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Education Foundation

Roundup on Cosmetic Dermatology

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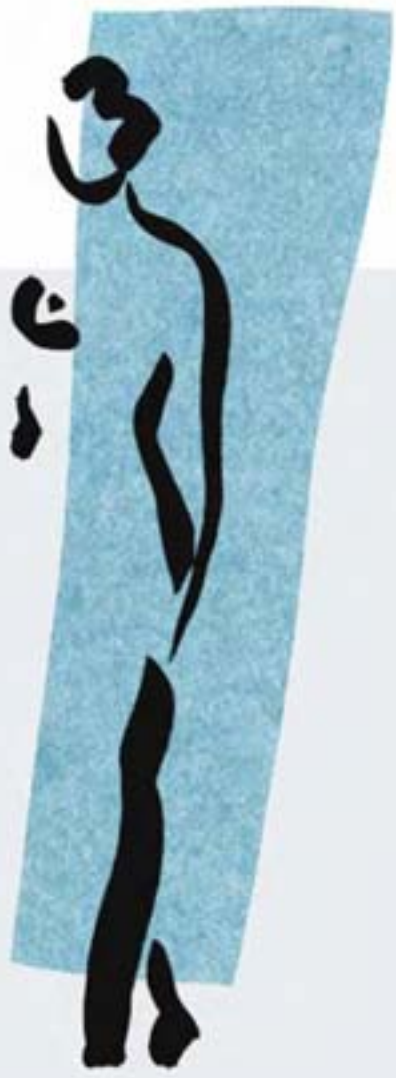

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New Technology Adds Tools to Cosmetic Dermatology

New technology recently has added to the variety of tools available to the cosmetic dermatologist, according to David Goldberg, MD, JD, Clinical Professor of Dermatology at Mount Sinai School of Medicine in New York.

Light-emitting diode (LED) treatment has provided new ways to treat aging skin. The therapy works through a process known as photomodulation.

"LED treatment can have a profound impact on various substances in the skin, and yet the treatment causes no pain and there is no wound," said Dr Goldberg.

LED Technology

LED technology comes in varying colors of light. The chosen color determines the impact on the skin. Current LED technology uses yellow, red, and infrared light.

Yellow light has been shown to promote collagen formation and to inhibit the breakdown of collagen.

Red light has been shown to have a tremendous effect on actual skin cells.

Infrared light penetrates deeper into the skin than do yellow and red light.

David J. Goldberg, MD, JD

"We are just beginning to evaluate what role LED technologies have in the noninvasive cosmetic arena," said Dr Goldberg. "It is clear, though, that in the future more and more cosmetic treatments will be undertaken with LED technology."

Over the past 20 years, filler agents for wrinkles have evolved considerably. The original filler was bovine collagen. Over the past 2 years, in particular, the number of available fillers has increased substantially.

"We now have human bioengineered collagen and various hyaluronic acid products," said Dr Goldberg. "These filler agents promote a very nice softening of nasolabial fold wrinkles and a variety of other wrinkles. No skin or allergy testing is required, and the results generally last about 6 months."

Longer-Lasting Fillers

Fillers that last even longer have recently become available in the United States. The new intermediate-lasting fillers include poly-L-lactic acid and calcium hydroxylapatite. Poly-L-lactic acid is more of a volume enhancer than a filler. The agent is currently approved for treatment of lipoatrophy in patients infected with the human immunodeficiency virus (HIV).

However, according to Dr Goldberg, poly-L-lactic acid is being used off-label in the United States and throughout Europe for the treatment of lipoatrophy in patients not infected with HIV.

"Poly-L-lactic acid is administered in a series of injections," said Dr Goldberg. "It nicely fills in sunken cheeks, and the results can last approximately 2 years."

Calcium hydroxylapatite treatment lasts 1 to 2 years. The filler is injected into the nasolabial folds and in acne scars. The results are immediate and no skin test is required.

Skin-Tightening Methods

Over the past few years, nonsurgical skin-tightening methods have attracted considerable interest. The most commonly used technique involves use of monopolar radiofrequency (RF) energy delivered to the skin.

"With this technique, large volumes of tissue are heated and tightened in a noninvasive manner," said Dr Goldberg. "Although the original FDA studies were done on the forehead, so as to lift the brow and eyelids, the technique is used most commonly today to treat jowls and sagging neck."

A second method of skin tightening involves use of a laser and bipolar RF energy. The technique does not produce the same degree of heating seen with monopolar RF, but the combination of bipolar RF and laser light can induce tightening and also improve skin quality.

A third method of skin tightening involves use of an infrared light source to heat the skin. Results with this newer technique are still being evaluated.

Laser resurfacing also has evolved considerably since it was first introduced 15 years ago. Traditional resurfacing does an exceptional job of improving skin wrinkles and photodamaged skin.

However, the treatment involves an open wound, the need to stay home after treatment for a week or 10 days, redness that can last for 6 months, and the risk of scarring and pigment changes.

Fractional resurfacing provides an alternative approach without the traditional downside to laser resurfacing.

"Fractional resurfacing is laser resurfacing without the production of an obvious wound," said Dr Goldberg. "Instead, microscopic wounds are created in the skin.

The treatment is given over a series of sessions and can produce improvement in an elegant manner to skin alterations due to photodamage and wrinkles." ■

Dr Goldberg is a consultant to Photo Therapeutics Limited and BioForm Medical, Inc. He discusses the off-label use of poly-L-lactic acid for the treatment of lipoatrophy in non-HIV patients and the off-label use of calcium hydroxylapatite as a cosmetic filler agent.

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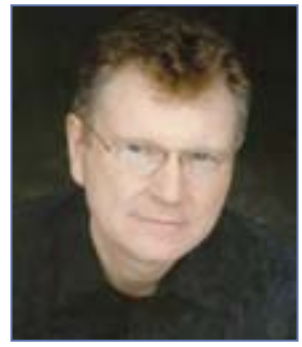
"Those older procedures were effective but, in many cases, cruder and less specific than the methods we have today," said Christopher Zachary, FRCP, a dermatologist at the University of California, San Francisco. "Now, just because the techniques were crude doesn't mean to say we should throw the baby out with the bathwater. Dermabrasion, chemical peels, and the CO_2 and erbium:YAG lasers are all techniques we used over the years to rejuvenate skin damaged by ultraviolet light, smoking, and natural aging. There is no doubt that we could dramatically improve the appearance, texture, and tone of the skin with these old and established techniques."



Christopher B. Zachary, FRCP

The older techniques have a notable downside, Dr Zachary continued. Abraded skin requires 1 or 2 weeks to reepithelialize. The procedures are sometimes associated with complications, such as infection, scarring, and persistent redness.

"Essentially, these procedures suspended both social and economic activities for at least 2 to 4 weeks," said Dr Zachary.

New Emphasis

The clinical and research emphasis in recent years has been on the so-called "lunchtime" procedures that are nonablative. These procedures can achieve significant improvement in appearance with very limited downtime in comparison with the traditional procedures.

An example is the intense pulse light, which is used to improve various types of dyspigmentation including brown spots associated with sun damage, telangiectases, and rosacea. If the problem is predominately redness or rosacea, an alternative is the V-beam, a 595-nm pulsed dye laser originally developed for the treatment of port wine stains.

"The V-beam has been found to be a very effective nonablative laser for the improvement of rosaceous skin and also for skin toning with better reflectance of light. Both latter characteristics are features of skin rejuvenation," said Dr Zachary.

The KTP lasers by Laserscope, Iridex, and other companies have proven useful for the treatment of lentigines and telangiectases. Despite the fact that KTP lasers have been around for many years, investigators have found new nonablative applications for the 532-nm laser, particularly with scanning devices or with large spot sizes.

"The KTP laser is very well absorbed by pigmentation and blood vessels and can give a very nice improvement in the texture and tone of skin," said Dr Zachary.

Wrinkle Treatment

For help with wrinkles, two nonablative laser devices have proven useful: the 1,320-nm CoolTouch and the 1,450-nm Smoothbeam. The CoolTouch device has the capability to ascertain the surface temperature of the skin with an infrared sensor and chill the surface before firing the laser to create a reverse thermal gradient, resulting in the top of the skin being cooler than the inside of the skin. The process protects the epidermis from excessive heat damage by the laser.

