56 - 61 Skin Manifestations of Internal Disease

61 Skin Manifestations of Internal Disease

■ ■FURTHER READING Bolognia JL et al (eds): Dermatology, 4th ed. Philadelphia, Elsevier,

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James WD et al (eds): Andrew’s Diseases of the Skin Clinical Dermatology, 13th ed. Philadelphia, Elsevier, 2020. Kang S et al (eds): Fitzpatrick’s Dermatology, 9th ed. New York, McGraw-Hill, 2019. Wolff K et al (eds): Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology, 8th ed. New York, McGraw-Hill, 2017. PART 2 Cardinal Manifestations and Presentation of Diseases Jean L. Bolognia, Jonathan S. Leventhal,

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Skin Manifestations of

Internal Disease It is a generally accepted concept in medicine that the skin can develop signs of internal disease. Therefore, in textbooks of medicine, one finds a chapter describing in detail the major systemic disorders that can be identified by cutaneous signs. The underlying assumption of such a chapter is that the clinician has been able to identify the specific disorder in the patient and needs only to read about it in the textbook. In reality, concise differential diagnoses and the identification of these disorders are actually difficult for nondermatologists because they are not well-versed in the recognition of cutaneous lesions or their spec trum of presentations. Therefore, this chapter covers this particular topic of cutaneous medicine not by simply focusing on individual dis eases, but by describing the various presenting clinical signs and symp toms that point to specific disorders. Concise differential diagnoses will be generated in which the significant diseases will be distinguished from the more common cutaneous disorders that have minimal or no significance with regard to associated internal disease. The latter disorders are reviewed in table form and always need to be excluded when considering the former. For a detailed description of individual diseases, the reader should consult a dermatologic text. PAPULOSQUAMOUS SKIN LESIONS (Table 61-1) When an eruption is characterized by elevated lesions, either papules (<1 cm) or plaques (>1 cm), in association with scale, it is referred to as papulosquamous. The most common papulosqua mous diseases—tinea, psoriasis, pityriasis rosea, and lichen planus—are primary cutaneous disorders (Chap. 60). When psoriatic lesions are accompanied by arthritis, the possibility of psoriatic arthritis or reac tive arthritis should be considered. A history of oral ulcers, conjuncti vitis, uveitis, and/or urethritis points to the latter diagnosis. Lithium, beta blockers, anti-

PD-1/PD-L1 antibodies, HIV or streptococcal infections, and a rapid taper of systemic glucocorticoids are known to exacerbate psoriasis; despite being used to treat psoriasis, tumor necro sis factor (TNF) inhibitors can paradoxically induce psoriatic lesions. Comorbidities in patients with psoriasis include cardiovascular disease and metabolic syndrome. Whenever the clinical diagnosis of pityriasis rosea or lichen planus is made, it is important to review the patient's medications because the eruption may resolve by simply discontinuing the offending agent. Pityriasis rosea–like drug eruptions are seen most commonly with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and metronidazole, whereas the drugs that can produce a lichenoid erup tion include thiazides, antimalarials, quinidine, beta blockers, TNF inhibitors, anti-PD-1/PD-L1 antibodies, and ACE inhibitors. In some populations (e.g., Europeans), there is a higher prevalence of hepatitis

