

## **Facial Resurfacing: Pharmacologic Skin Rejuvenation**

### **Retinoids, Alpha & Beta Hydroxy Acids, and other compounds**

“There are more lines today in the looking glass. Time is the warden of all flesh.”

*The Locket*, Richard Paul Evans

For centuries, cosmetics have been used on the facial skin of men and women for adornment and for other decorative purposes. During the 19<sup>th</sup> and 20<sup>th</sup> centuries cosmetics were used not only to enhance appearance and mask undesired features but cosmetic moisturizers and emollients were also purported to prevent and reverse aging skin. Today and for the future, cosmeceuticals\*, which include topical retinoids, hydroxy acids, and antioxidants serve in several roles: decorative, therapeutic, and chemopreventive. \* [Cosmeceuticals are hybrids of cosmetics and pharmaceuticals. There is no FDA recognition of the term “cosmeceutical”. The distinction between a cosmetic and a drug usually depends upon the **claims** in the marketing of the product and not upon the chemical action of the compound. Although a chemical compound may alter the structure or function of the skin (ie a drug), if it is marketed as a product to beautify, it is classified as a cosmetic].

Cosmeceuticals of the 20<sup>th</sup> century and beyond should be considered as “performance” and “treatment” products. Today’s cosmeceuticals have replaced products previously used for beautification which survived years of misinformation based on a dearth of science used to justify exaggerated claims and promises. The cosmeceuticals of today, if used appropriately, are truly a “dream in a bottle” as well as “elixirs of youth” and can produce predictable results if used consistently.

## **Introduction**

Topical retinoids have been the single most important group of compounds in the 20<sup>th</sup> century for skin and hair and have revolutionized the treatment of many skin disorders. The retinoids will likely remain the primary medical therapy and chemopreventive treatment for photoaged, intrinsically aged, and acne-prone skins in the 21st century and beyond. Reproducible microscopic, biochemical and ultrastructural data support retinoid-induced physical and cosmetic benefits for both the epidermis and dermis, and their effects seem to be cumulative. The long-term safety of retinoids has been established through continued use for over 30 years for the treatment of acne, severe psoriasis, and disorders of keratinization.<sup>1</sup>

For topical retinoids to be effective, they must be used consistently on a long-term continuing basis. Unfortunately, there are many misconceptions regarding the use of topical retinoids that often limit patient acceptability and compliance. The issue of compliance is complicated by an exaggerated emphasis on their side effects, perpetuated as much by well-meaning, yet not fully informed, physicians and by patients who have become biased through hearsay and misinformation. Both groups could benefit from understanding the scientific basis for the use of retinoids as therapeutic, chemopreventive, and cosmetic agents.

While peeling agents have been used much longer than topical retinoids to renew photoaged and chronologically aged skin, it is only within the last decade that the use of alpha and beta hydroxy acids and other related compounds have been refined to their present precise art for therapeutic and cosmetic enhancement. Epidermal and dermal wounding can be specifically controlled, depending on the depth of skin injury needed, and side effects can be predicted for most individuals. However there are no

double blind or comparative long-term clinical studies confirming cumulative positive effects with the hydroxyacids as have been done with topical retinoids. The ability to achieve prompt cosmetic enhancement through the use of hydroxy acids with little or no “downtime” has made the new generation of cosmetic creams and cosmeceuticals far more acceptable to all age groups and more appealing to men who have traditionally shunned most age reversing products.

This chapter discusses the historic development, kinetics, and uses of topical pharmacologic skin rejuvenating agents and reviews patient selection criteria as well as common misconceptions and myths regarding the use of these compounds. An instruction guide for patients with an overview of the science and mechanisms involved is included at the end of this chapter.

## **Historical Perspective**

The biologic significance of vitamin A was first recognized nearly one hundred years ago.<sup>2</sup> It wasn't until the mid-1940s that retinol (Vitamin A) was first synthesized and made available commercially to treat a variety of dermatologic disorders. Toxicity problems with oral retinol led to the development of a topical agent with the active metabolic product of retinol, all-*trans*-retinoic acid or tretinoin.<sup>3</sup> Retinoic acid (tretinoin, all-*trans*-retinoic acid) was initially introduced in the late 1960s for the treatment of acne.<sup>4</sup> The first report detailing cosmetic skin enhancement with tretinoin was published in 1983 in Argentina.<sup>5</sup> As the use of tretinoin became more widespread, certain serendipitous side effects were observed. The cosmetic benefits of tretinoin were equal to and sometimes exceeded other cosmetic procedures and topical modalities for cosmesis.

In 1986, Kligman et al<sup>6</sup> reported cosmetic improvement of photoaged skin of the face and forearm with topical tretinoin. Initially, their assertions that tretinoin could reverse aging were met with some skepticism. This could be attributed to the difficulty in distinguishing differences between photoaging and chronologic aging by noncritical observers. The clinical changes reported by Kligman et al were supported by histologic and ultrastructural reversal of human photoaging. There were specific changes documented in the epidermis as well as the dermis. A number of subsequent double blind, vehicle controlled studies of human photoaged skin<sup>7,8,9,10</sup> have confirmed tretinoin's benefits and provided ultrastructural details and other supporting data for reversal of photoaging. Consequently, tretinoin has been approved for this specific use in the United States and in several other countries.

### **Clinical and Histologic features of Aging Skin**

Our perception of "age" is obvious but difficult to define and is usually based on the appearance of the exposed skin of the face, neck, and hands. The skin is characteristically thin, loose, discolored, mottled, dry and wrinkled. Under a microscope, the epidermal cell layer is thinned and the individual cells have varying degrees of nuclear atypism as well as a dyskeratotic appearance. The thinning of the dermis and the degree of elastosis and degeneration of collagen are usually in proportion to the extent of photodamage and to the chronologic age of the individual. Melanin is clumped, rather than microdispersed, along the dermal-epidermal junction and may also be apparent in the superficial dermis.

