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Photoaging

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INTRODUCTION

Aging and photoaging of the skin are now well-accepted concepts, but formerly it was equivalent to heresy to propose that these were anything but natural events. Aging skin was to be accepted as an inevitable, irreversible, and trivial consequence of getting old.

It became obvious early on that skin damage was an inevitable sequela of the medical use of x-rays; only in the past two to three decades has the extremely damaging nature of ultraviolet radiation (UVR) become increasingly clear to both scientists and the general population, and attempts to circumvent and reverse such damage have become extremely popular. These observations have coincided with several pertinent phenomena: (1) the incredible growth of scientific knowledge in recent years; (2) people in western populations living longer and spending increased leisure time exposed to sun in outdoor activities; and (3) the rampant cosmetic claims for products that will ‘‘turn back the clock’’ to youth overnight.

In the midst of this chaos, there exist two opposing hemispheres. One is the northern hemisphere, where life is rigid, cold scientific proof is difficult, and only the hardiest survive in the frozen tundras of pharmaceutical bureaucracy and governmental regulation. The southern hemisphere is friendly and warm and things that make you ‘‘feel’’ better are considered good, rather than inherently evil because they are not ‘‘natural’’ and may prevent us from looking our age.

War has inevitably existed between these two spheres ever since south's cosmetics were defined as bad and the north's pharmaceuticals were defined as good. Advocacy of the term cosmeceutical, as an attempt to compromise and bridge the gap between cosmetic and pharmaceutical, greatly enlivened the debate.

In fact, the debate has forced us to reevaluate what we truly believe, even made us iconoclasts, willing to listen to new ideas. It has taken place during an era of unprecedented discovery about the structure and functioning of the skin, and the discussion has begun to rise above the former shrill hysteria and is now on a higher plane of logic and scientific facts.

Photoaging is the ideal skin condition to focus the debate. On one hand, appearance of the facial skin makes this condition so obvious to the subject and observers, which in turn makes the use of cosmetic products so appealing. On the other hand, only a pharmaceutical product can truly and meaningfully effect change in the substantial pathology of the condition. The clear demonstration of the clinical efficacy of tretinoin, a pharmaceutically active retinoid topically applied for a cosmetic condition, speaks to the utility of the term cosmeceutical.

BACKGROUND

The term cosmeceutical implies cosmetic utility with an activity of at least a mild pharmacological or pharmaceutical nature. Cosmetic effect should be at least a partial result of structural or functional change, which can be reproducibly demonstrated by some reliable, accurate, and validated methodology—be it clinical or instrumental. Topical products presently predominate in the discussion, yet nontoxic, systemic substances such as vitamins and naturally occurring substances should also be considered in the definition.

Distinction between intrinsic aging of the skin and photoaging has been repeatedly emphasized, but in the context of this discussion it has little relevance; skin that is visible and cosmetically deteriorated is invariably sun exposed and usually highly sun damaged. In the vast majority of individuals, photoaging overshadows intrinsic changes, especially in the skin of the face, neck, and dorsal forearms (1).

The terms photoaging and photodamage have frequently been used interchangeably, although we have previously preferred to define photoaging as a process and photodamage as a description of the clinical or histological condition at any point in time. Photoaging begins at a very early time point, even in infancy, as a result of repetitive, chronic exposure of the skin to ultraviolet radiation. Clinical changes recognizable as photodamage may appear in early childhood, especially where exposure is high. A study of teenagers' skin in Australia demonstrated that 70% of Australians have detectable sun damage by the age of 14

years (2). As the process of photoaging continues, additional clinical signs of wrinkling, texture, and pigmentary change become progressively noticeable. Cessation of exposure to UVR or treatment allows partial reversal of the clinical and histological change. Both from the clinical and chronological standpoints, the process is a continuum with change possible in either direction.

THE COSMECEUTICAL PERSPECTIVE

The concept of photoaging is scientifically and psychologically complex and inclusive of a broad perspective (Table 1). A subject's self-assessment of appearance, the marketing claim made for the product, and the physical attributes of the cosmetic product are frequently strong forces in the equation, yet to the practitioner, investigator, and regulator, a rigorous endpoint of cosmetic improvement or demonstration of pharmacological activity may be most central. Evaluation for cosmeceutical effect must account for the following specific and distinct needs.

The customer's perspective is more related to the individual's perceptions of their skin appearance than to a meticulously quantitated numerical assessment of its condition. These perceptions are more global than specific, and mandate an evaluation that is weighted toward overall appearance but adequately accounts for specific concerns of dryness, texture, wrinkling, skin color, and pigmentary unevenness. The consumer asks, ''How old do I look?'' first and ''How can I get rid of these wrinkles and liver spots?'' second, although much scientific investigation seeks to preferentially quantitate specific parameters.

Cosmetic or therapeutic effects produced by the product are important to the consumer, but so are physical aspects of the product itself. A product that is not cosmetically elegant or that is drying or irritating to the skin will be less acceptable to the consumer in spite of alleged pharmaceutical properties. These aspects and physical attributes of cosmetics can be well quantitated by both consumer panel testing of the product as well as by specific instrumentation.

Table 1 The Cosmeceutical Perspective

Subject's self-perceptions
Customer cosmetic expectations
Product physical attributes
Regulatory aspects
Marketing claims
Degree of pharmacological activity

Cosmeceutical properties of a therapeutic intervention are central to the discussion and may require both well-conducted studies of consumer satisfaction as well as adequate documentation and substantiation of cosmetic or therapeutic claims (e.g., improvement in overall appearance, percent reduction of wrinkles, improvement in roughness and pigmentary unevenness). Adequate methodology exists to evaluate rigorously these cosmeceutical aspects.

Pharmaceutical testing of pharmacological effect is, by definition, the most stringent, requiring not only adequate trial design and execution but substantially more documentation of statistically significant changes that are also clinically and consumer relevant. This is the area where proper application of biometrics to photoaging is most helpful and important (3).

THE CLINICAL CONDITION OF PHOTOAGING

Cosmetic Deficits

The subject or patient complains that they look ''old'' to themselves and others (Table 2). They note that their skin is rough, dry, wrinkled, and that their face and hands, in particular, have numbers of variously colored flat spots. Tanning no longer produces an even darkening of the skin and, especially on the legs, numerous white spots have appeared. Occasionally they are aware of a less resilient quality of their skin, which in some areas tends to sag and not bounce back when it is stretched. Raised unsightly growths of cosmetic or medical concern to the patient may have appeared.