"We can now deliver high laser energy into the skin with the protection of the cooling device and selectively put heat where we want it," said Dr Zachary.

The Smoothbeam, which has a very sophisticated dynamic cooling device, has proven useful for treatment of acne scarring. The improvement may require 6 to 12 treatments, but dermatologists around the country have reported 40% to 60% improvement in acne scarring. It is said by some that similar results can be achieved with the CoolTouch device.

"The concept with these newer devices is that the patient arrives, is treated, and walks out 30 minutes later with just a little bit of redness and swelling lasting for a few days," said Dr Zachary. "Now compare that with the CO_2 or erbium:YAG laser, where the patient loses the outer layer of the skin, it takes at least 2 weeks for complete reepithelialization, and redness is still present for 3 months after that. Plus there is a significant chance of infection, pigmentary changes, and scarring. Weigh one against the other, and if you can achieve with these newer devices what you can achieve with ablative devices, then that is a huge step forward."

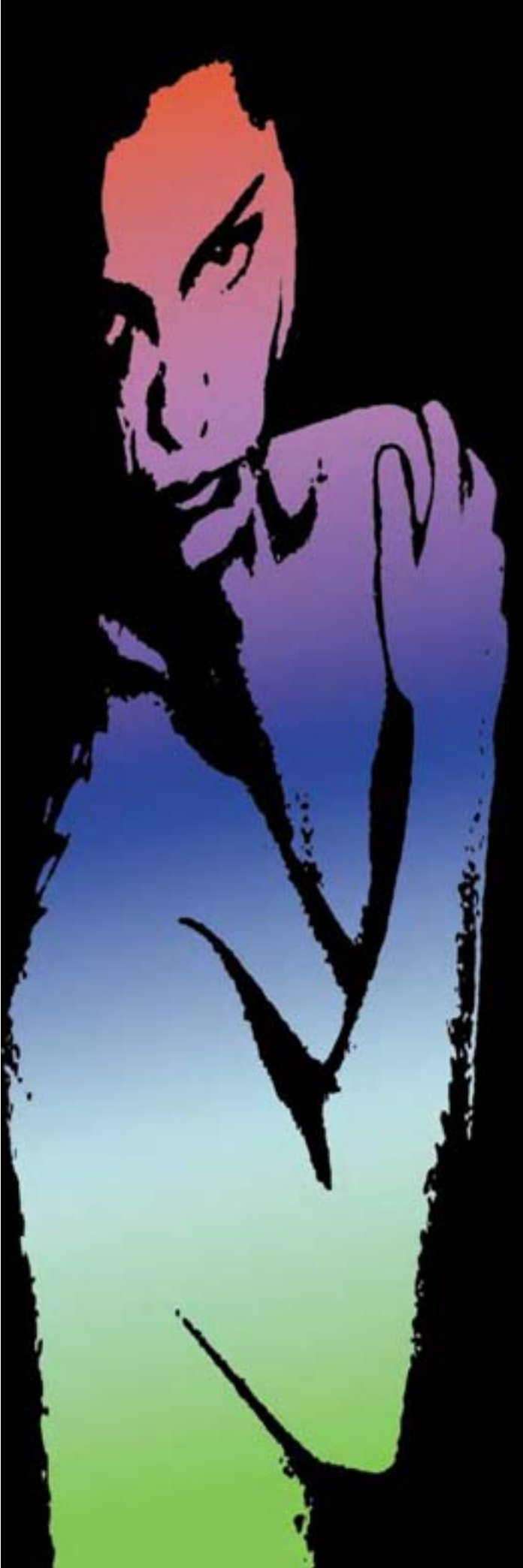
However, Dr Zachary offers a cautionary note about exceptional results that some users of the nonablative lasers have claimed.

"I don't want anyone to think that you can achieve with these nonablative devices the same benefits you can achieve with dermabrasion; I just don't buy it," he said. "For me, the old-fashioned dermabrasion is still the king for acne scarring."

In 2004, the Fraxel 1,550-nm laser was introduced. The device is used to perform fractionated rejuvenation or resurfacing of the face. The device creates a different sort of wound from that created by other types of lasers. Fraxel has a sophisticated scanning device that creates thousands of tiny vertical cylindrical areas of injury. In between the injured areas remains normal skin, which helps limit damage and speeds the healing process.

"There is some swelling, erythema, and desquamation," said Dr Zachary. "You don't get an ulcerated or eroded area unless you have been too aggressive. The results are still early in my opinion, but I have seen some nice improvement in skin texture and tone, in skin tightening, in reduction of blood vessels and pigmentation, and in improvement in recalcitrant melasma."

Continued on page 18



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A Refresher on Antioxidants

First hypothesized in 1956 by Dr Denham Harman, the free radical theory of aging is now the most widely accepted theory regarding the etiology of skin aging.

Both internal and external oxidative stressors create inflammatory pathways characterized by the formation of free radicals, which are highly reactive molecules with unpaired electrons. Left unchecked, free radicals can cause severe cellular damage to cell membranes, lipids, proteins, and DNA. Free radicals that are known to cause DNA damage, lipid peroxidation, and inflammation are also believed to cause skin aging.

Antioxidants are substances that protect cells from endogenous oxidative stress, which is a natural byproduct of cellular energy production. Antioxidants also offer protection from exogenous stressors, such as UV radiation from the sun, air pollution, cigarette smoke, ozone, and even oxygen itself.

Leslie S. Baumann, MD

The damage accumulation theory of aging suggests that a lifetime buildup of damage caused by unchecked free radicals is a primary mechanism leading to the manifestations of aging. The almost universal acceptance of both the free radical theory and the damage accumulation theory helps explain the intense interest of modern medicine in the capacities of antioxidants.

By scavenging and eliminating free radicals, antioxidants balance and thwart the deleterious effects of the free radical–mediated inflammatory pathways promoted by oxidative stress.

How Antioxidants Work

Several antioxidants are used as ingredients in topical skin care formulations, including vitamins C and E, lycopene, grape seed extract, green tea, coenzyme Q10, and alpha-lipoic acid. Each offers distinct advantages, but they all pose similar challenges in terms of harnessing their potency in topical products.

• **Vitamin C.** Although there is a dearth of research evaluating the effects of ascorbic acid (vitamin C) on wrinkles, one such study has garnered a good deal of attention. The topical application of Cellex C serum for 3 months was shown to reduce the size of wrinkles in a study of 19 patients (*Arch. Otolaryngol. Head Neck Surg.* 125[10]:1091-98, 1999). This study was not blinded, as a significant percentage of the participants experienced stinging on the treated side of the face.

Vitamin C is known to play an important role for the skin: It has been shown to increase collagen synthesis in neonatal and adult fibroblasts when added to the culture medium (*J. Invest. Dermatol.* 90[4]:420-24, 1988).

Topical vitamin C preparations have proven to be disappointing, however. Most preparations are unstable upon exposure to UV light and air, which renders them useless. Also, most topical vitamin C products, even the stable ones, fail to penetrate the stratum corneum.

• **Vitamin E.** The topical application of α-tocopherol (vitamin E) has been shown to confer significant protection against UV-induced damage to animal skin (*Free Radic. Biol. Med.* 22[5]:761-69, 1997; *J. Invest. Dermatol.* 104[4]:484-88, 1995).

Although immunostimulatory and antiinflammatory effects have been ascribed to vitamin E (*J. Am. Acad. Dermatol.* 39 [4, pt. 1]:611-25, 1998), several studies have cited adverse reactions to topical vitamin E (*Dermatol. Surg.* 25[4]:311-15, 1999; *Dermatology* 189[3]:225-33, 1994). A sun protection factor of 3 has been associated with the effects of topical application of vitamin E, which is believed to have the capacity to marginally absorb light (*Cosmet. Dermatol.* 12[9]:17-20, 1999). It appears likely, however, that vitamin E requires the interaction of other antioxidants to provide any photoprotective effect.

• **Coenzyme Q10.** A powerful antioxidant that combats free radical stress and assists in energy production, coenzyme Q10 is found in all cells. By inhibiting lipid peroxidation in plasma membranes—thus limiting free radical formation—coenzyme Q10 is believed to prevent oxidative stress–induced apoptosis.

