PRACTICAL AND CLINICAL INSIGHT INTO TODAY'S GENERAL DERMATOLOGY ISSUES

HMP COMMUNICATIONS LLC

February 2009

SKIN & AGING

www.skinandaging.com

BANISHING BURNOUT

Tips on managing stress, keeping positive and remaining engaged in medicine. Page 26

OTHER MUST-READ ARTICLES:

NEW DESIGN COMING SOON!

Treatment Strategies for Challenging Melasma Cases

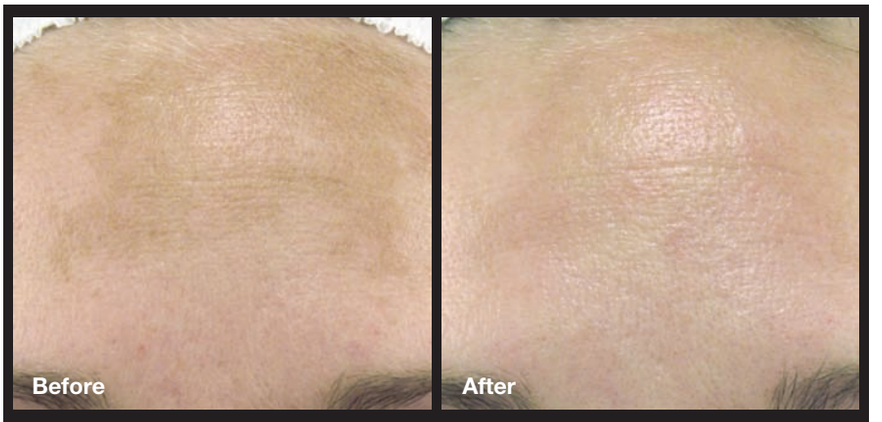
While many treatment options exist for this condition, the exact etiology is still not known, so treatment is difficult.

By Jennifer Linder, MD

Melasma, or hormonally induced hyperpigmentation, is one of the most common skin conditions in the United States, affecting nearly 6 million Americans annually.[1] Commonly referred to as the "pregnancy mask" due to its correlation with hormonal fluctuations and its mask-like appearance, melasma remains one of the most frustrating skin concerns for physicians and patients alike. While there are many treatment options for melasma, the exact etiology has not been completely determined, making it significantly more difficult to treat than other common hypermelanosis disorders. With new science unfolding each year, treatment is becoming better researched and deliberate, leading to more dramatic results. Proper diagnosis, knowledge of the latest innovations regarding possible etiology, and utilizing products formulated to clear the patches without worsening the condition are essential for ideal treatment choice and for setting realistic patient expectations.

Melasma typically appears in large, dense patches with distinct lines of demarcation. Most commonly seen on the centrofacial, malar and mandibular regions of the face, melasma may also affect other sun-exposed areas of the body such as the forearms.[2] While melasma affects women 90% of the time [3] and the condition is more prevalent in patients with darker skin, [4] anyone may be affected regardless of gender, pregnancy status or ethnic background.

The Melasma Area and Severity Index (MASI) was developed in 1994 to provide a consistent assessment of melasma cases. MASI characterizes hypermelanosis as follows: 0 = no abnormal; 1 = faint, barely visible; 2 = mild; 3 = moderate; and 4 = severe.[5,6] Each area of the face is categorized and an overall score is determined. This proven scale provides for greater consistency, which makes it easier to evaluate the efficacy of treatments. As with severity, the depth of hormonally induced discolorations also varies and may be epidermal, dermal, mixed or indeterminate. The depth of the pigment should be taken into consideration while developing a treatment plan and while explaining the condition to the patient.



Case 1: After 12 weeks
Received three PCA Peel with Hydroquinone treatments (14% lactic acid, 14% salicylic acid, 2% hydroquinone, 3% kojic acid and citric acid) in addition to daily use of PCA SKIN Facial Wash (aloe and lactic acid-based cleanser), Brightening Therapy with TrueTone (arbutin, undecylenoyl phenylalanine and phenylethyl resorcinol treatment lotion), ReBalance (nighttime hydrator) and Protecting Hydrator SPF 25 (sunscreen moisturizer).

