

# Topical therapies for melasma and disorders of hyperpigmentation

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**ABSTRACT:** Facial hyperpigmentation is usually a reflection of an increased amount of melanin either within the epidermis, the dermis, or both (mixed pattern). The increase in melanin content is due to an increased number of functioning melanocytes (melanocytosis), an increased amount of melanin production without a numerical alteration of melanocytes (melanosis), or both. Topical hypo/depigmenting agents are most effective in those disorders where the increased melanin pigment (secondary to melanocytosis or melanosis) is within the epidermis. In patients with melasma, one of the more common causes of facial hyperpigmentation, two major groups of hypo/depigmenting agents have been used: phenolic derivatives and nonphenolic compounds. Hydroquinone, a phenolic derivative, has been used most extensively. It is applied to areas of involvement, either alone or in combination with one or two of the following: tretinoin, salicylic acid, glycolic acid, or corticosteroid. Phenolic thioethers are a new class of phenolic derivatives, and they exhibit both cytoidal and cytostatic effects selectively on melanocytes. Nonphenolic depigmenting agents include azelaic acid and kojic acid. If the facial hyperpigmentation is not improved by first-line topical therapies, chemical peels may be used in combination. The precise cause of melasma is not known, and multiple factors have been implicated. However, a genetic predisposition and exposure to ultraviolet (UV) light are very important factors. Avoidance of direct exposure to sunlight and application of broad-spectrum sunscreens are required during and after the period of active treatment. In addition to melasma, other causes of facial hyperpigmentation include Riehl's melanosis, photocontact dermatitis, the sequelae of inflammatory diseases such as acne vulgaris and cutaneous lupus, and nevus of Ota.

**KEYWORDS:** chemical peels, hydroquinone, hyperpigmentation, melanin, melasma.

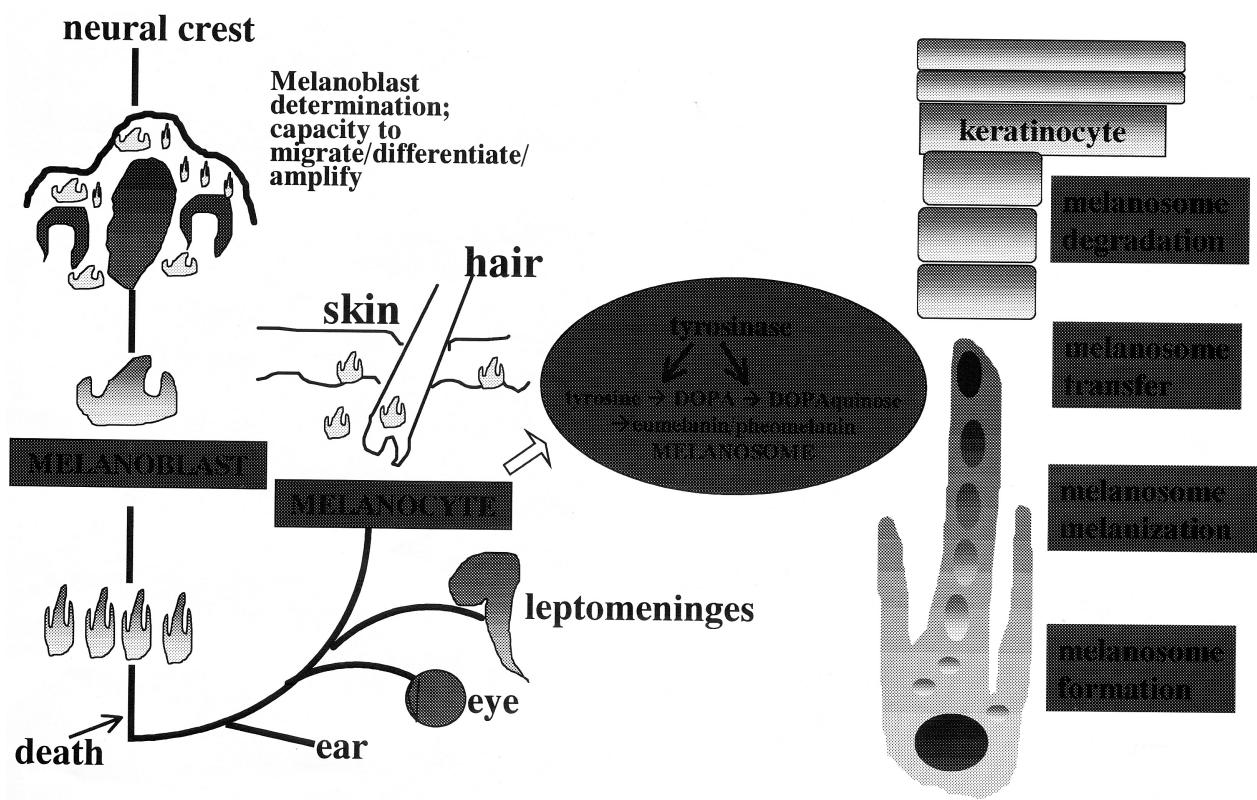
Designing a therapeutic regimen for facial hyperpigmentation that involves topical agents that are both safe and effective is often difficult. The first step is to try to understand the basic biology of pigmentation, and second, it is important to review the clinical characteristics of individual disorders in order to arrive at the correct differential diagnosis. Through these two steps, one may be able to anticipate the advantages as well as the limitations of each topical therapeutic agent.

