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Topical Exfoliation—Clinical Effects and Formulating Considerations

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EXFOLIATION

By definition, to exfoliate is to remove the surface in scales or laminae. Therefore, classical exfoliants are those agents that work at the skin's surface causing the removal of skin in layers. Exfoliation is characterized, based on its mechanism of action, into 3 categories:

1. physical/manual (loofah or microdermabrasion)
2. chemical/keratolytic agents (e.g., salicylic acid)
3. natural/exuviation (e.g., alpha-hydroxy acids)

Manual or physical exfoliation involves the use of physically abrasive devices such as loofahs and could also include instrumental techniques such as microdermabrasion. Manual exfoliants physically scrape and remove surface skin cells.

Salicylic acid represents the *chemical/keratolytic* class of exfoliants. Recent reviews of salicylic acid propose a change to the term "desmolytics" to more accurately reflect the action of these materials on skin (1,2); these agents dissolve the desmosomal bonds between cells beginning at the uppermost skin layers providing exfoliative effects from the top of the skin downward in a non-specific manner (1–5).

Natural exfoliation, also known as exuviation, is the naturally occurring process of epidermal turnover, which occurs approximately every 28 days. Compounds that enhance the natural process of exuviation include, the alpha-hydroxy acids (AHAs), polyhydroxy acids (PHAs), and bionic acids. These agents are frequently considered exfoliants; however, their effects differ from those of conventional keratolytics or desmolytics (6,7). They target the base of the stratum corneum, the layer identified as the stratum dysjunctum, and function by diminishing bonding strength between cells in a specific manner leading to normalization of cell turnover and, thus, exfoliation (6,8).

This chapter discusses the mechanisms, effects and formulating considerations of exfoliants, including physical implements, microdermabrasion, exuviating compounds (AHAs, PHAs, bionic acids), the keratololytic/desmolytic salicylic acid, and finally a newly emerging, non-acid, acetyl amino sugar known as N-acetylglucosamine.

PHYSICAL EXFOLIANTS: SCRATCHING THE SURFACE

Physical exfoliants involve the use of manual implements to erode away surface skin cells. Presumably, as rubbing is continued and additional force is exerted, skin cells will continue to forcibly desquamate in a non-specific manner. This can continue until the stratum corneum is removed and the "glistening" layer of the live epidermis is reached. A similar effect can be observed following repeated tape stripping, which could be thought of as a process of forced physical exfoliation.

Common methods of manual exfoliation include use of physically abrasive materials such as pumice, loofahs, and buff puffs. The repetitive action of shaving with a razor also serves to physically remove or exfoliate the stratum corneum (9). Newer methods of physical exfoliation, such as microdermabrasion, involve the use of sophisticated equipment which "sandblasts" the skin surface with particles.

Bathing Devices

Buff puffs, loofahs, mesh poofs, and, to a certain extent, washcloths are used by many people on a daily basis to provide varying degrees of exfoliation to the face and body. The amount of exfoliation is dependent on the force of application, the number of passes over the skin, and abrasiveness of the material being used. There is little information in the published literature discussing the effects of washing devices on skin physiology and function. A study by Grove showed that use of abrasive fiber sponges stimulates epidermal cell turnover and reduces the size of corneocytes, indicating an exfoliation effect on skin (10).

Another study by Bergfeld et al. directly compared the relative effectiveness of manual exfoliation with a loofah (controlled application twice daily) in comparison to topical application of the AHA, glycolic acid (10% lotion twice daily to one hand plus weekly, 3-minute 50% peels), in improving the quality of photoaged skin on the back of hands. Results on 21 women (mean age 44 years) indicated that glycolic acid treatment was superior to mechanical exfoliation in improving the quality of photodamaged skin. There was a greater than four-fold improvement in overall photodamage severity compared to the loofah treatment, and significant improvements ($p < 0.05$) in texture and wrinkling were also observed for the glycolic acid treatment. There were no significant changes to these characteristics on the loofah treated sites; however, loofah use resulted in significantly less irritation (11).

Shaving

Shaving with a razor blade removes hair as well as stratum corneum. As a result, there are many potential detrimental effects to skin including increased risk of irritation from other topically applied products, such as antiperspirants (9). Moreover, while shaving seems at first to make the skin smoother, this process actually generates uplifting scales and increased dryness, as well as diminished barrier function in the stratum corneum

and a pro-inflammatory environment in the epidermis (12). The amount of surface trauma and corresponding potential for irritation is increased with use of new razors, a non-optimal shaving angle, and insufficient use of lubricating products (9). Optimal shaving and minimal skin irritation can be achieved by following a few key steps including: (i) having clean skin, (ii) allowing warm water to soften hair, (iii) liberal use of shaving cream applied for two to three minutes to soften hair, and (iv) use of a wet, warm, sharp razor (13).

Microdermabrasion

The closed, self-contained procedure known as microdermabrasion was first developed in the mid-1980s by researchers in Italy to eliminate the risk of airborne blood generated during conventional dermabrasion treatments (14). Microdermabrasion was approved for use in the United States by the Food and Drug Administration (FDA) in 1997 and has become one of the most popular procedures used for aesthetic skin care (15).

This novel exfoliation technique utilizes a stream of aluminium oxide, sodium bicarbonate, or sodium chloride crystals that functions by "sandblasting" skin under mild suction, which serves to collect the aerosolized crystals and skin particulates for disposal (15,16). Depending on the power of the machine, the number of passes of the hand piece over the skin and/or the speed of the hand piece over the skin, microdermabrasion can cause superficial exfoliation of the uppermost layers of the epidermis or reach the dermis, as indicated by signs of bleeding (14). One study reported complete ablation of the stratum corneum after two passes with microdermabrasion and a resulting increase in vitamin C penetration by a factor of 20 compared to non-abraded skin, demonstrating the potential for significant exfoliation effects from microdermabrasion (17).

Microdermabrasion has been used to treat a variety of skin conditions including photoaged skin, acne, hyperpigmentation, striae distensa, actinic keratosis, and keratosis pilaris. Adverse events are infrequent and include pigmentation irregularities, which occur mainly in darker skin (Fitzpatrick skin types V and VI) and prolonged erythema lasting beyond 24 hours (15). Many microdermabrasion protocols suggest a series of superficial procedures on a monthly or half-monthly basis in order to achieve skin benefits while minimizing the likelihood for adverse events (15). Several publications support the safe and effective use of microdermabrasion, with both dermal and epidermal benefits, and corresponding patient satisfaction (18–21).

Due to the perceived benefits of microdermabrasion by patients and its success in dermatologist offices and spas/salons, a home care market is emerging. Accordingly, several cosmetic companies have tested and introduced home "microdermabrasion" kits; many of these kits incorporate use of scrubs or exfoliating moisturizers made by suspending physical particles, such as polyethylene beads or apricot kernels, in a cream emulsion or gel, rather than providing actual exfoliating devices (22,23).

CHEMICAL EXFOLIATION

Chemical exfoliants are substances that cause superficial skin cells to desquamate at an increased rate as a result of their ability to disrupt intercellular bonding within the stratum corneum. This effect on skin occurs through several different mechanisms as described below.

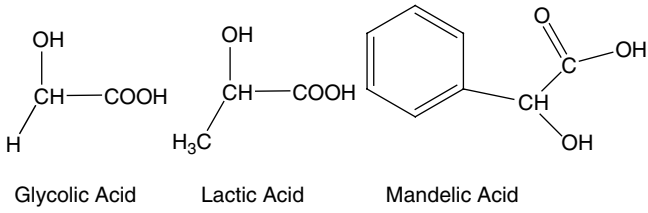

Figure 1 Alpha-hydroxy acids.

Exuviating Compounds: Alpha-Hydroxy Acids—Polyhydroxy Acids, and Bionic Acids

The alpha-hydroxy acid (AHAs), polyhydroxy acids (PHAs) and bionic acids are exvuviating compounds that enhance desquamation and cell turnover. Because of the differences in their molecular structures, these compounds provide some additional benefits to skin as described below.

Alpha-Hydroxy Acids—Anti-aging Plus Exfoliation

AHAs, such as glycolic acid, lactic acid, and mandelic acid (Fig. 1), have many beneficial effects on skin including enhanced exfoliation as well as reversal of photoaging (24–27). Upon topical application, AHAs have been shown to have a profound effect on desquamation and exuviation, the natural process of epidermal cell turnover (Fig. 2). When applied to severely hyperkeratotic skin, such as ichthyosis, AHAs at cosmetic strengths [defined by the Cosmetic Ingredient Review panel as a concentration of 10% or less with a minimum pH of 3.5 (28)] cause separation of abnormally thick stratum corneum at the base of the stratum corneum, the layer known as the stratum compactum (6,29). In severely hyperkeratotic skin, the thickened stratum corneum lifts off as a sheet (6). This observation distinguishes the effects of AHAs from traditional, non-specific exfoliating agents, such as salicylic acid, which diminish corneocyte cohesion thoughout the entire thickness of the stratum corneum (2).

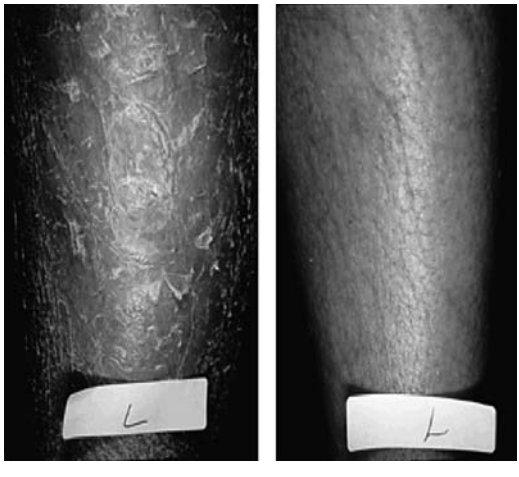

Figure 2 Lamellar ichthyosis before and after four weeks, with twice-daily topical application of an occlusive 10% AHA cream formulation containing glycolic acid, gluconolactone, tartaric acid, citric acid, and mandelic acid at pH 3.1.

AHAs have been shown to normalize the process of exuviation. As a result, continued use of AHAs results in a normalized rate of desquamation, and skin shedding becomes clinically lessened or non-apparent to the product user after two to three weeks (8). Effects of cosmetic strength AHA formulations on skin barrier function have been studied; Berardesca reported that twice-daily application of AHAs (8% lactic acid or 8% glycolic acid) over a period of four weeks resulted in maintenance of normal stratum corneum barrier function as measured by trans epidermal water loss (TEWL) and, therefore, excessive exfoliation of the stratum corneum was not apparent (30).

The mechanism of action of AHAs in promoting desquamation is postulated to be due to activation of the naturally-occurring enzyme steroid sulfatase to facilitate conversion of cholesterol-3-sulfate to cholesterol at the level of the stratum compactum. Exfoliation of normal, healthy skin requires the biochemical conversion of cholesterol-3-sulfate to free cholesterol in skin (31). When present at elevated levels, the more ionic molecule, cholesterol-3-sulfate, increases desmosomal bonding strength between corneocytes, thus prolonging the desquamation process. X-linked ichthyosis is known to be deficient in this critical enzyme (32).

AHAs also have stimulatory effects on dermal components. This, in conjunction with normalization of epidermal thickness and morphology, produces the anti-aging benefits of AHAs (26,33,34). Skin effects of AHAs include:

- *reduced* corneocyte cohesion at the stratum compactum (base of the stratum corneum) corresponding to fewer desmosomal attachments between cells
- *reduced* epidermal thickness especially in the case of abnormally thickened epidermis, e.g., lamellar ichthyosis
- *more even* distribution of melanin
- *increased* epidermal thickness of atrophic, photoaged skin
- *increased* synthesis of glycosaminoglycans (GAGs) and collagen fibers
- *normalization* of elastic tissue distribution and alignment
- *increased* dermal dendrocyte activity (8,33–37)

These effects together with their effects on exfoliation and cell turnover enable the AHAs to contribute significantly to the dermatologist's armamentarium in treating hyperkeratotic and photodamaged skin.

Polyhydroxy Acids and Bionic Acids—Gentler AHAs with Exfoliation Effects

PHAs are organic carboxylic acids that possess two or more hydroxyl groups on an aliphatic or alicyclic molecular structure. When one of the hydroxyl groups occurs in the alpha position, the PHA is a polyhydroxy AHA. In addition to the anti-aging and cell turnover benefits afforded by the alpha-hydroxy structure, the multiple hydroxyl groups of the PHAs, such as gluconolactone (gluconic acid), (Fig. 3) (29,38) and glucoheptonolactone, and polyhydroxy bionic acids, such as lactobionic and maltobionic acid (Fig. 4), impart humectant properties to these molecules. Studies indicate that PHA compounds can attract and bind water (38), which, on a practical level, provides moisturization to skin.

