Glycolic Acid Peels

edited by
Ronald Moy
Debra Luftman
Lenore S. Kakita

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Over the past decade, there has been a vast explosion in new information relating to the art and science of dermatology as well as fundamental cutaneous biology. Furthermore, this information is no longer of interest only to the small but growing specialty of dermatology. Scientists from a wide variety of disciplines have come to recognize both the importance of skin in fundamental biological processes and the broad implications of understanding the pathogenesis of skin disease. As a result, there is now a multidisciplinary and worldwide interest in the progress of dermatology.

With these factors in mind, we have undertaken to develop this series of books specifically oriented to dermatology. The scope of the series is purposely broad, with books ranging from pure basic science to practical, applied clinical dermatology. Thus, while there is something for everyone, all volumes in the series will ultimately prove to be valuable additions to the dermatologist's library.

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The latest addition to the series, edited by Drs. Ronald Moy, Debra Luftman, and Lenore S. Kakita, is both timely and pertinent. The authors are well known authorities in the fields of chemical peels and facial rejuvenation. We trust that this volume will be of broad interest to scientists and clinicians alike.

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Preface

Over the past several years we have witnessed an overwhelming plethora of glycolic acid products marketed for facial rejuvenation. Glycolic acids are currently being used by dermatologists as superficial chemical peel agents for the treatment of photodamaged and aged skin, dyschromias, rosacea, and acne. More recently they have proved to be safe and effective for ethnic skin types. These products are widely prescribed to patients in various formulations as part of their daily recommended skin care regimen and without a doubt have been a valuable addition to the dermatologist's armamentarium. Through aggressive marketing the annual sales of cosmetics containing glycolic acid are estimated to be in the range of billions of dollars.

Until recently, little research was available to substantiate many of the claimed benefits of the short- and long-term

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use of glycolic acid products. An increasing number of scientific studies have recently been published validating their therapeutic efficacy. These studies not only have demonstrated the clinical and histological improvement of the signs of photoaging achieved by the application of glycolic acid but have elucidated its role as a stimulant of fibroblast collagen production. Furthermore, glycolic acid has been shown to have both a photoprotective effect as well as anti-inflammatory capabilities. New applications in the use of glycolic acid have recently been formulated.

This book presents the most recent data available regarding the clinical and histological effects of glycolic acid. We believe that readers will benefit from this collection of studies and that the book will enhance their understanding of glycolic acid and its role in clinical practice.

Ronald Moy
Debra Luftman
Lenore S. Kakita

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1

Hydroxy Acids: Past, Present, Future

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I. INTRODUCTION

Over the course of the past few decades, increasing concern and attention has been directed to restoration and maintenance of environmentally damaged skin to more healthy states. In addition, greater concerns about aging and signs of aging have sparked enormous interest in means to rejuvenate the skin. The instinctive desire of humans to have normal appearing skin, free of disease; higher levels of a "healthy look"; and a more youthful appearance has been decidedly re-enforced.

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The current circumstance thus brings into focus a new category of desirable therapeutic and preventive agents, that is, agents that function to achieve and maintain states of optimal skin normalcy. Such a category of agents may be assigned the name of *eudermaceutics,* or perhaps simply topical *euceutics.* This group of agents would include ones to bind water and maintain optimal skin hydration; to normalize keratinization and desquamation; to enhance barrier efficiency; to reverse epidermal–dermal atrophy and maintain optimal skin morphology; and to decelerate the skin aging processes, especially those caused by oxidative damage. Candidate substances known today qualifying as topical *euceutics* would include water itself and adjuvant humectants; retinoids; alpha hydroxy acids (AHAs), some beta hydroxy acids (BHAs), and AHAs with multiple hydroxyl groups, poly hydroxy acids (PHAs); and sun screens to interfere with, or prevent completely, actinically induced damage that today accounts for so much skin unhealthiness.

This chapter is confined to hydroxy acids and related compounds.

Alpha hydroxy acids were first recognized and named as such in the publication of Van Scott and Yu in 1974 [1]. That publication identified AHAs as a special category of substances with special benefits in the treatment of disorders associated with or caused by abnormal keratinization. In the ensuing 25 years, clinical and laboratory investigations on an expanded array of hydroxy acids have revealed that the presence of additional hydroxyl groups on the molecule, which thereupon becomes a PHA, adds additional desirable properties to an AHA. Certain derivatives of AHAs, the o-acetyl derivatives, perform as antagonists to hydroxy acids, substances that may lead to new clues regarding controls determining epidermal cell maturation normally and in disorders wherein hyperkeratinization is predominant.

Findings that hydroxy acids not only affect epidermal form and function but also exert dermal effects now suggest

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that hydroxy acids may have wide and diverse roles in the skin.

Rather than present the history of AHAs in chronological fashion, it seems better to present relatedness of information on properties of hydroxy acids and the relevance of these properties to skin biology and clinical dermatology. This should help delineate the current status of our knowledge of these substances and what may be anticipated for their roles in the future.

II. SPECIFICITY OF AHA ACTIONS ON DESQUAMATION AND KERATINIZATION

Evidence of how AHAs affect desquamation and keratinization was initially derived from our clinical and histological studies of topical AHA effects on ichthyosis and later confirmed on normal skin. The initial action of topical AHAs applied in concentrations of 10% or less on desquamation seems to be a specific one, in which the stratum corneum is shed as variously large sheets, not as scales of small dimension. Such sheetlike shedding clinically suggests there has been uniform detachment of the stratum corneum at the innermost levels, not random loss of stratum corneum segments at more distal layers. This sheetlike desquamation is distinctly different from fine desquamation as occurs in dermatitis or coarse scale desquamation as in psoriasis. Histological findings reveal that detachment is immediately distal to the stratum granulosum, that is, in the zone of the stratum compactum. An immediate consequence is that the thickness of the stratum corneum is minimal but later is restored to thickness of normal stratum corneum, or even slightly thicker. In ichthyosis the thickened hyperplastic epidermis returns toward normal thickness with sustained topical applications of AHAs [1]. On the other hand, studies of topical effects of AHAs on adult skin beyond age 50 have shown that sustained

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applications cause the epidermis to become somewhat thicker than in control skin sites [2,3], where the epidermis is somewhat atrophic to begin with compared with the epidermis of younger individuals.

Whether these sequential stratum corneum/epidermal responses are due to direct influences of the AHA or whether the responses are normal homeostatic events secondary to desquamation is unknown. In either case, the sum consequence of topical AHA applications seems to be of a modulatory nature, wherein abnormal stratum corneum and epidermis are restored toward normal. Few agents known today can be viewed as being restorative-toward-normal agents. In such a frame of reference AHAs can be so viewed, that is, as *eudermaceutics,* when administered under conditions conducive to rendering modulating normalizing effects.

Although dermal effects from AHAs can and do occur [2–4], no attempt will be made herein to deal with dermal effects in any detail.

III. THE EXPANDING FAMILY OF HYDROXY ACIDS: SIMILARITIES AND DISTINCTIONS

The family of AHAs is composed of aliphatic (straight or branched carbon chain), alicyclic (closed carbon ring[s]), and (aralkyl aromatic ring[s] attached to aliphatic) organic acids, wherein an hydroxyl group is attached to the alpha carbon of the linear chain. A BHA is identified by an hydroxyl group on the beta carbon. Within the scope of this discussion, the presence of hydroxyl groups on carbons in addition to the one on the alpha position identifies a poly hydroxy–alpha hydroxy acid, or simply a PHA.

Although AHAs are similar in regard to their effects on desquamation, keratinization, and modulating epidermal and stratum corneum thickness as described previously, many have properties that distinguish them from the others. Distinguishing properties include solubility, inherent irritancy

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or gentleness to the skin, antioxidancy, humectancy, and propensity to form films on the skin surface.

A. Solubility

Two extremes of solubility are found in glycolic acid versus benzilic acid. Glycolic acid (aliphatic:alpha hydroxy acetic acid) is predominantly water soluble and only slightly lipid soluble. Aqueous solutions somewhat in excess of 70% can be readily prepared. Conversely, benzilic acid (aralkyl:diphenyl glycolic acid) is predominantly lipid soluble. Each has an advantage. Aqueous solutions of glycolic acid effectively penetrate the stratum corneum, effectively can normalize the stratum corneum, and effectively promote desquamation. Because benzilic acid is negligibly water soluble, it cannot perform precisely as glycolic acid does. Benzilic acid in appropriate lipid formulation can selectively penetrate into hair follicles because of its solubility in sebaceous lipids and can be used advantageously for dislodgement of comedones. Benzilic acid is very much like salicylic acid in regard to solubility characteristics; neither can be used as humectants, because they repel water, dehydrate, and harden the stratum corneum under most circumstances.

Among other commonly available AHAs are lactic acid, citric acid, malic acid, tartaric acid, and mandelic acid, each with its own solubility profile and each having special merit because of this or because of other properties or attributes. Mandelic acid (aralkyl:phenyl glycolic acid) seems to possess properties between glycolic acid and benzilic acid.

B. Inherent Irritancy or Gentleness to the Skin

Molecular peculiarities do exist in this regard. An example of this is found in a comparison of irritancy versus gentleness of 3-phenyl lactic acid (2-hydroxy-3-phenyl propanoic acid) an AHA and tropic acid (2-phenyl-3-hydroxy propanoic acid) a BHA. Each has the same empirical formula, and they differ from each other only by an exchange in positions of the phenyl

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group and hydroxyl group. Forty-eight–hour topical application under occlusion of 0.4M aqueous solution of 3-phenyl lactic acid reveals it to cause sheetlike separation of the stratum corneum but with substantial edema and erythema (i.e., irritation); tropic acid under the same conditions also causes sheetlike separation of the stratum corneum but with no signs of irritation whatsoever. This bioreactivity difference is rather intriguing, because it is not explainable on the basis of difference in bioavailability, because they both have a similar pKa.

In general, multiple hydroxyl groups attached to an AHA impart gentleness to the skin. Most PHAs studied by us thus far have this quality. Gluconolactone is an outstanding example. In solution it converts from its lactone form to its free acid form, gluconic acid, presenting a molecule with hydroxy groups at the alpha, beta, gamma, delta, and epsilon positions. There are virtually no skin irritations with this compound, even at concentrations up to 20–30% in unneutralized formulations [5]. Yet its performance as an AHA is superb, causing desquamation and reversal of hyperkeratinization with gentleness, even on hyperkeratotic eczematous lesions.

C. Antioxidancy

Avoidance and reversal of oxidative damage, which seems to be a major determinant of degenerative processes, including those of the skin associated especially with extrinsic aging, are recognized as being more and more important. Therefore, the search for and identification of physiological, nontoxic antioxidants for clinical use becomes more important also. We have used three systems to screen substances for antioxidant function because of their simplicity and relevance to dermatological development. The systems provide a measure of whether and to what degree the test substances directly exert antioxidant function but do not measure what antioxidant activity a substance might have within a metabolic circumstance.

In one system, anthralin in hydrophilic ointment is used to screen test substances added in aqueous solution. Rank order of antioxidancy of a substance is determined by its abil-

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ity to prevent or delay oxidative darkening of anthralin from bright yellow to shades of brown-purple-black. In the second system, hydroquinone in hydrophilic ointment is used similarly to screen whether test substances prevent or delay its oxidative darkening. In the third system, freshly cut squares of bright yellow ripe banana peel are immersed in aqueous solutions of test substances. Rank order of antioxidancy is determined by degree to which a substance prevents or retards oxidative browning or blackening of the banana peel. Vitamin C, a known antioxidant, is also included in the test as a positive control. Several AHAs have been found to very effectively prevent or retard oxidative darkening in all three screens. These AHAs include citric acid, gluconolactone, tartaric acid, and lactobionic acid.

D. Humectancy

The system we have found to differentiate consistently the ability of a substance to bind water is to expose a weighed amount of substance in glass containers to an atmosphere of near 100% relative humidity at 50°C for a fixed period of time (e.g., 4 hours). Sealed containers with substance contained therein are weighed before and at the end of the test period when they are again sealed and weighed. Water binding is determined by gravimetric difference and is expressed by weight of water asorbed per mole of substance.

The most avidly water-binding substance in this system is lactobionic acid, found to have approximately the same water-binding potential as glycerol. Ribonolactone, gluconolactone, tartaric acid, and sorbitol are next in order, roughly equivalent to each other; mandelic acid, benzilic acid, and salicylic acid have no potential for water binding.

E. Film Forming

The bionic PHA, lactobionic acid, has been found to be exemplary in this regard. The film-forming phenomenon can be demonstrated in several ways. One way is to place an amount

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of lactobionic acid in powder form on a glass slide or on a sheet of flexible plastic and expose it at 100% relative humidity in a closed chamber. As water is bound, the powder dissolves into a transparent film, which can be removed as an intact flexible sheet from the plastic. Another way is to expose a concentrated solution of lactobionic acid to very low humidity. Stepwise, the solution becomes a syrup, thence a soft resinlike substance that persists as such under room conditions of either high or low ambient humidity. Aqueous solutions of lactobionic acid applied to the skin leave a thin visible film on the skin on drying. Because lactobionic acid is a potent antioxidant PHA, gentle to tissues, it is used as a major component of preservation fluids for organ transplantation to suppress oxygen radical–induced tissue damage.

IV. APPLICATIONS OF HYDROXY ACIDS IN DERMATOLOGIC THERAPEUTICS

After our publications in 1989 on the therapeutic use of AHAs for diverse skin conditions [6,7], their clinical use gradually became more common. Maximum therapeutic value, however, is yet to be realized. In those publications, we related our experience with the use of AHAs for treatment of hyperkeratotic skin conditions such as dry skin, ichthyosis, follicular keratosis, seborrheic keratoses, and actinic keratoses. We called attention to the unique benefits of AHAs on acne when applied daily in home-use formulations and in high concentration for office use. We also related how AHAs could be used as comparatively gentle peeling agents to improve facial wrinkles and other signs of skin aging. Clinical resolution of wrinkles indicated that although AHAs could be used for effects limited to the epidermis, more vigorous extended use could bring about distinct effects on the dermis, later confirmed and reported in 1995 and 1996, [2,8,9]. Although a great deal of work will be required to fully use AHAs therapeutically and better understand their modes of action, it is gratifying that

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other workers report studies that confirm and extend our understanding of AHAs, their effects on the epidermis [10] and on dermal matrix components [3,4], and studies that sharpen our insights on clinical use [11].

V. CLUES TO POSSIBLE CONTROLS OF KERATINIZATION

In 1984 [12], we called attention to o-acetyl derivatives of AHAs, which induced hyperkeratinization that seemed to be precisely opposite that of AHAs. That is, instead of modulating hyperkeratinization toward normal, these derivatives modulated eukeratinization toward hyperkeratinization, both in the skin of hairless mice and in normal skin of humans, where the clinical and histological changes resembled those found in ichthyosis. We additionally commented in that publication that clinically we had found cheilitis, caused by therapy with oral 13-cis-retinoic acid, to be eradicated with topical applications of o-acetyl mandelic acid (OAMA) in petrolatum. Further clinical investigations of ours since then on this compound leads us to believe that it may provide another clue to possible controls of keratinization normally and disorders such as ichthyosis. These further studies have revealed that sustained applications of OAMA solutions to brittle nails, such as encountered in idiopathic onycholysis or in psoriasis, brings about hardening of the nail plate and a return toward normal nails in most cases. In designed clinical tests, OAMA has been shown to be directly antagonistic to agents now in use for treating hyperkeratinization. For example, glycolic acid, salicylic acid, and retinyl acetate, each in 5% concentrations in hydrophilic ointment placed on normal skin under occlusion for 84 hours, cause distinctly recognizable gross clinical effects. Glycolic acid causes characteristic separation of the stratum corneum in sheetlike fashion, without edema or erythema; salicylic acid causes the stratum corneum to desquamate as irregularly sized flakes with distinct edema and erythema; retinyl acetate causes fine scaling

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of the stratum corneum, with minor edema and no erythema. The addition of 5% concentrations of OAMA to the preceding formulations, applied concurrently on adjacent sites, causes degrees of hyperkeratinization, minor degrees of edema, no erythema, and no separation of stratum corneum or evidence of desquamation.

All the preceding therapeutic, clinical, and test results indicate that the prokeratinization influence of OAMA is paramount, predominating over or counteracting the modulating influence of an AHA, salicylic acid, and a retinoid. Can these events have relevance to disorders associated with hyperkeratinization, particularly ichthyosis? Defects in aryl-sulfatase and transglutaminase have been identified in X-linked ichthyosis and lamellar ichthyosis, respectively. Hypothetical biomechanistic consequences of this have been discussed by us and others, [12–14]. In view of our findings that an o-acetyl group in the alpha position on AHAs provokes ichthyotic-like hyperkeratinization, the possibility of an abnormality in acetylesterase enzyme(s) (i.e., overactive in the formation of o-acetyl AHAs and/or failure of de-acetylation in disorders associated with hyperkeratinization) needs to be considered.

VI. FUTURE ROLES OF HYDROXY ACIDS, ANALOGUES, AND DERIVATIVES

Because most hydroxy acids are physiological, natural, and nontoxic substances, we believe clinical use and applications of these fruit acids will continue to expand.

Because at this time we already know of some of the attributes of PHAs and bionic acids, we perceive potential benefits from these subgroups of AHAs for cosmetic and therapeutic uses. They are gentle molecules with small chance of causing skin irritation; at the same time they can be used in properly prepared formulations to achieve very susbtantial results.

We already know that combinations of AHAs and PHAs, each with different properties as described earlier herein,

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achieve better results, (e.g., on ichthyosis) than any one agent alone. We also know that even better results are achieved when adjuvant other ingredients are added. This perhaps should not be unexpected in view of similar results with combination therapy in other fields. We expect that further explorations of therapy with combinations of ingredients will show distinct advantages.

What has not yet been realized are benefits that can accrue from the use of AHAs as adjuvants with drug agents. For example, we have had a rather large experience with the use of AHAs as adjuvants in cortiosteroid topical formulations. In all instances, the combination has achieved substantially better results than the cortiosteroid alone. Repeated studies with combinations of AHAs and antifungal agents in topical formulations for treatment of onychomycosis have shown curative results with the combinations, whereas treatment with the antifungal agent alone does not eradicate the infection. In part because of unavoidable costs, formulations such as these have not made their way to become manufactured products to date. We are somewhat confident that this will change in the future.

Areas in which clairvoyance of the future is not so certain but distinctly possible involves interrelationships among other categories of substances found in metabolic charts. A simple example of such may be found in the interconvertability of alanine with pyruvic acid, which in turn is interconvertible with lactic acid. Some substances when applied together may work synergistically to achieve enhanced benefit. For example, retinoic acid, glycolic acid, lactic acid, and citric acid each enhance formation of dermal matrix components [2,3,15,16]. It seems quite possible that combinations of these substances could amplify dermal matrix formation and provide more optimal treatment of skin aging.

Complex molecules combining two or more subgroups of compounds that achieve special effects are exemplified by a molecule such as lactobionic acid, in which there is chemical union of the PHA gluconic acid with the saccharide galactose.

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Because this molecule has special beneficial properties, referred to earlier, we expect certain combination molecules will be found to have still other special properties with specific benefits.

Finally, numerous compounds, including hydroxy acids and derivatives as well as retinoids and derivatives, may play substantial roles in keratinization. Pursuit of clues provided by these compounds may lead to better understanding of keratinization and better ways to restore normalcy in disorder wherein keratinization is abnormal.

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Bioavailable Alpha Hydroxy Acid in Topical Formulations

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I. INTRODUCTION

Since our publication on alpha hydroxy acids (AHAs) for topical treatment of ichthyosis in 1974, AHAs have been used as primary ingredients or in combination with other topical agents for various cosmetic and dermatological indications, ranging from dry skin, skin smoothing, acne, age spots, fine lines, and wrinkles to photoaging [1–3]. Because of the acidic

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nature, a topical formulation containing an AHA usually has a pH of below 2.0, and the formulation might cause skin stinging and/or irritation on repeated topical application to sensitive or atopic skin. In most commercial products, the AHA is partially neutralized with an alkali to raise the pH to 3.5 to 4.5. One frequently asked, but very important, question is the relationship between the pH and topical efficacy of an AHA formulation. This chapter is intended to answer this question and also to discuss related issues, including a slow-release amphoteric system containing an AHA.

II. SKIN BARRIER AND TOPICAL FORMULATION

In normal or unaltered human skin, the stratum corneum consists of approximately 14 to 30 layers of keratin-enriched corneocytes embedded in a lipid matrix and is very resistant to penetration by large molecules with a molecular weight greater than 1000 [4] and most ionic compounds [5]. For example, unneutralized 50% glycolic acid at pH 1.2 causes erythema on topical application to human skin, but 50% sodium glycolate at pH 7.0 does not cause erythema or any other detectable reactions to the same individuals. Whereas unneutralized 10% glycolic acid, lactic acid, or pyruvic acid is therapeutically effective for topical treatment of severe dry skin, 10% sodium glycolate, sodium lactate, or sodium pyruvate is substantially less effective during the same period of topical application. Whereas these AHAs in free acid form are significantly more bioavailable, their metallic salts are much less bioavailable for topical treatment of most cosmetic and dermatological indications. The reason is that the metallic salt of an AHA dissociates almost completely into AHA ion (anion) and metallic ion (cation), and the anion cannot penetrate into the stratum corneum as readily as its free acid form.

The situation is slightly different when an AHA salt is formed from ammonium hydroxide or an organic amine. In this case, the neutralizer is a weak alkali in contrast to the

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strong alkali of metallic hydroxide, such as sodium hydroxide or potassium hydroxide. The AHA salt formed from a weak alkali does not dissociate completely into anion and cation; however, the salt still cannot penetrate into the stratum corneum of the skin as readily as the free acid form. In any case, it is essential that a topical formulation containing an AHA is still therapeutically effective after partial neutralization with an organic or inorganic alkali.

III. TOPICAL EFFICACY AND BIOAVAILABLE CONCENTRATION

The topical efficacy of a formulation containing an AHA for cosmetic and dermatological indications depends on two major factors: (1) bioavailable concentration of the AHA, and (2) the vehicle used [6]. The bioavailable concentration is obtained by initial concentration of the AHA used multiplied by bioavailability. In pharmacology, the bioavailability is defined as the fraction of unchanged drug reaching the systemic circulation after administration [7]. For topical administration, penetration of an AHA through the stratum corneum seems to be a major limiting factor, and the bioavailability or the potential bioavailability may be defined as the fraction or ratio of the AHA in free acid form. Thus, the bioavailability is the number of free acid molecules divided by the number of initial or total AHA molecules in the topical formulation. The following are discussions regarding topical formulations containing glycolic acid, and the same principles can also be applied to other AHAs.

IV. BIOAVAILABILITY AND DISSOCIATION CONSTANT

When glycolic acid is dissolved in aqueous solution, the free acid (HA) dissociates into glycolate ion (A^-) and hydrogen ion (H^+), and the reverse also occurs; the glycolate ion reacts with the hydrogen ion to form the free acid. At an equilibrium

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state, the dissociation constant (Ka) is defined as the concentration of glycolate ion [A^-] multiplied by hydrogen ion [H^+] and divided by undissociated free acid [HA]. The dissociation equilibrium may be converted to a negative logarithm, and the Henderson-Hasselbalch equation thus formed shows that logarithm of [HA]/[A^-] equals pKa of glycolic acid minus pH of the formulation as shown in Fig. 1. Because the pKa is known, the ratio of [HA]/[A^-] can be calculated from the pH of the formulation. One molecule of glycolate ion is derived from one molecule of dissociated glycolic acid, and the sum of the undissociated free acid [HA] and the glycolate ion [A^-] should represent the initial or total concentration of glycolic acid used. Therefore, the bioavailability is obtained from undissociated glycolic acid [HA] divided by the initial concentration, which

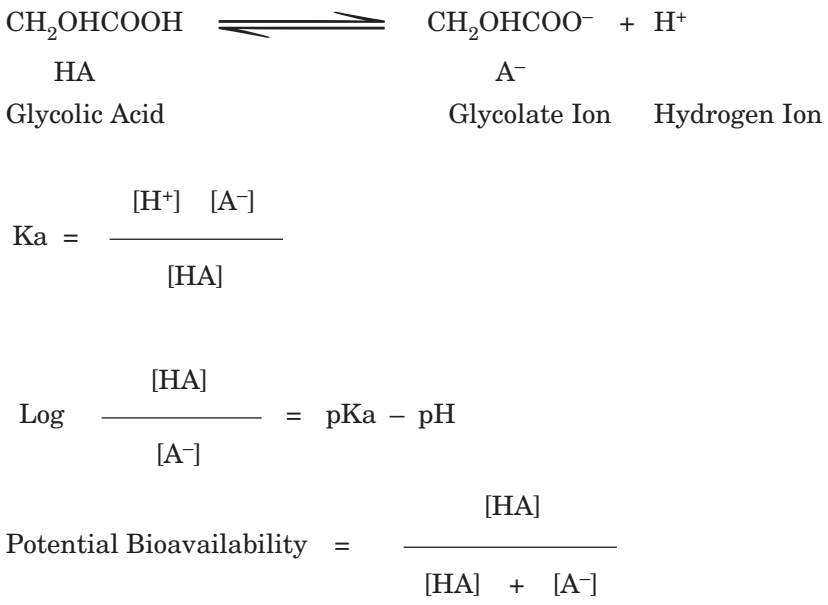

Fig. 1 Potential bioavailability and pKa of glycolic acid.

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is ([HA] + [A^-]). Useful to remember is that at the pKa of a given acid, 50% of it is in free acid form, and 50% is in dissociated ionized form.

Because dissociation constant is essential for calculation of bioavailability, it is appropriate to discuss its properties and implications in the following section.

V. ACID STRENGTH AND pKa

The relative strength of an acid is measured by its dissociation or production of hydrogen ions in solution [8]. An AHA is a stronger acid if it produces more hydrogen ions in solution. Because the concentration of hydrogen ions [H^+] is proportional to the dissociation constant [Ka] and the pKa is a negative logarithm of Ka, an AHA is a stronger acid if its pKa is lower. The difference of one unit (1.0) in pKa represents a ten-

Table 1 Acid Strength and pKa of AHA, BHA, and PHA

Hydroxyacids	pKa (pK_1)*	AHA	BHA	PHA
Atrolactic acid	3.53	+		
Benzilic acid	3.09	+		
Citric acid	3.13	+	+	
D-gluconic acid	3.86	+	+	+
DL-glyceric acid	3.64	+	+	
Glycolic acid	3.83	+		
2-hydroxybutanoic acid	3.65	+		
L-3-hydroxybutanoic acid	4.41		+	
L-lactic acid	3.86	+		
Malic acid	3.46	+	+	
Mandelic acid	3.41	+		
Methyllactic acid	3.72	+		
D-tartaric acid	3.04	+	+	
Tartronic acid	2.37	+		
Tropic acid	3.53		+	

**Source*: Lange's Handbook of Chemistry, 14th ed., New York: McGraw-Hill, 1992.
+Indicates the compound as AHA, BHA, and/or PHA.

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fold (10.0) difference in the acid strength. Relative acid strength and pKa of AHA, beta hydroxy acid (BHA), and poly hydroxy acid (PHA) are shown in Table 1. For those compounds containing two or more carboxyl groups such as malic acid, tartaric acid, tartronic acid, and citric acid, only the first dissociation pKa (pK_1) is shown in Table 1.

Hydroxy acids can be bona fide AHAs such as atrolactic acid, benzilic acid, glycolic acid, lactic acid, and mandelic acid or genuine BHAs, such as 3-hydroxybutanoic acid and tropic acid. Certain hydroxy acids can be AHAs and also BHAs because of an additional hydroxyl group at beta position (glyceric acid) and/or additional carboxyl group (s), and in the latter case the alpha position of a hydroxyl group can also be the beta position to the second or third carboxyl group in the molecule such as malic acid, tartaric acid, and citric acid. In the case of citric acid, the hydroxyl group is alpha position to one carboxyl group but beta position to two other carboxyl groups. Because gluconic acid contains five hydroxyl groups at alpha, beta, gamma, delta, and epsilon positions, it is an AHA, BHA, and PHA compound.

From Table 1, glycolic acid (pKa 3.83) is a slightly stronger acid than L-lactic acid (pKa 3.86), but methyllactic acid (pKa 3.72) is a much stronger acid than glycolic acid.

Among BHAs, L-3-hydroxybutanoic acid (beta hydroxybutanoic acid, pKa 4.41) is a much weaker acid than lactic acid, but the lipid-soluble BHA tropic acid (2-phenyl-3-hydroxypropanoic acid, pKa 3.53) is a much stronger acid than glycolic acid.

On the basis of our clinical studies, the acid potency of an AHA may not correlate to its topical action on keratinization. For example, benzilic acid (pKa 3.09) is much more acidic than glycolic acid (pKa 3.83), but the former is less potent than the latter for topical treatment of severe dry skin under the same conditions. The same is true between malic acid (pKa 3.46) and L-lactic acid (pKa 3.86). Both D-gluconic acid (PHA) and L-lactic acid (AHA) have the same pKa of 3.86, but

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the former seems to have gentler action for dry skin because of its slower penetration into the stratum corneum.

VI. BIOAVAILABLE GLYCOLIC ACID

Potential bioavailability of unneutralized AHA is always near 1.00, and bioavailable concentration of glycolic acid is the same as the initial concentration used. The initial concentration is the actual concentration of glycolic acid used. For example, if 70% commercially available aqueous solution is used, 50% of this solution used in the formulation means 35% actual or initial concentration of glycolic acid. It causes confusion and is misleading to indicate "50% of 70% glycolic acid" on product brochures or labels.

Potential bioavailability of unneutralized 70% glycolic acid peel is 1.00, and the bioavailable concentration is 70%. Partial neutralization of glycolic acid will lower the bioavailability and bioavailable concentration. The bioavailability of glycolic acid at different pH of the formulation can be calculated from the free acid concentration over the initial or total concentration. In general, the calculated bioavailability is less accurate at a pH of 2.0 below and above the pKa of glycolic acid, (i.e., below pH 1.83 and above pH 5.83).

Potential bioavailability and the bioavailable concentration of glycolic acid at different pH ranging from 2.8 to 4.6 is shown in Table 2. The bioavailability and bioavailable concentration are higher at lower pH of the formulation, and the bioavailability of any acid is always 0.5 at the pH of its pKa. For example, the bioavailability of glycolic acid is 0.5 at pH 3.83, that is, one half of glycolic acid is in free acid form and the other half is in glycolate ion form. When a formulation containing 1.0M (7.6%) glycolic acid is partially neutralized with an alkali to pH 3.2, 0.19M glycolic acid would dissociate into glycolate ion (0.19M) and hydrogen ion (0.19M). The undissociated glycolic acid in free acid form would be 0.81M,

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Table 2 Bioavailable Concentration of Glycolic Acid

pH	Bioavailability[a]	Bioavailable concentrations (%)				
		Initial concentration of (%)				
		4	5	8	10	20
2.8	0.915	3.7	4.6	7.3	9.2	18.3
2.9	0.895	3.6	4.5	7.2	9.0	17.9
3.0	0.871	3.5	4.4	7.0	8.7	17.4
3.1	0.843	3.4	4.2	6.7	8.4	16.9
3.2	0.810	3.2	4.1	6.5	8.1	16.2
3.3	0.772	3.1	3.9	6.2	7.7	15.4
3.4	0.729	2.9	3.7	5.8	7.3	14.6
3.5	0.681	2.7	3.4	5.5	6.8	13.6
3.6	0.629	2.5	3.2	5.0	6.3	12.6
3.7	0.574	2.3	2.9	4.6	5.7	11.5
3.83[b]	0.500	2.0	2.5	4.0	5.0	10.0
3.9	0.460	1.8	2.3	3.7	4.6	9.2
4.0	0.403	1.6	2.0	3.2	4.0	8.1
4.1	0.349	1.4	1.8	2.8	3.5	7.0
4.2	0.299	1.2	1.5	2.4	3.0	6.0
4.3	0.253	1.0	1.3	2.0	2.5	5.1
4.4	0.212	0.9	1.1	1.7	2.1	4.2
4.5	0.176	0.7	0.9	1.4	1.8	3.5
4.6	0.145	0.6	0.7	1.2	1.5	2.9

[a]At 25°C in water

[b]pKa of glycolic acid

and the bioavailability is 0.81. In the same manner, when a formulation containing 1.0M glycolic acid is partially neutralized with an alkali to pH 4.2, 0.701M glycolic acid would dissociate into glycolate ion (0.701M) and hydrogen ion (0.701M). The undissociated glycolic acid in free acid form would be 0.299M, and the bioavailability would be 0.299.

The bioavailability of glycolic acid is always constant at a given pH under standard conditions (such as at 25°C in water) and is independent of the initial concentration used.

For example, the bioavailability of glycolic acid is always 0.403 at pH 4.0, despite whether the initial concentration is 1.0M (7.6%) or 2.0M (15.2%). Bioavailable concentration diminishes rapidly at higher pH. For example, bioavailable concentration of 4% or 10% glycolic acid at pH 3.0 is 3.5% or 8.7%, respectively, but it diminishes to 0.7% or 1.8%, respectively, at pH 4.5. A similar reduction in bioavailable concentration applies to 70% glycolic acid peel. Bioavailable concentration changes from 70% at pH 0.6 to 35% at pH 3.83.

As discussed earlier, the topical efficacy of glycolic acid depends on bioavailable concentration and not the bioavailability. Because the bioavailable concentration is obtained by multiplication of the bioavailability and the initial concentration, identical topical efficacy may be obtained from two different parameters: higher bioavailability with lower initial concentration or lower bioavailability with higher initial concentration. For example, in the first phase of percutaneous penetration, 5% glycolic acid at pH 3.2 may have approximately the same efficacy as 10% glycolic acid at pH 4.0, because the potentially bioavailable concentration of glycolic acid in both cases is approximately the same 4%. However, the 10% glycolic acid at pH 4.0 may have two advantages: (1) less skin irritation with higher pH and (2) a reservoir for potential second phase of percutaneous permeation if the partial neutralization is made with a weak alkali. The second phase of percutaneous permeation may be viewed as follows.

During the first phase of permeation, free glycolic acid penetrates into the skin, and the concentration of the free acid decreases. To maintain the dissociation equilibrium, the glycolate ion and hydrogen ion in the formulation would react to form more free glycolic acid to compensate for the loss or the decrease in concentration. If the formulation in cream, lotion, gel etc. remains on the skin and is not wiped off by cloths or washing, a second phase of permeation from replenished glycolic free acid could take place.

In commercial practice, actual bioavailability and

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bioavailable concentration may differ from that in Table 2 because of various factors, including ingredients and solvents. Nevertheless, calculated numbers in Table 2 may be used as a basic approach to or a reference guide for predicting therapeutic potential of a topical formulation containing glycolic acid.

VII. FORMULATIONS AND VEHICLE

The type and category of carrier vehicle play important roles in topical efficacy of an AHA. Many AHAs such as glycolic acid, lactic acid, malic acid, tartaric acid, and citric acid are water soluble. Methyllactic acid, atrolactic acid, and mandelic acid are soluble in water and alcohol. Benzilic acid is insoluble in water and is soluble in lipid solvent. For water-soluble AHA a cream or lotion of oil-in-water emulsion is a preferred choice, because most AHA molecules are present in water phase, which is a continuous outer layer and in direct contact with the skin when the emulsion is topically applied. When 8% glycolic acid is partially neutralized to pH 3.8 with ammonium hydroxide in an oil-in-water emulsion, most glycolic acid and glycolate ions would be present in the water phase of the emulsion. Because water is a continuous outside phase of the oil-in water emulsion, most glycolic acid molecules in water phase would be in direct contact with the skin for optimal topical effects.

For lipid-soluble AHA, a cream or lotion of water-in-oil emulsion may be preferred, because most AHA molecules are present in outer oil phase, which would be in direct contact with the skin when the emulsion is topically applied. In addition, some skin conditions may require certain type of a formulation. For severe dry skin with heavy scales, the preferred choice of emulsion is an oil-in-water cream or lotion containing a water-soluble AHA. Most AHA molecules would be in the outside continuous water phase and would be bioavailable to the skin for optimal effects. On sustained topical applica-

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tion for a few days, most heavy scales from severe dry skin are easily washed off during a bath or shower.

A preferred formulation for eczematous skin is an ointment or a water-in-oil emulsion containing a gentle PHA, which is nonirritating to sensitive or inflamed skin.

Certain skin diseases such as psoriasis need occlusive vehicle components such as petrolatum and mineral oil to achieve a steady-state delivery of the active ingredients. Certain cosmetic ingredients seem to interfere with the topical effects of an AHA. Glycerin is a common humectant used in many cosmetic products, and it seems to have strong affinity with water-soluble AHAs on the skin surface after topical application. Because glycerin cannot substantially penetrate the stratum corneum, it affects the permeation of AHA molecules and compromises the topical effects of AHA except for moisturization. Another example is 70% glycolic acid peel containing a gelling agent such as hydroxyethyl cellulose. This gelling agent seems to interfere with the penetration and exfoliating effect of glycolic acid. Some ingredients on the other hand can have an enhancing effect on topical action of an AHA. Propylene glycol seems to enhance the penetration of an AHA by modifying the permeability of stratum corneum.

VIII. SKIN STINGING AND IRRITATION

A formulation containing glycolic acid or lactic acid with or without partial neutralization may provoke sensations of tingling, stinging, or even irritation when topically applied to sensitive or atopic skin. These side effects may be due to (1) lower pH and fast penetration of the AHA, (2) inherent property of the AHA, and/or (3) the alkali used in partial neutralization. Except for professional peels, most commercial products containing glycolic acid have pH adjusted to 3.5 to 4.5 with ammonium hydroxide to reduce skin stinging and irritation. However, many such products are still irritating to sensitive skin. Such skin irritation is not related to the pH of the

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formulation but is due to fast penetration and/or the inherent property of glycolic acid and ammonium hydroxide. It seems that a formulation containing glycolic acid or lactic acid is less irritating when certain organic amines are used for partial neutralization.

IX. SLOW-RELEASE AMPHOTERIC SYSTEM

For fast-penetrating AHAs such as glycolic acid and lactic acid, a slow-release formulation containing an amphoteric substance seems to eliminate or reduce irritations on sensitive or atopic skin. An amphoteric substance by definition should behave both as an acid and an alkali and may be an organic or inorganic compound. The preferred amphoteric substances are physiological organic compounds of amino acids such as glycine, glutamine, lysine, arginine, histidine, tryptophan, ornithine, and citrulline. Because the amino acid contains one or more alkaline group such as amino, imino, and guanido in addition to carboxyl group, it will form an ionic complex with an AHA in the formulation. For example, glycolic acid will form triple ionic complex with glycine and quadruple ionic complex with lysine, arginine, histidine, or tryptophan. The ionic complex in the formulation seems to act as a buffering system to control the release of glycolic acid into the skin, thus eliminating or reducing skin irritations without compromising therapeutic efficacies.

In formulating a slow-release composition, an amphoteric substance such as arginine or lysine 0.5M is reacted with 1M glycolic acid in cooled aqueous solution. The formation of amphoteric complex is completed as the pH changes from 1.9 to approximately 3.0 or 3.3, respectively. The amphoteric solution thus obtained is mixed with an oil-in-water formulation to make the final composition of glycolic acid 1M (7.6%) and arginine 0.5M (8.7%) or lysine 0.5M (7.3%), respectively. The bioavailable concentrations of glycolic acid in these amphoteric compositions are 0.871M (6.6%) and 0.772M (5.9%),

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respectively. Topical applications of these amphoteric compositions have provided equal or superior therapeutic efficacies for severe dry skin and other indications with negligible skin irritations to sensitive or atopic skin.