Coenzyme Q10 plays an important role in the energy-producing adenosine triphosphate pathways present in the mitochondria of each cell in the body. Energy production is an important component of cellular metabolism that is thought to diminish in efficiency with age. Coincidentally, levels of coenzyme Q10 also decline with age. Supplementation with this coenzyme is believed to have potential to stem the decline in energy production associated with senescence and illness.

A preponderance of clinical work with coenzyme Q10 has evaluated its systemic administration. However, topical coenzyme Q10 has been shown to penetrate the viable layers of the epidermis and lower the level of oxidation, measured by weak photon emission, and reduce wrinkle depth. In the same study, the coenzyme suppressed expression of collagenase in human fibroblasts following UVA irradiation. These results suggest that topical coenzyme Q10 may be effective in preventing the deleterious effects of ultraviolet radiation exposure (*Biofactors* 9[2-4]:371-78, 1999).

• **Grape seed extract.** By inducing vascular endothelial growth factor expression in keratinocytes, grape seed extract in one study appeared to exhibit the potential to confer beneficial results in dermal wound healing and related skin problems (*Free Radic. Biol. Med.* 31[1]:38-42, 2001).

In human volunteers, topical application of grape seed extract has been shown to enhance the sun protection factor (*Toxicology* 148[2-3]:187-97, 2000). Data suggest that grape seed extract is a significantly more potent scavenger of free radicals than either vitamin C or E (*Res. Commun. Mol. Pathol. Pharmacol.* 95[2]:179-89, 1997; *Toxicology* 148[2-3]:187-97, 2000). The bioflavonoids in grape seed extract appear to promote the body's ability to absorb vitamins, creating a symbiotic atmosphere for other nutrients.

• **Green tea.** Green tea is included in various skin care products because of the purported antioxidant and antiinflamma-

tory effects of polyphenols that occur naturally in the green tea leaf. The polyphenols have been shown to modulate the biochemical pathways important in cell proliferation, inflammatory responses, and responses of tumor promoters (*Arch. Dermatol.* 136[8]:989-94, 2000).

Oral consumption of green tea has actually been shown to increase green tea phenol levels in skin as indicated by tape-stripping analysis. Numerous studies support continuing interest in and use of green tea.

Unfortunately, when high levels of green tea are placed in a moisturizing vehicle, the cream often turns brown. One company (Topix) has avoided this problem by making their cream brown to begin with.

• **Lipoic acid.** Water- and lipid-soluble lipoic acid is a potent antioxidant and a promising option in the treatment of aging skin. It is believed to be effective in treating inflammatory diseases, and may slow the pace of skin aging.

Lipoic acid is absorbed in a stable form. After entrance into cells, however, it is immediately converted to its byproduct, dihydrolipoic acid, which has a stronger antioxidative effect (*Biochem. Biophys. Res. Commun.* 204[1]:98-104, 1994). The topical application of 3% lipoic acid in a lecithin base on human skin has been shown to decrease erythema caused by UVB twice as fast as lecithin base alone. This suggests that lipoic acid could potentially reduce the effects of photoaging or even thwart carcinogenesis.

Lipoic acid is another in the long line of antioxidants that show promise, but lack double-blind clinical trials showing their efficacy in available products. Lipoic acid can be irritating to those with sensitive skin.

• **Lycopene.** Naturally present in human blood and tissues, lycopene is a non–provitamin A carotenoid. It is best known as the pigment primarily responsible for the characteristic red color of tomatoes.

Lycopene is now drawing attention for its potential potency as an antioxidant. Lycopene may play a role in reducing oxidative damage to tissues, as suggested by a study in which a 31%-46% decrease in skin lycopene concentration was observed following a single intense exposure (three times the minimal erythema dose) of solar-simulated light on a small area of the volar arm (*J. Nutr.* 125[7]:1854-59, 1995).

In a separate study of oral consumption of lycopene, both lycopene and β-carotene failed to confer photoprotective effects to human dermal fibroblasts. Their stability was enhanced, however, by the presence of vitamin E, which contributed to the suppression of metalloproteinase-1 mRNA expression (*Free Radic. Biol. Med.* 32[12]:1293-1303, 2002).

This suggests that to deliver the benefits of lycopene in topical products, it may be necessary to combine the carotenoid with other antioxidant active ingredients. The literature is rife with evidence of the efficacy of ingested lycopene, but there is a paucity of double-blind, case-control studies evaluating the efficacy of topical products.

Measuring Efficacy

Millions of people are likely aware of many of the topical antioxidants currently marketed, given how popular the use of "anti-aging" cosmeceuticals containing such ingredients has become. Most consumers are clueless, however, as to how to rate the effectiveness of such formulations, as scant scientific data exist on the wide range of skin care products that contain highly touted antioxidants.

Until now, there have been no standard methods for comparing the relative efficacy of different antioxidants in a fashion readily accessible to consumers.

The almost universal acceptance of both the free radical theory and the damage accumulation theory helps explain the intense interest of modern medicine in the capacities of antioxidants.

Pharma Cosmetix Research, a cosmeceutical research and development company, has produced a protocol of in vitro and in vivo studies designed specifically to address the need to standardize efficacy measurement of topical antioxidants. In much the same way that the sun protection factor provides a measuring stick enabling the user to estimate the level of UV protection to expect from a sunscreen product, Pharma Cosmetix Research's environmental protection factor (EPF) is designed to provide the product user with an estimate of the level of oxidative/environmental stress protection to expect from an antioxidant skin care product.

In all of the antioxidant efficacy protocols, each antioxidant substance is scored, and the results are totaled for each antioxidant on an equal weighted basis. The overall total score for each antioxidant reflects the overall stress protection capacity, or EPF, of the antioxidant.

The bottom line is that EPF is to antioxidant environmental protection efficacy what SPF is to sunscreen UV protection efficacy. Consumers will now have a simple way to rate antioxidant strength and compare the efficacy of topical antioxidant cosmeceutical products. ■

Dr Leslie S. Baumann is director of cosmetic dermatology at the University of Miami. Reprinted from SKIN & ALLERGY NEWS*, May 2004.*

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How to Spot Neurosis in Cosmetic Candidates

Demanding cosmetic dermatology patients who are never satisfied might have underlying psychiatric conditions to identify and treat.

In addition to body dysmorphic disorder, "difficult" cosmetic patients can have narcissistic personality disorder or histrionic personality disorder, or they can be "self-destructive deniers," said Eva C. Ritvo, MD. Also possible are mood disorders, anxiety disorders, and substance abuse issues.

Certain red flags can help identify such patients. Dermatologists should be wary of people with unrealistic expectations or a history of numerous procedures. Other warning signs include routinely complaining about previous procedures or other providers, calling or visiting an office excessively, or spending money they do not have for cosmetic enhancement.

Take a careful history, get to know the patient, and be explicit about the plan and expected results, suggested Dr Ritvo, chief of the department of psychiatry at Mount Sinai Medical Center, Miami Beach.

Take before and after photographs, and have the patient sign a written contract, she added.

"Think like a shrink," Dr Ritvo said. Dermatologists should be aware of their reactions and check the emotions that arise when they deal with challenging patients, Dr Ritvo suggested.

If possible, use the "24-hour rule." If a patient calls a few days after a procedure to complain about the outcome, tell him or her to come in the next day to discuss any concerns, Dr Ritvo said. This delay allows a physician time to approach the patient more objectively and not act on impulse.

Dr Ritvo highlighted some common underlying psychiatric conditions in these patients:

- **Body dysmorphic disorder.** Patients with this disorder become preoccupied with an imaginary defect in their appearance or excessively concerned with a slight anomaly. The preoccupation causes significant distress or impairs functioning. The disorder usually begins during adolescence, and diagnosis often takes years. Contrary to the common perception, Dr Ritvo said, the disorder is equally prevalent in women and men.

Do not perform inappropriate procedures in these patients, Dr Ritvo emphasized. Instead, refer them to a mental health professional. She suggested that you say, "I would like you to see a colleague of mine before we proceed."