The sequential physical, molecular, and microscopic changes of the aging face and neck have been comprehensively organized in this text. (See volume II chapters 2 and 5). Elsewhere Dzubow<sup>11</sup>

has discussed each anatomic region of the face and neck individually and has integrated them as a whole since changes in the skin occurring both with the aging process and from environmental exposure are independent as well as interdependent. He correlates the physical changes with the histologic changes in graphic detail. Barbara Gilchrest has focused much of her research specifically on the aging skin.<sup>12</sup> Her work is an important resource for evolving details.

### Intrinsic and Extrinsic Aging

The clinical and microscopic descriptions of intrinsic and extrinsic aging skin have been detailed by the authors mentioned above. The most obvious clinical evidence of photoaging is much more pronounced on extrinsically aged fair-skinned individuals phototypes I and II (See Table I and Figures 1, 2, 3).

It is important to realize that structural damage to the dermal matrix, manifested by varying degrees of elastosis and degeneration of collagen, primarily develops on sun-exposed skin and occurs early in life. In fact, 80% of lifetime sun exposure is usually accumulated before age 18.<sup>13</sup> Epidermal and dermal changes from solar exposure are evidenced microscopically in most individuals as young as 15 years of age, long before photodamage is obvious clinically. In some skin types, especially phototypes I and II, photodamage can be observed in childhood without using skin biopsies or other invasive procedures. This photodamage is easily demonstrated with Woods light examination showing occult dyspigmentations which can then be documented by a special ultraviolet photographic process (See Figure 4).

## Altered Skin

As unscientific as the following descriptions and terminology may seem, the terms in quotations are those used by adults and teenagers to describe their skin complaints.

“*Altered skin*” is the result of cumulative sun damage, genetic predisposition, environmental exposure and other factors (See Figures 5,6, 7, 8).

Dermatoheliosis is sundamaged “altered skin”. It is characterized by dyspigmentation and thin, loose, muddy appearing skin with “yellowing” or “blotches”, poor texture, wrinkling, and dark spots. Enlarged follicles, open and closed comedones, and sebaceous papules are also characteristic of sundamaged, older, and *altered skin*. Loosening and darkening of the upper and lower eyelid skin (“dark circles”) is yet another feature of “*altered skin*”, as is the dyspigmentation of the sides of the neck (poikiloderma of Civatte). There is also a zone on the neck of well-circumscribed oval pale skin under the chin down to the epiglottis where the chin has shielded the mid neck from cumulative sun damage (See Figures 9, 10, 11).

Acne-prone skin is oily skin with enlarged follicles and open and closed comedones. Papules, pustules, and/or acne cysts may also be present. Discrete spots of hyperpigmentation of the post-inflammatory type either from resolved acne lesions or from self-manipulation of inflammatory lesions may be noticeable (See Figures 12, 13, 14, 15). Teenage skin may also have a muddy appearance or have nonspecific discolorations from photodamage, melasma, and/or environmental exposure.

## **Selection of Candidates for Pharmacologic Skin Rejuvenation**

Most adults and teenagers can benefit substantially from the chemopreventive and therapeutic uses of topical retinoids and various alpha or beta hydroxy acid compounds and antioxidants.

Chemoprevention and chemorestitution should be the primary goal of any specialist who deals with skin. The changes associated with altered skin, chronologic aging, and environmental aging can be precisely and gradually reversed by the consistent and appropriate use of the various cosmeceuticals discussed in this text. Routine daily use of sunscreens with broad spectrum UVA and UVB protection is also recommended for all age groups and all skin types on all exposed skin.

Candidates for topical retinoids who are younger than 15 years of age include those who have any of the following risk factors irrespective of normal appearing skin:

- a. Very fair skin that burns easily and does not tan (phototype I or II). These individuals usually have blue eyes, blond or red hair, and freckles and are of Celtic origin.
- b. History of one or more blistering sunburns during childhood.
- c. Individuals of any skin type who have unusually high exposure to sun because of lifestyles, recreational risks, occupation, or geographic location in certain latitudes.

Occult sun damage in any of the above individuals can be easily demonstrated by simple Woods light examination and/or UV photography (See Figure 4).

The best candidates for pharmacologic skin rejuvenation are those who can integrate retinoids or other products into their daily regimen and who are willing to commit to a lifelong avoidance of sun exposure. Appropriate candidates must also be advised that clinical benefits may not be evident for months. Adherence to a comprehensive skin care regimen is facilitated by open discussion regarding

the patient's often unrealistic expectations. Physicians can anticipate inquiries from their patients and should provide written handout material to minimize these inquiries (See Instruction Guide Page 25, 26, 27, and 28 of this chapter). Pretreatment photographs are beneficial in supporting subjective perceptions of improvement and optimally should be compared to mid and post-treatment photographs. Sequential photo-documentation, although not a cost-effective process, greatly enhances compliance.

### **Pharmacologic Intervention**

Tretinoin has been the most studied and the most commonly used prescription product for photoaging for the past 15 years. This chapter focuses on the effects of tretinoin and other retinoids used in pharmacologic skin rejuvenation. These effects have been substantiated by confirmed scientific studies and through numerous controlled clinical trials. This chapter also addresses the use of hydroxy acids and other compounds as alternative treatment options and companion products for skin rejuvenation.