X. SUMMARY

In the first phase of skin permeation, the topical efficacy of an AHA formulation depends on two major factors: bioavailable concentration and vehicle used. The bioavailable concentration is obtained from the initial concentration of the AHA multiplied by its bioavailability. The bioavailability is defined as a fraction obtained from the number of AHA molecules in free acid form divided by the number of total AHA molecules in the formulation. The bioavailability depends on the pKa of the AHA and the pH of the formulation. Therefore, the topical efficacy of an AHA formulation depends on (1) initial concentration of the AHA used, (2) pKa of the AHA, (3) pH of the formulation, and (4) the vehicle used. At the same concentration, the efficacy is higher at lower pH, and at the pH of its pKa the bioavailable AHA is one half of the initial concentration. Skin stinging or irritation is due to lower pH and fast penetration of the AHA, inherent property of certain AHAs, and/or the alkali used in partial neutralization. The slow-release amphoteric system seems to eliminate skin irritations from AHAs.

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Glycolic Acid

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The alpha hydroxy acids (AHAs), known by the media as the fruit acids because they occur naturally in various fruits, form a group of carboxylic acids that have actually been used in cosmetic treatments and products for many centuries. They are chemically characterized by having a hydroxyl group on the alpha carbon, the first carbon after the carbon contained in the carboxyl group. Glycolic acid is the smallest of the AHAs, the group's general formula being RCHOHCOOH, as seen in Fig. 1. With glycolic acid, R is H, making the formula for glycolic acid $C_2H_4O_3$ or $HOCH_2COOH$, also known as hydroxy acetic acid.

The strength of an acid is determined by the ease with which the H^+ or proton is donated or given up. The similarity of glycolic acid to acetic acid and trichloroacetic acid should be

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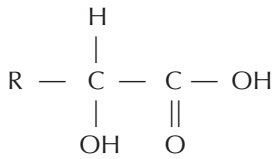

Fig. 1

noted. The relative strengths of the acids are directly related to their abilities to donate the proton. Acetic acid is a weaker acid than trichloroacetic acid, because the attraction of the electrons to the three chlorides is much greater than to the three hydrogen atoms, making the H^+ from the trichloroacetic acid much easier to go into solution than the one that is part of the acetic acid molecule. The hydroxyl group in the glycolic acid moiety, because it is basically negative, imparts less ability of the electrons to migrate toward that group, freeing up the hydrogen with more difficulty and, therefore, is a relatively weak acid.

The highest concentration attainable with glycolic acid is 70%, because it will precipitate out above that concentration. The pH of glycolic acid at this concentration as manufactured by DuPont (Glypure) is 0.5. Other characteristics of this acid made for cosmetic and medical purposes are a boiling point of 112°C, melting point of 10°C, a mild burnt sugar odor, and a density of 1.25 g/ml at 26°C. It is a clear liquid, light amber in color and will not decompose, polymerize, or burn.

It is not an easy task to work with this acid. Even though it is stable, its small molecular size, ability to penetrate the skin easily, makes it difficult to formulate. The office of Occupational Safety and Health Administration instructions are to "immediately flush the skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Call a physician. Wash clothing before reuse." Obviously, a degree of respect must be maintained when formulating with this material and when applying it to human skin.

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Some of the confusion arising from the use of glycolic acid peels and products is that some manufacturers claim that their product contains 100% glycolic acid, which in reality refers to the fact that they are starting with an undiluted product, which is 70% in concentration. Glycolic acid in its pure form is a relatively weak acid compared with other acids used to perform chemical peeling. Certainly, there is discomfort with this material if applied to the skin; however, permanent sequelae, such as scars and hyperpigmentation, would be very unlikely to occur unless the skin is damaged or prepared in some way to increase penetration of the acid.

A number of cosmetic products and devices have been on the market and available for the physician, aesthetician, and consumer for many years using this versatile acid. To make it more user-friendly, manufacturers have manipulated the concentration of the free acid and its pH. One of the most common ways to do this is to make use of basic chemistry and the acid/base reactions, producing salts. Salts are defined as compounds that contain a cation other than H^+ or an anion other than hydroxide ion OH^-. In the partial neutralization of products glycolic acid is combined with a base, most commonly ammonium hydroxide. This combination results in the presence of three chemicals in equilibrium in the solution—glycolic acid, ammonium hydroxide, and ammonium glycolate. In the event that the reaction were allowed to continue to completion, the only substance remaining would be ammonium glycolate. By adjusting the concentration of acid and base in the mixture, various concentrations of acid, base, and salt result, giving rise to pH adjusted concentration of free acid in the mixture. It is the free acid that actually produces the benefit of the particular product, and the product, because it no longer contains only acid, is said to be partially neutralized. This does not produce an ineffective product but instead allows a product to be both safe and effective.

Another term that has been introduced into the cosmetic industry is that of esterification. Esterification is the process by which casboxylic acids react with alcohols through a process

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of condensation. The general reaction is RCOOH + R′ – OH yields RCOOR¢ and H_2O. This reaction produces a covalent bond, which is a bond that results when atoms share electrons. This is a much stronger bond than the ionic or electrovalent bond that is formed by the transfer of one or more electrons from one atom to another. Once esterification occurs, the strength of the bond is so great that it is unlikely to dissociate in any solution or formulation. Any acidic activity demonstrated by the substance, therefore, must be due to free acid ptgsgpt in the formulation.

With this background information, it is possible to evaluate products and procedures that contain or use glycolic acid, and it becomes possible to compare one modality with another. The only information that is needed is the pH and concentration of the free acid in the system. All other information is secondary to these two key factors. This is also why a product that is said to contain a certain percentage of the acid may not be stronger than one with a lower concentration. It is very important to determine the free acid if at all possible, not just the concentration listed in the ingredients.

In addition, a number of products have to come to market that attempt to address the irritation of the products by addition of some substance or change in the formulation. Evaluation of these must take into consideration that changes could affect the efficacy of the product, and unless rigorous clinical trials have been carried out and published in peer review journals, much of the marketing must be treated as just that—marketing.

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4

Acne and Glycolic Acid

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One of the most common problems seen by dermatologists is acne in its many forms—teenage acne, adult acne, perioral dermatitis, rosacea, etc. The pathogenesis of acne involves the pilosebaceous apparatus—the hair follicle and sebaceous gland are referred to as the pilosebaceous unit or pilosebaceous apparatus. The development of acne begins when the functions within this unit are disrupted. If the follicle becomes irritated for some reason, keratinized cells are overproduced. This may be in response to trauma, material in the unit, hormonal factors, or vascular factors. Once this overproduction of keratinized cells occurs, the stratum corneum in the upper portion of the follicular canal thickens and becomes cohesive. There is no longer normal shedding but an accumulation of corneocytes (retention keratosis) with formation of

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the microcomedone. This precursor of all acne lesions produces obstruction of the canal. Sebum continues to be produced, and retention keratosis continues to progress.

The now anaerobic conditions in the plugged follicle and the lipids provided by the sebum enhance the growth of the already present organism, *Propionibacterium acnes,* which hydrolyzes fatty acids from the sebum. These fatty acids are irritating, leading to both inflammation and further proliferation of cells in the follicular canal. As the plug increases in size, the follicle becomes distended and forms a closed comedone that is visible on the skin. This lesion may or may not rupture.

Rupture of the lesion produces a very irritated pustule with significant inflammatory reaction. The papule and cyst may also form with little or no irritation if the lesion remains closed. Regardless of the progression of the lesion and whether it is open or closed, the basic pathogenic mechanism is always the same—the pilosebaceous unit retains a keratin plug.

The primary mechanism of action of glycolic acid on the skin is to decrease corneocyte cohesion, (i.e., it decreases the ability of skin cells to adhere to one another). This characteristic, as well as the small size of the molecule, make this acid the perfect material to aid in the removal of the keratinous plug in acne. The small size of the molecule is important, because it allows for even greater and easier penetration of the glycolic acid to get into the unit and decrease the cells' ability to maintain the plug.

One of the other prime characteristics of glycolic acid is the fact that because it decreases the ability of the epidermal cells to maintain attachments, the spaces between the cells open, thereby allowing better penetration of other substances applied to the skin. Most of the activity of glycolic acid is, therefore, intercellular. Drugs, such as Retin-A and other retinoids, act almost entirely intracellularly. The important concept is that by allowing better, faster, and more efficient

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penetration, retinoids are much more effective when used in conjunction with glycolic acid.

Although the mechanism by which retinoids reverse the plugging of the pilosebaceous unit and reverse acne has not been totally delineated, there are a number of clinical studies, and a tremendous amount of clinical data over the last 30 years, indicating both the efficacy and possible mechanism of action of the retinoids. Biopsy specimens have shown that there is a normalization of keratinization of the unit in the treatment of acne. Receptors for retinoids are known to occur in the keratinocyte, and the various retinoids interact with different receptors. All trans-retinoic acid interacts with the RAR alpha, beta, and gamma receptors, whereas adapalene and tazarotene interact only with RAR beta and gamma. The consequences of the various receptors is not appropriate for this discussion; however, it is important to note that there have not been any studies indicating receptors for glycolic acid. It is instead the direct effect of the acid on the corneocytes that produces the benefit in acne.

As in all uses of glycolic acid, there is both product use and the application of the acid in chemical peeling. Chemical peels with glycolic acid can be performed with various strengths and concentrations of the acid, and the reader is referred to the appropriate chapters on glycolic acid chemical peels in this text for more information. It should be pointed out here, though, that glycolic acid is particularly effective in benefitting comedonal acne and decreasing the hyperpigmentation often associated with acne in darker skin. Papules and pustules may be treated with direct application of the acid during chemical peeling of the whole face to provide extra benefit. The number of peels, as well as the time between peels, will vary from patient to patient.

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5

The Treatment of Rosacea with Glycolic Acid

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Rosacea is a common skin condition that affects an estimated 13 million Americans, with almost half of these patients between the ages of 30 and 50 years old [1]. It is a relapsing, chronic dermatosis that develops in stages and is characterized by a defect in vascular responsiveness [2,3]. Most often, fair-skinned individuals are seen first with flushing and blushing episodes followed by persistent erythema and telangiectasia with later recurrent eruptions of inflammatory papules and pustules involving the central face. These lesions nearly always occur on a backdrop of solar elastosis and dermatoheliosis [4]. Although there is a greater incidence of the milder, earlier stages of rosacea in women, men more fre-

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quently have the more severe form (i.e., rhinophyma) [5]. In most cases of rosacea, the standard therapy can be augmented by the addition of glycolic acid peels and home application of lower concentration glycolic acid preparations.

I. PATHOGENESIS

The pathogenesis of rosacea is most likely multifactorial. It is a polymorphic disease that seems to be precipitated by many causes, including genetic, vascular, immune-mediated, emotional, environmental, and infectious factors. Central to disease formation is the development of vascular hyperresponsiveness in genetically predisposed individuals. Even features of rosacea other than erythema and telangiectasia may derive from this same vascular abnormality [2]. It is hypothesized that rosacea is preceded by the degeneration of perivascular, vascular collagen, and elastotic tissues in susceptible persons when exposed to environmental stimuli like heat, humidity, friction, cold, or sunlight [4]. This deterioration can result in permanent dilation of dermal blood vessels (telangiectasia) with subsequent leakage of inflammatory mediators [2,4]. Elastin degradation caused by chronic actinic exposure may also lead to lymphatic insufficiency, which can create a sterile, low-grade dermal cellulitis [2]. All of these processes unfortunately promote even further flushing by means of vasodilatory mechanisms [2,4].

Other triggers precipitating flares of rosacea include emotional stimuli such as stress and excitement; physiological stimuli like exercise and ingestion of alcohol, hot beverages, and spicy foods; exogenous stimuli such as application of skin care products containing ingredients like alcohol, witch hazel, menthol, peppermint, eucalyptus and clove oils, or other potential irritants [1]. Factors that have been implicated in the development of rosacea include *Demodex folliculorum* mite infestation and *Helicobacter pylori* infection [6,7]. In one study, the mean *Demodex* mite count was significantly

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higher in subjects with rosacea than in controls. It is hypothesized that an increased mite load may play a role in the pathogenesis of rosacea by provoking inflammatory or allergic reactions either by mechanical blockage of follicles or by acting as a vector for microorganisms [6]. Other researchers have noted that subclinical *H. pylori* infection may also be involved in the genesis of rosacea and that eradication treatment may reduce the severity of skin disease [7]. Another organism, *Malassezia furfur* (*Pityrosprorum ovale*), which is routinely found on biopsy specimens of rosacea, may also play a role in pathogenesis. Unlike acne, the presence of bacteria within the hair follicle does not seem to affect rosacea [3].

II. CLINICAL STAGES

Rosacea can usually be subdivided into three clinical stages. Some patients may advance from mild to more severe disease, whereas others remain at a given stage. The first stage of rosacea is predominantly vascular. It is characterized by recurrent flushing on the central face, neck, and upper chest [2]. These brief episodes, which are usually provoked by the stimuli mentioned previously, slowly become less transient with time. Prolonged flushing also causes persistent facial edema to develop [2–4]. This chronic erythema and swelling are thought to be the result of increased numbers of erythrocytes within inflamed superficial vasculature [2]. Later, telangiectases also become prominent on the cheeks and nose.

The second stage, inflammatory rosacea, is marked by the appearance of crops of follicular-based inflammatory papules and pustules. In the background, there is persistent erythema, more numerous telangiectases, elastosis, dermatoheliosis, solar comedones, and prominent facial pores [2–4].

Only a minority of patients progress to the third stage, which is characterized by a proliferation of sebaceous, connective, and vascular tissue and results in bulbous hypertrophy of the nose called rhinophyma. These patients also have

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deep persistent erythema, dense telangiectases, papules, and pustules. Facial contours may become coarse and thickened because of the massive deposition of collagen and sebaceous hyperplasia [4]. This last stage of rosacea is more commonly found in men [5].

III. HISTOPATHOLOGY

In stage one, there is mainly vascular dilation of the upper and middermal venules and lymphatic vessels, with some perivascular and perifollicular lymphohistiocytic inflammation [8]. There is also slight edema and some elastic tissue hyperplasia present.

Likewise, in stage two there is more significant lymphohistiocytic infiltration around the follicles and the vasculature. Pustules appear as intrafollicular collections of neutrophils and chronic folliculitis. Inflammation is also prominent around sebaceous structures. Venous thickening and dilation along with marked elastosis are noted as well [4,8].

The rhinophyma of stage three rosacea is seen as hyperplastic, irregular sebaceous follicles and widespread dermal fibroplasia with connective tissue proliferation. Sebaceous ducts are dilated and filled with sebum and keratinaceous debris. In all stages, *Demodex folliculorum* can be found within sebaceous ducts and follicular infundibula [8]. Likewise, in our experience *Malassezia furfur* is also commonly observed within hair follicles in the biopsy specimens of rosacea.

IV. INDICATIONS FOR TREATMENT WITH GLYCOLIC ACID

Alpha hydroxy acids such as glycolic acid can be useful in the treatment of rosacea. Although rosacea can he seen in many forms, photodamage seems to be an almost universal associated feature. Studies have shown that glycolic acid (GA) peels and topical preparations can help repair and reverse changes

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such as fine wrinkling, coarse texture, and the overall severity of sun-damaged skin [9,10]. Furthermore, glycolic acid treatment can also provide a protective anti-inflammatory action by acting as an antioxidant in photodamaged skin [11]. Histological effects of GA treatment include reduction of stratum corneum thickness, increased epidermal thickness, more orderly differentiation, enhanced rete ridge pattern, and dispersal of melanin within the basal layer [12–14]. In addition, alpha hydroxy acid improvements within the dermis include a thickened papillary dermis, increased collagen synthesis, increased hyaluronic acid levels, and an increased amount and improved quality of elastic fiber tissue [12–16]. A recent study revealed that glycolic acid treatment, both in vitro and in vivo, increased the production of collagen by means of a direct effect on fibroblast proliferation that is independent of inflammatory mechanisms [17]. In patients with inflammatory lesions such as papules and pustules, GA peels can be an important adjunctive therapy. They act by promoting spontaneous "unroofing" of pustules by means of subcorneal epidermolysis secondary to more rapid penetration of acid through the thin epidermis and stratum corneum overlying the lesions [14].

Concerns regarding the compatibility of potentially irritating agents such as alpha hydroxy acids and the sensitive skin of rosacea patients are recognized. However, we have safely treated numerous rosacea patients in our clinics with GA peels and topical preparations. Recently, we performed an open-label, 12-week pilot study that investigated the safety and efficacy of gluconolactone, a new poly hydroxy acid, products on 15 women with rosacea. Exuviance® sensitive skin care products by NeoStrata, Inc.: Daytime Cream SPF 15 (gluconolactone 4%, pH 3.8) and Evening Cream (gluconolactone 8%, pH 3.8) were applied respectively in the morning and before bedtime. Significant improvement, as evaluated by physician clinical assessment, was noted for the following parameters: texture, fine lines, overall photodamage, dryness, and erythema. Similarly, 80% of patients rated the products

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as good to excellent in cosmetic acceptability [18]. (Figs. 5.1, 5.2, see color insert.)

In a safety assessment by the Cosmetic Ingredient Review (CIR), it was determined that even on normal skin alpha hydroxy acid ingredients can be dermal irritants. As expected at a given pH, higher concentrations of GA preparations tended to increase irritation. Meanwhile, an inverse relationship existed between the pH of the GA product and amount of irritation produced [19]. In most over-the-counter cosmetic products, the irritant potential of alpha hydroxy acids can be dampened by the vehicle and pH adjustors such as salts of the acids. The CIR also reported that GA and lactic acid, their common salts and simple esters, were safe for the use in cosmetic products at concentrations ≤10%, at final formulation pH ≥3.5. Cosmetic products for over-the-counter use include toners (astringents), cleansers, lotions, and creams. These same ingredients were deemed safe for use in salon-applied products at concentrations ≤30%, at a final concentration ≥3.0 in products designed for brief, discontinuous use followed by rinsing [19]. Designated salon-applied products are superficial alpha hydroxy acid chemical peels.

Because GA and other agents are potentially irritating, it is clear that special care must be taken by the dermatologist when selecting an alpha hydroxy acid regimen for the sensitive skin of rosacea patients. Our clinical and research study findings have confirmed that superficial peeling agents like GA can be safely and effectively used in the treatment of rosacea.

V. TREATMENT REGIMENS FOR ROSACEA

A. Flushing

Flushing is often the most troublesome symptom among rosacea patients. Because there are numerous "triggers" that may bring about a rosacea flare, it is important for patients to

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avoid these factors (environmental, food-related, psychological, and contact) that provoke flushing and other symptoms. Although no medication can completely suppress physiological flushing, some patients are helped by anticholinergics such as glycopyrrolate (at a dose of 2 mg b.i.d., whereas others may benefit from beta-blockers such as propranolol and naldolol or alpha-agonists like clonidine patches [20]. Sunscreens or sunblocks should also be used to prevent further photodamage and dilation of cutaneous vessels. Foundations and other makeup should be chosen to provide both adequate camouflage and sun protection (SPF 15 or greater) with minimal irritation. For patients with marked flushing and erythema, we often suggest a foundation cover-up with a green tint. Repeated laser treatments can also be helpful for persistent erythema and telangiectases.

B. Inflammatory Papules and Pustules

1. Antibiotics

Initial therapy for rosacea generally consists of a topical antibiotic metronidazole with or without an oral antibiotic in the tetracycline family, depending on the severity of the condition [21]. The mechanism of action of antibiotics in rosacea is most likely anti-inflammatory rather than antibacterial. Topical metronidazole (Metrogel™, Metrolotion™, and Metrocream™, 0.75% for b.i.d. application, and Noritate™, 1.0% for q.d. application) can be selected according to patient skin type. The mechanism of action of metronidazole has been attributed to antibiotic/antiparasitic activity on *Demodex folliculorum*. It also displays anti-inflammatory activity and immunosuppressive effects, being responsible for the inhibition of localized cutaneous cell-mediated immunity [22]. Alternate or additional topical antibiotics include sulfacetamide with or without sulfur (Sulfacet-R™ or Klaron™). These sulfur-based agents may help kill *Demodex* mites, as well as being anti-in-

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flammatory [20]. Topical clindamycin and erythromycin are also effective in rosacea.

Tetracycline, in doses of 250 to 500 mg b.i.d., or minocycline, in doses of 50 to 100 mg b.i.d., are often started with topical metronidazole in hopes of hastening recovery [20]. The therapeutic activity of the tetracyclines seems to be related to their anti-inflammatory effects. They also reduce neutrophil chemotaxis and macrophage phagocytosis, while also inhibiting complement activation and immune-mediated reactions [22]. Alternate oral agents include doxycycline, ampicillin, amoxicillin, clarithromycin, erythromycin, trimethoprim/sulfamethoxyazole, and metronidazole [20,22].

A recent study demonstrated that continued treatment with metronidazole alone can maintain remission of moderate to severe rosacea induced by treatment with oral tetracycline (250 mg q.i.d. for 12 weeks followed by a 4-week taper) and topical metronidazole 0.75% gel (b.i.d. application) [21].

2. Glycolic Acid

In our patients with stage one to two rosacea, we find that taking a combination approach by adding GA peels and topical GA products to an antibiotic regimen can dramatically improve the patient's condition.

Although the GA peels tend to provide maximal benefit for the inflammatory lesions and background photodamage, home application GA cleansers and lotions can help maintain the resultant positive changes. We try to tailor the regimen to the individual patient. In many cases, individual products of the "program" may be changed, depending on the particular needs and sensitivities of the patient's skin.

Over-the-counter GA products can be divided into the following categories: toners, cleansers, creams, and lotions. The purpose of a toners or astringents is to remove excess oil and temporarily tighten skin. Although most toners are now alcohol-free, ingredients like GA will still have a significant drying

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effect on the skin. Cleansers containing GA have a dual purpose in that they remove excess oil and tighten skin while also promoting gentle exfoliation. Glycolic acid–containing creams and lotions confer some degree of moisture to the skin while also suppressing acne and rosacea lesions by diminishing corneocyte cohesion and promoting normal keratinization.

For at least a month before initiating the GA peel series, we like our patients to use a GA-containing cleanser and oil-free, noncomedogenic GA lotion to prepare the skin. In our experience, topical preparations such as the MD Forte® facial cleanser and facial lotion, which have a 15% GA concentration and have been partially neutralized to a pH of 3.8, are efficacious and have low irritation rates in our rosacea patients. Patients will generally start out with once-daily cleansing and lotion application and work up to twice-daily use as tolerated.

After consistent application of GA products for 4 to 6 weeks with minimal to no irritation, we begin with the GA Peels. The Gly Derm® line of GA peels ("glycolic applicators") is well suited to the variable sensitivities of rosacea patients, because it comes in concentrations ranging from 20–70% and delivers a fixed quantity of GA per packet. The lowest concentration peel (20%) has a product pH of 1.4; whereas the highest concentration peel (70%) has a product pH of 0.1.

Before the peel, the patient's face is first prepared by cleansing with the Gly Derm gentle cleanser (GA concentration, 2%; pH, 5.7). Next, we lightly swab the area with an alcohol pad followed by acetone solution to degrease the skin. Initially, this part of the process is performed on a small area of the forehead to test for any potential irritation. If a patient does display some sensitivity, this step is foregone in the future. Now the glycolic peel is applied. Special care is taken to avoid excess rubbing, which would otherwise potentiate uneven absorption and undue irritation.

The length of contact time must be determined on an individual basis. Generally, for the first peel we allow half of the recommended time (2–3 min) to elapse before having the pa-

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tient rinse her face with tepid water. We can then gauge her degree of sensitivity and determine which concentration and the length of exposure to use subsequently. The interval between peels is also variable, ranging from 2 to 4 weeks. For optimal effect, we suggest a series of six to eight peels. Between peels and after completion of the series, patients continue to use their topical GA products. "Touch-up" peels may be performed at more distant intervals as they are required. (Figs. 5.3, 5.4, see color insert.)

3. Tretinoin

Tretinoin, a vitamin A derivative, has been shown to influence epidermal keratinization, reverse gross and microscopic changes of photoaging, and modulate epidermal differentiation and wound healing. It has long been used in the treatment of acne vulgaris and photoaged skin. Lower strength (0.025%) tretinoin (Retin-A™) cream applied nightly for 16 weeks has been shown to be beneficial in the treatment of severe or recalcitrant rosacea. Therapeutic benefits were measured in terms of reduction of papules, pustules, and erythema. Using a lower concentration of tretinoin can minimize the adverse effects such as dryness, stinging, scaling, and erythema seen with use of higher strength preparations [23]. In our experience, the benefits of tretinoin in rosacea can best be achieved using the lowest concentration of tretinoin, 0.025%, cream and decreasing the frequency of nightly application to two to three times per week. Irritation may further reduced by diluting the tretinoin with an oil-free moisturizer before use.

4. Isotretinoin

When rosacea is recalcitrant, isotretinoin in doses of 0.2–0.5 mg/kg/d has been used with good results [4]. The treatment period is usually between 3 and 5 months. Studies report primary improvement in inflammatory lesions, edema, and

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rhinophyma but negligible effect on erythema [4,24]. Because isotretinoin's mode of action is to alter keratinization in the skin and reduce sebaceous gland size by decreasing proliferation of basal sebocytes and suppressing sebum production, it is of particular benefit in patients with oily, large-pored skin with multiple sebaceous gland hyperplasias. Isotretinoin has also been shown to have anti-inflammatory, immunomodulatory, and antiangiogenic properties [24]. In addition to treating acne and rosacea, isotretinoin has been shown to be efficacious in cases of severe seborrhea and gram-negative folliculitis, which suggests a broad-spectrum antimicrobial effect. It may also have an effect on decreasing adrenal gland function.

As with any isotretinoin treatment regimen, full explanation of all potential adverse effects, especially teratogenicity, should be discussed before hand with the patient. Routine laboratory monitoring of liver function tests, lipids (cholesterol, triglycerides), qualitative beta-human chorionic gonadatropin levels (if applicable), and complete blood count should be performed at baseline and at 4- to 6-week intervals while on therapy. Unfortunately, some patients may note relapse of their rosacea once isotretinoin is withdrawn. Nonetheless, isotretinoin has a necessary place in managing the most severe or persistent cases.

C. Laser Surgery

Although peels predominantly improve underlying photodamage and inflammatory lesions, persistent erythema and telangiectases are best handled with laser surgery. For patients who have discrete sprays of telangiectases, effective vessel elimination can be achieved with the Versapulse (532 nm) laser. When persistent diffuse erythema and telangiectases are the problem, treatment with the flash-lamp–pumped tunable dye laser is preferable [25]. Most patients require at least 3 to 10 treatments to clear most of their vas-

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cular lesions. Interestingly, ablation of dilated vessels with the laser has been shown to reduce the number of subsequent inflammatory lesions [2,25].

With the rise of CO_2 resurfacing laser use, excellent cosmetic results have been obtained in patients with severe, disfiguring rhinophyma. Other surgical modalities include electrosurgery, dermabrasion, excision and skin grafting, scalpel shaving, and cryosurgery. Isotretinoin is often used preoperatively to shrink bulbous portions and is frequently continued postoperatively to maintain the improvement [4].

VI. CONCLUSION

In summary, rosacea is a potentially progressive, chronic dermatosis that deserves early and aggressive therapy. It is a polymorphic disease that is affected by genetic, vascular, immune-related, psychological, environmental, and infectious factors. With prompt intervention, patients can expect control of their symptoms and a significant improvement in the appearance of their skin. Because the manifestations of rosacea can range from vascular to inflammatory, optimal management should target treatment toward the specific lesion. The need to minimize or avoid contact with triggers that provoke flares of rosacea should be emphasized. Although laser surgery is the most effective treatment for persistent erythema and telangiectases, topical and oral antibiotics are the cornerstones of initial therapy for papulopustular lesions. Treatment of background photodamage, which is characteristic of all stages of rosacea, and mild to persistent inflammatory lesions can be augmented by the addition of a GA program. The synergistic combination of antibiotics and GA is highly effective and well tolerated by most all rosacea patients. Because alpha hydroxy acids can be potentially irritating, it is of paramount importance that the dermatologist carefully design a regimen that will have maximal efficacy with minimal adverse cutaneous effects. Collectively, a series of GA peels used in

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combination with daily use of GA cleanser and lotion will work above, below, and at the surface of the epidermis to rejuvenate and repair the stigmata of rosacea.

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6

Prepeeling Regimens

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I. INTRODUCTION

A good topical regimen is often the first step in the necessary behavior modification for the patient who desires procedural resurfacing. Not only do prepeeling topical programs set the stage for uniform resurfacing and faster healing, they train the patient in proper skin care maintenance. Combining sun protection measures and sunscreen with a good topical regimen also gives longevity to resurfacing procedures.

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II. WHAT DO WE ACCOMPLISH WITH TOPICALS BEFORE A PEEL?

The goal in topical use before peeling depends on the level of resurfacing anticipated. If a superficial peel is planned, topical products are used to maximize results with less morbidity than with medium depth resurfacing. If a medium depth or deep resurfacing is planned, the goal of the topical regimen is appropriate skin preparation without excessive irritation. With any prepeel topical regimen, erythema and desquamation are indications of disruption of skin barrier function and may lead to unpredictable uptake of the peel solution. It is important to recognize these signs, adjust the regimen, and modify or cancel the peel procedure.

III. ACNE

Three subsets of acne patients particularly benefit from a series of superficial peels. Patients with widespread open and closed comedones respond quickly to the keratolytic effect of light peels. In these patients acne surgery is a useful adjunct after the peel has loosened the comedones. Acne patients with a tendency toward postinflammatory pigmentation respond to a combination of peels and bleaching agents. Finally, acne patients who are sensitive to topicals and limited in what they can tolerate at home can benefit from peels as an alternative to other keratolytic agents.

When designing a prepeeling topical regimen (see Table 1), the primary objective is to enhance keratolysis to prevent comedone formation without causing irritation. Younger acne patients tend to have skin that is more sensitive, both to prepeel topicals and to peel solutions. This may be because active acne lesions create microbreaks in the skin barrier. Older acne patients often have a component of dermal scarring, which makes their skin more tolerant of a wide variety of topicals. If the patient is currently on a topical regimen, we con-

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Table 1 Prepeeling Regimen for Acne Patients

Syndet bar/mild cleanser
AHA lotion, twice daily or morning only
AHA exfoliant,[a] as needed
Tretinoin, adapalene
Bleaching agent[b]—hydroquinone, azelaic acid[c]

[a]In patients with an oily complexion.
[b]In patients with postinflammatory hyperpigmentation (can be given in combination with AHA (i.e., Lightening gel [Dermatologic Cosmetic Labs, East Haven, CT]).
[c]One of these agents.

sider this in planning the regimen before the peels. Many acne patients do not consider peels as a first-line therapy and have used a number of different topicals for acne therapy. It is important to discuss their past experiences with topicals to understand their tolerances and preferences.

A. Cleansing

A mild synthetic detergent bar soap or Syndet bar has a pH adjusted to that of normal skin (between 5 and 7) and is a gentle cleanser [1]. If the acne patient describes his or her complexion as oily, this cleaning can be followed with an astringent/exfoliant (i.e., Aqua Glyde, Herald Pharmaceuticals [now Allergan] Irvine, CA). An astringent has an alcohol base and is used to remove oil, giving the patient a light or clean feel [1]. An exfoliant is an astringent with an agent added (such as glycolic or salicylic acid) to increase epidermal turnover [1]. It is common for acne patients to use abrasive scrubbing products and mechanical scrubs such as a Buf-Puff or wash cloth. These products can compromise the epidermal barrier allowing peel solutions to penetrate unpredictably. They produce erythema and peeling but do not predictably improve comedones [1,2]. Abrasives also lower patient tolerance for other skin products.

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B. Alpha Hydroxy Acids

In acne patients with minimal scarring and more sensitive skin, we tend to use glycolic acid products at the lower end of the available range (8–10%) to avoid irritation. Chronic acne patients with some scarring and less sensitive skin will often tolerate topical glycolic acid products with a concentration ranging from 15–20%. It is important that the vehicle be noncomedogenic (predominantly water and propylene glycol) [3]. Propylene glycol can enhance the penetration of AHAs by affecting the permeability of the stratum corneum [4]. If a patient has an oily complexion, adding an exfoliant can provide both oil control and topical AHA delivery.

AHAs act on the nascent layers of the stratum corneum, creating a sheetlike separation of the proximal upper stratum corneum [5]. It is speculated that AHAs may compete for sulfate and phosphate with sulfate transferase, phosphotransferase, or other enzymes in the stratum granulosum [5]. This substrate competition would result in fewer electronegative sulfate and phosphate groups on the surface of the keratinocytes in the stratum corneum and would weaken ionic bonding at this level of skin [5]. Berardesca et al evaluated 8% glycolic acid (GA), lactic acid (LA), tartaric acid (TA) and gluconolactone (GLU) to evaluate how the decrease in thickness of the stratum corneum affected skin barrier function and resistance to irritation from a detergent, 5% sodium lauryl sulfate (SLS) [6]. They found that the applied AHAs increased the resistance of the skin to a topically applied irritant (SLS). Both of these pharmacological actions would be beneficial to acne patients. Decrease in corneocyte adhesion works to decrease follicular plugging. An increase in the resistance of the skin barrier to topical irritants makes AHAs a useful adjunct for a patient population that often has compromised barrier function and is using multiple topicals.

For patients with chronic acne and the resultant dermal fibrosis, the pharmacological actions of AHAs in the dermis may lead to collagen remodeling and improved skin appearance [7,8].

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C. Topical Retinoids

Tretinoin has been the cornerstone of most acne therapeutic regimens for the past several decades. Tretinoin promotes drainage of comedones through loosening of follicular impaction, normalizing desquamation of follicular epithelium, removing the microorganisms that stimulate inflammation, and providing an anti-inflammatory effect [9–11]. In addition to its multifaceted attack on the acne process, tretinoin has also been shown to lessen the time to re-epithelialization after skin resurfacing [12,13]. The biggest limitation to the use of tretinoin is the high incidence of retinoid dermatitis. The incidence of retinoid dermatitis decreases with use over time [14]. In addition one can decrease adverse effects by using lower concentration formulations and alternate-day application. Retin A-Micro (Tretinoin .1%, Ortho Pharmaceutical, Raritan, NJ) is a relatively new product in which tretinoin is encapsulated in porous acrylate copolymer microspheres that release tretinoin over time causing less skin irritation [15].

Unfortunately, even with these modifications, some patients are truly unable to tolerate tretinoin. Probably a larger segment of the patient population that claims to be intolerant is simply unwilling to try tretinoin because of a previous experience with dermatitis. If it is possible to use tretinoin in the prepeeling regimen, the concentration best tolerated in the past is prescribed. Patients are instructed to be vigilant in recognition of retinoid dermatitis, because the presence of any erythema or scaling can focally increase penetration of peeling solutions.

Adapalene (Galderma, Fort Worth, TX) is a reasonable substitution for tretinoin and has shown efficacy with less irritation in a study comparing it to tretinoin gel, 0.025%.

D. Bleaching Agents

The use of bleaching agents is important for those acne patients who have postinflammatory hyperpigmentation. Wang et al showed that the use of a combination of glycolic acid

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peels and glycolic acid topicals improved skin pigmentation in 77.5% of the 40 Asian patients treated for acne. They observed a generalized lighter and brighter skin tone and prominent bleaching of hyperpigmentation [17]. They postulated that the mechanism of pigment improvement might be epidermolysis of hyperpigmented skin followed by follicular replacement with more normally pigmented epithelium. In addition, they suggested that the structural similarity of glycolic acid to ascorbic acid might provide the chemical basis for a direct depigmenting effect.

Hydroquinone is a very effective bleaching agent and can be added to prepeeling and postpeeling regimens. A commercial formulation with 4% hydroquinone usually is adequate, although it is occasionally necessary to compound a high-percentage formulation. Patients using hydroquinone should be told to discontinue use if the area of application darkens. Although it is unlikely, there is a potential for development of exogenous ochronosis even with low concentrations of hydroquinone [18].

E. Azelaic Acid [19]

A recent study has evaluated the use of 20% azelaic acid in combination with a 15–20% AHA lotion compared with 0.025% tretinoin cream in the treatment of mild to moderate acne vulgaris. They found equivalent efficacy with a 25% global improvement in both groups. They found significantly less dryness, scaling, and erythema on the azelaic acid/glycolic acid–treated side.

IV. MELASMA (Table 2)

Melasma is a chronic pigmentary condition of facial skin. The cause is multifactorial; high estrogen states, genetic predisposition, sunlight, and autoimmune thyroid disease have all been identified as causative factors [20–22]. The three regional patterns of melasma are malar, centrofacial, and mandibu-

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Table 2 Prepeeling Regimen for Melasma

Sunscreen	Before makeup
Tretinoin	Before bed
Alpha hydroxy acid	Twice daily (night, 1/2 hour before tretinoin)
Bleaching agent	
Hydroquinone	Twice daily
Azelaic acid	

lar [22,23]. There are three histologic patterns of pigment distribution in melasma: (1) melanin in the basilar and suprabasilar epidermis; (2) melanin-laden macrophages in the perivascular area; (3) mixed. For the clinician melasma can be a very frustrating condition, because there is great variability in response to therapy. Even when it responds well to therapy, a small amount of sun exposure can flair the melasma. Because of this, the mainstay of topical therapy is a good sunscreen.

A. Efficacy of Glycolic Peeling in Melasma

The increase in pigment in melasma is in the basal layer of the epidermis and the dermis. If one thinks of the level of action of glycolic acid (stratum corneum), it is perplexing that it is efficacious in the treatment of melasma. This is probably because glycolic acid products do not "peel off" the pigment but rather have some intrinsic bleaching properties and increase the penetration of agents used in combination. Two recent studies confirm the efficacy of glycolic acid for melasma. Lim et al compared a topical regimen of 10% glycolic acid and 2% hydroquinone alone to these same topicals combined with a series of light peels over 26 weeks in 10 Asian women with moderate to severe melasma [23a]. Both sides showed improvement. The peel side showed greater improvement than the topical-alone side, but the difference was not statistically significant. Lawrence et al conducted a double-blinded split-face design study comparing a series of three peels with 70%

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glycolic acid and three peels with Jessner's solution in conjunction with tretinoin and hydroquinone for the treatment of melasma in 16 patients [23b]. The global melasma score decreased 63%, and the colorimeter analysis showed on average, lightening of 3 points. There was no statistically significant difference between the two sides.

B. Sunscreen

The portion of the ultraviolet (UV) spectrum responsible for stimulating melasma has not been explained. Therefore, it is important to block both UVB and UVA in the melasma patient. In the resurfacing patient physical sunblocks have a number of advantages. They provide broad-spectrum coverage (UVA and UVB). They are hypoallergenic and have an extremely low risk of irritancy. Micronized titanium dioxide and zinc oxide are two excellent physical sunscreens. Many products contain one of these ingredients but also have chemical sunscreens. It is important to advise the patient to look at the list of ingredients to ensure that the sunblock they choose contains only a physical block (see Table 3).

Physical blocks are preferable in the resurfacing patient, because they are less likely to irritate newly resurfaced skin.

Table 3 Nonchemical Sunscreens (for Patients with Allergy or Sensitivity)

Almay supersensitive SPF 30
Clinique City Block Oil-Free Daily Face Protection SPF 15
Clinique Special Defense Sun Block SPF 25
Estee Lauder Advanced Suncare Sunblock SPF 15 or 25
Estee Lauder Advanced Suncare Baby Block Lotion for Children SPF 25
Estee Lauder Advanced Suncare Sun Block Lotion Spray SPF 15
Neutrogena Sensitive Skin Sunblock SPF 17
Westwood-Squibb PreSun Block SPF 28
SkinCeuticals Daily Sun Defense 20 with zinc oxide
Roc Dermatologic Broad Spectrun Sunblock

Modified from Skin & Aging May 1999, Sunscreens: Friend or Foe? pages 31–36.

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When patients use a makeup with sunscreen, we advise them to put a sunscreen on before their makeup, because most people do not apply their makeup thick enough to provide adequate protection.