Clinical Presentations

Photoaging is most frequently progressive, yet modified by both environmental exposure and genetics (Table 3). The clinical presentation of photodamage is therefore highly polymorphic but with many characteristic signs and symptoms (4).

Table 2 Photoaging Signs and Symptoms

Overall appearance older than chronological age
Wrinkles, fine and coarse
Diverse pigmentary alterations
Rough texture
Dryness
Sallow complexion
Various neoplasms, benign and malignant

Table 3 Functional Abnormalities of Photoaging

Uneven tanning
Skin easily distends
Slow return to normal contour
Thinned skin easily traumatized
Sensory decrease
Decrease in immune competence

The most casual observation of the face or neck of an individual with photodamaged skin, even by the untrained observer, consciously and subconsciously gives an overall impression of a person older than their chronological age. Visually, wrinkles both fine and coarse are frequently the hallmark of sun-damaged skin in many individuals, although genetic differences may, in some, favor pigmentary alterations or thinning of the skin as the most prominent presenting sign.

An overall sallow, or yellowish hue, is common and presumably due to the complex interplay of light absorption and reflection in photodamaged skin that is characterized by uneven thickness of the stratum corneum and abnormalities of melanization. Additionally, circulatory alterations of endogenous origin or as a consequence of photodamage produce variable contributions of heme pigment to overall skin color.

Pigmentary alteration of photodamaged skin is very common but highly variable. Discrete alterations consistent with actinic lentigos, especially prominent on the face and hands, may alternate with mottled hyperpigmentation consisting of patchy and alternating lighter and darker macules due to diffuse abnormalities of melanogenesis and melanosome distribution in keratinocytes. Diffuse pigmentary change may also present as melasma on the face due to either epidermal melanin abnormalities or dermal macrophages containing melanin or heme pigment.

Hypomelanotic macules are vitiligenous and are frequently observed most prominently on the lower extremities.

Dryness and surface roughness, best perceived by tactile rather than visual means, are among the most common complaints related to aged and photoaged skin, but are not specific for either. Scaling due to dryness or perturbation in epidermal turnover is also common, but not specific to photodamage.

Multiple neoplastic lesions as a consequence of photodamage are common. Benign seborrheic keratoses are mostly cosmetic growths that appear in sun-exposed body areas.

Functional Alterations

Photodamage-related structural alterations in epidermis and dermis are mirrored by functional abnormalities that may be of either cosmetic or medical consequence. The skin no longer tans evenly and areas of hypopigmentation may sunburn after minimal UVR exposure. The skin is easily distended and does not quickly return to its original contour. Grossly observed thinning and histological stratum corneum irregularity, epidermal thinning, and abnormal collagen and elastin result in skin that is easily traumatized with abrasions, cuts, and tears. Blood vessels can be easily seen through the skin and, because of epidermal thinning and decreased dermal integrity, the skin bruises and bleeds more easily than normal.

Sensory decrease, not usually clinically obvious, has been partially documented in increasing age, though not specifically in photoaging. Utilizing skin compliance and a two-point discrimination testing on the pad of the index finger, increasing age was correlated with decreased tactile sensitivity and said to be likely related to change in the nervous system (tactile discrimination), rather than change in skin itself (skin compliance) (5). An actual increase in intraepidermal nerve fibers, correlated with severity of photodamage, was observed in a recent study of the ultrastructure of photodamaged skin and was theorized to be indicative of a neural involvement in the pathophysiology and/or repair of photodamaged skin (6). The known effects of capsaicin on skin sensory function as well as the observations of synthesis of nerve growth factor (NGF) and other biologically active factors by keratinocytes should stimulate further research in this interesting area.

A decrease in immune competence of aged skin has been repeatedly demonstrated and UVR is known to be highly immunosuppressive. This complicated interaction continues to be an extremely important area of research (7).

COSMECEUTICAL PRODUCT TESTING

Product Attributes

The consumer can personally judge certain charateristics of the product and, although there is a wide range of acceptable characteristics, certain general principles apply. Since the products will be applied at least to the face, and probably to other areas of the body, it must be cosmetically acceptable and preferably refined or elegant. Exceptions are those individuals who will use a greasy ointment or malodored product thinking it must be therapeutic if it has those undesirable characteristics.

Product qualities and potential acceptance can be tested more rigorously by using a panel of trained individuals who note the various properties of the

Table 4 Product Testing

Product attributes by dermatosensory panel
Claim substantiation
Instrumentation
Pharmaceutical testing

formulation (Table 4). Even untrained individuals may be able to distinguish overall acceptability but use of trained panelists allows much greater refinement of the overall and individual aspects of the product. Commercial testing is available (entitled the DermatoSensory Profile), which describes and grades or compares products for their characteristics of appearance and feel on the skin. Testing includes evaluation of the rate of absorption of the product into the skin, including spreadability and stickiness, immediate afterfeel, including shininess, greasy or oily feeling, drag (the sensation of resistance to motion over the skin), and residue (the sensation or perception of something remaining on the skin). Perception of residue after set periods of time such as 5, 15, and 30 min is called delayed afterfeel. Various descriptions of the product itself, aside from its characteristics on the skin such as color, odor, thickness, substantivity, consistency, grittiness, or smoothness can also be described. Many of these product characteristics are important in consumer acceptance of the cosmeceutical as well as in their perception of benefit.

Cosmeceutical Testing

No matter if cosmetic or pharmaceutical endpoints are sought, adequate trial design is critical for accurate, precise, consistent, reproducible, and valid observations in photoaging. The optimum trial for pharmaceutical, and to some extent cosmeceutical, purposes is double-blind, placebo (vehicle)-controlled, multicenter, and frequently, for the chronic process of photoaging, of at least several months' duration. Study of a relatively large, genetically homogeneous population of a narrow range of similar skin type (usually skin types I–III) is often required to observe statistically significant differences. Cosmetic testing may be of much shorter duration in fewer subjects but should optimally follow the same basic logic. Study of the parameter that is most important to the product is essential; a facial moisturizer designed for older females living in the north should not be artificially tested in male and female college students in the south. Similarly, establishment of change of transepidermal water loss (TEWL) is irrelevant if the product is claiming to affect wrinkles.