Diagnosing and Evaluating Melasma

Certain diagnostic tools offer assistance in evaluating the skin and determining the depth of the melanin. The Wood's Lamp has been used as a diagnostic tool in dermatology since 1925 [7] and is particularly beneficial in evaluating hyperigmentation. The lamp utilizes wavelengths of 340 nm to 400 nm and illuminates abnormal tissue in varying colors depending on the condition. For example, epidermal melasma exhibits increased melanophages in all layers of the epidermis and is easily detected with a Wood's Lamp as a highlighted area, while dermal melasma is an abundance of melanin in the dermal layers of the skin, and the affected area will not fluoresce compared to surrounding normal skin. Mixed melasma, however, is a combination of both epidermal and dermal distribution, and only certain areas of dyschromia will be intensified under the Wood's Lamp. Indeterminate melasma, as the name suggests, cannot be classified with the Wood's Lamp.

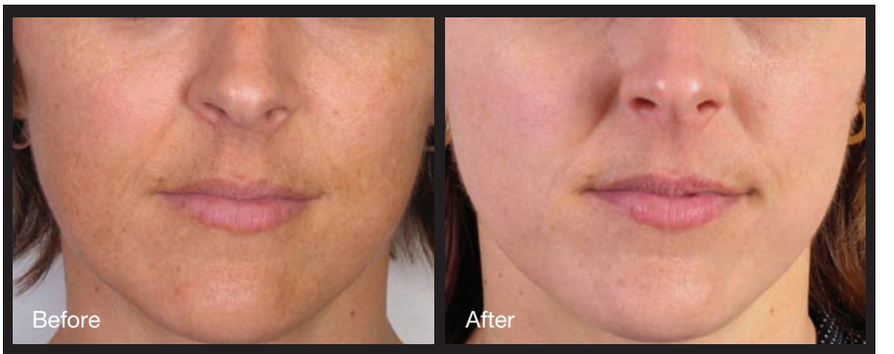
Advances in technology provide a wide variety of Wood's Lamps, ranging from simple hand-held models to larger full body variations. More advanced devices are also available, including some that offer bulbs with additional wavelengths to further highlight specific conditions and include digital photography capabilities. Regardless of the type, Wood's Lamps should be utilized in a dark room with the light approximately 5 inches from clean, dry skin. Once the depth of the melasma lesion is determined, treatment expectations may be set. In most circumstances, the deeper the melanin, the longer the treatment process. Setting realistic expectations with melasma patients is important, as treatment is often longer than with other skin conditions. On average, melasma sufferers may not see improvement for 3 to 6 months and, unfortunately, in some cases, dermal melasma cannot be lifted.

Etiological Advance and Understanding the Melanogenesis Process

Each year, new insights into the possible causes of melasma are uncovered, leading to more efficacious treatment options. Becoming familiar with recent etiological advances and an in-depth understanding of the melanogenesis process allows the practitioner to customize treatment plans for each individual patient.

Although not completely elucidated, new findings demonstrate underlying cellular variations possibly responsible for melasma discolorations. Melasma sufferers have been shown to have an increased number of epidermal melanocytes, keratinocytes and melanosomes in areas of melasma lesions.[8,9] Studies also indicate that increased branching of melanocytic dendrites is present in many cases.[9] All melanocytes contain nuclear estrogen receptors; however, melanocytes in patients with melasma have an increased number of estrogen receptors and may be more sensitive to the stimulatory effects of estrogens and other sex hormones.[9,10] It is well-documented that sun exposure worsens melasma patches,[11,12,13] and this is likely a result of a hypermelanogenic status due to a combination of UV radiation and hormone-related melanocyte excitement.[8] These and future findings will significantly increase the specificity and efficacy of melasma treatment options.