- **Narcissistic personality disorder.** Patients with this disorder are grandiose, seek admiration, and have fragile self-esteem. They can be preoccupied with fantasies of personal beauty, and although frequently dissatisfied, continuously return to the cosmetic dermatologist's office.

"These patients are the entitled demanders," Dr Ritvo said. They might call and demand an immediate appointment because their botulinum toxin type A is wearing off, for example.

Do not attack them, and never disparage their feelings. Instead, acknowledge their right to good health care, and try to restore their sense of control, Dr Ritvo suggested. Involve the person's family. Review realistic expectations, and set limits. If you refer them, make sure you document the reason carefully, she suggested.

- **Histrionic personality disorder.** Patients with histrionic personality disorder have a pervasive pattern of excessive emotionality and attention seeking. Some display inappropriate, sexually seductive behaviors. Others refer to doctors by their first names. Make the diagnosis, communicate clearly and carefully, and review expectations, Dr Ritvo suggested. Document everything, and stay alert for shifting moods in these patients.
- **Self-destructive deniers.** These patients include smokers, drinkers, sun abusers, skin pickers, and drug seekers, Dr Ritvo said. They are noncompliant, at a high risk for complications, and generally "out of control."

Avoid being judgmental or punitive, Dr Ritvo suggested. Remember the disease model for addiction. Set clear, realistic goals with the patient, and do not be seduced by their stories. Do not perform unnecessary cosmetic procedures, and consider a psychiatric consultation. ■

By Damian McNamara, IMNG News Service. Reprinted from SKIN & ALLERGY NEWS, *April 2005. Based on a presentation at a symposium sponsored by the Florida Society of Dermatology and Dermatologic Surgery.*

Cosmetic Procedures: Pros & Cons

Ablative Laser Resurfacing

Pros: Best results on deep rhytids; Significant tightening; Long-term results.

Cons: Painful; Lengthy healing phase; Risks; Hypopigmentation.

Photodynamic Skin Rejuvenation

Pros: Excellent results on red and brown pigmentation; Better tightening and remodeling; Minimal downtime ; Superb for actinic keratosis and damage; Acne and other applications; Long-term results; Can be used for skin types I-IV.

Cons: Photosensitivity; Some downtime.

Radiofrequency Toning and Tightening

Pros: Improvement for lax skin; Can be used for all skin types; Improvement of acne scars; No downtime ; Long-term results possible; Same day combination with ablative techniques.

Cons: Pain; Variability.

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Cons: No effect on actinic keratosis; Slight effect on rhytids.

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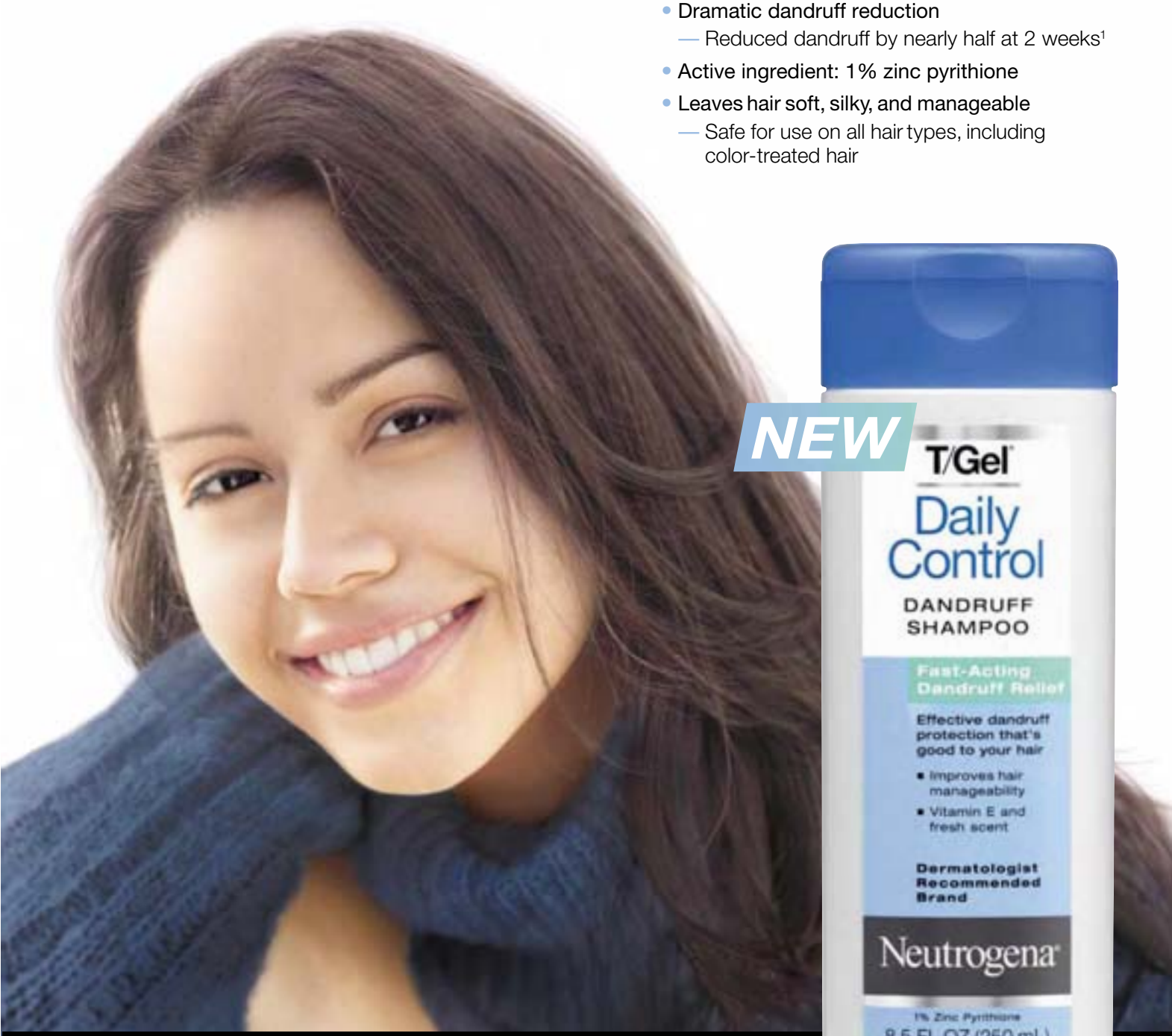

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Peptides

The use of peptides to treat aging skin is gaining favor among skin care enthusiasts. Consumers who have tried retinoids, hydroxy acids, and antioxidant creams are now turning to a group of biologically active compounds that promise to turn back the hands of time.

The natural healing process is dependent on biologic factors that signal cells to initiate the repair process. Macrophages secrete a host of substances, including growth factors that attach to cell surface receptors, thereby turning on a variety of cellular events. Vascular neogenesis and collagen synthesis are modulated by these factors and promote wound healing.

Patricia Farris, MD

The pathogenesis of skin aging is well defined; it is characterized by a decrease in collagen synthesis and an increase in collagen breakdown, mediated by metalloproteinases (*Arch. Dermatol.* 138[11]:1462-70, 2002). This net loss in dermal collagen is believed to cause wrinkling. Biologic factors that stimulate collagen production in wound healing might provide similar benefits for aging skin. Accordingly, growth factors, peptide fragments, and other biologically active molecules are being incorporated into antiaging cosmeceuticals.

Growth factors are high-molecular-weight peptides with diverse biologic effects. Five key growth factor families have been identified, including transforming growth factor-β (TGF-β), epidermal growth factor (EGF), insulinlike growth factor (IGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF).

Because most cell types have receptors for TGF-β, this is the most important growth factor family. TGF-β is a potent stimulator of collagen production and promotes the synthesis of ground substances like glycosaminoglycan and proteoglycan (*J. Biol. Chem.* 262[14]:6443-46, 1987). TGF-β inhibits matrix degradation by reducing protease activity (*J. Biol. Chem.* 264[3]:1860-69, 1989). Proliferation of various cell types, including leukocytes and keratinocytes, is also inhibited by TGF-β (*Am. J. Surg.* 165[6]:728-37, 1993).