Aside from their moisturizing effects, PHAs have also been shown to strengthen the skin's natural barrier against a chemical irritant (30), and provide non-irritating and non-stinging anti-aging skin benefits to clinically sensitive skin including rosacea and atopic dermatitis (39–41). Previous studies of gluconolactone and lactobionic acid have documented their ability to provide measurable anti-aging effects including skin smoothing, reduced appearance of fine lines and wrinkles, and improved clarity, without

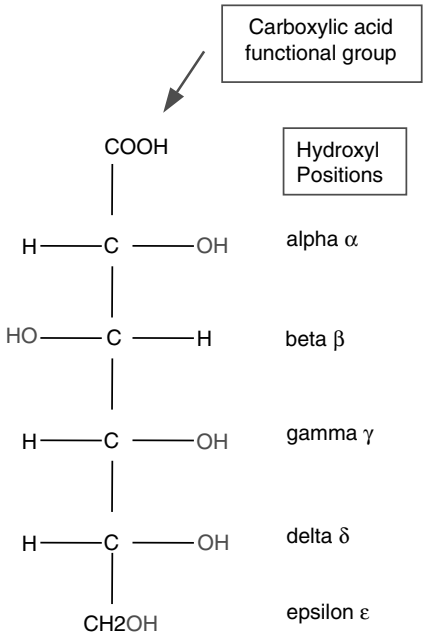

Figure 3 Gluconolactone hydrolyzes to gluconic acid in the presence of water in water-based formulations and skin. Gluconic acid is an alpha-hydroxy acid with additional hydroxyl groups (β, γ, δ, ε), thereby being a polyhydroxy acid (PHA).

causing irritation (42–44). These agents have also been shown to increase skin exfoliation and enhance cell turnover as demonstrated in dansyl chloride cell turnover studies (45).

AHA, PHA, and Bionic Acid Use in Dermatology

AHAs are used extensively as adjunctive agents in the treatment of hyperkeratotic disorders including psoriasis, callouses, acne, keratosis pilaris, and keratoses (6,8,27). They are considered among the best therapeutic options for the treatment of most forms of ichthyosis (24,25). These compounds are also used ubiquitously for the treatment of aging-related skin changes. AHAs are marketed in a variety of forms that are readily available to physicians including superficial peel reagents, cleansers, creams, lotions, and gels.

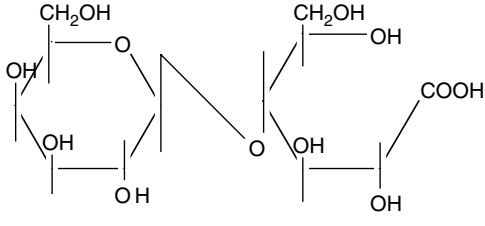

Figure 4 Lactobionic acid, a polyhydroxy bionic acid, is chemically defined as a bionic acid because it is comprised of two units: one gluconic acid molecule (*right*) and one galactose molecule (*left*).

Table 1 Chemical Exfoliants

Exfoliation class	Ingredient	Regulatory status	Solubility	pKa	Bioavailable (non-ionized) % at a selected formulation pH of 3.5[a]	Common concentration range in topical formulations, %
Alpha-hydroxy acid (AHA)	Glycolic acid	Cosmetic	Water-soluble	3.83	68%	Up to 10%
Alpha-hydroxy acid (AHA)	Lactic acid	Cosmetic or Rx (12% ammonium lactate form)	Water-soluble	3.86	70%	Up to 10%
Alpha- (and beta-) hydroxy acid (AHA)	Citric acid	Cosmetic	Water-soluble	3.13	30%	Up to 10%
Alpha-hydroxy acid (AHA)	Mandelic acid	Cosmetic	Water-/alcohol-soluble	3.4	44%	Up to 10%
Alpha-hydroxy acid (AHA)	Benzilic acid	Cosmetic	Slightly soluble in water, freely soluble in alcohol, ether	3.0	24%	Up to 10%
Polyhydroxy acid (PHA)	Gluconolactone/ gluconic acid	Cosmetic	Water-soluble	3.6	56%	Up to 15%
Bionic acid	Lactobionic acid	Cosmetic	Water-soluble	3.8	68%	Up to 15%
Salicylic acid	Salicylic acid	OTC drug or cosmetic depending on claims	Slightly soluble in water, freely soluble in alcohol, ether	2.97	23%	0.5–2.0% (OTC monograph)
Acetyl amino sugars	N-Acetylglucosamine	Cosmetic	Water-soluble	Neutral	N/A	Up to 10%

[a] Calculation based on Henderson-Hasselbalch equation: pKa = pH + log [Acid]/[Base].

The PHAs and bionic acids are gaining use in dermatology due to their significant skin normalizing effects and anti-aging benefits in conjunction with their non-irritating characteristics. These non-irritating agents are especially useful on the sensitive skin of rosacea, atopic dermatitis, and post-procedure (microdermabrasion, peels, non-ablative laser, etc.) when the skin barrier has been disrupted and irritation or stinging is likely to occur due to the increased potential for rapid absorption of skin care ingredients (38,44).

Formulating Factors for the Hydroxyacids

There are several factors to consider in the formulation process to optimally and safely deliver hydroxy acids to skin. The AHAs, PHAs, and bionic acids are mild, organic acids that are optimally absorbed into skin when present in the free acid, non-ionized form (46). As a result, formulation pH is extremely important. At a defined pH, the concentration of the acid and its pKa determine the amount of free acid and, thus, bioavailability, provided by a formulation (Table 1). As the pH of a formulation is reduced below the pKa of the acid, there is a significant increase in the amount of free acid that is available for penetration. As a result, the potential to cause sensory irritation and erythema increases and must be considered in the formulation process. Formulation technologies exist to facilitate the gradual penetration of free acid into skin, thereby diminishing irritation potential and stinging without reducing skin benefits (46). One such technology utilizes amphoteric amino acids during formulation pH adjustment to temporarily complex free AHA molecules and allow a more gentle delivery of the AHA with reduced irritation and stinging.

Another important factor in the hydroxy acid formulation process involves selection of the specific AHA ingredient. The relatively broad selection of ingredient options provides the formulator with the ability to customize AHA solubility parameters and modify potential skin benefits. For example, the more common AHAs, including glycolic acid and lactic acid, are readily soluble in water. In comparison, those with lipophilic side chains have increased oil solubility and the resultant increased potential to absorb into oily skin and pores. Examples include mandelic acid (phenyl glycolic acid) and benzilic acid (diphenyl glycolic acid) (Fig. 1).

Salicylic Acid—A Topical Desmolytic

Salicylic acid (orthohydroxybenzoic acid) (Fig. 5) is an aromatic hydroxyacid with the hydroxyl and carboxyl groups attached directly to a benzene ring (47,48). It is frequently referred to as a beta-hydroxy acid, but a more accurate description is a phenolic aromatic acid because the carboxyl and hydroxyl groups are present on the benzene ring; in this position, the hydroxyl group is acidic (2,47,48). This is to be compared to the hydroxyl group of conventional alpha- or beta- hydroxy acids, which have their attachment on an

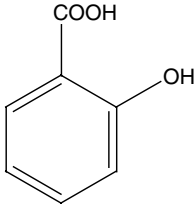

Figure 5 Salicylic acid, orthohydroxybenzoic acid.

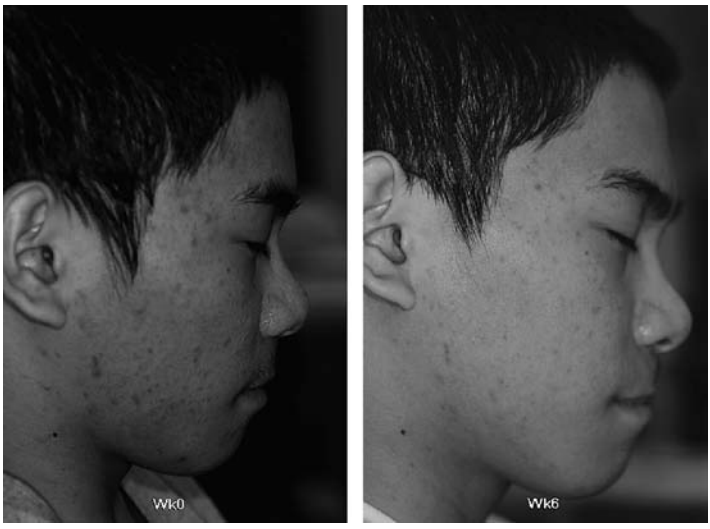

Figure 6 Mild acne: baseline and after six weeks. Twice-daily application of a topical solution containing 2% salicylic acid in combination with 4% alpha-hydroxy acids (benzilic acid, citric acid, tartaric acid, and O-acetylmandelic acid).

aliphatic or alicyclic structure, rendering the hydroxyl group chemically neutral (48). This chemical difference appears to differentiate the activity of salicylic acid from AHAs on the skin (8).

Salicylic acid has been used as a keratolytic since the 1800s, when it was first derived from the bark of the willow tree (49,50). Its effects on skin have been studied and determined to be primarily limited to enhanced shedding of the stratum corneum, with no increase in mitotic activity of the epidermis (3–5). Salicylic acid reportedly functions by decreasing corneocyte cohesiveness over the entire thickness of the stratum corneum via disruption of desmosomal attachments and denaturing glycoproteins, thus the term "desmolytic" (1,3–5).

The effects of salicylic acid are reported to be more extensive and clinically relevant on skin exhibiting conditions of increased corneocyte cohesiveness (3–5). As a result, dermatologists have used salicylic acid to treat various conditions of hyperkeratosis, including corns, warts, seborrheic dermatitis, psoriasis, and dandruff (2,51). Topical salicylic acid is also a mainstay in home care for acne; this is due to the comedolytic effect of salicylic acid (Fig. 6) (7,52). Aside from OTC formulations, there are products designed for use in dermatologists' offices including topical peels with concentrations of salicylic acid up to 30%. These products are primarily targeted for the adjunctive treatment of acne, and are also used in photoaging (53–55). Salicylic acid is frequently also used adjunctively in the treatment of psoriasis as a result of its keratolytic effects and its ability to enhance penetration of topical medications (56,57).

The anti-aging benefits of salicylic acid may be limited to the epidermis. Whereas alpha-hydroxy acids have been shown to stimulate biosynthesis of dermal components and increase dermal skin thickness upon topical application, salicylic acid has been shown to decrease dermal skin thicknness (8). Nonetheless, salicylic acid has been used extensively in anti-aging formulations (7), presumably due to its exfoliation effects.

Formulating Factors for Salicylic Acid

Salicylic acid is a somewhat stronger acid with a lower pKa compared to most AHAs due to the electron-withdrawing properties of the benzene ring. As a result, a lower pH should be considered to optimally formulate bioavailable products (Table 1). However, as pH is reduced, and penetration is increased, there is an increased likelihood to cause irritation. The concentration of use of salicylic acid in over-the-counter (OTC) treatments of acne, dandruff, seborrheic dermatitis, psoriasis, and wart formulations is governed by the FDA OTC monographs. These regulatory documents dictate product form, concentration, uses, directions, and warnings. Since these formulations are regulated as OTC drugs, chemical stability of salicylic acid must be proven over the shelf-life of the formulation. Cosmetic formulations that make cosmetic claims, on the other hand, are free to use varying strengths of salicylic acid; however, the upper concentration may be limited by irritation potential.

N-Acetylglucosamine—A Non-Acid Chemical Exfoliant for Aging Skin

N-acetylglucosamine (NAG) (Fig. 7) is a water-soluble, neutral compound that can easily be incorporated into skin care formulations. It is found naturally occurring as a repeating unit of the abundantly available material known as chitin (e.g., shrimp shells). In human skin, it is a natural component of GAGs, glycolipids, and membrane glycoproteins. Along with glucuronic acid (a polyhydroxy acid), NAG is a one of the repeating, alternating units in hyaluronic acid, the prominent GAG of skin (29).

NAG represents a new class of anti-aging and exfoliation compounds. Its reported beneficial effects on exfoliation occur as a result of its interaction with CD44 receptors on corneocytes, which prevents cross-linking between cells (58,59). Topical application of NAG has been shown to induce desquamation and epidermal cell turnover, as well as increase epidermal differentiation. In a pilot ($n=9$) dansyl chloride exfoliation study of NAG (8% cream, native pH 4.9) in comparison to glycolic acid (8%, pH 3.7) and an untreated control, NAG significantly reduced mean fluorescence scores significantly compared to the untreated control (82% and 62%, respectively), but not as effectively as the tested glycolic acid formulation (92%), $p<0.05$ (60).

NAG also provides moisturizing and anti-aging benefits to skin. As a component molecule in hyaluronic acid and a potential precursor to its synthesis, NAG has been shown to stimulate synthesis of hyaluronan in fibroblasts and keratinocytes (61–62).

