Common Hyperpigmentation Disorders in Adults: Part I. Diagnostic Approach, Café au Lait Macules, Diffuse Hyperpigmentation, Sun Exposure, and Phototoxic Reactions

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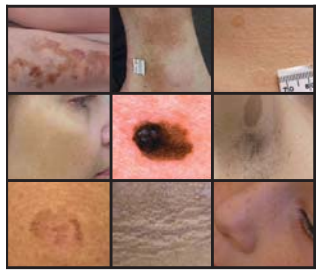
The cause of hyperpigmentation usually is traced to the activity and presence of melanocytes. Café au lait macules may be solitary benign findings or may indicate the presence of neurofibromatosis with its associated complications. Diffuse hyperpigmentation should prompt a search for offending medications or systemic diseases such as hemochromatosis, hyperthyroidism, and Addison's disease. In these instances, the hyperpigmentation may be ameliorated by discontinuing offending medications, performing serial phlebotomy in patients with hemochromatosis, instituting cause-specific treatments in patients with hyperthyroidism, and replacing deficient glucocorticoids and mineralocorticoids in patients with Addison's disease. Cosmetic treatment with bleaching agents or lasers can be used to decrease pigmentation of ephelides (freckles) and lentigines. (Am Fam Physician 2003;68:1955-60. Copyright© 2003 American Academy of Family Physicians.)



This is part I of a two-part article on hyperpigmentation in adults. Part II, "Melanoma, Seborrheic Keratoses, Acanthosis Nigricans, Melasma, Diabetic Dermopathy, Tinea Versicolor, and Postinflammatory Hyperpigmentation," appears in this issue on page 1963.

This article is one in a series coordinated by Daniel L. Stulberg, M.D., director of dermatology curriculum at the Utah Valley Family Practice Residency Program, Provo, Utah.

See page 1898 for definitions of strength-of-evidence levels.

Hyperpigmentation may be the sign of a benign or relatively easily treated condition, or it may indicate the presence of a life-threatening condition such as melanoma. This two-part article presents a suggested approach to adult patients with increased pigmentation and reviews various underlying causes.

Melanocytes and Pigmentation

Melanocytes are derived embryonically from neural crest cells that migrate into the basal layer of the epidermis. In the skin, melanocytes continuously produce melanosomes—organelles that are transferred to keratinocytes. The melanosomes convert tyrosine to melanin, giving skin its color. Under the stimulus of hormones or irritation, the production of melanosomes increases, leading to hyperpigmentation. In response to sun exposure or idiopathically in some disorders, hyperplasia of melanocytes occurs and causes hyperpigmentation.[1]

The same melanocyte concentration is present in persons of all races who have normal skin. However, some races have larger melanosomes, giving their skin a darker color.[2,3]

Diagnostic Approach

A simple way to approach hyperpigmentation is to consider whether the increase in color is caused by an increase of melanin, an increase in melanocytes, or the deposition of another substance that adds color to the skin *(Figure 1)*. Selected disorders and their characteristics are discussed in the following sections and summarized in *Table 1*; other disorders are discussed and summarized in part II of this article.

A directed history and physical examination offer clues to the underlying cause of hyperpigmentation. The history should address the time of onset of the lesion, because some disorders (e.g., neurofibromatosis) are congenital, while others develop in childhood (e.g., ephelides) or during pregnancy (e.g., melasma). Systemic symptoms may indicate the presence of hyperthyroidism, Addison's disease, or diabetes-related disorders. A review of medication use, supplement use, and exposure to plants and ultraviolet radiation can help determine whether hyperpigmentation is caused by a medication side effect or a phototoxic reaction.

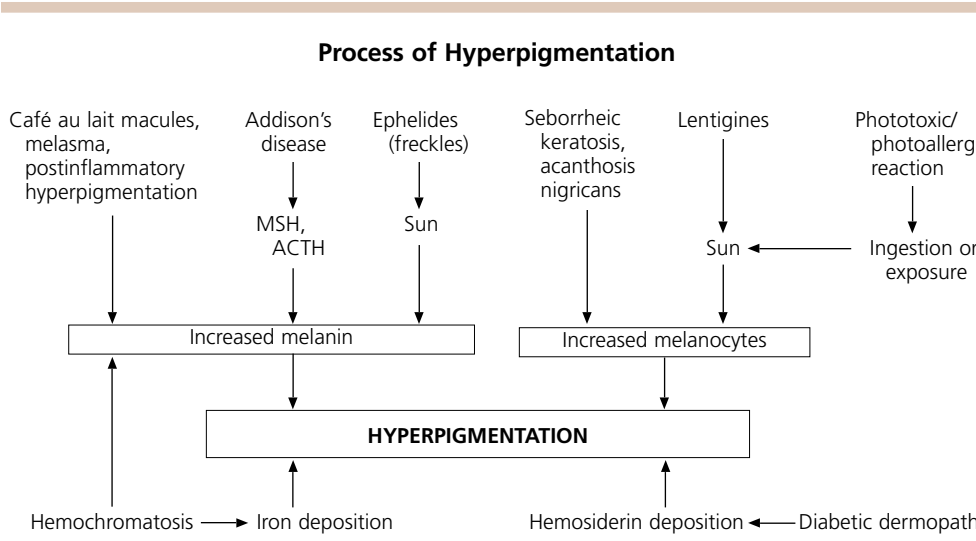


FIGURE 1. Selected disorders and associated processes that result in hyperpigmentation. (MSH = melanocyte-stimulating hormone; ACTH = adrenocorticotropic hormone)