Melanogenesis, or the biosynthesis of melanin, can be triggered by both inflammation and hormonal stimuli. Fluctuations in hormones, such as pregnancy, lactation, menopause, hormonal contraceptives, hormone replacement therapy or thyroid or ovarian disorders may be responsible for the initiation of melanogenesis. The catalyst for all types of hyperpigmentation is the release of melanocyte-stimulating hormone (MSH), which triggers a chain reaction within the melanocyte. The enzyme tyrosinase is released and bound with copper and simultaneously induces the oxidation of the amino acid tyrosine. This oxidation leads to the production of L-3-4-dihydroxyphenylalanine (L-DOPA), which then is oxidized into dopaquinone by the copper-bound tyrosinase. At this point, dopaquinone is converted to eumelanin or pheomelanin. This pigment is then collected into packets of pigment called melanosomes that are transferred along the dendrites of the melanocyte to the surrounding keratinocytes. Melanosomes are then distributed in a parasol-like pattern over the nucleus of the keratinocytes to protect the cell's DNA.[14,15]



Case 2: After 11 weeks
Received four PCA Peel with Hydroquinone and Resorcinol treatments (14% lactic acid, 14% salicylic acid, 14% resorcinol, 2% hydroquinone, 3% kojic acid and citric acid) in addition to daily use of PCA SKIN Facial Wash (aloe and lactic acid-based cleanser), Pigment Gel (2% hydroquinone, kojic acid and azelaic acid treatment gel), C-Quench (15% ascorbic acid serum), A&C Synergy Serum (retinol treatment serum), ExLinea (peptide wrinkle reducer), Apres Peel Hydrating Balm (nighttime hydrator), and Hydrator Plus SPF 25 (sunscreen moisturizer).

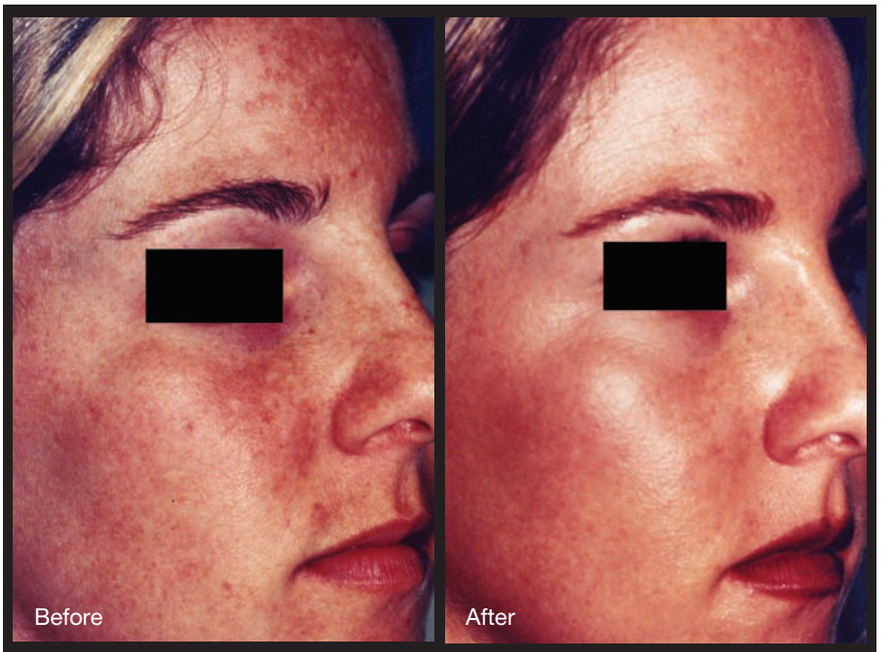
By understanding this process we are able to identify ingredients scientifically proven to counteract multiple steps of this melanogenesis pathway, and therefore accelerate treatment results.

Therapy Options for Melasma

Centuries of scientific research have uncovered multiple agents to reduce the appearance of this prevalent condition; however, through my own personal struggle with melasma and that of my patients, I feel there is no one ingredient that will completely clear this stubborn affliction. By determining the mechanism of action of the pigment-reduction ingredients currently available, ideal combinations can be found that work synergistically to interrupt melanin production at numerous points.