Overall severity rating for study entry and follow-up of global appearance has been accomplished with a photographically derived rating scale, with 0 =

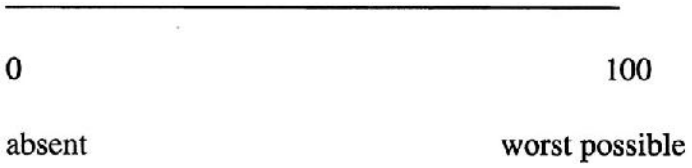

Figure 1

none, 1 to 3 = mild, 4 to 6 = moderate, and 7 to 9 = severe photodamage (8). These evaluations may be performed by the investigator, by the subject, or by third persons comparing photographs of before and after in a randomized and blinded manner.

This and similar rating scales may also be applied at baseline and follow-up to specific parameters such as wrinkles, surface roughness, mottled pigmentation, overall color, skin dryness, and texture.

A 100-mm visual analogue scale has been successfully utilized to rate the overall appearance of the skin and specific parameters of fine wrinkles, discrete pigmentation, shallowness, and texture. The scale may be continuous from 0 to 100 (Fig. 1), rating the condition as absent to severe, or balanced (Fig. 2) with a score of zero designating no change from baseline, improvement recorded to the right side of zero (to a maximum of +50 mm), and worsening recorded to the left side of zero (to a minimum of −50 mm).

A clinical panel evaluation technique has been described that potentially allows precise, consistent, and completely unbiased evaluations of clinical state (9). Very high-quality photographic slides are obtained, prepared in matched carousels, and placed on two random-access projectors in a rear-screen projection booth. Side-by-side comparison of each patient's time-randomized baseline and end-of-treatment photographic slides by trained, but uninvolved, evaluators is thus accomplished in a completely blinded and randomized manner. Both global response and specific parameters of overall appearance, fine wrinkles, and discrete pigmentation can be judged and graded on a 13-point balanced categorical

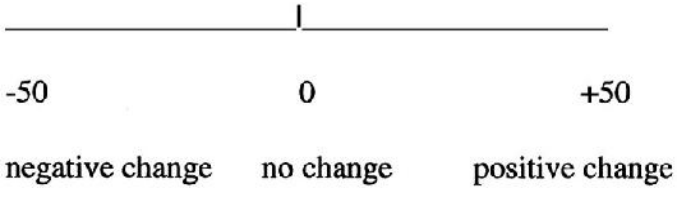

Figure 2

scale with zero representing no difference between the two photographs. A score of +1 to +6 is assigned when the end-of-treatment photograph is perceived to be better and a score of −1 to −6 when the baseline photograph is perceived to be better.

Trials of isotretinoin have successfully utilized the clinical panel and demonstrated the therapeutic effect compared to vehicle (10,11).

Claim Substantiation

If the above-described pharmaceutically oriented trials demonstrate significant effect, claim substantiation may be relatively easy and clear-cut.

However, distinction may be made among the various aspects of a claim for a product. There are, in each country, very different cultural and legal perspectives dictating what can be stated about a product designated for photoaging. These claims are generally related to the broad perception of whether the cosmetic or skin-care aspects, the potential cosmeceutical action, or a proven pharmaceutical effect is being claimed and advertised. In this regard, everything from consumer statements, consumer panel testing, instrumentation results, clinical testing results, to absence or presence of statements regarding alteration of structure or function of the skin must be considered in evaluating, regulating, and advertising a product.

Use of Instrumentation

With no other methodology is there the same potential for accurate, precise, reproducible, consistent data to used appropriately or to be nefariously manipulated to purport therapeutic effect as with the now-available and sophisticated instrumentation (12). Evaluation of the obtained instrumental data must take place in a clinically appropriate context for them to be truthful and meaningful (Table 5).

Table 5 Instrumentation

Optical profilometry
Fluorescent photography
Ultrasound
Transepidermal water loss
Skin hydration by capacitance/conductance
Laser Doppler
Colorimetry

Optical Profilometry

Profilometry is one of the most useful techniques in photodamage evaluation. A skin replica obtained with silflo dental impression material is oriented and side-illuminated to produce shadows of various widths and depths that are captured by high-resolution video interfaced to a computer containing image-analysis software (13). The width and depth of the ''peaks'' and ''valleys'' of the skin surface may correspond to roughness, wrinkling, or other surface contours or markings and can be differentiated by the analysis software. The technique is reproducible and blinded, can be utilized even in large clinical trials, and has correlation with the clinical condition. Evaluation of the cheek and crows feet area of the face consistently demonstrate approximately a 10% improvement in wrinkles after treatment with tretinoin (14). It can also be useful in evaluation of skin roughness that may change after tretinoin or alpha hydroxy acid treatments.

Fluorescent and Polarized Photography

Another highly informative technique utilizes photographs obtained with illumination of UVR of 365-nm wavelength to highlight differences in epidermal melanin content and distribution. The photographs of photoaged skin may be highly dramatic in accentuating mottled and diffuse pigmentary alterations and may also be quantitative, utilizing visual counting of macules and evaluation of diffuse change compared to a 20-point gray scale (15). Polarized photography allows selective enhancement of the appearance of wrinkles, pigmentary change, or erythema (16).

High-Resolution Facial Photography

A very sophisticated research tool, high-resolution facial photography allows direct visualization and measurement of individual wrinkles and appears to be potentially highly sensitive and precise for determination of this parametner (17). Present systems are proprietary, however, and have not been commercially available.

Ultrasound

High-frequency B-scan ultrasound consistently demonstrates an echo-poor band in the upper dermis corresponding to the location of dermal elastosis of photoaging (18). Refinement of ultrasound techniques may soon allow more precise definition of epidermal and dermal thickness and changes resulting from therapy.

Transepidermal Water Loss

Although a nonspecific technique, measurement of transepidermal water loss (TEWL) is frequently utilized. TEWL may be increased whenever barrier func-

tion of the epidermis is altered. The underlying changes of stratum corneum may be a result of acute or chronic insult and correlation of TEWL with a specific condition or its therapy is frequently not a simple matter. Aged skin has been variously demonstrated to have changes in TEWL (19). Nonspecific interventions, such as use of moisturizers, may quickly effect substantial changes in TEWL and more specific hydrating measures, such as the inclusion of humectants, hyaluronic acid, lactic or glycolic acid, and lipids, which can be absorbed into the intercellular space, may also affect TEWL.

Skin Hydration

Measured by capacitance or conductance, skin hydration may (similar to TEWL) demonstrate acute, chronic, narrow, or wide oscillations in a variety of skin conditions and experimental circumstances. Hydration status is not specific to photodamage but may be improved as a result of some treatments for photodamage.