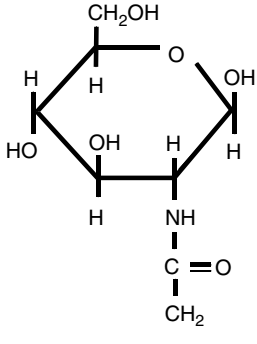

Figure 7 N-acetylglucosamine.

Oral supplementation of NAG (1 g orally per day vs. placebo for 60 days) reportedly reduced skin dryness and roughness, and increased moisturization (63).

Topical evaluation of 8% NAG was shown to provide significant, clinically-assessed improvements on mild to moderate photodamage with substantial improvements in skin firmness and skin thickness. The latter effect is thought to be due to an increase in the production of GAGs, which increases skin volume through water binding and plumping (64). In addition to its desirable cosmetic effects, NAG was shown to be well tolerated on skin (64), and therefore represents a desirable new class of compounds in the growing exfoliation and anti-aging ingredient technology market.

CONCLUSION

Dermatologists and patients are inundated with products and devices to assist the skin in its natural exfoliation process. The purest form of exfoliation is achieved through use of physically abrasive implements on skin. These devices, such as loofahs, buff puffs, and mesh poofs, can provide light exfoliation on a daily basis to slough away excess layers of stratum corneum, helping to keep the skin smooth and luminous. Additional clinical benefits to skin are few, if any, and have not been well documented. Microdermabrasion elevates the physical exfoliation process to the next level. Depending on how it is used, this procedure can simply provide mild exfoliation or, when used as part of a comprehensive skin care regimen, it can help the clinician to achieve meaningful cosmetic outcomes.

Chemical exfoliants have more to offer the dermatologist and patient in terms of flexibility and patient outcomes. When properly formulated for optimal bioavailability and safety, these agents penetrate the skin and disrupt binding between stratum corneum cells to facilitate exfoliation. This effect is beneficial in the treatment of various hyperkeratotic disorders including acne and dry skin. Some chemical exfoliants also provide significant anti-aging effects leading to smoother skin with the reduced appearance of fine lines and wrinkles and an increase in skin firmness. Careful selection of a chemical exfoliant facilitates customization of the formulation to skin condition including oily, dry, and sensitive skin. Furthermore, the chemical exfoliants can be readily formulated into products that can be used at home or in physicians' offices and spas/salons. The use of exfoliating procedures, including topical peels and microdermabrasion, is frequently combined with home application of skin benefit ingredients to achieve significant therapeutic outcomes.

REFERENCES

1. Leveque JL, Saint-Leger D. Salicylic acid and derivatives. In: Leyden JJ, Rawlings AV, eds. Skin Moisturization. New York: Marcel-Dekker, 2002:353–364.
2. Del Rosso JQ. The many roles of topical salicylic acid. Skin & Aging 2005; 13:38–42.
3. Roberts DL, Marshall R, Marks R. Detection of the action of salicylic acid on the normal stratum corneum. Br J Dermatol 1980; 103:191–196.
4. Davies M, Marks R. Studies on the effect of salicylic acid on normal skin. Br J Dermatol 1976; 95:187–192.
5. Huber C, Christophers E. Keratolytic effect of salicylic acid. Arch Dermatol Res 1977; 257:293–297.

6. Van Scott EJ, Yu RJ. Hyperkeratinization, corneocyte cohesion and alpha hydroxy acids. J Am Acad Dermatol 1984; 11:867–879.
7. Kligman AM. A comparative evaluation of a novel low-strength salicylic acid cream and glycolic acid products on human skin. Suppl Cosmet Dermatol 1997;11–15.
8. Yu RJ, Van Scott EJ. α-hydroxyacids, polyhydroxy acids, aldobionic acids and their topical actions. In: Baran R, Maibach HI, eds. Textbook of Cosmetic Dermatology. 3rd ed. New York: Taylor & Francis, 2005:77–93.
9. Draelos ZD. The mechanisms of shaving: a complex interaction between the blade and the skin. Cosmet Derm 1993; 6:54–55.
10. Grove GL. Effect of daily cleansing with a polyester sponge on epidermal cell renewal. Poster presentation, New Orleans, La, February, 53rd Annual Meeting of the American Academy of Dermatology, 1995:4–9.
11. Bergfeld W, Tung R, Vidimos A, et al. Improving the cosmetic appearance of photoaged skin with glycolic acid. J Am Acad Dermatol 1997; 36:1011–1013.
12. Marti VPJ, Lee RS, Moore AE, et al. Effect of shaving on axillary stratum corneum. Int J Cosmet Sci 2003; 25:193–198.
13. Draelos ZD. Re-evaluating the mechanics of shaving. Cosmet Dermatol 1996; 9:11–14.
14. Hopping SB. The power peel: its emergence and future in cosmetic surgery. Int J Cosmet Surg 1988; 6:98–100.
15. Sadick NS, Finn N. A review of microdermabrasion. Cosmet Dermatol 2005; 18:351–354.
16. Kist D, Flor M, Zelickson B. Vibradermabrasion—new technique for superficial exfoliation. Cosmet Dermatol 2005; 18:131–135.
17. Lee WR, Shen SC, Kuo-Hsien W, et al. Lasers and microdermabrasion enhance and control topical delivery of vitamin C. J Invest Dermatol 2003; 121:1118–1125.
18. Bridges MA, Chrzanowski DS, Garrett AB, et al. The efficacy of facial microdermabrasion. Cosmet Dermatol 2003; 16:19–21.
19. Alam M, Omura NE, Dover JS, et al. Glycolic acid peels compared to mircrodermabrasion: a right-left controlled trial of efficacy and patient satisfaction. Dermatol Surg 2002; 28:475–479.
20. Coimbra M, Rohrich RJ, Chao J, et al. A prospective controlled assessment of microdermabrasion for damaged skin and fine rhytides. Plast Reconstr Surg 2004; 113:1438–1443.
21. Shim EK, Barnette D, Hughes K, et al. Microdermabrasion: a clinical and histopathologic study. Dermatol Surg 2001; 27:524–530.
22. Sparacio RM, Voigt A, Maes D, et al. A study comparing a novel home microdermabrasion system with a standard microdermabrasion procedure. Cosmet Dermatol 2004; 17:431–435.
23. J&J study shows home microdermabrasion efficacy on par with professional. The Rose Sheet, March 7, 2005:3.
24. Van Scott EJ, Yu RJ. Control of keratinization with alpha hydroxyacids and related compounds. Arch Dermatol 1974; 110:586–590.
25. Bond M, Van Scott EJ. New hydroxy acid formula for ichthyosis and other severe dry skin. Cosmet Dermatol 1998; 11:32–33.
26. Edison BL, Green BA, Wildnauer RH, et al. A polyhydroxy acid skin care regimen provides antiaging effects comparable to an alpha-hydroxyacid regimen. Cutis 2004; 73:14–17.
27. Yu RJ, Van Scott EJ. Alpha-hydroxyacids and carboxylic acid. Cosmet Dermatol 2004; 3:76–87.
28. 34th Report of the CIR Expert panel—safety of alpha hydroxy acid ingredients. Int J Toxicol 1998; 17.
29. Yu RJ, Van Scott EJ. Hydroxycarboxylic acids, N-acetylamino sugars, and N-acetylamino acids. Skin Med 2002; 2:117–122.
30. Berardesca E, Distante F, Vignoli GP, et al. Alpha hydroxyacids modulate stratum corneum barrier function. Br J Dermatol 1997; 137:934–938.
31. Williams ML. Lipids in normal and pathological desquamation. In: Elias PM, ed. Advances in Lipid Research. New York: Academic Press, 1991:211–262.

32. Shapiro LJ, Weiss R, Webster D, et al. X-linked ichthyosis due to steroid sulphatase deficiency. Lancet 1978; 1:70–72.
33. Ditre CM, Griffin TD, Murphy GF, et al. Effects of alpha hydroxyacids on photoaged skin: a pilot clinical, histologic and ultrastructural study. J Am Acad Dermatol 1996; 34:187–195.
34. Bernstein EF, Underhill CB, Lakkakorpi J, et al. Citric Acid increases viable epidermal thickness & glycosaminoglycan content of sun-damaged skin. Dermatol Surg 1997; 23:689–694.
35. Bernstein EF, Uitto J. Connective tissue alterations in photoaged skin and the effects of alpha hydroxy acids. J Geriatr Dermatol 1995; 3:7A–18A.
36. Bernstein EF. Dermal effects of alpha hydroxyl acids. In: Moy R, Luftman D, Kakita L, eds. Glycolic acid peels. New York, NY: Marcel Dekker, 2002:71–113.
37. Griffin TD, Murphy GF, Sueki H, et al. Increased factor XIIIa transglutaminase expression in dermal dendrocytes after treatment with α-hydroxyacids. Potential physiologic significance. J Am Acad Dermatol 1996; 34:196–203.
38. Bernstein EF, Green BA, Edison B, et al. Poly hydroxy acids (PHAs): clinical uses for the next generation of hydroxy acids. Supplement to Skin & Aging. Skin Aging 2001; 9:4–11.
39. Bergfeld WF, Remzi BK, Green B. An evaluation of the gluconolactone sensitive skin care products. Poster presentation. February 1998: 56th Annual Meeting of the American Academy of Dermatology. FL: Orlando, 1998.
40. Rizer R, Turcott A, Edison B, et al. An evaluation of the tolerance profile of a complete line of gluconolactone-containing skin care fomulations in atopic individuals. Suppl Skin Aging 2001; 9:18–21.
41. Rizer R, Turcott A, Edison B, et al. An evaluation of the tolerance profile of gluconolactone-containing skin care fomulations in individuals with rosacea. Suppl Skin Aging 2001; 9:22–25.
42. Green BA, Edison BL, Wildnauer RH, et al. Lactobionic acid and gluconolactone: PHAs for photoaged skin. Cosmet Dermatol 2001; 9:24–28.
43. Grimes PE, Green BA, Wildnauer RH, et al. The use of polyhydroxy acids (PHAs) in photoaged skin. Cutis 2004; 73:3–13.
44. Briden ME, Green BA. The next generation hydroxyacids. In: Draelos Z, Dover J, Alam M, eds. Procedures in Cosmetic Dermatology: Cosmeceuticals. Philadelphia, PA: Elsevier Saunders, 2005:205–212.
45. Outwater S, Kohut BE, Greenspan AH, et al. An evaluation of the exfoliation efficacy of skin care formulations containing the poly hydroxy acid, gluconolactone. Suppl Skin Aging 2001; 9:26–30.
46. Van Scott EJ, Yu RJ. Bioavailability of alpha-hydroxy acids in topical formulations. Cosmet Dermatol 1996; 9:54–62.
47. Brackett W. The chemistry of salicylic acid. Therapeutic use of salicylic acid. Suppl Cosmet Dermatol 1997; 9:5–6.
48. Yu RJ, Van Scott EJ. Salicylic acid: not a beta-hydroxy acid. Cosmet Dermat 1997; 10:27.
49. Goldsmith LA. Salicylic acid. Int J Dermatol 1979; 18:32–36.
50. Lin AN, Nakatsui T. Salicylic acid revisited. Int J Dermatol 1998; 37:335–342.
51. Draelos ZD. Salicylic acid in the dermatologic armamentarium. Suppl Cosmet Dermatol 1997;7–8.
52. DiNardo JC. A comparison of salicylic acid, salicylic acid with glycolic acid and benzoyl peroxide in the treatment of acne. Cosmet Dermatol 1995; 8:43–44.
53. Elson ML. Salicylic acid peels in a new formulation for use in dermatologic surgery. J Clin Dermatol 1998; 1:36–39.
54. Lee HS, Kim IH. Salicylic acid peels for the treatment of acne vulgaris in asian patients. Dermatol Surg 2003; 29:1196–1199.
55. Kligman D, Kligman AM. Salicylic acid peels for the treatment of photoaging. Dermatol Surg 1998; 24:325–328.
56. Medansky RS, Duffie CA, Tanner DJ. Mometasone furoate 0.1% salicylic acid 5% ointment twice daily versus fluocinonide 0.05% ointment twice daily in the management of patients with psoriasis. Clin Ther 1997; 19:701–709.