The size and number of the lesions are useful in diagnosing neurofibromatosis, ephelides, and lentigines. The border, color, and character of a lesion help to distinguish melanoma from a benign lesion, while the distribution of skin changes assists in the diagnosis of melasma and acanthosis nigricans.

Congenital Lesions: Café au Lait Macules

Café au lait (coffee with milk) macules can be congenital, or they may develop in childhood. These flat macules usually occur on the trunk and can have a smooth or irregular border *(Figure 2)*. They range from 0.2 to 4 cm in diameter in infants but can reach 30 cm in diameter in adults.[3] The hyperpigmentation is caused by increased melanin in melanocytes and basal keratinocytes.[4]

Café au lait macules may be a sign of neurofibromatosis. The diagnosis of this disease requires the presence of at least two of seven criteria established at a National Insti-

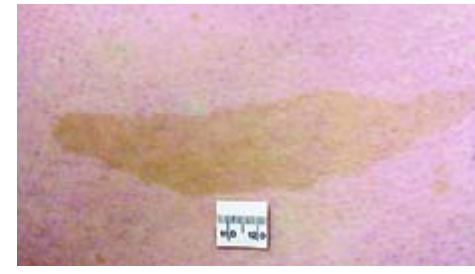


FIGURE 2. Smooth border of café au lait macule.

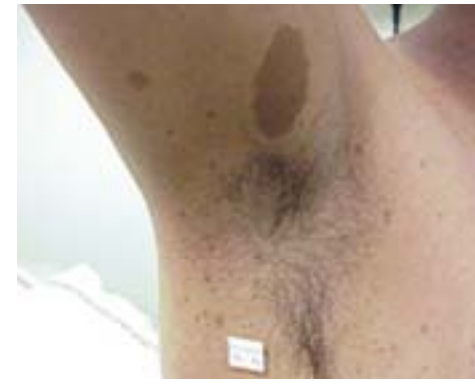


FIGURE 3. Axillary freckling with irregular but discrete border.

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TABLE 1
Characteristics and Treatments of Selected Hyperpigmentation Disorders

Disorder	*Appearance*	*Age of onset*	*Hormone or medication related*	*Sun or other exposure involved*	*Associated systemic complications*	*Treatment*
Café au lait macules	Multiple macules, 0.2 to 30 cm in diameter, with smooth or irregular, but discrete borders	Congenital or in childhood	Not related	Not involved	May indicate neurofibromatosis (see Table 2)	Treat skin lesions for cosmesis; use laser or surgical procedure if mass effect.
Addison's disease	Diffuse hyperpigmentation with "muddy" appearance, especially in sun-exposed areas, perineum, axillae, areolae, palms, and soles	Usually adulthood	Elevated adrenocorticotropic hormone and melanocyte-stimulating hormone levels	More prominent in sun-exposed areas	Blood pressure instability, fatigue, anorexia, depression	Use hydrocortisone and fludrocortisone (Florinef).
Hemochromatosis	Diffuse slate-gray or bronze hyperpigmentation	Adulthood	Not related	Not involved	Multiorgan dysfunction caused by iron deposition	Use phlebotomy to decrease iron load and address end-organ damage.
Ephelides (freckles)	Multiple red, tan, or brown macules, 1 to 3 mm in diameter, on sun-exposed areas	Childhood through adulthood	Not related	Increased number and pigmentation	None	Treat for cosmesis; avoid sun exposure; use sunscreen, bleaching or peeling agents, or laser.
Lentigines	Multiple tan, brown, or black macules, 2 to 20 mm in diameter, on sun-exposed areas	Childhood through adulthood	Not related	Increased in sun-exposed areas	If present on mucosa, consider Peutz-Jeghers syndrome (gastrointestinal polyposis and increased cancer risk)	Treat for cosmesis; avoid sun exposure; use sunscreen, bleaching or peeling agents, or laser therapy.
Photoallergic/phototoxic reaction	Diffuse inflammation followed by hyperpigmentation in sun-exposed areas	Any age	Not related	Combination of sun exposure and an offending medication, plant, or chemical	None	Treat for cosmesis; avoid sun exposure and the offending agent; may use bleaching agents, laser therapy, or dermabrasion.

