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Melasma: Epidemiology, pathogenesis, clinical presentation, and diagnosis

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INTRODUCTION

Melasma is a common, chronic, and recurring disorder of hyperpigmentation arising from hyperfunctional melanocytes that deposit excessive amounts of melanin in the epidermis and dermis [1]. Melasma is particularly common in females (especially those of reproductive age) and in body areas with high amounts of sun exposure (notably the face) [2-4]. Contributing factors involved in the pathogenesis of this condition include genetic influences, sun exposure, sensitivity to hormones, pregnancy, and, in some cases, medications. The treatment of melasma is challenging, and relapses are universal. Patients must adhere to a rigorous therapeutic regimen to avoid relapses [5,6].

This topic will discuss the pathogenesis and clinical manifestations of melasma. The management of melasma is discussed separately. Other acquired disorders of hyperpigmentation are discussed separately.

- (See "Melasma: Management".)
- (See "Acquired hyperpigmentation disorders".)
- (See "Postinflammatory hyperpigmentation".)

EPIDEMIOLOGY

Overall, the prevalence of melasma in the general population is approximately 1 percent, but it can be as high as 9 to 50 percent in high-risk populations [7]. Between 4 and 10 percent of people presenting to dermatology clinics in Central and South America may have melasma [4].

Melasma most frequently presents in females of reproductive age. The mean age of onset in two studies from Brazil was approximately 28 years [8,9]. The mean age of onset in 140 cases from India was 37 years [10]. A survey of 324 women being treated for melasma in nine countries reported a mean age of onset of 34 years [11]. The Fitzpatrick phototype of a patient may influence the age of onset. In a group of melasma patients from Brazil, the mean age of onset was 27 years in those with type II skin, 28 years in type III, 30 years in type IV, and 35 years in type V [12]. These results suggest that lighter skin may be a predisposing factor due to its susceptibility to photodamage.

The prevalence of melasma in males varies across studies. Studies from India report that 26 to 32 percent of patients with melasma are males [10]. In a Brazilian study of 953 adults with melasma, only 2.5 percent of the patients were males [12].

RISK AND TRIGGER FACTORS

Genetic predisposition, exposure to sunlight (including ultraviolet [UV] and, possibly, visible light), skin phototype, and hormonal factors (including pregnancy, hormonal therapies, and use of oral contraceptives) are the main risk and trigger factors for melasma [5,9,13]. Additional factors associated with the development of melasma may include some cosmetics, certain medicines (eg, photosensitizing drugs and anticonvulsants), and zinc deficiency [9,14,15].

In a study of 324 women from nine countries, 90 percent of patients with a family history of melasma had Fitzpatrick phototypes III to IV compared with 77 percent of those without a family history [11]. This multinational study also supported suggestions that hormonal changes might contribute to the etiology of melasma. For example, 42 and 26 percent of cases occurred after or during pregnancy, respectively, with UV exposure being a contributing factor; each additional 10 hours a week that the person spent working outside increased the risk of melasma during pregnancy by approximately 27 percent. Maternal age at pregnancy increased the risk by approximately 8 percent for each year older at primigravida. The number of pregnancies increased the risk that melasma would first emerge during pregnancy, doubling and tripling for two and three or more pregnancies, compared with primigravida. Moreover, 25 percent of women who used oral contraception said that melasma appeared for the first time after they used the pill. The risk of melasma associated with the contraceptive pill was more

than twofold higher in women with a family history of melasma compared with those without family history (odds ratio 2.45, 95% CI 1.10-5.46) [11].

A Brazilian study of 302 women with melasma reported that the most common triggers were pregnancy (36 percent), intense sun exposure (27 percent), and use of contraceptive pills (16 percent) [9]. Most patients were Fitzpatrick phototypes III (34 percent) and IV (38 percent). In another study of 953 Brazilian adults, UV exposure and pregnancy were identified as the most frequent triggers of melasma (in 44 and 24 percent of patients, respectively). This study also confirmed that melasma is most common in patients with Fitzpatrick III and IV phototypes (36 and 40 percent, respectively).

In another study, individuals with skin phototypes II and III and those with a family history of melasma had an earlier onset of melasma compared with those with skin phototypes IV, V, and VI; extrafacial melasma was more common in postmenopausal women than in premenopausal women (14 and 3.5 percent, respectively) [12].

Several studies suggest that melasma may be associated with abnormal thyroid function and thyroid autoimmunity [9,16]. A study of 45 women with melasma and 45 matched controls found increased levels in free thyroxine, thyroid-stimulating hormone (TSH), and thyroglobulin antibodies in women with melasma but not in controls [16]. Another study found a prevalence of increased TSH levels of 24 percent [9]. High levels of TSH were associated with UV-induced melasma (odds ratio 2.15, 95% CI 1.00-4.69). However, further studies are needed to elucidate the role of thyroid disorders in the pathogenesis of melasma.

PATHOLOGY

General features — The epidermis of melasma lesions shows hyperactive melanocytes without hyperplasia [2]. Although the melanocyte number is similar in lesional and perilesional skin, melanocytes in the affected skin are larger, contain more and singly dispersed melanosomes, and show more and very prominent dendrites that can extend into the basal layer (picture 1A-B) [1,17,18]. In lesional skin, keratinocytes also show an increased number of melanosomes compared with healthy skin [1].

Disruption to the basement membrane — The penetration of melanocytes and melanin into the dermis seems to be an important reason why melasma often proves difficult to treat and commonly relapses [6]. Estimates of the prevalence of disruption of the basement membrane in melasma lesions vary widely, depending on the experimental technique [6]. However, a study using sensitive methodologies reported that up to 83 to 96 percent of people with melasma

show disruption of the basement membrane in their lesions [19]. Increased levels of matrix metalloproteinases (MMPs) 2 and 9, which degrade collagen, also appear to facilitate the movement of melanocytes into the dermis [6].

Lymphohistiocytic infiltrates — In a study of 21 melasma patients, 75 percent of lesions showed mild lymphohistiocytic infiltrates [1]. The infiltrate was characterized by significant enrichment of inflammatory cells, including $CD4^+$ T cells, $CD68^+$ macrophages, and mast cells, and increased levels of the inflammatory cytokine interleukin 17 (IL-17) and the enzyme cyclooxygenase 2 (COX-2), which synthesizes proinflammatory prostaglandins from arachidonic acid, compared with unaffected skin [3,6].

In a histochemical and immunohistochemical study of biopsies from 20 women with malar melasma, levels of $CD4^+$ T cells and COX-2 expression were associated positively with the Melasma Activity and Severity Index (MASI) score. COX-2 expression was also associated positively with dermal elastosis and epidermal melanin deposition. The findings suggest that chronic inflammation may contribute to melasma, which may partly explain why recurrences are common [3]. Indeed, there seems to be an inflammatory phenotype of melasma [20]. These patients showed increased numbers of $CD68^+$ melanophages, leucocytes expressing the leucocyte common antigen, and $CD117^+$ mast cells than noninflammatory lesions [20].

Melasma lesions have shown increased mast cell infiltration compared with perilesional skin [19]. Mast cells contribute to dermal elastosis, disruption of the basement membrane, and vasodilation. Histamine released by mast cells seems to stimulate the proliferation and migration of melanocytes [6]. Further research needs to fully elucidate the role of mast cells in the pathogenesis of melasma.

Dermal elastosis — Melasma lesions show dermal elastosis, a hallmark of photoaging [19,21,22]. (See "Photoaging".)

In a study of 56 Korean patients with melasma, the involved skin showed moderate to severe elastosis in 93 percent of cases, while normal skin exhibited elastosis in 70 percent [21]. Indeed, photoaging seems to have a central place in the pathogenesis of melasma, mediated by ultraviolet (UV) and visible light, release of melanogenic cytokines (eg, stem cell factor, endothelin 1, hepatocyte growth factor) from fibroblasts, and upregulation of the Wnt signaling pathway [6,19]. In addition, melasma lesions show increased expression of *c-kit*, the gene that encodes the stem cell factor receptor, compared with perilesional skin [19]. In a study of 50 Indian females, skin biopsies from melasma and perilesional normal skin revealed significant solar elastosis in the lesional skin compared with the perilesional skin [22]. Other changes

included epidermal atrophy, basal cell hyperpigmentation, and pendulous melanocytes extending into the dermis.

Increased vascularization — Chronic UV exposure results in increased vascularization, and melasma lesions show greater numbers, size, and density of blood vessels in lesions compared with perilesional skin [6,23]. A study of 50 Korean women with melasma reported an increase in the number and size of dermal blood vessels in lesional skin compared with healthy skin [23]. The number of blood vessels correlated with the extent of hyperpigmentation. The expression of the proangiogenic vascular endothelial growth factor (VEGF) was significantly increased in lesions compared with healthy skin. VEGF also stimulates the release of arachidonic acid, which may affect melanogenesis. This observation dovetails with the increased expression of COX-2 in melasma lesions [3]. Indeed, melanocytes express VEGF receptors [23]. These results might support a role for antiangiogenic treatment in the management of melasma [6].

The signaling molecule nitric oxide mediates vascular tone as well as contributes to inflammation, skin immune function, and intracellular keratinocyte signaling [24]. UV radiation stimulates production of nitric oxide by upregulating expression of inducible nitric oxide synthase (iNOS) in keratinocytes. In turn, iNOS stimulates tyrosinase activity, which increases melanin synthesis. Lesions from nine melasma patients showed colocalization and a highly correlated association between iNOS protein and phosphorylated Akt (also called protein kinase B), part of an intracellular signaling pathway linked to the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). The results suggest that melasma lesions show increased iNOS expression, probably mediated by activation of the Akt/NF-kB pathway [25].

Senescent fibroblasts — Fibroblasts are essential for dermal integrity and pigmentation. They release stem cell factor and its epidermal receptor c-kit, transforming growth factor (TGF)-beta-1, and Dickkopf-related protein 1.

Senescent fibroblasts have been reported in lesional skin of patients with melasma. In a study of lesional and perilesional skin from 38 patients with melasma, using the senescence marker p16Ink4a, lesional skin demonstrated a significant increase in senescent fibroblasts. Fractional laser resurfacing therapy was shown to decrease the proportion of senescent fibroblasts in the aged dermis and improve pigmentation [26,27].

A study of cultured fibroblasts from melasma skin showed that fibroblasts were less fusiform in appearance and had a slowed growth rate, further supporting a senescent phenotype [28]. Such cells have the ability to secrete inflammatory cytokines, causing collagen degradation in the lesional skin of melasma. These findings support a photoaging phenotype.

PATHOGENESIS

Genetics and transcriptomic studies — Melasma shows strong familial occurrence, especially in first-degree relatives [8,9,11,12], implicating a genetic basis for the hyperpigmentation. Nevertheless, relatively few genomic analyses (eg, genome-wide association studies) have identified genetic risk factors, although melasma is likely to show polygenic inheritance.