While topical retinoids have revolutionized the medical treatment of skin for acne and photoaging, these compounds are also used for many other skin conditions and abnormalities.<sup>14 15 16</sup> New generations of retinoids and new vehicles for tretinoin continue to emerge while new uses and newly synthesized compounds are evolving exponentially. Some of the newer synthetic retinoids target different nuclear receptors than tretinoin does. It is possible that using a combination of several retinoid compounds may yield even better clinical results in the future.

### **Effects on Photoaging**

Tretinoin has been shown both clinically and histologically to partially and gradually reverse photodamage in skin in a cumulative manner.<sup>17 18</sup> These effects are mediated by the ability of retinoic

acid to not only repair existing photodamage but also, at the same time, to prevent further UV damage.<sup>19 20</sup> Concomitant use of sunscreens enhances these effects since the dermal repair process has been shown to occur in laboratory animals while being irradiated if sunscreens have been reapplied. These findings have also been documented in humans (See Table II). The inherent mechanisms causing acne, sebaceous hyperplasia, and follicular dilatation are also altered by the consistent use of retinoic acid.

Obvious clinical response to topical tretinoin results from improvement in both epidermal and dermal components of photoaged skin (See Figures 16, 17). Long-term studies have shown the most noticeable skin changes with tretinoin treatment result primarily from the increase in dermal collagen, decrease in abnormal elastin, increase in epidermal and dermal mucin, decrease in abnormal clumped melanin, and repair of the dermal-epidermal junction.<sup>21 22</sup> Not all clinical features of photoaging respond equally to tretinoin, but dyspigmentation, surface roughness, and fine wrinkles demonstrate the most consistent and significant improvement and occur quite early (See Figure 18). Interestingly, physical changes are much more obvious in the most severely sundamaged skins, and these are often seen within a few weeks of use. The correlation of histologic and clinical changes is summarized in Table III and in Figure 17.

### Epidermal Photoaging

Improved skin texture and a “rosy glow” are the first and most noticeable clinical changes in tretinoin-treated photoaged skin. It is because of this “rosy glow” that before and after photographs of patients using topical retinoids are viewed with some skepticism, as the after shots appear to have been taken under different lighting exposures (See figures 18, 19, 20, 21, 22). Interestingly, the perceived difference in lighting is universally apparent in every set of photographs. The changes of a brighter,

lighter, more even-toned skin may become apparent within a few days in most individuals compared to pre-therapy, although some skin types do not show obvious changes for weeks or months. It is possible that there is a vehicle and/or a compound specificity for some skin types. Occasionally that desired luminous glow becomes more apparent when the subject switches from one retinoid formula to another. There are no comparative studies documenting vehicle specificity. Since nuclear retinoid receptors are controlled by genes that are part of a larger gene family controlling many hormones, it seems reasonable that clinical and molecular responses will vary among individuals. Some of the newer retinoid compounds are mediated by different sets of nuclear receptors; thus, it is possible that a combination of retinoid compounds with different chemical structures may produce even better results clinically.

#### Dermal Photoaging

Not enough emphasis has been placed on the profound and cumulative dermal repair resulting from consistent use of topical retinoids. The progressive synthesis of new collagen and repair of dermal micro blood vessels may be one of the major mechanisms by which skin is tightened (See Figure 24). This effect can be likened to the importance of a sound foundation or infrastructure.

The diminution of dermal appendages, all of which enlarge during the aging process, is gradually achieved with topical retinoids. Hyperplastic sebaceous papules, dilated follicular orifices, and enlarged sebaceous glands (sources of rhinophyma), syringomas, and xanthelasma are all located in the dermis and can almost completely involute with aggressive use of topical retinoids (See Figures 25, 26, 27, 28, 29, 30, 31). Few, if any, of these dermal growths are structurally altered by most other cosmetic modalities, although follicles may appear smaller while the skin is edematous and taut after chemical peeling or laser resurfacing.

Any trauma to the skin, including chemical peeling and laser resurfacing, will stimulate remodeling of collagen and other dermal elements, but without the continued stimulus to the dermis, the remodeled collagen is static and short-lived when compared to the cumulative effects from consistent use of topical retinoids. By stressing the aggressive and constant use of topical retinoids after laser resurfacing or chemical peeling, it is possible that cumulative and lasting cosmetic benefits will exceed most expectations, but there are no studies that demonstrate these results.

### **Mechanism of action and Pharmacokinetics**

Retinoids as a chemical entity were previously defined as substances having structural relationships to the parent compound retinol. Retinol has been a chemist's dream molecule, readily modified by substitutions at the carboxylic end group, the polyene chain, or the aromatic ring. As modern chemistry has progressed, compounds have been developed with little structural resemblance to retinol but with retinoid-like effects, due to their molecular mechanism of binding retinoic acid receptors.

Retinoid physiology is mediated by multiple pathways and is highly complex.<sup>3</sup> Retinoids are known to produce their biologic effects at the molecular level by binding to specific nuclear receptors, retinoic acid receptors (RARs), which have molecular makeup and function similar to the steroid/thyroid superfamily of receptors. The retinoid-receptor complex binds to specific DNA sequences located in the promoter region of the target gene, which activates gene transcription and generates protein products that cause the characteristic clinical and histologic changes associated with retinoid use. More than 300 genes are activated by tretinoin. Some proteins give rise to desired pharmacologic effects while some give rise to side effects. These effects may be carried out directly or indirectly. Furthermore, formation of protein products may in turn activate other genes in a cascading manner.

Retinoids also have high affinity for another family of proteins, the cytosolic retinoid acid-binding proteins, types I and II. These have been thought to be simply transport proteins; however, new research suggests other roles, possibly important ones in control of cell proliferation.