tutes of Health (NIH) consensus development conference *(Table 2)*.[5] The presence of six or more café au lait macules is one of the diagnostic criteria; axillary or groin freckling is another *(Figure 3)*. Hence, the presence of axillary or groin freckling should prompt a search for café au lait macules, and vice versa. If neurofibromatosis is suspected or confirmed, an ophthalmologist can detect optic gliomas and iris hamartomas, which are additional criteria for the diagnosis of neurofibromatosis. The American Academy of Dermatology has practice guidelines based on the NIH definition.[5] [Evidence level C, consensus opinion]

Café au lait macules themselves require treatment only if cosmesis is requested. Surgical or laser treatment by a cosmetic dermatologist may be considered on an individual basis. From a practical standpoint, neurofi-

The treatment of solar-radiation–induced ephelides or lentigines is for cosmesis only and includes avoidance of the sun and use of sunscreens, make-up, moisturizers, bleaching and peeling agents, and laser therapy.

bromas, which can occur throughout the body, pose more of a cosmetic and functional concern *(Figure 4)*.

Consultation with a geneticist may be prudent because neurofibromatosis is an autosomal dominant condition, although spontaneous mutations cause 50 percent of cases.[6] Some patients have café au lait macules without neurofibromatosis; their children are not at increased risk for the disease.

Diffuse Hyperpigmentation

Diffuse hyperpigmentation may have a systemic cause, such as Addison's disease, hyperthyroidism, or hemochromatosis. It also may occur because of a medication side effect.

In Addison's disease, the adrenal glands fail to produce adequate amounts of mineralocorticoids and glucocorticoids. When elevations of melanocyte-stimulating hormone and adrenocorticotropic hormone (also referred to as corticotropin) levels occur as the pituitary gland tries to stimulate the adrenal glands, melanin production increases, causing hyperpigmentation with a "muddy" appearance.[7] The hyperpigmentation is diffuse, but more pronounced in sun-exposed areas and in the perineum, axillae, areolae, palms, and soles.[8] Patients with Addison's disease should be treated with mineralocorticoid and glucocorticoid replacement to reduce the drive for excess production of adrenocorticotropic hormone and melanocyte-stimulating hormone.

Hyperthyroidism causes a pattern of hyperpigmentation similar to that in Addison's disease, especially in patients with darker complexions.[9] Treatment is specific to the cause of hyperthyroidism and may involve antithyroid medications, surgical resection of the thyroid, or radioactive iodine therapy.

Hemochromatosis, a disorder of iron storage and deposition, can cause a slate-gray hyperpigmentation (because of hemosiderin deposition). Hyperpigmentation is present in 70 percent of affected patients at diagnosis.[10] Bronzing resulting from increased melanin production is common, although the mechanism for this effect is not known.[11] Hemochromatosis is treated with repeated phlebotomy to reduce excessive iron stores.[12]

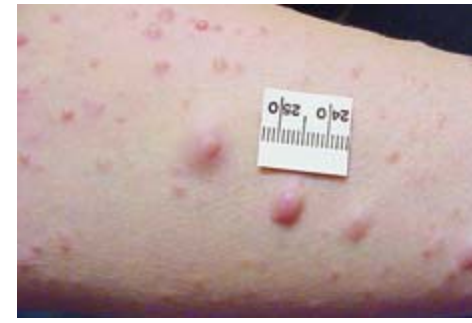

FIGURE 4. Prominent neurofibromas on the arm.

TABLE 2
Diagnostic Criteria for Neurofibromatosis

Diagnosis requires the presence of two or more of the following:
1. Six or more café au lait macules larger than 5 mm in greatest diameter in prepubertal persons and larger than 15 mm in greatest diameter in postpubertal persons
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal region
4. Optic glioma
5. Two or more Lisch nodules (iris hamartomas)
6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
7. A first-degree relative (i.e., parent, sibling, child) with neurofibromatosis type 1 by the above criteria

Information from reference 5.

Lesions from Chronic Sun Exposure

The normal response to solar radiation (or tanning beds) is an increase in melanin production, which causes uniform tanning in most persons but leads to freckling in some. Ephelides, or freckles, are small (usually less than 3 mm in diameter), red or light- to dark-brown macules that appear on sun-exposed areas of the body *(Figure 5)*. Lentigines are tan, brown, or black macules, 2 to 20 mm in

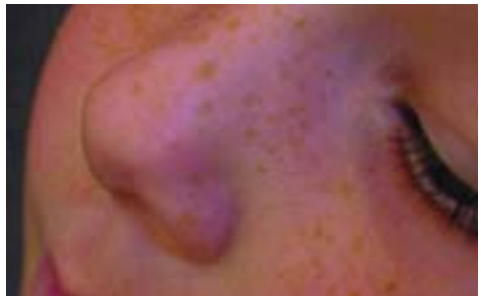

FIGURE 5. Ephelides (freckles).

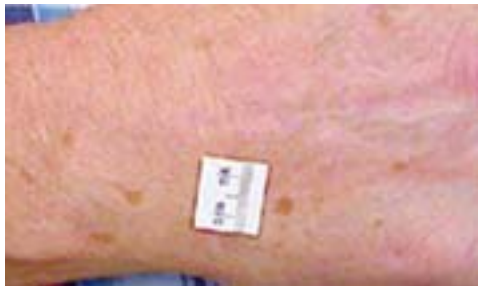

FIGURE 6. Lentigines.

diameter, that occur anywhere on the body *(Figure 6)*.