Pigment Reduction Ingredients

- ***Hydroquinone***(HQ) is the most prescribed bleaching agent world-wide and inhibits tyrosinase activity by suppressing the binding of copper and tyrosinase. HQ also decreases the formation of melanosomes, promotes the degradation of melanosomes and induces melanocyte-specific cytotoxicity.[8,16,17] HQ should be used in lower percentages to avoid inflammation and the possible subsequent post-inflammatory hyperpigmentation (PIH). Spot testing should be utilized to determine patient tolerance.
- ***Arbutin*** is a natural beta-D-glucopyranoside derivative of HQ that allows controlled release of HQ.[8,17] Arbutin inhibits the activity of tyrosinase and melanosome maturation.[17,18]
- ***Kojic acid*** inhibits melanogensis by chelating the copper bound to the tyrosinase.[8,17,19] It also decreases the number of melanosomes and melanocytic dendrites[20] while inhibiting nuclear factor-kappa B (NF-kB) activation in keratinocytes, mitigating the inflammatory response.[21]
- ***Retinol*** inhibits tyrosinase activity, decreases the amount of melanosomes and inhibits the transfer of melanin from melanocyte to keratinocytes. Retinol also enhances the penetration of actives through the stratum corneum and increases cell turnover, accelerating the pigment-lifting process.[8,22]
- ***Ascorbic acid*** is the bioavailable form of vitamin C and works to prevent the binding of copper to tyrosinase and also converts dopaquinone back to L-DOPA.[23]
- ***Lactic acid*** is a widely used alpha-hydroxy acid (AHA) that increases exfoliation of melanin-filled keratinocytes and suppresses the formation of tyrosinase.[8,24]
- ***Azelaic acid*** provides melanocyte-specific anti-proliferative and cytotox-



Case 3: After 8 weeks
Received one PCA Peel with Hydroquinone treatments (14% lactic acid, 14% salicylic acid, 2% hydroquinone, 3% kojic acid and citric acid) in addition to daily use of PCA SKIN Facial Wash (aloe and lactic acid-based cleanser), Pigment Gel (2% hydroquinone, kojic acid and azelaic acid treatment gel) and Hydrator Plus SPF 25 (sunscreen moisturizer).

ic effects while inhibiting tyrosinase activity as well as DNA synthesis and mitochondrial activity in hyperactive and abnormal melanocytes. [8,25]

- ***Glycyrrhiza glabra extract*** (licorice) suppresses the activity of tyrosinase while preventing inflammation. [26]
- ***Morus bombycis root extract*** (mulberry) inhibits the conversion of L-DOPA to dopaquinone and provides anti-inflammatory and antioxidant benefits. [16]
- ***Phenylethyl resorcinol*** is a synthetically produced resorcinol derivative that inhibits the conversion of tyrosinase to L-DOPA and provides antioxidant effects. [27]
- ***Undecylenoyl phenylalanine*** works very early in the melanogenesis response by inhibiting the release of melanocyte-stimulating hormone. [28]

Exfoliation and Cellular Turnover

These ingredients, combined with gentle exfoliation and increased cellular turnover, will lead to a reduction in pigmented macules and an overall more even skin tone.

Exfoliation

Exfoliation may be induced by ***chemical*** peeling ingredients such as alph hydroxy acids, trichloroacetic acid, salicylic acid or resorcinol or may be ***mechanical*** as with microdermabrasion or scrubs. Although both may be effective, caution should be taken when utilizing these methods, as overly aggressive exfoliation can create inflammation within the skin and can initiate further melanogenesis. Prepping the skin with melanogenesis inhibitors prior to treatment and using professional treatment products that include these ingredients may prevent the occurrence of treatment-induced discolorations. [29]

Cell Turnover

Along with promoting the shedding of melanin-filled keratinocytes, cell turnover should also be stimulated to accelerate the lifting of pigmented cells. ***Retinoids*** are the most effective topical agents to induce cellular turnover, [30] and while retinoic acid is very powerful, it is also potentially irritating and should be used cautiously. ***Retinol*** is often a suitable alternative, as it is successfully converted to retinoic acid within the skin and creates no topical inflammation.