57. Tost A, Piraccini BM, Cameli N, et al. Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. Br J Dermatol 1998; 139:655–659.
58. Brysk MM, Rajaraman S, Penn P, et al. Glycoproteins modulate adhesion in terminally differentiated keratinocytes. Cell Tissue Res 1988; 225:657–663.
59. Hudson DL, Sleeman J, Watt FM. CD44 is the major peanut lectin-binding glycoprotein of human epidermal keratinocytes and plays a role in intercellular adhesion. J Cell Sci 1995; 108:1959–1970.
60. Data on file, NeoStrata Company, Inc., 2004.
61. Sayo T, Sakai S, Inoue S. Synergistic effect of N-acetylglucoseamine and retinoids on hyaluronan production in human keratinocytes. Skin Pharmacol Physiol 2004; 17:77–83.
62. Breborowicz A, Kuzlan-Pawlaczyk M, Wieczorowska-Tobis K, et al. The effect of N-acetylglucosamine as a substrate for in vitro synthesis of glycosaminoglycans by human peritoneal mesothelial cells and fibroblasts. Adv Perit Dial 1998; 14:31–35.
63. Kikuchi K, Matahira Y. Oral N-acetylglucosamine supplementation improves skin conditions of female volunteers: Clinical evaluation by a microscopic three-dimensional skin surface analyzer. J Appl Cosmet 2002; 20:143–152.
64. Green BA, Edison BL, Wildnauer RH, et al. Derivatives of sugar compounds provide anti-aging effects. Poster presentation, Washington DC, February 2004: 62nd Annual Meeting of the American Academy of Dermatology.

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Over-the-Counter Acne Medications

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INTRODUCTION

Acne vulgaris is an extremely common condition affecting more than 80–90% of adolescents and young adults (1,2). It typically starts in late childhood or early teens, but onset may be delayed in some people well into their 20s and 30s (3). The incidence rate of acne is roughly the same in males and females but, males tend to have more serious conditions (4). Even later in adulthood, roughly 25% of adult men and 50% of adult women can have acne at some time in their adult lives.

Acne can be difficult to cope with no matter what age, and can cause depression and social anxiety in an adult the same way it can in a teen. Kellett and Gawkrodger (5) found that acne patients reported levels of social, psychological, and emotional problems as great as those reported by patients with chronic disabling asthma, epilepsy, diabetes, back pain, or arthritis. This study also reported that the impact on quality of life did not correlate with acne severity. To a teenager, acne can be one of the worse things that ever happened. Acne frequently makes teens feel embarrassed and lowers their self-esteem. A recent survey of British teenagers found that the emotional toll could be significant (6). This survey found:

- About two out of five teenagers with acne claimed to have skipped school because of embarrassment.
- Between 11- to 18-year-olds, over half said acne prevented them from having a boyfriend or a girlfriend.
- One-third indicated acne hurt their ability to make friends.

Proper care and intervention help improve the life quality by alleviating the negative emotional impacts and building up self-esteem. Treatment can also prevent acne from getting worse and deter scarring.

When it comes to treatment, one study conducted in 2000 indicated that 75% of patients waited about one year before seeking professional help for acne (7). Another survey estimates that only a third of acne sufferers consult their physicians at all. Thus, the majority of acne sufferers apparently opt for the over-the-counter (OTC) acne products to treat their acne. This is most likely due to the fact that most acne cases are mild to moderate in severity for which OTC acne products—readily available and not requiring a prescription and an appointment to the doctor's office—are perfectly suited. And many of today's new OTC acne products are not only clinically effective and safe but also aesthetically elegant and pleasant to use. Non-prescription products tried most frequently were medicated cleansers, washes, pads, gels, and lotions (8). A 2001 report estimates that consumers of all ages spend approximately $100 million per year on OTC remedies for acne (9). The actual market figure today is probably much higher than that as evidenced by the sheer number of OTC acne products that have since come on the market in the recent years. Given the large variety of acne OTC products, this chapter attempts to provide a comprehensive overview while focusing on the recent OTC advances of the two most-widely used acne OTC medications, salicylic acid (SA) and benzoyl peroxide (BPO).

CLINICAL CONSIDERATIONS

Acne affects mainly the face, although other regions rich in sebaceous glands can also be affected (chest, back, upper arms). The lesions can be distinguished into non-inflammatory (open and closed comedones or blackheads and whiteheads) and inflammatory lesions (papules, pustules and nodules).

Four main factors are known to influence the development of acne, namely: (i) sebaceous gland hyperplasia with excess sebum production (seborrhea); (ii) follicular epidermal hyperproliferation and altered differentiation; (iii) follicular colonization by *Propionibacterium acnes* (*P. acnes*); and (iv) inflammation and immune response. Altered epidermal growth and differentiation, combined with seborrhea, is responsible for the formation of the primary lesion in acne: The microcomedo. The development of inflammatory lesions, instead, is often triggered by the effects of *P. acnes* with release of inflammatory mediators.

The first entity in the development of an acne lesion is a tiny invisible plug (microcomedone) of the pilosebaceous duct; skin that is at one time apparently unaffected may subsequently develop lesions if not treated. Generally speaking, it may take up to four weeks for an untreated papule or pustule to complete its life cycle from start to end. Therefore, an acne therapy that significantly reduces lesion counts during the first four weeks is recognized as having treated existing lesions, while therapies effective in reducing acne lesions count during the following four weeks are considered also effective in preventing the appearance of new lesions.

Because of the multiple pathogenetic factors, dermatologists recommend treating acne with combinations of agents that act at different levels. It is widely recognized that an effective acne treatment should not only clear current acne lesions but also prevent the appearance of new ones.

HIGHLIGHTS OF OVER-THE-COUNTER ACNE MONOGRAPH

The Food and Drug Administration (FDA) is the regulatory agency that oversees the marketing of non-prescription acne products. In the Final Acne Monograph, an "acne drug product" is defined as: "A drug product used to reduce the number of acne blemishes, acne pimples, blackheads and whiteheads" (10).

The following ingredients and concentrations are currently allowed in OTC acne products.

- Salicylic acid 0.5–2%
- Sulfur 3–10% alone, or 3–8% in combination with resorcinol
- Resorcinol 2% or resorcinol monoacetate 3% in combination with sulfur 3–8%
- Benzoyl peroxide 2.5–10%

Salicylic acid, sulfur alone, or sulfur in combination with resorcinol are included in the Final Monograph for meeting the monograph conditions of being "generally recognized as safe and effective and not misbranded (Category I)" for the treatment of acne. Although the final rule on benzoyl peroxide is still pending, FDA has allowed its continued use in OTC acne products (11).

In the Final Acne Monograph, it also lays down the requirements for the labeling of OTC acne products. The labeling requirements include a statement of identity that contains the established name of the drug and identifies the product as an acne medication or treatment and the dosage form, a statement for the indications that the drug product is intended to treat; additional statements of treatment benefits; appropriate warnings; and directions of product usage. In the absence of a final ruling on the use of benzoyl peroxide in OTC acne products, manufacturers are referred to the proposed rules (12,13).

FORMULATION OF OVER-THE-COUNTER ACNE PRODUCTS

Manufacturing of OTC acne products is both a science and an art. An OTC acne product must abide by the rules and regulations set in the Acne Monograph in the choice of an allowed active ingredient or combination of active ingredients and the allowable concentration ranges.

Amongst the approved OTC acne ingredients, BPO and SA are the most widely used. Both are topical comedolytics that help dry excess sebum and make the excreted sebum less sticky. This prevents occlusion of the pores and consequent formation of comedones. Topical comedolytics also cause sloughing of the stratum corneum and help remove existing sebum plugs along with loose keratinocytes. They also help normalize keratin turnover in the follicle (14). Interestingly, in the Final Acne Monograph, the agency notes that only BPO has known comedolytic activity and considers the other monograph ingredients as exfoliating agents that can evoke superficial peeling, thereby "aiding in unroofing superficial pustular lesions and causing spontaneous drainage" (15).

Benzoyl peroxide and SA come in a variety of products and in several different delivery systems, such as creams, washes, gels, and cleansing pads (16). Skin reactions to topical treatments may vary depending on the skin types. Thus, formulating the right OTC product that can work best for the majority of acne population is a formidable task. The main concern should be minimization of irritation on all skin types. The formulator should also take into account the time an individual has to care for the skin, the lifestyles of consumers, and the cost of individual products.

Another important consideration for formulation is the effects of the vehicle on the skin. Gels and solutions such as astringents can have higher alcohol contents and may increase the drying effect, while creams and lotions delivered in an emollient base tend to be moisturizing to the skin. "A proper vehicle is one that will deliver the drug to the site of action at a rate that will allow maximum benefit without causing or allowing toxic effects" (17). Given that all OTC acne drugs are keratolytics and can be somewhat drying and irritating, the ability of a vehicle that can mitigate the irritancy potential and allow delivery of the maximum drug benefits is all the more important.

What this also translates into is that in order to provide sustainable treatment benefits, OTC acne treatment should be developed in such a way that the consumers can and will like to use on a consistent, long-term basis. In other words, OTC acne products should be effective in delivering the clinical improvements as indicated, cause little or no irritation, be aesthetically pleasant, and be easy to use.

TRENDS IN OVER-THE-COUNTER ACNE FORMULATIONS

In the last decade, no new OTC ingredient has been approved for the treatment of acne. However, much research effort has led to the development of better vehicles and delivery forms designed to reduce skin irritation and improve efficacy. The common product forms are gel, lotion, cream, and cleanser.

In addition, other delivery methods have appeared, which include masks, scrubs, pads and even makeup foundation and concealing sticks. Body acne has also been gaining notices: Body washes and leave-on sprays have been developed to address delivery to hard-to-reach areas such as the back. The varieties in forms and delivery systems make it possible to design OTC treatment programs that are tailored to an individual's needs.

At the same time, there is an increasing desire to provide patients with a comprehensive product system or regimen that is easy to follow on a daily basis. This approach has two potential advantages: Encouraging usage compliance by consumers, and ensuring a product system that has been tested and proven to be compatible and may even be synergistic to deliver optimal efficacy and safety profiles. Multi-step systems that consist of combinations of products from cleanser to lotion or cream have been designed to provide a full range of products to use in daily routines. Typically one or two of the products in the system contain an OTC active ingredient. Cleansers, toners, masks, cosmoceuticals, emollients and sunscreens can be incorporated as adjunctives in the system. Some products even go beyond acne to try to address both acne and aging, targeting those adults who are concerned about both conditions on their skin.

ADVANCES IN OVER-THE-COUNTER ACNE FORMULATIONS

Salicylic Acid

SA is a keratolytic agent. It is used to treat a variety of hyperkeratotic skin disorders such as psoriasis, ichthyoses, seborrheic dermatitis, palmoplantar keratosis, keratosis pilaris, and pityriasis rubra pilaris (18). In acne, SA may reduce comedones (comedolytic) and prevent the formation of new ones by breaking down the comedonal follicular plug and by reducing follicular desquamation. It is an effective alternative for patients who do not tolerate topical retinoids. SA is approved for use in pediatric acne.

Concentrations of SA ranging from 0.5–10% from various manufacturers have been recommended for acne, but 2% is the maximum strength allowed in non-prescription acne products in the U.S. It is commonly found in acne cleansers.

The effectiveness of 0.5–2% SA as an acne treatment was originally demonstrated in two studies submitted to the FDA during the OTC approval phase (50 FR 2174, 1/15/85). The first study was a 12-week, double-blind investigation on 180 subjects comparing the efficacy of 2% SA solution versus vehicle solution and active control (5% benzoyl peroxide) in the treatment of acne. Forty percent of the subjects treated with 2% SA showed a good or excellent decrease in total lesions compared to 5% of the subjects in the vehicle group and 2% of the subjects in the benzoyl peroxide group. The study reported that SA was significantly more effective than vehicle and benzoyl peroxide in the reduction of total lesions, inflammatory lesions, and open comedones (but not closed comedones) (19). The second study was conducted on 187 subjects. Two SA formulations at 0.5% and 2% were tested against the vehicle. The results showed that both 0.5% SA and 2% SA were superior to the vehicle in reducing inflammatory lesions, open and closed comedones, and total lesions (20).

The efficacy of the cleanser form was investigated by Shalita in a cross-over study. He compared a 2% SA cleanser and a 10% benzoyl peroxide wash in 30 acne subjects. Subjects were randomly treated for two weeks with either SA or benzoyl peroxide. At the end of the first two weeks they switched treatment. The study concluded that only SA cleanser induced a significant reduction in comedones (21). More recently, a study by Pagnoni et al. (22) showed a significant reduction from baseline in open comedones count after four weeks of treatment using a 2% SA scrub or a 0.5% SA toner with 1% glycolic acid. The scrub induced a significant improvement as early as two weeks after treatment.

SA pads were investigated by Eady et al. (23). They compared 2% SA lotion versus placebo impregnated into pads. They found that the SA pads were significantly better than the control in reducing the total lesion count, starting at the fourth week of treatment. The superiority in improving comedones was also noted. Zander and Weisman reviewed three placebo-controlled studies and reported that SA pads were effective in reducing the number of primary lesions and thereby the number and severity of all lesions associated with acne (24). They also reported that SA was superior to benzoyl peroxide in reducing the total number of acne lesions.