Lentigines have increased numbers of melanocytes that produce dense epidermal deposits of melanin. In contrast to lentigines, ephelides have a normal number of melanocytes but an increased number of melanosomes.[13] Because both lentigines and ephelides are benign, differentiation is not critical.

Ephelides and lentigines can be too numerous to count. This factor and their relative uniformity of color help to distinguish them from nevi, which have more serious implications. If lesions are larger than several millimeters or display abnormal coloration, the differential diagnosis includes nevi, which may require surgical removal because of possible malignancy.

Multiple lentigines in the skin, lips, and mucous membranes should raise suspicion for Peutz-Jeghers syndrome. This autosomal dominant syndrome is associated with polyposis of the gastrointestinal tract and an increased risk of cancers of the pancreas, lung, breast, ovary, and uterus.[14] [Evidence level B, retrospective cohort study]

Treatment of ephelides and lentigines is for cosmesis only. Avoidance of sun exposure and the use of sunscreens and make-up or moisturizers that contain sunscreens can decrease the development of additional lesions. If desired, patients can be treated with bleaching solutions or with peeling agents by a professional who is experienced in their use, such as a dermatologist. However, results are slow, and complications such as irritation and hyperpigmentation can occur. Bleaching agents include hydroquinone (Eldoquin Forte), which is available in 2 to 4 percent creams and gels. Laser therapy also is an option, but because of the frequency and broad distribution of these lesions, referral to a cosmetic dermatologist is appropriate.

TABLE 3
Medications That May Cause Phototoxic Reactions

- Anthranilic acids
  - Meclofenamic acid
- Antibiotics
  - Ceftazidime (Fortaz)
  - Fluoroquinolones
  - Griseofulvin (Grisactin)
  - Ketoconazole (Nizoral)
  - Nalidixic acid (NegGram)
  - Sulfonamides
  - Tetracyclines
  - Trimethoprim (Proloprim; also, in Bactrim, Septra)
- Antineoplastic agents
  - Dacarbazine (Dtic-Dome)
  - Fluorouracil (Adrucil)
  - Methotrexate
  - Vinblastine (Velban)
- Coal tar
- Diuretics
  - Bendroflumethiazide (Naturetin)
  - Furosemide (Lasix)
  - Hydrochlorothiazide (Esidrix)
- Dyes
  - Eosin
  - Fluorescein
  - Methylene blue
  - Rose bengal
- Miscellaneous
  - Amiodarone (Cordarone)
  - Desipramine (Norpramin)
  - Diltiazem (Cardizem)
  - Fibric acid derivatives
  - Imipramine (Tofranil)
  - Phenothiazines
  - Quinidine
  - Quinine
  - Sulfite food derivatives
- Nonsteroidal anti-inflammatory drugs
  - Arylpropionic acid derivatives
  - Benoxaprofen (Oraflex)
  - Carprofen (Rimadyl)
  - Ibuprofen (Motrin)
  - Ketoprofen (Orudis)
  - Nabumetone (Relafen)
  - Naproxen (Naprosyn)
  - Tiaprofenic acid (Surgam)
- Porphyrins
- Psoralens
- Pyrazolidinediones
  - Oxyphenbutazone (Phenabid)
  - Phenylbutazone (Butazolidin)
- Retinoids
  - Etretinate (Tegison)
  - Isotretinoin (Accutane)
- Salicylic acids
  - Aspirin
  - Diflunisal (Dolobid)

Adapted with permission from Gould JW, Mercurio MG, Elmets CA. Cutaneous photosensitivity diseases induced by exogenous agents. J Am Acad Dermatol 1995;33:551-73.

Lesions from Phototoxic Reactions

Hyperpigmentation can be caused by phototoxic reactions from the use of systemic or topical medications *(Table 3)*[15] or from contact with certain plants or foods in conjunction with sun exposure[16] (phytophotoder-

TABLE 4
Medications That May Cause Hyperpigmentation

Amiodarone (Cordarone)
Amitriptyline (Elavil)
Arsenic
Bismuth
Bleomycin (Blenoxane)
Busulfan (Myleran)
Clofazimine (Lamprene)
Cyclophosphamide (Cytoxan)
Daunorubicin (DaunoXome, Cerubidine)
Doxorubicin (Adriamycin)
Gold (may cause chrysiasis)
Mercury
Minocycline (Minocin)
Nitrogen mustard (topical)
Phenothiazines
Silver (may cause argyria)
Zidovudine (Retrovir)

Information from references 17, 19, and 20.

matitis). Initially, patients develop an erythematous allergic reaction. There can be an inflammatory response with lymphocytes, eosinophils, and edema, which can result in a bullous reaction on sun-exposed skin. Over time, hyperkeratosis and melanocytic hyperplasia develop, causing hyperpigmentation.[1] Some medications result directly in hyperpigmentation, without sun exposure, in a diffuse pattern[17,18] *(Table 4)*.[17,19,20] Examples of plant materials and foods that may be associated with phytophotodermatitis include lemons, limes, fig leaves or stems, celery, dill, parsnips, and carrot juice.[16]

Patients with phototoxic reactions should discontinue use of the offending medication or contact with the offending substance. If necessary, exposure to sunlight should be avoided. For cosmetic concerns, phototoxic reactions that fail to resolve spontaneously should be managed similarly to melasma, which is discussed in part II of this article.