In animals, TGF-β has been shown to accelerate wound healing after incision (*Science* 237[4820]:1333-36, 1987) and to improve healing of full-thickness ulcers (*J. Clin. Invest.* 87[2]:694-703, 1991).

PDGF can stimulate extracellular matrix deposition and blood vessel formation, and has been shown to stimulate granulation tissue formation in animal models (*J. Clin. Invest.* 87[2]:694-703, 1991). EGF and IGF are referred to as invasion growth factors; they induce keratinocyte migration into the dermis, presumably by up-regulating matrix metalloproteinase activity (*Invasion Metastasis* 16[1]:11-18, 1996). IGF-1 stimulates epidermal proliferation and induces TGF-β activity (*J. Cell. Physiol.* 174[3]301-09, 1998).

Currently available cosmeceuticals contain either a single recombinant growth factor or multiple growth factors.

The TNS Recovery Complex with NouriCel-MD (SkinMedica Inc.) is derived from bioengineered skin and contains multiple growth factors, including TGF-β. RéVive Sensitif Cellular Repair Cream (Bays Brown Laboratories) contains recombinant EGF, while products in the Transformation Line (Jan Marini Skin Research Inc.) contain recombinant TGF-β1. Natura Bissé's Facial Day Cream (Natura Bissé USA) is derived from placental extracts and contains 4% skin growth factor, while Citrix CRS Serum contains TGF-β1 (Topix).

Compared with other cosmeceuticals, growth factor products are relatively expensive and can cost as much as $180 for 2 ounces.

Although topically applied growth factors are sold extensively, there are few published studies confirming their efficacy for treating aging skin.

Probably the most widely studied formulation is the TNS Recovery Complex with NouriCel-MD. Preliminary in vitro studies confirm that this growth factor product is capable of stimulating collagen production by fibroblasts, stimulates cellular proliferation of keratinocytes and fibroblasts, enhances vascular formation, and has potent antiinflammatory effects.

In an open-label clinical trial of 14 patients applying TNS Recovery Complex gel with NouriCel-MD twice daily, 8 of 14 patients said their wrinkles were improved and optical profilometry on seven of eight specimens showed significantly less wrinkling at the end of 60 days (*J. Cosmet. Laser Ther.* 5[1]:25-34, 2003). Skin biopsies revealed an average increase in epidermal thickness of 30% and a 37% increase in grenz zone collagen.

These preliminary studies are promising, but larger, more objective clinical trials are needed. It is also uncertain whether single recombinant growth factors can provide the same benefits as multiple growth factors.

The newest peptide to be marketed as a treatment for aging skin is the procollagen fragment Lys-Thr-Thr-Lys-Ser, also called KTTKS.

Studies conducted at the University of Tennessee and sponsored by the National Institutes of Health confirmed that this pentapeptide can promote the synthesis of collagen types I and III and fibronectin by cultured fibroblasts (*J. Biol. Chem.* 268[14]:9941-44, 1993). To enhance penetration of this hydrophilic peptide, palmitoyl—a 16-carbon fatty acid moiety—was added.

Pal-KTTKS, also called Matrixyl, has been shown to penetrate human skin and remains in the dermis, according to unpublished reports.

Currently, several products contain Pal-KTTKS, including Olay's Regenerist, StriVectin-SD, and Strixaderm-MD. Matrixyl is patented, manufactured, and sold for commercial use by the French company Sederma.

In a double-blind, vehicle-controlled study of 49 women

Continued on page 18

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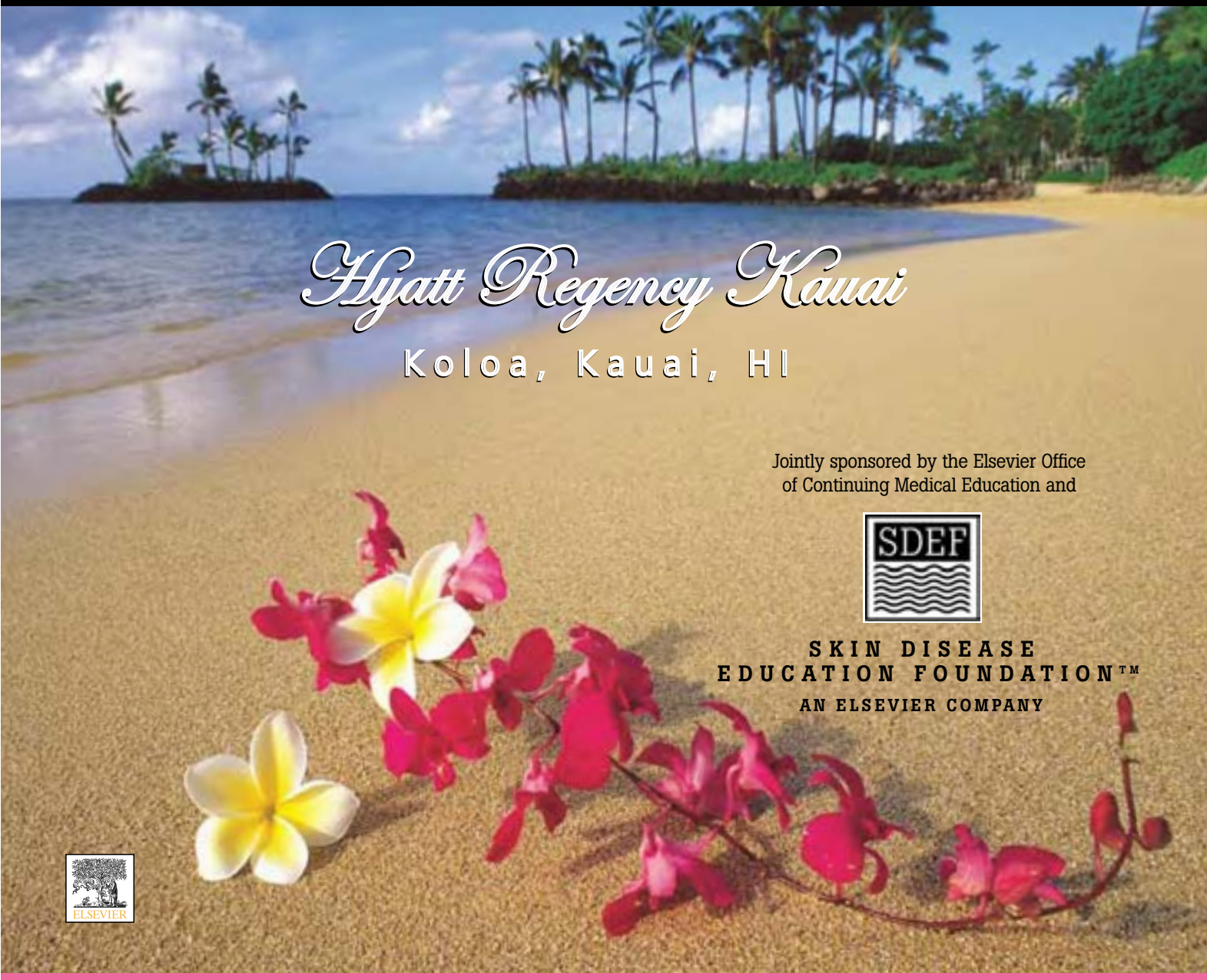

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Cosmetic Practice: Follow Tips to Get Started

Dr Joel Schlessinger's cosmetic dermatology practice and medical spa occupy a dramatically impressive building in suburban Omaha, Neb. Large signs proclaim his name and his Web site address, www.lovelyskin.com.

But the confidence that exudes from one of the Midwest's most successful cosmetic dermatologists grew gradually, from nervous beginnings.

Dr Schlessinger tells the story of returning home from an American Academy of Dermatology meeting in 1995 with the receipt for a $65,000 skin resurfacing laser—his first significant financial step toward building a cosmetic dermatology practice.

His wife, who balanced the checkbook and was used to his AAD splurges of $3,000 for forceps and gold-tipped scissors, was aghast. "Do you think it was worth it? Was there a person who said you should buy this laser?" she asked.

"I said, 'Yes,' " he explained, " 'The laser guy.' "

Dr Schlessinger forged his way into cosmetic dermatology on gut feeling rather than on any sophisticated market analysis.