One study comparing 10 sample pairs of lesional and perilesional skin found differential expression of 279 genes in lesional and perilesional skin, with 187 genes upregulated and 152 genes downregulated in lesional skin [17]. Notably, expression of four genes associated with melanogenesis (*SILV*, *TYRP1*, *MLANA*, and *TYR*) and a subset of modulators of the Wnt pathway, which is critical for melanocyte development, were upregulated in lesional skin. Moreover, the gene encoding Wnt inhibitory factor 1 (*WIF-1*) was downregulated in melasma lesions compared with normally pigmented skin [17]. Further support for the involvement of Wnt signaling in melasma pathogenesis comes from a study of *WIF-1* knockdown fibroblasts and keratinocytes, which showed increased tyrosinase expression and melanosome transfer; in contrast, cells that overexpressed *WIF-1* attenuated these changes [29].

Increases in melanin biosynthesis underlie all hyperpigmentation diseases. However, while hyperpigmentation triggered by inflammation and ultraviolet (UV) light generally resolves spontaneously, melasma tends to be chronic and recurrent. One hypothesis to explain the different phenotypes focuses on the *H19* gene, which encodes a noncoding ribonucleic acid (RNA) that seems to control gene expression.

Ultraviolet and visible light — Multiple studies suggest that ultraviolet (UV) light and visible light play a key role in the pathogenesis of melasma [30-32]. Melasma is most common in the tropics and areas with the highest UV radiation. The condition often improves during the winter months and with intense efforts to avoid exposure to UV radiation but relapses with exposure to UV radiation and visible light.

- UV radiation triggers a spectrum of events in the epidermis and dermis, including melanin synthesis; activation of tyrosinase, tyrosinase-related protein 1, and dopachrome tautomerase; and secretion of alpha-melanocyte-stimulating hormone (alpha-MSH), corticotrophin, and the ligand stem-cell factor [33,34]. UV radiation also triggers erythema, angiogenesis, and oxidative stress [35]. Studies document a role for visible light in triggering and sustaining melasma [36]. In a study evaluating the effectiveness of a broad-spectrum sunscreen in the prevention of melasma in 185 pregnant women, only 2.7 percent developed melasma when the anticipated rate was greater than 50 percent [37].

- Visible light activates the opsin 3 sensor receptor, triggering calcium-dependent microphthalmia transcription factor (MITF) signaling and the formation of *TYR*/dopachrome tautomerase protein complexes associated with long-lasting skin hyperpigmentation [38]. Investigations support the role of iron oxide's ability to mitigate hyperpigmentation induced by visible light [39]. Moreover, studies in melasma comparing the efficacy of photoprotection protocols incorporating iron oxide plus a broad-spectrum sunscreen with a broad-spectrum sunscreen alone showed superior outcomes in patients using the iron oxide and broad-spectrum photoprotection [36,40].

Hormones — Epidemiologic studies implicate hormones in the pathogenesis of melasma. (See 'Risk and trigger factors' above.)

For example, melasma is most common in females of reproductive age, and lesions often emerge following oral contraceptive use, pregnancy, menopause (for extrafacial involvement), or hormonal replacement therapy [8-12]. One study comparing gene and protein expression for estrogen receptor-beta (ER-beta) and progesterone receptor (PR) in facial melasma and adjacent healthy skin failed to find a difference in the expression of these genes in lesional skin compared with perilesional skin [8]. However, the epithelium of the lesions showed higher protein expression of these receptors, suggesting that female hormones contribute to the hyperpigmentation [8]. Estrogens stimulate melanogenesis by increasing the expression of alpha-MSH and inducing the synthesis of tyrosinase and tyrosinase-related proteins 1 and 2.

One study found that downregulation of *H19* in melasma skin induced tyrosinase overexpression and increased melanosome transfer [41]. Levels of *H19* RNA were at least twofold lower in melasma lesions than control skin. In cell culture, estrogens, but not UV irradiation, seemed to increase tyrosine overexpression mediated by *H19* RNA. However, this effect was apparent only in coculture of melanocytes and keratinocytes but not in melanocyte monoculture, underscoring the importance of intercellular signaling.

A study from Pakistan assessed blood levels of estrogen, progesterone, and prolactin in two consecutive follicular and luteal phases (day 9 and 18 of the menstrual cycle) in 138 women with melasma and 40 controls [42]. Only four melasma patients had normal values for all three hormones in all four phases. Nearly all patients (89 percent) had abnormal estrogen values (usually increased) in one or more of the four phases, whereas only 7.5 percent of controls had increased estrogen levels during both follicular and luteal phases. Fifty-five percent of melasma patients showed abnormal progesterone levels in all four phases; prolactin levels were normal in 97 percent.

Low testosterone levels have been observed in men with melasma [43].

Barrier function and oxidative stress — Chronic UV exposure reduces synthesis of epidermal free fatty acids and triglycerides, which are important in maintaining the skin's barrier function [44]. Studies suggest that skin from melasma lesions shows downregulation of several genes linked to lipid metabolism, a finding supported by the impaired barrier function characteristic of melasma [17]. A study of 16 melasma patients from Korea reported no difference in basal transepidermal water loss (TEWL), a marker of barrier function, or sebum content between lesions and healthy skin. However, after the barrier was disrupted by repeated tape stripping, TEWL was higher in lesional skin compared with healthy skin. The barrier function also took longer to recover in lesions. A trend suggesting thinner stratum corneum correlated with the rate at which barrier function recovered [44].

In the same study, the immunoreactivity of peroxisome proliferator-activated receptor-gamma (PPAR-gamma), which regulates lipid catabolism, was lower in the lesions of 6 of 11 patients with melasma [44]. PPAR-gamma seems to modulate skin aging, melanogenesis, and antioxidant balance [45].

Oxidative stress may contribute to melasma. An Indian study reported significantly higher blood levels of the antioxidants malondialdehyde, superoxide dismutase, and glutathione in 50 patients with melasma compared with the same number of matched controls [46]. Levels of these antioxidants correlated positively with the Melasma Activity and Severity Index (MASI) score, reaching statistical significance with malondialdehyde. Increasing PPAR-gamma activity might offer a new approach to the management of photo-oxidative skin damage and melasma [45].

Neural involvement — Melasma lesions often follow the path of the trigeminal nerves, which implies a neural component to the pathogenesis [2]. A study of six Korean women reported that melasma lesions showed increased expression of nerve growth factor receptor and neural endopeptidase compared with healthy skin. The authors suggest that nerve growth factor may modulate the microenvironment around melanocytes. The increased neural endopeptidase expression could influence melanogenesis. Therefore, an antagonist against these targets might offer a novel melasma therapy [2].

CLINICAL PRESENTATION

Melasma typically presents with irregular, light-brown to gray-brown macules and patches on sun-exposed skin [2]. The lesions are usually symmetric and may affect the forehead, nose, cheeks, upper lip area, and chin [2]. In most patients, melasma is asymptomatic. However, one study suggested that itching, tingling, dryness, erythema, or telangiectasia may herald

inflammatory melasma, which is characterized by increased vascularization with telangiectasias and erythema [20].

- **Facial melasma** – Common facial patterns of distribution for melasma include (figure 1):
  - **Centrofacial pattern** – Centrofacial melasma commonly affects the forehead, cheeks, nose, upper lip, and chin areas (picture 2A-D).
  - **Malar pattern** – Malar melasma predominately involves the lateral cheek areas (picture 2E).
  - **Mandibular pattern** – Mandibular melasma affects the lower jawline (picture 3).

  In a Brazilian study of 302 women with melasma, most patients had at least six facial regions affected, most commonly the zygomatic (84 percent), labial superior (51 percent), and frontal (50 percent) regions [9]. Another Brazilian study reported that melasma first appeared in the malar region in 70 percent of patients. Overall, the malar (90 percent), frontal (53 percent), upper lips (52 percent), and nose (34 percent) were the most commonly affected areas [12]. A study from India also found that the malar was the most common region affected (68 percent), followed by the central face (25 percent) and mandible (7 percent) [10].

- **Extrafacial melasma** – Some patients, predominantly females, develop extrafacial melasma, which is less common than the facial phenotype and is usually difficult to treat (picture 4). Extrafacial melasma tends to emerge at an older age than the facial form and may be associated with menopause. In one study, 81 percent of women with extrafacial melasma had reached menopause, and the mean age at presentation was 56.7 years [47].

  In one study, approximately 8 percent of patients with facial involvement showed extrafacial occurrence [9]. In a study of 45 patients with extrafacial melasma, the sites of involvement were the arms (95 percent), forearms (80 percent), chest (47 percent), or back (11 percent) [47]. The lesions, which were present for more than five years in approximately one-half of the patients, tended to show moderate intensity and homogeneity [47].

CLINICAL COURSE

Melasma is a chronic and recurrent condition. Although spontaneous remission may occur after pregnancy, pregnancy-related melasma can persist for several months after birth or indefinitely [4]. Independently from the trigger event for melasma, relapses occur with mild to intense sun exposure. While spontaneous remission may occur after pregnancy, such patients may have subsequent flares of the melasma.

In one study of 245 women with melasma who had had at least one pregnancy, 15 (6 percent) experienced spontaneous remission after each pregnancy [11]. Of note, spontaneous remission occurred more frequently among women whose melasma first appeared during a pregnancy than in those whose melasma started at some other time (16 versus 2 percent).

Melasma associated with hormonal therapies can remain after treatment ceases. Melasma with an inflammatory component may be associated with a worse outcome using conventional treatments compared with melasma without a marked inflammatory component. A Korean study found that approximately 25 percent of 197 patients might have had the inflammatory subtype [20].

IMPACT ON QUALITY OF LIFE

Multiple studies have documented the detrimental and psychologically devastating effects of melasma on quality of life. Emerging data suggest that melasma represents a photoaging skin disorder [10,48,49]. A seminal study reported that 65 percent of patients with melasma were dissatisfied by their hyperpigmentation all or most of the time [48]. Moreover, 57 percent of patients reported embarrassment, 55 percent experienced frustration, and 42 percent said that melasma affected interpersonal relationships. A study of 140 individuals with melasma from India found that 75 percent were bothered or frustrated by the disease most or all of the time [10]. Many of these patients reported that melasma was associated with depression (72 percent), embarrassment (71 percent), and negative appearance (42 percent) and had a negative impact on relationships with other people (42 percent) most or all of the time. In a systematic review and meta-analysis of 14 studies that included 1398 patients, melasma caused significant emotional distress and had a negative impact on patients' social lives [50].

DIAGNOSIS

Melasma is generally diagnosed based on the clinical presentation and classified as epidermal, dermal, or mixed, depending on the location of melanin [4]. However, in most cases, there is pigment deposition in the epidermis and dermis. Elements of history that support the diagnosis

include onset in relation to pregnancy or use of oral contraceptives, family history of melasma, and exposure to phototoxic drugs.

Wood's lamp examination may assist in identifying the location of pigment, especially in individuals with lighter complexions (Fitzpatrick phototypes I to III) [4,51]. Epidermal melanosis often manifests as well-circumscribed pigmentation with accentuated borders. In contrast, dermal melanosis typically appears poorly circumscribed and is not accentuated under Wood's lamp illumination. Wood's lamp examination is less reliable in Fitzpatrick phototypes IV, V, and VI. In these patients, the density of melanin can make variations between the skin layers difficult to differentiate [4,51].