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

Figures 2 through 6 from the Utah Valley Family Practice Residency Program, Provo.

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Common Hyperpigmentation Disorders in Adults: Part II. Melanoma, Seborrheic Keratoses, Acanthosis Nigricans, Melasma, Diabetic Dermopathy, Tinea Versicolor, and Postinflammatory Hyperpigmentation

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Nevi, or moles, are localized nevocytic tumors. The American Cancer Society's "ABCD" rules are useful for differentiating a benign nevus from malignant melanoma. While acanthosis nigricans may signal an underlying malignancy (e.g., gastrointestinal tumor), it more often is associated with insulin resistance (type 2 diabetes, polycystic ovary syndrome) or obesity. Melasma is a facial hyperpigmentation resulting from the stimulation of melanocytes by endogenous or exogenous estrogen. Treatments for melasma include bleaching agents, laser therapy, and a new medication that combines hydroquinone, tretinoin, and fluocinolone acetonide. Lesions that develop on the shins of patients with diabetic dermopathy often resolve spontaneously; no treatment is effective or recommended. Tinea versicolor responds to treatment with selenium sulfide shampoo and topical or oral antifungal agents. Postinflammatory hyperpigmentation or hypopigmentation can occur in persons of any age after trauma, skin irritation, or dermatoses. (Am Fam Physician 2003;68:1963-8. Copyright© 2003 American Academy of Family Physicians.)

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See page 1898 for definitions of strength-of-evidence levels.

Hyperpigmentation usually can be traced to the presence and activity of melanocytes. Part I of this two-part article presents a suggested approach to patients with increased pigmentation. Part II continues the review of conditions associated with hyperpigmentation.

New, Changing, or Symptomatic Localized Lesions

A localized hyperpigmented or irregularly pigmented lesion that is new in onset, arises within a congenital nevus, or causes pain or itching could be a malignant melanoma *(Figures 1 through 3)*. The American Cancer Society has developed useful guidelines for identifying suspicious nevi *(Table 1)*.[1] [Evidence level C, consensus/expert guidelines]

When possible, suspicious lesions should be excised totally for pathologic evaluation. If size or location precludes complete excision, incisional biopsy (usually punch biopsy) is performed.[2]

Seborrheic keratoses are localized, benign, hyperplastic, hyperpigmented lesions that may mimic melanomas. The hyperpigmenta-

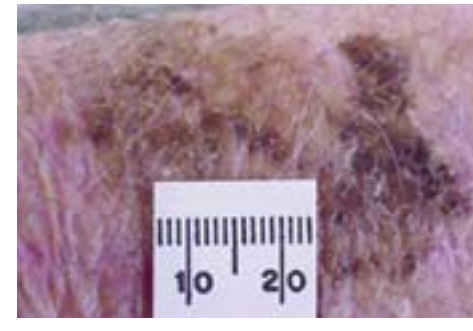

FIGURE 1. Lentigo maligna before vertical growth phase into lentigo maligna melanoma.

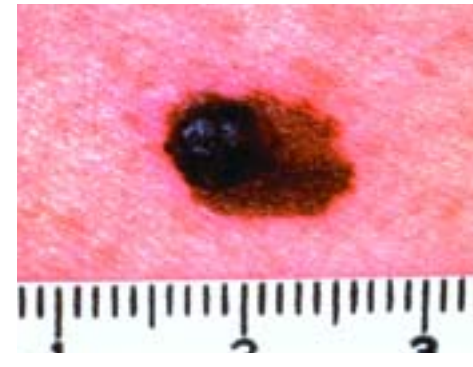

FIGURE 2. Nodular malignant melanoma.

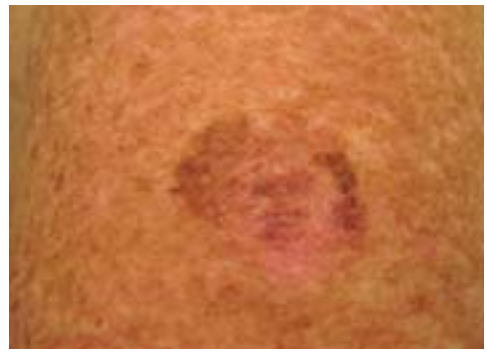

FIGURE 3. More subtle appearance of malignant melanoma.