### **Percutaneous absorption and vehicles**

The importance of vehicles, or bases, used in topical formulations cannot be overemphasized. The overwhelming majority of a topical formulation is comprised of its vehicle, which can directly impact absorption of the therapeutic agent into the skin. The vehicle can also influence the therapeutic efficacy and tolerability of the formulation. This may explain why some formulations are more effective on some skin types, while others will be more suitable for a different subject.<sup>23 24</sup>

Traditional vehicles for skin treatment include lotions, ointments, creams, and gels. Recent innovations include liposomes and microparticles. Liposomes are concentric spherical shells of phospholipids layered in a water medium, comparable to the skins of an onion. The application of topical formulations which include liposomes results in two stages of drug release. First, the preparation remains in a liquid state, reducing the rate of absorption. Second, the compound dries allowing the drug that has not entered the skin to slowly diffuse into the stratum corneum by intercalating into skin surface lipids. The main disadvantages of such a compound is limited shelf-life stability since water-soluble molecules leak out of the liposomes during storage.

Microparticles are polymer-based microstructures in which drugs can be entrapped, and which deliver a metered release of active compound on the skin. Such formulations produce less irritation of the skin surface than other retinoid formulations do.

## Formulations

Retinoids have revolutionized the treatment of abnormal skin, whether the changes are the result of genetic predisposition, hormonal abnormalities, or environmental and physical damage. In the armamentarium of topical treatments for photoaging, the retinoids have been the most studied and the most commonly used compounds.

### Tretinoin

Retin-A is the original trade name for tretinoin available in cream at strengths of 0.025%, 0.05%, and 0.1%, in gel form at 0.01% and 0.025% strengths, and in liquid form at 0.05%.

Renova is a more emollient formulation of tretinoin 0.05% cream, developed to alleviate the retinoid dermatitis associated with topical tretinoin and was developed specifically for treatment of the aging face.

Retin-a micro is tretinoin 0.1% gel encapsulated in porous acrylate copolymer microspheres that release tretinoin over time, causing less skin irritation than Retin A or Renova.

Avita is tretinoin 0.025% in a cream or gel vehicle incorporating polyolprepolymer-2, a material designed to help retain drug molecules in and on the skin when applied in topical vehicles. If irritation from tretinoin is related to the rate of initial penetration and if efficacy is more a consequence of total dose, this preparation represents an advantageous delivery system, allowing better compliance due to fewer side effects.<sup>25</sup>

New generations of retinoids and new vehicles for tretinoin continue to emerge.

### Adapalene

The initial question was how could retinoic acid be chemically modified to improve its side-effect profile? Differin (adapalene) is a synthetic naphthoic acid retinoid that is lipophilic, so it

concentrates in the pilosebaceous follicles and other oily areas. This synthetic retinoid binds to slightly different nuclear receptors than tretinoin. Studies comparing adapalene with other tretinoin products show adapalene to be less irritating.<sup>26</sup> Adapalene also does not produce the burning or stinging sensation upon exposure to sun that is attributed to tretinoin. Most studies with adapalene have focused on improvement in acne patients, but definite cosmetic effects do also occur.

### Tazarotene

Tazorac is a synthetic acetylenic retinoid that appears valuable in the treatment of psoriasis and acne, and it has cosmetic benefits for photoaging as well. Its actions are targeted on two specific retinoid receptors, again with the aim of efficacy with increased tolerability.<sup>27</sup>

### Retinol

Vitamin A (Retinol) itself has seen resurgence in topical use. Originally, retinol's instability limited its use, although, because retinol is metabolically converted to retinoic acid, efficacy could be predicted with a stable formulation. Retinol is now available without prescription in many skin care products. Unfortunately, some cosmeceuticals claiming to contain retinol may have concentrations too miniscule to have any beneficial effects. Products containing "retinoid imitators" (ie retinol palmitate or retinyl acetate) have not been shown to have any measurable therapeutic or cosmetic benefits.

## **Myths and Misconceptions**

**MYTH:** *Topical retinoids are very irritating and produce erythema and desquamation (exfoliation) within a few days of initiating therapy.*

Desquamation is a retinoid-mediated response but decreases with repeated use. Erythema varies with individuals and does not appear to be a direct receptor-mediated event.<sup>28</sup> However, because desquamation is a desired and direct effect of tretinoin, claims of efficacy without any peeling response should be viewed with some skepticism. By stimulating exfoliation of dull epidermal cells, skin cell turnover time is accelerated from the standard 30 to 35 day cycle down to 5 or 6 days. It is this process which is producing younger cells that gives the skin a radiant rosy glow, because a younger DNA is being inserted into each cell's nucleus. The desquamating skin can be controlled with moisturizers, mild exfoliants or simply by applying the retinoid a 2<sup>nd</sup> or 3<sup>rd</sup> time over the scaling sites. (See Figures 32, 33, 34, 35 and also patient instruction guide). The skin exfoliation is a much desired effect and should not be misinterpreted as "dry skin" as it is actually a way of gently removing dull and damaged cells so that younger cells can emerge. Erythema and desquamation due to contact allergy to topical tretinoin is uncommon.<sup>29</sup>

**MYTH:** *Clinical improvement is really subjective and correlates with the degree of irritation and erythema.*

Irritation by itself is not necessary for improvement. Evidence for this was substantiated by Griffiths et al in 1995.<sup>30</sup> This study showed equivalent responses with 0.025% and 0.1% tretinoin cream although the 0.1% cream was more irritating. Because only two specific formulations of tretinoin were

compared in this study, it is possible that therapeutic responses would differ if other vehicles and formulations of tretinoin were compared.

**MYTH:** *To minimize possible irritation, it is best to dilute tretinoin with a cream or lotion.*

Retinoids are unstable compounds and are not soluble in water (lotions and creams are oil in water and water in oil compounds). Pharmaceutical companies have spent years in developing vehicles that maintain stability and efficacy of their compounds, thus, diluting the preparations may very well inactivate or minimize their effects. Light also inactivates retinoids, so patients should be advised to apply these products at bedtime and to leave them in their own closed containers.