In disorders of hyperpigmentation, the amount of melanin in the skin is of primary importance

(1). Melanin is produced inside melanosomes, specialized organelles within the cytoplasm of melanocytes; the melanocytes, which reside in the basal layer of the epidermis, secrete melanosomes into surrounding keratinocytes. The estimated melanocyte:keratinocyte ratio is 1:36 and the partnership is known as the epidermal melanin unit. After the melanosomes have been transferred into the keratinocytes, they fuse with lysosomes (Fig. 1). When there is inflammation of the skin and subsequent cellular damage, some of the melanosomes drop into the dermis and are engulfed by macrophages; these cells are then referred to as melanophages.

Cutaneous hyperpigmentation is caused by the direct stimulation of melanocytes by exogenous factors such as ultraviolet (UV) light or indi-

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**Fig. 1.** Embryonic development of melanocytes from neural crest and their migration to the skin. Melanoblasts migrate to not only the skin and hair, but also the leptomeninges, inner ear, and eye. In the epidermis there is a symbiotic relationship between a melanocyte and a neighboring group of keratinocytes (epidermal melanin unit). There is a marked difference in the number, degree of melanization, size of melanosomes, and distribution (single versus complex pattern) of degrading melanosomes in keratinocytes between hyperpigmented skin (e.g., melasma) and control nonpigmented skin.

rect stimulation of melanocytes by keratinocytes or other cells (such as fibroblasts) via the release of a number of cytokines and growth factors. The latter include basic fibroblast growth factor, endothelins (I and III), transforming growth factor (TGF)- $\alpha$ , epidermal growth factor, nerve growth factor, platelet-derived growth factor, and hormones such as insulin, melanocyte-stimulating hormone (MSH), and hydrocortisone.

The biologic process of cutaneous pigmentation is divided into two primary components: melanin production determined by cellular genetic programs in the absence of exposure to UV light, that is, constitutive skin color; and immediate and delayed tanning reactions elicited by direct exposure of the skin to UV light, that is, facultative color. Facultative color changes are elicited by a complex interplay of light, hormones, and other factors, including the capacity for tanning established by the individual's genetic constitution. The marked variation in the ability of very light-skinned individuals to tan suggests that fac-

ultative changes in skin color involve gene actions beyond that which determines constitutive skin color. Topical therapeutic agents used for hyperpigmentation effect primarily facultative pigmentation of the skin.

### Clinical features and pathophysiology of melasma and other disorders of facial hyperpigmentation

Facial hyperpigmentation is a fairly common disorder, especially in darkly pigmented individuals, and it can represent a complex diagnostic problem. A myriad of factors may be responsible for facial hyperpigmentation, and the increased pigment may reflect a localized phenomenon or it may be a manifestation of a more generalized disorder. In addition, the hyperpigmentation may be acquired, congenital, or inherited. Histologically, the increased pigment can be found within

**Table 1.** Classification of facial hyperpigmentation

Level of pigmentation	Clinical features		
	Histogenesis	Circumscribed/limited	Diffuse/widespread
Epidermal	Melanocytosis <sup>a</sup>	Lentigines and lentigo-based syndromes (e.g., centrofacial, Peutz-Jeghers); lentigo, senilis, and maligna	Lentigines and lentigo-based syndromes [LEOPARD syndrome, Carney's complex (NAME/LAMB syndrome)]; dysplastic nevus syndrome
	Melanosis <sup>b</sup>	Melasma (epidermal type); Riehl's melanosis; erythromelano-follicularis faciei et colli; postinflammatory hyperpigmentation; drugs (e.g., phenytoin, oral contraceptives, estrogens); ephelides	Porphyria cutanea tarda; Addison's disease; systemic diseases (hyperthyroidism, renal insufficiency, biliary cirrhosis); hemochromatosis; POEMS syndrome; drugs; urticaria pigmentosa
Dermal	Melanocytosis <sup>c</sup>	Nevus of Ota; blue nevus; extrasacral Mongolian spot	
	Melanotic	Periorbital hyperpigmentation	Metastatic melanoma with melanogenuria; fixed drug eruption; erythema dyschromium perstans; pinta; chronic nutritional deficiency
	Nonmelanotic/ nonmelanocytotic	Tattoos; ochronosis, exogenous; drugs (e.g., mercury-containing cosmetics)	Drugs (e.g., amiodarone, antimalarials); heavy metals (e.g., bismuth, chrysiasis, argyria); hemosiderin; alkaptoururia

<sup>a</sup>Increased number of epidermal melanocytes.<sup>b</sup>Increased amount of melanin pigment in the epidermis, but no alteration in melanocyte population.<sup>c</sup>Functioning melanocytes in the dermis.

Adapted from Salopek and Jimbow (27).

the epidermis, dermis, or both. As outlined in Table 1, there may be an increased number of melanocytes (i.e., melanocytosis), an increased amount of melanin without an alteration in the number of melanocytes (i.e., melanosis), or the presence of non-melanin pigments (e.g., tattoo pigment).