FIGURE 5. Thickening and hyperpigmentation of the skin in acanthosis nigricans.

TABLE 1
Signs and Symptoms of Melanoma

Asymmetry. One half of the mole does not match the other half.
Border irregularity. The edges of the mole are irregular, ragged, blurred, or notched.
Color. The color over the mole is not the same. There may be differing shades of tan, brown, or black, and sometimes patches of red, blue, or white.
Diameter. The mole is larger than 6 mm (about 1/4 inch or about the size of a pencil eraser), although in recent years, physicians are finding more melanomas between 3 and 6 mm.
Other important signs of melanoma include changes in size, shape, or color of a mole or the appearance of a new spot. Some melanomas do not fit the ABCD rule described above, so it is particularly important to be aware of changes in skin lesions or new skin lesions.

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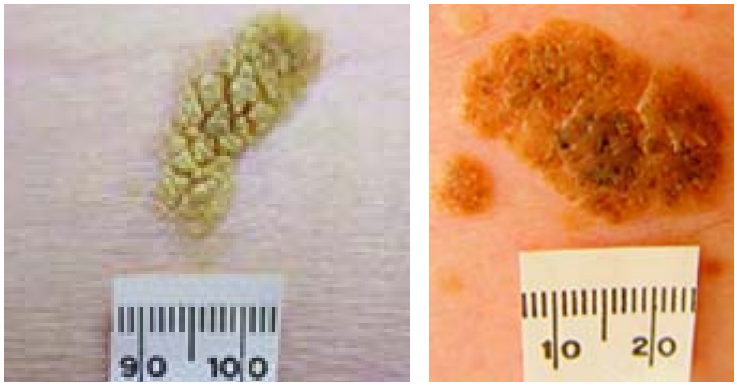

FIGURE 4. Seborrheic keratosis. *(Left)* Rough, craggy surface. *(Right)* Smooth surface with keratin "pearls."

tion is associated with hyperplasia of melanocytes.[3] Experienced physicians usually can differentiate seborrheic keratoses based on their sharp borders; tan, brown, or black color; and typical appearance. These lesions have a "stuck-on" appearance, with a surface that is rough and craggy *(Figure 4, left)* or smooth with small keratin "pearls" *(Figure 4, right)*.[4]

If seborrheic keratoses are symptomatic or there is a question about possible malignancy, the lesions should be removed and sent for pathologic evaluation.

Acanthosis Nigricans

Acanthosis nigricans, usually related to insulin resistance or obesity, ranges in appearance from a thickened, velvety brown streaking to a leathery, verrucous, papillomatous lesion *(Table 2)*. The condition commonly occurs on the neck or in skin folds (e.g., in the axilla, under the breast, at the belt line, in the groin), but it may develop in other parts of the body. Patients with this condition may complain that they have a "dirty area" that cannot be cleansed *(Figure 5)*.

Microscopically, acanthosis nigricans is characterized by an increased number of melanocytes, with papillary hypertrophy and hyperkeratosis.[5] Associated hypertrophy and hyperkeratosis cause acanthosis nigricans to be palpable rather than macular.

It is important for physicians to recognize acanthosis nigricans, because the condition

Acanthosis nigricans can be associated with insulin resistance (type 2 diabetes, polycystic ovary syndrome), obesity and, occasionally, malignancy.

can be associated with insulin resistance (as occurs in type 2 diabetes and polycystic ovary syndrome), obesity and, occasionally, malignancy. Type 2 diabetes is increasing in incidence in the United States, especially among black and hispanic children; 60 to 92 percent of these children have acanthosis nigricans.[6] According to one study[7] that compared 50 children with type 2 diabetes and 50 children with type 1 diabetes, acanthosis nigricans was present in 86 percent of the children with type 2 diabetes but in none of the children with type 1 diabetes.[7] [Evidence level B, retrospective cohort study]

If a patient rapidly develops acanthosis nigricans, especially on the palms or soles, occult malignancy is a possibility. A thorough physical examination, a review of systems, a complete blood count, fecal occult blood testing, and chest radiography should be consid-

TABLE 2
Characteristics and Treatments of Selected Hyperpigmentation Disorders

Disorder	*Appearance*	*Age of onset*	*Hormone or medication related*	*Sun or other exposure involved*	*Associated systemic complications*	*Treatment*
Acanthosis nigricans	Velvety brown color, located in axillae, on neck, and in areas of skin folds With acute onset (especially on palms or soles) in nonobese adults, evaluate carefully for malignancy.	Adolescence to adulthood	Insulin resistance	Not involved	Increased risk of diabetes, polycystic ovary syndrome, dyslipidemia and, possibly, underlying malignancy	Treat underlying disease or condition.
Melasma	Macular hyperpigmentation of cheeks, forehead, and upper lip	Adulthood	Pregnancy, use of oral contraceptive pills, phenytoin (Dilantin) therapy	Increased by sun exposure	None	Treat for cosmesis; avoid sun exposure; use bleaching agents, laser therapy, or dermabrasion.
Diabetic dermopathy	Papular pink or brown eruption evolving to macular, sometimes confluent brown eruption on anterior shins	Adulthood	Uncertain	Not involved	Multiorgan dysfunction related to underlying diabetes	Treat underlying diabetes.
Tinea versicolor	Dark or light scaly lesions, single or confluent patches on trunk	Adolescence through adulthood	Increased sebum production starting in adolescence	Hypopigmented appearance because tanning process is blocked	None	Treat with topical selenium sulfide shampoo, or topical or oral antifungal agents.
Postinflammatory hyperpigmentation	Localized, macular, brown hyperpigmentation at site of inflammation	Any age	Not related	Reaction to trauma (physical or chemical injury), skin irritation, or dermatoses	Inflammation of skin because of underlying injury or condition	Refer patient to cosmetic dermatologist.