**MYTH:** *Dermatitis from retinoid therapy is not safe on darkly pigmented skin because of increase risk of dyspigmentation.*

Controlled studies and more than thirty years of clinical application demonstrate quite the opposite occurrence. Improvement and resolution of melasma and of dyspigmentations of various causes are some of the most dramatic changes seen following the use of retinoid compounds (See Figures 36 A1, 2, 3 and B 1,2, 3, and Figures 37, 38, 39, 40, 41, 42).

**MYTH:** *Tretinoin causes photosensitivity because skin is thinned.*

Fisher et al<sup>31</sup> showed that skin treated with tretinoin had no increased sensitivity to ultraviolet light, confirming that tretinoin has no phototoxic effect. During the initial few weeks of use, the stratum corneum is thinned, rendering the skin more susceptible to sunburn, but susceptibility to sunburn (minimal erythema dose - MED) returns to normal with continued use of tretinoin. Paradoxically, the viable epidermis is thickened with use of topical retinoids (See Figure 43).

Patients do occasionally complain of uncomfortable sensations on exposure to sunlight, often within minutes of being in the sun, which suggests that the reaction is quite different from sunburn reactions that normally occur hours after sun exposure. Furthermore, the sensations are more noticeable in hot environments than in cold ones, suggesting that heat (infrared radiation) rather than UV radiation, may contribute to this response.<sup>32</sup> Also important, some patients attribute having a “red face” to an irritant reaction to the tretinoin. Actually, tretinoin thickens the epidermis and repairs the dermal microvasculature which can have quite the opposite effect.

**MYTH:** *Tretinoin causes birth defects.*

When administered systemically, tretinoin is a potent teratogen. The data on routine use of topical tretinoin indicate that there is no increased risk for pregnant women.<sup>33</sup> Jensen et al<sup>34</sup> showed negligible absorption of isotretinoin even after excessive topical application in acne patients. However, tretinoin is classified as a Pregnancy Class C drug.

## **Hydroxy Acids**

The historical use of hydroxy acids spans many centuries. Cleopatra applied sour milk to her face, while Arabian women favored yogurt as their source of lactic acid. Polynesian women preferred glycolic acid from sugar cane, whereas ladies of the French court used tartaric acid from red wine.<sup>35</sup> Modern interest in hydroxy acids surfaced with the work of Van Scott and Yu,<sup>36</sup> who investigated their use in disorders of keratinization.

The efficacy of a topical hydroxy acid is mediated by two major factors: the bioavailable concentration and the vehicle used.<sup>37</sup> The bioavailability of a hydroxy acid, or the fraction that permeates

the stratum corneum, is the fraction of free acid present in the formulation. The amount of free acid in a formulation is determined by the inherent pKa of the hydroxy acid and the pH of the formulation. If the pH of the formulation is less than the pKa of the acid, the free acid form predominates. If the pH of the formulation is greater than the pKa of the acid, the less effective salt form predominates.

It is important to understand that, although two products may contain equal percentages of a hydroxy acid, the bioavailability of that hydroxy acid may not be equal between the two products if the pH values of the vehicles are different. For example, glycolic acid's pKa is 3.83. A 10% glycolic acid cream formulated at pH 3.0 has a bioavailability of 0.96 and is quite effective on skin. On the other hand, a 10% glycolic acid cream formulated at pH 5.0 has a bioavailability of 0.06 and is much less effective.

The second major factor affecting efficacy is the vehicle, which determines the solubility of a hydroxy acid and the bioavailability through its pH, as discussed above. For water soluble hydroxy acids, such as glycolic, lactic, malic, tartaric, and citric acid, an oil-in-water emulsion is the vehicle of choice. For more lipid soluble hydroxy acids, such as mandelic, benzilic, and salicylic acid, a water-in-oil formulation is the vehicle of choice.

### Alpha Hydroxy Acids

AHAs are organic carboxylic acids with a hydroxy group in the alpha position. Epidermal changes seen with AHA use include a decrease in corneocyte cohesion above the stratum granulosum, an increase in epidermal thickness, a reversal of basal cell atypia, a dispersal of melanin pigmentation, and a return to a more normal rete pattern. Dermal changes include increases in papillary dermal thickness, acid mucopolysaccharide synthesis, fibroblast proliferation, and collagen synthesis.<sup>38</sup>

Ultrastructural changes include an increased number of desmosomes, increased tonofilament

aggregation, decreased clumping of tonofilaments within the cytoplasm, increased perinuclear localization of tonofilaments, and the formation of microvilli.<sup>39</sup>

AHAs are useful in the treatment of photoaged and intrinsically aged skin by reducing fine lines and wrinkles, and evening out pigmentation. Besides improving the appearance of photoaged skin, they are useful in pigmentary disorders such as melasma, ephelides, and post inflammatory hyperpigmentation (PIH).

In addition to treating PIH, AHAs are often incorporated into a post-op regimen for skin resurfacing to decrease the likelihood of developing PIH. They may be used as adjunctive treatments prior to chemical peels, to decrease the corneal layer, thereby allowing a more even penetration of chemicals. In high concentrations, glycolic acid may be used alone as the chemical peel agent itself.

AHAs also improve acne by inducing exfoliation and enhancing the comedolytic action of retinoids. The multitudinous applications of AHAs provide a strong foundation for the treatment of an assortment of skin conditions.