TABLE 61-1 Selected Causes of Papulosquamous Skin Lesions

1. Primary cutaneous disorders a. Tineaa—widespread disease may be sign of immunosuppression b. Psoriasisa—widespread or resistant disease may be sign of HIV infection c. Pityriasis roseaa d. Lichen planusa e. Parapsoriasis, small plaque and large plaqueb f. Bowen's disease (squamous cell carcinoma in situ)c
2. Drugs
3. Systemic diseases a. Lupus erythematosus, primarily subacute or chronic (discoid) lesionsd b. Cutaneous T-cell lymphoma, in particular, mycosis fungoidese c. Secondary syphilis d. Reactive arthritis e. Sarcoidosisf—with scale less common than without scale f. Bazex syndrome (acrokeratosis paraneoplastica)g aDiscussed in detail in Chap. 60; cardiovascular disease and the metabolic syndrome are comorbidities in psoriasis; primarily in Europe, hepatitis C virus is associated with oral lichen planus. bSome authors view large plaque parapsoriasis as a form of early mycosis fungoides. cAssociated with chronic sun exposure more often than exposure to arsenic; usually one or a few lesions. dSee also Red Lesions in "Papulonodular Skin Lesions." eAlso cutaneous lesions of HTLV-1-associated adult T-cell leukemia/lymphoma. fSee also Red-Brown Lesions in "Papulonodular Skin Lesions." gPsoriasiform lesions of the helices, nose, and acral sites; squamous cell carcinoma of the upper aerodigestive tract most common underlying malignancy. Abbreviation: HIV, human immunodeficiency virus. C viral infection in patients with oral lichen planus. Lichen planus–like lesions are also observed in chronic graft-versus-host disease. In its early stages, the mycosis fungoides (MF) form of cutaneous T-cell lymphoma (CTCL) may be confused with eczema or psoriasis, but it often eventually fails to respond to appropriate therapy for those inflammatory diseases. MF can develop within lesions of large-plaque parapsoriasis and is suggested by an increase in the thickness of the lesions. The diagnosis of MF is established by skin biopsy in which collections of atypical T lymphocytes are found in the epidermis and dermis and is supported by TCR gene rearrangements. As the disease progresses, cutaneous tumors and lymph node involvement may appear. In secondary syphilis, there are scattered pink to red-brown papules with thin scale. The eruption often involves the palms and soles and can resemble pityriasis rosea. Associated findings are helpful in making the diagnosis and include nonscarring alopecia, annular plaques on the face, mucous patches, condyloma lata (broad-based and moist), and lymphadenopathy, as well as malaise, fever, headache, and myalgias. The interval between the primary chancre and the secondary stage is

usually 4–8 weeks, and spontaneous resolution without appropriate therapy occurs. ERYTHRODERMA (Table 61-2) Erythroderma is the term used when the majority of the skin surface is erythematous (red in color). Erythema may be more dif ficult to appreciate in darkly pigmented skin. There may be associated scale, erosions, or pustules as well as shedding of the hair and nails. Potential systemic manifestations include fever, chills, hypothermia, reactive lymphadenopathy, peripheral edema, hypoalbuminemia, and high-output cardiac failure. The major etiologies of erythroderma are (1) cutaneous diseases such as psoriasis and dermatitis (Table 61-3); (2) drugs; (3) systemic diseases, most commonly CTCL; and (4) idio pathic. In the first three groups, the location and description of the initial lesions, prior to the development of the erythroderma, aid in the diagnosis. For example, a history of red scaly plaques on the elbows and knees would point to psoriasis. It is also important to examine the skin carefully for a migration of the erythema and associated second ary changes such as pustules or erosions. Migratory waves of erythema studded with superficial pustules are seen in pustular psoriasis.