Cutaneous Blood Flow

Blood flow through the skin can be measured by laser Doppler instrumentation and may reflect local flow as with increased capillary growth or as a result of local inflammation or overall vascular response to environmental factors such as exercise. As with many other techniques mentioned herein, interpretation of results is critical to reliable conclusions about pharmacological effect of a product.

The Dansyl Chloride Technique

This relatively simple method allows estimation of epidermal turnover by staining stratum corneum with dansyl chloride (or other stains) and subsequently evaluating the time to elimination of the stain from the skin by visual or instrumental observation. The time to elimination of the stain (in days) reflects the rate at which the desquamating stratum corneum has been replaced by underlying proliferative epidermis. Agents purporting skin ''rejuvenation'' are frequently evaluated with modifications of this technique.

Skin Color by Colorimetry

With the use of appropriate filter, this technique is more specific, sensitive, and reproducible than visual observation of skin color. It offers an instrumental approach to enable separation of skin color effects related to melanin or heme pigments and is especially useful in precisely quantitating erythema.

Miscellaneous Instrumentation

Mechanical properties of the skin measured by twistometry, indentometry, levarometry, and ballistometry reflect some of the most important aspects of the mechanical functioning of the skin such as elasticity, ability to reconform after deformation, strength to resist torsional and abrasive trauma, etc. Although many techniques exist to evaluate these characteristics, in the absence of notable products that improve these functional aspects, they are not yet of widespread pharmaceutical testing utility.

PRODUCTS POTENTIALLY CLASSED AS COSMECEUTICALS

It is clear from the above-described diversity of product testing that many extremely sensitive and reproducible clinical and instrumental techniques are widely available to study products for their potential cosmeceutical effect. The issue of classification of any product thus becomes partly definitional and partly perceptual. As beauty is in the eye of the beholder, so the consumer, investigator, or regulator may view any objective fact in disparate fashion. There is not a single or universally defined and accepted endpoint with any of the above-elaborated techniques that determines if a product is cosmetic, cosmeceutical, or pharmaceutical. Most of the below products described are accepted as at least cosmetic in effect, many as pharmacologically active, and most as cosmeceutical as defined above (Table 6).

Moisturizers

As pointed out in a previous chapter, it is now clear that even simple occlusion of the skin, with a ''moisturizer'' such as petrolatum, has definite effects on skin

Table 6 Potential Cosmeceuticals

Moisturizer
Retinoids
Estrogens
Various vitamins and minerals
Alpha-hydroxy acids
Beta-hydroxy acids
Hydroquinones
Hyaluronic acid
Natural cartilage polysaccharides

structure and probably on function and thus it is appropriate to begin the discussion of potential cosmeceuticals with this seemingly simple product (see Chap. 1). In fact, however, the matter is far from simple, as modern moisturizers have achieved a sophistication and multiplicity of potential effects in parallel with our increasing knowledge of stratum corneum barrier function and kinetics of skin hydration and transepidermal water loss.

There is no universally accepted clinical or biomechanical definition of dry skin, although photoaged skin is frequently described as dry. Dry skin may be clinically rough, scaly, less flexible, and dry to the touch. Instrumental measurements may reveal changes in skin surface topography such as irregularity of stratum corneum and abnormal desquamation by profilometric evaluation or sticky tape application. An increase in TEWL indicative of impaired barrier function of the stratum corneum may be due to stratum corneum disruption and loss of intercellular lipids. A decrease in moisture of the viable epidermis can be determined by capacitance (Corneometer) or conductance (Skicon®-100)techniques.

Although older or photodamaged skin is frequently perceived as ''dry,'' there is substantial evidence that TEWL is actually decreased in chronologically aged skin, possibly due to increase in stratum corneum barrier function or decreased moisture content of the viable epidermis (20).

Moisturizers and emollients may exert their positive effects in several ways. Simple occlusion effects may acutely allow retention of more water in the skin and acutely lead to lowered TEWL. Healing of damaged stratum corneum and replacement of intercellular lipids may reestablish normal barrier function and allow normalization of TEWL. Strictly cosmetic effects of change in perception of dryness and skin smoothness also may be noted.

Retinoids

Retinoids, with pleotropic biological effects including modulation of epidermal cell differentiation and sebocyte dedifferentiation, have been extensively studied and have, in a way, become the prototypic cosmeceutical by which others are judged in treatment of photoaging. Without an immediately perceived and clinically obvious pharmacological effect, after many weeks of application they produce a number of definite, observable, and quantifiable improvements in photodamaged skin; these changes are best described clinically as cosmetic in appearance but with definite, modest, chronic pharmacological effect on epidermis and dermis.

Tretinoin has been well studied in multiple, large, open, and blinded clinical trials over the past 20 years and is unquestionably active in reversing some of the clinical, histological, and instrumentally determined manifestations of photodamage. This molecule can be considered as a prototypic cosmeceutical with clear pharmacological action producing a definite cosmetic effect. The various

clinical and histological grading systems consistently demonstrate improvement (21–23). Excellent, good, or fair responses were obtained in 5%, 21%, and 42% of 76 tretinoin emollient cream–treated patients and in 0%, 11%, and 32% of 72 vehicle-treated subjects—results that were clinically obvious, cosmetically meaningful, and statistically significant ($p < 0.001$) (24). The mean percent change from baseline in this study was 16.5%, a cosmetically noticeable change indicative of a modest long-term pharmacological effect. The individual parameters of fine wrinkling, roughness, and mottled pigmentation are consistently improved and can be observed and quantitated by the subject. The investigator or a third party can confirm this utility with any and all of the clinical grading systems, visual analogue scoring, clinical panel assessment, fluorescent and polarized photography, optical profilometry, and histological assessments described above.

Some months of treatment are necessary to reach meaningful clinical effect and the treatment, while generally adequately tolerated, does frequently produce some undesired dryness and erythema especially at the onset. Roughness, fine wrinkles, and mottled pigmentation respond but meaningful improvements in skin function, such as elasticity have not been consistently described. A small study of six women aged 68 to 79 years who applied 0.025% tretinoin cream to the nonsun-exposed skin of the inner thigh for 9 months demonstrated alteration of the involutional structural changes in intrinsically aged sun-protected skin (25). Thus, the reparative abilities of retinoids may not be limited only to photodamage.

Isotretinoin has also been adequately documented in double-blind, vehicle-controlled trials to improve the same parameters of photoaging as tretinoin and appears to be well tolerated.

Adapalene has been proven effective in treatment of acne (26). It most likely will be studied and proven efficacious in reversing some of the stigmata of photoaging.