ered if the patient does not fit the typical clinical pattern of insulin resistance.[8] [Evidence level C, consensus/expert guidelines] Adenocarcinomas are the most common malignancies found in patients with acanthosis nigricans; the tumors are most often present in the stomach (60 percent), followed by the colon, ovary, pancreas, rectum, and uterus.[9]

Treatment of acanthosis nigricans is directed at the underlying cause, rather than the appearance of the skin. If present, insulin resistance should be managed appropriately. Screening for hypercholesterolemia and coronary artery disease may be appropriate, depending on the clinical picture.

Melasma

Pregnancy or the use of hormones (e.g., oral contraceptive pills) can cause melasma, a localized facial hyperpigmentation *(Figure 6)*. Melasma may be seen in patients who take phenytoin (Dilantin). While melasma may regress after pregnancy, it may increase with each subsequent pregnancy and become quite obvious. Because of the facial location, melasma may be quite disturbing to patients.

Frequently called the "mask of pregnancy," melasma (chloasma) differs from the ruborous glow of pregnancy. Histologically, women who have this condition develop an increased number of melanocytes, with the deposition of additional melanin and a background of solar elastosis, typically on the cheeks, forehead, and upper lip.[10] Examination using a Wood's light in a darkened room demonstrates enhanced contrast if hyperpigmentation affects the epidermal layer of skin.[11]

Patients with hyperpigmentation of the superficial epidermal layer who desire treatment may attempt a trial of bleaching agents after patch testing elsewhere on the body to confirm low levels of inflammation. Use of bleaching agents on inflamed skin could lead to postinflammatory changes and further hyperpigmentation.

Tretinoin 0.1 percent (Retin-A) cream and hydroquinone (Eldoquin Forte), a bleaching agent available in 2 to 4 percent creams and gels, have been the mainstays of topical treatment. Combining tretinoin and hydroquinone (applied at different times during the day) can potentiate the effect.

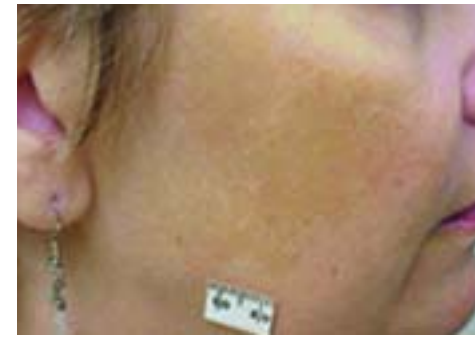

FIGURE 6. Facial hyperpigmentation of melasma.

A new medication that contains tretinoin, hydroquinone, and fluocinolone acetonide (Tri-Luma) has been effective in the treatment of melasma. In a company-sponsored, double-blind, randomized controlled trial of the triple-combination agent, 77 percent of patients showed complete or nearly complete clearing of melasma, compared with 47 percent for hydroquinone and tretinoin, 42 percent for fluocinolone acetonide and hydroquinone, and 27 percent for tretinoin and fluocinolone acetonide.[12] [Evidence level B, lower quality randomized controlled trial] The triple-combination agent should be applied daily, 30 minutes before bedtime. Azelaic acid (20 percent), kojic acid formulations, and alpha-hydroxy acids also have been useful in the treatment of melasma.[13]

Side effects of all topical treatments include allergic and contact dermatitis, depigmentation of surrounding normal skin, and postinflammatory hyperpigmentation. Tretinoin alone or combined with hydroquinone and fluocinolone acetonide should not be used during pregnancy.

If no increase in contrast is seen with use of the Wood's light, the deeper dermal tissues usually are involved, and bleaching agents will not help.[11] Laser therapy may be used for superficial epidermal or deeper dermal melasma, but strict avoidance of sun exposure is important to prevent recurrence.[14] [Evidence level C, expert opinion]

Diabetic Dermopathy

Diabetic dermopathy (pigmented pretibial papules) develops in up to 70 percent of

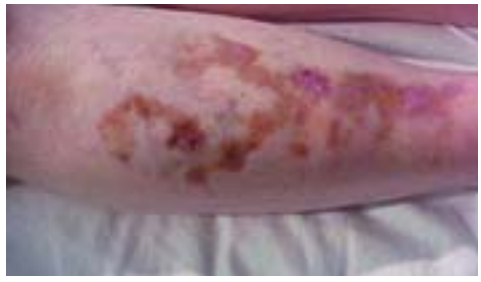

FIGURE 7. Diabetic dermopathy.