In the evaluation of a patient, it is important to try to distinguish epidermal from dermal hyperpigmentation by clinical examination and inspection with a Wood's lamp. Epidermal pigmentation is usually dark brown or black in color, and it is accentuated under Wood's lamp illumination. In contrast, dermal pigmentation is often slate gray or blue in color, and it becomes less prominent by Wood's lamp examination. However, in darkly pigmented individuals, changes in color intensity with Wood's lamp illumination may be more difficult to appreciate. Nonetheless, if possible, this distinction should be made because medical treatment modalities are best suited for the treatment of epidermal causes of hyperpigmentation.

### Melasma

Melasma presents in one of three, usually symmetric, facial patterns. The most common one is

the centrofacial pattern involving the cheeks, forehead, upper lip (sparing the philtrum), nose, and chin (Fig. 2). Less common are the malar pattern, involving the cheeks and nose, and the mandibular pattern, involving the ramus of the mandible. Melasma also occurs on other parts of the body, for example, the forearms, but this is unusual. The macular lesions have irregular and geographic borders and usually display a remarkable degree of symmetry. Melasma occurs exclusively in sun-exposed areas and is more apparent after a period of solar exposure. It is consistently less obvious in winter months when solar exposure is usually kept to a minimum. Multiple factors have been reported to exacerbate melasma, including pregnancy, oral contraceptives, endocrine dysfunction, genetic factors, medications, nutritional deficiency, and hepatic dysfunction. Melasma may become apparent during pregnancy or following childbirth or the use of oral contraceptives. Although a few familial cases have been described, melasma is usually not considered an inherited disorder in the classic sense. There is, however, a genetic predisposition in that melasma is seen more commonly in patients with skin types III–VI. At least a third of cases in women and the majority in men are idiopathic in nature.



Fig. 2. Clinical features of melasma lesion on the face of a female patient. The centrofacial pattern involving cheeks, forehead, and chin.

Histologically, biopsy specimens of melasma reveal increased melanin pigmentation in the epidermis (epidermal type), dermis (dermal type), or both (mixed type). In the epidermal type, there is an increased amount of melanin in both the basal and suprabasal layers. An increased number and activity of melanocytes also may be seen. A consistent finding is an increase in the formation, melanization, and transfer of melanosomes to surrounding keratinocytes. In the dermal type of melasma, melanin pigments produced by epidermal melanocytes drop off into the papillary dermis and are taken up by macrophages (melanophages) (2,3).

#### Riehl's melanosis

Riehl's melanosis is an acquired pigmentary disorder characterized by reticular pigmentation of the face; the areas of involvement are brown-violet to black in color. It is most commonly seen in middle-aged women, but men may be affected (Fig. 3). In 1917, Riehl suggested that the ingestion of "noxious substances" was the etiologic

factor. Exposure to external substances, for example, mineral oil and tar, was also thought to be able to produce a similar condition. Hoffman and Habermann (4) referred to this condition as "melanodermatitis toxica."

Riehl's melanosis occurred during and after both World Wars, primarily in the populations that were defeated, and exposure to tar was thought to be a primary factor. Because patients suffering from Riehl's melanosis frequently demonstrated positive patch-test reactions to cosmetics or their ingredients, the disorder was also referred to as "pigmented cosmetic dermatitis." Similarly, this condition has been called "female facial melanosis" inasmuch as the majority of patients with Riehl's melanosis are middle-aged women. While the etiology of Riehl's melanosis remains undetermined, it may be the result of contact or photocontact dermatitis due to a chemical or chemicals present in cosmetics.

Hayakawa (5) found that the lipoperoxide content of sebum from Riehl's melanosis patients was 19 times that of normal controls. Nagao et al. (6) reported the following light and electron mi-



Fig. 3. Riehl's melanosis of a female patient, showing brown to slate gray pigmentation on the face.

croscopic findings in Riehl's melanosis: edema within the epidermis, active melanocytes, a multilayered basal lamina, and marked pigmentary incontinence. These authors suggested that exposure to various "irritations," for example, the chemicals within cosmetics, UV light, or rubbing of the skin at the time of application of cosmetics, caused edema within the epidermis, activated the melanocytes, and destroyed the barrier function of the epidermis, leading to the production of Riehl's melanosis.

### **Photocontact dermatitis**

Photocontact dermatitis often leads to hyperpigmentation of the skin that is usually epidermal in nature. It occurs when the application of photosensitizing compounds is followed by exposure to sunlight. In the case of phototoxic reactions, the photosensitizing compounds include psoralen-containing vegetables, fruits, plants, and cosmetics, as well as coal tars. Examples of such vegetables, fruits, and plants include limes, lemons, figs, parsley, carrot greens, celery, ferns, and clover. Application of psoralen-containing perfumes and colognes followed by sunlight exposure also leads to photodermatoses, for example, Berloque dermatitis. In some cases, only hyperpigmentation appears in sites of exposure, whereas in others the pigmentation is preceded by an erythematous and/or bullous eruption.

### **Nevus of Ota**

Nevus of Ota, also known as oculodermal melanocytosis, is a reflection of melanin-producing melanocytes within the dermis in addition to epidermal hyperpigmentation. The disorder was first reported by Ota in 1937 and 1940, and is frequently observed in Asians. In Japan, up to 0.2–0.8% of all visits to dermatologists involve the evaluation or treatment of nevus of Ota (7). There are two major peaks of incidence, one in infancy and the other in the late teens/early 20s. No explanation exists, however, for the observation that women are affected five times more frequently than men.