Dermoscopy has become increasingly popular as an aid for diagnosing melasma and identifying the levels of pigment deposition. Dermoscopy can reveal accentuation of the normal pseudoreticular pigmentary network, increased vascularity, telangiectasia, pigment structures, and owl's eye structures [52]. Moreover, dermoscopy may be helpful to assess melasma severity, based on the pattern and density of pigmented structures [52].

The existence of true dermal melasma remains controversial. It is to be distinguished from Hori's nevus, a dermal melanocytosis commonly observed in Asian individuals. (See 'Differential diagnosis' below.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of melasma encompasses a wide range of disorders characterized by facial hyperpigmentation, including [7]:

- **Hori's nevus** – Nevus of Hori is a common, acquired, dermal melanocytosis seen in Asian populations, primarily in young and middle-aged Chinese and Japanese females [53]. It presents as multiple speckled, blue-brown or slate-gray macules occurring bilaterally on the malar regions. Hori's nevus is recalcitrant to topical agents used to treat melasma. (See "Acquired hyperpigmentation disorders", section on 'Nevus of Hori'.)

- **Riehl's melanosis** – Riehl's melanosis, also called pigmented contact dermatitis, is a dermal melanosis involving the face and neck caused, in most cases, by chemicals in cosmetics (picture 5) [54]. (See "Acquired hyperpigmentation disorders", section on 'Riehl's melanosis'.)

- **Erythema dyschromicum perstans** – Erythema dyschromicum perstans is an uncommon, slowly progressive dermatosis characterized by hyperpigmented macules of

variable size and shape of an ashen-gray color (picture 6 and picture 7). (See "Acquired hyperpigmentation disorders".)

- **Lichen planus pigmentosus** – Lichen planus pigmentosus is a rare form of lichen planus that presents with oval or irregular, brown to gray-brown macules and patches most often located on sun-exposed areas of the skin, such as the face, or flexural areas. (See "Lichen planus", section on 'Cutaneous variants'.)

- **Fixed drug eruptions** – Fixed drug eruption is a cutaneous drug reaction that characteristically recurs in the same locations upon re-exposure to the offending drug. It typically presents with solitary, round to oval, dusky red to brown/black macules (picture 8). (See "Fixed drug eruption".)

- **Discoid lupus erythematosus** – Discoid lupus erythematosus lesions of the face may present with postinflammatory hyperpigmentation as well as violaceous hyperpigmentation. However, hyperpigmented lesions are often interspersed with hypopigmented, scar-like areas (picture 9). (See "Overview of cutaneous lupus erythematosus", section on 'Discoid lupus erythematosus'.)

- **Phototoxic dermatitis** – Phototoxic reactions may occur to a number of systemic drugs, including tetracyclines, thiazide diuretics, fluoroquinolones, and nonsteroidal anti-inflammatory drugs. It usually presents as an exaggerated sunburn limited to the sun-exposed areas that may be followed by postinflammatory hyperpigmentation. Amiodarone may cause a slate-gray pigmentation in a photodistribution of the face (picture 10). (See "Photosensitivity disorders (photodermatoses): Clinical manifestations, diagnosis, and treatment", section on 'Phototoxicity'.)

- **Phytophotodermatitis** – Phytophotodermatitis is a cutaneous, phototoxic eruption caused by the contact with plant-derived substances, such as lemons or limes. It may present with hyperpigmented macules or patches with a bizarre shape corresponding to the areas of contact with the sensitizing substance. (See "Photosensitivity disorders (photodermatoses): Clinical manifestations, diagnosis, and treatment", section on 'Phototoxicity'.)

- **Postinflammatory hyperpigmentation** – Postinflammatory hyperpigmentation manifests as hyperpigmented macules or patches on the skin that match the distribution of the preceding inflammatory dermatosis or injury (picture 11). (See "Postinflammatory hyperpigmentation".)

- **Lentigines** – Solar lentigines present with multiple tan to dark brown macules, often with irregular borders (picture 12). They typically occur in older adults on areas that are chronically exposed to the sun (eg, the face, dorsal hands, extensor forearms, and upper trunk). (See "Acquired hyperpigmentation disorders", section on 'Solar lentigines'.)

Additionally, clinicians should exclude exogenous ochronosis due to chronic topical treatment with, for example, hydroquinone [55]. It manifests as a localized, symmetric, blue-gray discoloration of the skin, with characteristic hyperchromic, pinpoint, caviar-like papules in photo-exposed regions. (See "Topical skin-lightening agents: Complications of use in the nonmedical setting", section on 'Exogenous ochronosis'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Melasma and hyperpigmentation disorders".)

SUMMARY

- **Definition** – Melasma is a chronic, therapeutically challenging, and universally relapsing condition that arises from hyperfunctional melanocytes that deposit excessive amounts of melanin in the epidermis and dermis. It typically occurs in females of reproductive age but may also be seen in males. (See 'Introduction' above.)

- **Risk factors** – Genetic predisposition, exposure to sunlight (including ultraviolet [UV] and, possibly, visible light), skin phototype, and hormonal factors (including pregnancy, hormonal therapies, and oral contraceptives) are the main risk and trigger factors for melasma. (See 'Risk and trigger factors' above.)

- **Clinical presentation** – Melasma typically presents as light brown to gray-brown macules and patches on sun-exposed skin. Lesions are usually symmetric and may affect the forehead, nose, cheeks, upper lip area, and chin (picture 3 and picture 2A, 2E). Less commonly, melasma may occur on extrafacial sites, such as the forearms, chest, and back (picture 4). Melasma has a chronic and recurrent course. Relapsing occurs with mild to intense sun exposure even after successful treatment. (See 'Clinical presentation' above and 'Clinical course' above.)

- **Diagnosis** – Melasma is generally diagnosed based on the clinical presentation. Wood's lamp examination may assist in identifying the location of pigment (epidermal or dermal), especially in individuals with lighter complexions (Fitzpatrick phototypes I to III). Dermoscopy is increasingly used as an aid for diagnosing melasma and identifying the level of pigment deposition. (See 'Diagnosis' above.)

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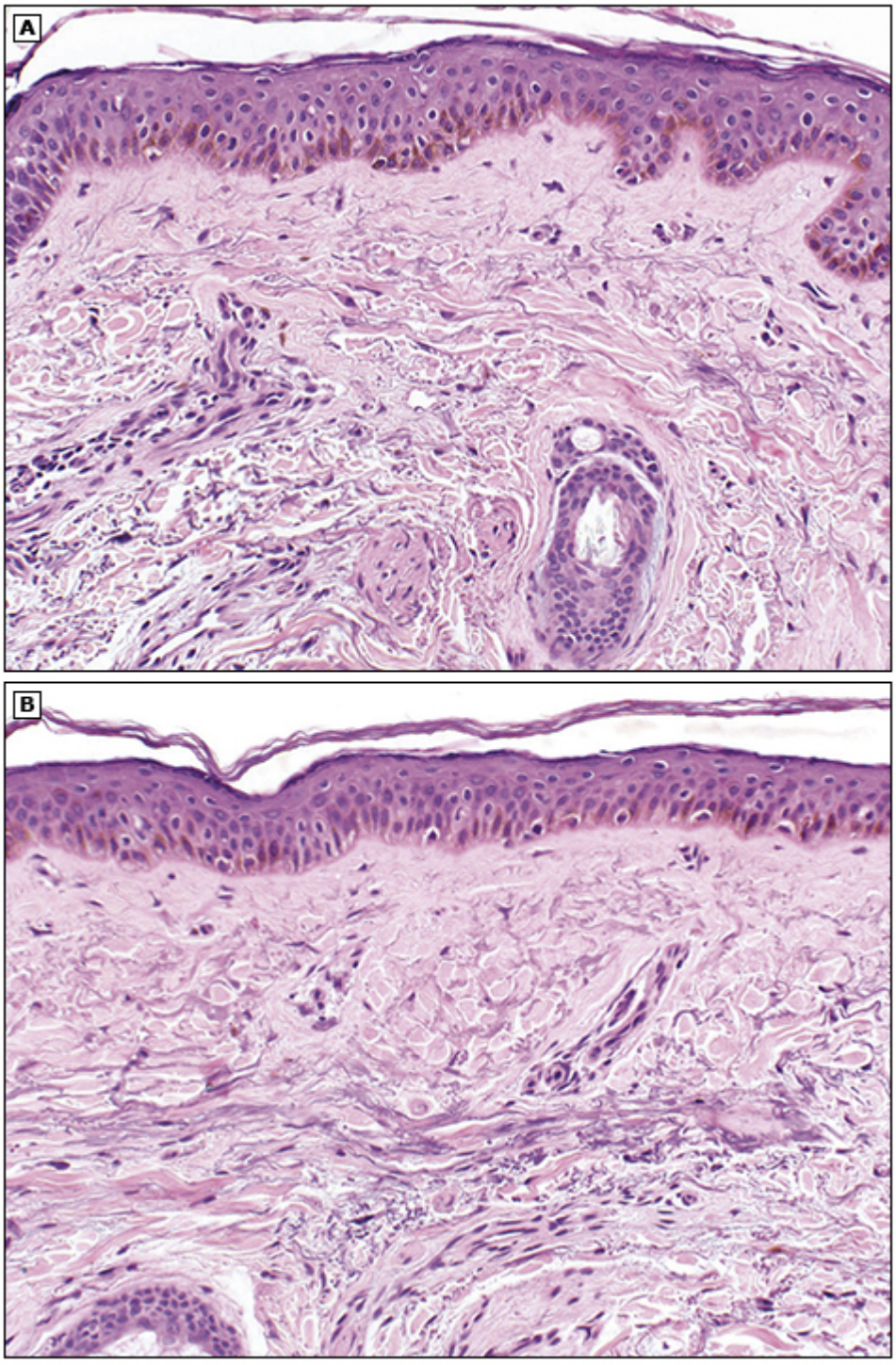
GRAPHICS