Prevent Cellular Oxidation, Inflammation

Cellular oxidation and inflammation from internal and external factors should be prevented in all patients prone to melasma. Inflammation is one of the main causes and exacerbating factors in hyperpigmentation. Anti-inflammatory and antioxidant agents such as ascorbic acid, EGCG from green tea and resveratrol reduce both inflammation and free radical damage.[31,32,33] Adding antioxidants to a pigment control routine can accelerate results.

UV Protection

The last and possibly most important step in the treatment of melasma is daily use of broad-spectrum UV protection. Not only will the sun's damaging UV rays stimulate more inflammation and dyschromias, but many of the melanogenesis inhibitors increase photosensitivity. Reducing the melanin content in the skin depletes the skin's natural defense against the sun;[17] therefore, patient compliance regarding sun protection and avoidance is imperative and will determine individual outcomes.

Combination Therapy

While several methods of treatment have proven to be effective, the most beneficial, in my experience, is combination therapy. I prefer superficial chemical peels formulated with a combination of acids, such as the PCA SKIN PCA Peels, which are Jessner's solutions enhanced with pigment inhibitors. These peels should be used in conjunction with daily care products designed to inhibit melanogenesis, inflammation and oxidation, and provide daily UV protection. Superficial chemical peels provide gentle exfoliation without inducing unwanted trauma, and while several treatments may be needed for clearing, dependant on the severity and depth of the melasma, I recommend this route over more aggressive treatments that can over-stimulate the skin and exacerbate the condition.

Avoid Overtreatment of Melasma

The most common mistake I see in the treatment of melasma is the worsening of the problem or a delayed outcome due to overly aggressive treatment such as pure TCA peels, high percentage HQ or laser therapy. Studies show that light therapy treatments such as IPL or laser, while beneficial for sun-induced hyperpigmentation, will frequently worsen melasma.[34,35,36] High percentages of acids and chemical lighteners may also stall clearance by stimulating additional discolorations in the form of post inflammatory hyperpigmentation (PIH) in the area of treatment.

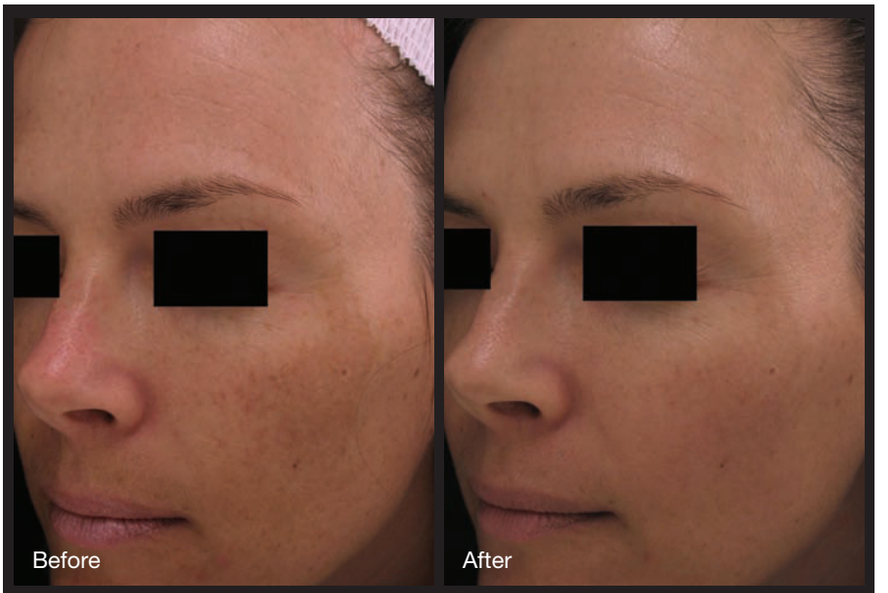
Consider peel depth and the inflammation associated with deeply penetrating treatments before over-treating hypermelanosis disorders. Another component to consider is the irritation caused by home care ingredients. For example, if a patient is on greater than 2% of HQ and does not seem to be improving, consider the possibility that the HQ has triggered enough irritation to induce PIH. One should also consider the irritation associated with topical tretinoin usage and explore less aggressive alternatives such as retinol.