C. Alpha Hydroxy Products

The melasma population is usually able to tolerate a higher concentration alpha hydroxy topicals. If they have never used AHAs, one can start them with a 10% AHA formulation. However, the AHA can also be in a more emollient formulation, because these patients (unless they have acne) do not have to be concerned about comedogenesis or oiliness. If they have been using over-the-counter AHAs, we start at 15%.

D. Tretinoin

The melasma patient often tolerates a higher concentration tretinoin than the acne patient. Unless they have a history of previous difficulties with tretinoin or sensitive skin, one can start with a 0.05% tretinoin. When the patient finishes the first tube of tretinoin, 0.05%, if they have tolerated that percentage without regimen modification (every-other-day application or avoidance of application to areas prone to peel like the chin), they will be advanced to tretinoin, 0.1% (Retin A-Micro, Ortho Pharmaceutical, Raritan, NJ).

E. Bleaching Agents

Hydroquinone is a hydroxy phenolic compound that targets tyrosinase inhibiting the conversion of dopa to melanin [24]. Hydroquinone bleaches indiscriminantly and therefore must be carefully applied, because it will bleach skin with normal pigmentation. Patients should be given specific instructions on application (see Instruction Sheet below). It is important to caution the patient that the gel formulations often sting on initial application, but this transitory sensation is not a true

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irritant dermatitis and not an indication for discontinuing use.

Bleaching gel or cream instruction sheet

1. Apply a thin layer twice a day to darkened areas of skin. If also using Retin A, use bleaching gel morning and dinner time and Retin A at night.
2. This is a bleaching cream, it must be applied carefully *only* to dark spots. It will bleach the normal skin if applied.
3. If darker pigment clears, then use the bleach only as needed for recurrences.
4. Sun must be avoided, and sunscreen, SPF of 15 or greater, must be used. See sun tip information sheet for further advice.
5. Avoid getting gel or cream in your eyes.
6. If a skin irritation, allergy, or darkening of pigment develops, call immediately.

Azelaic acid also has antityrosinase activity but is more specific for hyperfunctioning or proliferating melanocytes. It does not affect normal melanocytes and is not associated with ochronosis. Kakita et al performed a double-blinded split-face design study comparing a combination of azelaic acid, 20%, and glycolic acid, 15 to 20%, to hydroquinone, 4%, in the treatment of facial hyperpigmentation in dark-skinned patients [25]. The conditions of hyperpigmentation in the study included severe melasma, postinflammatory hyperpigmentation, idiopathic melanosis, and drug-induced hyperpigmentation. Patients were evaluated by physicians using a graded scale. Patients completed an exit survey for subjective assessment. After 24 weeks, there were equivalent overall improvement scores for both treatments, with a slightly higher incidence of irritation on the azelaic acid/glycolic acid–treated side.

Kojic acid is a pyrone compound that chelates the copper moiety of tyrosinase, causing suppression of this enzyme

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[24,26]. Garcia et al conducted a double-blinded split-face design trial comparing a 2% hydroquinone/glycolic acid gel to a 1% Kojic acid/glycolic acid gel in 39 patients with melasma [24,27]. They found an average pigment reduction of 58% and no statistically significant difference between the two treatments. Patients found the Kojic acid more irritating.

V. PHOTOAGING

Photoaging is the result of chronic sun exposure. The histological changes include the following:

1. Stratum corneum thickening, epidermal acanthosis, epidermal dysplasia [28]
2. Discrete pigmented lesions—solar lentigines and seborrheic keratosis, as well as heterogencity in pigmentary activity of melanocytes [29].
3. Reduction in collagen and collagen precursors, solar elastosis with abnormal deposition of glycosaminoglycans on the elastotic material, and chronic inflammation with an increase in mast cells, macrophages, and lymphocytes [30,31].

Ridge et al evaluated the use of 12% ammonium lactate (Lachydrin, Westwood-Squibb Pharmacy Inc., Buffalo, NY) in 21 patients with photoaging ranging from mild to severe. They found an improvement in fine wrinkling and skin texture in most of the patients [32]. Ditre et al performed a double-blinded placebo-controlled trial on severely damaged forearm skin in 17 patients [33]. They used a 25% AHA, pH 3.5, for 6 months and found an increase in skin thickness by pinch test and changes under both light and electron microscopic (LM, EM) examination. By LM examination there was increased epidermal thickness, improved rete pattern, better dispersal of melanin, and better quality elastic fibers. On EM examination there was a decrease in desmosomes and in increase in anchoring fibrils. In another double-blinded placebo-

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Table 4 Prepeeling Regimen for Photoaging

Sunscreen	Before makeup
Tretinoin	Before bed
Alpha hydroxy acid	Once or twice daily

controlled trial using 20% citric acid on photodamaged forearms, there were statistically significant improvements in skin thickness, epidermal thickness, dermal hyaluronic acid, and dermal chondroitan sulfate [34]. Two studies have demonstrated that even very low concentrations of AHAs (8% or 5%) can effect a modest improvement in photodamage over time [35,36].

Bergfeld et al compared the application of glycolic acid topicals in conjunction with light peels to mechanical irritation with a loofah sponge in a 16-week study on photodamaged dorsal hand skin. There was a significant improvement on the AHA side, which supports a pharmacological rather that an irritant mechanism for AHA improvement in photodamage.

The prepeel regimen for photoaging is detailed in Table 4. The patient's history is reviewed, including any previous history of precancerous lesions, product use, skin type, and sensitivity, and placed on the highest strength product they can tolerate without irritation. As they tolerate both tretinoin and alpha hydroxy acid products, they are put on increasing strengths until they are using tretinoin, 1% (Retin A-Micro, Ortho Pharmaceuticals, Raritan, NJ) and AHA of 20%.

VI. SPECIAL CONSIDERATIONS IN PREPEELING CARE

A. Seborrhea

Patients with seborrhea are usually placed on a low-potency steroid cream such as 1% hydrocortisone. Glycolic peel solutions will penetrate more deeply in an area with inflamma-

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tion. When this happens, the patient gets an uneven, deeper-than-expected peel. Patients are often intolerant of greater than expected morbidity when they expect the minimal morbidity of a light peel.

B. Tretinoin-Induced Dermatitis

Tretinoin-induced dermatitis is very common and if severe and can allow a deeper, uneven peeling as described with seborrheic dermatitis. If it is mild, this is usually not a concern. It is important to counsel the patients that if they are getting considerable erythema and peeling, they should call and have their regimen adjusted so that it is not necessary to cancel their peel.

VII. SUMMARY

A good prepeel regimen can maximize results and minimize complications. The same topicals are often used for maintenance. The prepeel regimen begins good skin care habits before a procedure.

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7

Dermal Effects of Alpha Hydroxy Acids

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Alpha hydroxy acids (AHAs) are naturally occurring organic carboxylic acids, which are commonly found in foods. The first reported therapeutic benefit of these agents was reported more than two decades ago [1]; however, only recently have they been used in a myriad of skin products. AHAs were initially used to treat disorders of keratinization, including ichthyosis, xerosis, and psoriasis [2]. Despite the recent surge in AHA use, relatively little has been written regarding their mechanism of action.

Their safety has been well documented since they have been established as nontoxic fruit substances and participate in our bodies in the formation of metabolic energy and are building blocks for carbohydrates and other essential molecules. They have been used for more than a quarter of a cen-

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tury as topical agents and have proven to be both safe and effective. Despite their ability to strip even grossly thickened stratum corneum, as seen in lamellar ichthyosis (Figs. 1 and 2), their use in dermatology was still rather limited until recently. Only a single prescription AHA has been marketed for the treatment of dry skin, 12% ammonium lactate. The discovery that AHAs improve sun-damaged skin led to investigation of the dermal effects of these agents. Their somewhat limited use in medical dermatological practice is quite surprising, given the demonstration that these agents can prevent both dermal and epidermal atrophy resulting from long-term topical corticosteroids use [3]. These would seem to be ideal agents to use in conjunction with corticosteroids for treating a number of chronic conditions in which topical corticosteroids are used for prolonged periods of time, such as morphea.

I. THE DERMIS

To understand the effects of AHAs on photoaged dermis, we must first understand the normal biology of the dermis and the alterations that result from chronic sun exposure. The major structural component of skin is the dermis, also know as the cutis. This forms the bulk of the skin, where the resident cells of the dermis reside and the blood vessels transport a myriad of circulating cells to the skin. The dermis may be divided into a superficial papillary dermis, which contains fine whisps of collagen and elastic fibers with an associated vascular plexus, and a deeper reticular dermis, with its wider collagen bundles and associated elastic fibers. The collagen of the reticular dermis is easily distinguished from the papillary dermis because of the orientation of the thicker collagen fibers parallel to the epidermis.

The border between the papillary dermis and the epidermis is delineated by the dermal–epidermal basement membrane zone. This zone is comprised of a number of extracellular matrix molecules, and is quite metabolically active. The epidermis needs to derive all its nutrients through this zone,

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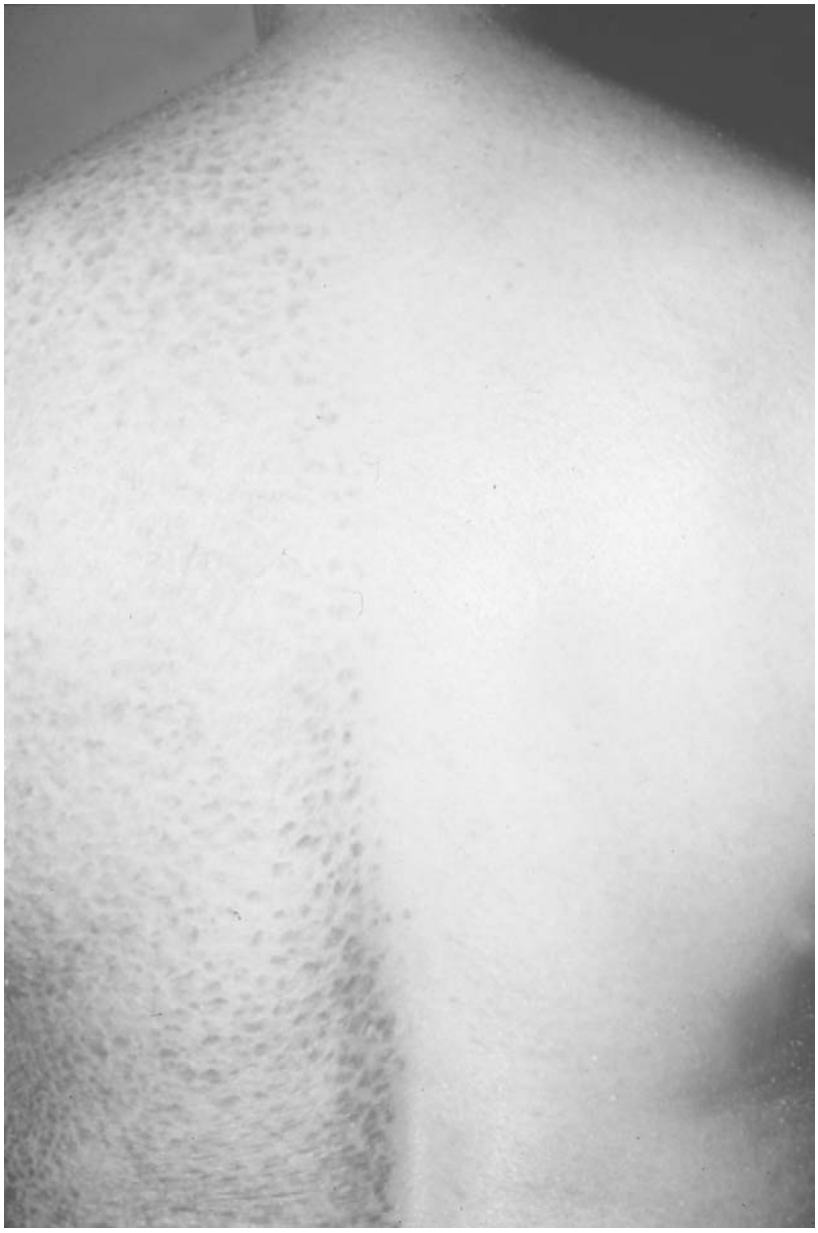

Fig. 1 A patient with lamellar icthyosis who has been treated on the right side of his back with a combination of alpha hydroxy acids. (Courtesy of Eugene Van Scott, M.D.)

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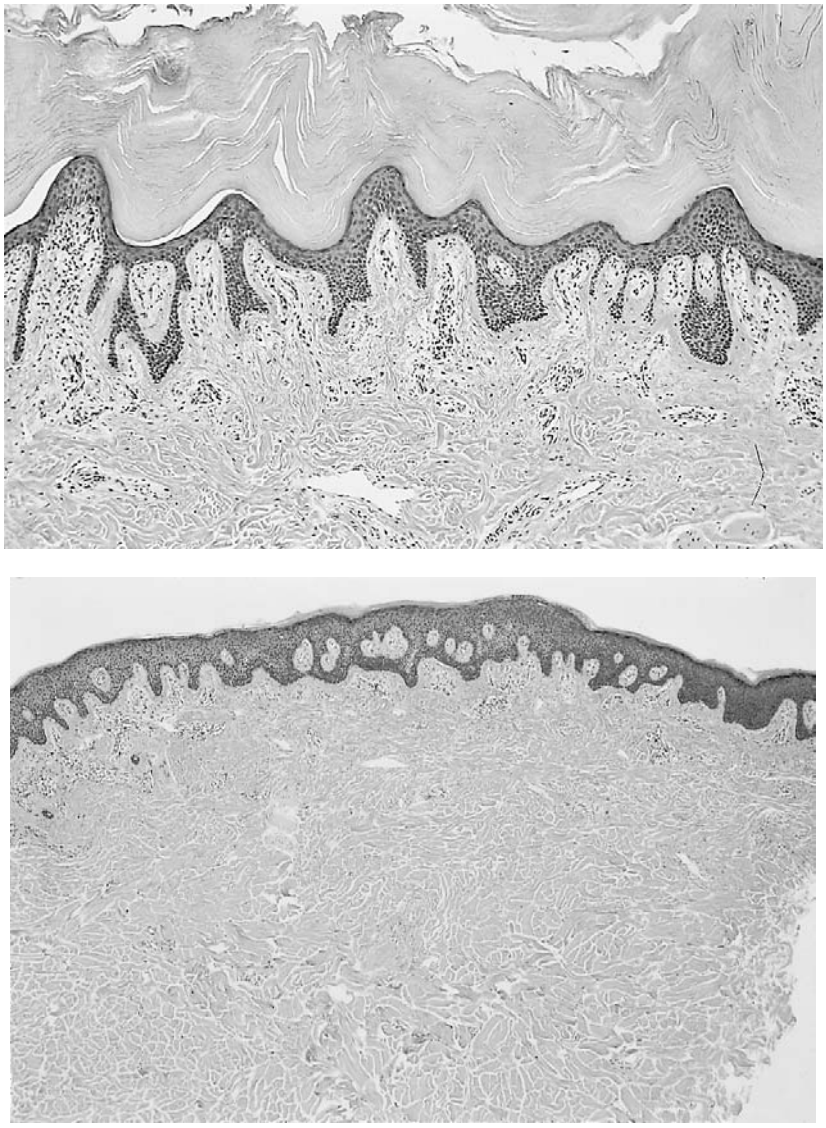

Fig. 2 *Top*, A punch biopsy taken from the untreated side of the patient shown in Fig. 1 demonstrates a greatly thickened stratum corneum. *Bottom*, A biopsy taken from the treated area shows a more normal-appearing stratum corneum (magnification ×128). (Courtesy of Eugene Van Scott, M.D.)

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because the epidermis contains no blood supply of its own. The border of the deeper reticular dermis and the underlying adipose tissue is less well defined, with adipose lobules intermixed with the lower reticular dermis. The resident cells of the dermis are relatively sparse, but they play a crucial role in maintaining dermal integrity and responding to outside insults, such as sunlight. They also exert their effects by recruiting circulating inflammatory cells to alter dermal architecture. The major extracellular matrix component of the dermis is collagen, with intermingled elastic fibers, proteoglycans, and glycosaminoglycan. Enmeshed in the extracellular matrix are blood vessels, lymphatic channels, and nerves. Some of the nerves traverse the dermal–epidermal junction and communicate with the epidermis. In addition, the adnexal structures of the skin participate in maintenance of dermal architecture, or alter it in response to exogenous stimuli. These include hair follicles, sebaceous glands, and sweat glands with their associated epithelium. The extracellular matrix components of skin provide the properties that allow skin to adapt to a constantly changing environment. Collagen provides strength, and the strength of healing wounds is largely proportional to the collagen content and maturity. Elastic fibers supply the ability to stretch (elasticity) and the ability of skin to snap back to its original shape after distention (resilience).

A. The Extracellular Matrix

The dermis is composed of extracellular matrix, which is largely maintained and remodeled by resident fibroblasts. These fibroblasts are under the regulatory control of the surrounding cells, including circulating inflammatory cells, resident mast cells, epidermal keratinocytes, and vascular endothelial cells, among others. Together this conglomeration of cells functions to maintain the homeostasis of the dermis.

Collagen is by far the most abundant extracellular matrix component. Collagen makes up 80% of the dry weight of the dermis [4]. Although the most abundant collagen, type I collagen, forms the bulk of the dermis, together with the less

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abundant type III collagen, collagens serve a number of other functions in the dermis. Type VII forms the anchoring fibrils that help attach the epidermis to the underlying dermis. In addition, other collagen types help form more superficial portions of the dermal–epidermal basement membrane zone.

Although elastic fibers are by weight a minor component of the dermal extracellular matrix, forming only 2–4% of the dry weight of the dermis, they are functionally critical. Elastic fibers provide most of the elasticity and resilience to skin. Elastic fiber alterations are one of the major findings associated with chronic sun exposure, leading to dramatic alterations in the skin's appearance and ability to respond to the environment.

Collagen and elastic fibers form the fibrillar component of the extracellular matrix. Polysaccharides and glycosaminoglycans are large extracellular matrix molecules, which form the bulk of the nonfibrillar component. Although these molecules represent a relatively small portion of the total extracellular matrix, 0.1–0.3%, they provide hydration by binding large amounts of water. In addition, they function to allow cell migration and mitigate cell–matrix interactions, helping form normal-appearing collagen and elastic fibers. Normal functioning of the skin requires an interplay between all the extracellular matrix components, resident cells of the dermis, and inflammatory cells. External stimuli such as sunlight can alter normal homeostasis and result in an altered dermal structure and function.

II. COLLAGEN

The collagens makeup a family of related molecules, which share certain similarities, but may differ widely in their function and use. They are named using Roman numerals in the order in which they were discovered. Collagens are composed of three polypeptide chains, which are designated alpha chains. These chains may be distinct or identical. Distinct chains are numbered one and/or two and/or three. All collagen

molecules contain a characteristic triad of amino acids termed the Gly-X-Y sequence. Gly refers to the amino acid glycine, and X and Y refer to other amino acids. The X and Y positions are often occupied by the imino acids, proline and hydroxyproline, respectively [5]. These Gly-X-Y sequences repeat in the collagenous segment of a collagen molecule. This repeating sequence confers a characteristic triple-helical configuration to the collagen molecule. This triple helix configuration results from having glycine in every third position of this polypeptide. Proline and hydroxyproline help stabilize the triple helix helping form a stable collagen fibril [5]. Patients who have severe vitamin C deficiency, or scurvy, are characterized by poor wound healing, fragile skin, and bruising and bleeding tendencies. Vitamin C is crucial to hydroxylation of prolyl residues forming hydroxyproline, which cross-links and stabilizes collagen fibers [5].

Collagen alpha chains are synthesized as precursor polypeptides, on the ribosomes of cells, which produce collagen. The main such cell in the dermis is the dermal fibroblast. These newly made precursor alpha chains associate with one another in the rough endoplasmic reticulum. These associated chains are then stabilized by interchain disulfide bonds. The three associated alpha chains then fold into the triple-helical confirmation. These procollagen molecules are then secreted into the extracellular space by way of the Golgi apparatus in Golgi vesicles. In the extracellular space, the collagenous extensions at the end of the molecule are removed. Further formation and processing of collagen takes place in the extracellular space. The molecules align to form fibers, which are initially weakly stabilized by noncovalent interactions and disulfide bonds. Subsequently, molecules are linked by the formation of covalent cross-linking, involving oxidative deamination of lysyl and hydroxylysyl residues by lysyl oxidase [6].

A. Type I Collagen

Type I collagen is expressed in a variety of connective tissues, including bones, tendons, and ligaments. It is the single most

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abundant structural protein in the body. Type I collagen is also the major collagen in the dermis and accounts for approximately 80% of the collagen in skin (Fig. 3) [4]. Type I collagen fibers have a characteristic banding pattern with an interval between bands of 68 nm. It consists of three polypeptide chains that are arranged in the typical alpha helical configuration. Two of these chains are identical and thus labeled α 1(I) chains, whereas the third unique chain is labeled α 2(I). The procollagen molecules form a triple helix composed of the two α 1(I) and one α 2(I) chains. This procollagen mol-

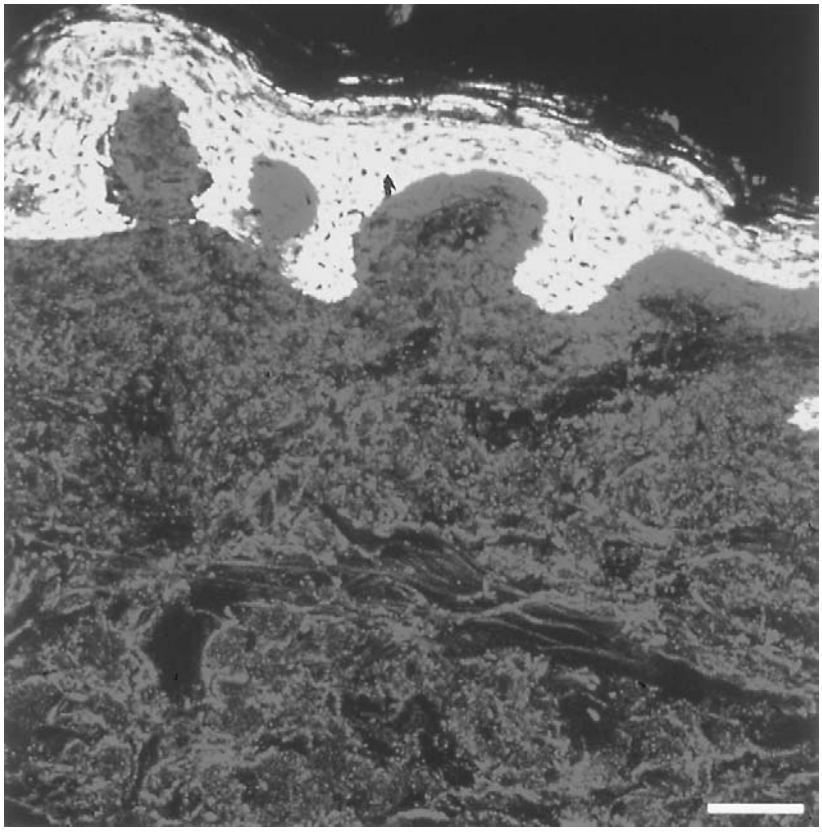

Fig. 3 Laser scanning confocal microscopy demonstrates the dense collagen network in sun-protected skin. The epidermis is stained white (magnification ×490).

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ecule is secreted at the extracellular space, and the nonhelical extensions on the *N* terminal and C terminal ends of the protein are removed by proteases.

B. Type III Collagen

Type III collagen is also called fetal collagen because of its great abundance in fetal tissues [7]. Type III collagen forms approximately one half of the total collagen in fetal skin. However, after birth, production of type I collagen moves ahead of type III collagen, with the resulting ratio of type I collagen to type III collagen in adult human skin being 6:1 [8]. Unlike type I collagen, which is composed of two types of alpha chains, type III collagen is composed of three identical α 1(III) chains. These chains also arrange themselves in the triple helix confirmation, which typifies collagens. Type III collagen is distributed similarly to type I collagen throughout the skin. In addition, type III collagen is abundant in extensible tissues such as the gastrointestinal tract and arterial blood vessels [9,10]. The function of type III collagen is highlighted in disorders such as Ehlers-Danlos syndrome type IV. In this disorder, mutations are present in type III collagen that give individuals with this condition fragile skin and the propensity to develop ruptures of the gastrointestinal tract and arteries [9,10]. This demonstrates the importance of type III collagen to stability of these tissues. Because type III collagen fibers have been found to distribute throughout the dermis with type I collagen fibers [11], it is speculated that they help direct the formation of mature type I collagen fibers. This is also evidenced in wound healing, where type III collagen is the first collagen identified in a healing wound, soon to be followed by type I collagen, which as it matures confers strength to the dermis.

C. Type IV Collagen

Type IV collagen makes up the bulk of the basement membrane zone at the dermal–epidermal junction. It also forms the basement membrane zone of blood vessels in the dermis and elsewhere, (Fig. 4). Like type I collagen, type IV collagen

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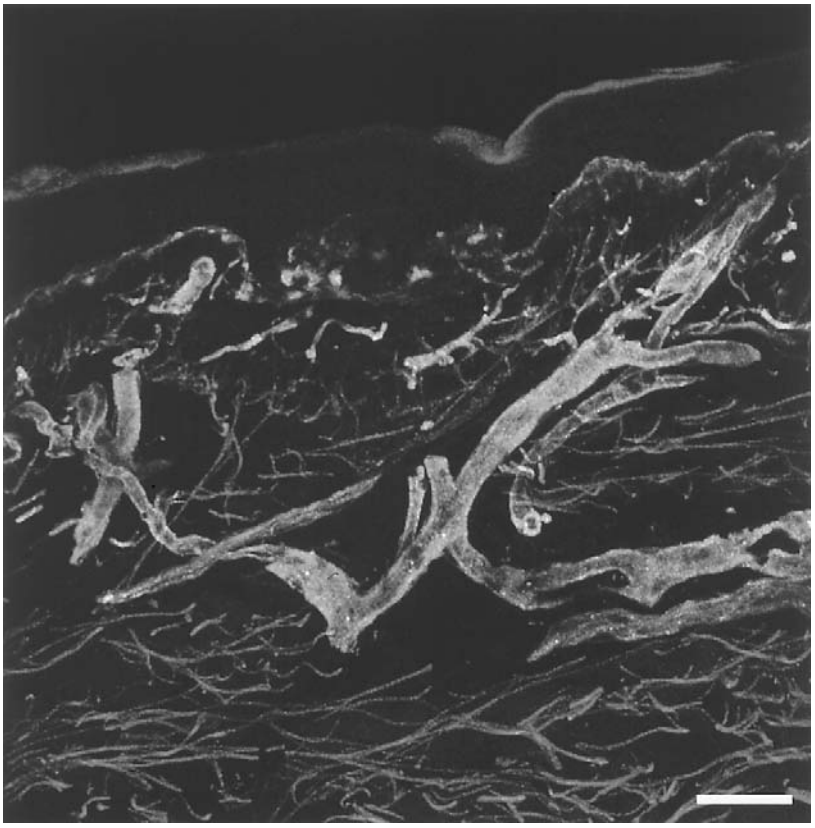

Fig. 4 Laser scanning confocal microscopy demonstrates the basement membrane zone surrounding dermal blood vessels and separating the dermis from the epidermis. Elastic fibers are seen as thin fibrillar structures (magnification ×480).

is a trimer composed of two α 1(IV) chains and one α 2(IV) chain. Unlike the fibrillar type I and type III collagens, type IV collagen in between its triple helical collagenous regions has noncollaginous segments that lack the typical Gly-X-Y sequences. This is thought to allow type IV collagen to be flexible and serve as a scaffold for formation of the basement membrane zone [12].

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D. Type VI Collagen

Type VI collagen contains a short triple-helical segment, but has large amino- and carboxy-terminal globular domains. Type VI collagen is composed of three distinct polypeptide chains, α 1(VI), α 2(VI), and α 3(VI). It is largely present in the dermis as microfibrils [13]. Type VI collagen is located between the dermal collagen fibers. It also has cell adhesion properties that suggest that it may be involved in mature collagen fiber formation and with other extracellular matrix components. Fibroblast cultures produce significant amounts of type VI collagen [14].

E. Type VII Collagen

Like type III collagen, type VII collagen is composed of three identical α 1(VII) chains. The type VII collagen chains are much longer than the chains of the most abundant dermal collagens, types I and III [15]. Type VII collagen forms the anchoring fibrils, which extend from the basement membrane zone at the dermal–epidermal junction to the upper papillary dermis. Type VII collagen also has interruptions in the Gly-X-Y structure, like type IV collagen, which probably confers flexibility [16]. The crucial role played by anchoring fibers composed of type VII collagen is demonstrated by the severe blistering disorder, dystrophic epidermolysis bullosa. This disorder is a hereditary blistering disorder, which results from mutations in type VII collagen. Patients form blisters at areas of friction, which results in severe scarring (Fig. 5).

F. FACIT and Other Collagen Types

Fibril Associated Collagens with Interrupted Triple helices (FACIT) contain interruptions in the triple helical sequence as the name suggests [17]. Collagen types XII and XIV are part of this family of collagens and have been found to associate with type I collagen fibers in the dermis. These collagen

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Fig. 5 Separation between the epidermis and dermis is evident in this child with dystrophic epidermolysis bullosa.

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types, as well as collagens type III and VI, may participate in regulation of collagen fiber formation. Type XVII collagen is a component of the basement membrane zone. This collagen is also known as bullous pemphigoid antigen, type 2 [18].

III. ELASTIC FIBERS

Elastic fibers make up only 1–2% of the dry weight of non-sun-exposed skin. However, functionally they contribute to the

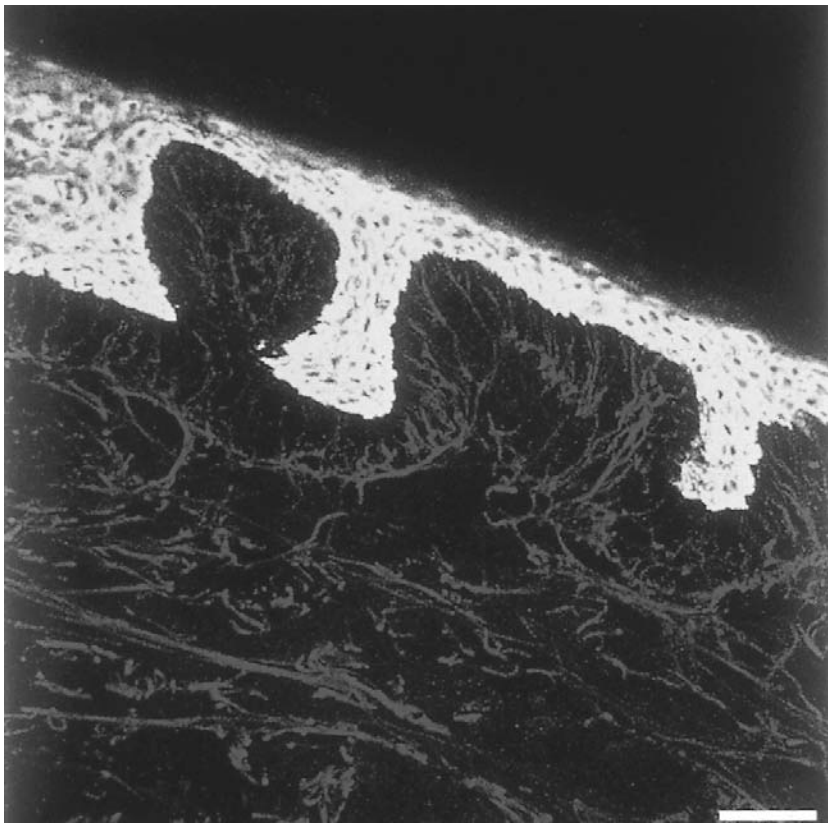

Fig. 6 Laser scanning confocal microscopy demonstrates the fine elastic fiber network present in skin. The epidermis appears white (magnification ×480).

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elasticity and resilience of skin (Fig. 6) [19–21]. Elastic fibers are composed of elastin, a fibrillar protein aptly named fibillin, and a large chondroitin sulfate proteoglycan named versican. In the deeper reticular dermis, elastic fibers run parallel to the collagen fibers and are intimately associated with them

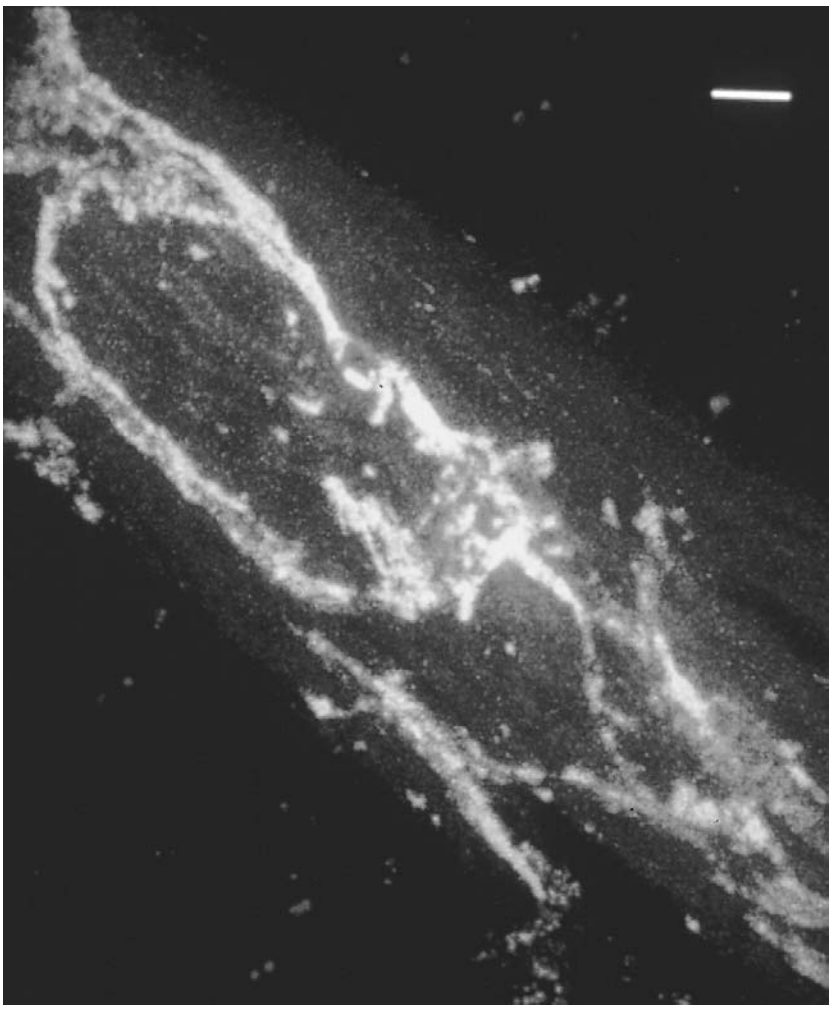

Fig. 7 Laser scanning confocal microscopy demonstrates a collagen fiber (gray) closely associated with elastic fibers (white) (magnification ×2320).

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(Fig. 7). In the superficial papillary dermis a plexus of thin elastic fibers also runs parallel to the dermis. These fibers are called elaunin fibers and contain very small amounts of cross-linked elastin. Other fine fibers, called oxytalan fibers, extend upward from the papillary network of elaunin fibers to the dermal–epidermal junction. These fibers are composed solely of fibrillin, the fibriller protein present in elastic fibers.

The elastic fibers form a meshwork, which is intermingled with the collagen fibers of the dermis. Transmission electron microscopy shows elastic fibers to be composed of electron-lucent elastin, as well as an electron-dense fibriller component known as fibrillin.

Like collagen, elastin is synthesized as a precursor, tropoelastin. Elastin is rich in hydrophobic amino acids such as glycine, valine, proline, and alanine, which may contribute to its ability to stretch and recoil. Approximately one third of the amino acids making up elastin are glycine residues, as is the case with collagen. However, unlike collagen these residues do not appear as every third amino acid. Elastin does not have the collagenous Gly-X-Y sequence. The glycine residues present in elastin are grouped with the other hydrophobic amino acids. Elastin also contains unique amino acid derivatives, desmosine and its isoform, isodesmosine [19]. These amino acid derivatives are uniquely found in elastic fibers among all mammalian proteins. Thus, they may be used to measure the amount of cross-linked elastic fibers present in skin or other tissue.

A possible explanation for the way elastic fibers stretch and recoil relates the hydrophobic amino acids that elastic fibers are rich in. When an elastic fiber is stretched, the hydrophobic domains, which are normally folded within elastin, are exposed to the aquous extracellular milieu. Because these domains wish to leave the aquous environment, they seek to fold back to their original confirmation with the hydrophobic amino acids in the interior.

Fibrillin is analogous to the string surrounding a bungee cord. The elastin represents the stretchy inner portion of the elastic fiber, whereas the strong outer woven string would be

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the fibrillin. Fibrillin may direct the formation of elastic fibers, forming fibers of a specific diameter and orientation. Abnormalities of fibirllin-1 are associated with Marfan syndrome, a disease that affects the skin and the aorta [22]. In addition, fibrillin-2 has been associated with a Marfan-like condition [23]. Fibrillin is a highly insoluble protein, hindering its study and discovery until relatively recently.

Versican is a large chondroitin sulfate proteoglycan, which codistributes with elastic fibers. Versican is thought, like fibrillin, to participate in elastic fiber formation [24].

IV. GLYCOSAMINOGLYCANS AND PROTEOGLYCANS

Glycosaminoglycans are polysaccharides that are composed of repeating disaccharide units, the structure of which determines the nature of the proteoglycans. Glycosaminoglycans are widely distributed throughout the skin. Despite their widespread distribution, they account for a very small fraction of the dry weight of the dermis, less than 0.5%. Glycosaminoglycans bind a very large amount of water relative to their weight and thus modulate hydration of the dermis. Hyaluronic acid may be found free in the dermis unattached to a protein. All other glycosaminoglycans are linked to a protein by the terminal reducing sugar residue, thus forming proteoglycans [25,26]. Proteoglycans are distributed between and on collagen and elastic fibers, on cell surfaces, and form significant components of basement membrane zones. They have a variety of functions that include regulating cell movement within tissues, maintaining basement membrane integrity, and serving as sites for cell attachment.

Hyaluronic acid is the largest glycosaminoglycan composed of repeating D-glucuronic acid and *N*-acetylglucosamine residues. Unlike other proteoglycans, it does not contain sulfate, can be found free in the dermis unassociated with a core protein, and is found in high concentrations in the skin [27].

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Chondroitin sulfate is attached to a core protein, thus forming a proteoglycan. Chondroitin sulfate is composed of alternating uronic acid and *N*-acetylgalactosamine residues. Chondroitin sulfate is sulfated at the C4 or C6 of the *N*-acetylgalactosamine. Heparin sulfate and the related compound heparin are composed of alternating *N*-substituted glucosamine and uronic acid [27].

Decorin is a small chondroitin sulfate proteoglycan, which is widely distributed in the dermis in association with collagen fibers (Fig. 8) [28]. It is the major proteoglycan that is produced by human fibroblasts in tissue culture [29]. Only one chondroitin sulfate chain is attached to the core protein of decorin. Decorin has been found to bind to specific regions on the collagen fiber, and has been show to affect collagen fiber formation. In vitro, decorin results in a specific lateral alignment of collagen fibrils. Decorin is believed to regulate assembly of collagen fibers and may affect collagen fiber diameter [28–30]. It has also been shown to affect binding of transforming growth factor-beta, a growth factor involved in wound healing, regulating inflammation, and dermal remodeling [31].

In contrast to tiny decorin, versican is a very large chondroitin sulfate proteoglycan also present in significant amounts in the dermis (Fig. 9). Keratinocytes and fibroblasts both express versican mRNA in vitro, however, the protein has only been found by immunohistochemical localization in the dermis [24]. Versican has a hyaluronic acid–binding domain, as well as two epidermal growth factor–like repeats [30]. Versican's association with the elastic fibers of the dermis suggests a role for versican in elastic fiber formation, although the details remain to be explained.