When it comes to deciding whether to start a cosmetic dermatology practice, "I don't think the scientific method always has merit," he said. "Do you think your practice is ready? I think you either have to know it or not."

Dermatologists can evaluate their training, the potential willingness of their staffs, and the basic makeup of their patient populations when weighing the decision about whether to add cosmetic services. "If 95% of your patients are Medicare patients and 5% are pediatric patients, you may not want to consider Botox," Dr Schlessinger quipped.

His practice, on the other hand, largely drew from suburbia. The patients with warts, rashes, and acne were delivered to his waiting room by their mothers: potential clients, as he saw it, for cosmetic services.

"I'm not saying you should jump in and say, 'Absolutely, if I buy it, they will come,' " he said, "but when we bought it and marketed it, they did come."

Once you've made the decision, there are ways to increase your likelihood of success, Dr Schlessinger said. Here are his tips for starting out:

• **Find a great patient coordinator.** "Cosmetic dermatology basically boils down to customer service," he said. He has two patient coordinators: a bubbly former telemarketer who loves people and enjoys talking on the phone, and a woman who worked at a cosmetics counter at a local department store.

A patient coordinator may already work for you.

Do you have a secretary with amazing people skills and a flair for organization?

• **Be up front with your staff.** Discuss your plans with your existing staff.

Are they skilled in relevant procedures? Are they interested in cosmetic dermatology? Dr Schlessinger lost several staff members when the focus of his practice changed.

When a nurse told him, "I didn't become a nurse to sell creams to people," Dr Schlessinger gave her his blessing to look elsewhere for work.

• **Set aside time in your week for cosmetic patients.** You may have to add practice hours or drop borderline insurance plans to carve out room for cosmetic patients, but do it.

A woman who decides to devote one lunch hour of her busy week for a Botox injection does not want to wait 3 months for an appointment. When she gets to her 12:15 p.m. appointment, she wants to be seen.

• **Develop a reasonable plan.** Decide which services to offer first and prepare to offer them.

Design a long-term plan for measured, not exponential, growth.

Obtain the necessary training for each new service, devise a marketing plan, and begin.

Dr Schlessinger added a few services each year. ■

By Betsy Bates, IMNG News Service. Reprinted from Skin & Allergy News, *February 2003. Based on a presentation at the American Society of Cosmetic Dermatology and Aesthetic Surgery.*

A Timeline for Cosmetic Dermatology

Dr Schlessinger added services gradually to his cosmetic dermatology practice:

• **Years 1 and 2.** Began offering one line of skin care products. Performed sclerotherapy and offered collagen filler procedures. Later, added peels.

• **Year 3.** Hired aesthetician for one room of clinic (who helped with filing and stocking until her client list grew). Added laser skin resurfacing.

• **Year 4.** Bought laser for leg veins and telangiectasias. Attended course and added liposuction. Hired patient coordinators. Added computer imaging.

• **Year 5.** Opened freestanding day spa and hired second aesthetician. Began offering Botox and laser hair removal. Launched informational Web site.

• **Year 6.** Added more lasers for hair removal. Added liposonic sculpting and hired staff member to perform procedure. Incorporated Web site product sales. Began plans for new site to bring spa and practice under one roof.

• **Year 7.** Moved into new site and obtained state certification as ambulatory surgical center. Added CoolTouch laser, more hair removal lasers. Hired staff for Web site.

• **Year 8.** Added diode laser and product sales specialist.

• **Year 9.** Added VascuLight and Palomar E2000 lasers, more product lines, and massage therapist.

• **Year 10.** Expanded day spa and hired third full-time aesthetician and additional Web site personnel. Began offering clay masque peels.

Source: Dr Gary D. Monheit.

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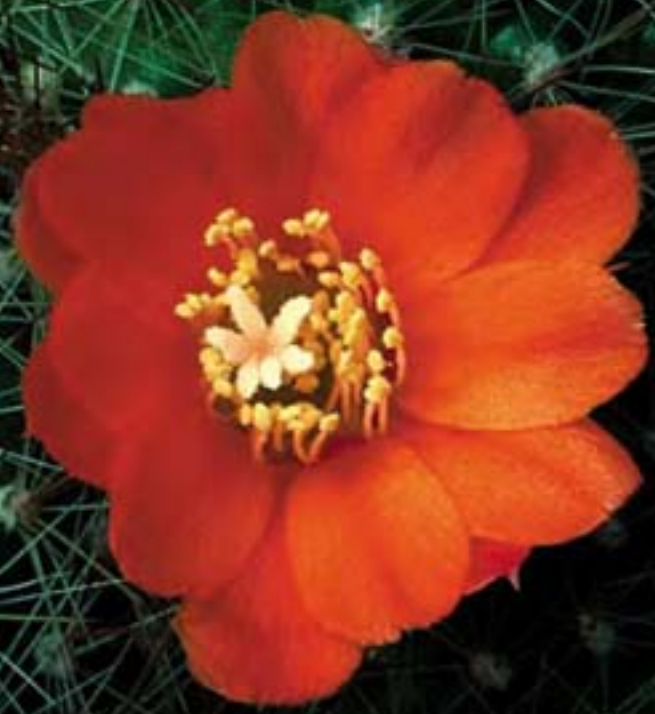

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Extensive Experience Produces Array of Cosmetic Dermatology Devices

Continued from page 6

Radiofrequency Devices

Still another area of advancement is radiofrequency (RF) treatment, which includes monopolar and bipolar devices. Dr Zachary is particularly impressed with the monopolar ThermaCool system. Initially plagued by problems due to overzealous use of high energies resulting in fat depression, the manufacturer has introduced a new protocol to address the problem. The device is used primarily for tissue tightening.

"I think people are seeing significant results in somewhere between 25% and 50% of cases," said Dr Zachary, who emphasized that he has no financial stake in any of the devices he mentioned. "Some people say they see significant results in 90% to 100% of cases, but this is clearly an exaggeration. The device has been extremely well studied, and the company has put more than $30 million into research and development, an extraordinary investment, but one that is paying off in the development of newer, faster, safer, and more effective treatment tips."

RF treatment is not a substitute for a facelift. The procedure is ideally suited for people who do not want surgery and prefer a procedure that takes an hour or so to perform and produce a moderate degree of tightening. It is said that one treatment can significantly and progressively improve the skin's appearance over 9 to 12 months. The cost for a single RF procedure might be in the $2,500 to $3,000 range, and patients have to face the possibility that they might not see any improvement at all!

"Patients and physicians have to be realistic about the results that can be achieved with any of these devices and procedures," said Dr Zachary. ■

Dr Zachary has nothing to disclose.

Peptides

Continued from page 14

sponsored by Sederma and presented in a poster at the 2002 World Congress of Dermatology in Paris, Pal-KTTKS (3 ppm) decreased skin roughness by 13%, reduced wrinkle volume by 36%, and decreased wrinkle depth by 27% after 4 months of twice-daily application on the face and neck. Skin biopsies performed on six women at 2 and 4 months demonstrated increased density and thickness of elastin fibers, while collagen type IV was improved at the dermal-epidermal junction.

Clinical studies sponsored by Procter & Gamble supported the benefits of Pal-KTTKS on photoaging skin.

Ninety-two women with moderate to severe photodamage participated in a split-face, randomized, double-blind, vehicle-controlled study. Subjects were treated for 12 weeks with twice-daily applications of facial moisturizer containing 3 ppm of Pal-KTTKS. Pal-KTTKS significantly improved facial lines and wrinkles as measured by image analysis of digital photos and expert grading, and did not negatively affect the skin barrier as measured by transepidermal water loss.

Additional studies were performed to compare the effects of Pal-KTTKS (3 ppm) to retinol (700 ppm) in the same vehicle. Sixteen women applied Pal-KTTKS to crow's-feet on one side of the face and retinol to the other for 4 months.

At the end of 2 months, Pal-KTTKS provided greater benefit than did retinol; at 4 months, both agents performed similarly and had reduced wrinkles as much as 50%. The investigators noted that Pal-KTTKS offered these benefits without the irritation that is often associated with retinol use.

Argireline, or acetyl hexapeptide-3, is a synthetic peptide that is touted as a topical alternative to botulinum toxin injections.