Based on these previous studies, SA is generally considered less effective than benzoyl peroxide in the treatment of inflammatory acne but more effective in the treatment of comedonal acne.

Recently a new paradigm on SA has been ushered in when an acne treatment gel containing 2% SA was shown to be as effective as a 10% benzoyl peroxide lotion in all acne-related parameters. Because of the drying and irritating potentials of acne active

Table 1 Anti-acne Efficacy Comparison of a 2% Salicylic Acid Treatment Gel Containing Skin Soothing Naturals with a 10% Benzoyl Peroxide Lotion

	Mean change from baseline (%)			
	2% Salicylic acid gel (N = 44)		10% Benzoyl peroxide lotion (N = 46)	
Acne lesion type	Week 2	Week 4	Week 2	Week 4
Open comedones	−31	−43	−34	−56
Closed comedones	−30[a]	−26[a]	−13	−6
Inflammatory (papule + pustules)	−26[a]	−23	−15	−6
Total lesions	−28[a]	−27	−17	−15

Shading indicates a significant change from baseline ($p < 0.05$).
[a] Significantly higher improvement compared to the other treatment ($p < 0.05$).

ingredients, some of today's acne treatment products are formulated with cosmetic ingredients or cosmoceuticals that can help soothe the skin and reduce irritation. This approach has proven very effective in optimizing efficacy for OTC acne products containing SA.

A SA gel formulated with a proprietary soothing blend of naturals was compared to a 10% benzoyl peroxide treatment lotion, to the vehicle and also to no treatment control in double-blind and randomized clinical studies (25,26). The 2% SA treatment gel was found to be at parity to 10% benzoyl peroxide in target lesion resolution and on par or even superior in reducing closed comedones and inflammatory lesions (Table 1).

The effects on the target lesion resolution was evaluated by assessing lesion erythema, size and elevation and surrounding erythema. Significantly faster resolution was observed with the active treated group versus the vehicle group and the untreated group in blinded and randomized clinical evaluation (Fig. 1).

When it comes to irritancy, the 2% SA gel was superior to the 10% benzoyl peroxide lotion in mildness. Skin soothing benefits were evidenced in the reduction of pimple associated discomfort and the lessening of global erythema. These effects were observed in the majority (70–90%) of the study subjects. Similar gentle yet effective treatment benefits were also noted with another SA treatment in a lotion base (27).

Yamamoto et al. (28) have reported diminished water barrier function in acne patients. The strong vehicle effects often observed in acne clinical studies might be due to the vehicles being less drying. Thus, having a delivery vehicle that helps improve skin moisturization can have a positive impact in the treatment.

Recently, Chantalat et al. (29) reported the use of a microgel complex to optimize SA's anti-acne efficacy through solubilizing sebum and enhancing the delivery of SA. This microgel complex is a multiple-phase system consisting of micro-droplets in an aqueous phase. High-performance liquid chromatography (HPLC) analysis of

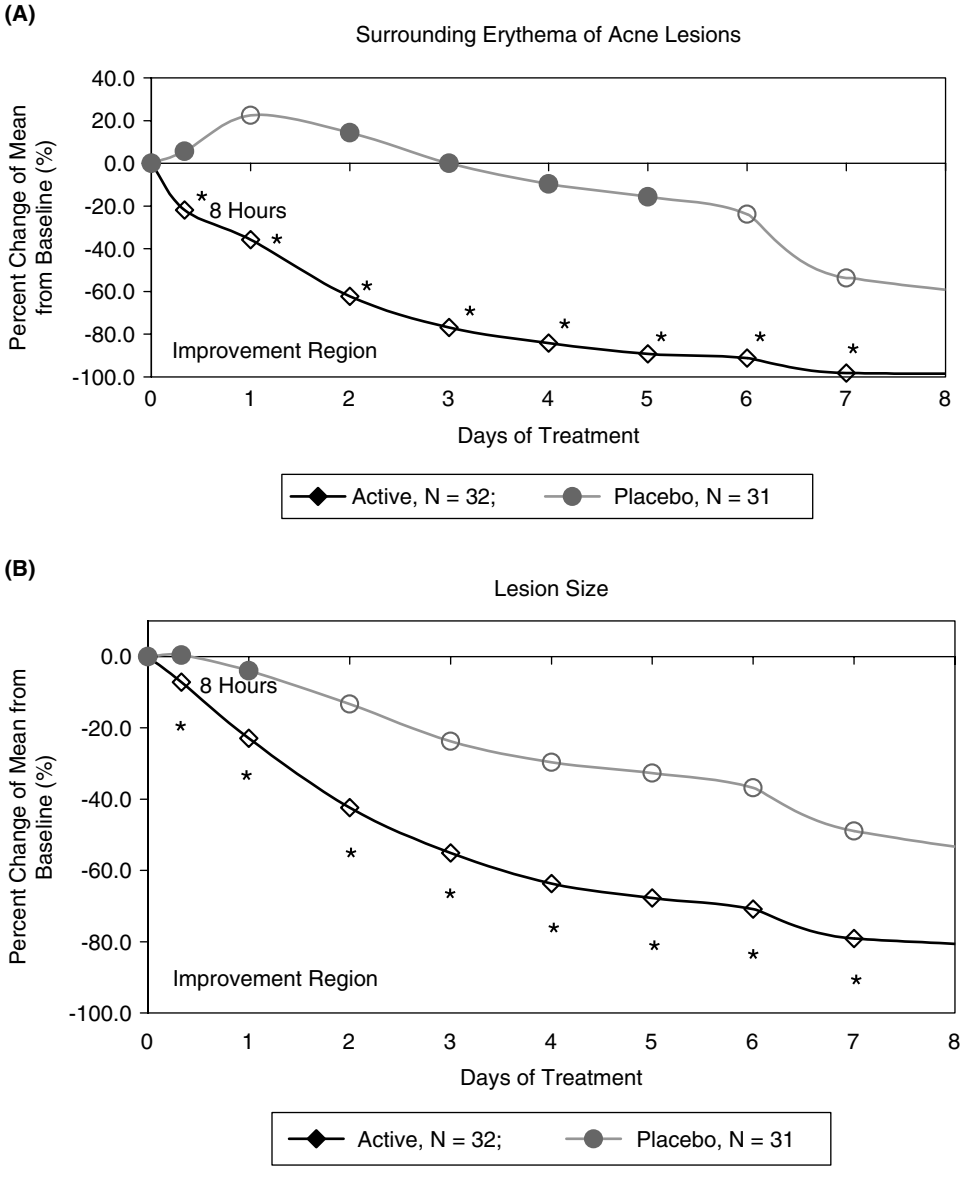

Figure 1 Blinded clinical expert grading of (**A**) surrounding erythema and (**B**) lesion size comparing a salicylic acid gel with a synergistic blend of skin soothing naturals (active) and its vehicle control (placebo). Note: open symbols denote mean values that are significantly different from baseline ($p < 0.025$). Asterisks next to the data points denote between treatments difference in favor of the labeled treatment ($p < 0.01$).

microgel complex formulations with SA shows that the distribution of SA is significantly higher in the hydrophobic phase than the aqueous phase. In vitro investigations with model sebum compositions showed that certain components of the microgel complex solubilize sebum. Using fluorescence spectroscopy, ultraviolet (UV) light imaging, and confocal microscopy, they demonstrated in vivo that the depth of SA penetration in the skin was increased, as was the extent of deposition. Furthermore, skin conductance and transepidermal water loss (TEWL) measurements showed that formulations with the microgel complex delivered greater moisturization benefits versus placebo. This microgel formulation containing SA was shown to be highly effective not only at treating existing acne lesions but also at ameliorating emerging acne pimples—the sub-surface acne lesions that are not yet visible on the skin surface (30).

Benzoyl Peroxide

Benzoyl peroxide has been one of the most important topical acne agents for a long time. It has a combination of antibacterial, anti-inflammatory and comedolytic properties. Benzoyl peroxide can penetrate through the follicular duct deeply into the infundibulum where it then releases oxygen to inactivate anaerobic bacteria that cannot live in its presence, *P. acnes* being one of those bacteria. A study by Bojar et al. (31) reported an almost 2-$\log_{10}$ decrease in the density of *P acnes* after two days of 5% benzoyl peroxide treatment. Pagnoni et al. (32) confirmed this rapid effect in their investigation that showed *P. acnes* count decreased by an average of 2-log after a three-day treatment with a 10% benzoyl peroxide cream, without any further decline by day 7. In contrast to the bacterial resistance known to be associated with the use of oral and topical antibiotics, the antibacterial activity of benzoyl peroxide occurs without the induction of bacterial resistance.

The anti-inflammatory effect of benzoyl peroxide is probably directly related to the decrease of *P. acnes* density in the sebaceous follicles. It is known that *P. acnes* induces monocytes to secrete pro-inflammatory cytokines such as tumour necrosis factor α (TNF-alpha), interleukin-1β (IL-1β), and IL-8 through a Toll-like receptor 2-dependent pathway (33,34).

Benzoyl peroxide is commonly available as a liquid cleanser (2.5–10%), bar cleanser (5–10%), pads (3–9%), mask (2.5–5%), lotion (5–10%), cream (5–10%), and gel (2.5–20%). A report from the Global Alliance to Improve Outcomes in Acne (35) indicates that gel formulations may be more stable and may release benzoyl peroxide more consistently than creams and lotions.

Specific cleanser forms of benzoyl peroxide (5% and 10%) have been shown to reduce *P. acnes* density and inflammatory lesion counts. To increase the cleanser's benefits, patients should be instructed to gently massage the cleanser into moistened skin and allow a 20-second contact time followed by a 10-second gentle rinse (36). Recently a benzoyl peroxide cleanser mask takes this one step further by allowing the patients to use the product either as a cleanser or as a mask that allows for even longer contact time (37).

Benzoyl peroxide can enhance the efficacy of concomitant antibiotic therapy and reduces the development of antibiotic-resistant *P. acnes*. When used in combination with oral antibiotics, it has been shown to reduce the resistance of bacteria to the systemic drug. Recently, new drugs have combined benzoyl peroxide with other topical antibiotics. These

formulations are available only by prescriptions and include erythromycin 3%–benzoyl peroxide 5% and clindamycin 1%—benzoyl peroxide 5% combinations. These products have been shown to have some additive effect compared to either drug alone and to reduce the resistance to the antibiotic.

Once absorbed by the skin, benzoyl peroxide is metabolized to benzoic acid and excreted in the urine as benzoate. There is no evidence of systemic toxicity caused by benzoyl peroxide in humans (38). Side effects of benzoyl peroxide may include mild to moderate irritation and skin dryness. Contact allergy has been reported in approximately 1% of patients. Additionally, benzoyl peroxide formulations may bleach fabrics and hair. It is the controversy over tumor-promoting reports from animal studies on benzoyl peroxide that caused the FDA to delay ruling on its monograph status. In the interim, the agency has issued proposed rules that recommend sun avoidance and the use of a sunscreen when using a benzoyl peroxide product to treat acne (39).

Many peer-reviewed studies have been published supporting the efficacy and safety of benzoyl peroxide in acne. This ingredient is the main OTC treatment suggested by dermatologists because of its undisputed efficacy in inflammatory lesions. In fact, a review of the literature by Eady et al. (40) showed that none of the topical antibiotics used in various studies was clinically better than benzoyl peroxide. A direct comparison between a 10% benzoyl peroxide gel, a 1% clindamycin lotion, and a 20% azelaic acid cream found that the 10% benzoyl peroxide gel was significantly superior in reducing *P. acnes* at two and four weeks of treatment (41). Clinically, benzoyl peroxide has also additive benefits when combined with other topical antibiotics (such as clindamycin or erythromycin) (42,43).

Several previous studies have originally documented the efficacy of 2.5–10% benzoyl peroxide, which were reported in the Advance Notice of Proposed Rulemaking for Topical OTC Acne Drugs and accepted as support for the efficacy of benzoyl peroxide in acne (44). It is interesting to note that higher concentrations of benzoyl peroxide have not been shown to be more effective in acne, but may actually increase the risk of irritation. An eight-week study (45) compared the efficacy of 2.5% benzoyl peroxide versus 10% benzoyl peroxide in 50 acne subjects. The results showed that both treatments significantly decreased the total number of papules and pustules, with no difference in effectiveness between the two concentrations. There was also basically no difference in the reduction of total lesions between the two concentrations, while the incidence and severity of adverse events was much higher in the 10% benzoyl peroxide group. Similar findings were reported by Mills et al. (46), in which they compared a 2.5% benzoyl peroxide against its vehicle, and against a 5% and a 10% benzoyl peroxide gel in three double-blind studies involving 153 patients with mild to moderately severe acne vulgaris. The 2.5% benzoyl peroxide formulation was more effective than its vehicle and equivalent to the 5% and 10% concentrations in reducing the number of inflammatory lesions.