Employing a progressive, rather than aggressive, approach when treating all types of hyperpigmentation allows for effective lifting of dyschromias without exacerbating the condition. In general, I have found it is better to utilize gentler treatments and lower percentages of effective ingredients. The avoidance of irritation and inflammation insures a consistent, beneficial outcome.

The Keys to Treatment Success

Although melasma continues to be one of the most difficult conditions to treat, proper diagnosis, improved technology, patient education and breakthrough ingredients have enabled melasma treatments to progress significantly in recent years. Through better understanding of this stubborn condition, new treatment options are sure to arise in the future that will assist the practitioner in developing the most beneficial treatment plans available. ■

Dr. Linder, a board-certified dermatologist and fellowship-trained Mohs skin cancer surgeon, is a volunteer Clinical Instructor in the Department of Dermatology at the University of California, San Francisco. Dr. Linder is currently in private practice in Scottsdale, AZ.



Case 4: After 14 weeks

Received seven PCA Peel with Hydroquinone treatments (14% lactic acid, 14% salicylic acid, 2% hydroquinone, 3% kojic acid and citric acid) in addition to daily use of PCA SKIN Facial Wash (aloe and lactic acid-based cleanser), Nutrient Toner (antioxidant and lactic acid-based astringent), Pigment Gel (2% hydroquinone, kojic acid and azelaic acid treatment gel), Brightening Therapy with TrueTone (arbutin, undecylenoyl phenylalanine and phenylethyl resorcinol treatment lotion), ReBalance (nighttime hydrator) and Protecting Hydrator SPF 25 (sunscreen moisturizer).