TABLE 61-2 Causes of Erythroderma

1. Primary cutaneous disorders a. Psoriasisa b. Dermatitis (atopic > contact >> stasis [with autosensitization] or seborrheic [primarily infants])a c. Pityriasis rubra pilaris
2. Drugs
3. Systemic diseases a. Cutaneous T-cell lymphoma (Sézary syndrome, erythrodermic mycosis fungoides) b. Other lymphomas c. Rarely, late-stage solid tumors, autoimmune bullous diseases
4. Idiopathic (usually older men) aDiscussed in detail in Chap. 60. TABLE 61-3 Erythroderma (Primary Cutaneous Disorders) LOCATION OF INITIAL LESIONS OTHER FINDINGS DIAGNOSTIC AIDS TREATMENT INITIAL LESIONS Psoriasisa Pink-red, silvery scale, sharply demarcated Elbows, knees, scalp, presacral area, intergluteal fold Nail dystrophy (e.g., pits, oil drop sign), arthritis, pustules, SAPHO syndromeb Dermatitisa Atopic Acute: Erythema, fine scale, crust, indistinct borders, excoriations Chronic: Lichenification (increased skin markings), excoriations Antecubital and popliteal fossae, neck, hands, eyelids Pruritus Personal and/or family history of atopy, including asthma, allergic rhinitis or conjunctivitis, and atopic dermatitis Exclude secondary infection with Staphylococcus aureus or HSV Exclude superimposed irritant or allergic contact dermatitis Contact Local: Erythema, crusting, vesicles, and bullae Depends on offending agent Irritant—onset often within hours Allergic—delayed-type hypersensitivity; lag time of 48 h with rechallenge Patient has history of allergic contact dermatitis to topical agent and then receives systemic medication that is structurally related, e.g., formaldehyde (skin), aspartame (oral) Systemic: Erythema, fine scale, crust Generalized vs major intertriginous zones (especially groin) Seborrheic (rare in adults) Pink-red to pinkorange, greasy scale Scalp, nasolabial folds, eyebrows, intertriginous zones Flares with stress, HIV infection Associated with Parkinson’s disease Stasis (with autosensitization) Erythema, crusting, excoriations Lower extremities Pruritus, lower extremity edema, varicosities, hemosiderin deposits, lipodermatosclerosis History of venous ulcers, thrombophlebitis, and/or cellulitis Exclude cellulitis Exclude superimposed contact dermatitis, e.g., topical neomycin Pityriasis rubra pilaris Orange-red (salmon-colored), perifollicular papules Scalp When generalized, characteristic “skip” areas of uninvolved skin Wax-like palmoplantar

keratoderma Exclude cutaneous T-cell lymphoma aDiscussed in detail in Chap. 60. bSAPHO syndrome occurs more commonly in patients with palmoplantar pustulosis than in those with erythrodermic psoriasis. Abbreviations: Ab, antibody; HSV, herpes simplex virus; IL, interleukin; IM, intramuscular; MTX, methotrexate; PUVA, psoralens plus ultraviolet A irradiation; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis (a subtype is chronic recurrent multifocal osteomyelitis); TNF, tumor necrosis factor; UV-A, ultraviolet A irradiation; UV-B, ultraviolet B irradiation.

Drug-induced erythroderma may begin as an exanthematous (mor billiform) eruption (Chap. 63) or may arise as diffuse erythema. A number of drugs can produce an erythroderma, including penicil lins, sulfonamides, aromatic anticonvulsants (e.g., carbamazepine, phenytoin), and allopurinol. Fever and peripheral eosinophilia often accompany the eruption, and there may also be facial swelling, hepa titis, allergic interstitial nephritis, myocarditis, and delayed thyroiditis; this constellation is frequently referred to as drug reaction with eosino philia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS). In addition, these reactions, especially to aromatic anticonvulsants, can lead to a pseudolymphoma syndrome with adenopathy and circulating atypical lymphocytes, while reactions to allopurinol may be accompanied by gastrointestinal bleeding.

Skin Manifestations of Internal Disease CHAPTER 61 The most common malignancy that is associated with erythroderma is CTCL; in some series, up to 25% of the cases of erythroderma were Skin biopsy Topical glucocorticoids, vitamin D analogues, aryl hydrocarbon receptor agonist, PDE4 inhibitor; UV-B (narrowband) > PUVA; oral retinoids; MTX; anti-TNF agents, anti-IL-12/23 Ab, anti-IL-23 Ab, anti-IL-17A, anti-IL-17F, or anti-IL-17 receptor A Ab; TYK2 inhibitor; apremilast; cyclosporine; anti-IL-36 receptor Ab for generalized pustular psoriasis Skin biopsy Topical glucocorticoids, tacrolimus, pimecrolimus, crisaborole, JAK inhibitors, and antipruritics; oral antihistamines for sedation; open wet dressings; UV-B ± UV-A > PUVA; anti-IL-4R alpha Ab, anti-IL-13 Ab; JAK inhibitors, e.g. abrocitinib, upadacitinib; oral/ IM glucocorticoids (short-term); MTX; mycophenolate mofetil; azathioprine; cyclosporine Topical or oral antibiotics Patch testing; repeat open application test Remove irritant or allergen; topical glucocorticoids; oral antihistamines; oral/ IM glucocorticoids (short-term) Patch testing Same as local Skin biopsy Topical glucocorticoids and imidazoles Skin biopsy Topical glucocorticoids; open wet dressings; leg elevation; pressure stockings; pressure wraps if associated ulcers Skin biopsy Isotretinoin or acitretin; MTX; anti-IL-12/23 Ab, anti-IL-23 Ab, anti-TNF agents, anti-IL17A, anti-IL-17F, or -IL-17 receptor A Ab