Melasma histopathology: Hematoxylin and eosin staining

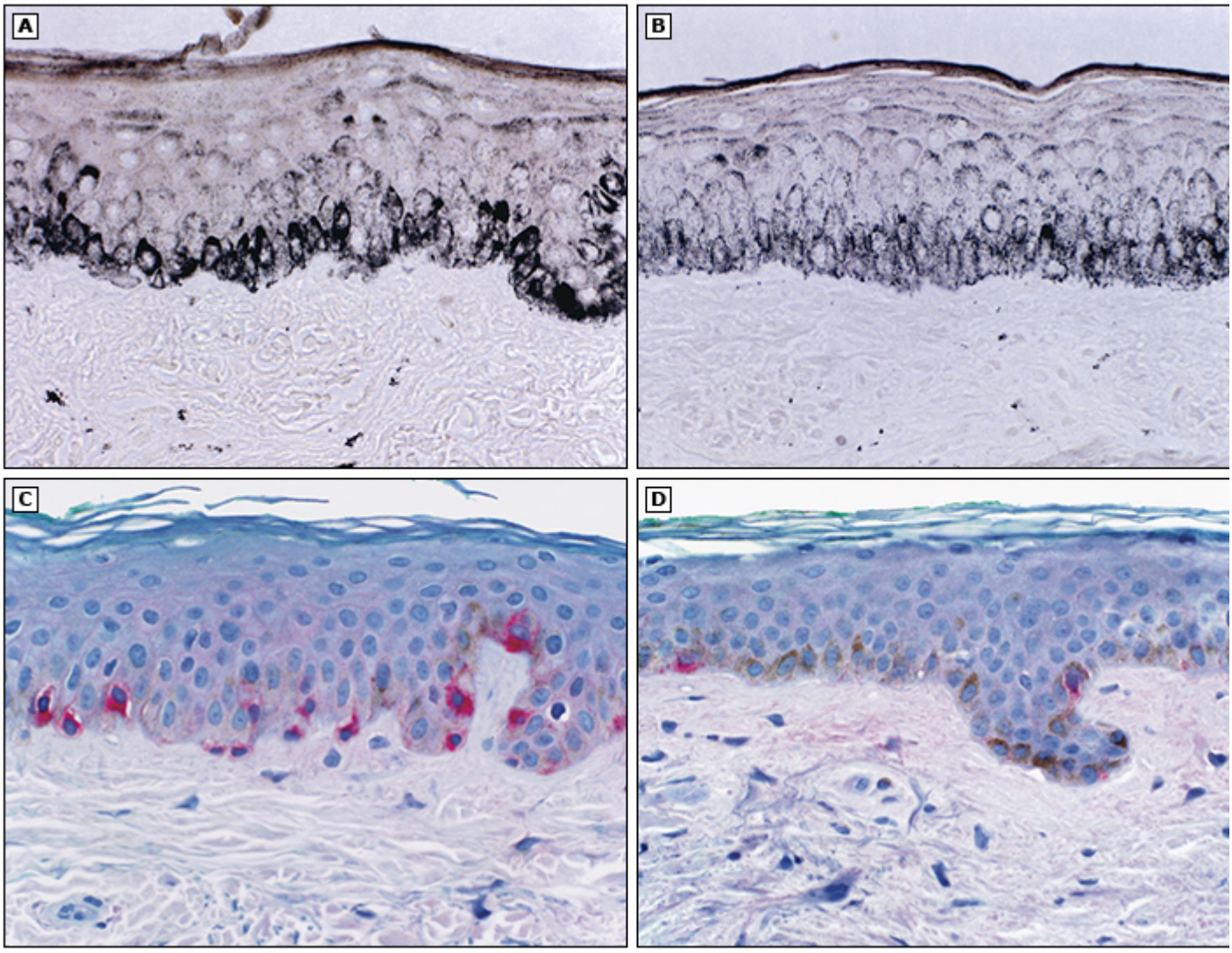


(A) Photomicrograph of melasma. Hematoxylin and eosin stain. Increased epidermal melanin and mild, perivascular, lymphohistiocytic infiltrate (original magnification 340).

(B) Hematoxylin and eosin stain. Normal skin for comparison. Same patient (original magnification 340).

Graphic 122973 Version 5.0

Histopathologic features of melasma: Fontana-Masson and Mel-5 staining



(A) Fontana-Masson stain of melasma skin showing increased epidermal melanin and dermal melanophage (original magnification ×40).

(B) Fontana-Masson stain of normal adjacent skin for comparison (original magnification x40).

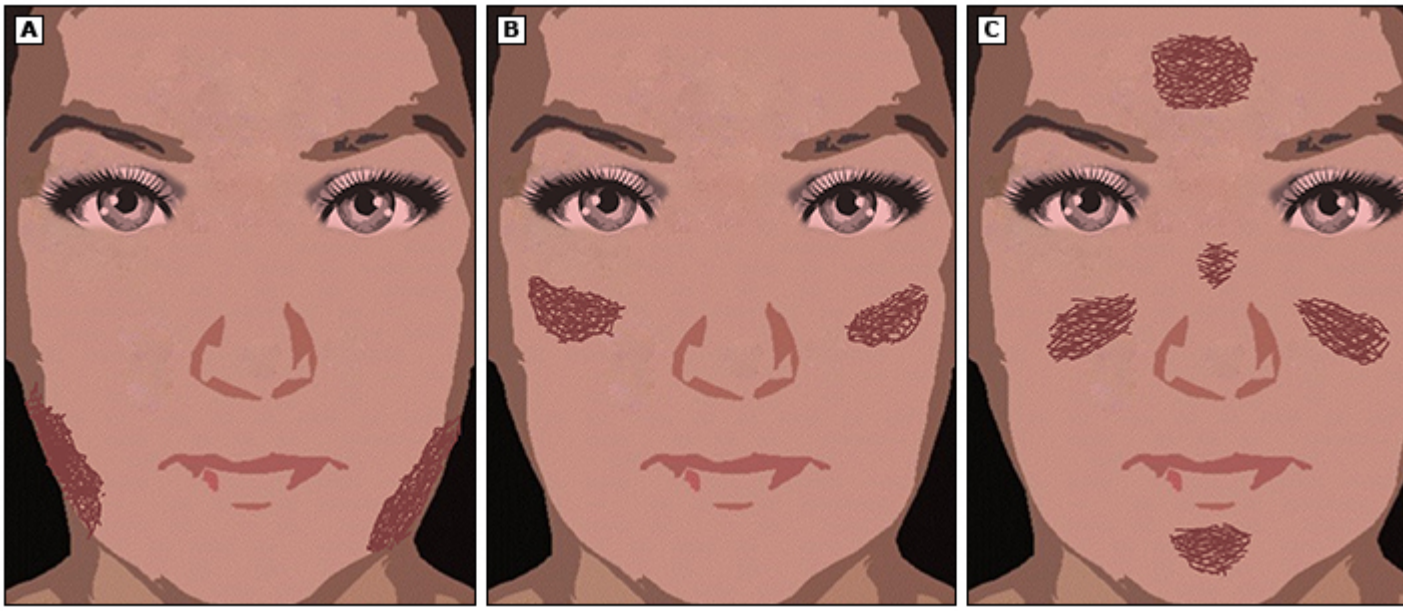
(C) Mel-5 immunostain of melasma skin showing enlarged, intensely stained melanocytes with prominent dendrites (original magnification ×40).

(D) Mel-5 immunostain of adjacent normal skin for comparison (original magnification ×40).

From: Grimes PE, Yamada N, Bhawan J. Light microscopic, immunohistochemical, and ultrastructural alterations in patients with melasma. Am J Dermatopathol 2005; 27:96. DOI: 10.1097/01.dad.0000154419.18653.2e.

Graphic 122093 Version 5.0

Facial melasma patterns

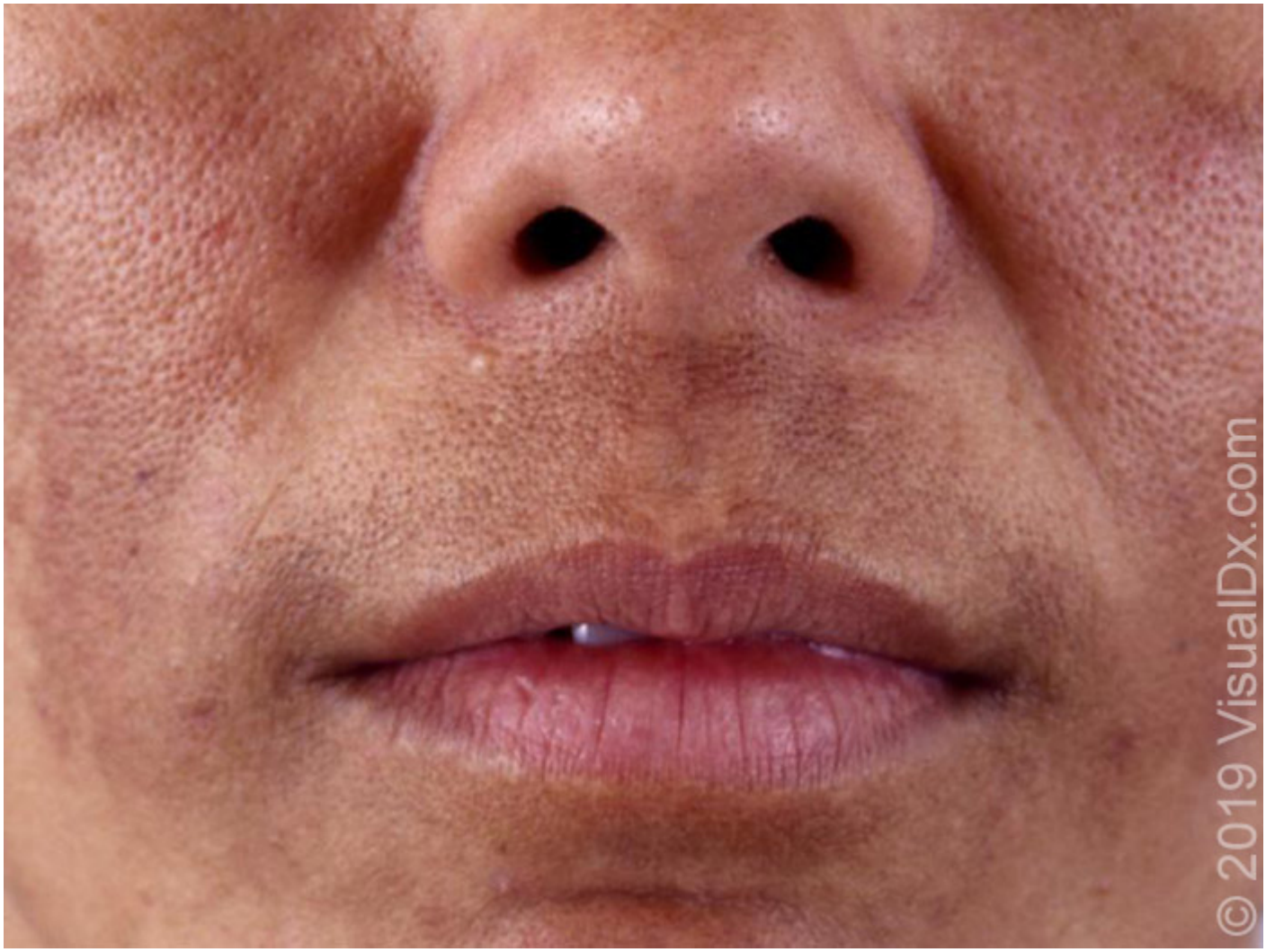


Graphic depictions of (A) mandibular, (B) malar, and (C) centrofacial melasma.

Courtesy of Pearl E Grimes, MD.