This peptide was developed and synthesized by Lipotec S.A. in Barcelona, Spain, and is distributed in the United States by Centerchem Inc. Argireline is found in several cosmeceuticals, including Avotox, DDF's Wrinkle Relax (HDS Cosmetics Inc.), and Inhibit (Natura Bissé). Most products contain 5%-10% argireline; Inhibit may have the highest concentration at 20%, and costs $135 for 0.5 ounce.

Extensive in vitro studies have been performed to elucidate argireline's mechanism of action (*J. Biol. Chem.* 272[5]:2634-39, 1997). One such study demonstrates that the peptide acts by preventing formation of the soluble N-ethylmaleimide–sensitive fusion attachment protein (SNAP) receptor complex, and thus inhibiting vesicle docking. Catecholamine release, including epinephrine and norepinephrine, was inhibited by argireline in vitro. The investigators suggested that this synthetic peptide may have practical medical applications because it mimics the action of clostridial neurotoxins in vitro.

Clinical trials on the efficacy of topically applied argireline are limited. An open-label trial of 5% argireline and an oil- and-water emulsion, applied twice daily, was conducted on 10 women.

Silicone replicas of periorbital rhytides were analyzed using confocal laser scanning microscopy, and demonstrated a 17% improvement after 15 days of treatment and a 27% improvement after 30 days of treatment.

Although argireline clearly demonstrates interesting in vitro activity, larger, more objective clinical studies are necessary to confirm its efficacy. Permeability studies performed on human skin would also be necessary, because this peptide would have to penetrate to the muscles to exert its proposed mechanism of action.

The use of biologically active peptides continues to be an area of interest. Ongoing research validating their mechanisms of action and clinical efficacy will be necessary to confirm their usefulness in our armamentarium for treating aging skin. ■

Dr Patricia Farris is a clinical assistant professor at Tulane University in New Orleans, and she has lectured internationally on topical treatments for aging skin. Reprinted from Skin & Allergy News, *July 2004. Based on data presented in 2001 in a poster at a meeting of the Society for Investigative Dermatology, a study presented in a poster at the 2003 American Academy of Dermatology annual meeting in San Francisco, and a study presented at the 2002 World Congress of Dermatology in Paris.*

RENOVA®
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THE ART OF SUN DAMAGE TREATMENT

FOR TOPICAL USE ON THE FACE. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Brief Summary

RENOVA (tretinoin cream) 0.02% contains the active ingredient tretinoin in a cream base.

IMPORTANT NOTE — This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from the complete prescribing information certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.

INDICATIONS AND USAGE:

(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)

RENOVA (tretinoin cream) 0.02% is indicated as an adjunctive agent (see second bullet point below) for use in the mitigation (palliation) of fine facial wrinkles in patients who use comprehensive skin care and sunlight avoidance programs. **RENOVA DOES NOT ELIMINATE WRINKLES, REPAIR SUN-DAMAGED SKIN, REVERSE PHOTOAGING, or RESTORE MORE YOUTHFUL or YOUNGER SKIN.** In double-blinded, vehicle-controlled clinical studies, many patients in the vehicle group achieved desired palliative effects on fine wrinkling of facial skin with the use of comprehensive skin care and sunlight avoidance programs including sunscreens, protective clothing, and non-prescription emollient creams.

- RENOVA 0.02% has NOT DEMONSTRATED A MITIGATING EFFECT on significant signs of chronic sunlight exposure such as coarse or deep wrinkling, tactile roughness, mottled hyperpigmentation, lentigines, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.
- RENOVA should be used under medical supervision as an adjunct to a comprehensive skin care and sunlight avoidance program that includes the use of effective sunscreens (minimum SPF of 15) and protective clothing.
- Patients with visible actinic keratoses and patients with a history of skin cancer were excluded from clinical trials of RENOVA 0.02%. Thus the effectiveness and safety of RENOVA 0.02% in these populations are not known at this time.
- Neither the safety nor the effectiveness of RENOVA for the prevention or treatment of actinic keratoses or skin neoplasms has been established.
- Neither the safety nor the efficacy of using RENOVA 0.02% daily for greater than 52 weeks has been established, and daily use beyond 52 weeks has not been systematically and histologically investigated in adequate and well-controlled trials. (See **WARNINGS** section.)

CONTRAINDICATIONS:

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS:

- RENOVA 0.02% is a dermal irritant, and the results of continued irritation of the skin for greater than 52 weeks in chronic use with RENOVA are not known. There is evidence of atypical changes in melanocytes and keratinocytes and of increased dermal elastosis in some patients treated with RENOVA 0.05% for longer than 48 weeks. The significance of these findings and their relevance for RENOVA 0.02% are unknown.
- RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of RENOVA because of heightened sunburn susceptibility. Patients should be warned to use sunscreens (minimum SPF of 15) and protective clothing when using RENOVA. Patients with sunburn should be advised not to use RENOVA until fully recovered. Patients who may have considerable sun exposure, e.g., due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using RENOVA and follow the precautions outlined in the Patient Package Insert.

RENOVA should be kept out of the eyes, mouth, angles of the nose, and mucous membranes. Topical use may cause severe local erythema, pruritus, burning, stinging, and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether and consider additional appropriate therapy.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used only with caution in patients with this condition.

Application of larger amounts of medication than recommended has not been shown to lead to more rapid or better results, and marked redness, peeling, or discomfort may occur.

PRECAUTIONS:

General: RENOVA should be used only as an adjunct to a comprehensive skin care and sunlight avoidance program. (See **INDICATIONS AND USAGE** section.)

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of RENOVA should be discontinued.

Weather extremes, such as wind or cold, may be more irritating to patients using tretinoin-containing products.

Information for Patients: See Patient Package Insert

Drug Interactions: Concomitant topical medications, medicated or abrasive soaps, shampoos, cleansers, cosmetics with a strong drying effect, products with high concentrations of alcohol, astringents, spices or lime, permanent wave solutions, electrolysis, hair depilatories or waxes, and products that may irritate the skin should be used with caution in patients being treated with RENOVA because they may increase irritation with RENOVA.

RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of this clinical formulation (0.02%). A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day. These doses are 10 and 20 times the maximum human systemic dose, when adjusted for total body surface area. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.5 times the maximum human systemic dose, adjusted for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose is defined as 1 gram of 0.02% RENOVA applied daily to a 50 kg person (0.004 mg tretinoin/kg body weight).

Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

In dermal Segment I fertility studies in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (20 times the maximum human systemic dose adjusted for total body surface area), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day (10 times the maximum human systemic dose adjusted for total body surface area) and above were observed. A dermal Segment III study with RENOVA has not been performed in any species. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (83 times the human topical dose adjusted for total body surface area).

Pregnancy:

Teratogenic effects: Pregnancy Category C.

ORAL tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and subhuman primates. It was teratogenic and fetotoxic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (42 times the maximum human systemic dose normalized for total body surface area). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which, metabolically, is closer to humans for tretinoin than the other species examined, fetal malformations were reported at doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (417 times the maximum human systemic dose adjusted for total body surface area), although increased skeletal variations were observed at all doses. A dose-related increase in embryolethality and abortion was reported. Similar results have also been reported in pigtail macaques.

TOPICAL tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (42 times the maximum human systemic dose adjusted for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was dermally applied.

There are other reports in New Zealand White rabbits administered doses of greater than 0.2 mg/kg/day (17 times the maximum human systemic dose adjusted for total body surface area) of an increased incidence of domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species.

In contrast, several well-controlled animal studies have shown that dermally applied tretinoin may be fetotoxic, but not overtly teratogenic, in rats and rabbits at doses of 1.0 and 0.5 mg/kg/day, respectively (42 times the maximum human systemic dose adjusted for total body surface area in both species).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty human cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin (Retin-A). Although no definite pattern of teratogenicity and no causal association has been established from these cases, 5 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Non-teratogenic effects:

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered 0.5 mg/kg/day (42 times the maximum human systemic dose normalized for total body surface area). Oral tretinoin has been shown to be fetotoxic, resulting in skeletal variations and increased intrauterine death, in rats when administered 2.5 mg/kg/day (104 times the maximum human systemic dose adjusted for total body surface area).