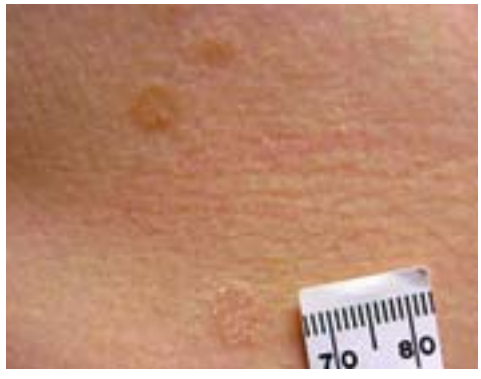

FIGURE 8. Tinea versicolor, with scaling on the inferior lesion and hyperpigmentation in the two superior lesions.

patients with diabetes.[15] This condition usually affects the skin of the anterior tibial area, where it starts as a papular pink or brown eruption and progresses to a macular, sometimes confluent, brown dermatitis, with the coloration caused by hemosiderin deposition *(Figure 7)*. The exact cause of the lesions is unknown.

The lesions of diabetic dermopathy may resolve spontaneously, even as new lesions arise. Treatment should focus on the patient's diabetes. No treatment for the asymptomatic cutaneous lesions is effective or recommended.[16]

Tinea Versicolor

While tinea versicolor is not truly a hyperpigmentation disorder, it is included in this review because affected skin on the trunk may appear darker than normal. Tinea versicolor rarely occurs until after adolescence, when production of sebum increases, especially in the skin of the anterior trunk and back. The increased sebum production allows the proliferation of *Pityrosporum ovale* or *Pityrosporum orbiculare (Malassezia furfur)*,[17] which can cause a brown, pink, or reddish discoloration of the skin.

Technically a papulosquamous eruption, tinea versicolor presents as numerous macules or slightly raised papules with subtle scale. Patients may have a coalescence of lesions or a single patch with an irregular border. The lesions of tinea versicolor may be several centimeters in diameter, or they may cover most of the trunk.

Over time, the Pityrosporum species can block the conversion of tyrosine to melanin,[18] leading to hypopigmented patches instead of increased coloration. The scale on the surface of the affected skin *(Figure 8)* and the "spaghetti and meatball" appearance of fungal forms on a potassium hydroxide preparation help to clarify the diagnosis.

Tinea versicolor may be treated with topical selenium sulfide shampoo in a daily or weekly treatment regimen. Once a day for one week, the selenium sulfide shampoo is allowed to dry on the affected skin for 10 minutes before the patient showers. Alternatively, once a week for four weeks, the selenium sulfide shampoo is left on the skin for 12 to 24 hours, after which time the patient showers.

Topical antifungal agents (e.g., allylamines, azoles, undecenoic acid) also are effective therapies for tinea versicolor.[19] [Evidence level A, Cochrane review] Because of the amount of topical medication required and the length of treatment (several weeks), orally administered agents have been studied and found to be effective.[20] [Evidence level A, Cochrane review] A 2 percent ketoconazole shampoo, left in place for five minutes, has been shown to have a cure rate of 69 percent after one application.[21]

Postinflammatory Hyperpigmentation

Trauma (physical or chemical injury), skin irritation, and dermatoses can lead to postinflammatory hyperpigmentation or hypopig-

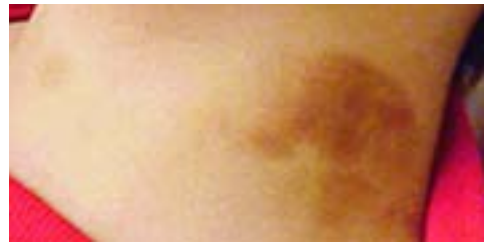

FIGURE 9. Postinflammatory hyperpigmentation.

mentation in persons of any age. Investigators in one study[22] theorized that some persons have an inherited tendency for weak melanocytes that respond to inflammation by decreasing melanin production, or for strong melanocytes that respond by increasing melanin production. While more effect is evident when lighter-skinned persons respond with hyperpigmentation *(Figure 9)* or darker-skinned persons respond with hypopigmentation, persons of all races can respond to inflammation with hyperpigmentation or hypopigmentation.

With time and resolution of the inflammation, the pigmentary changes usually tend to normalize. If cosmesis is desired, it should be performed by a physician with experience in cosmetic dermatology, because treatments such as bleaching agents can cause further postinflammatory pigmentary changes.

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

Figures 1 and 4 through 9 from the Utah Valley Family Practice Residency Program, Provo. Figure 2 from the Skin Cancer Foundation, New York City. Figure 3 from Adam Goldstein, M.D., University of North Carolina at Chapel Hill School of Medicine.

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