A. Fibronectin

Fibronectin is a glycoprotein that plays a significant role in cell movement and attachment, as well as wound healing. Circulating fibronectin may be deposited in a wound directly

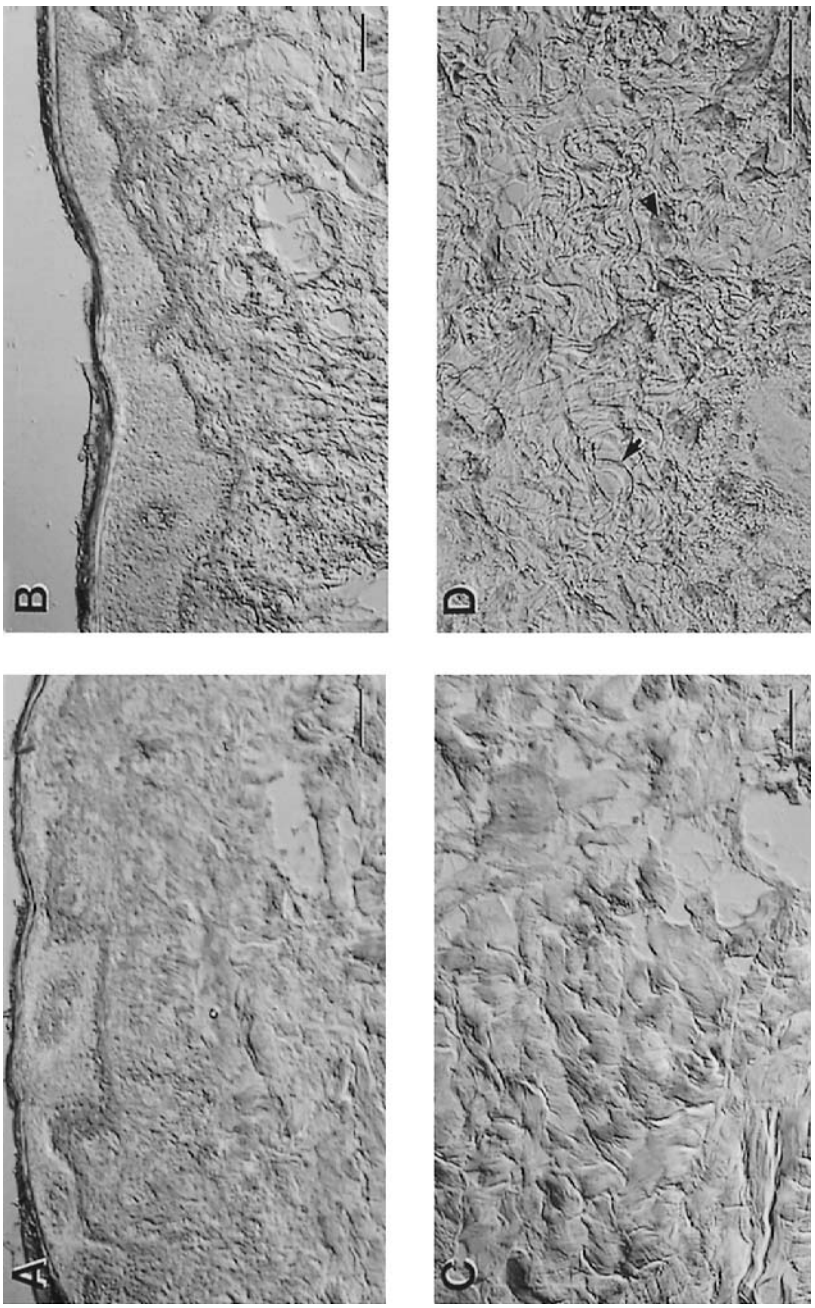

Fig. 8

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from plasma or may be produced at a wound site by the resident fibroblasts. Fibronectin contains an amino acid sequence, Arg-Gly-Asp-Ser (RGDS) sequence, that is the active cell-binding domain of fibronectin [31,32]. Other adhesion proteins, which may play a role in cutaneous remodeling and wound healing, are vitronectin, laminin, and thrombospodin.

V. RESIDUAL CELLS OF THE DERMIS

The dermal fibroblast is the cell most responsible for producing the dermal extracellular matrix and maintaining dermal integrity. Skin is constantly being remodeled by fibroblasts, with production and degradation of collagen and other extracellular matrix components. In response to outside insults such as sunlight, fibroblasts will degrade the superficial dermis and replace it with an altered arrangement and distribution of extracellular matrix proteins.

Mast cells are derived from the bone marrow and serve a number of functions in the dermis [32]. They release vasoactive substances that can recruit circulating cells to respond to an injury or outside insult. Mast cells are mostly found surrounding blood vessels in the dermis [33,34]. They contain prominent granules that contain large amounts of heparin

Fig. 8 The effect of chronic photoaging on decorin immunohistochemical staining. *A.* Staining of sun-protected skin for decorin reveals a thin, linear band of staining just below the epidermis. Below this is almost confluent staining of the dermis. The medium-sized collagen fibers of the papillary dermis that give way to the thicker fibers of the deeper reticular dermis are easily seen. *B,* Photoaged skin from the same individual as in *A* also reveals a narrow band of staining below the epidermis. Within the superficial dermis, there is sparse staining of some fibers among numerous clumped fibers that do not stain. *C,* The deep dermis shows near confluent staining of the thick collagen fibers of the reticular dermis in both non-sun-exposed (shown here) and photoaged skin. *D,* On higher magnification, the papillary dermis of photoaged skin reveals the clumped fibers that make up solar elastosis that do not stain (arrow), whereas what seems to be remnants of other fibers stain positively for decorin (triangle). *Scale bar,* 50 μm. (Reprinted with permission from reference 56).

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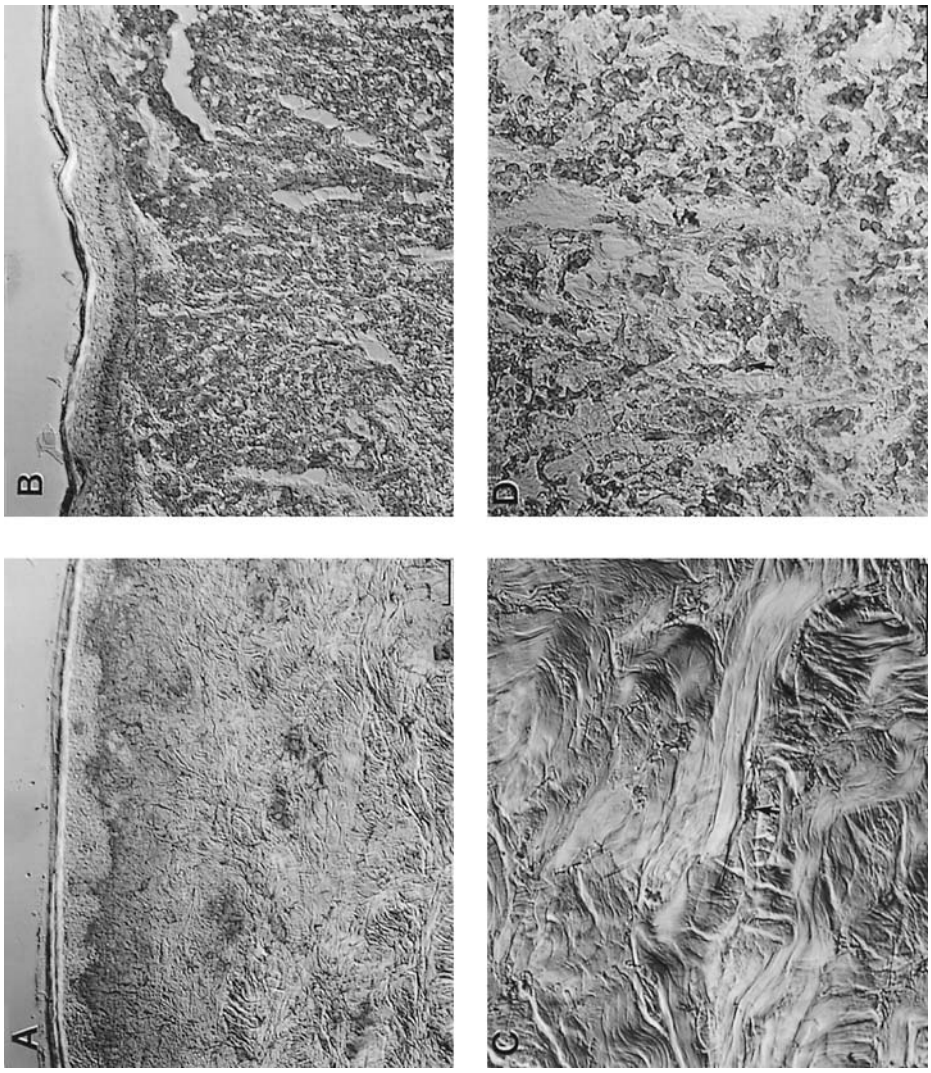

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and histamine. These granules stain metachromatically purple with the Giemsa stain and have a characteristic appearance when viewed under the electron microscope. Numerous stimuli may elicit release of mast cell granules, including cytokines, trauma, drugs, heat and cold, and laser irradiation. Once stimulated, mast cells release vasoactive mediators, including histamine and prostaglandines, chemotatic factors, enzymes, and heparin. Mast cells play a primary role in wound healing and in fibrotic disorders such as scleroderma [35,36].

Dermal dendrocytes are also bone marrow–derived cells, which are predominately located surrounding blood vessels. They stain positively with an antibody to clotting factor XIIIa, [37–39]. These cells may function in some situations like macrophages and as antigen-presenting cells. These cells are thus capable of interacting with a number of inflammatory cells and thus may contribute to maintaining homeostasis in the dermis or respond to various stimuli altering the characteristics of the dermis. They are involved in wound healing and thus participate in dermal remodeling [40,41].

Another cell that originates in the bone marrow is the tissue macrophage, which develops from circulating monocytes once they migrate into the skin. These cells function as phagocytes using large quantities of lysosomal enzymes that they

Fig. 9 The effect of chronic photoaging on versican immunohistochemical staining. *A,* Staining of sun-protected skin for versican reveals a network of thin, mostly vertically oriented fibers in the papillary dermis. In addition, diffuse staining is present at the dermal–epidermal junction. *B,* Photoaged skin from the same individual as in *A* demonstrates intense versican staining in the superficial dermis, revealing large, clumped fibers characteristic of solar elastosis. *C,* The deep dermis shows partial staining of a thin fiber network with versican Ab (arrow) in both sun-damaged (shown here) and non-sun-exposed skin. Thicker, unstained, fibers are dermal collagen. *D,* On higher magnification, versican immunostaining of photoaged skin shows the medium-sized, clumped fibers in areas of solar elastosis (arrow). *Scale bars,* 50 μm. (Reprinted with permission from reference 56).

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produce. Thus macrophages play an important role in repair and dermal remodeling in response to a variety of insults.

A. Influence of Cytokines on Remodeling of Extracellular Matrix

Both resident dermal cells and circulating inflammatory cells produce and release a myriad of soluble factors that influence production and degradation of the extracellular matrix. In addition, epidermal keratinocytes and vascular endothelial cells produce numerous cytokines that may exert an effect on the nearby dermal extracellular matrix. Among these cytokines are the interleukins, tumor necrosis factor-alpha, and growth factors such as epidermal growth factor, platelet-derived growth factor, and transforming growth factor-beta, among others.

Cytokines have been shown to stimulate or inhibit extracellular matrix deposition by fibroblasts. In human skin, a large number of cytokines are released simultaneously, and the effects may be additive or synergistic to extracellular matrix deposition, as well as inhibitory [42,43]. In addition, cytokines may also be modulating the expression of matrix metalloproteinases (MMPs). Matrix metalloproteinases are a family of enzymes that are capable of degrading the extracellular matrix. Matrix metalloproteinases have been divided into three categories, which include the collagenases, stromelysins, and the gelatinases. Matrix metalloproteinases in the same family have similar structural domains and amino acid sequences. Matrix metalloproteinases are secreted as zymogens and thus require activation to express their activity. Once MMPs are activated and degradation is taking place, they may be inhibited by specific tissue inhibitors of metalloproteinases, TIMPs. Dermal remodeling takes place by simultaneous degradation and deposition of extracellular matrix components. Cytokines, cell-to-cell interactions, and even the extracellular matrix components themselves all interact to endogenous and exogenous stimuli to result in a

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steady state of dermal extracellular matrix components arranged in a specific way.

B. Aging of the Dermis

Dermal aging occurs as the result of two very different processes. Chronological aging occurs with the natural passage of time. This aging process is perhaps regulated by the length of telomeres at the end of our chromosomes and continues independent of influences from outside agents. The environment is also capable of aging our skin. Smoking, pollution, as well as the daily stresses associated with living in our environment, all contribute to our aging process. By far the single largest factor responsible for aging of our skin is sunlight. Specifically, the ultraviolet portion of the solar spectrum produces numerous changes in the skin, which are interpreted as resulting in an aged appearance [44,45]. Our bodies have systems for fighting off the constant assault of ultraviolet radiation coming from the sun. These systems include our endogenous melanin pigment, which responds to ultraviolet radiation by altering its composition, in addition to increasing synthesis and distribution of melanin. In addition, endogenous antioxidants that include superoxide dismutase, glutathione pathways, as well as the antioxidant vitamins C and E provide protection against oxidative damage.

Although most people attribute the facial features we associate with aging to the passage of time, sun-protected skin demonstrates very few visible changes when viewed under the microscope until the eighth or ninth decades of life. Skin that is chronologically aged has a decreased number of cells with fewer fibroblasts, mast cells, and thinning of the dermis [46]. In addition, a loss of dermal elastic fibers occurs in chronologically aged skin [47–48]. This loss of elastic fibers may contribute to the fine wrinkling seen in sun-protected skin in older individuals. As a result, a decrease in skin resilience has been measured. Fibroblasts taken from the skin of more aged individuals demonstrates a decrease in collagen

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and collagenase gene expression. In addition, fibroblasts are less responsive to cytokines and thus may respond poorly to stimuli that injures the skin [49].

Although the changes resulting from chronological aging are often undetectable under the microscope, dermal changes as a result of chronic sun damage are quite pronounced. In comparing severely sun-damaged skin to sun-protected skin in the same individual, the results of chronic sun damage are quite evident. Superimposed on the subtle changes associated with chronologically aged skin are the thickened leathery appearance and deep troughs in sun-damaged sites. Most of the features that people attribute to chronological aging are actually due to chronic sun exposure. The main alteration evident on sun-damaged skin is a massive acculmuation of abnormally arranged elastic fibers termed *solar elastosis* (Fig. 10) [50–55]. The composition of solar elastotic material seems to be the same as normal elastic fibers. The elastotic material is composed of elastin, fibrillin, and versican with its associated hyaluronic acid—all present on normal elastic fibers [56–60]. However, the arrangement of these fibers is quite different from normal elastic fibers. Solar elastotic material consists of large clumps of haphazardly arranged elastic material (Fig. 11). The fine elastic fibers extending vertically to the epidermis may be all or partially removed [61]. The normal collagen-rich dermis has been replaced with large amounts of elastotic material and only remnants of the collagen, which was previously present (Fig. 12). These changes may occupy a substantial portion of the superficial to mid dermis.

Fig. 10 *A,* Sun-protected skin is rich in collagen (gray) with intermingled fine elastic fibers (black). The finer collagen present in the papillary dermis is distinctly separated from the deeper, thicker collagen bundles in the deeper reticular dermis. *B,* Severely sun-damaged skin demonstrated a dramatic alteration of the superficial dermis. The collagen has largely been replaced by black-staining clumps of elastic tissue or solar elastosis. A thin grenz, or boarder zone, of normal-appearing collagen is present between the solar elastotic material and the epidermis (original magnification ×100; Verhoeff-van Gieson).

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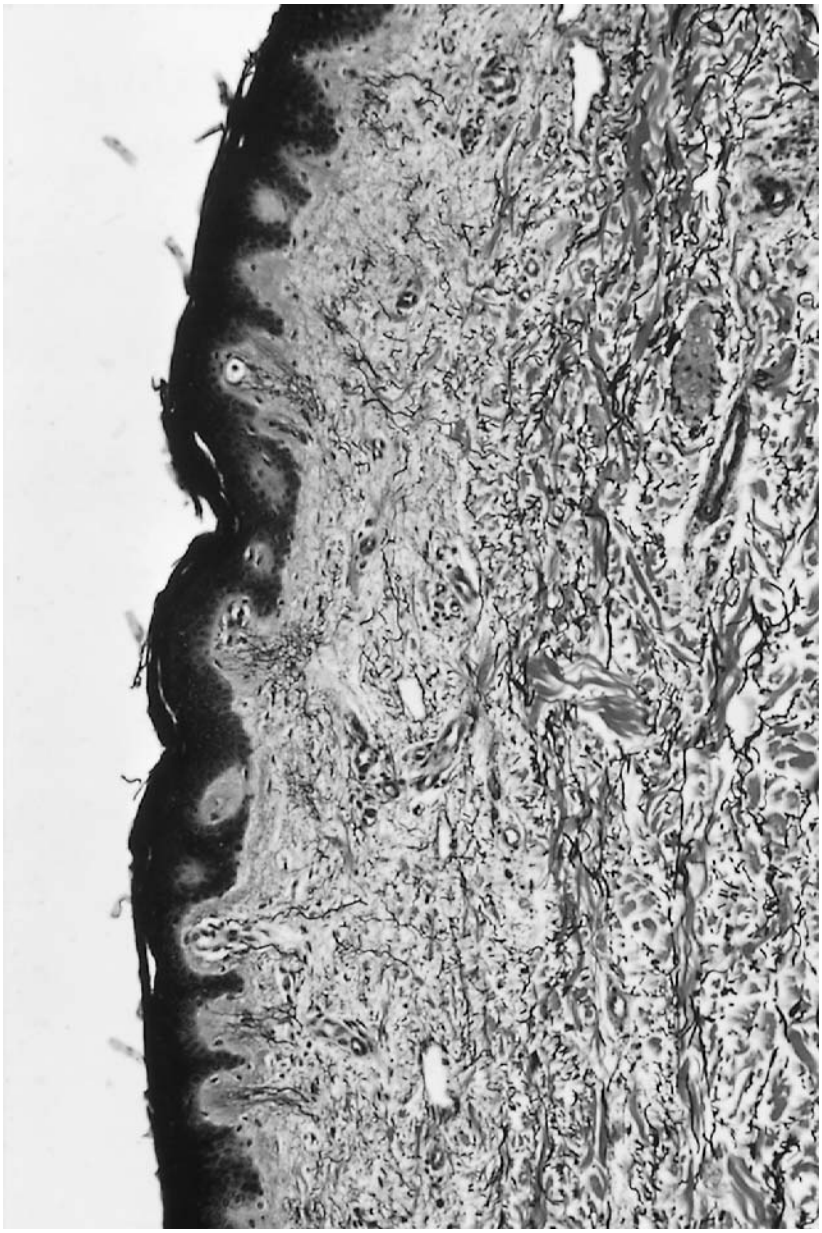

(A)

Fig. 10

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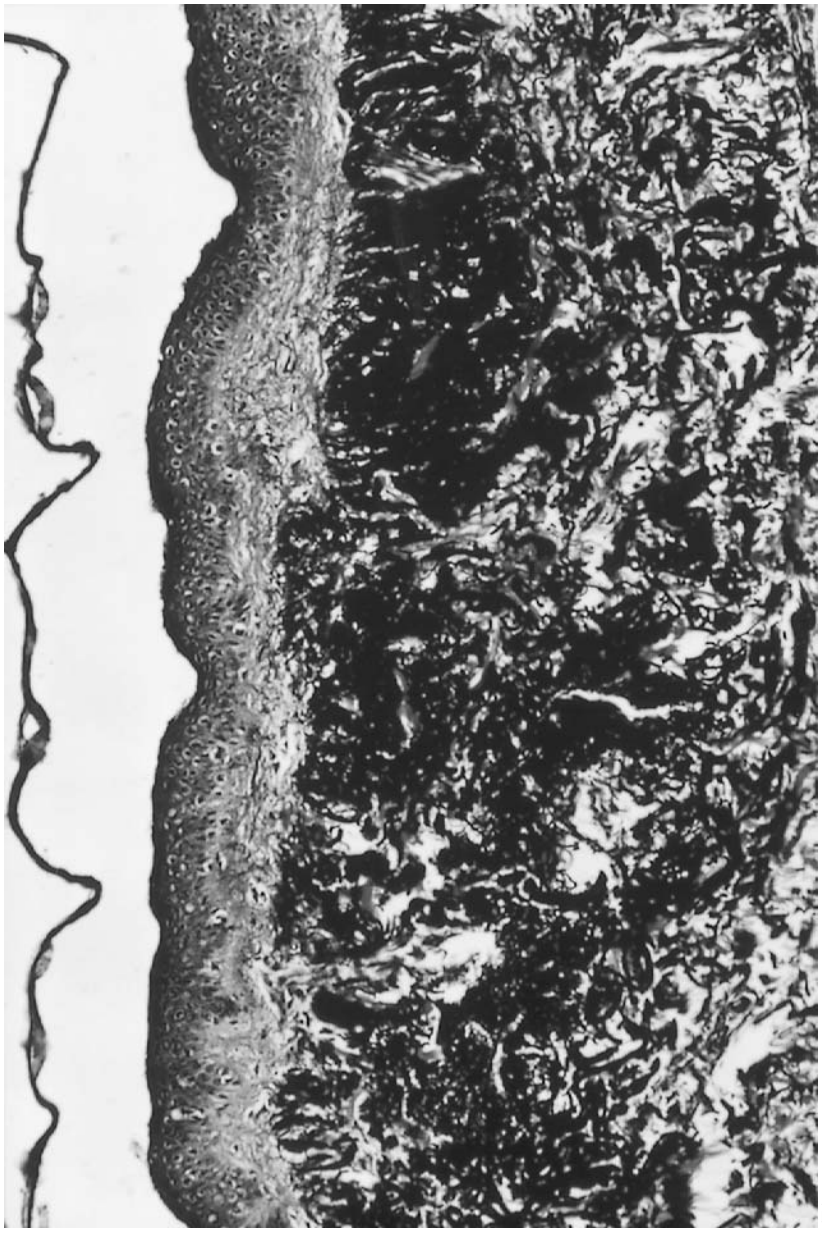

(B)

Fig. 10 (Continued)

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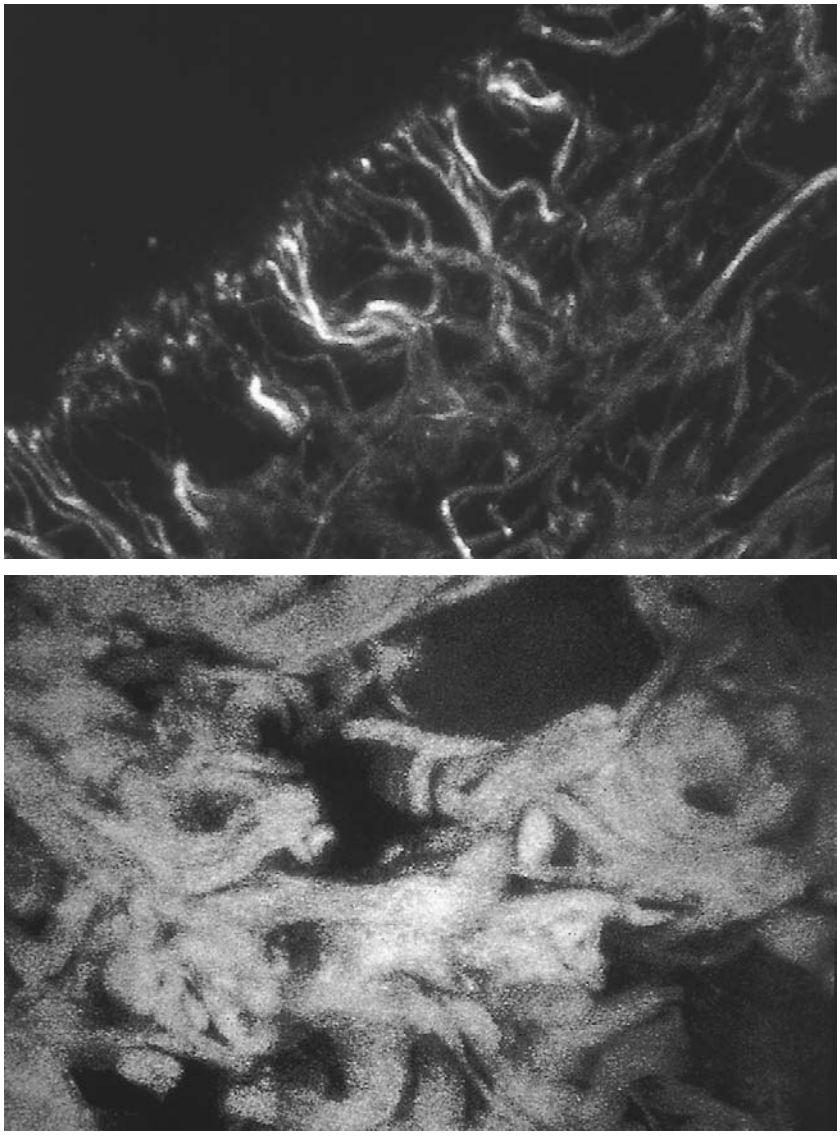

Fig. 11 *Top*, The elastic fiber network is demonstrated by laser scanning confocal microscopy of an immunostained section. *Bottom*, The well-formed fibers present in sun-protected skin seen in *A* are sharply contrasted with the large, tangled, clumps of elastotic material present in sun-damaged skin (magnification ×640).

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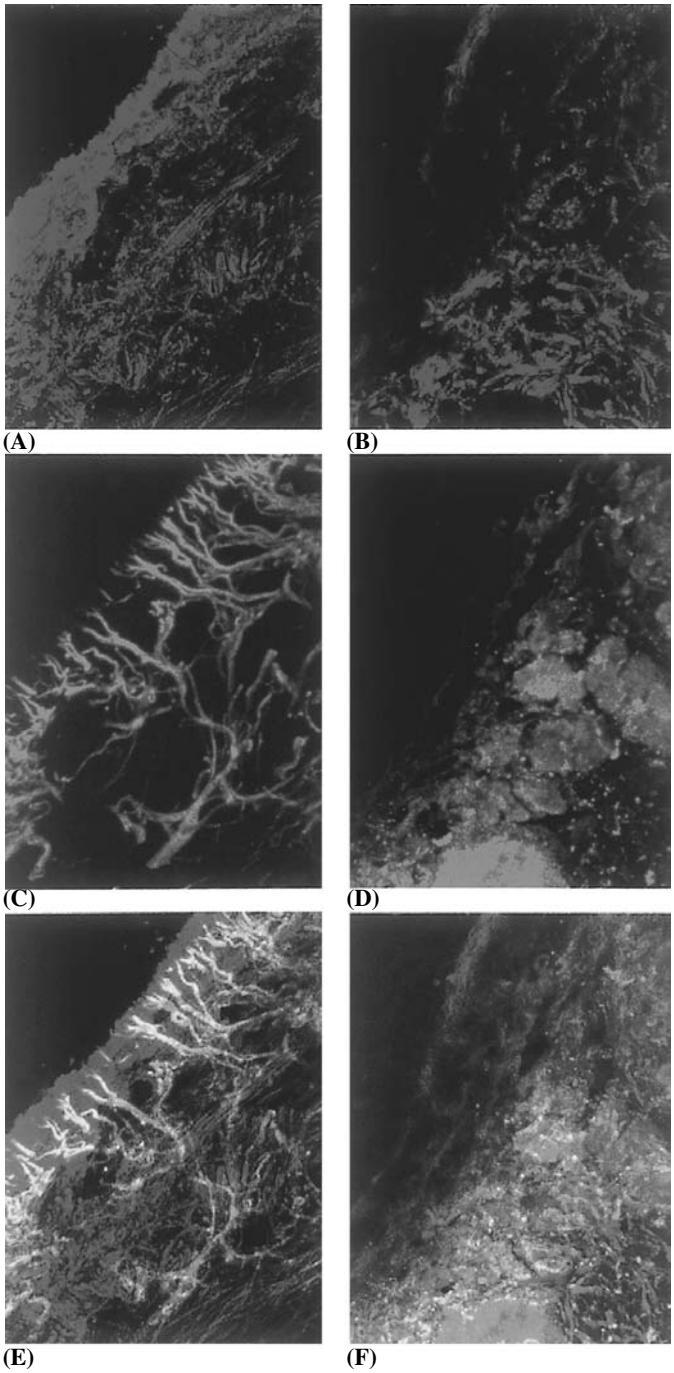

(A) (B)

(C) (D)

(E) (F)

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Separating the zone of solar elastotic material from the epidermis in sun-damaged skin is a thin zone of normal-appearing collagen referred to as a *grenz,* or border zone. This grenz zone is essential for maintenance of a healthy epidermis. The epidermis is avascular and thus depends on the underlying dermis for diffusion of nutrients. Thus it is quite likely that the epidermal keratinocytes secrete cytokines that stimulate the underlying dermal fibroblasts to produce the grenz zone. Keratinocytes have been shown to produce a wide range of growth factors capable of stimulating the underlying dermis. In addition, studies have demonstrated nerves extending from the dermis into the epidermis emphasizing the potential for communication of these two skin compartments [62].

C. Repair of Photoaged Skin

After tissue injury, a wound-healing response takes place. This response occurs in a very orderly and interrelated series of steps. The complex interactions that take place between

Fig. 12 Confocal scanning laser microscopy comparing sun-protected with sun-damaged skin from same person reveals profound alterations of collagen and elastic fibers of the superficial and mid dermis of photoaged skin. *A,* Collagen staining of normal skin reveals a zone of intense signal just below epidermis, with a dense network of collagen fibers mainly oriented parallel to the epidermis. Note that the epidermis serves as an internal negative control. *B,* Photoaged skin also has an intense band of collagen staining just below epidermis, beneath which lies a very sparse network of collagen fibers. *C,* Elastin staining of the superficial dermis of normal skin reveals a network of thin, interconnecting fibers that attach perpendicularly to the dermal–epidermal junction. *D,* Photoaged skin reveals a dense collection of elastic fibers beneath the epidermis many times the diameter of normal elastic fibers, replacing the normal elastic fiber network in the superficial dermis. Fibers are arranged in randomly oriented, tangled clumps. *E,* Dual immunofluorescent staining for collagen and elastic fibers in normal skin reveals a dense band of collagen below the epidermis in gray, with a network of fine white elastic fibers attaching vertically to the dermal–epidermal junction. *F,* Dual staining of sun-damaged skin shows large, tangled, elastic fibers composing solar elastosis in white beneath a dense band of collagen in gray. *Scale bar,* 10 μm. (Reprinted with permission from reference 58).

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cells and the cytokines and degradative enzymes they secrete, and the extracellular matrix components themselves, results in the formation of new dermis. These events occur in a way that is analogous to the interaction of instruments in an orchestra. Alterations in one or another step during this process will affect the entire event in ways that may not be predicted. The initial provisional extracellular matrix in a healing wound is composed largely of hyaluronic acid. Hyaluronic acid provides an initial matrix that enables cell migration and proliferation, thus enabling further dermal repair. Next, angiogenesis takes place producing granulation tissue that is rich in blood vessels and their associated basement membrane zone. This basement membrane zone contains large amounts of chondroitin sulfate. With further tissue remodeling, this matrix is then replaced with type III collagen that gives way to the final matrix composed largely of type I collagen. This collagen network then matures over time with cross-linking of type I collagen. Normal elastic fibers may begin to appear, although in many mature, healed wounds they only partially return.

Although photoaged skin does not contain what we classically consider to be a wound, the dermal matrix is radically altered and is in many ways analogous to a wound. Skin will begin to repair itself if it is removed from the sun. This repair process may be enhanced by the addition of AHAs or retinoids. Other attempts to improve photodamaged skin include controlled wounding such as laser resurfacing, dermabrasion, or deep chemical peels. After these more severe insults, the skin regenerates itself.

VI. EFFECTS OF AHAS ON THE DERMIS

Long before AHAs were used to treat photoaging, their effects on the stratum corneum were used to treat a number of dermatological disorders. As early as 1974, Drs. Van Scott and

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Yu demonstrated profound improvement of ichthyotic disorders by topical application of AHAs [1,63]. Alpha hydroxy acids have been shown to affect corneocyte cohesion. The separation between corneocytes occurs just above the granular layer. It is well known that changes in the stratum corneum can affect the underlying epidermis at least, and most likely result in changes in dermal architecture as well. Our ability to measure these changes is the function of the sensitivity of the technology used to ascertain alterations in dermal extracellular matrix. For example, because the dry weight of the dermis is composed of almost 80% collagen, newly manufactured collagen may be difficult to detect because of this background sea of collagen. However, measurements of procollagen, the precursor to mature collagen, may be a more sensitive indicator of newly manufactured collagen. Measurements of procollagen have been used to demonstrate the effect of topically administered retinoids on photodamaged skin [64]. To gain an indication of collagen production that may be even more sensitive, researchers can look earlier at steps leading to collagen production. Collagen messenger-RNA (mRNA) levels may be an indicator of collagen production, and mRNA production precedes formation of procollagen. To look even earlier at the steps leading to collagen production, one may measure collagen promoter activity, perhaps giving an even more sensitive indication of collagen production. Of course, as one moves further and further away from a desired end point such as mature collagen production, the ability of a given measure to reflect that end point decreases. Thus in many situations, one may sacrifice some specificity for increased sensitivity. Use of newer laboratory techniques enables closer glimpses at the mechanisms behind improvements in skin resulting from AHAs, retinoids, antioxidants, and other agents.

One of the most noticeable histopathological changes that occurs after AHA treatment is an increase in epidermal thickness. Increases in viable epidermal thickness have been

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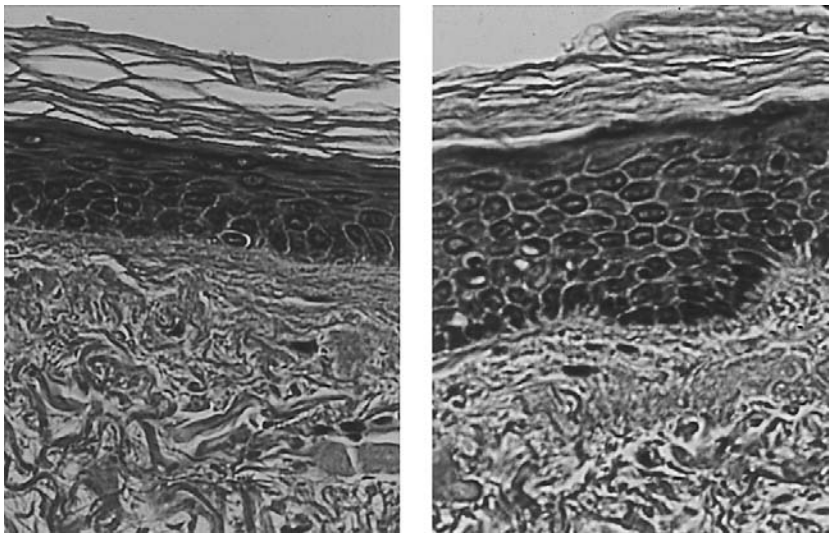

Fig. 13 In contrast to vehicle-treated skin on the left, skin treated with a relatively high concentration AHA for 3 months demonstrates an obvious increase in epidermal thickness (hematoxylin–eosin; magnification ×320).

demonstrated by a number of investigators after relatively short periods of treatment with AHAs (Fig. 13). The increase in thickness ranges from 19–62% [65–67]. Because many of the alterations resulting from chronic photodamage are epidermal, the effect of AHAs on epidermal morphology undoubtedly contributes to the improvement seen after AHA treatment.

In addition to increases in epidermal thickness, epidermal hyaluronic acid is also increased after AHA treatment. Hyaluronic acid is mainly deposited between keratinocytes in the viable epidermis. Increased epidermal hyaluronic acid may facilitate cell growth and diffusion of nutrients and cell movement during active growth. Tretinoin treatment results in almost identical changes to those seen after AHA treatment when measuring both epidermal thickness and epider-

mal hyaluronic acid content [68–70]. Although there is much speculation as to the differing mechanisms of action behind these changes, the histopathological changes are virtually identical after AHA and retinoid treatment of photoaged skin. Because widespread AHA use in clinical practice has occurred relatively recently, little research to explain the mechanism of action of AHAs has been performed.

Although the mechanisms behind improvements by AHAs have not been fully worked out, their positive effects on photodamaged skin have. Topical AHA preparations have been demonstrated to improve the appearance of photoaged skin [71,72]. At concentrations typically used in over-the-counter preparations, AHAs have been shown to improve photodamaged skin in a double-blind vehicle-controlled clinical trial [72]. The ability of AHAs to improve fine lines and wrinkles most likely results from the formation of new dermal extracellular matrix. The first changes measured after AHA or retinoid treatment are increases in dermal glycosaminoglycans [65,67,70]. Dermal glycosaminoglycans have been shown to increase approximately 50% after relatively short periods of AHA treatment (Fig. 14) [65,67]. Increases in dermal glycosaminoglycans result in increased dermal hydration, producing greater skin thickness (Fig. 15). Deposition of dermal glycosaminoglycans most likely leads to increases in dermal collagen. Glycosaminoglycans and proteoglycans can affect the amount and arrangement of other extracellular matrix components, such as collagen and elastin. Thus, changes in a single component of the dermis may have far-reaching effects. Increases in the precursor to mature collagen, procollagen, have been demonstrated after retinoid treatment for a period of 9 months [64]. Similarly, after 3 months of relatively high concentration AHA treatment, collagen gene expression is increased, demonstrating an increase in a marker of collagen production that is earlier in the cycle of collagen production [73]. Dermal dendrocytes are fibroblast-like cells associated with dermal vasculature. These cells increase in number after a few months of AHA treatment (unpublished data) (Fig. 16).

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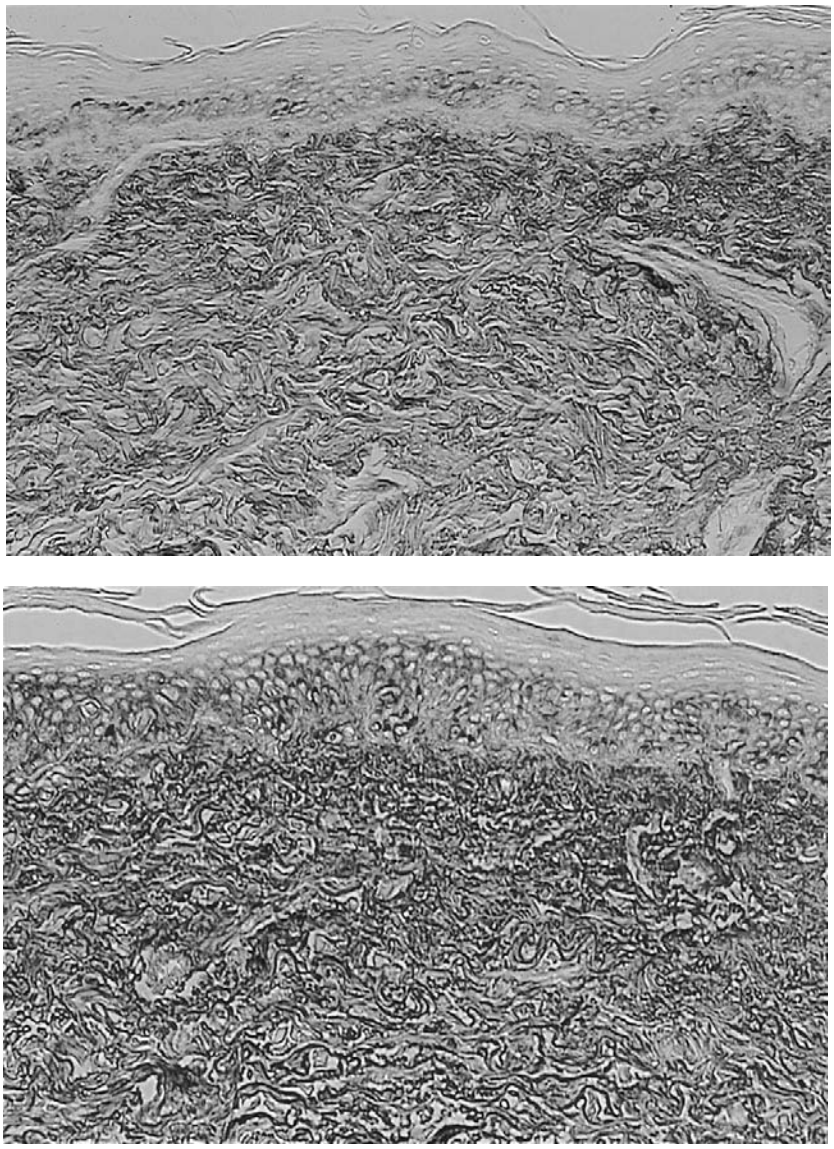

Fig. 14 *Top*, A punch biopsy taken from a vehicle-treated site demonstrates hyaluronic acid staining, which is greater in the papillary dermis. There is relatively little staining of the epidermis. *Bottom*, In contrast treated skin demonstrates significant hyaluronic acid deposition between keratinocytes in the epidermis, as well as throughout the superficial dermis (immunoperoxidase staining; magnification ×320).