Orth et al. (47) investigated the penetration of a 2.5% and a 10% benzoyl peroxide formulation into the sebaceous follicles using cyanoacrylate follicular biopsy. The results showed that benzoyl peroxide penetrated into the follicles within a few hours and that the 2.5% formulation delivered a similar amount of benzoyl peroxide as the 10% product. The authors suggested that the vehicle of the 2.5% formulation played a significant role in enhancing the delivery of benzoyl peroxide.

One of the few studies comparing benzoyl peroxide to topical retinoids was conducted by Belknap (48). He compared 5% benzoyl peroxide twice daily versus 0.05%

retinoic acid once daily in an eight-week study. Both treatments were "extremely effective" for all types of lesions and significantly reduced open and closed comedones after two weeks of treatment. Somewhat higher number of patients in the benzoyl peroxide group showed excellent results.

A study by Shalita et al. showed the additive effect of the cleanser in acne treatment (49). They compared the efficacy of a combination of benzoyl peroxide 6% cleanser and tretinoin 0.1% microsphere gel versus tretinoin alone during a 12-week study. Fifty-six subjects with moderate acne completed the study. Both treatments showed a significant reduction in inflammatory and non-inflammatory lesions from baseline. However, the combination regimen produced a greater reduction of inflammatory acne lesions than the monotherapy without increasing local irritation.

Recently, a British study compared the efficacy and treatment costs of benzoyl peroxide versus oral antibiotics (50). This 18-week study evaluated five antimicrobial acne treatments in approximately 650 participants: oral oxytetracycline; oral minocycline; benzoyl peroxide; separate administration of topical erythromycin and benzoyl peroxide; and a combination of topical erythromycin and benzoyl peroxide. The authors found that topical 5% benzoyl peroxide used twice daily as single active agent was similar in efficacy to 100 mg minocycline once daily. The analysis of cost-effectiveness found that the cheapest treatment (benzoyl peroxide) was 12 times more cost-effective than minocycline. Additionally, the authors noted that pre-existing propionibacterial resistance compromised the clinical efficacy of oral tetracyclines. In contrast, regimens combining benzoyl peroxide with erythromycin were unaffected by resistance. The authors concluded that topical benzoyl peroxide and benzoyl peroxide/erythromycin combinations are similar in efficacy to oral antibiotics (oxytetracycline and minocycline). The more significant message is that the clinical equivalence comes without being affected by propionibacterial antibiotic resistance.

Sulfur and Sulfur/Resorcinol Combinations

Sulfur has been used to treat acne for hundreds of years for its peeling and drying actions, and it is found in various washes, soaps, and creams. It is an antifungal and antibacterial agent. Its keratolytic activity is somewhat controversial, with some authors showing even a comedogenic effect (51). It is not fully understood how sulfur works in the treatment of acne lesions. The claimed keratolytic properties may derive from the interaction between sulfur and keratinocytes, producing hydrogen sulfide. Smaller sulfur particles could allow greater interaction with keratinocytes and, therefore, produce greater therapeutic efficacy (52). Because of its unpleasant odor, sulfur is rarely used alone. As an OTC ingredient, it is most frequently found in combination with resorcinol. Sulfur is also present in prescription acne products in combination with sodium sulfacetamide.

Resorcinol has antibacterial, antifungal and mild keratolytic activity. When used as resorcinol monoacetate, this slowly liberates resorcinol, generating a milder but longer lasting effect. In the Acne Monograph, the OTC panel concluded that resorcinol is safe for human applications but did not find it efficacious in acne as a single ingredient (53). Therefore, resorcinol and resorcinol monoacetate are currently approved as OTC acne ingredients only in combination with sulfur. Side effects of sulfur and of resorcinol include

mostly mild irritation. Unpleasant odor (sulfur) of the formulation may also be a problem for patients.

Sulfur preparations for acne treatments are not as popular as they were in the past decades. Although sulfur is found in the forms of cream, lotion, ointment, spot-treatment mask, and bar soap, the more common use is in its prescription combination with sodium sulfacetamide.

Published peer-reviewed studies on the efficacy of sulfur, alone or in combination with resorcinol, are basically non-existent. Few controlled efficacy studies are, however, described in the OTC Acne Monograph and were presented to the OTC panel as substantiating material for the approval of these ingredients (54). Based on these studies, sulfur was approved as an acne ingredient in the concentrations of 3–8%. Resorcinol (2%) and resorcinol monoacetate (3%), however, were not found to be effective as single ingredients, and they were approved only in combination with sulfur 3–8% (55). The Acne Monograph reports that in a 12-week study (56), more subjects treated with 3% sulfur showed a good to excellent response, compared to the vehicle group, although no statistical analysis was conducted. A series of split-face, vehicle-controlled studies (57) showed a better reduction in lesion count in the subjects treated with a 5% sulfur product compared to vehicle.

Another study compared an 8% sulfur-2% resorcinol cream against placebo cream in 25 subjects using a split-face design (58). After eight weeks of treatment sulfur-resorcinol was significantly better in reducing open comedones, papules and pustules compared to placebo. A third study compared four treatment cells of 60 acne subjects each. The treatments were applied three times daily for eight weeks and consisted of: (i) 2.66% sulfur–1% resorcinol; (ii) 8% sulfur–2% resorcinol; (iii) 2.66% sulfur; and (iv) placebo. The two combinations of sulfur-resorcinol were found equivalent and were superior to both the placebo and the sulfur alone in the reduction of papules and "whiteheads" (59).

While the effect of sulfur on non-inflammatory lesions is not clear, its combination with resorcinol seems to increase its efficacy in both inflammatory and comedonal lesions.

Adjunctive Acne Products

A few adjunctive products have been promoted for the treatment of acne. Since these are not sold as OTC drugs, well-controlled studies are usually missing and it is difficult to interpret their true benefit as acne treatments.

Tea Tree Oil

Tea tree oil (TTO) is extracted from the Melaleuca alternifolia and in the past decade has become a popular topical antimicrobial for skin conditions such as tinea pedis and acne. The three major components of TTO responsible for anti-*P. acnes* activity have been found to be alpha-terpineol < terpinen-4-ol < alpha-pinene (listed in order or increased minimum inhibitory concentration (MIC) values) (60). Besides its anti-*P. acnes* properties, TTO has been found to have a significant and rapid (within 10 minutes) anti-inflammatory activity when applied to histamine-induced weals (61). This could be an additional pathway through which TTO improves inflammatory acne.

One of the few clinical studies conducted in acne compared a 5% TTO gel with a 5% benzoyl peroxide lotion in 124 acne patients. Both treatments had a significant effect in improving both inflamed and non-inflamed acne lesions, although benzoyl peroxide produced faster results. Fewer side effects, though, were experienced in the TTO group (62).

Botanicals

Although products cannot be sold bearing an anti-acne label unless they contain an OTC approved ingredient, many botanical formulations are marketed towards the acne-prone consumer claiming to "heal," "purify," or "cleanse" the skin and pores. Companies promote their proprietary formula of herb extracts, but well-conducted clinical studies are lacking, and therefore it is difficult to understand the true efficacy of these products. The formulation may include different herb extracts with various activities (antimicrobial, anti-oxidant, anti-inflammatory, soothing, etc.).

Retinaldehydes

A novel European acne formulation combines 6% glycolic acid and 0.1% retinaldehyde. In a study on mild to moderate acne patients, the combination led to "important/very important" global improvement at two months (63). This formulation has been also suggested to prevent post-inflammatory pigmentation (64).

Capryloyl Salicylic Acid

A lipophilic derivative of SA (capryloyl SA or LHA) has been proposed as a new anti-acne agent by a European firm. In a recent study, they showed that the LHA cream was well tolerated and significantly more effective than a control moisturizing cream throughout the 87-day period as per the global evaluation scale (65). However, no comparison with its vehicle cream or with any approved SA drug was presented.

Oral Supplements (Nutraceuticals)

Oral supplements have recently become more popular as a way of promoting total well-being. Some supplements are marketed as part of a multi-step aging or acne treatment. Nutraceuticals marketed for acne typically contain either herb extracts or specific vitamins (especially vitamin A and vitamin B-complex).

Alpha-Hydroxyl Acids

Alpha-hydroxy acids (AHAs) such as glycolic acid and lactic acid have been used for many years by dermatologists at concentrations of 20% to 30% for facial peel procedures. More recently, AHAs have been added to OTC washes and moisturizers at concentrations of 4% to 6%. AHAs have been found to soften the stratum corneum, remove dead cells, and change free radicals on the skin. These products combine well with both topical comedolytics and topical antibiotics. They can be used as the daily facial cleanser or moisturizer before application of prescription medication. AHAs in the 20% to 30% strength help to improve discoloration and scarring. Mild benefit can also be seen at the 4% to 6% strength. As with all other topical products, irritation may be a problem, especially during the initial few weeks of usage. AHAs are sometimes used

alone in mild acne. Various products, though, add glycolic acid to SA formulations claiming an increase in the exfoliation benefits. A 2% lactic acid cream gel preparation has been reported to be effective in both inflammatory and non-inflammatory acne lesions compared to placebo (66).

Over-the-Counter Combination Therapy

Since acne is a multi-factorial disorder, dermatologists recommend the use of combination therapy. In analogy, an OTC combination therapy was recently developed to treat multiple pathogenic factors of acne. This system combines a 2.5% benzoyl peroxide lotion with an SA cleaner that also contains glycolic acid. A daytime broad-spectrum sunscreen containing a proprietary blend of skin soothing naturals is included in the system as per FDA recommendation (67).

This OTC combination therapy system was compared to a benzoyl peroxide only system in a double-blind, randomized, placebo-controlled clinical study on 90 subjects with mild to moderate acne. Both systems were well tolerated, although the benzoyl peroxide–only system had slightly higher irritation. The clinical results showed that the OTC combination therapy system with both SA and benzoyl peroxide treatment products rapidly improved acne within one week and continued to further ameliorate over the course of treatment. Target pimple size, edema and erythema were significantly reduced within two days (first time point). Significant reduction of full-face total acne lesion counts was seen as early as day 4. In contrast, the benzoyl peroxide only system did not show significant reduction of full face acne lesions until week 2 and global acne severity until week 4 (68). The time course kinetics of the treatments (charts in Fig. 2) show that the main difference clinically appeared to be in the superior reduction of the closed comedones or the primary lesions by the SA + BPO OTC combination therapy system.

These results demonstrate the value of using the combination therapy approach in OTC acne treatments as in Rx.

Clinical Imaging in the Development and Evaluation of Over-the-Counter Acne Products

Photography has been a useful tool for evaluating and documenting treatment benefits (Fig. 3 for example). Several acne-grading methods have even been proposed based on photographs. Recent advancement in digital imaging has made image capture and evaluation much more convenient. The techniques that have been applied to clinical imaging go beyond just regular photography that mainly utilizes the visible light spectrum. Photographers have used polarized filters to either cut through the surface specula for a matted appearance with cross-polarized light (Fig. 4 for example), or to enhance the surface specula to make the shine shinier or the surface texture more 3-dimensional–like with the help of parallel-polarized light. Skin redness and pigmentation are highlighted in cross-polarized light images, while parallel-polarized light images bring out the surface luminosity and make the height of a pimple or the depth of a wrinkle more distinctive.