Tazarotene, another recently studied retinoid, has been shown to be effective in psoriasis and acne will likely be effective in photoaging (27).

Retinol, the prototypic retinoid, is the alcohol of retinoic acid and has been shown to be somewhat active in animal models of photodamage. It has recently been incorporated into two products marketed as AFIRM and as Healthy Skin Anti-Wrinkle Cream with claims relative to photoaging in humans stating ''. . . a retinol product . . . clinically proven effective at reducing the appearance of fine lines, wrinkles, and mottled hyperpigmentation, while improving skin texture and tone'' (28). Data to substantiate this cosmetic claim (not the same as pharmaceutical efficacy substantiation) are not included in the advertisements.

Hormones and Vitamins

As many hormone and vitamin deficiencies adversely affect the skin and as many of the skin functions and structures have been shown to be affected by hormonal

or vitamin treatment, it is surprising that there has not recently been more quality research in the area of hormonal and vitamin effects or attention focused on the therapeutic use of androgen, thyroid, or growth hormones topically applied in photoaging.

Androgens

Androgens play a major role in skin physiology and are especially important in regulation of hair growth and sebum secretion. Less is known about their anabolic capabilities in skin but one would conclude that they should produce beneficial effects on aging and photoaging skin although conclusive proof is presently lacking.

Estrogens

A modest literature does exist, however, supporting the utility of estrogens in reversing at least some of the sequelae of skin aging. An open study of 98 postmenopausal women found a skin difference of 7 to 15% thickening of the skin and a 35% increase in sebum in those women who had been using estradiol gel or hormone replacement therapy (HRT) compared to the women who had not been receiving HRT (29). The mean duration of HRT was 58 months.

A pilot comparative study of eight perimenopausal women treated with 0.3% estriol, and 10 perimenopausal women treated with 0.01% estradiol to the face for 6 months duration showed improvement in symptoms of skin aging in both groups, with no changes in vaginal epithelium or in serum estradiol, follicle stimulating hormone, or prolactin (30). Clinically, improvement of elasticity, firmness, skin moisture, vascularization, and wrinkling were noted. Instrumental determination of skin moisture (Corneometer CM 420) showed increases from 55.9 ($\pm$ 30.5 S.D.) to 80.0 ($\pm$ 28.4 S.D.) in the estradiol group and comparable results in the estriol group. Optical profilometry (Hommeltester T 2000) results in five patients (estradiol group) and seven patients (estriol group) showed statistically significant changes in wrinkling in both groups with mean RZ-D measurements of 38.6 μm pretreatment and 24.8 μm at end of treatment in the estradiol group, and means of 40.7 and 28.2 μm in the estriol group.

A randomized, double-blind study of 54 women aged 52 to 70 years with moderate-to-severe facial cutaneous aging compared treatment with either 1 g Premarin cream (0.625 conjugated estrogens per gram) or placebo vehicle cream applied to the face for 24 weeks (31). A statistically significant difference in skin thickness measured by B-scan ultrasonic echography was demonstrated at week 24 in the Premarin-treated group. Skin thickness of epidermis plus dermis increased from a mean of 1.56 $\pm$ 0.20 mm at baseline to 1.68 $\pm$ 0.19 mm at end of treatment with Premarin ($p = 0.013$). At weeks 12 and 24, Premarin cream was significantly ($p = 0.010$ and $p = 0.012$) more effective in improving fine wrinkles as measured by mechanical profilimetry. Clinically, significant improve-

ments in roughness, laxity, and mottled hyperpigmentation were noted by the investigator, but no differences from baseline or between the two groups were noted in subjects' self-evaluations of overall facial appearance or wrinkling of the crow's feet area. Although pre- and posthormone determinations were not obtained in this study, a significant difference from baseline in the vaginal maturation index was noted in the Premarin-treated group, indicating probable systemic effect.

A 6-month study compared the effects of 0.01% estradiol and 0.3% estriol topically applied to the facial skin of 59 preclimacteric women with skin aging symptoms (32). Both groups demonstrated significant decreases of wrinkle depth measured by optical profilimetry as well as clinical improvement in elasticity and firmness of the skin. Significant increases of type III collagen labeling by immunohistochemistry and increased collagen fibers were noted. No evidence of systemic hormonal effect was noted except for an increase in prolactin levels.

Vitamins

Vitamin D

Many vitamin D analogues have demonstrated effects on epidermal cells and fibroblasts and they have achieved quick acceptance in treatment of psoriasis. As some of their properties resemble those of retinoids, modulation of epidermal differentiation is possible and should be investigated in photoaging.

Vitamin C

As with claims for retinol in cosmetic products, the claims made for topical vitamin C are still more cosmetic than documented pharmaceutical.

Vitamin E

Vitamin E is an antioxidant in many systems and has been proposed, studied, and promoted for a large number of diverse systemic and skin conditions (33). On a theoretical basis, the concept of utility of the antioxidant effect of vitamin E is appealing, but, although the literature is voluminous, it is not completely convincing of a pharmaceutical effect in most conditions including skin disease, photoprotection, or photoaging. A 4-week study of 5% RRR alpha-tocopherol oil-in-water cream applied to the crows feet area demonstrated, by optical profilometry, decreased skin roughness, length of facial lines, and depth of wrinkles compared to placebo (34). A 10-day study by the same investigators claimed

enhanced skin smoothness with topical vitamin E. Larger, longer trials are needed to substantiate a true and long-lasting effect.

Miscellaneous Agents

Alpha-Hydroxy Acids

A now substantial literature demonstrates a definite cosmeceutical effect of alpha-hydroxy acids (AHA). In a pilot study, a 25% increase in skin thickness was noted, comprised of both epidermal and dermal contributions. Increased acid mucopolysaccharides, improvement in elastic fiber quality, and increase in collagen density were also noted (35). A 22-week double-blind study confirmed utility of both 8% glycolic and 8% lactic acid in treatment of photodamaged skin in overall appearance and in specific parameters of mottled pigmentation, sallowness, and roughness (36).

The beta-hydroxy acid, salicylic acid, has been studied for its effects on photodamage in a large number of women during a home-use trial versus a proprietary glycolic acid cream and was observed to be superior on global improvement of appearance (37).

Hydroquinones

These agents, as weak depigmenting agents, may occasionally be of some utility in treatment of the epidermal pigmentary irregularities associated with photoaging. Higher concentrations, better delivery systems, and combination with other active products may enhance their utility in treatment of pigmentary abnormalities related to photoaging.