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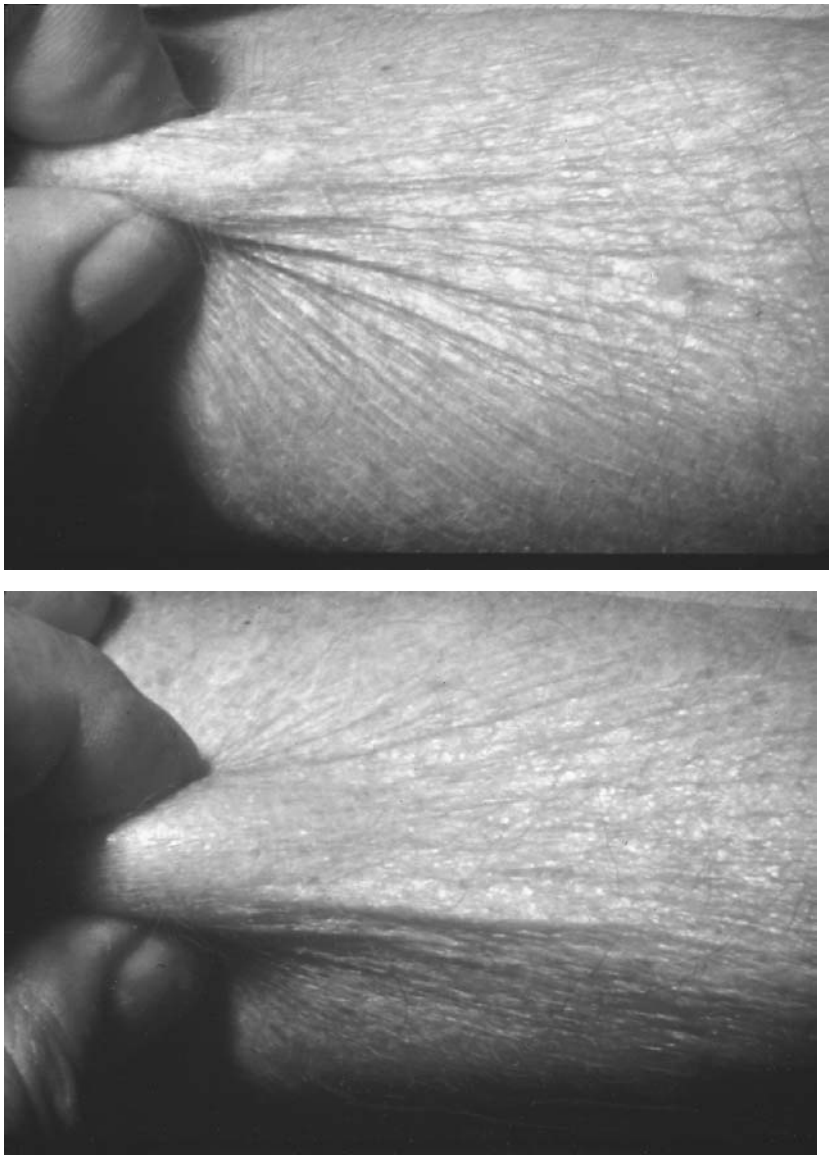

Fig. 15 Skin thickness is increased in skin treated for 3 months with an AHA lotion. Top figure demonstrates vehicle-treated skin, whereas bottom figure shows the effect of 3 months of AHA treatment. (Courtesy of Eugene Van Scott, M.D.)

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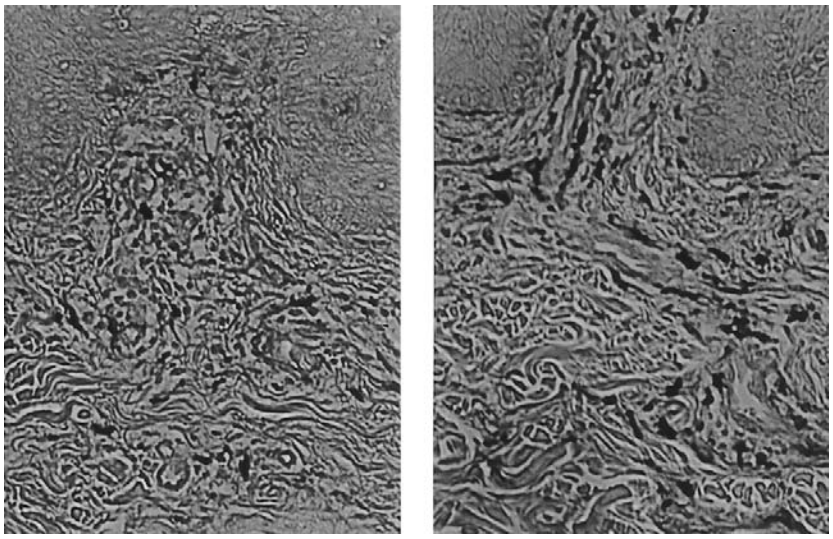

Fig. 16 Immunoperoxidase staining for dermal dendrocytes in vehicle-treated, left, and AHA-treated skin demonstrates a significant increase in dermal dendrocytes in the papillary dermis of treated skin (immunoperoxidase staining; magnification ×640).

The ability of AHAs to affect dermal architecture may result from a direct effect of AHAs on the dermis. Because changes in the more superficial components of skin may affect the underlying dermis, more complex interactions may also be taking place. It has recently been demonstrated that keratinocytes can affect underlying dermal extracellular matrix. Communication between the epidermis and dermis occurs continuously, because the epidermis is devoid of blood vessels and must depend on the underlying dermis for nutrients. Nerves that traverse the dermal-epidermal basement membrane zone have been shown, providing yet another avenue for communication between these two very active cutaneous compartments [74]. Further studies of the mechanisms behind improvement of photoaged skin by AHAs should suggest far greater roles for these versatile compounds in treating and preventing cutaneous aging.

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8

The Use of Alpha Hydroxy Acids in Xerosis and Photoaging

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In 1974 Van Scott and Yu first described the effects of alpha hydroxy acids (AHAs) on keratinization disorders. However, it was not until the 1990s that AHA products gained acceptance and popularity [1]. In this last decade, multiple reports showed the beneficial effects of AHAs in patients with xerosis and hyperkeratotic conditions [2–5]. As a result, AHA use by dermatologists and consumers increased dramatically. The

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main benefits of products containing these fruit-acid derivatives are the normalization of the keratinization process, replacement of water content, and stimulation of the epidermal cell renewal process [6].

I. XEROSIS

Dry skin (xerosis) affects at least 75% of men and women older than age 64. It is characterized histologically by a thickened compact stratum corneum. This thickness is a consequence of enhanced corneocyte cohesion resulting from dehydration and lack of humidity. For these reasons, dry skin tends to improve in the summer and worsen in the winter [7,8].

Xerosis manifests itself clinically by irritation, uncomfortable pruritus, and abnormal scaling. Intrinsic factors, including advanced age and normal dehydration associated with aging, and extrinsic factors, such as environmental exposure and photoaging, have been associated with the development of xerosis. Treatment involves attacking the cause of the condition by replacing the water content of the skin, thereby alleviating irritation and normalizing the keratinization process [9].

A. The Pathology of Xerosis

1. Hyperkeratinization

Hyperkeratinization is a result of thickened stratum corneum caused by a decreased rate of desquamation and, in some cases, an increased rate of corneocyte cohesion. The strength of corneocyte cohesion is determined by the strength of its intercellular bonding. Intercorneocyte attachments (desmosomes, gap junctions, and intercellular substances) provide a firm structural support between adjacent keratinocytes

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[10,11]. It is, therefore, necessary to understand the factors that control and affect corneocyte cohesion and to observe how certain substances and conditions influence the physical properties and structural aspects of this skin barrier.

Corneocytes bind to each other through convalent bonds (disulfides, peptides, polysacharides) or noncovalent bonds (ionic or nonionic hydrogen bonds). The hydrogen bonds can be diminished by dilution with water molecules. They can also be broken or denatured by irritating agents, such as alkalis and urea [5].

Ionic bonds occur between positively charged groups (amino acids) and negatively charged groups (carboxy, sulfate, and phosphate acids) found in the outer surfaces of the corneocytes [12]. Such charged groups are assumed to be present in the glycoproteins, proteins, mucopolysaccarides, sterols, and lipids found on the outer surface of keratinocytes. Three factors affect ionic bonds: (1) the distance between positive and negative charges, (2) the size of the groups, and (3) the medium occupying space between the corneocytes. The distance between the charges has a negative effect on these ionic bonds. Superhydrating the stratum corneum increases the distance between bonds, facilitating the desquamation process. On the contrary, dehydration decreases the distance between the opposing charged groups on the outer cell walls, increasing corneocyte adhesion.

Epidermal hydrolytic sulfatase and phosphatase enzymes hydrolyze the sulfate and phosphate groups located in the outer cell wall of keratinocytes, decreasing the number of glycoprotein, mucopolysaccharide sterols, and lipid phospatides [13]. Destruction of the sulfate group decreases cohesion forces, a fact clearly evidenced in X-linked ichthyosis patients, who lack sulfatase activity [1,14,15]. So cohesion forces increase with outcome of severely dry skin or ichthyosis. Because of the decline in sulfatase levels in ichthyosis, the sulfur content in the stratum corneum of these patients is also higher.

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2. The Effect of Stratum Corneum Lipids

Changes in stratum corneum lipids are another important mechanism by which xerosis can occur. These lipids, which include cholesterol, fatty acids, cholesterol sulfate, glucosyl ceramides, phospholipids and, most importantly, the ceramides [12], also add to the barrier function of the stratum corneum and play an important role in the mechanical and enzymatic desquamatory process. By their effects on water permeability, they prevent the formation of xerotic skin [16].

In elderly patients, a significant decline in free fatty acids and triglycerides can be noted. This may well explain the high incidence of dry skin in the elderly population [17]. The level of stratum corneum lipids, especially ceramides, is influenced by the season of the year, the age of the individual, and the presence of any desquamatory disorder.

Increasing the level of stratum corneum lipids can lead to an improvement in barrier function, maintenance of stratum corneum flexibility, and regulation of enzymatic activity. These characteristics are vital for the desquamation process and may help the stratum corneum resist xerosis.

B. The Effects of AHAs on Xerosis

It is thought that AHAs probably exert their effects by inhibiting the biosynthesis of sulfatated and phosphorylated cell surface molecules. This causes fewer electronegative sulfate and phosphate groups to be located on the outer wall of corneocytes, where they diminish cohesion [13–15]. Certain AHAs also inhibit the enzymatic activity of phosphotranferase and the kinases. They have been known to react with phosphate groups to form phosphorylated AHA in certain metabolic pathways. This may explain some of the beneficial effects of AHAs on the stratum corneum. The effects of these biochemical mechanisms are seen with certain topical medications such as retinoids. Retinoids break off from already formed sulfate and phosphate groups and reduce corneocyte cohesion, resulting in irritation and dryness [18].

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It is thought that the beneficial effects of vitamin A and AHAs are counteracted by endogenous molecules called alpha acetoxy acids (AAAs), which are formed by the acetylation of the alpha hydroxyl groups of AHAs. The function of AAAs in normal or hyperkeratotic conditions is unknown; however, they increase corneocyte cohesion and stratum corneum thickness.

Keratolytic agents such as urea, strong acids, and alkali disaggregate the mature cells on the upper levels of stratum corneum, reducing the thickness and improving the appearance of hyperkeratotic skin. Although AHAs detach at the lower, newly forming levels of the stratum corneum, they also promote a thinner stratum corneum and improving skin surface and flexibility [19]. Topical AHA use causes the stratum corneum to separate from severely dry areas of ichthyotic skin in a sheet, leaving a smoother appearance (Figs. 1, 2) [20]. In addition to epidermal effects, high concentrations of AHAs have profound dermal effects, which will be discussed later in this chapter. In general, they reduce keratinocyte cohesion, causing epidermolysis and epidermal separation, thereby improving epidermal regeneration [21].

C. Use of AHAs in the Treatment of Xerosis

AHAs and their salts are especially effective in the most severe dry skin problems that do not respond to standard moisturizers. Most studies have been conducted with lactic acid and glycolic acid [1,3–9]. Several of these have shown that ammonium lactate in a 12% lotion provides a greater beneficial effect on dry skin than other topical moisturizing agents [3,4,22]. Sodium lactate and lactic acid are reported to be among the most effective natural humectants for human skin [15], preventing water loss, increasing dermal ground substance, and improving the proliferative rate of basal keratinocytes [23].

Another important mechanism by which lactic acid improves dry skin is through its metabolization to acetyl coen-

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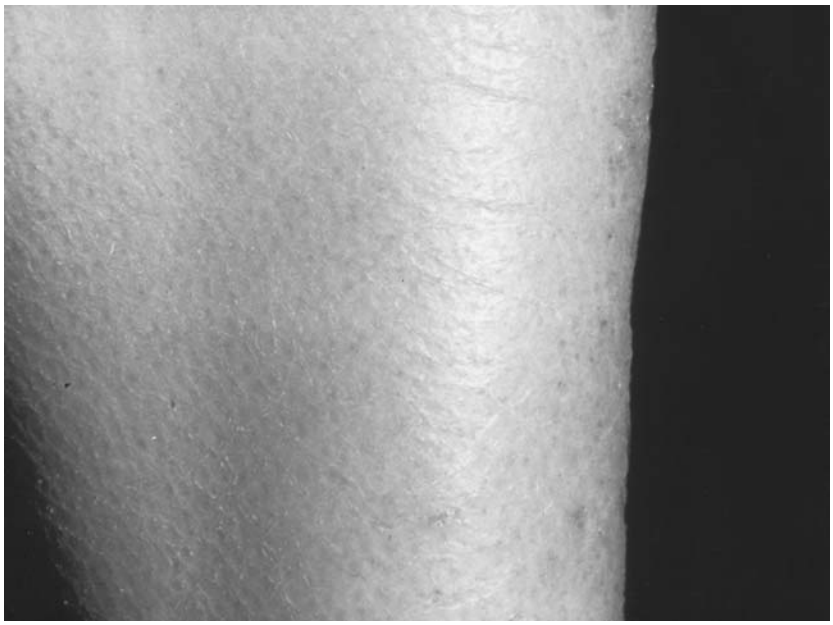

Fig. 1 Dry skin before AHA treatment. Note presence of scaling, uplifting scales, and fissures. (Courtesy of Neostrata Co.)

zyme, which may be used as a carbon source for lipid biosynthesis. This leads to increased ceramide levels. Increasing the lipid levels in the stratum corneum improves the barrier function [24]. The result is reflected not only by an increase in the skin's resistance to irritating challenge but also by the reduced expression of xerotic skin during the posttreatment period (Figs. 3, 4) [16].

Lactate is a natural metabolite of glucose. Absorbed lactate enters the Krebs cycle at the lactate step and is metabolized readily. Topical lactic acid rarely produces adverse effects. Systemic toxic effects immediately after application may include stinging, itching, or mild irritation. For these

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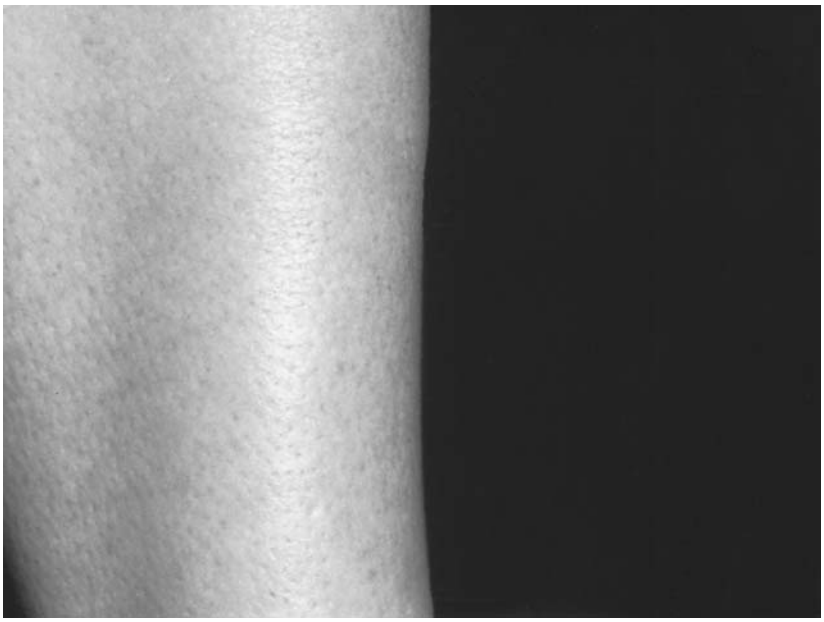

Fig. 2 Three weeks twice daily application of 15% glycolic acid lotion treatment. All of the symptoms had resolved. (Courtesy of Neostrata Co.)

reasons, contact with eyes, lips, mucous membranes, and broken or inflamed skin should be avoided [25].

Alpha hydroxy acids can be used unneutralized or partially neutralized with ammonium hydroxide or organic amine. Lactic acid formulations that are partially neutralized with ammonium hydroxide to a pH of 4.5–5.5 provide optimum effectiveness in concentrations of 8–12% [6]. For large body areas and the palms, soles, and scalp, patients can have large quantities prepared in gallon containers. These compounded formulations should be applied thinly two to four times daily for 1 to 3 weeks with a household sponge or to the scalp with a plastic squeeze bottle. The frequency of applica-

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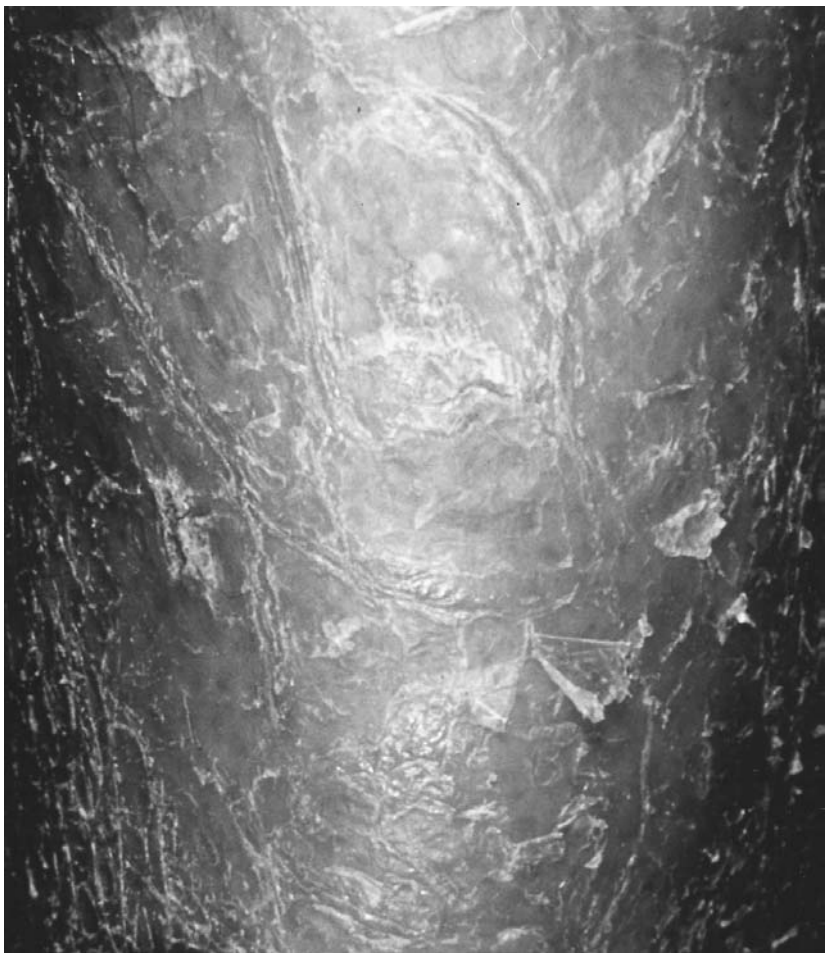

Fig. 3 Lameller ichthyosis before treatment. Note presence of rough texture, scaling, and fissuring. (Courtesy of Neostrata Co.)

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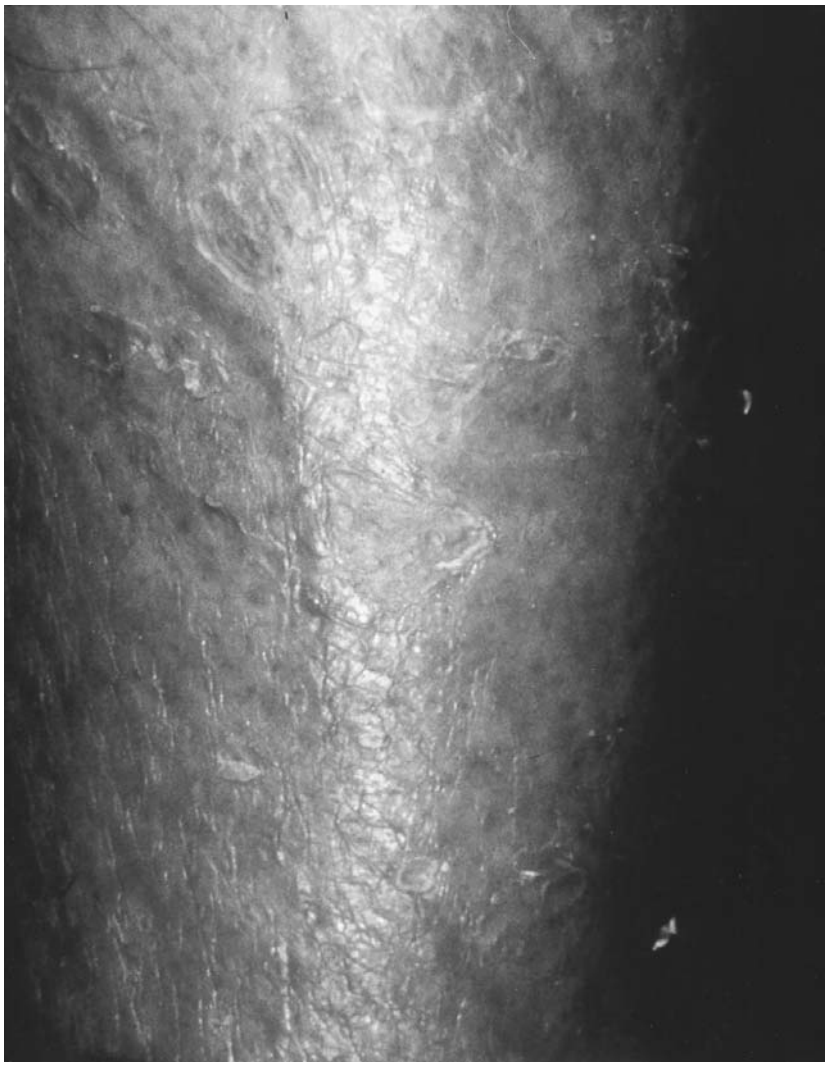

Fig. 4 Two weeks twice daily after alpha hydroxy–poly hydroxy complex treatment (Ingredients: water, petrolatum, propylene glycol, stearyl alcohol, gluconolactone, glycolic acid, PEG-40 stearate, sorbiton stearate, triethonolamine, ethyl pyruvate, arginine, citric acid, tocopherol acetate(vitamine E), retinyl acetate(vitamine A), cetyl alcohol, dimethicone, C 10–30 cholesterol, lanosterol esters, mandelic acid, tartaric acid, acetyl cysteine, beeswax, polysorbate 80, spearmint oil, hydroxycellulose, disodium EDTA, phenoxyethanol.).

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tion can diminish once improvement is noted. Unneutralized formulations of glycolic, mandelic, tartaric, and malic acid have also proven effective in other dermatological conditions, such as acne, photoaging, warts, keratosis pilaris, and others.

All symptoms of skin dryness can be decreased by lactic acid and glycolic acid lotions and creams. Cream formulations are generally more effective in moderate to severe xerosis, but lotions have better patient compliance, more cosmetic attributes, and are more useful in mild xerosis.

The concentration of AHA is important in its effectiveness. Leyden et al reported that 4 weeks of treatment with 12% lactic acid (ammonium lactate) lotion caused a 19% increase in epidermal thickness and increased amounts of dermal glycosaminoglycans. This occurred without inflammation or irritation [21]. Rogers et al compared a 5% lactic acid lotion with a 12% formulation. The 12% was significantly more effective on severe dry skin problems and had a significantly greater duration of effect, lasting 2 to 3 weeks after discontinuation of use [22].

Numerous products are on the market containing a single AHA ingredient. In these products, concentration of AHA and pH-free acid, degree of neutralization, and overall formulation differ. Products vary widely in their efficacy according to the variations in these factors. When evaluating AHA products, it is important to look at the entire formulation along with the concentration of ingredients. Studies have shown that mixtures of AHAs with poly hydroxy acids have enhanced benefit in dry skin problems [4].

D. Xerosis Skin Care

The most important consideration in managing dry skin is patient education. In most cases, proper bathing techniques and moisturizing can solve the problem. Patients must be taught to avoid hot water, overuse of soap, and unnecessary scrubbing with washcloths and towels.

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Dry skin should be hydrated with topical application of any number of formulas. Moisturizers can alleviate the unpleasant symptoms of dry skin, and petrolatum is ideal. However, many patients find petrolatum or other pure grease moisturizers too occlusive or cosmetically unacceptable. In these cases, hydrophilic creams are a reasonable substitute [27,28].

Season and latitude may influence the choice of moisturizers. During the cold, dry winter months with relatively low humidity indoors and outdoors, patients prefer ointments. For obvious reasons, the same occlusive ointments are not well tolerated in the summer months.

Compounds combining AHAs and poly hydroxy acid products are especially effective on dry skin (Figs. 5, 6). The AHAs play an important role in the treatment of dry skin conditions, because they are naturally occurring humectants for human skin. These acids normalize the process of keratinization, thereby reducing symptoms of dryness. However, further work is needed to fully understand their mechanism of action to incorporate them more effectively into the therapeutic armament for other diseases in which the skin barrier is disrupted.

II. PHOTOAGING

Cutaneous aging consists of two distinct process: chronological or intrinsic aging, which refers to the biological clock that keeps ticking regardless of outside influences, and extrinsic aging, a process caused by external actors such as sunlight, radiation, air pollution, wind, humidity, heat, chemicals, and cigarette smoke. Solar aging—also known as photoaging—reflects our exposure to ultraviolet radiation, as well as our skin's ability to protect itself from damaging ultraviolet rays.

Chronological aging results in a decrease in dermal thickness [29–31]. In addition, the number of fibroblasts, mast cells, and blood vessels in the dermis decrease [29].

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Fig. 5 Severe ichthyosis before AHA treatment.

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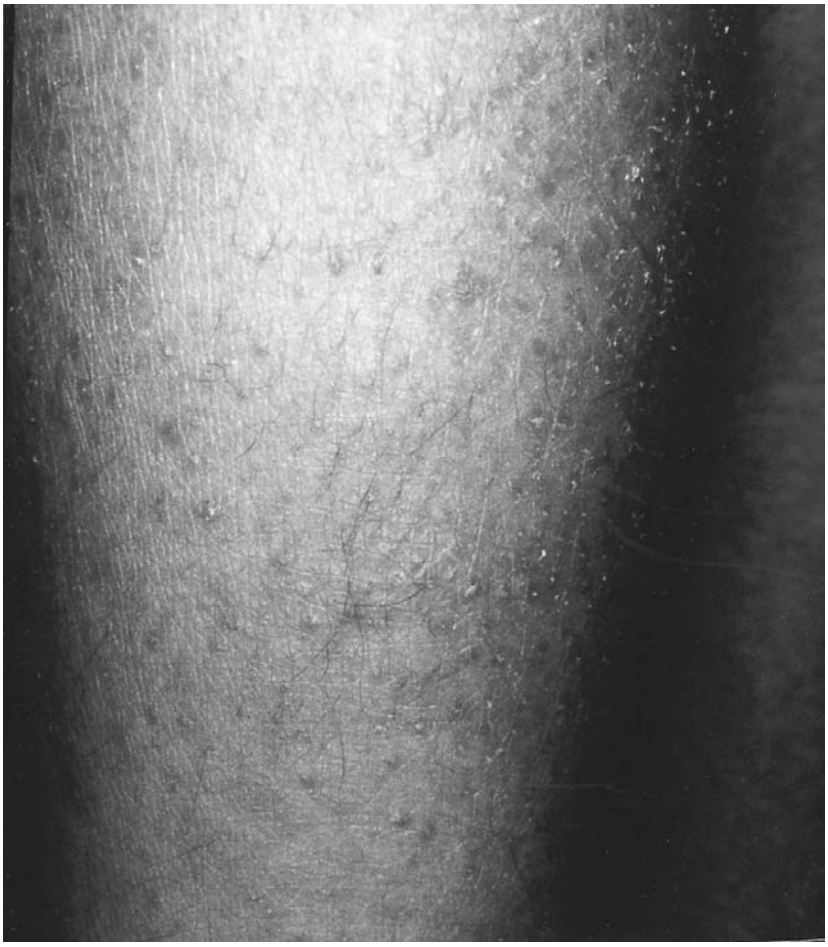

Fig. 6 Three weeks twice daily application of alpha hydroxy–poly hydroxy acid treatment. (Ingredients: water, petrolatum, propylene glycol, stearyl alcohol, gluconolactone, glycolic acid, PEG-40 stearate, sorbiton stearate, triethonolamine, ethyl pyruvate, arginine, citric acid, tocopherol acetate(vitamine E), retinyl acetate(vitamine A), cetyl alcohol, dimethicone, C 10–30 cholesterol, lanosterol esters, mandelic acid, tartaric acid, acetyl cysteine, beeswax, polysorbate 80, spearmint oil, hydroxycellulose, disodium EDTA, phenoxyethanol.)

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There is also a decrease in the ability to clear substances absorbed through the epidermis, which may be a reflection of alterations in the vascular or lymphatic system in aged skin [32]. There is an age-associated loss of normal elastic fibers responsible for maintaining the skin's ability to return to its original shape and position after physical distention, contributing to loss of elastic recovery [33,34]. Fibroblasts taken from more aged donors have shown that collagenase gene expression also decreases along with collagen production [35]. These histological changes are manifested clinically by fine wrinkling and laxity.

Most of the characteristics we associate with an aged appearance result from chronic photodamage and not from intrinsic aging [33]. The effects of chronic sun exposure on exposed skin are easily identifiable when comparing sun-exposed skin to sun-protected sites on the same individual. The deep furrows, pigmented alterations, benign and malignant growths, and thickened leathery appearance characteristic of sun damage can be superimposed on the sagging and fine wrinkling of chronologically aged skin.

Histopathological examination of sun-exposed skin reveals a massive accumulation of material that stains similarly to elastin when examined in routine hematoxylin-eosin–stained sections. This is termed solar elastosis [36–57]. Immunohistochemcial analysis of sun-exposed skin has shown that solar elastosis is composed of elastin [52–54] and fibrillin [52,54,55], the normal constituents of elastic fibers. Although these fibers are composed of the same proteins as normal elastic fibers, they are present in greatly increased amounts and arranged in an abnormal and haphazard manner.

Accompanying the alterations in elastic fiber formation are changes in the amount and organization of collagen fibers within the area of solar elastosis in sun-damaged skin. These changes have been suggested as a cause of the clinical changes observed in photoaged skin [56]. Previous studies have suggested that degradation of collagen takes place in

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areas of solar elastosis [5]. Direct assays of collagen content [57], immunohistochemical staining for collagen [52,57,58], and studies on the evaluation of collagen maturation [59] have revealed collagen abnormalities in photodamaged skin. Most studies have shown that the amount of collagen is reduced in areas of solar elastosis, a finding that may be indicative of variable amounts of collagen degradation and/or alterations in collagen production. Thus, alterations in steady-state collagen levels accompany the massive deposition of elastic fibers, which takes place in sun-damaged skin.

A. Mechanism of Action of AHAs on Photoaging

As discussed earlier in reference to xerosis, AHAs function at the lower and newly forming levels of the stratum corneum by promoting a thinner stratum corneum and improving skin surface and flexibility [14]. AHAs increase the thickness of the viable epidermis and increase proliferation of the epidermis and glycosaminoglycan production in the dermis. One theory on how AHAs diminish corneocyte cohesion is that they interfere with the formation of ionic bonds. This action is mediated by interference with the functions of enzymes that form sulfate and phosphate bonds, respectively [32].

Lavker and others [63] have noted that AHAs increase the receptor protein of hyaluronic acid. They also increase fibronectin. Other studies [23] have shown that AHAs selectively activate messenger RNA, interleukin-1 (IL-1), and levels of protein in keratinocytes. IL-1 has been reported to be mitogenic for keratinocytes and fibroblasts [23] and is capable of inducing fibrocytes to produce collagen and glycosaminoglycans.

One specific action of AHAs is its effect on keratinization. It seems to exert this action at the junction of the stratum granulosum, the lowermost level of the stratum corneum. Here, it decreases the cellular cohesion between corneocytes. Clinical studies have shown that lower concentrations of

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AHAs (5–10%) result in significant improvement in skin texture, smoothness, and mosturization [66].

In photodamaged skin, AHA use enables the atrophic epidermis to regain normal or near normal thickness and appearance. Dermal effects seem to be related to the bioavailability of the AHA used: Such changes have been observed after prolonged use of lower concentration AHA products or repeated application of higher concentrations in procedures such as those used in chemical peels [9].

Histological studies of glycolic acid, lactic acid, and citric acid after topical application on photoaged skin demonstrated an increase in mucopolysaccharides, an increase in density of collagen, improved quality of elastic fibers, and an increase in the total thickness of the papillary dermis [63]. These dermal responses occur more slowly than the epidermal response, first appearing within 2 to 3 months and becoming more apparent thereafter [31,33]. Either alteration in the parenchyma might be responsible for the improvement in tone and texture, decrease in dryness, and generally plumper and healthier looking skin. The results are more noticeable with higher concentrations of AHAs, such as those used in glycolic acid peels [9]. At lower concentrations, the improvements are achieved more slowly.

B. AHAs in the Treatment of Photoaging

Glycolic acid and lactic acid are the most widely studied AHAs and, for these reasons, are the most popular in cosmetic and therapeutic products. Glycolic acid has the smallest molecule of any AHA, which presumably gives it the best penetration capability. It is very soluble in water.

Lactic acid is part of the normal carbohydrate metabolism in the skin. Aqueous solutions have different pHs, depending on the acid concentration. Formulations containing malic, tartaric, and mandelic acids recently entered the market with similar claims to those of other AHA products. Various combinations of AHAs are also available. There is a need for more

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scientific data to support the claims made by manufacturers of all AHA products. It is possible that the acids have different mechanisms of action at different levels of the skin. For example, malic acid, tartaric acid, and gluconolactone have antioxidant properties, whereas glycolic acid and lactic acid do not. Gluconolactone, a poly hydroxy acid, has natural antioxidant properties that strengthen the skin barrier, making it an ideal compound for sensitive skin. Interestingly, gluconolactone has been used with success in patients with atopic dermatitis and rosacea [65]. Its use in photoaging was documented by improvement in sallowness, fine wrinkles, mottled pigmentation, and pore size at 6 and 12 weeks [64].

Interestingly, some parameters of irritation present at baseline can be reduced with AHA product use. This demonstrates product compatibility with this self-assessed sensitive skin population. In place of traditional AHAs, gluconolactone can be used to achieve smoothing benefits and reduce the signs of aging. It is also appropriate for sensitive skin.

C. AHAs as Peeling Agents

At high concentrations, AHAs are used as chemical peeling agents and are particularly useful in the treatment of photoaging. Their potency can be controlled by modifying their exposure time on the skin. They are considered superficial peeling agents, because they cause no epidermal injury. When used in combination with other peeling agents, such as trichloroacetic acid (TCA) or solid CO_2, they achieve a medium-depth response. In these cases, injury extends through the papillary dermis down to the upper reticular dermis. Deeper peels, such as phenol, cause injury through to the midreticular dermis.

The amount of free acid delivered to the skin, duration of contact with the skin, preparation of the skin before the peel, body site being treated, and condition of the skin (presence of photodamage, acne scars, etc.) all play extremely important roles in determining the outcome [60–63]. In chemical peels,

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glycolic acid is used in concentrations of 20–70%. Studies to date [60,63] have shown that sustained applications of AHAs in high concentrations over periods of a few months will induce measurable changes suggestive of photodamage reversal. Moy et al and others [60,61,63] have reported improvements in wrinkling, coarse wrinkling, pigmentation, and overall skin texture [60]. Response depends not only on the concentration of AHA and pH but also on the vehicle and final formulation. Because so many variables exist, it is important for the physician to become familiar with a product to ensure consistent outcomes.

AHA peels can be performed in the office easily and safely. Side effects, such as hyperpigmentation, persistent erythema, and scarring are minimal compared with those caused by other chemical peeling agents.

D. Recommended Program for Skin Protection on Sunny and Cloudy Days*

1. Apply a broad-spectrum sunscreen with SPF of 15 or higher to all exposed skin including lips.
2. Plan outdoor activities early or late in the day to minimize sun exposure between 10 am and 4 pm.
3. Wear a broad-brimmed hat, sunglasses, and protective clothing that blocks UVB.

III. CONCLUSION

As naturally occurring humectants for human skin, AHAs provide a welcome new treatment option for patients with xerosis, ichthyosis, and other skin conditions that resist conventional treatment. These acids normalize the process of keratinization, thereby reducing symptoms of dryness and

*A good sun protection program is indispensable in the treatment of photoaging.

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improving the thickness and appearance of the epidermis. They make an excellent skin peeling agent because of easy control of potency and absence of severe side effects associated with other chemical peeling agents.

In only a few years, AHAs have produced consistently excellent results with few side effects. Creams and lotions containing AHAs have been readily accepted by the public and are routinely used in medical and cosmetic skin care regimens.

AHAs other than glycolic acid can be formulated for greater specificity of action (such as enhanced desquamation of the stratum corneum) or enhanced potency for greater dermal response (such as greater depth of peeling).

Further work is needed to fully understand their mechanism of action and enable them to be incorporated more effectively into the therapeutic armament for additional diseases in which the skin barrier is disrupted.

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9

The Use of Glycolic Acids in Asian Skin

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I. INTRODUCTION

Asian populations are very sensitive socially and culturally to pigmentation of the skin. The degree of color can have social implications related to status and beauty. Fair and evenly pigmented skin is a sign of nobility and purity. Flaws in skin pigmentation take on significant importance. The reduction or elimination of postinflammatory hyperpigmentation, ephelides, lentigines, and melasma is preferred.

