel sheets flattened and resolved keloid and hypertrophic scars, undertook a functional analysis of the horny layer overlying these scars [68]. Having found that the horny layer over scars was more hydrated than the surrounding skin, they questioned the prevalent idea that water retention induced by occlusion could be a factor in the efficacy of silicone sheets. They compared silicone sheets to an impermeable plastic, Saran Wrap, renewed daily for 1 week, having established that the TEWL of both devices was equal, 0.5 g m^2/h. They first studied two subjects, one on the normal forearm of a young woman and another on a split-thickness donor graft site. They undertook a functional analysis of the stratum corneum on days 1 and 7, using qualitative non-invasive methodologies described by Tagami. The stratum corneum changes were strikingly different for the two impermeable dressings. After 1 day, water uptake (hygroscopicity) was much greater with Saran Wrap than the silicone sheet, indicating increased hydration. After 7 days, the hydration level fell with the silicone sheet and stayed the same with Saran Wrap. After 1 day, TEWL was measured 30 min after removal of the dressings and was much greater with Saran Wrap than with silicone, increasing further after 7 days, staying the same after 7 days and again reflecting greater uptake of water by Saran Wrap. The capacity to hold water (hydrophilicity), revealed by sorption–desorption kinetics, was as expected greater after Saran Wrap than silicone, increasing further after 7 days of Saran Wrap. Additionally, two subjects with hypertrophic scars were subjected to the same analysis of stratum corneum functions, with

results comparable to those described previously for normal skin. Interestingly, these investigators likened the Saran Wrap results to those that were characteristic of the changes induced by an effective moisturizer (Tagami).

The conclusion was that silicone sheets maintained a mild level of hydration, falling with continued exposures, compared to excessive hydration and water-holding capacity with Saran Wrap. Clinicians were aware that excessive exposure to water in such occupations as hair tending, cannery workers and dishwashers experienced adverse effects that Kligman described under the heading of 'hydration dermatitis' [69].

Finally, Elias et al. [70] (P.M. Elias, unpublished data) treated six keloid patients with silicone gel sheets for 24 weeks and demonstrated unequivocal benefits in regard to reductions in itching, pain, redness and elevation, already evident by 4 weeks, with steady improvements over 24 weeks, with complete disappearance of itching and pain.

My group performed pilot studies on two young men with extremely dense and elevated hypertrophic scars associated with severe acne conglobata of the upper back. We compared three treatments on 3-in. squares with symmetrical scars: (1) silicone gel sheets changed daily for 4 weeks, except on weekends; (2) Saran Wrap changed every 3 days for 4 weeks, sealed under occlusive Blenderm tape; and (3) water-saturated non-woven cotton pads (Webril) sealed under Blenderm tape, changed every 3 days. By the end of 4 weeks, we estimated a modest flattening of the scars with fading of erythema with silicone sheets, somewhat less so with Saran Wrap. By contrast, we had to stop the wet Webril applications after 6 and 9 days, respectively, owing to a fierce exacerbation of inflammation, pain, exudation, maceration and oedema, signs that slowly resolved after b.i.d. applications of 0.05% clobetasol propionate cream. This was a dramatic illustration of 'hydration dermatitis'.

Perhaps the most instructive finding of the study by Elias et al. [70] (P.M. Elias, unpublished data) was a decreased density of mast cells throughout the upper and lower dermis, revealed by toluidine blue staining. Mast cells are known to secrete a number of chemical mediators, especially histamine and substance P, which presumably explains the relief of itching, pain and redness by silicone sheets, which are valuable not only for treatment but for the prevention of emerging scars after surgical excisions (Fulton).

Elias et al. [70] (P.M. Elias, unpublished data) have synthesized these findings into a plausible hypothesis of the mechanisms by which silicone sheets exert their beneficial effects, starting with the proved demonstration that the horny layers overlying keloid and hypertrophic scars are defective, structurally deranged and functionally more permeable, known also to be a reservoir or storage depot of pro-inflammatory substances. Accordingly, primary cytokines are released that 'stimulate the formation of additional cytokines, resulting in a downstream cascade of additional cytokines, adhesion molecules and other mediators'. Fibroplasia and angiogenesis are subsequently engendered, which lead to increased production of collagen and GAGs, prominent features of scars. The therapeutic end game is restoration of the impaired barrier that would interrupt this pathogenic sequence.

Conclusions

Corneobiology refers to that broad range of experimental studies that are focused on the anatomy, physiology and biology of the stratum corneum, centred particularly on the human horny layer that has features uniquely different from other mammals. Corneobiology has a very broad reach, encompassing studies that deal with immunology, endocrinology, neurobiology and psychology, comprising a network of complex interactions that have connections to the central nervous system. It has attracted the attention of a confederation of scientists from very different disciplines, including molecular biologists, anatomists, physiologists, pharmacologists, geneticists, psychologists and still others. Corneotherapy refers to preventive interventions that are primarily directed to the correction and restoration of the stratum corneum barrier that has been rendered defective and impaired by disease, genetics and a variety of mechanical, physical, chemical and psychological exogenous insults and stresses. Contributors to building the edifice, we now call corneobiology, are a motley, diverse crew of investigators, mainly situated in industry and academia from around the world.

AV Rawlings has recently named me as 'the father of corneobiology' [71], a high tribute that I hope represents the consensus of the world of corneobiologists.

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