References

1. Scheinfeld NS. Melasma. *SKINmed: Dermatology for the Clinician.* 2006;6(1):35-37.
2. Montemarano AD. "Melasma" emedicine from WebMD 2008 http://www.emedicine.com/DERM/topic260.htm
3. Pandya AG, Guevara IL. Disorders of hyperpigmentation. *Dermatologic Clinics* 2000;18(1):91-98.
4. Freitag FM, Cestari TF, Leopoldo LR, et al. Effect of melasma on quality of life in a sample of women living in southern Brazil. *J Eur Acad Dermatol Venereol.* 2008;22(6):655-662.
5. Kimbrough-Green CK, Griffiths CE, Finkel LJ, et al. Topical retinoic acid (tretinoin) for melasma in black patients. A vehicle-controlled clinical trial. *Arch Dermatol.* 1994;130:727-33.
6. Bhor U, Pande S. Scoring systems in dermatology *Indian J Dermatol Venereol Leprol.* 2006;72(4):315-321.
7. Gupta L, Singi M. Wood's Lamp. *Indian J Dermatol Venereol Leprol.* 2004;70(2):131-136.
8. Lotti T. *Dermatologic Clinics: Pigmentary Disorders* Philadelphia: Elsevier Saunders, 2007.
9. Costin G, Hearing VJ. Human skin pigmentation: melanocytes modulate skin color in response to stress. *FASEB J.* 2007;21:976-994.
10. Lieberman R, Moy L. Estrogen receptor expression in melasma: results from facial skin of affected patients. *J Drugs Dermatol.* 2008;7(5):463-465
11. Katsambas A, Antoniou C. Melasma. Classification and treatment *J Eur Acad Dermatol Venereol.* 1995;4(3):217–223.
12. Victor FC, Gelber J, Rao B. Melasma. A review. *J Cutan Med Surg.* 2004;8(2):97-102.
13. Tung RC, Bergfeld WF, Vidimos AT, et al. Alpha-hydroxy acid-based cosmetic procedures: guidelines for patient management. *Am J Clin Dermatol.* 2000;1(2):81-88.
14. Bolognia JL, Jorizzo JL, Rapini RP. *Dermatology*: 2-Volume Set. Philadelphia: Mosby, 2007
15. Jimhnez-Cervantes C, Solano F, Kobayashiq T, et al. A new enzymatic function in the melanogenic pathway. *J Biol Chem* 1995; 269(27):17993-18000.
16. Badreshia-Bansal S, Draelos ZD. Insight into skin lightening cosmeceuticals for women of color. *J Drugs Dermatol.* 2007;6(1):32-39.
17. Bennett S, Chaudhuri RK, Closs B, et al. *Anti-aging: Physiology to Formulation*. Carol Stream, Illinois: Allured Publishing Corporation, 2006.
18. Maeda K, Fukuda M. Arbutin: mechanism of its depigmenting action in human melanocyte culture. *J Pharmacol Exp Ther.* 1996;276(2):265-269.
19. Kim YM, Yun J, Lee CK, et al. Oxyresveratrol and hydroxystilbene compounds: inhibitory effect on tyrosinase and mechanism of action. *J Biol Chem.* 2002;277(18):16340-16344.
20. James AJ. Skin lightening and depigmenting agents. emedicine from WebMD 2006. http://www.emedicine.com/derm/topic528.htm
21. Draelos ZD. *Cosmetic Formulation of Skin Care Products.* New York: Taylor and Francis Group LLC, 2006.
22. Draelos ZD. Retinoids in cosmetics. *J Cosmet Dermatol.* 2005;18(s1):3-5.
23. Goh, CL. Medical treatment for acquired pigmentary disorders in Asians. AAD 66th Annual Meeting, February, 2008.
24. Ando S, Suemoto Y, Mishima Y, et al. Tyrosinase gene transcription and its control by melanogenic inhibitors. *J Invest Dermatol.* 1993;100(2s):150s-155s.
25. Fitton A, Goa KL. Azelaic acid. A review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary disorders. *Drugs.* 1991;41(5):780-798.
26. Yukota T, Nishio H, Kubota Y, et al. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. *Pigment Cell Res.* 1998;11(6):355-361.
27. SymRise AG. Symwhite Product Information. Frankfurt, Germany (2007).
28. SEPPIC SA. Sepiwhite Product Information. Paris, France (2003).
29. Atkins D, Frodel J. Skin rejuvenation in facial surgery. *Facial Plast Surg.* (2006);22(2)129-139.
30. Elias PM. Epidermal effects of retinoids: supramolecular observations and clinical implications. *J Am Acad Dermatol.* 1986;15(4 Pt 2):797-809.
31. Ferris PK. Topical Vitamin C: A Useful agent for treating photoaging and other dermatologic conditions. *Dermatol Surg.* (2005);31(s1):814-818.
32. Hsu S, Bollag WB, Lewis J, et al. Green tea polyphenols induce differentiation and proliferation in epidermal keratinocytes. *The J Pharmacol Exp Ther.* 2003,306;29-34.
33. Baxter RA. Anti-aging properties of resveratrol: review and report of a potent new antioxidant skin care formulation. *J Cosmet Dermatol.* 2008;7(1):2-7.
34. Suzuki H, Anderson RR. Treatment of melanocytic nevi. *Dermatol Ther.* 2005;18(3):217-226.
35. Goldberg DJ. Laser removal of pigmented and vascular lesions. *J Cosmet Dermatol.* 2006;5(3):204-220.
36. Wang CC, Hui CY, et al. Intense pulsed light for treatment of refractory melasma in Asian persons. *Dermatol Surg.* 2004;30:1196-1200.

DISCLOSURE: Dr. Linder is Chief Scientist, PCA SKIN, is National Instructor, Dermik Aesthetics (Sculptra), and National Instructor, Allergan Facial Aesthetics.