Graphic 122094 Version 1.0

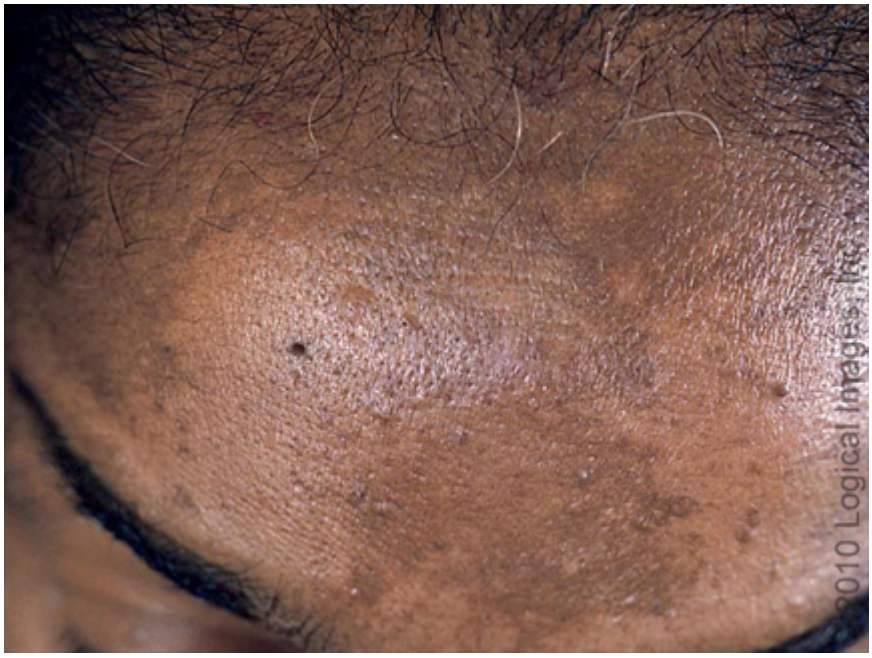
Melasma



Brown patches with irregular borders involving the cheeks, upper lip, and chin.

Graphic 122098 Version 1.0

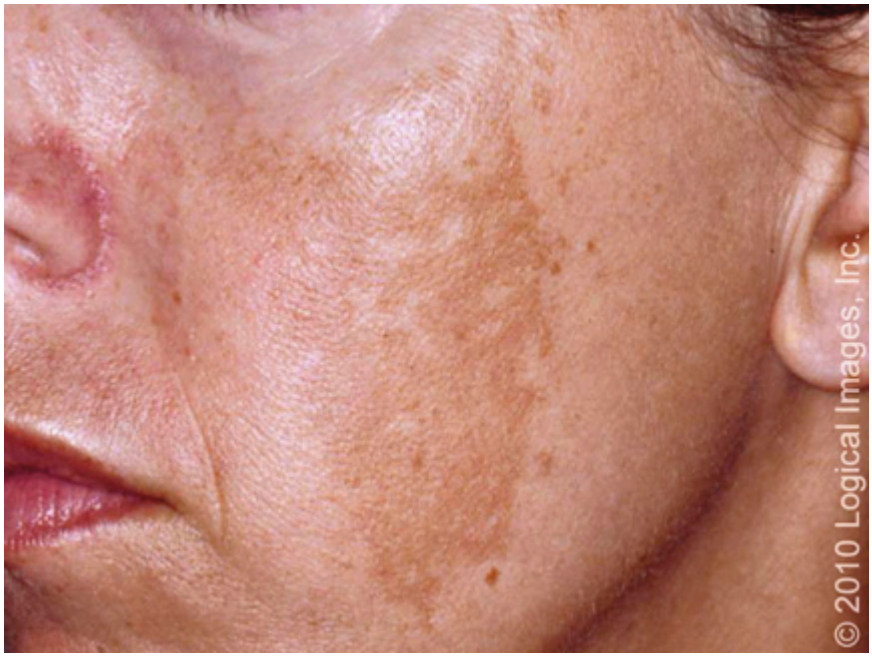
Melasma



Mottled hyperpigmented patches are present on the forehead.

Graphic 75884 Version 6.0

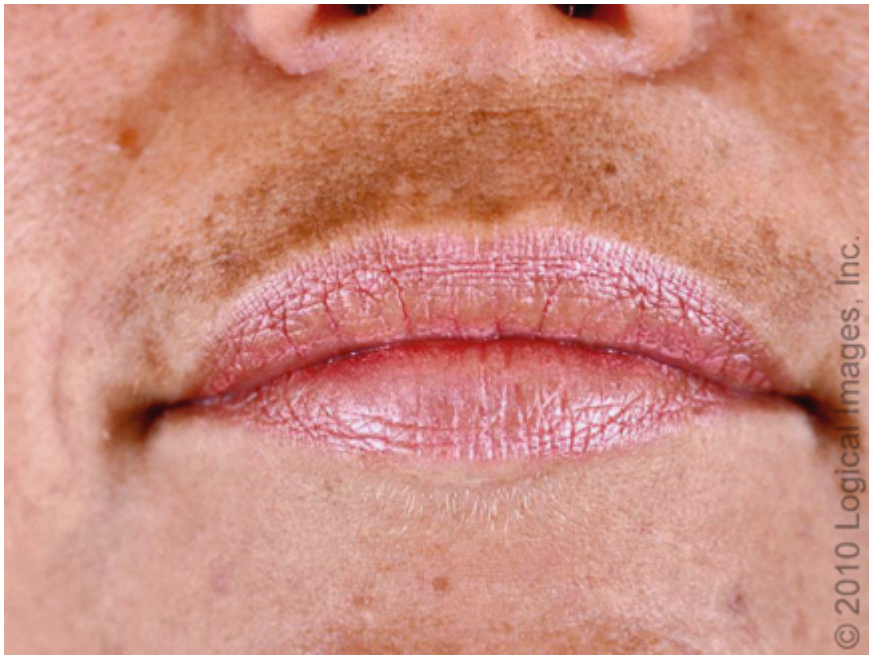
Melasma



A mottled hyperpigmented patch is present on the cheek.

Graphic 64109 Version 7.0

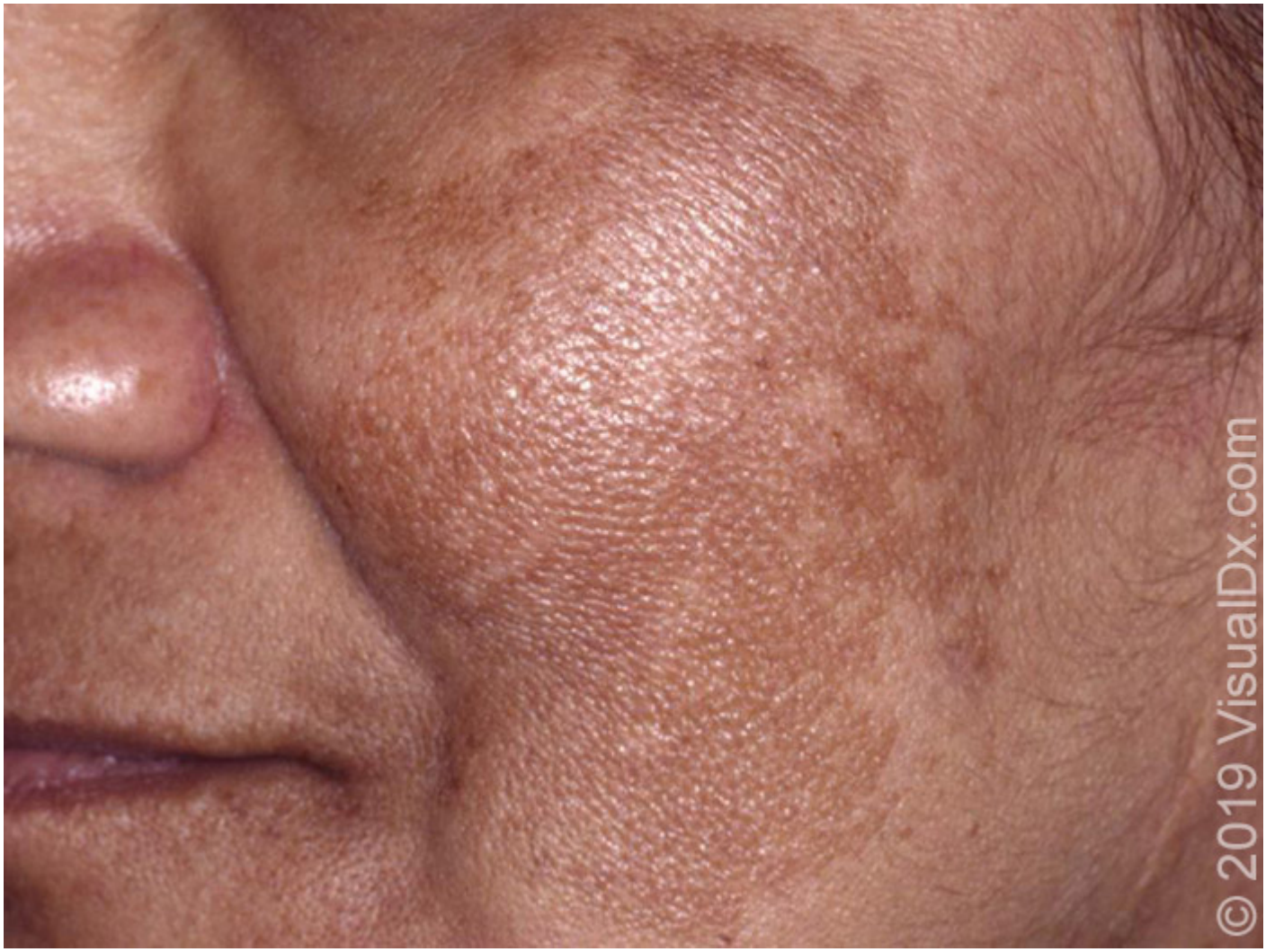
Melasma lip



A hyperpigmented patch is present on the upper lip in this patient with melasma.