Alpha-Interferon

An interferon-containing cream was demonstrated to increase cutaneous CD1a+ cells and HLA− DR+ cells in aging skin and in skin treated with PUVA implying that this increase in epidermal Langerhans cells may benefit photoaging-reduced immunosurveillance (38). Substantiation of clinical effect requires additional study.

Minerals

The legends surrounding Cleopatra, the ancient Queen of Eygypt, are numerous. Frequently referenced in advertising of cosmetics, she is said to have claimed the rights to the Dead Sea's mineral ingredients and, most naturally, these ingredients have claimed numerous cosmetic properties (39). Cosmetics derived from this source are varied in their composition. Some contain a high concentration of divalent cations, magnesium, and calcium and a lower concentration of mono-

valent cations sodium and potassium as well as miscellaneous other cations and anions. Zinc and selenium have been frequently studied in dermatological conditions, most often inconclusively for true pharmacological effect, but these and other minerals unquestionably play major roles in normal physiology of the mammalian organism. Most notably, their vital roles as cofactors in enzymatic processes means that they cannot be completely dismissed in spite of sometimes extravagant marketing claims. Much confirmatory work is needed to fully substantiate cosmeceutically oriented claims of skin penetration, restoration of moisture because of hydroscopic characteristics, and, importantly, actual participation as cofactors in enzymatic regulation activities in the metabolism of healthy or photoaged skin.

Hyaluronic Acid

Hyaluronic acid plays a key role in both epidermis and especially dermis. Its water-holding properties are well established and, more recently, its involvement in control of cell growth, membrane receptor function, and adhesion have been demonstrated. A progressive reduction in electron-dense granules of hyaluronic acid has been observed with increasing age (40). Numerous observations support the concept that application of exogenous HA may be beneficial in various types of tissue remodeling, repair, and healing (41). Furthermore, application of topical tretinoin to photoaged skin has been demonstrated to increase both epidermal and dermal hyaluronic acid theoretically increasing water-holding capacity and possibly facilitating other intercellular transports (42).

Hyaluronic acid stimulation by electrorydesis has been demonstrated. Retinoids have long been known to stimulate HA in epidermis and dermis, but recently a cosmeceutical device that produces a specific, pulsed electromagnetic field (electrorydesis) has been studied in three patients and demonstrated ability to stimulate a significant increase in electron-dense granules corresponding to hyaluronic acid in collagen, elastic fibers, and soluble matrix (43). Clinically, swelling of skin and decrease in prominence of wrinkles was noted, apparently related to increased hydration of the dermis related to increased GAGS.

Natural Cartilage Polysaccharides

Vivida, an oral formulation containing 500 mg/day of purified natural polysaccharides from cartilage of marine fish was compared with a placebo in a study of 30 women aged 40 to 50 years with sun-damaged skin (44). No changes were noted in the placebo group, but in the Vivida group, after 90 days, the epidermal thickness increased from 0.11 to 0.29 mm, dermal thickness from 0.74 to 1.39, skin elasticity index from 44 to 73%, and the erythemal index decreased from 0.301 to 0.205.

Imedeen, a different commercial preparation of natural cartilage polysaccharides containing 380 mg of active substance was compared to Vivida 500 mg/

day in a second study of 30 women aged 40 to 60 years (45). After 90 days, statistically significant differences ($p < 0.001$) in favor of Vivida were demonstrated, with mean epidermal thickness increased from 0.14 to 0.26 mm, dermal thickness from 0.90 to 1.51 mm, and elasticity index from 47 to 71%.

Confirmation of these results in larger, controlled multicenter studies, as well as explanation of how an oral preparation of polysaccharides would survive the digestive system and reach the systemic circulation and, therefore, the skin, is needed.

The substances and products described above are at least partially clinically substantiated as having a cosmeceutical action in photoaging and in many cases have a theoretical basis for action. A host of additional putative agents has been described with new additions monthly. A recent review discusses potentially skin-active naturally occurring botanicals including familiar substances such as chamomile, ginseng, hops, etc. (46). Substantiation of effect in photoaging is not available, but in view of the long-standing folklore surrounding some, an open mind and meticulous investigation are prudent.

Minoxidil

Topically applied minoxidil provides another example of modest pharmacological action with cosmeceutical impact and is modestly effective in treatment of androgenetic alopecia by conversion of some telogen follicles to anagen possibly via K-channel mechanisms. It would be interesting to study this class of molecule in photoaging to see if the ''resting'' aged epidermis and dermis could be similarly stimulated to a more active state.

Last, although it is not the specific purvue of cosmeceuticals, multiple interventions from conventional surgery to laser techniques have been detailed to affect photoaging. One new device has recently been described which may foretell the future treatment of many diseases and conditions of the skin. A depth-targeted gene delivery and expression in the skin utilizing pulsed electric fields has been discussed in the context of skin aging (47). It has become increasingly clear that manipulation of gene action by various techniques, be they indirect such as hormonal, receptor-mediated up- or downregulation of genetic control, or direct intervention by substitution of new gene material into the cell nucleus, are feasible and productive in regulation of various skin dysfunctions. A new and important frontier is being explored that will have profound effects on the future treatment of human disease.

SUMMARY AND CONCLUSIONS

In the face of raging clinical, regulatory, and philosophical debates over whether photoaging is a condition, a disease, or a strictly cosmetic view, science has

been progressing. The cosmetic and pharmaceutical efficacy of tretinoin and other molecules has been unequivocally established by cosmetic, clinical study, and instrumentation methods. That the inherent structure and function of the skin can be modified to produce essentially and primarily cosmetic change is indisputable and the term cosmeceutical is the ideal designation for many of the above products advocated for the care and treatment of aged and photodamaged skin. Whatever the cultural, political, scientific, and regulatory polemics, the cosmeceutical in treatment of photoaging remains a fact.

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4
Hydroxyacids

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INTRODUCTION

Hydroxyacids are organic carboxylic acids classified into the α- and β-types (AHA and BHA) according to their molecular structure. Both AHAs and BHAs are used worldwide and most probably for centuries as active dermatological drugs and cosmetic ingredients. Their acceptance by physicians, cosmetologists, and consumers contrasts with the few independent, well-controlled studies demonstrating long-term effects. In addition, little is known about the relevance of distinguishing AHAs and BHAs as far as the biological consequences of their application onto the skin is concerned.