Clinically nevus of Ota is usually characterized by unilateral discoloration of facial skin; blue-brown or slate gray macules intermingle with areas of brown pigmentation. The most common location is the area of the face innervated by the first and second branches of the trigeminal nerve (e.g.,

eyelids, zygomatic and maxillary regions) (Fig. 4). Ocular involvement is common (up to 60% of patients) (Fig. 5) and its incidence correlates with the extent of cutaneous involvement. Blue to blue-gray discoloration of mucosal surfaces, for example, oral and nasal, also may be seen.

Based on the distribution and extent of pigmentation, four clinical types of nevus of Ota have been proposed: 1) mild/type I—subdivided into common A and B forms (orbital and zygomatic involvement, respectively) and less common C and D forms (forehead and ala nasi involvement, respectively); 2) moderate/type II—discoloration involving the upper and lower eyelids, periocular and zygomatic regions, cheek, and temple; 3) intensive/type III—distribution of type II plus the scalp, forehead, eyebrow, and nose; and 4) bilateral/type IV—bilateral distribution of pigmentation (Fig. 6).

## **Topical therapies for melasma and other disorders of facial hyperpigmentation**

### **Hydroquinone**

Currently hydroquinone (HQ) is the most commonly used topical therapy for melasma and other disorders of facial hyperpigmentation. Although there are a number of formulations of HQ, the concentrations usually vary from 2 to 5% and are usually compounded in a vanishing cream or hydroalcoholic base. A decrease in skin color may be observed after 4 weeks of therapy, and the optimal effect on pigmentation is achieved after 6–10 weeks of therapy. The effectiveness of HQ is enhanced by concomitant daily use of an effective broad-spectrum sunscreen cream. However, daily and prolonged use of HQ at a concentration of 4–5% leads to a high incidence of primary irritant reactions. In addition, there is the risk of exogenous ochronosis and further darkening of the skin (8). Two-percent HQ (which is available without a prescription) is not effective for the treatment of melasma, but can be used for maintenance therapy. In 1975, Kligman and Willis (8) reported good results with a combination of retinoic acid (RA; 0.1%), HQ (4%), and triamcinolone acetonide (0.025%), and similar combinations are still used today. Formulations containing 2% HQ plus 0.05% or 0.1% RA also can lead to a lightening of melasma. Higher concentrations



Fig. 4. Nevus of Ota in a female patient affecting eyelid, forehead, nose, and zygomatic area.



Fig. 6. Nevus of Ota in a male patient affecting eyelid, zygomatic area, and nose (bilateral).

of RA (>0.5%) should be avoided, as they can be irritating and result in “paradoxical” postinflammatory hyperpigmentation. Patients with dermal melasma often do not respond satisfactorily to HQ therapy (9).

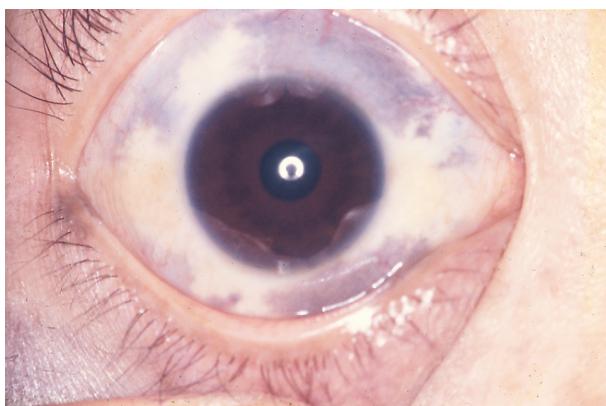


Fig. 5. A female patient with nevus of Ota, showing ocular pigmentation.

#### Azelaic acid

Azelaic acid (AA) is a dicarboxylic acid originally isolated from *Pityrosporum ovale*, the organism responsible for pityriasis versicolor. In vitro, AA has been shown to be a competitive inhibitor of tyrosinase, and it can be used successfully to treat melasma. However, a detailed mechanism of action has yet to be elucidated. In a randomized, double-blind study of 155 patients who suffered from melasma, those who were treated with 20% AA cream responded much better than those treated with 2% HQ cream (10). After 24 weeks of treatment, 74% of the AA-treated patients showed good to excellent results. In contrast, only 19% of the HQ-treated patients had a similar response. Patients with both epidermal and mixed (i.e., epidermal and dermal) types of melasma responded to treatment with AA.

Another study comparing the efficacy of 20% AA cream with 4% HQ cream for the treatment of melasma failed to demonstrate any superiority of AA. In a 24-week, double-blind study of 329 women, 65% of the AA-treated patients showed good to excellent results, whereas 73% of the HQ-

treated group had similar results (11). Azelaic acid was associated with fewer side effects, however, which suggested that its use might be beneficial if prolonged treatment is anticipated.

### Retinoic acid

Tretinoin has been shown to lighten hyperpigmented macules associated with photoaging and to inhibit melanogenesis (12). In a 40-week, randomized, double-blind, vehicle-controlled study of 54 black patients with postinflammatory facial hyperpigmentation, there was significant lightening of affected areas in patients treated with topical tretinoin cream (0.1%). On histologic examination, there was a corresponding reduction in the epidermal melanin content within the lesions. Fifty percent of the tretinoin-treated patients developed contact dermatitis; however, it did not alter the efficacy of the treatment and gradually diminished as the study progressed (13).