There are, however, no adequate and well-controlled studies in pregnant women. RENOVA should not be used during pregnancy.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since many drugs are excreted in human milk, mitigation of fine facial wrinkles with RENOVA 0.02% may be postponed in nursing mothers until after completion of the nursing period.

Pediatric Use: Safety and effectiveness in patients less than 18 years of age have not been established.

Geriatric Use: In clinical studies with RENOVA 0.02%, patients aged 65 to 71 did not demonstrate a significant difference for improvement in fine wrinkling when compared to patients under the age of 65. Patients aged 65 and over may demonstrate slightly more irritation, although the differences were not statistically significant in the clinical studies for RENOVA 0.02%. Safety and effectiveness of RENOVA 0.02% in individuals older than 71 years of age have not been established.

ADVERSE REACTIONS:

(See **WARNINGS** and **PRECAUTIONS** sections.)

In double-blind, vehicle-controlled studies involving 339 patients who applied RENOVA 0.02% to their faces, adverse reactions associated with the use of RENOVA were limited primarily to the skin. Almost all patients reported one or more local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus. In 32% of all study patients, skin irritation was reported that was severe, led to temporary discontinuation of RENOVA 0.02%, or led to use of a mild topical corticosteroid. About 7% of patients using RENOVA 0.02%, compared to less than 1% of the control patients, had sufficiently severe local irritation to warrant short-term use of mild topical corticosteroids to alleviate local irritation. About 4% of patients had to discontinue use of RENOVA because of adverse reactions.

Approximately 2% of spontaneous post-marketing adverse event reporting for RENOVA 0.05% were for skin hypo- or hyperpigmentation. Other spontaneously reported adverse events for RENOVA 0.05% predominantly appear to be local reactions similar to those seen in clinical trials.

OVERDOSAGE:

Application of larger amounts of medication than recommended has not been shown to lead to more rapid or better results, and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

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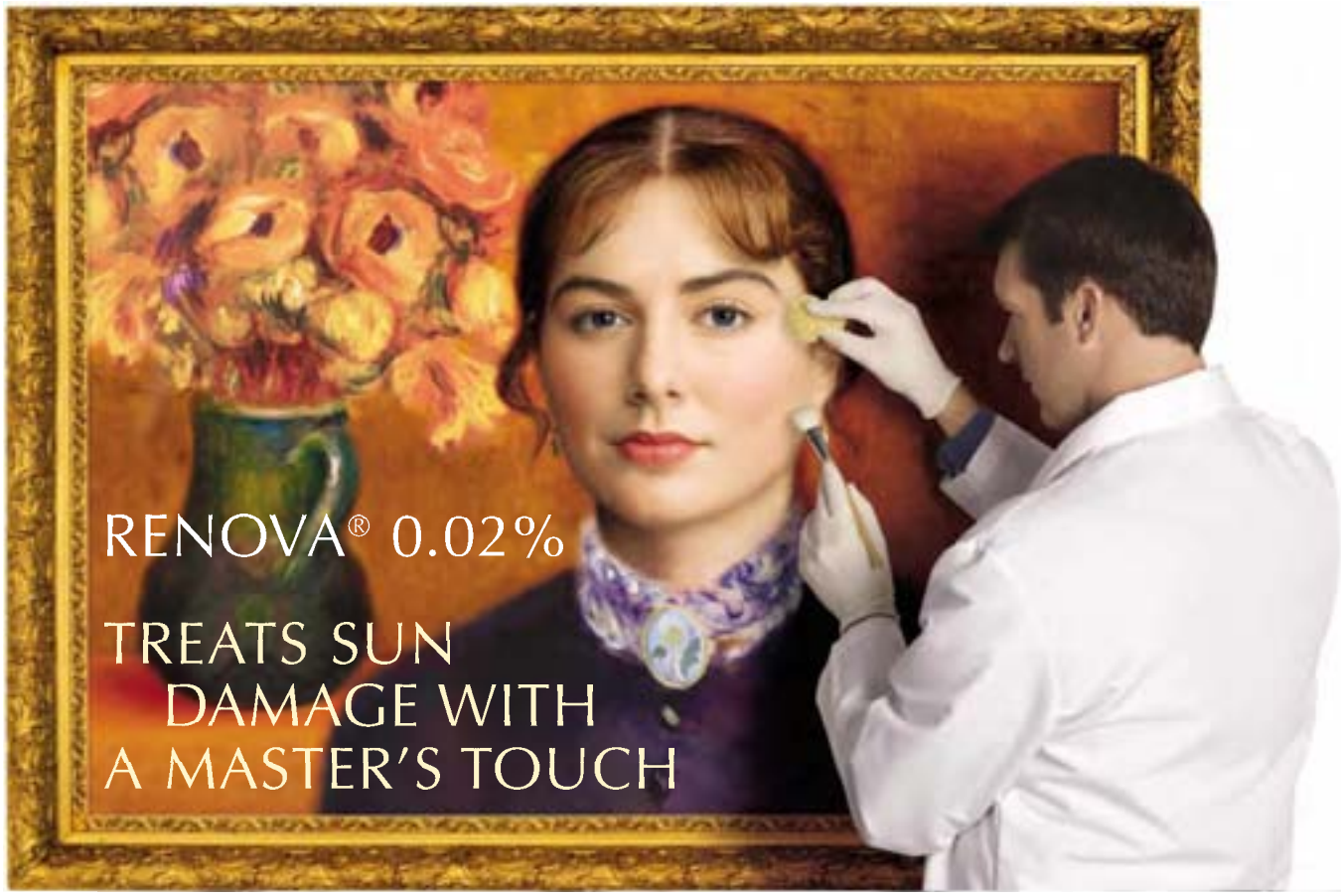

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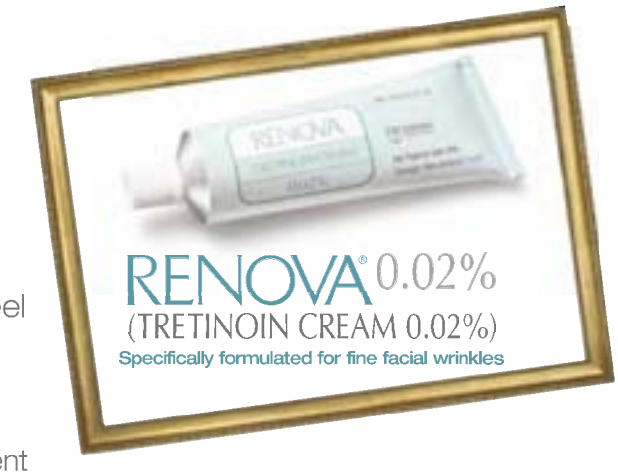
- Efficacious fine wrinkle reduction with less irritation[1,2]
- Patented water-base is cosmetically elegant for a light, silky, non-greasy feel



RENOVA 0.02% is indicated as an adjunctive agent for use in the mitigation (palliation) of fine wrinkles in patients who use comprehensive skin care and sunlight avoidance programs. RENOVA 0.02% does not eliminate wrinkles, repair sun damaged skin, reverse photoaging, or restore more youthful or younger skin.

The safety and efficacy of using RENOVA 0.02% daily for greater than 12 months have not been established. RENOVA 0.02% is proven effective on lightly pigmented skin, Fitzpatrick skin types I, II, and III.

Do not use RENOVA if the patient is taking drugs known to be photosensitizers, pregnant, attempting pregnancy, or nursing.

RENOVA 0.02% is a dermal irritant. Almost all patients experience skin reactions, including dryness, peeling, burning/stinging, erythema, and itching. In some patients this may be severe.

REFERENCES: 1. Nyriady J, Nighland M. Assessment of the cumulative irritation potential of six topical retinoids. Poster presented at: The American Academy of Dermatology 61st Annual Meeting; March 21-26, 2003; San Francisco, CA. 2. Nyriady J, Bergfeld W, Ellis C, et al. Tretinoin cream for the treatment of photodamaged facial skin: a review of 2 double-blind clinical studies. *Cutis*. 2001;68:135-142.

Please see next page for full Prescribing Information.