Health care and cosmetic regulations differ among countries, although skin biology is the same throughout the world. In general, physicians consider that the current legal definitions of drugs and cosmetics are archaic and unworkable in some countries. It is evident that any environmental threat and topical product may exhibit some biological effect on the skin. Hence cosmetics should be viewed as skin physiology modifiers. Should they all be classified as real bioactive agents? This is a matter of definition because bioactivity differs by several degrees of magnitude among product categories. There is a huge difference between decorative, supplement, and real active compounds in cosmetology (1).

Nowadays, there is much controversy about the concept of cosmeceuticals. What is in a name? The term was coined by Kligman to describe products that fall between the two groups: cosmetics and pharmaceuticals. This concept received immediate acceptance by many dermatologists. However, some corporate leaders contend that cosmeceuticals are neither scientifically sensible nor juridically necessary. In fact, with the exception of Japan, national regulatory agencies have not formally recognized the class of cosmeceuticals, or ''quasidrugs.'' The lack of clarification might in time have negative effects. Some products are at risk of being banned, although they could be valuable in cosmetology; the reverse might also be true, and some products could be used in cosmetology without adequate evaluation of their potential biological effects. One example is the widespread use of AHAs. Despite the obvious antixerotic and caustic effects of AHAs at given concentrations, there is little information available about their general toxicity and secondary biological effects. In contrast, the toxic effect of the BHA salicylic acid is well known when the percutaneous absorption is high.

CHEMICAL STRUCTURE AND NATURAL SOURCES OF AHAS

AHAs range from simple aliphatic compounds to complex molecules. Many of these substances can be derived from natural sources and are often referred to as fruit acids. However, a number of synthetic sources provides access to new structural analogues. The AHAs used in dermatology and cosmetology are usually produced by chemical synthesis. They are characterized into chemical groups based on the number of incorporated carboxylic groups (Table 1).

According to their configuration, AHAs may be present under different stereoisomeric structures called enantiomers termed ''l'' and ''d'' or ''R'' and

Table 1 Hydroxyacid Classification

α-Hydroxyacids	
monocarboxylic acids:	glycolic acid
	lactic acid
	mandelic acid
dicarboxylic acids:	malic acid
	tartaric acid
tricarboxylic acid:	citric acid
β-Hydroxyacids	
salicylic acid (ortho hydroxybenzoic acid)	
2-hydroxy-5-octanoyl benzoic acid	
tropic acid	

''S.'' Some of the common AHAs occur naturally in an enantiomerically enriched form and both enantiomers may be available.

Glycolic acid (2-hyroxyethanoic acid) is a constituent of sugar cane juice. Lactic acid (2-hydroxypropanoic acid) was first isolated in 1780. The l-lactic acid is produced by the microorganism *Lactobacillus* and is responsible for the taste and odor of sour milk. The other enantiomer, d-lactic acid (also called sarcolactic acid) is formed during anaerobic muscular contraction and is also found in apples, ergot, foxglove, opium, and tomatoes. Mandelic acid (2-hydroxy-2-phenylethanoic acid) can be obtained from hydrolysis of an extract of bitter almonds. Malic acid (2-hydroxy-1,4-butanedioic acid) was first isolated from unripened apples in 1785. Tartaric acid (2,3-hydroxy-1,4-butanedioic acid) was first isolated in 1769. It is widely distributed in plants, particularly in grapes and lees of wine. Citric acid (2-hydroxy-1,2,3-propanetricarboxylic acid) was first isolated from lemon juice in 1784. It is also found in pineapples and other citrus fruits.

BIOLOGICAL ACTIVITIES OF HYDROXYACIDS

Many aspects concerning the mechanisms of action of hydroxyacids still remain unknown. During the past few years numerous cosmetics containing hydroxyacids have appeared on the market with unfounded claims of performance. Hasty conclusions have been drawn from uncontrolled studies. Erroneous information and incorrect statements flourished behind promotional objectives obscuring the facts.

At least one facet of the hydroxyacid biological activities may be ascribed to the native acid strength of the compounds. Such physicochemical characteristics are measured by the proton dissociation in solution and are expressed as the pKa. A hydroxyacid has a stronger acid strength when its pKa number is lower. A decrease of 1 unit in pKa represents a tenfold increase in the strength. If the acid strength influences some of the biological effects of hydroxyacids, it does not, however, correlate with the potency of all their biological actions.

The pH of the formulations varies with both the nature of the hydroxyacid and its concentration. In order to avoid irritation as much as possible, it is desirable to formulate a cosmetic preparation with a pH close to the normal pH range of the skin. This may be achieved by partial neutralization and by the addition of an effective buffer. However, data suggest that neutral pH AHA products induce little effect on skin.

In order to prevent misunderstandings and misstatements about the effects of hydroxyacids, one should also consider biological actions related to their chemical structure regardless of their acidity. Such a hypothesis is not yet supported by scientific data. The exquisite enantioselectivity exhibited by many biological systems suggests that enantiopurity is an important parameter in any phar-

macological effect, including pharmacokinetics, metabolic rate, and toxicity. Thus the components of a racemate can differentially interact with biomolecules of the skin. Whether such concern is of importance for some effects elicited by AHAs is not settled.

Both AHAs and BHAs exert indisputable direct effects on the stratum corneum, at least when it is affected by xerosis, ichthyosis, and analogous conditions. Comedonal hyperkeratosis in acne-prone subjects might also be improved by the same compounds. In the field of tumors, benign keratoses and viral warts may also be affected by high-concentration formulations. The efficacy is largely related to the pH-related chemical burn. Such caustic effect is also induced in order to realize AHA skin peeling. The effect of hydroxyacids, if any, on heliodermatosis appears more complex, involving multifaceted mechanisms boosting physiological aspects of aging skin.

Most of the aforementioned effects are in part hydroxyacid dose-dependent. In the present review, we arbitrarily define the category low concentration when there is less than 4% of active compound in the formulation. Medium concentration is applied in the range 4 to 12%, and high concentration for dosages higher than that.

EFFECTS ON CORNEOCYTE COHESION AND STRATUM CORNEUM FUNCTIONS

During the formation and maturation of the stratum corneum the intercorneocyte linkages corresponding to desmosomes become modified into so-called corneosomes. Their numbers normally decrease toward the surface of the skin, most notably during the stratum compactum to stratum disjunctum transition (2). In xerotic and ichthyotic conditions, ordered desquamation is impaired because desmosomes persist up to the outer stratum corneum leading to the unruly accumulation of corneocytes and to skin scaling and flaking (3).