Orlow et al. (14) showed that RA is a potent inhibitor of the induction of the pigmentary pathway by melanocyte-stimulating hormone (MSH), cholera toxin, or L-tyrosine. However, the RA did not affect the associated growth or morphologic changes of the melanocytes, nor did it alter the basal levels of tyrosinase or dopachrome tautomerase activity. In a recent study in Korean patients by Kauh and Zachian (2), a topical regimen consisting of 0.1% tretinoin cream plus 3% HQ lotion followed by sunscreen use for 5 months led to significant improvement of melasma with few side effects. Histologic examination of treated sites demonstrated a significant decrease in epidermal pigmentation and improvement of solar damage in the dermis.

### Kojic acid

Kojic acid (5-hydroxy-2-[hydroxymethyl]- $\gamma$ -pyrone) is a fungal metabolite produced by many species of *Aspergillus* and *Penicillium* that is structurally related to maltol. Like maltol, it is a good chelator of transition metal ions and has been shown by several investigators to inhibit tyrosinase activity. Mishima et al. (15) reported that kojic acid inhibited the activity of tyrosinase isolated from the integument of black- and gold-colored fish; suppressed melanogenesis in cultured pigment cells; and when fed to black goldfish for 49 days, resulted in a decrease in pigment such that the fish became yellow-brown in color. The authors attributed these findings to the ability of kojic acid to chelate copper (tyrosinase is a copper-requiring enzyme).

Further studies by Kahn (16) showed that preincubation of tyrosinase with kojic acid did not result in an inactivation of tyrosinase, suggesting that kojic acid cannot remove copper from the active site of tyrosinase. These latter authors proposed that kojic acid may inhibit the formation of pigment by inhibiting the uptake of oxygen that is required for the oxidation of melanin precursors. An alternative hypothesis is that a chemical interaction occurs between kojic acid and *o*-quinones, preventing *o*-quinones from being polymerized to melanin pigment (16). Kojic acid, however, has significant sensitizing potential, and a comparatively high frequency of contact dermatitis has been observed in patients using kojic acid-containing products.

### Phenolic thioethers

Phenolic thioethers such as 4-S-cysteaminylphenol (N-acetyl or N-propionyl) represent a new family of depigmenting compounds related to phenols.

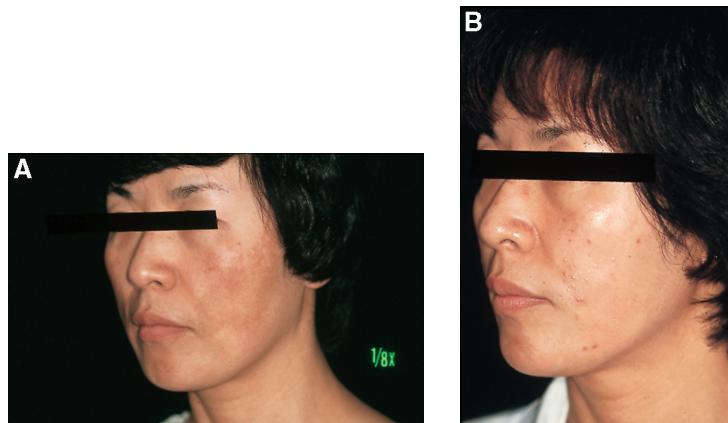


Fig. 7. A female melasma patient showing pigmentation and depigmentation of the skin (A) before and (B) after treatment with N-acetyl-4-S-cysteaminylphenol.