Graphic 52220 Version 5.0

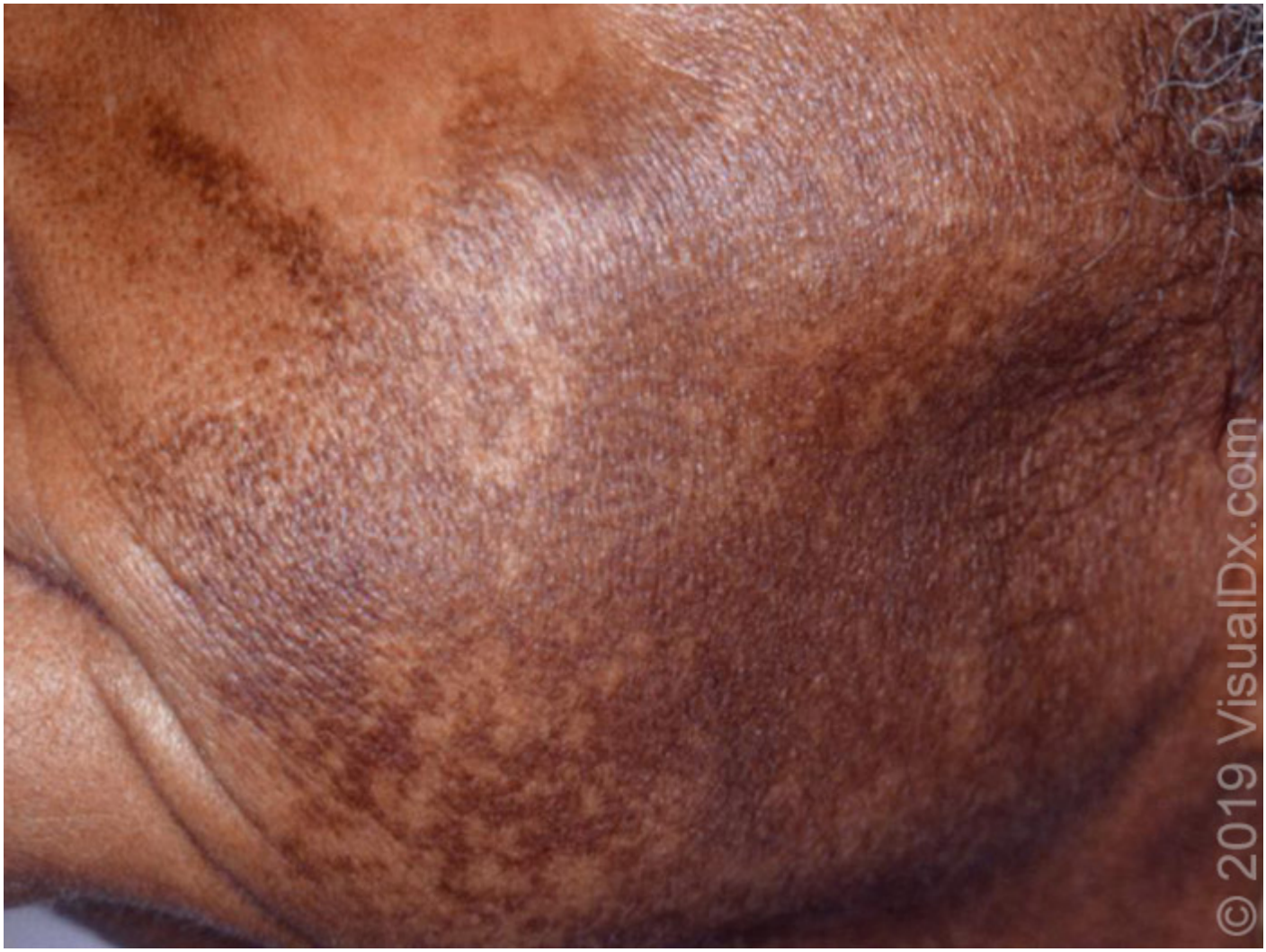
Melasma



A broad, evenly pigmented, tan patch with feathered borders on the cheek.

Graphic 122095 Version 1.0

Melasma



A large, evenly pigmented patch with feathered borders involving the cheek and the mandibular area.

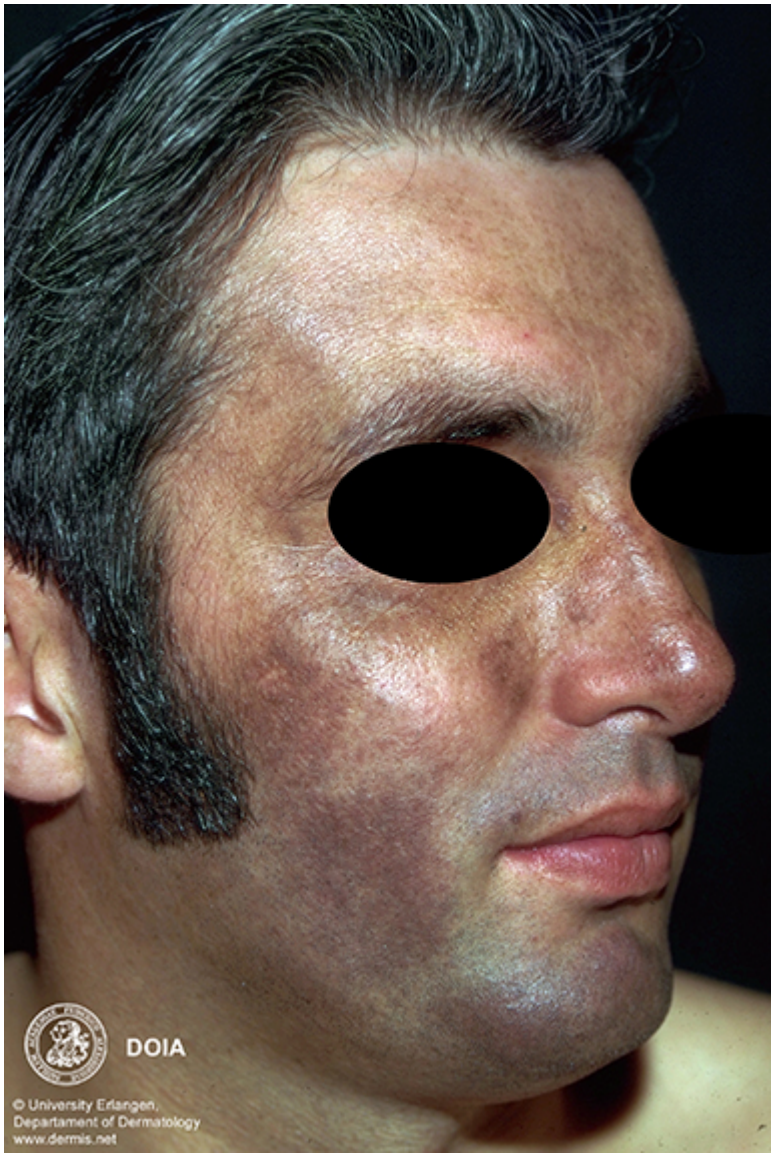
Graphic 122097 Version 1.0

Melasma

Splotchy, symmetric hyperpigmentation on the forearms, upper chest, and face in a 30-year-old woman. Shortly after starting oral contraceptives, she developed melasma after intense sun exposure.

Graphic 89286 Version 4.0

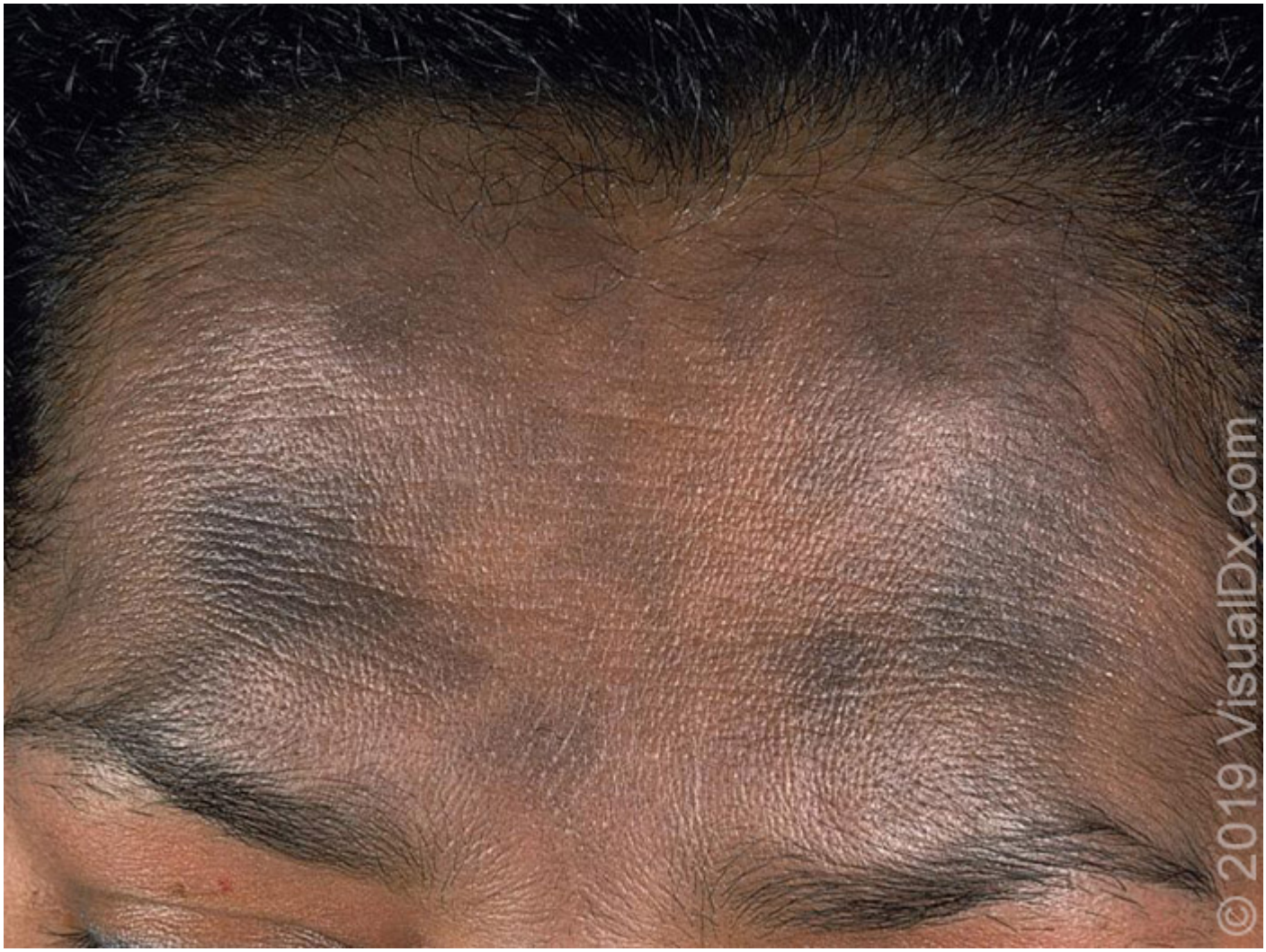
Pigmented contact dermatitis (Riehl's melanosis)



Gray-brown, reticular facial pigmentation in a 33-year-old man with Riehl's melanosis.