Drs. Eugene Van Scott and Ruey Yu introduced the concept of the alpha hydroxyacids (AHAs) in 1974 [1]. Their findings indicated that the AHAs had a profound effect on keratinization and corneocyte cohesion [2]. When the corneocyte cohesion is reduced, there is a desquamation of the stratum

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corneum. Further studies [3] demonstrated an improvement of barrier reactivity and function in addition to resistance to skin irritation [3] with repeated use of AHAs. Studies with the application of 25% glycolic acid, lactic acid, or citric acid to photodamaged skin indicated clinical improvement and histological changes [4]. The epidermal changes revealed an increase in thickness, reversal of basal cell atypia, a more normal rete ridge pattern, and a dispersal of melanin pigmentation. This latter effect has been helpful when treating Asian skin with AHAs. Changes in the dermal thickness with thickening of the papillary dermis is seen after the epidermal response. Treatment of photoaged skin with 25% AHAs (either glycolic, lactic, or citric acids) revealed approximately 25% increase in epidermal thickness [5]. The papillary dermal thickening was associated with increased mucopolysaccharides and an increase of elastic fibers and collagen density. The clinical benefit is the improvement of fine wrinkling.

The cosmetic benefits from the use of AHA are many. When consumer home products are combined with glycolic acid peels, a variety of skin conditions are improved. Benefits are the improvement of fine lines caused by the photoaging process and improvement of acne scars and irregular pigmentation, including ephelides, solar lentigines, melasma, and sallow complexions [6,7]. Other dermatological conditions are also benefited, such as dry skin [8], ichthyosis, hyperkeratosis of the palms or soles, keratoses [9], and rosacea [10]. One study [11] revealed a photoprotective effect of glycolic acid. Low concentrations of glycolic acid were helpful in reducing the erythema of UVB-exposed skin. This study is important to disprove the belief that a thinner stratum corneum would lead to greater sun sensitivity.

II. GLYCOLIC ACID PEELS

There are currently a number of companies [12,13] that have produced glycolic acid peel formulations. The factors that in-

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fluence the effect on the skin relate to the concentration of the acid, the pH of the product, the vehicle, the amount of free acid present depending on the formulation, duration of exposure, and level of dryness of the skin [14–16]. The patient's skin type has a major influence on the action of AHAs. Even with Asian skin there are different degrees of oiliness, thickness, laxity, fragility, and pre-existing erythema or irritation. Among the factors that affect Asian skin are the environment, concurrent therapy (such as with retinoic acid products), and existing conditions (such as atopic dermatitis, rosacea, and seborrheic dermatitis).

Glycolic acid chemical peels on Asian skin can be more reactive [17]. It is recommended that glycolic acid peels are started from the lowest percentage formulation and slowly advanced to the higher concentrations. Some Asians only require the lowest concentration with treatment for a few minutes (e.g., 2 min) to accomplish effectiveness of the glycolic acid on the skin. Other Asians are able to tolerate the highest concentrations without any deleterious effects. Many factors determine the sensitivity of the skin. Some factors that may increase skin responsiveness are known tendencies toward skin sensitivity, a history of atopic dermatitis, exposure to windy or cold weather, or a recent procedure that may make the skin more sensitive, such as a recent hair epilation or waxing. Factors that may make the skin less responsive to the glycolic acid peels depend on skin that is inherently less sensitive. Postinflammatory hyperpigmentation is always a possible side effect of glycolic acid peels associated with strong exfoliation and epidermolysis. Crusting and necrosis of the skin should be avoided. It has been noted that the younger individual has more sensitive skin than the older person with photodamaged skin [16].

Because glycolic acid peels are considered "mild" chemical peels, they can be used on all Fitzpatrick skin types, I–VI. Moreover, in addition to the face, glycolic acid peels may be applied to many areas of the body, including the neck, chest, back, arms, and legs. Many Asians who have damage to pig-

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mentation on the back and arms from overexposure to the sun seek to reduce or eliminate the pigmentary changes. However, the main focus of treatment is on the face for postinflammatory hyperpigmentation (from acne or dermatoses), ephelides, lentigines, or melasma.

To reduce hyperpigmentation, a series of glycolic acid peels is optimal. The patients must be educated that one chemical peel will not be effective. Frequently, four to eight peels are required to obtain the beneficial reduction of color. Peels may be repeated after 1-week. Frequently, an interval of 2–4 weeks is a comfortable time interval. Many individuals continue a maintenance program after the improvement occurs. Maintenance peels may be applied every few months.

A. Chemical Peels in Asians

Glycolic acid peels are very beneficial for Asian skin [18]. For two or more weeks before a chemical peel, many physicians have their patients use an AHA home preparation (cream, lotion, or gel). The AHA helps to thin the stratum corneum, providing for a more effective and even peel and also improving the tolerance to the glycolic acid peel [11]. Patients should be cautioned to avoid procedures that may cause irritation for a 1-week period before and after the peel. These procedures include waxing, electrolysis, masks, aggressive hair treatments (e.g., dyes and chemicals that may touch the face), abrasive products, and retinoic acids. If Asian skin is irritated with these combined procedures, postinflammatory hyperpigmentation may occur. Avoidance of excessive sun after peels should be emphasized. Moreover, if the patient has a history of herpes simplex infections on the face, then prophylactic therapy may be given. It is advisable to place petrolatum at the corners of the eyes, folds of the nose, and the corners of the mouth. This will prevent excessive irritation to the folds of the face. Petrolatum may also be applied to active acne lesions so as not to produce an erosive posttreatment lesion and the possibility of scarring.

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Before using the glycolic acid for peeling, the patient's skin is cleansed with a solution that removes some of the oils and debris and prepares the skin pH. For Asian skin this preparation should be done gently, otherwise you may have a resultant deeper peel [19]. With glycolic acid peeling systems that have more free acid released, a close observation of the patient's response is imperative when dealing with Asian skin. This is done by the clinician's judgment of the effect of the glycolic acid on the skin, namely, the level of erythema or if any epidermolysis is occurring. One can ask the patient to state what level of pain they are experiencing. You ask "on a scale of 1 to 10, 10 being the worst pain, what level of pain are you experiencing." Occasionally, the painful location may be around the nose, eyes, or another specific area of the face. If the pain is significant (e.g., level 5 or 6 out of 10), then the glycolic acid reaction can be neutralized. Most glycolic acid peeling systems have a sodium bicarbonate–neutralizing solution to end the reaction. Water can also be used for this purpose. Treatment is usually from 2 to 5 minutes a session. Frequently, if the patient has tolerated 5 minutes of one strength without bothersome side effects, then the next chemical peel can be at the next higher level.

B. Chemical Peels for Acne Vulgaris

For those patients with comedones and papulopustular lesions, acne surgery is an excellent therapeutic modality after completing the glycolic acid peels. The lesions are unroofed by the peel and the comedonal contents are expressed with gentle pressure with a comedone extractor. If acne cystic lesions are present, intralesional corticosteroid therapy may be applied after the chemical peel.

A study [20] of 40 Asian (Taiwanese) Fitzpatrick type IV patients with moderate to moderately severe acne vulgaris were divided into two groups. The two groups were treated with 35% and 50% glycolic acid peels, respectively, repeated serially four times at 3-week intervals. Both groups applied a

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formulation containing 15% glycolic acid between peels. Good results were assessed from 80.0–97.1% with patients in each category of acne; comedones, papules, pustules, cysts, and scars. Eighty-nine percent of patients with postinflammatory hyperpigmentation had good results. One hundred percent of the patients demonstrated smoother skin texture at week 11. Sixty-seven percent of the patients noted smaller pores. There were three cases in each category of side effects, including skin irritation, postinflammatory hyperpigmentation, and mild local herpes simplex infection.

For patients with acne scarring or hyperpigmentation conditions, fingertip massaging where the damage is the greatest is very helpful to increase the penetration of the glycolic acid into the skin. This allows a greater chemical reaction locally, which leads to more rapid improvement of the condition.

In many mild acne vulgaris patients with comedones and papulopustular acne, good control of their acne is evidenced with periodic (e.g., once a month) use of glycolic acid peels [21]. Cystic acne patients tend to decrease the number of cystic lesions that occur when doing repeated peels. For patients with acne scarring, a higher free acid preparation will improve the soft depressions. Patients with oiliness of the skin, especially those living in humid climates will be helped by glycolic acid products and peels. Glycolic acid peels may also be used for patients who are pregnant or are breastfeeding.

C. Postchemical Peel

As the last step of the glycolic acid peel, a restorative, emollient cream is applied. It is recommended that retinoic acid products be avoided until the skin recovers. Recovery time is approximately 5 days or less to return to a normal level of oiliness. Because the peels are light, the patient may return to normal activities immediately after the procedure. Makeup can be applied if necessary. This peel is frequently called a "lunch time" peel, because the patient can return to work the same day.

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D. Chemical Peels for Hyperpigmentation

The number one problem of Asian skin is the splotchy pigmentation of the face. The most common persistent lesions are lentigines and melasma. Lentigines frequently are removed by light electrodesiccation, liquid nitrogen, or laser therapy, which successfully stop their growth. Often with these therapies mild postinflammatory hyperpigmentation is improved by the use of glycolic acid products and peels along with a depigmenting agent(s). The specific area will lighten in color with glycolic acid treatments. If lentigines are left untreated, the base lesion will slowly continue to grow larger with time. Darkening of these lentigines easily occurs with a small amount of sun exposure.

Melasma is more complicated. Only the epidermal melasma is amenable to reduction in color. The deep dermal melasma is very difficult to treat. Most patients have a mixed type of melasma with a combination of epidermal and dermal pigmentation. Use of the Wood's lamp can assist in the differentiation of the type of melasma. The epidermal pigmentation will darken with exposure to the Wood's lamp. No change in the color is detected with dermal pigmentation. Melasma is most frequently the result of chronic sun exposure. Occasionally, it can be due to hormonal changes, such as those resulting from pregnancy or the use of oral contraceptives.

Many individuals with hyperpigmentation conditions use a complementary depigmenting program at home [22,23]. This usually consists of an AHA cream, lotion, or gel with bleaching agent(s); a retinoid (e.g., tretinoin) [24]; and a sunscreen that protects against both UVB and UVA. Most bleaching agents are compatible with the use of AHAs. Chemicals used for depigmenting include hydroquinone, azelaic acid, kojic acid, and arbutin. The use of a series of glycolic acid peels allows for a more rapid resolution of hyperpigmentation.

In one study, 16 women with melasma, mainly a mixed epidermal and dermal type of melasma, were treated on one side of the face with 70% glycolic acid and on the other side of the face with Jessner's solution [22,25]. No statistically sig-

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nificant difference between the two acid peels was detected. However, the overall decrease of severity of the melasma was 63% for both.

Another study [26] of 10 Asian (Singaporean) women, Fitzpatrick type IV and V, with moderate to severe melasma, used a cream containing 10% glycolic acid and 2% hydroquinone on both sides of the face. Glycolic acid peels (Neostrata) were performed on one half of the face every 3 weeks for 26 weeks. A sunscreen with an SPF of 15 was used during the study. Although the melasma and fine wrinkling improved more on the glycolic acid–peeled side of the face, the treatments were not statistically significant.

Relatively low concentrations of AHAs can improve photodamaged skin. A study [27] of 74 women with moderately severe photodamaged facial skin used 8% glycolic acid or 8% lactic acid creams compared with vehicle cream. This cream was applied to the face and the outer aspect of the forearms each day for 22 weeks. Photodamage was shown to improve significantly with both the glycolic acid and lactic acid 8% creams. Mottled hyperpigmentation, sallowness, roughness (especially on the forearms), and overall photodamage appearance all improved significantly.

A randomized study [28] of 65 patients with Fitzpatrick skin type III–V were treated for mixed epidermal and dermal melasma. The duration of the study was 24 weeks, with half of the patients treated with 20% azelaic acid plus a 15% or 20% glycolic acid lotion and the other half treated with 4% hydroquinone. The study showed an equivalent reduction of hyperpigmentation for both groups. A slight degree of skin irritation was noted with the glycolic acid–treated group.

III. USE OF APPROPRIATE SUNSCREEN

All the effort in improving hyperpigmentation conditions will be for naught if a sunscreen is not used. The sunscreen must

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protect against both UVB and UVA rays [29]. The popular sunscreen products currently on the market have a combination of non-PABA sunscreen chemicals containing avobenzone (Parsol 1789) to protect against UVA, titanium dioxide, and zinc oxide. To be practical, the sunscreen should be effective for 6 to 8 hours after application. Many sunscreens must be applied every 90–120 min to be effective.

Sunscreens are only a part of the entire sun-protection program. The use of hats, caps, clothing, and sun umbrellas are important additions. Gardening, golf, and other outdoor activities should be scheduled before 10 AM and after 3 PM. Periodic reapplication of sunscreen is imperative to be effective. For Asian skin, the greater the protection from ultraviolet radiation, the better.

IV. NEWER CHEMICALS FOR THE SKIN

Newer products and peels have recently added a new dimension for treating photodamaged skin, hyperpigmentation conditions, and acne vulgaris. Poly hydroxy acids have been extremely effective for Asian skin. The molecules contained in poly hydroxy acids are larger. The penetration of these larger molecules (e.g., gluconolactone) into the epidermis is slower and does not cause the burning and irritation that occasionally occurs with AHA products. These poly hydroxy acids can be easily used around the eyes and on patients with atopic dermatitis, acne vulgaris, seborrheic dermatitis, or acne rosacea. Chemical peels with poly hydroxy acids are less irritating and are useful in treating Asian patients.

The salicylic acid peels (e.g., 20% and 30%) are similar to mild glycolic acid peels in action [30]. The reaction stops on its own and is easier to use without being as careful with the end point reaction on the skin.

Combinations of the AHAs (e.g., glycolic acid, malic acid, and citric acid) are becoming more common on the market.

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The AHAs have been combined with the poly hydroxy acids for greater efficacy. The possibility of combining glycolic acid (which is hydrophilic) with beta hydroxy salicylic acid (which is lipophilic) might create a very good moisturizer [31].

The advancement of the hydroxy acids has been accelerated in the past 5 years. Newer products that are less irritating without burning, stinging, and erythema are optimal for the Asian skin. The understanding of the efficacy of these hydroxy products in producing collagen and elastic fiber production in the dermis and in improving the epidermal skin characteristic must await further scientific studies.

V. CONCLUSION

Glycolic acid products and peels have a major role to play in the improvement of Asian skin. Because the glycolic acid peels are light, the peels may be applied serially on Asian skin. It is important not to be too aggressive with darker-skinned individuals when using these peels. Excessive therapy will cause postinflammatory hyperpigmentation, which may aggravate the original problem of pigmentation. In addition to postinflammatory hyperpigmentation, ephelides, lentigines, and epidermal melasma may benefit from the use of glycolic acid products and peels. These products and peels also help acne vulgaris and fine wrinkling. Improvement of the photodamaged Asian skin is always a goal. Products or procedures that cause the least amount of irritation but still provide benefits are the ultimate objective in dealing with Asian skin.

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10

Body Peels

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I. INTRODUCTION

Traditionally, most practitioners have tended to limit the use of chemical peeling procedures to the facial skin and possibly the neck [1,2]. Although chemical peeling techniques can be highly beneficial to skin that has been damaged by sun exposure and/or aging, the nonfacial skin can be problematic to treat. Traditional chemical peeling techniques when applied to the nonfacial skin may give unpredictable or undesirable results, such as depigmentation and/or scarring, and may penetrate beyond the desired depth. In some cases, postinflammatory pigmentation and other undesirable sequelae may occur.

Despite the practical difficulties, interest in body peeling has persisted, because the potential benefits are great. The nonfacial skin, particularly in sun-exposed areas, often dis-

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plays epidermal and dermal lesions and cosmetic defects. These may include irregular pigmentation, lentigines, keratoses, wrinkling, crepiness, roughness, striae distensae, and so on. Experience with facial peeling demonstrates that skin resurfacing in properly selected patients can help to decrease wrinkling, smooth the skin texture, and lighten pigmented lesions. Skin resurfacing can also help give the skin a more vigorous, glowing, and youthful quality because of the formation of new collagen and reorganization of the elastic fibers in the skin.

Peels of the nonfacial skin have been reported using glycolic acid alone [3,4]; however, I generally prefer a deeper peel for moderately to severely sun-damaged skin. Body peels have been reported using 20–30% trichloroacetic acid (TCA) [5], but in my experience this agent may produce an undesirable redness after treatment and may cause postinflammatory pigmentation. Other agents reported have been Jessner's solution [6], salicylic acid ointment [7], and salicylic acid liquid [8].

After much research, I have developed a chemical peeling technique for the nonfacial skin that has demonstrated consistently good results [9,13]. This method combines glycolic acid gel with TCA liquid in such a way as to permit a "controlled" peel. I coat the area to be peeled with a layer of glycolic acid gel and then apply TCA directly over the gel. This seems to combine the benefits of both agents—the deeper penetration of TCA and the avoidance of undesirable sequelae that are characteristic of TCA. An important factor in the use of this technique is to permit the peeling process to proceed only to a predetermined end point and then to stop the process by removing the peeling agents and neutralizing the area. In my practice, this method has proven to be quite safe and effective in peeling nonfacial skin.

I call this technique the Cook Total Body Peel™. The term "total body peel" does not mean that the entire body is treated, but rather that the technique can be used on most

parts of the body. I have used this technique successfully on the neck, chest, arms, hands, legs, back, abdomen, and balding scalp. The technique may also be used on the face when a somewhat lighter peel is desired than that achieved by 40% TCA alone. It is suitable for any area of the body that may be subject to sun damage and aging changes.

The Cook Total Body Peel uses a combination of 40% TCA and 70% glycolic acid gel as peeling agents. It is important to use glycolic acid gel, rather than liquid, because the gel acts as a partial barrier to the TCA penetration. Liquid glycolic acid does not act as a barrier to the TCA, so that combining it with TCA can result in too deep a peel on the body. I have found the 40% TCA formulation to be preferable to a lower strength, because it enables the TCA to penetrate deep enough into skin lesions such as keratoses and lentigines.

A copious amount of sodium bicarbonate solution is used to neutralize the acids and stop the peeling at a time determined by the physician. The method permits precise timing, so that the extent and depth of the peel are almost entirely technique dependent. The result is a peel that can range in depth from superficial to deep and can be used on most areas of the body and most skin types. I have given this treatment to more than 3,000 patients to date, with consistently good results and high patient satisfaction.

A. Technique

1. General Considerations

Most patients in this office who receive a facial peel of any type are also given a TCA/glycolic acid gel peel (Cook Total Body Peel) to the neck, chest, and hands. Other body areas such as the arms, legs, abdomen, and back are also treated when appropriate.

I use this technique at the same time as a traditional peel of the face. For the facial peel I generally use either a laser or a TCA chemical peel, depending on the patient; in some cases, I

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use the TCA/glycolic acid gel technique to peel the patient's face and selected areas of the body. The combination of nonfacial skin peeling with a facial peel allows good blending from one area to another. It can reduce or eliminate the sharp, rather unnatural-looking contrast that may sometimes occur between treated facial skin and untreated neck and chest skin.

2. Preoperative Considerations

Patients are evaluated carefully before treatment. Factors to be considered include the patient's general health; the Fitzpatrick skin type [10]; the degree of actinic or age damage [11]; current medications, including isotretinoin (Accutane, Roche Pharmaceuticals, Nutley, NJ) and tretinoin (Retin-A, Ortho Dermatological, Raritan, NJ); the degree of sun exposure that the patient currently experiences and will experience in the future; and the degree and extent of poikiloderma on the neck. Relevant history must be obtained, including any history of prior cosmetic surgery, hypertrophic scarring, keloids, allergies (including "sensitive skin"), or acne.

Most lentigines and irregular pigmentation can be expected to improve after a peel or series of peels. Wrinkles and crepiness of the arms and midchest will also generally respond well to a series of peels. Patients need to understand that the blood supply, and therefore the healing ability, of the body skin is much less than that of the face, so that several light peels are safer than a single deeper peel.

The most problematic area to peel is the legs. The skin area is extremely large, and the skin type varies from sensitive inner thigh to tough, sun-damaged lower leg. Patients always hope for elimination of skin lesions like flat seborrheic keratoses, hyperkeratotic actinic keratoses, and porokeratosis, which on the legs are notoriously unresponsive to peeling without postinflammatory erythema or hyperpigmentation. Patients expect perfection, and it is important to emphasize realistic expectations, particularly on the legs.

As with any cosmetic surgery, it is important that pa-

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tients have realistic expectations. In particular, they need to realize that certain skin lesions, particularly keratotic lesions, may persist after treatment, and that striae distensae may or may not be improved by this procedure.

Before this or any skin resurfacing procedure, patients are placed on prophylactic antibiotics and antiviral medication, starting the day of the peel and continuing for 2 weeks. If patients can tolerate Retin-A, they will benefit from preoperative application to the face. Alpha hydroxy acids and hydroquinone may also be used. However, care must be taken if patients use high concentrations of alpha hydroxy acids or tretinoin on the nonfacial skin during the week before the procedure, because these substances can increase the speed of penetration of the peeling chemicals. I advise patients to stop using these agents at least 1 week before their peel.

3. Peeling Technique

I prefer to peel one individual area of skin all the way to neutralization, then the next area, and so on, treating each area separately to increase my control of the end point.

No pretreatment with local anesthetic is needed before this peel. No sedation is required for procedures that include just the face, neck, chest, hands, and arms. Patients who are undergoing a more extensive body peel, covering greater areas of the body such as legs, back, and abdomen, may prefer to receive intramuscular or sublingual sedation, because this is a more lengthy procedure. Appropriate monitoring equipment and personnel are necessary when using sedation. Sedation agents may include intramuscular midazolam (Versed, Roche Pharmaceuticals Nutley, NJ), 2.5–5 mg; meperidine (Demerol, Sanofi Winthrop, New York, NY), 50–100 mg; or hydroxyzine (Vistaril, Pfizer Inc., New York, NY), 25–50 mg. In addition, diazepam (Valium, Roche Products, Manati, Puerto Rico), 5 mg, may be administered sublingually.

Glycolic acid gel 70%, nonneutralized, is purchased in ready-to-use form (Sun Laboratories, Roslyn, PA).

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TCA, 40% weight/volume, unbuffered, is made to order by a local pharmacy.

Sodium bicarbonate, 10% weight/volume, is also made up by a local pharmacy (Fig. 1).

The skin to be treated is cleansed with acetone. Then 70% glycolic acid gel is applied to one selected area with a folded 3×3 gauze (Nu-Gauze, Johnson & Johnson, Fort Washington, PA).

Immediately, 40% TCA is applied to the same area with a folded 3×3 gauze (Fig. 2).

I observe the skin carefully throughout the process, so as to achieve the desired depth of peel. When the particular area being peeled has reached the desired end point (see visual staging criteria, later), I immediately stop the peeling process by neutralizing the entire area. If only a small part of the area has reached the desired end point, that part may be neutralized and the remaining areas watched carefully until they also reach the desired end point.

If the desired end point is not reached after approxi-

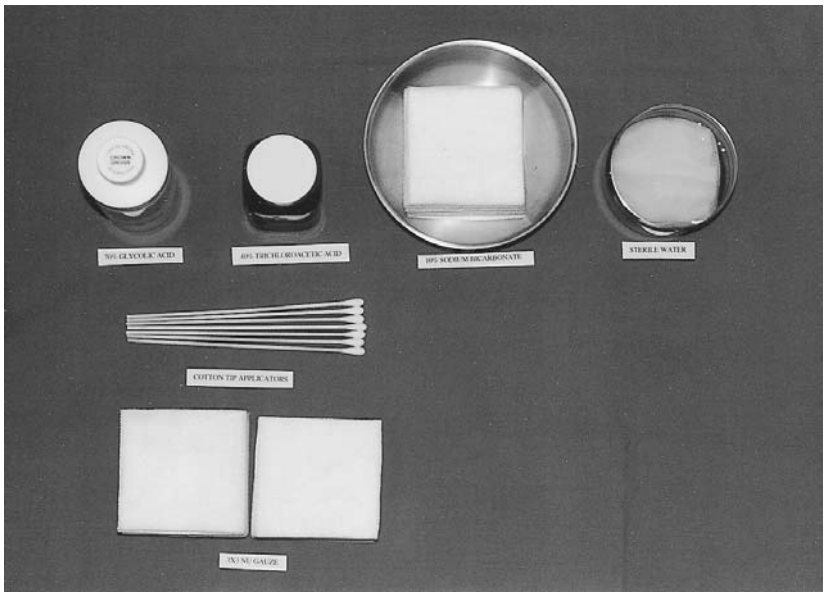

Fig. 1 Peeling supplies and equipment ready for use.

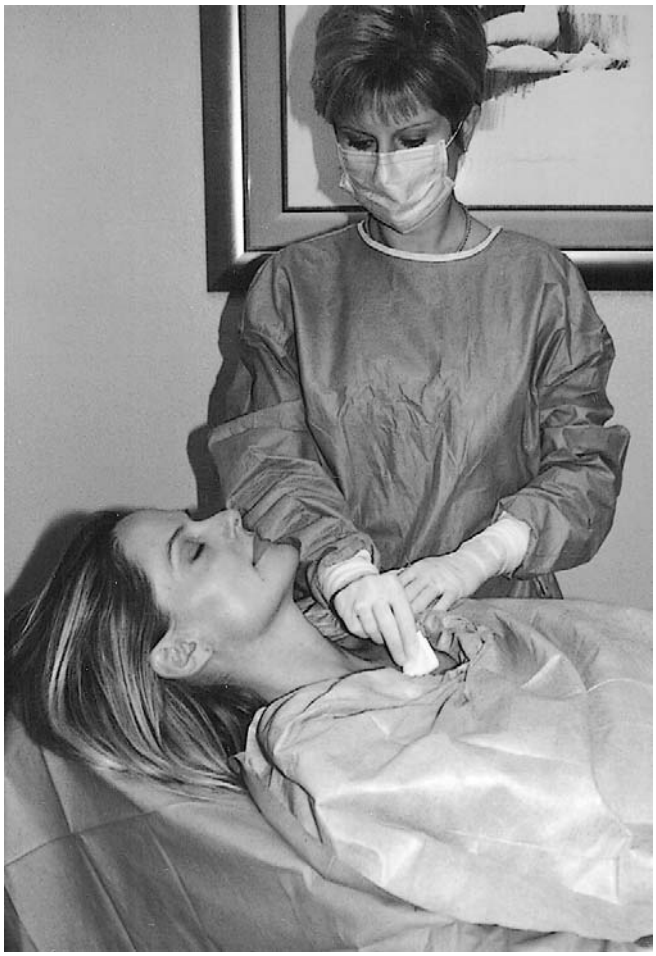

Fig. 2 Chemical peeling solution being applied to the chest.

mately 3 minutes, a small test area of the skin is neutralized by wiping it clean with the corner of a 3×3 gauze soaked in 10% sodium bicarbonate solution, and the area is observed visually. In approximately one fourth of patients, the test area will show signs of a deeper end point only after it is neutralized. In these cases, the rest of the area is immediately neutralized as well. The entire area will usually show a similar

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reaction to the test spot—that is, it will show visual evidence of end point only after being neutralized.

Approximately one third of patients will reach end point within 3 mins. If after 3 mins the skin has not yet reached the desired end point and a small neutralized test spot does not show end point and the patient is not complaining of a burning sensation, then an additional coat of TCA may be applied and the process allowed to continue. Several additional coats of TCA may be applied at 3-min intervals, after again evaluating a different test spot and if the patient is still not experiencing a burning sensation, to attain the desired end point.

When the end point is reached, I stop the process by neutralizing with a copious amount of 10% sodium bicarbonate solution. The sodium bicarbonate solution is applied at least five times with 3×3 gauze and gentle wiping. Sodium bicarbonate solution is used rather than water, because of its neutralizing effect. Care should be taken to remove all glycolic acid gel from the skin and to neutralize at least 3 inches beyond the treated area on all sides.

4. Visual End Point

Determination of the proper end point is crucial for this technique to be successful. The physician must determine the appropriate end point for each area according to the patient's skin type, actinic damage, and "age damage." The primary method for determining the end point is direct observation of the skin (Table 1).

When undergoing a chemical peel, the skin goes through a series of color changes, primarily caused by the TCA in the formulation. Careful attention to the color change is key to obtaining the best cosmetic result. These color changes have been described by Rubin ([2] pp 118–119) as "levels of frost." First, the skin may become pink or erythematous (stage I; Rubin's level O). Then small white speckles develop (stage II, Rubin's level 1; Fig. 3A). The speckles increase in number and size until the skin reaches a "frosted" appearance, with the underlying pink still showing through (stage III, Rubin's level 2; Fig. 3B). If a peel is taken even further, the skin will

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Table 1 Visual Staging to Determine End Point for Chemical Peel of the Skin

Stage	"Level of frost" (Rubin)	Description	Illustration	Clinical application
I	0	Pink or erythematous skin		Dark skin with minimal actinic damage; face and/or body
II	1	Pink skin with small white speckles	Fig. 2A	Fair to medium skin with medium actinic damage; face and/or body
III	2	"Frosted" appearance with pink skin showing through	Fig. 2B	Fair skin with moderate to severe actinic damage; face and/or body
IV	3	"Blanched" appearance with an opaque white color	Fig. 2C	Fair skin; face only, or fair skin of upper neck blending into face
V		"Blanched" appearance with a yellowish white color	Fig. 2D	Severe actinic damage; face only (rarely needed because laser peels may be preferred)
VI		"Blanched" appearance with a grayish white color	Fig. 2E	Severe actinic damage; face only (rarely needed because laser peels may be preferred)

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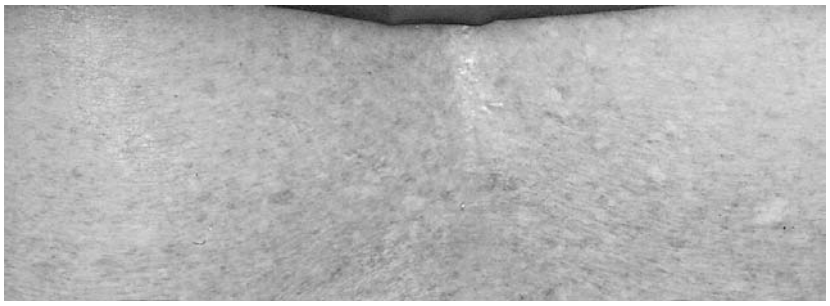
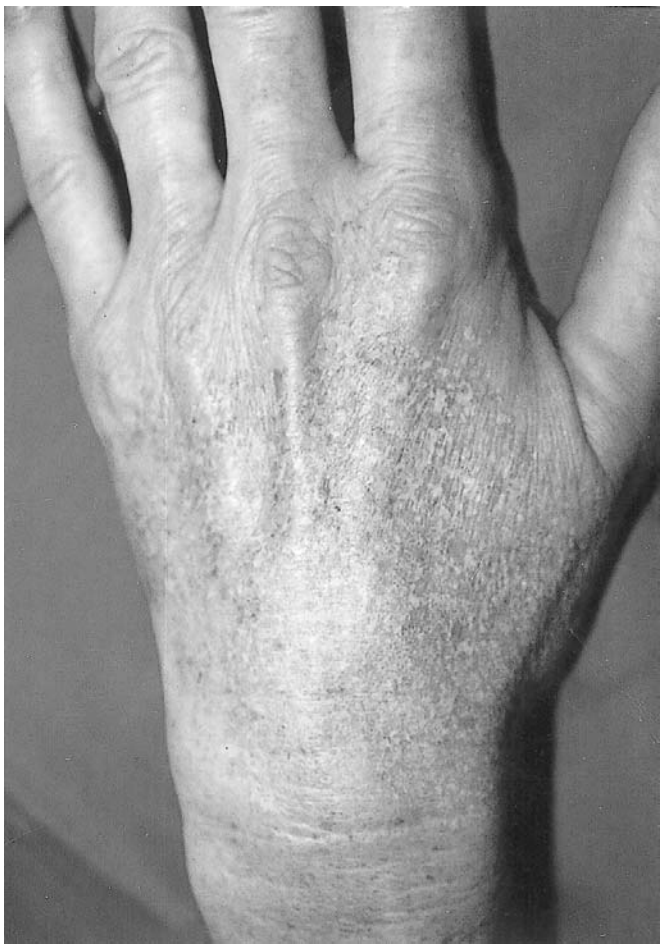


A



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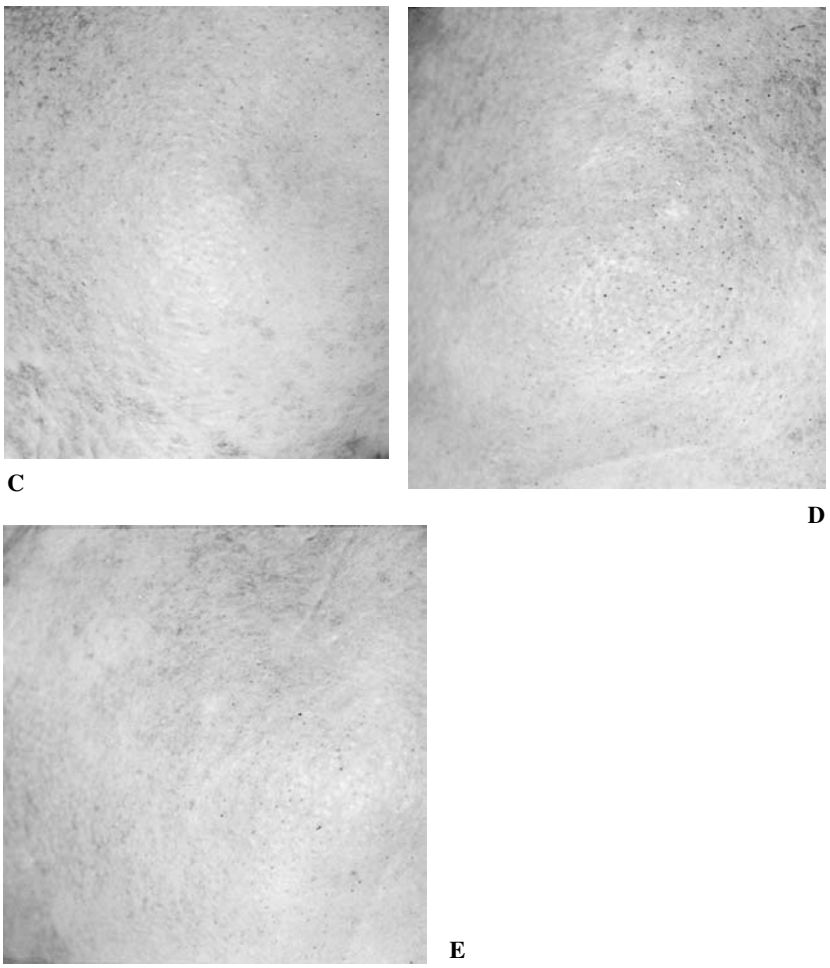

Fig. 3 Visual appearance of the skin during a chemical peel. *A,* Stage II, erythema with scattered white speckles. *B,* Stage III, erythema with a moderate number of speckles, giving a "frosted" appearance. *C,* Stage IV, "blanched" appearance with an opaque white color. *D,* Stage V, "blanched" appearance with a yellowish white color. *E,* Stage VI, "blanched" appearance with a grayish white color.

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"blanch," becoming first opaque white (stage IV, Rubin's level 3; Fig. 3C), then yellowish white (stage V; Fig. 3D), and finally grayish white (stage VI; Fig. 3E).

A typical end point for this technique is in the range of stage II to stage III, depending on the degree of skin sensitivity and the amount of skin damage that has occurred. Sensitive skin with mild to moderate sun damage should be peeled only to stage II, which is characterized by erythema with small scattered white speckles, or an expression by the patient of a slight burning sensation. "Tough," weathered, or sun-damaged skin can be taken to a more speckled or lightly frosted end point (stage III), which indicates a deeper peel. In general, the nonfacial skin is rarely peeled past stage III, to the point where it would begin to blanch to an opaque white.

In most patients, I peel the upper neck more deeply than the more distal areas of the neck, so as to blend better with the treated areas of the face. The upper neck may sometimes be taken slightly beyond stage III to an early stage IV.

In patients with darker skin types, I usually limit the depth of the peel by neutralizing at stage I.

Some skin areas may require more time or more TCA than neighboring areas to peel to the same stage. Similarly, different areas of the body may require different degrees of treatment to reach the same end point. I generally peel more deeply in areas that have suffered more damage. If there are a few spots that need additional peeling after most of the area has reached end point, I may neutralize the rest of the area but leave the peeling agents on the spots that need additional treatment. It is even possible to "spot" additional TCA onto small areas that need deeper penetration, using a cotton-tipped applicator. The process may be compared with scrubbing a floor, where some spots are dirtier than the rest of the floor, needing additional scrubbing or a longer "soak" to get a uniformly clean floor.

Thicker lesions on the upper body may be given additional treatment at the time of the peel if they do not blanch sufficiently after several TCA applications. Gentle cryo-

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surgery may be applied to hyperkeratotic actinic keratoses or seborrheic keratoses. Gentle electrocautery or laser treatment may be used for cutaneous polyps and sebaceous hyperplasia. Lentigines will generally not need any additional treatment, because they will usually blanch even sooner than adjacent skin.

After neutralization, it may seem that one area has been peeled somewhat deeper than an adjoining area. If necessary to prevent an "unbalanced" appearance, I may reapply the agents briefly to the less peeled area to achieve the same end point. However, this should be done with great care. Physicians should beware of emulating the stock comedy figure of the incompetent hedge-trimmer, who keeps trimming one end of the hedge and then the other to "even it up," eventually winding up with nothing but stumps. If an area of skin reaches a deeper stage than I would prefer, I do not deepen the other areas. Instead I apply a strong cortisone ointment such as betamethasone dipropionate (Diprolene, Schering Pharmaceuticals, Kenilworth, NJ) or halobetasol propionate (Ultravate, Westwood-Squibb Pharmaceuticals, Plainsboro, NJ) immediately postoperatively, and I instruct the patient to continue applying it twice a day.

The artistry of this technique lies in the blending, so as to achieve consistency in the final appearance of the skin in the various body areas. This blending between one cosmetic unit and another is important to achieve a uniform outcome.

5. Postoperative Considerations

Immediately after the procedure, an emollient such as Theraplex (Medicis Dermatologics Inc., Phoenix, AZ) is applied to the treated areas. Patients are also given 20 mg triamcinolone acetonide (Kenalog, Apothecon, a Bristol-Myers Squibb company, Princeton, NJ) and 6 mg betamethasone sodium phosphate and betamethasone acetate (Celestone Soluspan, Schering Pharmaceuticals, Kenilworth, NJ) intramuscularly to reduce inflammation.

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Patients will continue to apply the Theraplex emollient twice a day until peeling is completed. They are told to wash the areas gently, without trying to remove all the emollient, and not to pick at the area as it peels.

On subsequent postoperative visits, intralesional Kenalog, 2 mg/ml, and topical cortisone ointment are used in any healing areas that are pink or eroded to reduce inflammation.

Depending on the area treated, the skin will flake and scale for 2 to 4 weeks postoperatively (Fig. 4). Patients can return to work and normal activities promptly after this procedure but should strictly avoid sun exposure for at least 1 month. They are advised to use retinoic acid and hydroquinone after the skin has peeled.

This peel can be repeated as often as every month, as soon as the flaking process is complete. In my practice, most patients are satisfied with the improvement seen after a single peel to the face, neck, chest, and hands. Approximately 10% desire further treatment of the body skin. One or two additional peels to the arms and legs are usually sufficient; however, some patients with severe sun damage have received up to 10 peels of the arms over a period of several years, with improvement each time and no complications. In my experience, a repeat peel is more effective if it is performed as soon as the previous peel has healed (generally around 1 month after the initial peel) compared with a repeat peel done after 6 months or more.

For patients with moderate to severe sun damage, I usually recommend a series of three peels, 1 month apart. However, I usually wind up performing only one or two peels, because the patient is generally satisfied with the result before completing the entire course of three peels.