### Polyhydroxy Acids

PHAs are organic carboxylic acids that contain two or more hydroxyl groups. Many possess antioxidant properties and are more moisturizing than AHAs. Gluconolactone and gluconic acid, the more commonly used PHAs, are larger molecular compounds than glycolic acid and are often formulated to limit dermal penetration in an effort to decrease irritation. They exfoliate on the skin surface but not within the sebaceous unit. PHAs theoretically cause less stinging, burning, and irritation than other types of hydroxy acids. Individuals with sensitive skin, such as those with rosacea or atopic dermatitis, may prefer these products.<sup>40</sup>

## Beta Hydroxy Acids

Salicylic acid is a hydroxyl derivative of benzoic acid and represents a carboxylic acid attached to the aromatic alcohol phenol.<sup>41</sup> Although salicylic acid is not a beta-hydroxy acid by definition, it is referred to as a BHA in the cosmetic arena because it contains a hydroxy group in the beta position.<sup>42</sup> It is a lipid soluble molecule, restricting its site of action to the superficial epidermis and follicles.<sup>43</sup> This lipid solubility accounts for its ability to expel comedones from follicles. Salicylic acid promotes exfoliation by dissolving intercellular cement and reducing intercorneocyte adhesion<sup>44 45</sup> but it has no effect on the mitotic activity of the epidermis.<sup>46</sup> As a salicylate, it contains anti-inflammatory properties via its effects on the arachadonic acid cascade.<sup>47</sup>

Salicylic acid's unique comedolytic and anti-inflammatory properties make it a good agent for treatment of comedonal and inflammatory acne vulgaris. It is also useful for the treatment of papular rosacea, photodamage, fine lines, and surface roughness, as well as for melasma with primarily epidermal deposits of melanin pigment.

### Side effects and their management

The most common side effects of all topical hydroxy acid preparations are irritation and peeling skin. If excessive irritation does occur, decreasing the frequency of application or the strength of the formulation will ameliorate this unwanted side effect. Because this side effect is very common, patients should start with a low strength product and increase the strength of the formulation as tolerated.

Patients may also notice a tendency to sunburn more quickly than they did prior to starting hydroxy acid treatment. They should be instructed to wear appropriate sunscreens and also to minimize sun exposure.

## Myths

There are two main misconceptions involving the hydroxy acids. The first involves erroneous concerns for photoallergic reactions. Because the stratum corneum will thin with hydroxy acid use, patients may notice a tendency to sunburn more quickly. Patients should be educated that this is not an allergic reaction, but rather an expected pharmacologic effect. The second misconception involves hydroxy acids being incorrectly included in the group of keratolytic agents. Because keratin proteins are not hydrolysed, it is more accurate to refer to this group of acids as “exfoliants”<sup>48</sup>. The hydroxy acids loosen the intercellular cement facilitating exfoliation of corneocytes, and also actually repair the horny layer at the level it is formed rendering the keratin layer more compact. Most important, it is the repaired horny layer that gives the skin its moist and normal appearance. (See Figures 44, 45, 46, 47).

## **Vitamins**

### Vitamin C

L-ascorbic acid, the active form of vitamin C, is presented as ascorbate, a water-soluble molecule, in most biologic settings. Vitamin C is not synthesized by the body and must be provided by the diet. Ascorbic acid is an important antioxidant, scavenging free radicals and regenerating vitamin E from its radical form.<sup>49</sup>

UV radiation generates free radicals that damage cell membranes, various enzymes, and DNA. These changes are known to play a role in many of the histologic changes seen with acute photodamage and with chronic photoaging. Topical antioxidants, including vitamin C, help photoprotect against UVR because of their antioxidant and anti-inflammatory properties<sup>50</sup>. Most studies are in animal models but do support biologic antioxidant activity.<sup>51 52</sup>

The major hurdle in developing topical vitamin C preparations, is insuring stability. Exposure to light, moisture, and oxygen inactivates vitamin C. Patients should keep any preparations tightly closed and away from light, and discard any discolored (oxidized and thus inactive) product. Because Vitamin C is unstable, multiple confirming studies have yet to fully confirm its efficacy.

### Vitamin E

The most biologically active form of vitamin E is alpha-tocopherol. Vitamin E is a naturally occurring lipid-soluble antioxidant. Vitamin E and vitamin C work synergistically, since vitamin E can regenerate its antioxidant capabilities in the presence of vitamin C. As previously mentioned, topical application of these antioxidants to the skin has been shown to reduce acute and chronic photodamage. In one study comparing topically applied 5%RRR alpha-tocopherol to a control vehicle in the treatment of periorcular rhytides, the vitamin E-treated side of the face<sup>53</sup> showed a reduction of skin roughness, length of facial lines, and depth of wrinkles.

Both vitamin antioxidants C and E appeal to the general public as natural products and are sometimes referred to as “nutraceuticals”. They are also loosely classified as cosmeceuticals. However, both vitamin C and E require more extensive study in human, double-blind, vehicle-controlled studies with scientific quantification of their effects before widespread acceptance by doctors and patients.

### **Kinerase** (furfuryladenine)

Furfuryladenine is a plant cytokinin, one of a group of substances important in various aspects of plant growth and differentiation. Furfuryladenine has been shown to retard senescence in plants, to regulate plant growth under environmental extremes, and to act as an antioxidant.<sup>54</sup> The addition of

furfuryladenine to cultures of human fibroblasts delayed biochemical and morphologic changes associated with cell aging.<sup>55</sup> A controlled study of 96 subjects showed improvement in 100% of the treated subjects at week 24, with a mean improvement in tactile smoothness in 63% and of fine lines in 17%. Less than 1% of the subjects had clinical irritation.<sup>56</sup> No histologic studies have been reported and there have not been any other studies confirming these results.