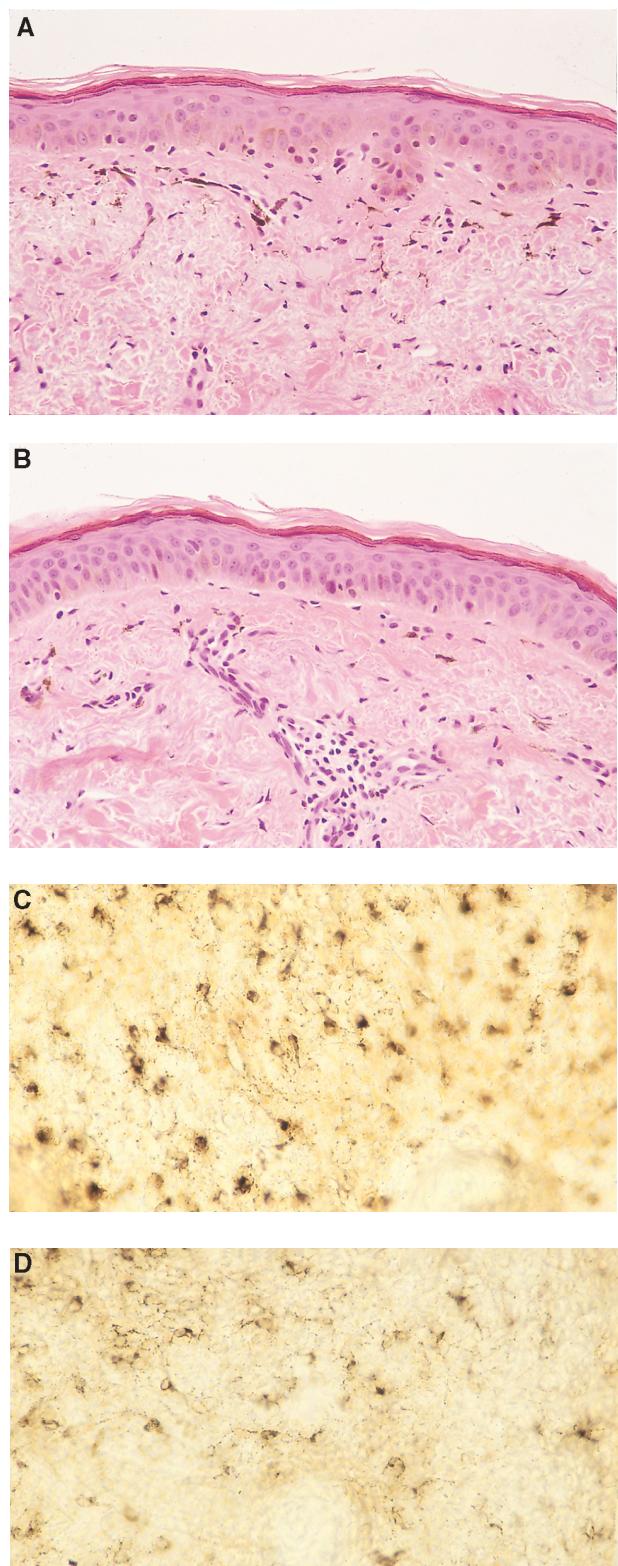
These melanocytotoxic agents are derived from the sulfur homologues of phenols, producing cysteinylphenol and cysteaminylphenol. A preliminary clinical study utilizing a 4% preparation of N-acetyl-4-S-cysteaminylphenol was conducted in patients with melasma. Marked to moderate improvement was seen after 2–4 weeks of topical application (Fig. 7). Compared to HQ, the compound appeared to be less irritating to the skin (17). Side effects were minimal. The decrease in hyperpigmentation was associated with a decreased number of functioning melanocytes as well as a decrease in the number of melanosomes transferred to keratinocytes (Fig. 8). N-acetyl-4-S-cysteaminylphenol is a tyrosinase substrate, and following incubation with tyrosinase, it forms a melanin-like pigment. A new N-propionyl derivative, N-propionyl-4-S-cysteaminylphenol, has been developed recently. This compound is also a substrate for tyrosinase and has more potent melanocytotoxic effects than the related N-acetyl form (Fig. 9). In vitro studies (18,19) have shown that it has both cytostatic and cytoidal properties with respect to melanocytes.

#### Topical agents used in conjunction with chemical peels

Chemical peels, also referred to as chemexfoliation, has become an established technique for improving or treating disorders of facial hyperpigmentation, including melasma. Superficial, medium, and deep chemical peels are often used to treat melasma (20). The following is a brief description of topical agents used as chemical peels.

**Glycolic acid.** Chemical peels consisting of the application of glycolic acid represent a safe and effective method for treating facial hyperpigmentation (21). The effectiveness of these peels can be enhanced by pretreatment with 10–15% glycolic acid lotion plus 2% HQ (Table 2). Darkly pigmented skin does not appear to be a contraindication to the use of glycolic acid peels (22). The combination of HQ plus glycolic acid peels at 3-week intervals is an effective means of lightening the hyperpigmentation of melasma.

**Resorcinol.** An isomer of catechol, it was one of the first chemical peels to be used. At a concentration of 50%, resorcinol results in medium-depth peels and has been useful in the treatment of patients suffering not just from melasma, but also freckles and solar lentigines (23).



**Fig. 8.** Light microscopic and split-DOPA preparations of melasma lesion before and after the treatment with N-acetyl-4-S-cysteaminylphenol. (A) Hematoxylin and eosin-stained section before treatment. (B) Hematoxylin and eosin-stained section after treatment. (C) Split-DOPA preparation before treatment. (D) Split-DOPA preparation after treatment.

## TYROSINASE KINETICS OF N-ACETYL AND N-PROPYONYL-4-S-CYSTEAMINY PHENOLS AND THEIR RELATED COMPOUNDS

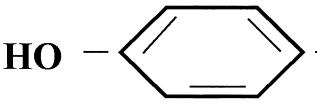
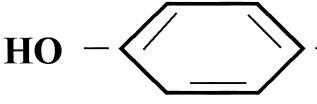
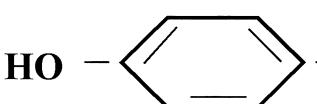
COMPOUND	$V_{max}$ ( $\mu$ mol/min/mg)	$K_m$ (mM)
 <b>Tyrosine</b>	0.164	0.021
 <b>4-S-cysteaminylphenol</b>	0.117	0.039
 <b>N-acetyl-4-S-cysteaminylphenol</b>	1.05	0.375
 <b>N-propionyl-4-S-cysteaminylphenol</b>	1.37	0.340

Fig. 9. Chemical structure and tyrosinase kinetics of phenolic thioethers.