Abdominal striae may be treated with a series of three peels, provided that improvement was seen after the first peel. Striae that do not show improvement after a single peel will generally be unresponsive to repeat peels (see "Results").

The result of this method is a lighter peel than a typical peel using 40% TCA alone. In contrast, Coleman's medium-

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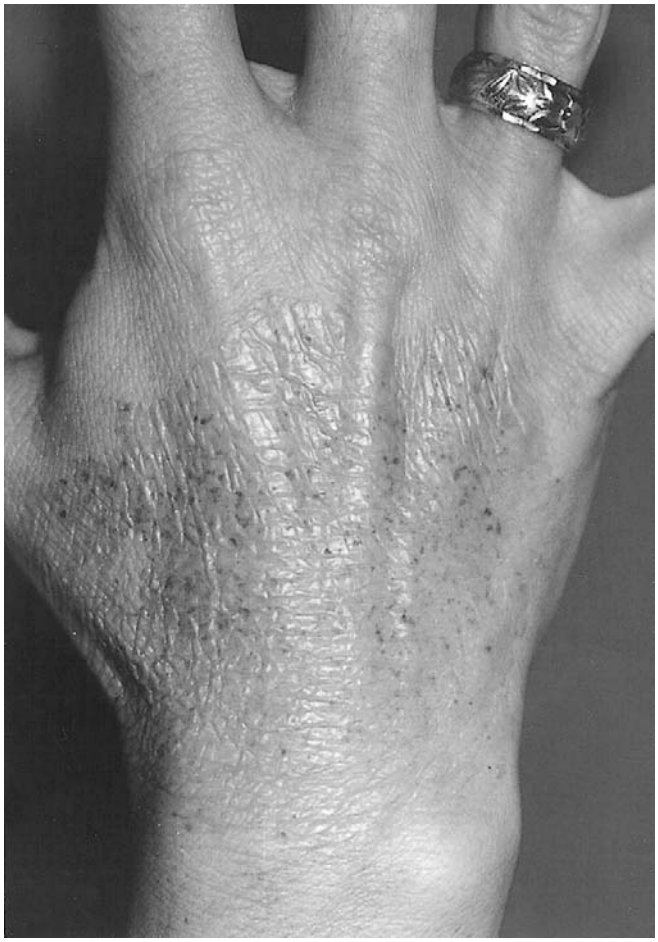

Fig. 4 TCA/glycolic acid cell peel of the hand. Patient 10 days postoperatively. Note decreased pigmentation on areas already peeled.

depth facial peel using TCA plus the liquid form of glycolic acid produces a heavier peel [12].

B. Results

I have performed the Cook Total Body Peel on thousands of patients. Virtually all of my facial peel patients receive this

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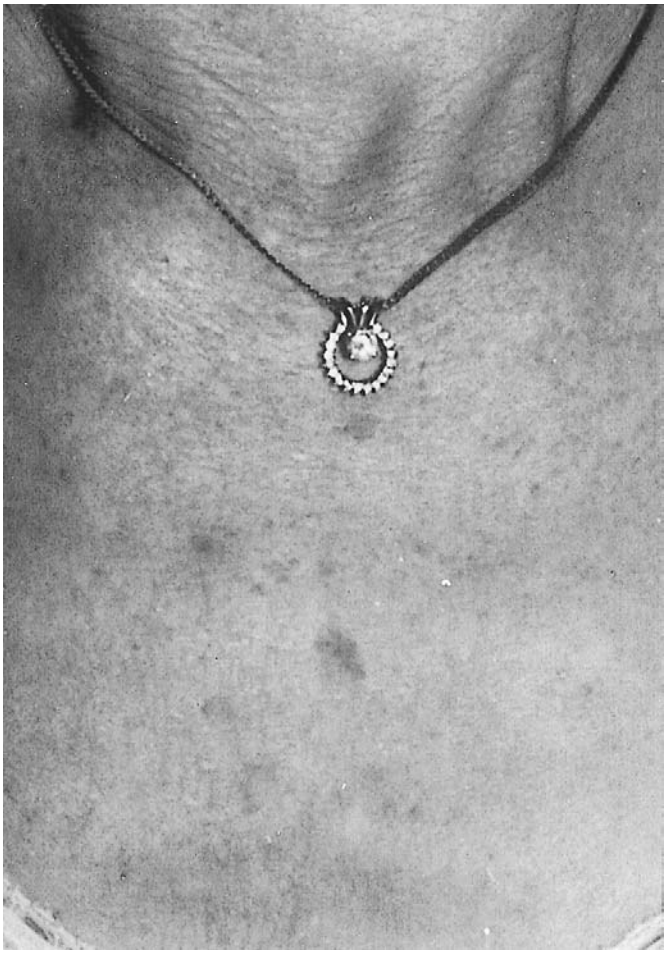

A

Fig. 5 TCA/glycolic acid gel peel of neck and chest. Patient (*A*) before and (*B*) after one peel. Pigmented lentigines are greatly reduced, and the texture of neck and chest is smoother. Peel results are even in color and texture.

treatment on their neck, chest, and hands. When appropriate, I may also treat the scalp, legs, abdomen, and back.

This method has produced consistently good results on the neck, chest (Fig. 5), hands (Fig. 6), arms (Fig. 7), legs, back, abdomen, scalp, and face. The skin has a smoother tex-

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B

ture, and there is a significant decrease in irregular pigmentation, lentigines, wrinkling, and actinic keratoses. However, "flat" seborrheic keratoses usually show less improvement.

Striae distensae of the abdomen can be decreased in many cases, even if they have been present for many years. Of course, striae do improve naturally over time, but in some patients this peel seems to speed up the process markedly. Some patients report that atrophic, hypopigmented striae are

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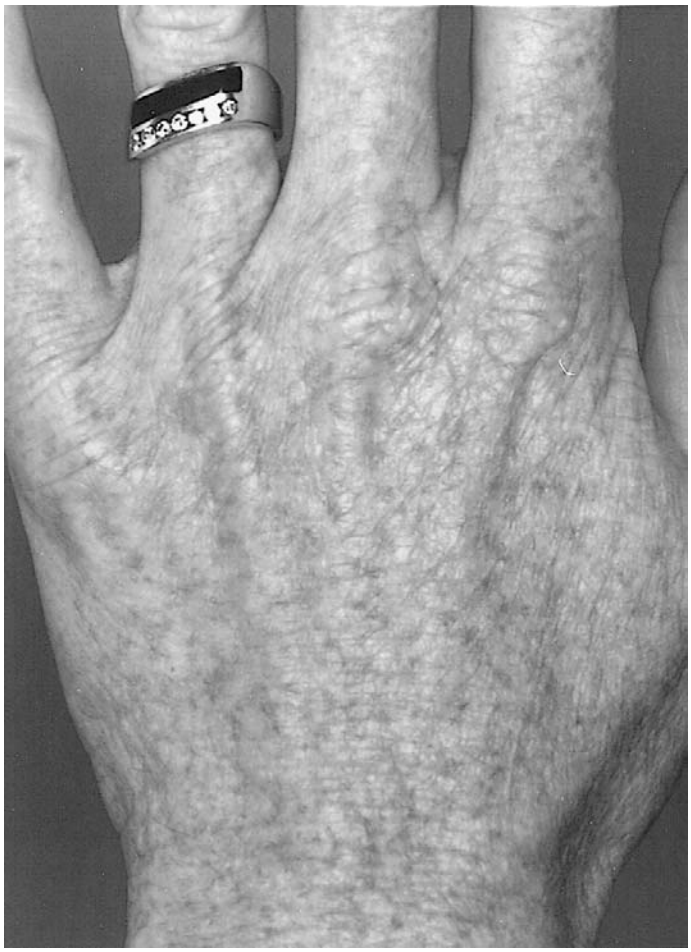

A

Fig. 6 TCA/glycolic acid gel peel of hands. Patient (*A*) before and (*B*) after one peel. Pigmented lentigines are greatly reduced. Peel results are even in color and texture. Scratch on hand is unrelated to peel.

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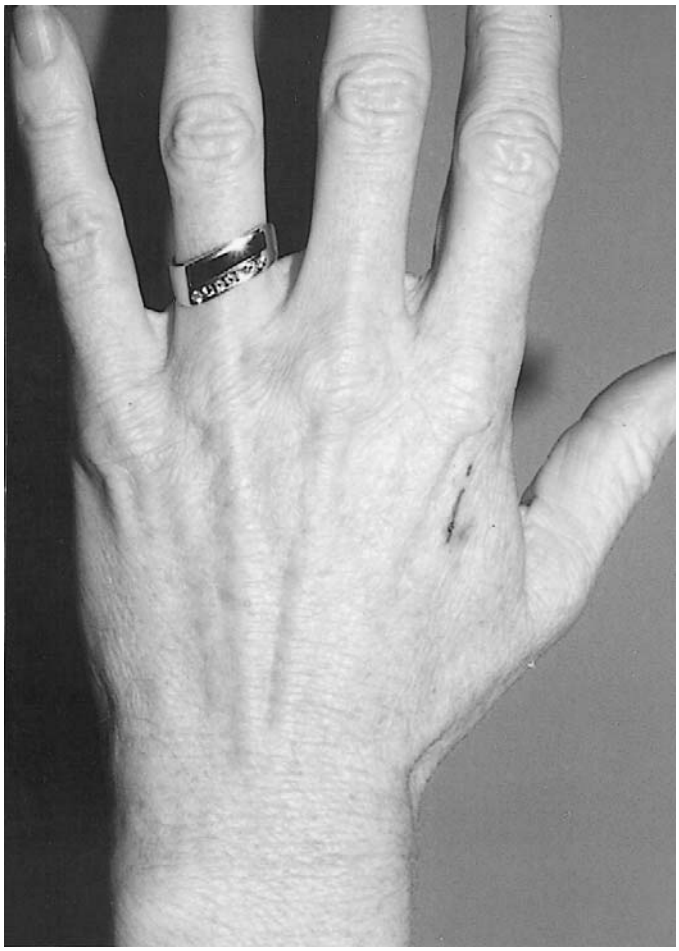

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greatly improved after a single treatment, and in these patients the striae will generally continue to become less noticeable with successive treatments. In other patients the first peel has little or no effect, and in these cases, subsequent peels will generally not be effective either. Patients need to understand that striae are not always improved by peeling.

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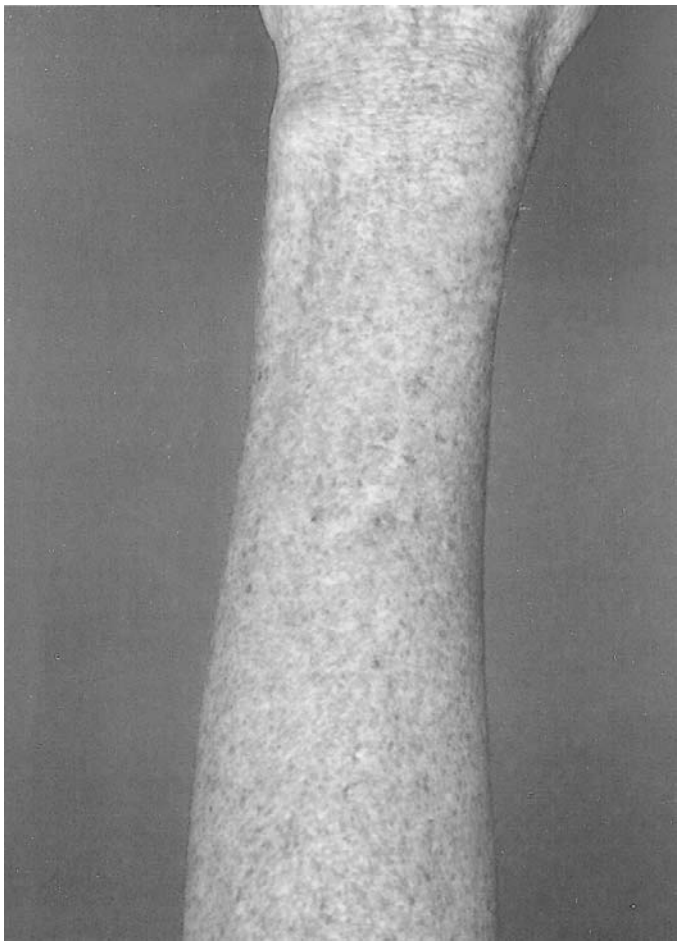

A

Fig. 7 TCA/glycolic acid gel peel of arms. Patient (*A*) before and (*B*) after one peel. Pigmented lentigines are greatly reduced, and skin texture is smoother. Peel results are even in color and texture.

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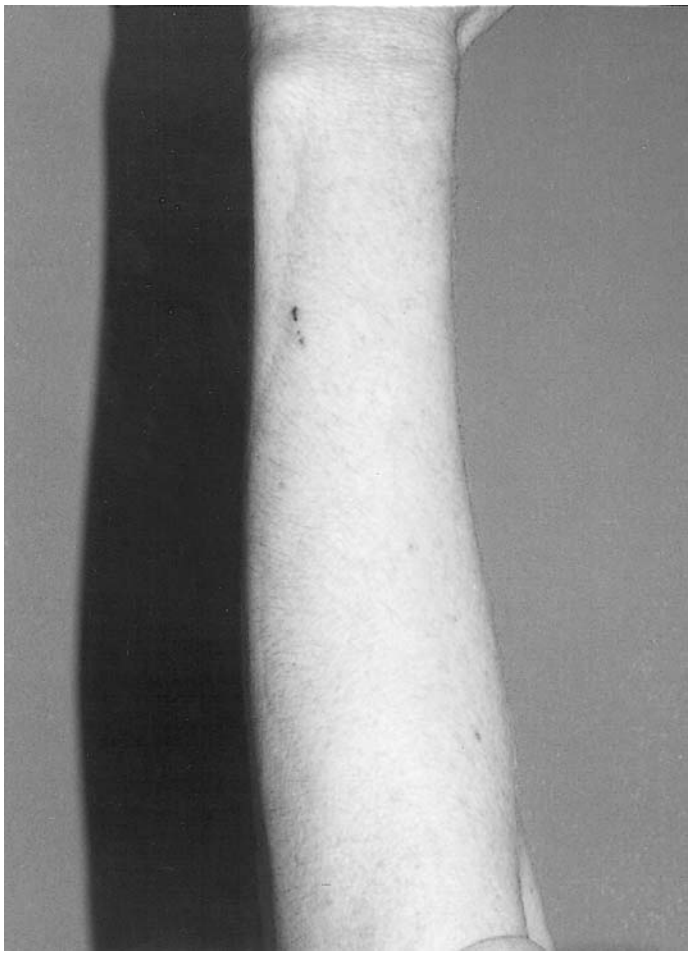

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The results of this peel are particularly impressive in patients with freckled or sun-damaged necks, chests, and hands. The technique promotes good blending between the peeled facial skin and the skin of the neck. Patients can achieve a more youthful appearance while avoiding an abrupt "demarcation line" between treated facial skin and adjacent untreated skin (Fig. 8).

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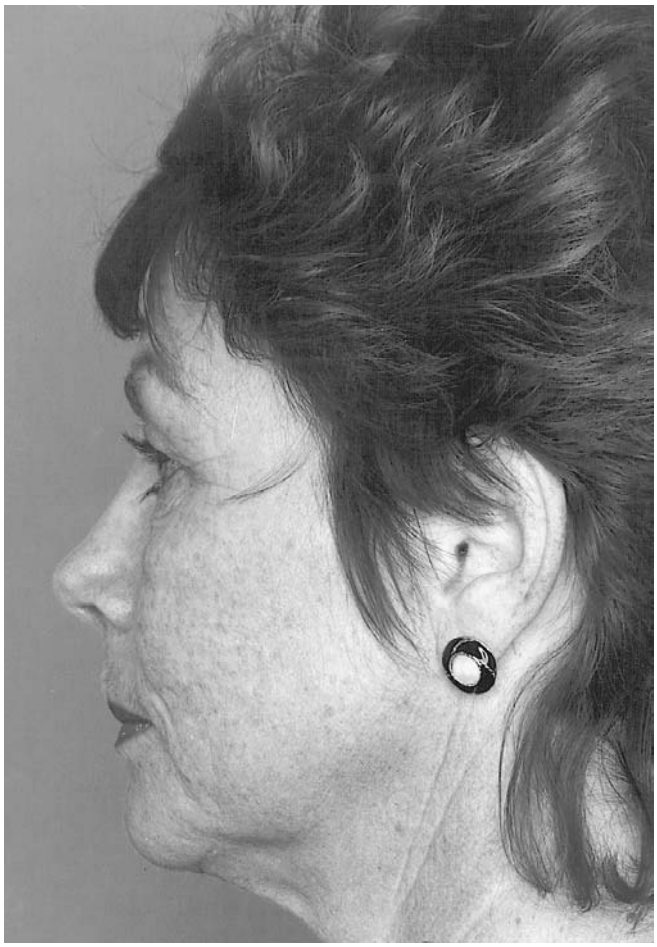

A

Fig. 8 CO_2 laser peel of the face with TCA/glycolic acid gel peel of the neck. Patient (*A*) before and (*B*) after one peel. Clinical results show excellent blending of previously freckled skin of face and neck.

This technique shows a minimal incidence of postinflammatory pigmentation. In my experience approximately 1 patient in 1000 may have postinflammatory pigmentation develop, limited to the arms and legs, which resolves readily with local hydroquinone treatment. I have not seen any de-

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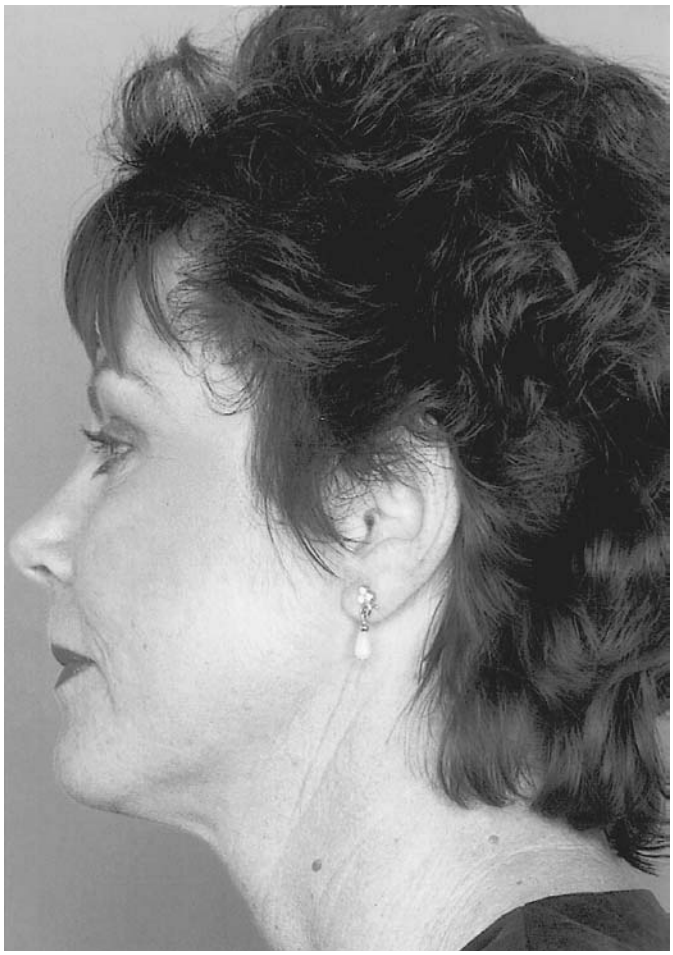

B

pigmentation, scarring, or other major complications in my patients.

In summary, I have found this to be an excellent peel for the nonfacial skin, giving consistently good results when properly performed. Careful physician attention to the timing of the peel and prompt neutralization at the proper end point are critical to the consistent success of this technique.

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11

Glycolic Acid Peels in Blacks

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I. INTRODUCTION

Chemical peeling procedures are commonly performed in Caucasian skin (Fitzpatrick's skin types I, II, and III) for photodamage, actinic keratoses, rhytides, acne, scarring, and dyschromias [1]. Despite the general popularity of chemical peels in lighter complexioned racial–ethnic groups, cosmetic surgeons have been reluctant to perform these procedures in darker racial–ethnic groups, in particular, skin types V and VI. Historically, there have been major concerns regarding the induction of dyschromias and scarring. Recent data, however, suggest that peeling procedures are indeed safe and efficacious for darker racial ethnic groups [2].

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When considering chemical peeling procedures in darker-skinned, racial–ethnic groups, the treating physician must first possess an in-depth knowledge of morphological and physiological racial skin differences. Second, the clinician should have an adequate knowledge base regarding issues of paramount cosmetic concern for darker skin types. Although no quantitative differences in melanocytes have been demonstrated among different racial–ethnic groups, the melanocytes of darker-skinned individuals (blacks) produce greater quantities of melanin, and melanosomes are singly dispersed within the cells. The melanocytes often demonstrate labile, exaggerated responses to cutaneous injury [3]. In addition, other reported differences in black skin include increased stratum corneum cell layers, increased desquamation, increased lipid content, decreased ceramide content, and increased recovery after tape stripping [4–6]. Multinucleated fibroblasts are more commonly observed in black skin [3], and hypertropic scars and keloids are significantly more common [7]. The studies that have assessed sodium lauryl sulfate irritation, transepidermal water loss, and percutaneous absorption of chemicals have reported variable results [5,6].

In view of the quantitative increased levels of photoprotective melanin, darker skin demonstrates significantly greater intrinsic photoprotection. Clinical photodamage, actinic keratoses, rhytides, and skin malignancies are less common problems in deeply pigmented skin. However, darker skin types are frequently plagued with dyschromias because of the labile responses of cutaneous melanocytes [8]. In a survey of 2,000 black patients seeking dermatological care in a private practice in Washington, DC, the third most commonly cited skin disorders after acne and eczema were pigmentary problems other than vitiligo [9]. Of those patients, most had a diagnosis of postinflammatory hyperpigmentation, followed in frequency by melasma. Grimes et al (personal database, Vitiligo and Pigmentation Institute) conducted a survey of 100 African-American and Hispanic women. The survey as-

sessed issues of cosmetic concerns for darker skin types. The most commonly cited problems were dark spots or blotchy skin, texturally rough skin, and increased sensitivity to topical products. The patients surveyed also complained of oily skin. Wrinkles and photodamage were significantly less frequent when the data were compared with an age-matched Caucasian population of 141 women.

II. INDICATIONS FOR CHEMICAL PEELING

The aforementioned data suggest that the indications for peeling procedures differ in darker racial–ethnic groups, in particular blacks. Key indications in darker skin types include postinflammatory hyperpigmentation and melasma unresponsive to topical bleaching agents, texturally rough skin, oily skin, and acne vulgaris. Peeling procedures also improve pseudofolliculitis barbae. Clinical experience suggests that the benefits of chemical peeling in dark skin can be maximally achieved with superficial peels while minimizing risks. This chapter specifically addresses the use of glycolic acid as a peeling agent for black skin (skin types V and VI).

III. GLYCOLIC ACID PEELS

The alpha hydroxy acids (AHAs) are organic carboxylic acids having one hydroxyl group attached to the alpha position of the carboxylic carbon atom. Alpha hydroxy acids are naturally occurring products present in sugar cane juice, sour milk, tomato juice, grapes, and apples. Glycolic acid, a 2-carbon molecule, and the smallest of the AHA compounds, has gained widespread acceptance as a superficial peeling agent [10,11]. It has, indeed, become the most widely used organic carboxylic acid for skin peeling. Glycolic acid formulations include buffered, partially neutralized, and esterified products. Concentrations for peeling range from 20–70%.

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The topical effects of glycolic acid include decreased corneocyte adhesion, increased skin thickness, and increased collagen and glycosaminoglycan production [12]. Several published studies have assessed the efficacy of glycolic acid peels in darker racial–ethnic groups. Lim et al [13] treated 10 Asian women with melasma and fine wrinkles with 2% hydroquinone and 10% glycolic acid applied to both sides of the face. A series of 20–70% glycolic peels were performed on one side for comparison. Greater improvement with minimal side effects were noted on the side treated with the series of glycolic acid peels. Wang et al [14] treated 40 Asian patients with moderate to moderately severe acne with a series of 35–70% glycolic acid peels. The investigators noted significant improvement in skin texture and acne. Side effects were reported in 5.6% of patients.

Burns et al [15] treated 19 black patients with postinflammatory hyperpigmentation. The control group was treated with 2% hydroquinone/10% glycolic acid twice daily and tretinoin 0.05% h.s. whereas the active peel group received the same topical regimen plus a series of six serial glycolic acid peels. Although not statistically significant, greater improvement was noted in the chemical peel group.

Lawrence, Cox, and Brody [16] compared the efficacy of Jessner's solution and 70% glycolic acid in a split-face study of 16 patients. Of the total group, five were skin type IV, three were skin type V, and one had skin type VI. There was no statistically significant difference in improvement between the two groups. The investigators did not report an increased frequency of side effects in patients of skin types IV through VI. Glycolic acid has been used extensively as a superficial peeling agent in my practice. Despite some general predictable outcomes with glycolic acid, there can be tremendous variability and reactivity when peeling dark skin. Superficial peeling can cause hyperpigmentation and scarring in susceptible individuals. Therefore I always perform a series of glycolic peels beginning with a low concentration of glycolic acid to assess the patient's sensitivity and reactivity. My standard

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protocol involves initial pretreatment for 1 to 2 weeks with bleaching agents such as hydroquinone, 4% or higher (extemporaneously compounded), azelaic acid, 20%, or kojic acid formulations. Bleaching agents are essential components of the peeling protocol, otherwise there is indeed a greater risk of paradoxical hyperpigmentation.

A series of four to six glycolic acid peels are performed at 2- to 4-week intervals. After cleansing with degreasing agents such as acetone or alcohol, glycolic peels are applied with wedge sponges, gauze sponges, or peel brushes for 3 to 5 mins. Cautious titration is appropriate. Glycolic acid peels are titrated from concentrations of 20–35%, 50%, and finally 70%. Postpeel care includes the use of bland cleansers and emollients until irritation subsides. The patient then resumes the use of their regular topical skin care products and bleaching agents. Postpeel adverse reactions such as excessive desquamation and irritation are treated with low- to high-potency topical steroids.

Tretinoin often increases the depth of peeling agents and peel complications such as postinflammatory hyperpigmentation in black skin. Hence, if the patient is using tretinoin, it should be discontinued at least 2 to 4 weeks before and during the series of chemical peels.

Grimes (database, Vitiligo and Pigmentation Institute) assessed the efficacy of serial glycolic acid peels in 40 dark-skinned patients using the aforementioned protocol. Thirty were African-American and 10 were Hispanic. Conditions treated included acne, melasma, and postinflammatory hyperpigmentation (Figs. 11.1–11.3, see color insert). Significant improvement occurred in 15 (34%), moderate improvement in 18 (45%), and mild improvement in 7 (18%). Transient hyperpigmentation occurred in 8%. None of our patients experienced persistent hyperpigmentation. None had scarring. Of the patients treated, maximal improvement occurred in the patients with dyschromias.

Glycolic acid peels are well tolerated in darker racial–ethnic groups. Side effects are substantially minimized when con-

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centrations are gradually titrated from the 20–30–35%, 50%, and finally to the full-strength 70% peel. When compared with other superficial peeling agents such as salicylic acid, glycolic acid peels are advantageous for darker-skinned individuals with dry-sensitive skin. Disadvantages include hyperpigmentation and scarring. However, such side effects are uncommon if the patient is appropriately titrated and treated concomitantly with bleaching agents.

Grimes (database, Vitiligo and Pigmentation Institute) assessed the histological alterations induced by 70% glycolic acid peels in patients with skin types IV, V, and VI. Peels were applied to the back and preauricular facial areas of 17 subjects. Biopsies were performed at 24 hours. Glycolic acid induced the stratum corneum necrosis. Other epidermal and dermal changes were minimal at 24 h.

IV. SUMMARY

Cosmetic procedures including chemical peels have become increasingly popular among blacks. These individuals often are skin types IV through VI. Serial superficial glycolic acid peels offer substantial benefits for postinflammatory hyperpigmentation, melasma, acne, oily skin, and texturally rough skin. Glycolic acid peels are indeed generally safe and efficacious for black skin when concentrations are appropriately titrated. However, in light of the labile responses of melanocytes of darker-complexioned individuals, the clinician must always weight the indication/necessity and benefit/risk ratio of the chemical peeling agent. These procedures should be performed with care and caution.

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12

Comparing AHA Products

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The topical glycolic acid products available fall into two general categories: those formulated and supplied only to physicians offices and those on the general market supplied to drug stores and department stores.

Table 1 lists the cosmetic topicals formulated for physicians. The active ingredient in these products is the *free acid* in the righthand column. Although most physicians are accustomed to looking at percentage as a measure of the strength of the product, it is really the biologically available free acid that determines the strength. This can vary, depending on the pH according to the equation seen in Fig. 1 [1]. The Physician's Choice products have a combination of lactic and citric acid. This author could not find anyone at this company that could

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Table 1 Cosmetic Topicals Formulated for Physicians

Company name	Product name	Lactic and citric	Lactic	Salicylic	Glycolic	pH	Free
Procter & Gamble	Oil Olay Daily Renewal Cream			1.50%		2.8	
Derm Cosmet Labs	AHA Lightening gel				10%	3.6–4.0	6.3
	AHA Oily & Acne Solution 8				8%	3.7–4.2 4.0	3.2
	AHA Revitalizing Cleanser 4				4%	4.0–4.4	1.6
	AHA Revitalizing Cream 15				15%	3.7–4.0 3.8	7.8
	AHA Revitalizing Cream 8				8%	3.7–3.9 3.8	4.2
	AHA Revitalizing Cream HP 20				20%	3.7–3.9 3.8	10.4
	AHA Revitalizing Eye Cream					4.1–4.5	
	AHA Revitalizing Gel 20				20%	3.8–4.2	10.4
	AHA Revitalizing Gel 15				15%	3.8–4.2 4.0	6
	AHA Revitalizing Lotion 10				10%	3.7–3.9 3.8	5.2
	AHA Revitalizing Lotion 15				15%	3.7–4.0 3.8	7.8
	AHA Revitalizing Lotion HP 20				20%	3.7–3.9 3.8	10.4
	AHA Shampoo 3				3%	4.0–4.4	1.2
	20% Glycolic Acid Pads				20%	2.3–3.0 2.5	19.2
Allergan	MD Forte						
	Facial Lotion I				15% (.6)	3.8	4.7
	Facial Lotion II				20% (.6)	3.8	6.2
	Facial Cream I				15% (.6)	3.8	4.7
	Facial Cream II				20% (.6)	3.8	6.2
	Glycare I				15% (.6)	4.4	1.9
	Glycare II				20% (.6)	4.4	2.5
	Glycare Perfection Gel			1%	5% (.6)	4.4	1
	Facial Cleanser				15% (.6)	3.8	4.7
	Glycare Cleansing Gel				15% (.6)	3.8	4.7
	Bleaching Gel				10% (.6)	4.4	1.3
	Hand & Body Cream				20% (.6)	12	

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Herald Pharmacal	Aqua Glycolic					
	Facial Cleanser			12%	4.4	2.52
	Face Cream			10%	4.4	2.1
	Hand & Body Lotion			14%	4.4	2.9
	Shampoo & Body Cleanser			14%	4.4	2.9
	Astringent			11%	4.5 4.4	2.31
Collagen Aesthetics	Refinity					
	Lotion		15%		3.2	12.3
	Hydrogel		15%		3.2	12.3
	Cream		15%		3.2	12.3
	Cleanser				3.2	12.3
	Toner				3.2	12.3
	Strontium Nitrate Ointment		70%		4	29.4
Neutrogena	Healthy Skin Face Lotion			8%	3–4 buff 3.6	5.4
	Healthy Skin Face Lotion			4%		
Physicians Choice	Facial Wash	5%			6	<1
	Facial Wash for Oily/Problem	7%			5	1
	Balancing Toner	10%			4.5	
	Balancing Toner for Oily/Problem	10%			4.5	
	The Peel	15%			5	1
	Gentle Exfoliant	4%			6	<1
	Collagen Hydrator	5%			6	<1
	Hydrator Plus	5%			6	<1
	Protecting Hydrator	5%			6	<1
	Eye Wrinkle Cream	5%			6	<1
	ReBalance	2%			7	<1
	Clearskin	5%			6	<1

(Continued)

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Table 1 Cosmetic Topicals Formulated for Physicians (Continued)

Company name	Product name	Lactic and citric	Lactic	Salicylic	Glycolic	pH	Free
NeoStrata	15 Face Cream				15%	3.6	9.4
	15 Body & Face Lotion				15%	3.6	9.4
	15 Enhanced Gel				15%	4	6
	15 Foot Gel				15%	4	6
	Solution for Olly & Acne Prone Skin				8%	4	3.2
	Gel for Age Spots & Skin Lightening				10%	4	4
	Skin Smoothing Lotion				10%	3.8	5.2
	Skin Smoothing Cream				8%	3.5	5.5
	Daytime Skin Smoothing Cream				8%	3.7	4.4
ICN	Gly Derm						
	Cream				5%	1.5–2.0	4.9
	Cream Plus				10%	1.4–1.8	10
	Cream Plus			12%		1.4–1.8	
	Lotion				5%	1.6–2.2 2.0	4.9
	Lotion Plus				10%	1.4–1.8	10
	Lotion Plus			12%		1.4–1.8	
	Lotion Lite				5%	1.7–2.3 2.0	4.9
	Lotion Lite Plus				10%	1.4–2.0	9.9
	Lotion Lite Plus			12%		1.4–1.8	
	Solution				5%	2.3–2.9 2.5	4.8
	Solution Plus				10%	1.9–2.5	9.6
	Solution Plus			12%		1.7–2.3	

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Fig. 1 Formula to determine biologically free acid.

break down the percentage between these two acids or provide a bioavailability chart for citric acid. One can surmise that if the pKa of lactic acid is 3.86 and the pKa of citric acid is 3.13, these products that have a pH ranging from 4.5 to 6 have very little free acid in them. The numbers in the table are based on the total percentage consisting of lactic acid.

The MD Forte line (Allergan) is prepared using "Herald Glycolic compound," which is a complex pH-balanced mixture of glycolic acid, ammonium glycolate, purified water, and higher molecular weight oligomers of glycolic acid with an activity level of approximately 60%. Because of this, it is necessary to multiply the percentage listed for each product by .6 to get the true percentage of glycolic acid before using that number to solve the equation for the free acid in the product [4].

Obtaining detailed information on products on the general market is difficult. Most of the companies are unwilling to give out any information on the ingredients in their products. They consider all of this information "trade secrets" and would not discuss their products even in broad terms. The only company that would send any information on their product was Procter & Gamble. They sent all their material safety data sheets and explained that they have removed all AHAs from their products and only have beta hydroxy acids. Estee Lauder and its subsidiary company Clinique have no AHAs in their products. They use patented poly hydroxy acids that decrease dermal penetration and irritation [2]. Revlon and its subsidiary Almay have no AHAs but have "ingredients with similar function" according to the companies. The same is true of Chanel and Lancome. According to Dr. Draelos, the

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cosmetic companies have developed exfoliants that improve skin smoothness and tone without glycolic acid. There is a trend toward higher molecular weight hydroxy acids that cause epidermal exfoliation and minimize dermal effects. Dr. Van Scott maintains that increasing the length of the carbon chain decreases the efficacy of these products [3].

NeoStrata (Princeton, NJ) now offers a line of skin care products with gluconolactone a poly hydroxy alpha hydroxy acid (PHA). The multiple hydrophilic hydroxyl groups bind water, creating a large molecule with the acid component masked causing slower penetration and less irritation. Berardesca et al compared glycolic acid, lactic acid, tartaric acid (TA), and gluconolactone (GLU) in their effects on skin barrier function and irritation response to sodium lauryl sulfate [5]. They found that the PHAs (TA and GLU) had a more pronounced effect in enhancing skin barrier function to prevent skin irritation. Green et al also looked at the use of GLU for photoaging and found a greater than 30% reduction in fine lines and wrinkles over 12-week use and a low level of irritation [6].

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13

8% Glycolic and 8% Lactic Acid

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I. INTRODUCTION

There are currently hundreds of over-the-counter skin care products that contain glycolic acid and lactic acid in concentrations of 8%. Claims made by cosmetic and pharmaceutical companies include reduction of fine lines and wrinkles, skin moisturization, improvement of skin firmness, and generally diminishing the visible signs of aging. The *Wall Street Journal* reported that sales of two glycolic acid products approached $300 million in 1994 [1]. In addition, alpha hydroxy acids (AHAs) have contributed to the 10% annual growth in recent years of the hand and body skin care market, with sales in 1994 reaching $5.4 billion [2]. One naturally must

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question whether this billion dollar industry is based on scientific evidence or driven by clever marketing.

Research has continued over the last two decades to build on the original work of Eugene Van Scott and Ruey Yu in the 1970s. Low-dose AHAs have been studied to ascertain clinical effects of these molecules, and studies have begun to attempt to explain their mechanism of action. The question arises, however, are AHAs cosmetics or drugs?

A drug is defined as a substance that alters structure or function of the body or prevents or treats disease [2]. A product that alters skin tissues that are not alive such as the stratum corneum and terminal hair follicle is classified as a cosmetic. Over the last few years the term "cosmeceutical" has surfaced to describe products such as AHAs that supposedly have a cosmetic and pharmaceutical effect. This term has been largely abandoned by the medical community, because it is vague and clouds the line between a drug and a cosmetic. The Cosmetic, Toiletry, and Fragrance Association (CTFA), on behalf of the cosmetics industry, states that current glycolic acid and lactic acid products are cosmetics [2]. The Food and Drug Administration (FDA) has concerns that the AHAs may be functioning as drugs, but has yet to classify AHAs and antagonize the CTFA. Currently, to the best of our knowledge, the only prescription AHA product is 12% lactic acid and ammonium lactate (Lac-Hydrin).

The Cosmetic Ingredient Review (CIR), a committee of the CTFA, recommended in 1996 that glycolic acid and lactic acid in cosmetic products not exceed concentrations of 10% and have a pH less than 3.5 [3]. The difficulty is that few cosmetic companies reveal concentration and pH (Table 1). Pharmaceutical companies that market low-dose AHAs tend to be more forthright with concentration, pH, and vehicle (Table 1). Although it is difficult to be exact, glycolic acid and lactic acid cosmetics currently contain concentrations ranging from 4–20% and have pH ranging from 1.4–8. One can then understand the difficulty for the consumer to ascertain first, what

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Table 1

Product name	Acid & % (if available)	pH	Size (oz)	Retail price	Product claims
Avon All-in-One Perfecting Complex SPF 15	"Alpha-hydroxy acid"	N/A	1.7	$16.00	"Look of fine lines and wrinkles visibly reduced"
Alpha-hydrox AHA Facial Treatment	8% of 70% glycolic acid solution	N/A	2	$8.99	
Aqua Glycolic Face Cream (Herald Pharmacal)	10% glycolic acid	4.4	2	$12.09	"Removes the dead skin cells from rough, dry, sun-damaged skin"
Elta AHA 10	10% of 70% glycolic acid solution	3.4	2	$13.90	"Can help deep-clean stubborn clogged pores and remove blemishes"
Estee Lauder Fruition Extra	"Four interactive acids"	N/A	1.7	$70.00	"55% improvement in the evenness of skin color"
ICN Cream Plus	10% glycolic acid	1.4–1.8	1	$21.00	
Mary Kay Skin Revival Cream	"Alpha and beta hydroxy"	N/A	1.5	$25.00	"38% reduction in surface fine lines"
MD Formulations Facial Cream	14% glycolic acid	3.8	2	$60.00	
Neutrogena Healthy Skin Facial Lotion	8% glycolic acid	3.6	4	$10.69	"Improves the texture and appearance of the skin"
Ponds Age Defying Complex	"Alpha hydroxys"	N/A	2	$9.89	

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product they are buying and, more importantly, whether the companies' claims are based on sound clinical studies.