Graphic 89290 Version 2.0

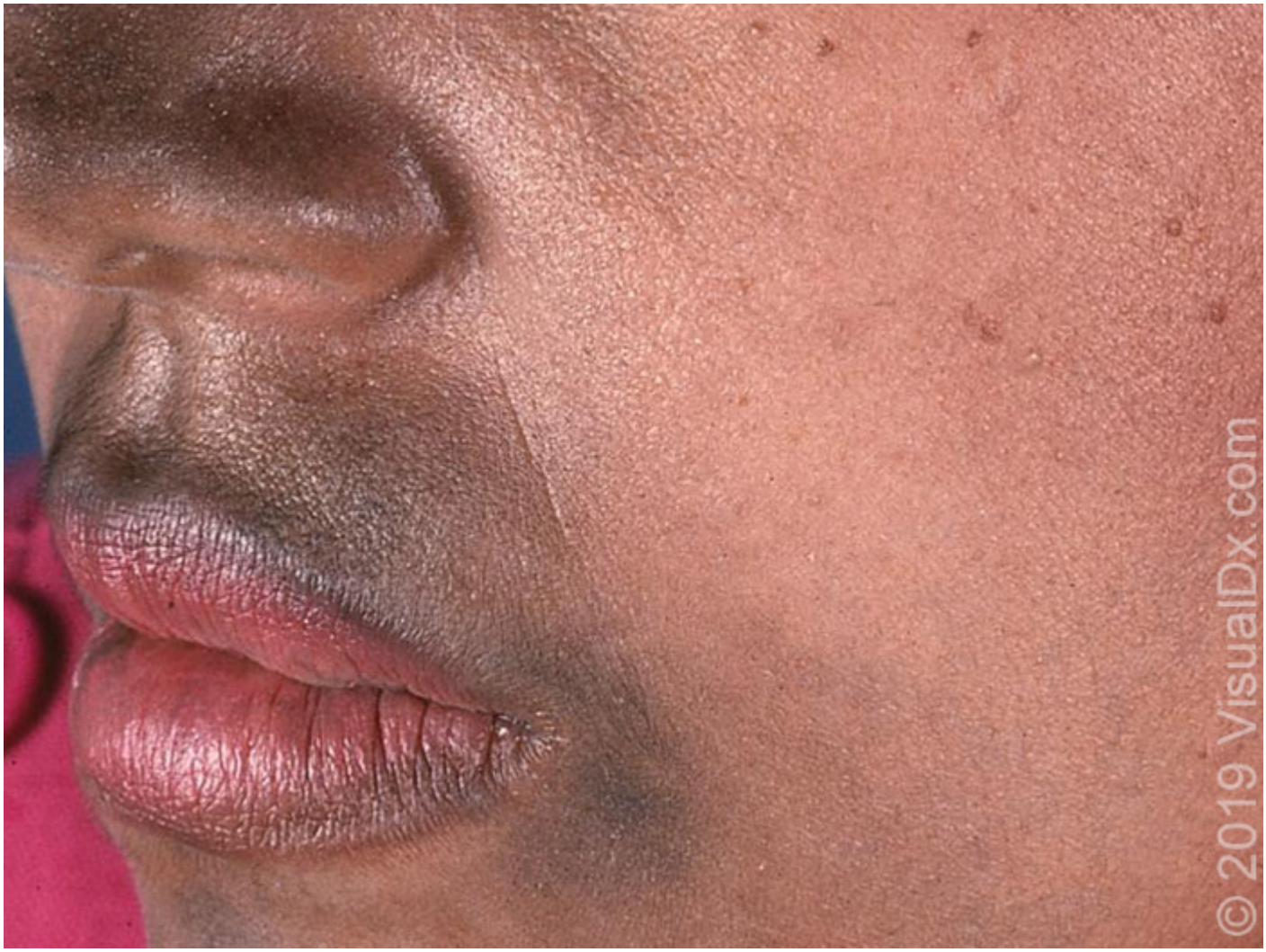
Erythema dyschromicum perstans (ashy dermatosis)



Dark gray macules and patches on the forehead.

Graphic 122117 Version 1.0

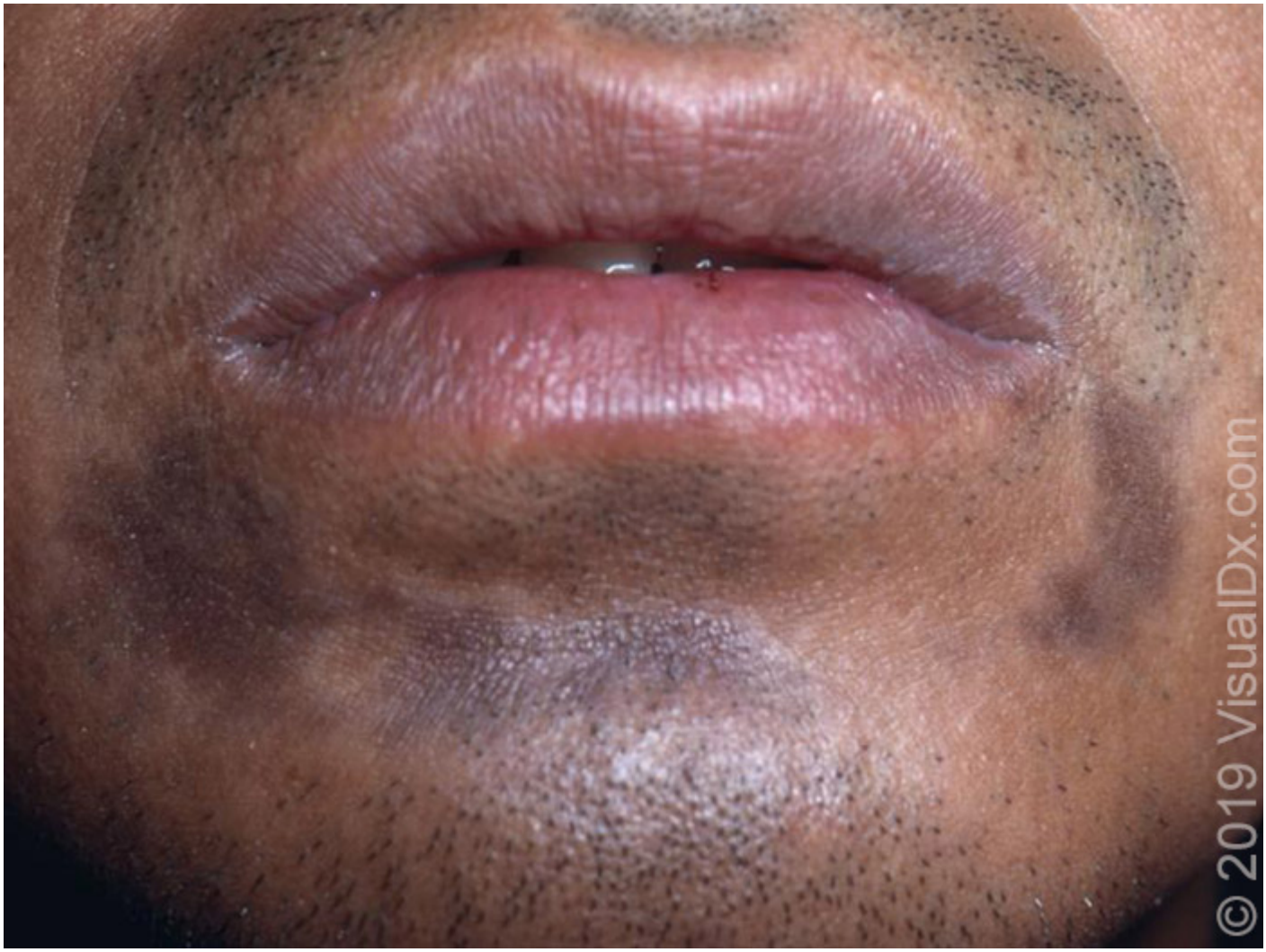
Erythema dyschromicum perstans (ashy dermatosis)



Dark gray patches on the central face.

Graphic 122119 Version 1.0

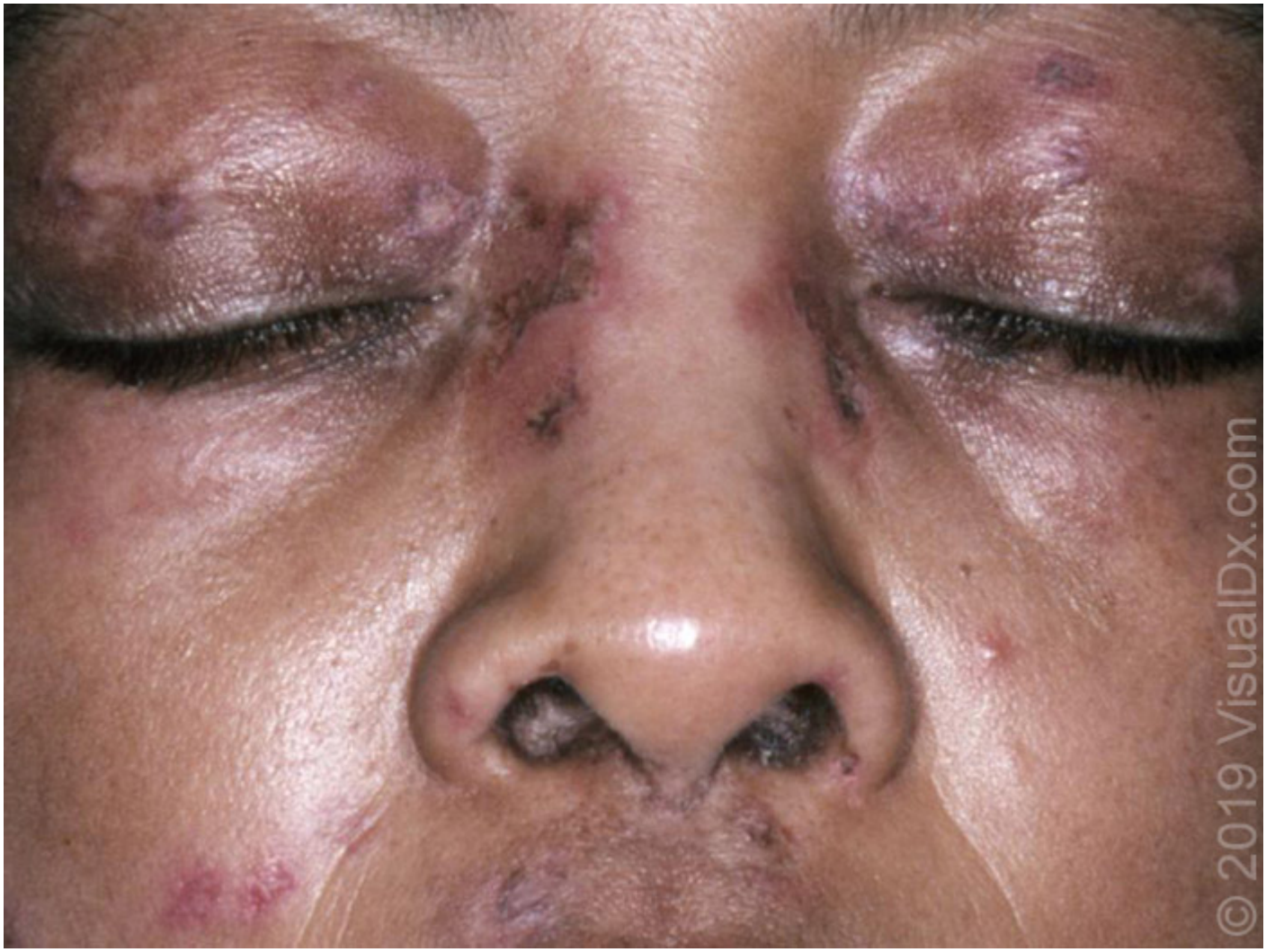
Fixed drug eruption



Brownish-gray macules on the chin.