Salicylic acid is the reference BHA used since the early days of dermatology to improve xerotic conditions. Although this compound at low and medium concentrations seems to have little or no effect on the normal stratum corneum, there is growing evidence that complete desmosomal degradation is helped in various xerotic and ichthyotic disorders (4–6). It appears, therefore, that applying the term keratolytic to such a compound is a misnomer, while desmolytic agent is more appropriate and explicit.

Quite recently, a lipophilic derivative of salicylic acid was tested on normal human skin (6,7). It corresponds to the 2-hydroxy 5-octanoyl benzoic acid, also called β-lipohydroxyacid (β-LHA). One of its main targets is clearly the corneosomes, which appear to be weakened following altered chemical bonds in the junctional complexes. Subtle differences in desmolytic activity of salicylic acid

and β-LHA have been described and ascribed to the respective hydrophilic and lipophilic natures of these compounds (6).

Various AHAs, particularly lactic acid and glycolic acids in the medium range of concentrations, have profound effects on corneocyte cohesion (8–11). The usefulness of such formulations in xerotic and allied conditions is beyond doubt (12–17). The mechanisms of action of AHAs at that level are poorly documented. A desirable pH for inducing desquamation with AHA application lies between 2.8 and 4.8. The cutaneous surface pH changes cannot be taken lightly because they can persist several hours following applications and can affect a number of stratum corneum layers according to the product concentration. A discrete superficial desmolytic effect occurs in response to low dosages (6). However, in other circumstances, when an appropriate amount of a given AHA is topically applied, within a couple of days the stratum corneum abruptly becomes detached at its lower-most levels, and desquamates as large flakes or sheets (8,9,17). In such instances, no disaggregation of corneocytes at upper levels of the stratum corneum is apparent (17). Speculation has been made on the interaction between AHAs and various enzymatic processes involved in the maturation and disaggregation of the stratum corneum (17).

In addition to the therapeutic effect of the various hydroxyacids improving hyperkeratotic disorders, the same products yield cosmetic benefits by increasing plasticization and flexibility of the stratum corneum (18) without impairing the barrier function (7,11,19). This barrier function was even reported to be improved by some AHAs leading to increased resistance to SLS-induced skin irritation (20). The latter beneficial effect was not equal for all hydroxyacids, being more marked for AHAs characterized by antioxidant properties (20,21). A similar protection was not evidenced after applications of salicylic acid (22).

CAUSTIC EFFECTS

When applied to the skin in high concentration, AHAs cause necrosis and detachment of keratinocytes leading to epidermolysis (12,23,24). Such injury is a chemical peeling depending primarily upon the disruption of the skin pH. The farther away from the physiological pH, the greater the caustic effect, the greater the risk of side effects, but the more likely the patient is to receive the benefits of the peeling agents. A tolerable sense of burning itch is often experienced by patients.

The indications of such treatment encompass the destruction of slightly elevated seborrheic and actinic keratoses (12,25). The full-strength preparation must be applied carefully and exactly to the keratosis in an office procedure. After a few minutes, the entire lesion can be curetted off. Common warts can also be eradicated by hydroxyacids in a home-administered treatment with

applications made daily for several days. To shorten the treatment period, the outer portion of the hyperkeratosis can be removed with a scalpel in an office setting.

ACNE AND PSEUDOFOLLICULITIS TREATMENT

Salicylic acid is listed among active products to treat acne (26,27). However, clearcut evidence for a significant benefit at low concentration in well-controlled experimental and clinical trials is scanty. Similarly, medium concentrations of AHAs, such as glycolic acid, lactic acid, and mandelic acid, are employed twice daily to improve mild acne (12). Such a treatment awaits validation by independent controlled studies. In our experience, the lower AHA concentrations present in some cosmetic products have no effect whatsoever on acne and comedones.

Another modality of acne treatment has been proposed using high concentrations of glycolic acid in an office setting (12). The procedure has to be repeated weekly or so. Improvement has been reported to be precipitous while patients were also taking tetracyclines (12). Discomfort, mild diffuse erythema, and fine scaling are often experienced by patients. In addition, there is a risk for stronger irritation leading to a papular and perifollicular erythema that can persist for a few weeks.

Pseudofolliculitis is another related disorder that can be improved by topical AHA treatment (28).

BOOSTING PHYSIOLOGICAL ASPECTS OF SKIN

One fascinating aspect in the effects of hydroxyacids is the boosted physiology that has been claimed to occur in the epidermis and dermis (29–35). Accordingly, some of these compounds have been used to correct skin atrophy (36) and to induce a gradual reduction in signs of aging, including dispigmentations (37) and wrinkles of fine and moderate depth (12,33,38–40). However, only a few controlled clinical trials and experimental studies have been conducted so far to validate these observations, and currently fuel controversies.

After a few days of application of 12% glycolic acid at low pH, fine wrinkles of the face may vanish as a result of irritation and dermal edema (41). Besides the untoward immediate effect of stinging, such smoothing effect is rapidly alleviated upon stopping topical treatment. Furthermore, in long-term applications, there is some concern regarding the presence of a chronic low-grade inflammation producing reactive oxygen species damaging collagen and elastic fibers. However, signs of reversal of aging and photoaging have been reported during long-

term therapy (12,33,38–40). Such findings were not confirmed in other studies, however, which indicated almost an absence of AHA effects on major skin aging parameters (42–44). In fact, new deposits of glycosaminoglycans in the dermis represent a result of inflammation that has been mistakenly interpreted as a correction of aging. A comparative controlled study has shown that tretinoin is more active than medium concentrations of glycolic acid in the improvement of the facial skin tensile properties (42). It should be noted that the combination of tretinoin and AHAs may be beneficial as therapy for photoaged skin (39,45).

In contrast with salicylic acid, low concentrations of β-LHA elicit a dermoepidermal stimulation (7,44,46–48) that leads to increased keratinocyte proliferation and epidermal thickness. Such effect is more evident in older skin and remains within the physiological range of normal skin. The difference between this and other AHAs and BHAs is that angiogenesis is moderately increased by β-LHA. An increased number of Factor XIIIa-positive dermal dendrocytes has been seen after topical applications of AHAs and β-LHA (34,47). Adverse reactions are mostly represented by stinging sensations without any other clinical and histological signs of irritation.

CONCLUSIONS

AHAs and BHAs enjoy tremendous interest in dermatology and cosmetology. They also attract media attention and consumer curiosity. Claims and proven effects are sometimes contradictory. Much remains to be learned and speculation must be turned to fact. Improved regimens capitalizing on the various beneficial effects of hydroxyacids should be explored.

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