II. OVERVIEW OF AHAS

The efficacy of AHAs has been studied in many disorders. Van Scott and Yu first showed that low-dose AHA (glycolic acid 5%) was effective for ichthyosiform dermatoses with their pioneering studies in the early 70s. They found that AHAs and related compounds influenced keratinization, but were only able to speculate as to how this occurred [4–6]. Dahl, Rogers, and Buxman illustrated that 12% lactate lotion was effective in treating xerosis and ichthyosis, respectively [7–9]. Twelve percent ammonium lactate was shown to be useful in counteracting the atrophic effects of clobetasol propionate by Lavker [10]. In addition, Smith showed that treatment with 12% lactic acid resulted in increased epidermal and dermal firmness and thickness with clinical improvement of skin smoothness and appearance of fine lines and wrinkles [11]. In the last decade numerous articles have addressed the clinical efficacy of low-dose AHAs; however, few are controlled studies. The handful of controlled studies, including Stiller and Drake who studied in vivo effects of 8% glycolic and lactic acid and Kim et al who revealed enhanced collagen synthesis in vivo and illustrated the dermal proliferative effect of glycolic acid 10% [12,13]. These studies have given us insight into the effects of AHAs at different concentrations and pH including histological correlations.

The clinical effects often assessed in AHA studies are intimately involved in the process of skin aging. Aging is a dynamic process that is divided into intrinsic and extrinsic components [12,14]. Intrinsic aging is a genetically determined deterioration in skin function and capacity. Signs of intrinsic aging are loss of elasticity, atrophy, and deepening of the expression lines. Histological correlates include epidermal atro-

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phy and flattening of the rete ridges. Photoaging or extrinsic aging-induced changes include wrinkling, tactile roughness, diffuse sallowness, mottled hyperpigmentation, laxity, and telangiecstasia [7,14–19]. The histological correlates include epidermal atrophy with atypia of keratinocytes and loss of keratinocyte polarity, increased melanocytic activity, dermal elastosis, and loss of collagen, and an increase in synthesis of glycosoaminoglycans [7,14–19].

Van Scott and Yu illustrated impressive changes in the stratum corneum in patients with lamellar ichythosis treated with glycolic acid and lactic acid ranging in concentrations from 5–12% [4–6]. The patients had an abrupt loss in abnormal stratum corneum. They found that AHAs altered corneocyte cohesion in skin disorders that displayed hyperkeratinization resulting in a decrease in abnormal stratum corneum and an increase in the thickness of viable epidermis [4–6]. Hyperkeratinzation can be due to two distinct processes. First, as in some of the ichthyoses and psoriasis, there can be an increased rate of keratinocyte production. More commonly, however, hyperkeratinzation is secondary to decreased rates of desquamation [20]. Application of daily low-dose AHAs results in diminished intercellular bonding because of alteration in ionic bonding at the lower levels of the stratum corneum, hence a thinner stratum corneum [6]. In addition, a thinner stratum corneum bends more readily without a propensity to crack or fissure [6]. AHAs have also been shown to alter enzymatic function of the stratum corneum. Diminished cohesive forces have resulted from AHA's inhibitive action on sulfate transferase, phosphotransferase, and kinases, resulting in less electronegative sulfate and phosphate groups on the outer surface of cells in the lower stratum corneum [6,21].

Lavker and colleagues reported that 12% lactic acid–ammonium lactate lotion caused a modest increase in epidermal thickness and increased amounts of glycosoaminoglycans in the dermis [10]. There was some speculation before this study

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and others that followed that increased skin thickness was the result of edema, but histological studies of low-dose AHA-treated skin have showed little to no inflammation present [10,16,22]. These data were confirmed by further studies that showed similar increases in epidermal thickness without inducing an inflammatory response [17,23].

Ditre has extensively studied the histological effects of AHAs, however, using 25% glycolic and lactic acid. Although this is a much higher dose than 8% AHA, her data may be important in understanding the ultrastructural effects of low-dose AHA. Her data revealed a statistically significant reduction in basal cell atypia, dispersal of melanin pigmentation, and more orderly rete pattern in skin treated with 25% glycolic and lactic acid versus controls [16]. In addition, her study showed ultrastructural correlates, including more uniform basal keratinocyte nuclei, less clumping of tonofilaments, more perinuclear localization of tonofilaments, and the formation of microvilli when compared with vehicle control [16].

Kim and colleagues in 1998 studied 10% glycolic acid (pH 3.9) and lactic acid (pH 6.0), respectively, in vivo and in vitro to assess their effects on collagen synthesis [13]. They hypothesized that there is a functional activation of fibroblasts and that increased dermal thickness with production of collagen, improved quality of elastic fibers, and increased acid mucopolysaccharides was not simply the result of an inflammatory response. After 14 days of application to hairless mice, they performed punch biopsies. Masson-trichrome staining revealed increased collagen production in glycolic acid– and lactic acid–treated mice with a more remarkable effect in mice treated with glycolic acid. In addition, they revealed increased collagen mRNA expression, however, admitted the proliferative effect of the AHAs needs further biochemical study to ascertain the mediators that resulted in fibroblast stimulation. Finally, the differences in pH between glycolic and lactic acid made head-to-head comparison difficult in this study. Moy had earlier studied the effect of glycolic acid on

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collagen production in human fibroblast cultures in vitro and showed similarly increased collagen production [23].

III. 8% GLYCOLIC AND 8% LACTIC ACID

As mentioned earlier in the chapter, there are few double-blind controlled studies of 8% glycolic and lactic acid. Stiller and Drake first studied the effects of 8% glycolic acid and 8% lactic acid in patients with photodamage (extrinsic skin aging) [12]. They assessed seven clinical signs of photodamage, including mottled hyperpigmentation, fine wrinkling, coarse wrinkling, laxity, sallowness, telangiecstasia, and tactile roughness. The subjects were given the same soap and sunscreen and screened so they had not received topical retinoids or AHAs in the prior 6 months. They were treated on the face and dorsal aspects of the forearms with either 8% glycolic acid (2-hydroxyethanoic acid), 8% 1-lactic acid (S-2-hydroxypropionic), or an oil-in-water emulsion vehicle for a period of 22 weeks. The study revealed that both glycolic acid and lactic acid improved signs of photodamaged skin more than emollients and sunscreen alone. Mottled hyperpigmentation was the most improved of the clinical signs on skin treated with 8% glycolic and lactic acid.

Dinardo et al found similar results when they reported 8% glycolic acid lessened skin roughness when treating the legs of subjects with xerosis or ichthyosis [22]. The histological evaluation of the subjects confirmed previous studies of higher dose glycolic acid exhibiting thinning of the stratum corneum, thickening of viable epidermis, increased glycosaminoglycans in the dermis, and increased dermal collagen deposition [22].

There have been concerns that AHAs may alter skin barrier function, resulting in susceptibility to insults including UV irradiation. Retinoids have been studied extensively in relation to barrier function. Retinoic acid thins the stratum

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corneum similar to low-dose AHAs [14,17,24–25]. In addition, retinoic acid results in altered barrier function, which can induce epidermal hyperplasia and dermal inflammation [26,27]. Do AHAs, having similar clinical effects to tretinoin, cause alterations is barrier function?

Several studies have addressed AHAs and barrier function. Berardesca et al treated the volar arm and forearm with an 8% concentration of glycolic acid and lactic acid for a period of 4 weeks [28]. The sites were then challenged with 5% sodium lauryl sulfate (SLS) at the end of 4 weeks. Erythema was reduced in sites treated with AHAs compared with vehicle controls [28]. Also, transepidermal water loss (TEWL) was followed at baseline, weeks 1, 2, 3, and 4, and before and after irritation with SLS. TEWL is known to be a measurable marker of skin barrier function. TEWL was significantly lower in skin treated with 8% glycolic and lactic acid compared with untreated and vehicle-controlled sites [28]. These data were consistent with data reported by Leyden [29]. Researchers are attempting to explain the mechanisms of improved barrier function of skin treated with low-dose AHAs. Increased ceramide production may be important in improvement of the barrier function in skin treated with lose-dose AHA [28]. Other possibilities include the alteration in cytokine release after irritant challenge or increased strength of cohesiveness at the basal and spinous layer of the epidermis induced by AHAs [28].

Although decreased irritation has been reported with 8% glycolic acid and lactic acid with SLS challenge, others have concerns that AHAs may cause irritation. It is believed that irritation is largely due to the pH of the formulation and the amount of free acid that is delivered [30,31]. The pH of low-dose glycolic and lactic acid products is not usually readily available to the consumer; however, it seems to play a significant role in efficacy the more we understand about AHAs. There have been no large, well-controlled double-blind studies of 8% glycolic and lactic acid at different pH levels. However, in a small study, Dinardo showed that increasing the pH

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of 8% glycolic acid resulted in trends toward increasing the efficacy in relation to reducing skin roughness, increasing thickness of viable epidermis, and collagen deposition [22]. Clearly, further studies are needed on the complex interaction between pH and free acid with end points assessing clinical signs of photodamage.

The thinning of the stratum corneum may make one speculate that 8% glycolic acid and lactic acid could result in the epidermis being more vulnerable to UV irradiation. In unpublished data from the FDA there are reports that skin treated with low-dose AHAs had an increased incidence of apoptotic keratinocytes, and questions arose as to whether these "sunburn cells" were due to a more susceptible epidermis (personal communication, John Bailey, FDA). However, published data have shown that 8% glycolic and lactic acid are actually photoprotective [29–32]. Perricone's data revealed that in skin pretreated for 3 weeks before UVB exposure there was a sun protection factor (SPF) of 2.4 elicited by the AHA application. In addition, Perricone showed that skin treated after a erythemogenic dose of UVB had a small reduction in irritation.

Erythema after UV irradiation is a seqeulae of the arachidonic acid cascade, which results in generation of free radicals. Glycolic acid may attack these free radicals by acting as an antioxidant. Perricone speculates that glycolic acid acts as a antioxidant by two possible mechanisms. First, glycolic acid has a structure similar to ascorbic acid. Ascorbic acid is thought to act as an antioxidant by its enediol structure [33]. The double bond of the carboxylic group in glycolic acid may resonate between the two carbons, producing a transient enediol structure [32]. Second, glycolic acid is known to chelate metals [32]. Glycolic acid may chelate the pr-oxidant, ferrous iron, resulting in decreased free radical production [32]. Despite Perricone and Leyden's fascinating research, this is an area that clearly needs further studies and histological correlations as well, especially to address the possible induction of apoptotic keratinocytes by AHAs.

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IV. CONCLUSION

Topical tretinoin has been studied more extensively than low-dose AHAs. Topical tretinoin is known to clinically reduce fine wrinkling, mottled hyperpigmentation, roughness, and laxity [24]. Histologically, tretinoin has been shown to increase epidermal thickness, increase granular layer thickness, decrease melanin content, and enhance stratum corneum compaction [17]. Also, studies are underway to explain tretinoin's possible inhibition of nonmelanoma skin cancer. Despite the similar effects clinically and histologically, there have been no studies comparing topical tretinoin with, or used in conjunction with, 8% glycolic acid. It would be interesting to compare tretinoin to AHAs, because they have comparable clinical effects.

Beta hydroxy acids, such as salicylic acid, despite being around for decades, have been more aggressively marketed the last 5 years. However, no studies known to the authors have compared them with AHAs, despite similar claims in regard to efficacy made by cosmetic and pharmaceutical companies.

The cost of cosmetic glycolic and lactic acid preparations ranges from less than $10 to up to $100 [34]. Unfortunately, promotion of products has relied on marketing and advertising more than well-controlled studies. With vague labeling that largely lacks inclusion of pH or concentration, the consumer is forced to depend on advertising and marketing when buying a product from a cosmetic company. In addition, many cosmetic companies simply cite that their product includes "alpha-hydroxy acid," failing to clarify the specific fruit acid. In 1999, the authors compared the preparations of low-dose glycolic acid and lactic acid offered at two large department stores, a drug store, and several pharmaceutical companies, including cost, pH, concentration, base, and scientific claims when available on packaging or supplied literature that was readily available to the consumer (Table 1). One can see that the clinical claims made are based on a paucity of scientific evidence for this billion dollar business.

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It is clear that all AHAs are not created equal. Many variables exist, such as pH, concentration of free acid, type of acid, and vehicle. Also, the questions remain as to how these variables affect efficacy, skin irriation, and photoprotection. On the other hand, it is clear that daily use of 8% glycolic acid and 8% lactic acid can produce clinical effects improving the signs of photoaging, including reduction of fine lines and skin roughness, improved sallowness, and lightening of mottled hyperpigmentation. In addition, histological studies have been done to ultrastructurally support these clinical findings. In conclusion, it should be stressed that although daily application of 8% glycolic and lactic acid can produce modest benefits on photodamaged skin, they are only part of a complete skin care armentarium. Photodamaged skin can be treated with many modailities, but photoprotection should remain the cornerstone of any treatment plan.

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14

Formulating and Marketing AHA Products for the Global Market

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I. INTRODUCTION

The market for alpha hydroxy acid (AHA) skin care products has grown with unprecedented momentum during the decade of the 1990s [1] (See list *AHA growth statistics* following). And with good reason—the AHAs have repeatedly been shown to provide significant benefits to a variety of skin disorders that require both therapeutic and cosmetic treatments [2–6]. Their benefits are easily perceived by consumers and patients, producing a strong purchase incentive, especially by those with hyperkeratotic disorders such as ichthyosis [7,8]. By removing embarrassing and often disfiguring scales, and softening rough, hardened skin, the AHAs have become one of the primary agents to cosmetically improve ichthyotic skin condi-

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tions. Furthermore, the benefits of AHAs extend into the seemingly limitless, yet highly competitive, "antiaging" skin care market as a result of their ability to minimize, and even reverse, the visual signs of photoaging [2–6].

AHA Growth Statistics

- AHAs can be credited with reviving the fortunes of the stagnant cosmetic industry—*Wall Street Journal.*
- In 1990, five AHA products were on the market. In 1992, 11 new products were introduced. In 1993, more than 50 products were introduced, and in 1994 more than 200 new AHA-containing products were launched into the skin care market.
- By 1994, nearly every known brand contained at least one AHA-containing skin care product.
- Today, AHAs continue to be the most widely used antiaging benefit ingredient. (From Ref. 1.)

The AHAs have numerous cosmetic and therapeutic adjunctive uses. These uses are based on their multiple effects as (1) stratum corneum exfoliants by means of their specific effect on the desmosomes of the stratum compactum, (2) normalizers of the epidermal cell turnover cycle, and (3) promoters of normal cellular structure in the dermis [9–12]. As a result of their multifunctionality and ability to address a broad range of skin care needs, products containing AHAs are marketed in every major channel of distribution, including the mass (Ponds®, Lubriderm®) and prestige (Exuviance®, Elizabeth Arden®) consumer markets primarily for antiaging and moisturization effects, direct to consumer (Avon's Anew®), the unique market of direct-dispensing by physicians for adjuvant therapeutic and skin rejuvenation benefits (NeoStrata®, MD Forte®), and by prescription (Lac-Hydrin®) for therapeutic moisturization of severely dry skin. Some companies have successfully marketed AHAs using infomercials to promote antiaging claims and correction of mild to moderate acne. In

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recent years, products containing poly hydroxy acids (PHAs) and beta hydroxy acids (BHAs) have been introduced into the cosmetic skin care market.

The consumer's decision to purchase AHA "treatment" cosmetics is determined by a host of factors, including professional or peer recommendation, company/product image, advertising and benefit claims, and product formulation and packaging. All of these factors and more must be considered when developing a new line of skin care products.

II. FORMULATING AHA SKIN CARE PRODUCTS FOR A GLOBAL MARKET

A. Who is the Consumer? What is the Need?

The first objective in creating a new line of skin care products is to define the desired characteristics, intended uses, and anticipated clinical benefits of the products, (Fig. 1). To complete this exercise, the consumers and their needs must be identified and fully understood. This information can be gathered using consumer research techniques designed specifically to meet the objectives of the project (see *Define the Target Consumer and Market* list following). In addition to determining the geographical location of the marketplace and consumer, the channel of distribution must be considered before formulating. What are the economic conditions and dynamics in the target market? Can prestige products be afforded, or is a mass market line more likely to be successful? Should the products be oriented toward one gender or unisex? What is the age range of the intended user and what are the skin care deficiencies that need to be addressed? Cultural factors often provide information to guide product development. For example, many women of Asian descent are highly discomforted by the appearance of dyspigmented skin and are continually seeking effective treatments to even skin tone. Are visual signs of aging a representation of respectable maturity and knowledge, or are they viewed negatively, thereby creating an opportunity

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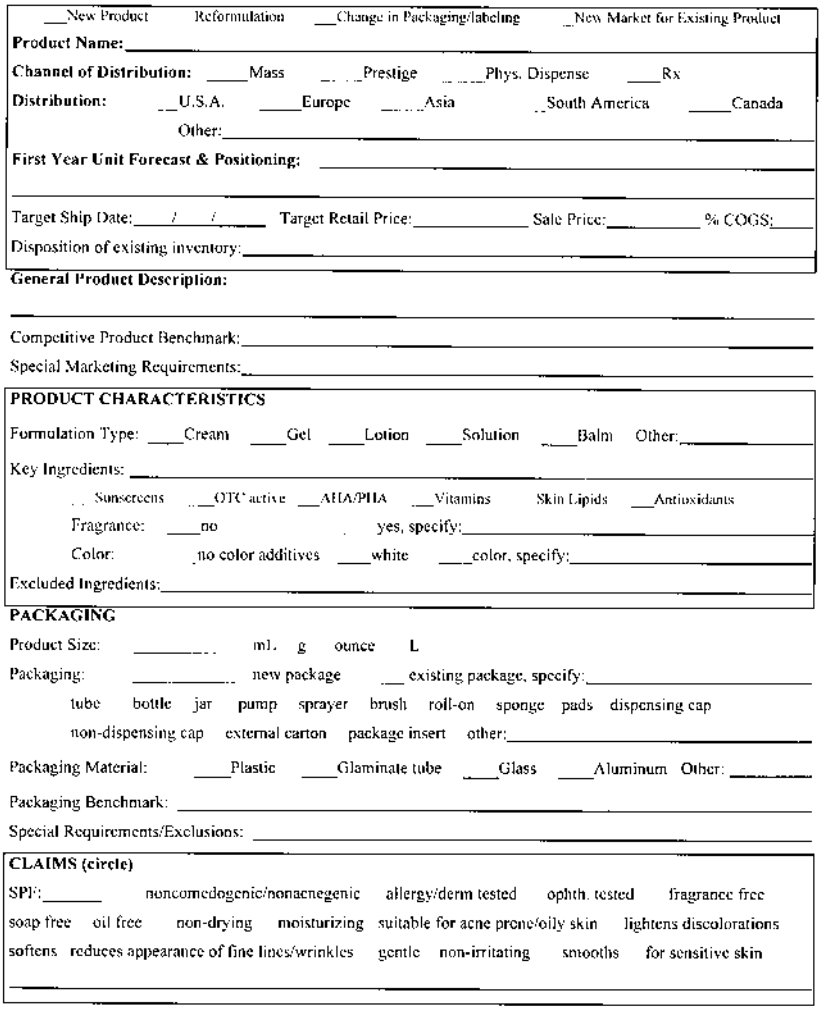

___New Product Reformulation ___Change in Packaging/labeling ___New Market for Existing Product

Product Name:_____

Channel of Distribution: _____Mass _____Prestige _____Phys. Dispense ____Rx

Distribution: __U.S.A. _____Europe _____Asia __South America _____Canada

Other:_____

First Year Unit Forecast & Positioning: _____

Target Ship Date:____/____/_____ Target Retail Price:_____ Sale Price:_____ % COGS:____

Disposition of existing inventory:_____

General Product Description:

Competitive Product Benchmark:_____

Special Marketing Requirements:_____

PRODUCT CHARACTERISTICS

Formulation Type: ____Cream ____Gel ____Lotion ____Solution ____Balm Other:_____

Key Ingredients: _____

__ Sunscreens ___OTC active ___AHA/PHA ___Vitamins Skin Lipids ___Antioxidants

Fragrance: ____no yes, specify:_____

Color: ___no color additives ____white ____color, specify:_____

Excluded Ingredients:_____

PACKAGING

Product Size: _____ mL g ounce L

Packaging: _____ new package ___ existing package, specify:_____

tube bottle jar pump sprayer brush roll-on sponge pads dispensing cap

non-dispensing cap external carton package insert other:_____

Packaging Material: ____Plastic ____Glaminate tube ____Glass ____Aluminum Other: _____

Packaging Benchmark: _____

Special Requirements/Exclusions: _____

CLAIMS (circle)

SPF:_____ noncomedogenic/nonacnegenic allergy/derm tested ophth. tested fragrance free

soap free oil free non-drying moisturizing suitable for acne prone/oily skin lightens discolorations

softens reduces appearance of fine lines/wrinkles gentle non-irritating smooths for sensitive skin

Fig. 1 Product development form.

for skin rejuvenation techniques? Native environmental conditions also affect product development, particularly regarding formulation type. Is the market a hot, humid climate that is more appropriate for light lotions and gels than heavy creams? What are the specific skin care needs caused by the local environment—sunscreens, moisturizers, oil absorbers, heavy emollients? All of these elements should be considered in defining the target consumers and their needs.

Define the Target Consumer and Market

- Age range
- Ethnicity
- Skin care needs
- Economic status
- Regulatory climate
- Gender
- Culture
- Available channels of distribution
- Level of disposable income
- Importation requirements

B. Ingredient Selection

After establishing the consumer needs and defining the basic characteristics of the product line, the formulation chemist endeavors to formulate products that meet the objectives set forth by marketing. The first and most important step in this process is identifying functional ingredients to support product claims that stay within the budgeted cost of goods and are approved for use in the target markets.

1. AHAs as "Active" Ingredients

Cosmetic formulations do not contain *active drug* ingredients, but in many cases they do contain *active cosmetic* ingredients. The difference is that drug ingredients and accompanying claims are regulated in the United States by the Food and

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Drug Administration (FDA) and by other regulatory authorities outside of the United States because of their ability to alter the structure or function of skin. These products, their claims, safety records, and manufacturing standards are all closely monitored. Cosmetic active ingredients are not regulated as drugs, because they do not alter skin structure and function. Cosmetic products are nonetheless required to undergo adequate testing to support safety and benefit claims [13].

The hydroxy acids (AHAs, PHAs, etc.) are classified as cosmetic ingredients when used at lower strengths, typically up to 10%, as long as claims are made using cosmetic verbiage. The AHAs provide consumer perceivable and clinically measurable benefits to skin, including pigmentation evening, reduced roughness, moisturization, and reduced appearance of fine lines and wrinkles [4,5,14], Alpha hydroxy acid products are also used by physicians therapeutically to enhance the efficacy of drug and/or procedural (i.e., laser microdermabrasion) regimens for acne [15], photoaging [16], and ichthyosis among others. In addition, AHAs are often included in consumer antiaging, skin smoothing, and moisturizing products, even at low levels, because these ingredients provide wide consumer recognition and a strong incentive to purchase.

Numerous AHAs can be selected for use in cosmetic formulations. As is appropriate for any technology, all patent rights must be fully investigated before ingredients and/or claims relating to the use of the ingredients or technology can be marketed. Because the uses of AHAs are heavily patented, utilization of AHA technology with respect to specific product claims may require a license.

The most widely used AHA in cosmetic formulations is glycolic acid. Because of its small molecular size, and therefore enhanced skin penetration, and its versatility in base vehicles, glycolic acid is used in antiaging formulations, acne preparations, moisturizers, and skin lighteners. Although glycolic acid provides significant skin benefits, other AHAs may be more appropriate depending on the needs of the consumer (Table 1). For example, a lipophilic AHA may be more

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Table 1 AHA Ingredient Profile

Name	Class	pKa	Solubility profile	Clinical features
Glycolic acid	Alpha hydroxy acid	3.83	Hydrophilic	Antiaging, enhancement of cell turnover, exfoliation, and moisturization
Lactic acid	Alpha hydroxy acid	3.86	Hydrophilic	Antiaging, enhancement of cell turnover, exfoliation, and moisturization
Citric acid	Alpha and beta hydroxy acid	3.13	Hydrophilic	Antioxidant, antiaging
Gluconolactone (gluconic acid)	Poly hydroxy AHA (PHA)	3.86	Hydrophilic	Antiaging, moisturizing, exfoliant, antioxidant, nonirritating, no stinging or burning
Benzilic acid	Aralkyl AHA	3.09	Increased lipophilicity over traditional AHAs	AHA benefits in oily regions of skin (pores, etc.)
Mandelic acid	Aralkyl AHA	3.41	Increased lipophilicity over traditional AHAs	AHA benefits in oily regions of skin (pores, etc.)

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suitable for use in acne and oily skin preparations if penetration into the sebum-rich follicle is desired. The neutralized form of lactic acid, ammonium lactate, is the active drug ingredient in the prescription product Lac-Hydrin®, which is a highly successful, therapeutically positioned moisturizer. Lactic acid is also used in cosmetic formulations and probably does not provide any significant advantages over glycolic acid, because it is only one carbon unit larger in size than glycolic acid and possesses nearly the same level of acidity (i.e. pK_a).

Skin sensitivity in the target population must be considered during product development, particularly with regard to the AHAs. Because up to 70% of women report having sensitive skin, stinging and burning sensations from traditional AHAs must be addressed. Fortunately, there are formulation approaches to minimize irritation and sensory responses through careful ingredient selection, controlled delivery to the skin surface, and by understanding the interaction of the key ingredients in the formulations. Use of lower AHA concentrations and raising the pH to minimize the concentration of free acid are the most common answers to targeting the sensitive skin population, although this approach may compromise product efficacy. While antiaging claims are often made with these products, there may be reduced effectiveness compared with the corresponding full-strength formulation. Alternatively, the selection of a PHA, such as gluconolactone, can provide reduced levels of stinging and burning even at high concentrations, along with antioxidant and skin barrier–conditioning benefits [17–19]. The mode of neutralization may also contribute to the irritation potential of the product. Because product pH plays an important role in balancing safety with efficacy, most home-use AHA formulations are partially neutralized; pH adjustment with an alkali is reportedly more irritating than the use of amphoteric neutralizing agents [17,20,21].

Successful selection of the AHA ingredient requires careful planning. First, AHA ingredients should be chosen to satisfy product claims of efficacy and to meet the needs of the tar-

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get consumer. In choosing the most appropriate AHA ingredient, a variety of physical and chemical parameters should be considered, including, solubility, pK_a, stinging/burning potential, and available safety and efficacy data. In some cases, the *best* AHA for a product may be a *blend* of several AHAs and PHAs, each providing a benefit to the product formulation. Ingredient selection must also involve a review by regulatory personnel to ensure the use of commercially salable ingredients. Regulatory limitations controlling ingredient use often vary from country to country. These may include an ingredient ban (negative lists) or a restriction in use such as a requirement to adhere to maximum concentration limits, use required directions and warnings on labeling, conduct mandatory premarketing clinical studies, and register with governmental health ministries.

2. Vehicle Components

After the *cosmetic actives* have been determined, vehicle components are carefully selected. The formulation vehicle plays an important role in developing efficacious AHA products. A well-performing vehicle can enhance AHA penetration and minimize sensory irritation, whereas a poorly designed vehicle can contribute to irritation or inhibit AHA penetration and diminish topical efficacy. Alpha hydroxy acid products that are used by consumers in an unsupervised environment must be safe when applied to the skin, even under exaggerated conditions. As a result, home use formulations are usually partially neutralized to provide only a portion of the total AHA content in the free acid form to penetrate the skin and provide cosmetic benefit (Table 2). The remaining neutralized, salt form of an AHA has reduced penetration potential; the penetration of this form would occur as a "second phase" of AHA delivery (this volume, chapter by Yu and Van Scott, Bioavailable Alpha Hydroxy Acid in Topical Formulations).

To maintain efficacy and provide a comfortable safety profile, AHA formulations should target a pH value that is

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roughly equivalent to the pKa (glycolic acid = 3.83) of the AHA ingredient [17,22]. At this point, approximately 50% of the AHA will be present in the free acid form and 50% as the neutralized salt form. Depending on the intended uses of the product and especially if the products are physician dispensed, a higher amount of free acid may be available in the products. This is the case with some of the higher strength glycolic acid products available from physicians for use at home by patients. In addition, many physicians use glycolic acid peels that are marketed as higher strength, free acid clinical reagents. On the other hand, some formulations are adjusted to a pH greater than 3.8 to minimize free acid penetration, for example, in sensitive skin formulations.

No matter how effective the product is, consumers demand elegant aesthetics to strengthen product loyalty. Some critical vehicle attributes include fast rub-in and absorption, nonsticky feel, a pleasant scent, which can be a challenge in fragrance-free formulations, and a smooth, nongreasy after feel. In many cases, the formulator must overcome significant negative aesthetic qualities from AHAs or other active ingredients. Organic sunscreens, for example, impart an oily feel and shine to cosmetic formulations. For beach products, this is not a major concern, because the products are worn less fre-

Table 2 Concentration of Free Glycolic Acid Contained in an 8% Formulation

Formulation pH	Free glycolic acid (% concentration)	Formulation pH	Free glycolic acid (% concentration)
2.0	8	3.83	4.0
2.5	7.7	4.0	3.2
3.0	7.0	4.4	1.7
3.6	5.0	5.0	0.5

Calculated using Henderson-Hasselbalch equation.
pKa = pH + log[acid form]/[base form].
pKa glycolic acid = 3.83.

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quently. For daily-use cosmetic formulations, including AHA moisturizers with sunscreens and AHA foundations with sunscreens, an oily effect can be detrimental to product success. Use of titanium dioxide as the sunscreen agent can be a nonoily alternative. Formulating with zinc oxide, another nongreasy sunscreen alternative, is a challenge, because this sunscreen active ingredient is difficult to stabilize in low pH systems.

The optimum product vehicle must deliver an appropriate amount of AHA in the active, free-acid form to the skin surface and provide acceptable aesthetics. The vehicle form, lotion, gel, solution, or cream, is often important to enhance efficacy and user compliance. For example, treatment of severe dry skin generally requires a highly emollient, petrolatum-based cream compared with a less-occlusive lotion formulation. In addition to providing enhanced efficacy, a heavier formulation is generally preferred by this population, because the added emolliency is comfortable to hyperkeratotic skin. On the other hand, a light lotion or gel is generally preferred when treating oily and acne-prone skin or for use in regions with high humidity.

Finally, the ingredients that are selected for the product formulation must be accepted by the regulatory authorities of the target markets and meet predetermined cost restrictions. Formulators and regulatory authorities around the world continually strive to improve global harmonization of ingredients, their label names and required ingredient standards, and testing. Nonetheless, each country maintains its own health authority, which ultimately decides the acceptability of product formulations and claims.

3. AHA—Drug Combinations

Many over-the-counter (OTC) and prescription drug products contain AHAs in combination with a drug active ingredient. Although a drug ingredient provides the labeled therapeutic effect, an AHA can serve several cosmetic functions, including

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skin smoothing and surface textural improvements, exfoliation, moisturization, and antioxidant effects. Combination OTC drug products that follow the FDA OTC Drug Monographs must be manufactured and marketed according to requirements established by FDA in the Code of Federal Regulations. The cosmetic benefits of AHAs can be promoted on OTC drug labeling provided there is a distinct separation of drug therapeutic activity from the cosmetic benefits afforded by the vehicle ingredients, including the AHAs. Prescription drug products must first either be filed as New Drug Applications (NDA) or as an Abbreviated New Drug Application (ANDA) and show bioequivalence to a previously approved pharmaceutical product. For the latter, the active ingredient system must remain the same, but the vehicle may be slightly modified.

III. SUPPORTING PRODUCT SAFETY AND CLAIMS

Safety and benefit claims of AHA formulations are determined by several approaches. Many companies use exaggerated use, human patch testing models to establish baseline safety. In addition, in vitro tests, consumer use tests, and, to a limited extent, animal tests are conducted to further support product safety. If available, companies also use historical marketing data of similar formulations to predict product safety.

A. Establishing AHA Product Effectiveness

Efficacy claims for finished products may be supported through human use studies, consumer evaluations with self-assessment, in vitro studies, published literature, and/or patents. Human use studies are designed to provide objective data to support product claims [23]. Most studies involve some form of expert grading to evaluate the visual or tactile effect of the product on the test condition. Whether conducted in a physician's office or through a contract research organi-

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zation, expert graders can readily assess changes in acne, scaling conditions, and aging signs, including fine lines and wrinkles, pigmentation evening, roughness, sallowness, telangiectasia, and so forth. Scores are generated for evaluable conditions at specified time points and are usually compared with baseline scores and/or a treatment control using the appropriate parametric or nonparametric statistical methods ($p < 0.05$).

Instrumental techniques are used to quantify various skin parameters, including firmness, elasticity, fine lines and wrinkles, coarse and fine flaking, rate of cell turnover, stratum corneum barrier function, and skin coloring (Table 3). Baseline values are collected, and measurements are repeated at predetermined time points for statistical comparison to baseline scores. The benefit of using instrumental data derives from the ability to collect data that are not dependent on the human eye (although consistent use of the instrument is subjective) and provide numerical values for percent im-

Table 3 Claim Support Models

Claim	Evaluation technique
Improvement in skin surface smoothness, fine lines, and wrinkles	• Clinical grading • Silicone replicas with image analysis
Moisturization	• Moisturizer efficacy study (regression test) • Instrumental measurement of conductance, impedance, or capacitance
Skin barrier function	• Transepidermal water loss (TEWL) • Patch test challenge
Irritation, skin pigmentation	• Clinical grading • Colorimetry • Melanin meter
Firmness, elasticity	• Clinical grading • Pinch recoil (Ballistometer) • Instrumental measurements
Scaling, flaking	• Clinical grading • D'squame tape disks

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provement claims. For example, silicone replicas are used to collect topographical data of skin on the crow's feet or other textured regions. The replicas are analyzed using image analysis, and numerical values representing degrees of wrinkling are obtained and compared with other treatments or baseline scores. Many times, quantitative advertising claims such as "achieve over 20% improvement in skin smoothness" are obtained using instrumental techniques. Quantitative claims continue to be popular in the marketplace, and instrumental assessments provide valuable complementary data to expert grading to support these claims. Photography is a strong tool for claim support and advertising; however, it is difficult to standardize and observe incremental improvements in signs of photoaging. Improvements in skin conditions that are more visually apparent, such as acne and rosacea, are more easily documented with photography.

Consumer use studies are frequently designed to assess product aesthetics and collect self-assessment data with regard to product efficacy. This element of study design is important to ensure that claim support data are relevant to, and perceived by, the consumer. Although a 20% improvement in skin smoothness may sound impressive, it is only meaningful if the change is consumer perceivable. Furthermore, compliant use of skin care products requires desirable formulation aesthetics and immediately perceivable benefits. True "antiaging" benefits may not occur until after many weeks of use, however, skin softness and radiance are often realized with 1 week of AHA product use.

Product claims are supported using other techniques, as well. Some products feature benefit ingredients, such as the AHAs, that can be promoted within the product. For example, products often make claims such as "contains glycolic acid—an ingredient known to reduce the symptoms of aging." In this way, the product purports to provide antiaging activity without actually having to perform the testing to support the claim. Instead, published literature and patents covering the benefit ingredient are used as claim support. As benefits for a

compound become better documented, companies rely on commonly known data for claim support. This is exemplified by the AHAs. There are many products containing AHAs that make bold claims, which seem to be supported by little clinical data.

B. Product Integrity

Before a new product is launched, a variety of testing methods are used to ascertain physical and chemical stability and resistance to microbial contamination. Most cosmetic products are launched with an established shelf-life of 2 years. (In the United States, expiration dates are not required to be stamped on cosmetic product packaging, whereas in the European community shelf-life must be indicated on packaging if the expiration date is less than 30 mo.) The expiration date is often extended once appropriate testing can be done to support a longer shelf-life. Stability studies during product development are usually conducted according to accelerated stability conditions defined by the United States Pharmacopoeia (USP). Stability is conducted in final packaging to ensure compatibility with packaging material. Once the product is produced in a manufacturing setting, it is monitored using real-time, ambient conditions.

Similarly, preservative efficacy is conducted using USP guidelines. This test requires the inoculation of product formulations with five common microorganisms representing gram-positive and gram-negative bacteria, yeast, and mold. To pass preservative challenge, products must demonstrate a sharp decline in organism counts within the specified period of time, as outlined in the USP procedure.

IV. MARKETING AHA SKIN CARE PRODUCTS

Preparation of formulated products for launch into the consumer market requires packaging and labeling, a marketing

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"story" to facilitate positioning within the market, and appropriate support materials.

A. Packaging and Labeling

The benefits of an effective formulation may go unnoticed unless the product is provided in suitable and enticing packaging that encourages product use. Not only must the package ensure the integrity and quality of the product, it should be easy to use and provide the appropriate image for the product. Physician-dispensed products are usually therapeutic in appearance and function, devoid of the obvious glamour and expensive packaging frequently seen in the prestige market. Conversely, women shopping in department stores, spas, and salons expect to purchase products that convey luxury and wealth.

1. Packaging

Selection of the most appropriate and desirable packaging requires consideration of cost, product function, delivery options (pump, tube, aerosol, etc.), product stability, shipping requirements, and international size requirements. To meet regulations for labeling, additional packaging such as a carton may be needed to provide space for mandatory labeling; this is often an issue for cosmetics that are also OTC drug products such as foundations and lipsticks with sunscreens. Stability requirements of the product can limit packaging selections, because the formulation must be compatible with the packaging material (usually plastics or glass), and exposure to the environment must be considered. Many formulations require protection from UV light and air and therefore have special packaging requirements. For example, to ensure the stability of an AHA plus hydroquinone-containing formulation, a laminate tube filled under nitrogen is recommended to prevent oxidation of the active ingredient. Finally, many companies strive to harmonize packaging, enabling the use of one package worldwide. As a result, international size re-

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quirements must be adhered to, and packaging must be selected to withstand the rigors of shipping.

2. Labeling

Labeling on AHA products usually describes the benefits that can be achieved with continued product use. Because labeling requirements in the United States are enforced by the FDA, claims made on product labels are usually mild compared with those made in advertising, which fall under the authority of the Federal Trade Commission (FTC). Although the FDA is concerned with the safe use of skin care products and the orientation of claims made on the labels (drug versus cosmetic), FTC ensures fair competition in advertising and promotion by requiring appropriate claims support regardless of whether the claim is cosmetic or drug. Harmonized labeling for worldwide use requires a thorough understanding of the regulations in all of the target markets. In general, the following areas are included on labels: product name and function, benefit claims, directions for use, warnings/cautions, ingredient disclosure, net weight, and a statement of manufacture. An excellent reference for cosmetic and OTC product labeling can be found in the *CTFA* (Cosmetic, Toiletry, Fragrance Association) *Labeling Manual—A Guide To Labeling and Advertising Cosmetics and OTC Drugs.*

B. Marketing Support Materials

Accompanying materials may be necessary to facilitate the sale of AHA skin care products in some markets. In the physician-dispensed marketplace, for example, physician customers expect marketing services to be available for their use, including the provision of patient brochures and in-office videos that describe product benefits in lay language, staff training, product display cases, inventory management systems, and extensive customer service for both the physician and patient. Department store sales are supported by seasonal promotions and free gifts with purchase. Success in this

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setting is highly dependent on the enthusiasm and knowledge of the beauty advisor behind the counter, and programs are implemented to motivate and educate the sales staff. Advertising and store promotions are important to the success of most consumer brands, although brand recognition can be achieved without expensive advertising campaigns.

V. CONCLUSION

The AHAs have enjoyed tremendous success in cosmetic and therapeutic skin care. Competition is great in each of the markets, between other AHA products, as well as new technologies that promise to be the next "AHA." Because of the high level of competition, successful entrance into the AHA market requires superior products that provide advanced formulation technology and aesthetics, strong topical benefits, desirable packaging, and a positive product image.

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