### **Copper**

Recently, copper based topical anti-aging preparations have been developed. Copper-dependent enzymes are instrumental in basic cellular metabolism. These include superoxide dismutase, an antioxidant, and lysyl oxidase, which functions in the cross-linking of collagen and elastin. One small noncontrolled study<sup>57</sup> reported some collagen production with the use of topically applied copper binding cream when compared to tretinoin.

### **Conclusion**

There is voluminous supporting scientific literature confirming the use of topical retinoid compounds as an important and vital infrastructural addition to any daily regimen for adult skin care. It should also be used in the maintenance and chemopreventive care of teenaged skin. When used consistently and responsibly these compounds may preclude the need for many cosmetic procedures in subsequent years.

Hydroxy acids have also been extensively studied in photoaging, but studies comparing antiaging compounds are rare. Pierard et al<sup>58</sup> compared the effects of retinoic acid, glycolic acid, and a lipophilic derivative salicylic acid on photodamaged epidermis and found retinoic acid to be superior to the

hydroxy acids, and the lipophilic derivative of salicylic acid to be superior to glycolic acid. More comparison studies are needed to determine the comparative efficacy of these compounds. Lack of standardization of these non-FDA monitored products limits advising patients accurately about true effectiveness.

Vitamins and other supplements are and will continue to be important additives in anti-aging and anti-photoaging preparations. Researchers are continually developing new compounds using sophisticated methods and strategies . The hope is that future research, with an emphasis on more stable formulations and on more controlled clinical trials, will yield yet another generation of important products that can be used independently as well as interdependently with existing retinoids, hydroxy acids, antioxidants, and other new “treatment” compounds.

## Sample Patient Instruction Guide for using Topical Retinoids

Retinoids are vitamin A derivatives that have the potential of reversing sun damage and other age related changes in skin. When used consistently and appropriately, maximum improvement can be obtained for most, but not all, skin types.

Tretinoin is an active prescription form of topical vitamin A. Retinol is the non prescription form of topical vitamin A and is now found in low concentrations in many skin care products. Some retinol-containing products are more active and effective than others, but there are no specific criteria available for making the best selection. For example, “retinoid imitators” like retinol palmitate and retinyl acetate are actually ineffective topically but are found in many cosmetic products. It is best to allow your skin care specialist to advise you on appropriate product choices.

### How do retinoids work and what will they do for you?

- Retinoids:
- 1) stimulate exfoliation of dull-looking epidermal cells by accelerating skin cell turnover time from the standard 30-35 days down to 5 or 6 days .
  - 2) repair DNA damage gradually in the epidermal cells as well as repair the dermal collagen and small blood vessels. The repair process effectively tightens skin, diminishes wrinkles, and lightens discolorations.
  - 3) actually shrink oil glands, resulting in reduced pore size, diminished scars, and generally tightened skin.

- 4) build an “infrastructure” by providing new collagen and a new thicker and plumper epidermis.

As a result of all of the above: Retinoids make skin look younger and have a rosy glow.

The importance of vehicles, or bases, used in topical formulations cannot be overemphasized. The overwhelming majority of a topical formulation is comprised of its vehicle, which can directly impact absorption into the skin of the therapeutic agent. The vehicle can also influence the therapeutic efficacy and tolerability of the formulation. This may explain why some formulations are more effective than others and why comparing the concentration of retinoids between products is meaningless.

#### How to use retinoids

- 1) For maximum benefit, use tretinoin (prescription form) or retinol (non prescription) in the evenings when possible, as these compounds can easily be inactivated by light. For some individuals (especially men), it may be more practical to apply them in the morning after a bath or shower - or after shaving.
- 2) After gentle cleansing with a mild soap or cleanser, apply a small amount to the entire face, initially avoiding the eye and neck areas. Start using the product every other night for one to two weeks and gradually increase to every night as tolerated. Don't be in a hurry, it may take several weeks for some skin types to adjust to the product. Once tolerance is achieved some individuals can use the retinoid sparingly more than once daily - even under make-up or sunscreen.
- 3) Avoid using astringents or toners to prevent overdrying.

- 4) If side effects like burning or stinging sensation, redness or a mild rash occur, discontinue use of the product for a few days and apply a bland moisturizer or mild hydrocortisone cream or lotion as needed. Discontinue the latter when symptoms are improved.
- 5) Expect your skin to peel initially. This is a desired effect, as dull, sun-damaged cells are being shed while new and younger cells are being produced. You may use a mild exfoliant followed by a bland moisturizer when needed to help shed the peeling skin. Paradoxically, the retinoid can also be reapplied once or twice within a few minutes over the flaking skin to improve and resolve the flaking.

NOTE: Other cosmeceuticals and nutraceuticals (ie glycolic acid, lactic acid and Vitamin C, Selenium, furfuryladenine, etc.) can be used to compliment as well as to augment the effect of the retinoids. It is best to gradually introduce only one new product at a time. It is always best to consult your skin care specialist before adding a new compound to your regimen.

**IMPORTANT:**

- Because of the initial exfoliation with retinoids and hydroxy acids, it is imperative to wear a broad spectrum sunscreen consistently every day. Multiple studies have confirmed that, if a sunscreen is worn daily, the retinoid will prevent future sun-damage as well as repair damage already present, even while you are in the sun.

- If the chemicals in some sunscreen products irritate your sensitive skin, switch to a non-chemical sunscreen which contains microdispersed zinc oxide or titanium dioxide. Consult your physician if your sensitive skin persists and you cannot develop a tolerance for retinoids.

While retinoids may not be for everyone, with guidance, a formula can be found that is suitable for most skin types, including some individuals with sensitive skin.