**Kojic acid.** If hyperpigmentation of melasma persists after treatment with topical kojic acid gel, kojic acid chemical peels can be performed. The kojic acid chemical peels consist of kojic acid at a 2% concentration in combination with three other  $\alpha$ -hydroxy acids (salicylic acid, citric acid, and lactic acid). In their study of patients with melasma, Ellis and Tan (24) found that kojic acid peels produced less dryness of the skin than glycolic acid chemical peels. Garcia and Fulton (25) described the combination of glycolic acid and kojic acid as a mild chemical peel for patients with melasma and related conditions. They found that both glycolic acid/kojic acid and glycolic acid/hydroquinone combinations were highly effective in reducing the hyperpigmentation of melasma. However, the kojic acid preparation was found to be more irritating than HQ.

**Salicylic acid.** Salicylic acid chemical peels, at concentrations of 20–30%, are also used to treat the hyperpigmentation of melasma. These peels can be performed at 2-week intervals. In a study by Grimes (26), salicylic acid chemical peels resulted in mod-

erate to significant improvement of postinflammatory hyperpigmentation and melasma.

**Trichloroacetic acid (TCA).** When treatment of facial hyperpigmentation by kojic acid peels is not satisfactory, TCA medium-depth peels can be used as an adjuvant to treat diffuse, persistent hyperpigmentation of melasma.

## Conclusion

In the treatment of melasma and other disorders of facial hyperpigmentation, the major objectives for the topical depigmenting agents are retardation of the proliferation of melanocytes, inhibition of the formation of melanin and melanosomes by melanocytes, and enhancement of the degradation of melanin pigments by keratinocytes or melanophages (27). Hydroquinone has been the most commonly used topical agent for melasma. It reduces the number of functioning melanocytes, inhibits melanin formation, and enhances the degradation of melanosomes (28). Prolonged use of

**Table 2.** Topical hypo/depigmenting agents for melasma and other disorders of facial hyperpigmentation

Phenolic derivatives
Hydroquinone
Hydroquinone/tretinoin
Hydroquinone/tretinoin/triamcinolone
Hydroquinone/salicylic acid
Hydroquinone/glycolic acid
Hydroquinone/azelaic acid
Isopropylcatechol
Acetyl and propionyl-4-S-cysteaminylphenol
Nonphenolic compounds
Tretinoin
Azelaic acid
Kojic acid
Pantetheine-S-sulfonate <sup>a</sup>

<sup>a</sup>From Franchi et al. (34).

HQ and higher strengths of HQ may result in irritant contact dermatitis and subsequent postinflammatory hyperpigmentation, and less commonly exogenous ochronosis. Tretinoin has been used in combination with HQ (29), but this therapeutic regimen (30) often leads to adverse reactions such as erythema, desquamation, edema, pruritus, and burning sensations. Other topical agents commonly employed include AA and kojic acid. If the hyperpigmentation is persistent despite the use of these topical agents, chemical peels may be added to the regimen (31). Topical corticosteroids are also frequently used in combination with topical agents such as HQ, AA, tretinoin, and kojic acid in order to reduce irritation and subsequent adverse reactions such as postinflammatory hyperpigmentation. However, the addition of corticosteroids may potentially produce a new set of side effects including atrophy, telangiectasias, and acneiform eruptions. The preliminary use of newly described phenolic derivatives, N-acetyl and propionyl-4-S-cysteaminyl phenol, has met with success. They appear to selectively target melanocytes, having both cytostatic and cytoidal effects on actively proliferating and functioning melanocytes (32). Strict avoidance of direct exposure to sunlight and daily application of sunscreen are mandatory for any patient with facial hyperpigmentation, both during and after treatment (33).

## References

1. Jimbow K, Quevedo WC Jr, Fitzpatrick TB, et al. Biology of melanocytes. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, eds. Melanocytes in dermatology in general medicine, 4th ed. New York: McGraw-Hill, 1993:261–289.
2. Kauh YC, Zachian TF. Melasma. In: Mallia C, Uitto J, eds. Rheumaderm. New York: Kluwer Academic/Plenum, 1999:491–499.
3. Pandya AG, Guevara IL. Disorders of hyperpigmentation. *Dermatol Clin* 2000; **18**: 91–98.
4. Hoffmann E, Habermann R. Arzneiliche und gewerbliche Dermatosen durch Kriegserzätmittel (Vaseline Schmieröl) und eigenartige Melanodermatiden. *Deutsch Med Wochenschr* 1918; **4**: 261–264.
5. Hayakawa R. Relation with facial skin diseases and lipids and lipoperoxide of serum and sebum, pH on the face and buffering power [in Japanese]. *Jpn J Dermatol (Series A)* 1971; **81**: 11–29.
6. Nagao S, Tan-no K, Iijima S. Riehl's melanosis and pigmentation after patch testing: light and electron microscopic study. In: Fitzpatrick TB, Kukita A, Morikawa F, Seiji M, Sober AJ, Toda K, eds. Biology and diseases of dermal pigmentation. Tokyo: University of Tokyo Press, 1981:209–223.
7. Kukita A, Hori K, Ohhara K, Kawashima M, Takehara K. Nevus of Ota. In: Fitzpatrick TB, Kukita A, Morikawa F, Seiji M, Sober AJ, Toda K, eds. Biology and diseases of dermal pigmentation. Tokyo: University of Tokyo Press, 1981:67–76.
8. Kligman AM, Willis I. A new formula for depigmenting human skin. *Arch Dermatol* 1975; **111**: 40–48.
9. Pathak MA. Clinical and therapeutic aspects of melasma: an overview. In: Fitzpatrick TB, Wick MM, Toda K, eds. Brown melanoderma: biology and disease of epidermal pigmentation. Tokyo: University of Tokyo Press, 1986: 161–172.
10. Verallo-Rowell VM, Verallo V, Graupe K, Lopez-Villa-fuerte L, Garcia-Lopez M. Double-blind comparison of azelaic acid and hydroquinone in the treatment of melasma. *Acta Derm Venereol Suppl* 1989; **143**: 58–61.
11. Balina LM, Graupe K. The treatment of melasma: 20% azelaic acid versus 4% hydroquinone cream. *Int J Dermatol* 1991; **30**: 893–895.
12. Bahawan J. Short- and long-term histologic effects of topical tretinoin on photodamaged skin. *Int J Dermatol* 1998; **37**: 286–292.
13. Bulengo-Ransby SM, Griffiths CE, Kimbrough-Green CK, et al. Topical tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. *N Engl J Med* 1993; **328**: 1438–1443.
14. Orlow SJ, Chakraborth AK, Pawelek JM. Retinoic acid is a potent inhibitor of inducible pigmentation in murine and hamster melanoma cell lines. *J Invest Dermatol* 1990; **94**: 461–464.
15. Mishima Y, Hatta S, Ohyama Y, Inazu M. Induction of melanogenesis suppression: cellular pharmacology and mode of differential action. *Pigment Cell Res* 1988; **1**: 367–374.
16. Kahn V. Effect of kojic acid on the oxidation of DL-DOPA, norepinephrine, and dopamine by mushroom tyrosinase. *Pigment Cell Res* 1995; **8**: 234–240.
17. Jimbow K. N-acetyl-4-S-cysteaminylphenol as a new