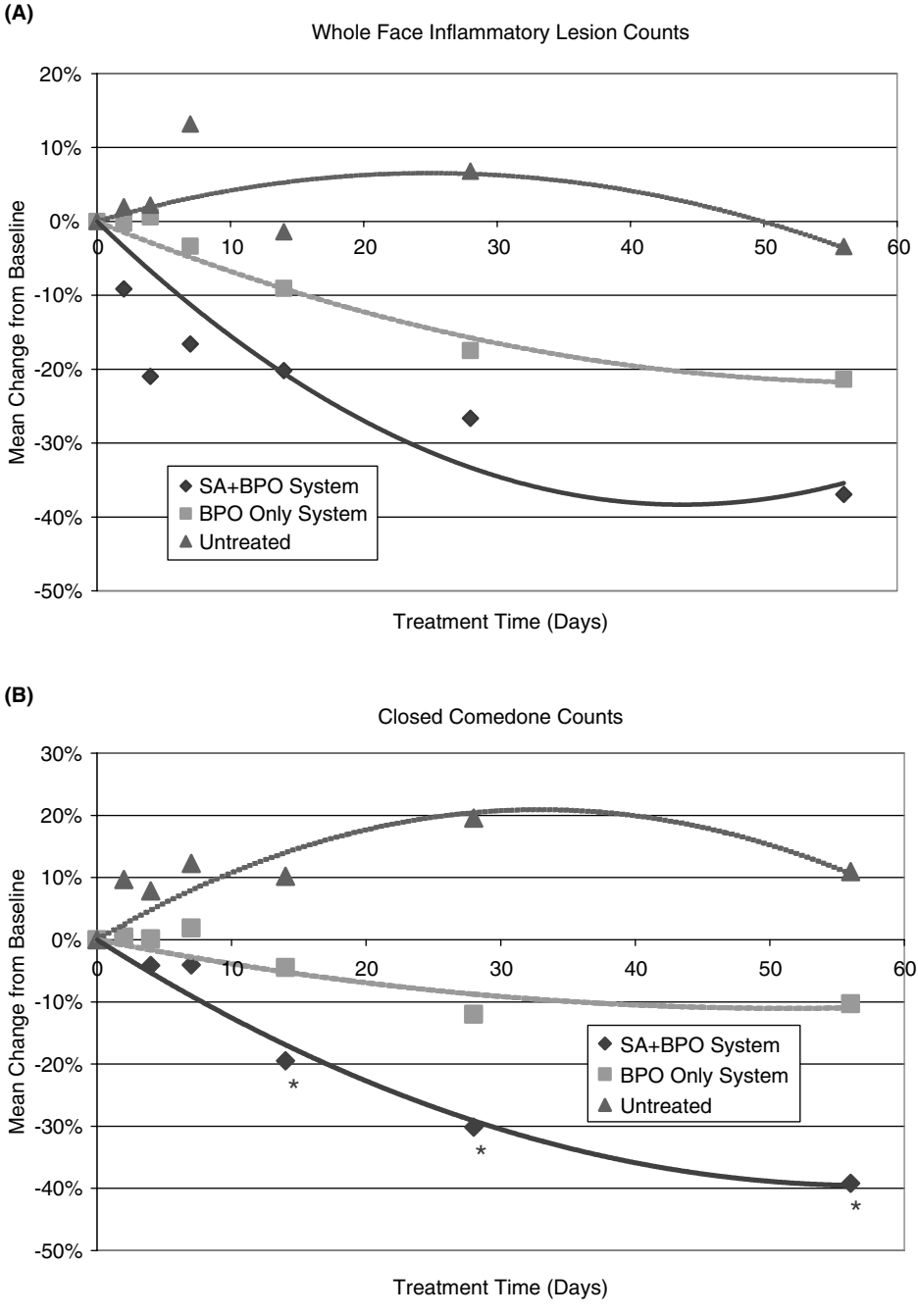

Figure 2 Treatment effects of an over-the-counter regimen containing salicylic acid and benzoyl peroxide versus a regimen containing only benzoyl peroxide. Upper chart (**A**) shows the changes in the total inflammatory lesion counts and the lower chart (**B**) shows the changes in closed comedone counts. Asterisks denote significantly greater reduction among treatments in favor of the labeled treatment.

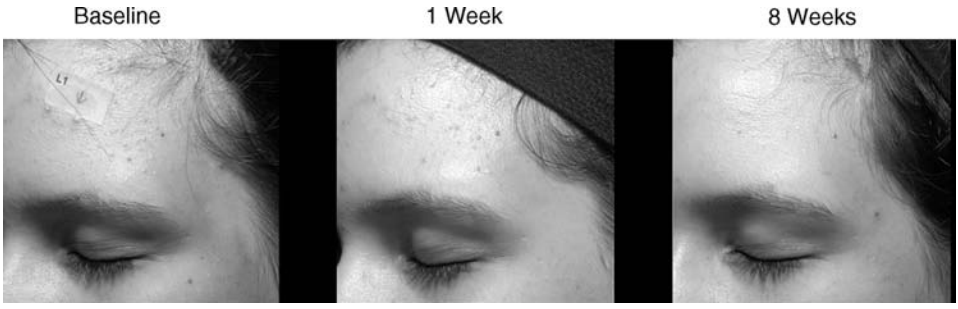

Figure 3 Acne skin images from visible light photography comparing the skin conditions before, during and after treatment with an over-the-counter combination therapy system (salicylic acid + benzoyl peroxide). Note the marked improvements in skin texture, bumpiness and clarity. Skin redness was also reduced (data not shown).

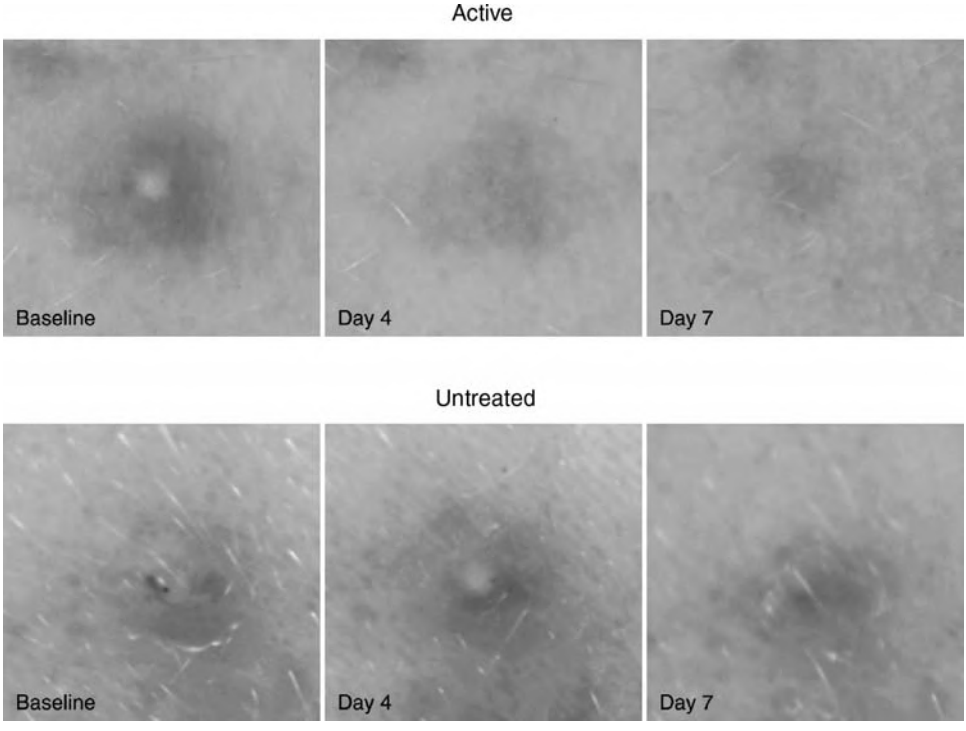

Figure 4 Cross-polarized light images tracking pimple resolution and redness reduction of a pimple treated with a 2% SA gel (active) and of an untreated pimple. Blinded analysis of individual pimple images showed pimple resolution by the 2% SA gel was faster than by the placebo (the vehicle gel) and the untreated control, and similar to that of a 10% benzoyl peroxide lotion. *Abbreviation*: SA, salicylic acid.

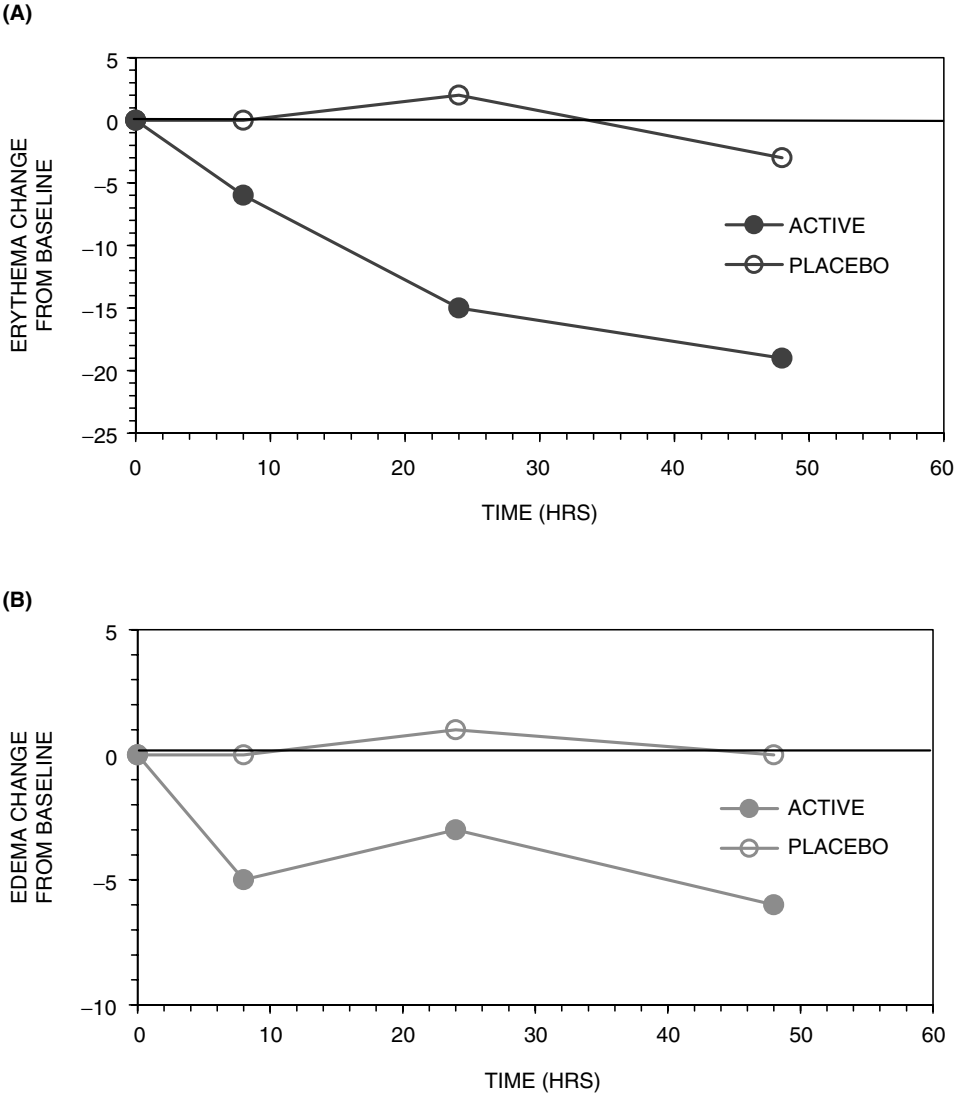

Figure 5 Time Course of target Lesion resolution as measured by hyper-spectral image analysis quantifying (**A**) Erythema, and (**B**) Edema (water).

Another imaging technique involves the use of UV-enriched lamp or blue light. When the skin is illuminated in this manner, the pilosebaceous glands glow as intensely yellow-green or orange-red fluorescent spots (69). Partially or totally clogged pilosebaceous glands all show particularly intense fluorescence of different sizes and brightness, reflecting the degrees to which they are blocked. While the yellow-green fluorescence is associated with the pore plug materials, the orange-red fluorescence is shown to be the emission at wavelengths of 620 and 680 nm by the *P. acnes* under

385–415 nm light (70–73). The intensity of this orange-red fluorescence is proportional to the density of *P. acnes* and declines under effective antibiotic treatment (74,75). Fluorescence photography is thus a quick way to assess the antibacterial efficacy of benzoyl peroxide formulations (76).

A powerful method has recently been developed that incorporates all of the above imaging techniques to enable concurrent evaluation of clinical and sub-clinical conditions in the skin (77,78).

The most recent advancement in the clinical digital imaging field is the hyper-spectral imaging technique (79). This technique uses narrow-band filters in front of the camera to acquire a series of images (called a hyper-spectral cube). The narrow band filters are selected to detect different chromophores in the skin, the distribution of which is captured in the corresponding images. Each pixel in an image, thus, contains spectral information of the corresponding imaged site on the skin. Reflectance data can be analyzed on a pixel-by-pixel basis to yield chromophore concentrations (oxy-hemoglobin, deoxy-hemoglobin, melanin, water, and light scattering). Increased local oxy-hemoglobin concentrations are manifested as erythema. Increased local water concentrations are related to interstitial fluid accumulation due to edema. Chen et al. (80) studied the progression of acne lesion maturation by monitoring lesion erythema and edema with hyperspectral imaging. An example of the results that can be obtained is shown in Fig. 5. Chantalat et al. (81) applied hyperspectral imaging to detect sub-clinical acne lesions that were not yet visible on the skin surface, and tracked the effects of treatments on resolving inflammation associated with the sub-clinical lesions. These studies demonstrate the unique potential of hyperspectral imaging in the evaluation of clinical and sub-clinical acne non-invasively.

SUMMARY

Majority of acne sufferers rely upon OTC acne medication to treat their acne. Therefore it is incumbent upon the OTC manufacturers to improve OTC formulations in response to the unmet needs of the average acne patients. While no new OTC acne ingredients have emerged since FDA issued the Final Acne Monograph in 1991, step change has taken place in terms of improved delivery of actives, the choices of vehicles, and the forms of treatments. This is particularly true with daily regimen. It has changed the paradigm of OTC acne therapy from reactive, occasional and irregular usage to routine daily treatment providing the ultimate acne control.