Graphic 122129 Version 1.0

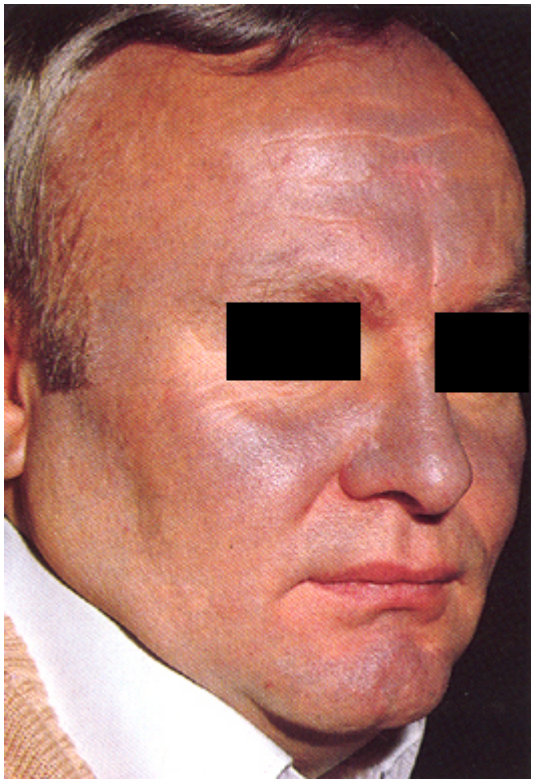
Discoid lupus erythematosus



Violaceous, erythematous plaques scattered on the central face with postinflammatory hypo- and hyperpigmentation on the eyelids and upper lips.

Graphic 122120 Version 1.0

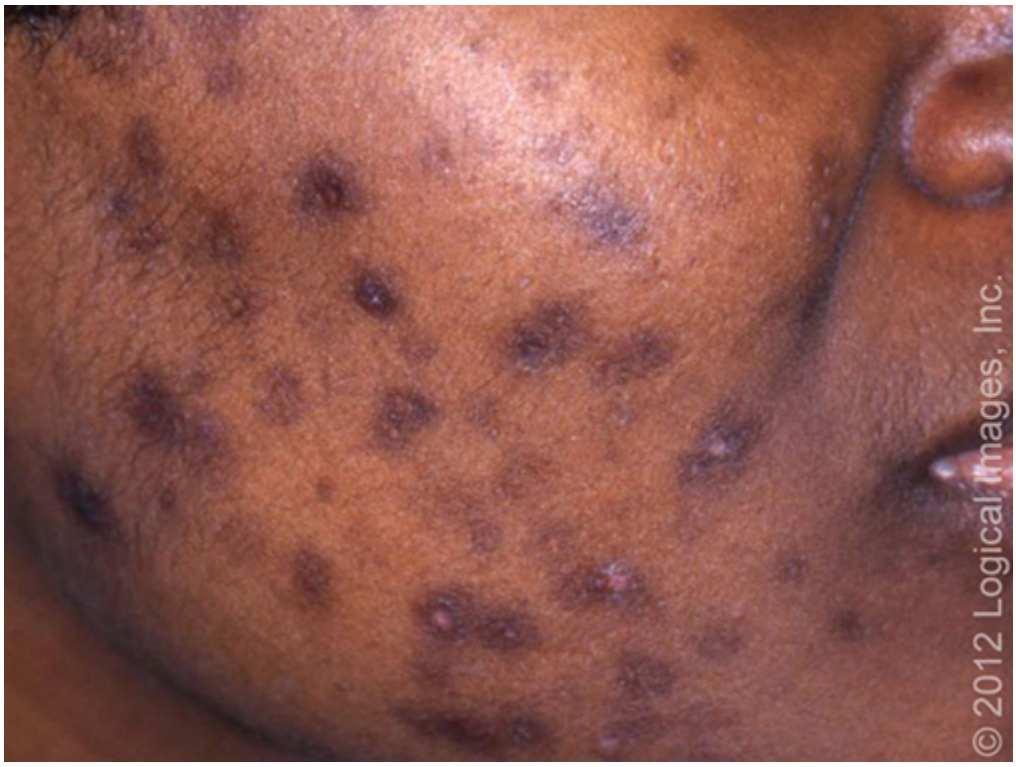
Amiodarone-induced pigmentation



Amiodarone causes a striking slate-gray pigmentation in a photodistribution of the face. The blue color (ceruloderma) is due to the deposition of melanin and lipofuscin contained in macrophages and endothelial cells in the dermis. The pigmentation is reversible, but it may take up to a year or more to complete resolution.

Graphic 70419 Version 6.0

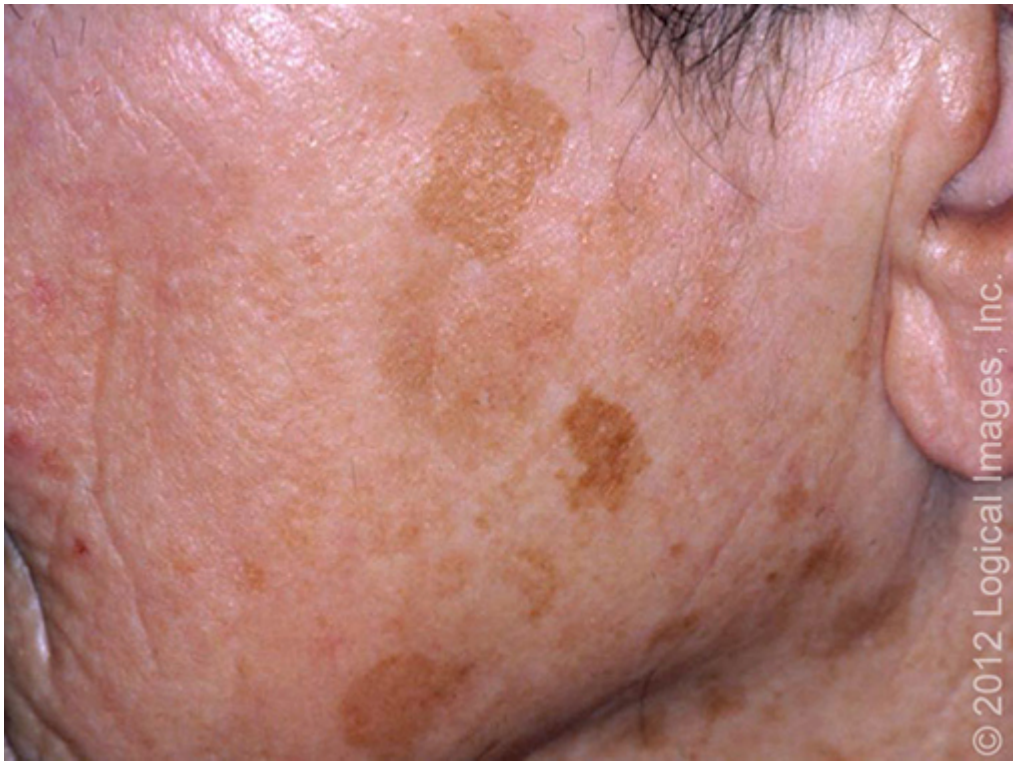
Postinflammatory hyperpigmentation and scarring in acne vulgaris



Multiple hyperpigmented macules and scars on the lower face of a woman with acne vulgaris.

Graphic 58817 Version 6.0

Solar lentigines



Multiple irregular, light brown macules are present on the face of this patient.

Graphic 81287 Version 7.0

Contributor Disclosures

Pearl E Grimes, MD Grant/Research/Clinical Trial Support: Clinuvel Pharmaceuticals [Pigmentation, vitiligo]; Incyte [Hypopigmentation, vitiligo]; LaserOptek [Hypopigmentation]; Pfizer [Hypopigmentation, vitiligo]; SkinBetter Science [Vitiligo]; VT Technologies [Pigmentation]. Consultant/Advisory Boards: Clarify Medical [Vitiligo]; Dermaforce [Hyperpigmentation]; Incyte [Vitiligo]; L'Oréal [Hyperpigmentation]; Procter & Gamble [Hyperpigmentation, cosmetics]. Speaker's Bureau: Incyte [Hypopigmentation, vitiligo]. All of the relevant financial relationships listed have been mitigated. **Robert P Dellavalle, MD, PhD, MSPH** Equity Ownership/Stock Options: Altus Labs [Itch, eczema]. Grant/Research/Clinical Trial Support: Pfizer [Patient decision aids, inflammatory and immune-mediated skin disease]. Other Financial Interest: Cochrane Council meetings [Expense reimbursement]. All of the relevant financial relationships listed have been mitigated. **Andrew F Alexis, MD, MPH** Grant/Research/Clinical Trial Support: AbbVie [Rhytides, melasma]; Almirall [Acne]; Amgen [Psoriasis]; Arcutis Biotherapeutics [Seborrheic dermatitis, atopic dermatitis]; Bausch Health Companies [Acne]; Bristol Myers Squibb [Psoriasis]; Cara Therapeutics [Pruritus]; Castle Biosciences [Atopic dermatitis, psoriasis]; Dermavant Sciences [Atopic dermatitis]; Galderma [Acne]; LEO Pharma [Atopic dermatitis]; Novartis [Psoriasis]; VYNE Therapeutics [Acne]. Consultant/Advisory Boards: AbbVie [Atopic dermatitis]; Allergan [Aesthetics]; Almirall [Acne]; Alphyn Biologics [Atopic dermatitis]; Amgen [Psoriasis]; Apogee Therapeutics [Atopic dermatitis]; Arcutis Biotherapeutics [Seborrheic dermatitis]; Bausch Health Companies [Acne]; Beiersdorf [Hyperpigmentation, photoprotection]; Bristol Myers Squibb [Psoriasis]; Canfield Scientific [Psoriasis]; Cara Therapeutics [Psoriasis]; Castle Biosciences [Skin cancer]; Cutera [Acne]; Dermavant Sciences [Atopic dermatitis]; Eli Lilly and Company [Atopic dermatitis]; EPI Health [Rosacea]; Galderma [Acne]; Janssen Pharmaceuticals [Psoriasis]; LEO Pharma [Atopic dermatitis]; L'Oréal [Atopic dermatitis, acne, psoriasis, skin care]; Ortho Dermatologics [Acne]; Pfizer [Atopic dermatitis, alopecia areata]; Regeneron Pharmaceuticals [Atopic dermatitis]; Sanofi [Atopic dermatitis]; Sol-Gel [Acne]; Swiss American [Skin care]; UCB [Psoriasis]; VisualDx [Dermatology education]; VYNE Therapeutics [Acne]. Speaker's Bureau: Bristol Myers Squibb [Psoriasis]; Pfizer [Atopic dermatitis]; Regeneron Pharmaceuticals [Atopic dermatitis]; Sanofi [Atopic dermatitis]. Other Financial Interest: Springer [Textbook]; Wiley-Blackwell [Textbook]. All of the relevant financial relationships listed have been mitigated. **Rosamaria Corona, MD, DSc** No relevant financial relationship(s) with ineligible companies to disclose.

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