- type of depigmenting agent for the melanoderma of patients with melasma. *Arch Dermatol* 1991; **127**: 1528–1534.
- 18. Thomas PD, Kishi H, Cao H, et al. Selective incorporation and specific cytoidal effect as the cellular basis for the antimelanoma action in sulphur containing tyrosine analogs. *J Invest Dermatol* 1999; **113**: 928–934.
  - 19. Minamitsuji Y, Toyofuku K, Sugiyama S, Jimbow K. Sulphur containing tyrosine analogs can cause selective melanocytotoxicity involving tyrosinase-mediated apoptosis. *J Invest Dermatol* 1999; **4**: 130–136.
  - 20. Matarasso SL, Glogau RG. Chemical face peels. *Dermatol Clin* 1991; **9**: 131–150.
  - 21. Moy LS, Murad H, Moy RL. Glycolic acid peels for the treatment of wrinkles and photoaging. *J Dermatol Surg Oncol* 1993; **19**: 243–246.
  - 22. Lim JT, Tham SN. Glycolic acid peels in the treatment of melasma among Asian women. *Dermatol Surg* 1997; **23**: 177–179.
  - 23. Karam PG. 50% resorcinol peel. *Int J Dermatol* 1993; **32**: 569–574.
  - 24. Ellis DAF, Tan AKW. How we do it: management of facial hyperpigmentation. *J Otolaryngol* 1997; **26**: 286–289.
  - 25. Garcia A, Fulton JE Jr. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. *Dermatol Surg* 1996; **22**: 443–447.
  - 26. Grimes PE. The safety and efficacy of salicylic acid chemical peels in darker racial-ethnic groups. *Dermatol Surg* 1999; **25**: 18–22.
  - 27. Salopek TG, Jimbow K. New treatment options for the patient with facial hyperpigmentation. In: Dahl MV, Lynch PJ, eds. *Current opinion in dermatology*. Philadelphia: Current Science, 1995:61–65.
  - 28. Jimbow K, Obata H, Pathak MA, Fitzpatrick TB. Mechanism of depigmentation by hydroquinone. *J Invest Dermatol* 1974; **62**: 436–449.
  - 29. Griffiths CE, Finkel LJ, Ditre CM, Hamilton TA, Ellis CN, Voorhees JJ. Topical tretinoin (retinoic acid) improves melasma. A vehicle-controlled, clinical trial. *Br J Dermatol* 1993; **129**: 415–421.
  - 30. Yoshimura K, Harii K, Aoyama T, Shibuya F, Iga T. A new bleaching protocol for hyperpigmented skin lesions with a high concentration of all-trans retinoic acid aqueous gel. *Aesthetic Plast Surg* 1999; **23**: 285–291.
  - 31. Lawrence N, Cox SE, Brody HJ. Treatment of melasma with Jessner's solution versus glycolic acid: a comparison of clinical efficacy and evaluation of the predictive ability of Wood's light examination. *J Am Acad Dermatol* 1997; **36**: 589–593.
  - 32. Jimbow M, Marusyk H, Jimbow K. The *in vivo* melanocytotoxicity and depigmenting potency of N-2,4-acetoxyphenyl thioethyl acetamide in the skin and hair. *Br J Dermatol* 1995; **133**: 526–536.
  - 33. Grimes PE. Etiologic and therapeutic considerations. *Arch Dermatol* 1995; **131**: 1453–1457.
  - 34. Franchi J, Coutadeur MC, Marteu C, Mersel M, Kupferberg A. Depigmenting effects of calcium D-pantetheine-S-sulfonate on human melanocytes. *Pigment Cell Res* 2000; **13**: 165–172.