Table I Skin Types (Phototypes)

Skin Type	Baseline Skin Color	Sunburn and Tanning History
I	White	Always burns, never tans
II	White	Always burns, tans minimally
III	White	Burns moderately, tans gradually
IV	Olive	Minimal burning, tans well
V	Brown	Rarely burns, tans darkly
VI	Dark Brown	Never burns, tans darkly black

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Figure 1, 2, 3

Examples of extrinsic aging in 3 generations. Note that sunexposed skin appears much older than protected skin in each of the age groups

Figure 4

Example of ultraviolet photography demonstrating occult photodamage – photographs reprinted with permission from Canfield

Figure 5, 6, 7, 8

Individuals of several age groups showing many of the features of “altered” skin: telangiectasia, poor texture, blotches, yellowing, dyspigmentation, wrinkling, and dark circles

Figure 9, 10, 11

Examples of “poikloderma of Civatte” (sun induced dyspigmentation on the sides of the neck). Note the white area of skin over the epiglottis where the midneck was shielded from the sun by the chin

Figure 12, 13, 14, 15

Acne prone skin showing enlarged follicles, papules, pustules, and post-inflammatory hyperpigmentation (Figure 14) from self manipulation of pustules and cysts. Both subjects have successfully used topical retinoids with dramatic improvement.

Table II. Scientific Basis for Use of Retinoids

- Tretinoin can Reverse photoaging
- Tretinoin can Reverse intrinsic aging
- Tretinoin can Prevent photoaging as it occurs
- Tretinoin can Retard photoaging as it occurs

Figure 16

Photomicrographs of epidermis and papillary dermis of severely photodamaged facial skin before and after 8 months of treatment with tretinoin. Note that the loose dry skin layer has resolved in the treated skin on the right. Also on the treated skin the epidermal cells are plump and more normal appearing and the treated epidermis is also thicker.

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Figure 17

Clinical photos and schematic of microscopic features of photodamaged skin before and after treatment with tretinoin. Reprinted with permission from Albert M. Kligman, M.D.

Table III. Correlating the Histologic and Clinical Changes seen with Tretinoin

Histologic Changes	Clinical Changes
Compaction of stratum corneum	Tactile smoothness
Spongiosis in the epidermis	Tactile smoothness
Hyaluronic acid within spongiotic areas (with resultant water retention)	Tactile smoothness
Increase in granular layer	
Decrease in melanin and more uniform dispersion	Reduction in mottled hyperpigmentation
Decrease in cytologic atypia	Decrease in actinic keratoses
Improved dermal-epidermal junction (presumably from increased production of type VII collagen, the anchoring fibrils)	Less skin fragility
Decrease in elastic tissue content	Decrease in sallowness
Increased collagen synthesis	Improvement in wrinkles and skin looseness
Increase in blood vessels	Rosy glow

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Figure 18, 19, 20, 21, 22

Improved skin texture, tighter skin and a “rosy glow” is obvious in each set of photographs. All

of the subjects were using tretinoin in the respective second set of photographs and all photographs were taken under the same lighting conditions

Figure 24

Upper and lower frames show alkaline phosphatase staining for small blood vessels, upper frame depicts vasculature in severely sun-damaged skin. Note expansion of microvasculature in lower frame after treatment with tretinoin for 14 months.

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Figure 25, 26

Note diminished sebaceous papules (forehead) smaller follicles and tighter, brighter skin

Figure 27, 28, 29

Note diminished appearance of follicles with use of topical retinoids. In frame #29 scars also appear smaller.

Figure 30, 31

More evidence of smaller dermal skin appendages with long term use of tretinoin:

- syringomas under eyes are smaller
- glabella lines are diminished and nose is less bulbous because of smaller follicles and smaller sebaceous glands

- eyelids are no longer loose and are not as dark

Figure 32, 33

Example of skin desquamation often seen with retinoid use and misinterpreted as dry skin. In Figure 33 (photo was taken within 5 minutes of photo #32). The tretinoin was reapplied over the left face to facilitate exfoliation of the loose skin cells. Note that the skin on the left side of the face (Figure 33) appears moist and well hydrated.

Figure 34, 35

Congenital lamellar ichthyosis – severest form of “dry skin” (Figure 34). Note loose desquamating skin cells after 1 month of topical tretinoin. The skin is noticeably moist and more normal appearing after tretinoin in spite of the desquamating skin cells. The desquamation is actually a desired effect and can be controlled with emollients and should not be viewed as a harmful occurrence. Also note the pink, luminous glow of the retinoid treated skin. The desquamating cells are uncovering normal, plump, and young skin cells.

Figure 36 A<sub>1</sub> A<sub>2</sub> A<sub>3</sub>

B<sub>1</sub> B<sub>2</sub> B<sub>3</sub>

NOTE gradual resolution of melasma/dyspigmentation over a 9 month period while using tretinoin.

Scars also appear diminished, as follicles become smaller. Skin bleaches were not used.

Figure 37, 38, 39, 40, 41

Examples of resolution of melasma and dyspigmentation while using topical retinoids.

Figure 42

Fontana stain showing melanin distribution in skin before and after treatment with tretinoin. Note that melanin granules become microdispersed throughout the hyperproliferative epidermis (right side of photo) and keratinocytes subsequently have no opportunity to accumulate pigment in large quantities.

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Figure 43

Normal skin (upper frame) before treatment with topical retinoids. Bottom frame shows thickened epidermal response. The keratin layer is thinner and more compact.

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Figure 44, 45

Severe congenital form of dry skin (ichthyosis) before treatment (Figure 44)

Same child after treatment of ichthyosis with 12% lactic acid lotion (Figure 45)

Figure 46, 47

Response on one leg to 12% lactic acid lotion (Figure 46). The left leg was not treated (Figure 47)

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