The body of works mentioned in this chapter clearly demonstrates that both benzoyl peroxide and SA are two powerful acne-fighting ingredients. Even though benzoyl peroxide has been the mainstay in OTC acne therapy, our recent work indicates that SA has been under-appreciated. With proper formulation, SA can provide rapid acne clearance with overall efficacy comparable to a 10% benozyl peroxide treatment, while providing high degree of skin compatibility.

In parallel, we have developed powerful, non-invasive imaging and spectral techniques to track acne clinically and sub-clinically at the follicular level. These advanced acne diagnostic methods will enable dermatologists and scientists to develop a much clearer understanding of the acne life cycle in vivo and control its emergence.

REFERENCES

1. White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. J Am Acad Dermatol 1998; 39:S34–S37.
2. Krowchuk DP, Stancin T, Keskinen R, Walker R, Bass J, Anglin TM. The psychosocial effects of acne on adolescents. Pediatr Dermatol 1991; 8:332–338.
3. Pochi PE. The pathogenesis and treatment of acne. Ann Rev Med 1990; 41:187–198.
4. Kraning KK, Odland GF. Analysis of research needs and priorities in dermatology. J Invest Dermatol 1979; 73:395–513.
5. Kellett SC, Gawkrodger DJ. The psychological and emotional impact of acne: the effect of treatment with isotretinoin. Br J Dermatol 1999; 140:273–282.
6. Jancin B. Teens with acne cite shame, embarrassment about skin. Skin Allergy News 2004; January:28.
7. Woodard I. Adolescent acne: a stepwise approach to management. Topics in Advanced Practice Nursing eJournal 2002; 2(2).
8. Malus M, LaChance PA, Lamy L, Macaulay A, Vanasse M. Priorities in adolescent health care: the teenager's viewpoint. J Fam Pract 1987; 25:159–162.
9. Agency for healthcare research and quality. Management of acne. Evidence report/technology assessment: number 17. Agency for healthcare research and quality (AHRQ) publication No 01-E018; March 2001.
10. 21CFR Part 333.350(b)(2), Federal Register, 1991; 56:41020.
11. Federal Register, 1995; 60:9555.
12. Federal Register, 1982; 60:9554–9558.
13. Federal Register, 1982; 47:12443–12447.
14. Fitzpatrick TH, Freedberg IM, Eisen AZ, et al. In: Dermatology in General Medicine. New York: McGraw-Hill, 1999:769–784.
15. Federal Register, 1991; 56:41015.
16. Scheman AJ, Severson DL. 6th ed Pocket Guide to Medications Used in Dermatology. New York: Lippincott Williams & Wilkins, 1999.
17. 21 CFR Part 333 Section II.I.3, Federal register, 1982; 47:12443.
18. Olin B, ed. Facts and Comparisons. St. Louis (MO): JB Lippincott Co., 1990.
19. Shalita AR. "Double-blind investigation of 2% salicylic acid solution versus vehicle solution and active control (benzoyl peroxide 5%) in the treatment of acne vulgaris Pillsbury grades I to III," included in Comment No C00002, Docket No.81N-0114, Dockets Management Branch.
20. Leyden J. "Double-blind investigation of 0.5% and 2% salicylic acid solutions (medicated pads) versus vehicle solutions (pads) in the treatment of acne vulgaris pillsbury grades I to III," included in comment No SUP, docket No.81N-0114, dockets management branch.
21. Shalita AR. Comparison of a salicylic acid cleanser and a benzoyl peroxide wash in the treatment of acne vulgaris. Clin Ther 1989; 11:264–267.
22. Pagnoni A, Chen T, Duong H, Wu IT, Appa Y. Clinical evaluation of a salicylic acid containing scrub, toner, mask and regimen in reducing blackheads. 61st meeting, American academy dermatology, Feb 2004, Poster#97.
23. Eady EA, Burke BM, Pulling K, Cunliffe WJ. The benefit of 2% salicylic acid lotion in acne—a placebo-controlled study. J Dermatol Treat 1996; 7:93–96.
24. Zander E, Weisman S. Treatment of acne vulgaris with salicylic acid pads. Clin Ther 1992; 14:247–252.
25. Herndon JH, Stephens TJ, Singler M, Asuncion A, Chen T, Appa Y. Rapid acne resolution by a 2% salicylic acid gel containing a complex of naturals. J Am Acad Dermatol 2004; 50:23.
26. Ok Kim H, Galzote CJ, Estanislao RB, Asuncion A, Chen T, Appa Y. Clinical assessment of a salicylic acid formulation containing a complex of naturals for the treatment of acne vulgaris in Asian subjects. J Am Acad Dermatol 2004; 50:24.

27. Miller D, Smith G, Kurtz ES, Berger RS. Gentle and fast-acting relief from a salicylic acid acne treatment with soothing natural extracts. J Am Acad Dermatol 2004; 50:12.
28. Yamamoto A, Takenouchi K, Ito M. Impaired water barrier function in acne vulgaris. Arch Dermatol Res 1995; 287:214–218.
29. Chantalat J, Wu J, Lu JC. Characterization of a synergistic microgel complex that improves acne treatment efficacy. Presented at the annual meeting of American academy of dermatology, San Francisco, CA, 2006.
30. Chantalat J, Lu JC, Chen T, Appa, Y. Treating emerging acne. Presented at the annual meeting of American academy of dermatology, San Francisco, CA, 2006.
31. Bojar RA, Cunliffe WJ, Holland KT. Short-term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflora. Br J Dermatol 1995; 132:204–208.
32. Pagnoni A, Kligman AM, Kollias N, et al. Digital fluorescence photography can assess the suppressive effect of benzoyl peroxide on Propionibacterium acnes. J Am Acad Dermatol 1999; 41:710–716.
33. Kim J, Ochoa MT, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. J Immunol 2002; 169:1535–1541.
34. Vowels BR, Yang S, Leyden JJ. Induction of proinflammatory cytokines by a soluble factor of Propionibacterium acnes: implications for chronic inflammatory acne. Infect Immun 1995; 63:3158–3165.
35. Gollnick H, Cunliffe W, Berson D, et al. Management of acne. A report from a global alliance to improve outcomes in acne. J Am Acad Dermatol 2003; 49:S1–S37.
36. Del Rosso J. Keeping it clean. Skin Aging 2003; August:82–87.
37. Neutrogena corporation clear pore cleanser mask.
38. TRIAZ® (Medicis) prescribing information.
39. Federal Register, 1995; 60:9554.
40. Eady EA, Cove JH, Joanes DN, Cunliffe WJ. Topical antibiotics for the treatment of acne vulgaris: a critical evaluation of the literature on their clinical benefit and comparative efficacy. J Dermatol Treat 1990; 1:215.
41. Leyden JJ, Gans EH. Evaluation of the antimicrobial effects in vivo of triaz gel (benzoyl peroxide special gel), Cleocin-T® lotion (clindamycin phosphate lotion), and Azelex® cream (azelaic acid cream) in humans. J Dermatolog Treat 1997; 8:S7–S10.
42. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. J Am Acad Dermatol 1997; 37:590–595.
43. Chalker DK, Shalita A, Smith JG, Jr, Swann RW. A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. J Am Acad Dermatol 1983; 9:933–936.
44. FR 1982, 12445–12446.
45. OTC Volume 070270.
46. Mills OH, Jr., Kligman AM, Pochi P, Comite H. Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. Int J Dermatol 1986; 25:664–667.
47. Orth DS, Widjaja J, Wortzman MS. Benzoyl peroxide concentration in follicular casts. Cosmetics Toiletries Mag 1997; 112:87–90.
48. Belknap BS. Treatment of acne with 5 percent benzoyl peroxide gel or 0.05 percent retinoic acid cream. Cutis 1979; 18:485–488.
49. Shalita AR, Rafal ES, Anderson DN, Yavel R, Landow S, Lee WL. Compared efficacy and safety of tretinoin 0.1% microsphere gel alone and in combination with benzoyl peroxide 6% cleanser for the treatment of acne vulgaris. Cutis 2003; 72:167–172.
50. Ozolins M, Eady EA, Avery AJ, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. Lancet 2004; 364:2188–2195.

51. Mills O, Kligman A. Drugs that are ineffective in the treatment of acne vulgaris. Br J dermatol 1983; 108:371–374.
52. Lin AN, Reimer RJ, Carter DM. Sulfur revisited. J Am Acad Dermatol 1988; 18:553–558.
53. FR 1982; 12459–12460.
54. FR 1982; 12447–12448.
55. FR 1982; 12468–12469.
56. OTC Volume 070099.
57. OTC Volume 070168.
58. OTC Volume 070236.
59. OTC Volume 070256.
60. Raman A, Weir U, Bloomfield SF. Antimicrobial effects of tea-tree oil and its major components on Staphylococcus aureus, Staph epidermidis, and Propionibacterium acnes. Lett Appl Microbiol 1995; 21:242–245.
61. Koh KL, Pearce AL, Marshman G, Finlay-Jones JJ, Hart PH. Tea tree oil reduces histamine-induced skin inflammation. Br J Dermatol 2002; 147:1212–1217.
62. Bassett IB, Pannowitz DL, Barnetson RS. A comparative study of tea-tree oil versus benzoyl peroxide in the treatment of acne. Med J Aust 1990; 153:455–458.
63. Poli F, Ribet V, Lauze C, Adhoute H, Morinet P. Multicentre, double-blind, randomized, vehicle-controlled trial. Dermatology 2005; S1:14–21.
64. Boisnic S, Branchet-Gumila MC, Nocera T, Verriere F. RALGA (Diacneal) decreases melanin content in a human skin model. Dermatology 2005; S1:35–38.
65. Rougier A, Richard A, Stengel F, Cannavo A. New advances in the treatment of inflammatory acne. J Am Acad Dermatol 2005; 52:11.
66. Presto S, Wehmeyer A, Rippke F, et al. In vivo assessment of the efficacy of an innovative face care system (Eucerin® impure skin) in subjects with mild acne vulgaris. J Eur Acad Dermatol Venereol 2000; 14:207.
67. Federal Register, 1995; 60:9554.
68. Chen T, Herndon JH, Stephens T, Appa Y. Constant attenuation of acne by a 2-step regimen containing both salicylic acid and benzoyl peroxide treatments. J Am Acad Dermatol 2005; 52:P16.
69. Bommer S. Hautuntersuchungen im gefilterten quarzlicht. Klin Wochenschr 1927; 6:1142–1144.
70. Cornelius CE, III, Ludwig GD. Red fluorescence of comedones: production of porphyrins by Corynebacterium acnes. J Invest Dermatol 1967; 49:368–370.
71. Melö TB, Johnsson M. In vivo porphyrin fluorescence from Proprionibacterium acnes. A characterization of the fluorescing pigments. Dermatology 1982; 164:167–174.
72. Lee WL, Shalita AR, Poh-Fitzpatrick MB. Comparative studies of porphyrin production in Propionibacterium acnes and Propionibacterium granulosum. J Bacteriol 1978; 13:811–815.
73. Sauermann G, Ebens B, Hoppe U. Analysis of facial comedos by porphyrin fluorescence and image analysis. J Toxicol Cutan Ocular Toxicol 1989; 8:369–385.
74. McGinley KJ, Webster GF, Leyden JJ. Facial follicular porphyrin fluorescence: correlation with age and density of Propionibacterium acnes. Br J Dermatol 1980; 102:437–441.
75. Martin RJ, Kahn G, et al. Cutaneous porphyrin fluorescence as an indicator of antibiotic absorption and effectiveness. Cutis 1973; 12:758–764.
76. Pagnoni A, Kligman AM, Kollias N, et al. Digital fluorescence photography can assess the suppressive effect of benzoyl peroxideon Propionibacterium acnes. J Am Acad Dermatol 1999; 41:710–716.
77. Merola K, Chen T, Appa Y. U.S. patent, filed Nov. 2001, serial no. 10/008 579.
78. Chen T, Stamatas G, Kollias N, Appa Y. High resolution imaging of acne. J Am Acad Dermatol 2005; 52:P22.
79. Stamatas GN, Balas C, Kollias N. Hyperspectral image acquisition and analysis of skin. Proc SPIE 2003; 4959:77–82.

80. Chen T, Stamatas G, Kollias N, Appa Y. High resolution imaging evaluation of acne. Poster #22 presented at the 63rd annual meeting of American academy of dermatology, Febuary 18–22, 2005, New Orleans, LA. Abstract published in J Am Acad Dermatol 2005; 52:P22.
81. Chantalat J, Lu JC, Chen T, Appa Y. Treating emerging acne. Poster #128 presented at the 64th annual meeting of American academy of dermatology, San Francisco, CA, March 3–7, 2006.