TABLE 61-4 Causes of Alopecia I. Nonscarring alopecia A. Primary cutaneous disorders

1. Androgenetic alopecia (female pattern, male pattern)
2. Telogen effluvium
3. Alopecia areata
4. Tinea capitis
5. Traumatic alopeciaa
6. Psoriasiform alopecia, including tumor necrosis factor (TNF) inhibitor–induced B. Drugs PART 2 Cardinal Manifestations and Presentation of Diseases
7. Telogen effluvium—see text for most common causes
8. Anagen effluvium—chemotherapeutic agents (e.g., anthracyclines) C. Systemic diseases

9. Systemic lupus erythematosus
10. Secondary syphilis
11. Hypothyroidism
12. Hyperthyroidism
13. Hypopituitarism
14. Deficiencies of protein, biotin, zinc, and perhaps iron II. Scarring alopecia A. Primary cutaneous disorders
15. Cutaneous lupus (chronic discoid lesions)b
16. Lichen planus, including frontal fibrosing alopecia
17. Central centrifugal cicatricial alopecia
18. Folliculitis decalvans
19. Dissecting cellulitis
20. Linear morphea (linear scleroderma)c B. Drugs
21. Chemotherapeutic agents (e.g., taxanes, busulfan) C. Systemic diseases
22. Discoid lesions in the setting of systemic lupus erythematosusb
23. Sarcoidosis
24. Cutaneous metastases aMost patients with trichotillomania or early stages of traction alopecia and some patients with pressure-induced alopecia. bWhile the majority of patients with discoid lesions have only cutaneous disease, these lesions do represent one of the criteria in the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) [2019] and ACR [1982] classification schemes for systemic lupus erythematosus. cCan involve underlying muscles and osseous structures, and rarely in linear morphea of the frontal scalp (en coup de sabre), there is involvement of the meninges and brain. due to CTCL. The patient may progress from isolated plaques and tumors, but more commonly, the erythroderma is present throughout the course of the disease (Sézary syndrome). In Sézary syndrome, there are circulating clonal atypical T lymphocytes, pruritus, and lymphade nopathy. In cases of erythroderma where there is no apparent cause (idiopathic), longitudinal evaluation is mandatory to monitor for the possible development of CTCL. ALOPECIA (Table 61-4) The two major forms of alopecia are scarring and non scarring. Scarring alopecia is associated with fibrosis, inflammation, and loss of hair follicles. A smooth scalp with a decreased number of follicular openings is usually observed clinically, but in some patients, the changes are seen only in biopsy specimens from affected areas. In nonscarring alopecia, the hair shafts are absent or miniaturized, but the hair follicles are preserved, explaining the reversible nature of nonscar ring alopecia. The most common causes of nonscarring alopecia include androge netic alopecia, telogen effluvium, alopecia areata, tinea capitis, and the early phase of traumatic alopecia (Table 61-5). In women with andro genetic alopecia, an elevation in circulating levels of androgens may be seen as a result of ovarian or adrenal gland dysfunction or neoplasm. When there are signs of virilization, such as a deepened voice and/or

enlarged clitoris, the possibility of an ovarian or adrenal gland tumor should be considered. Exposure to various drugs can also cause diffuse hair loss, usually by inducing a telogen effluvium. An exception is the anagen effluvium observed with chemotherapeutic agents such as daunorubicin. Alope cia is a side effect of the following drugs: warfarin, heparin, propyl thiouracil, carbimazole, isotretinoin, acitretin, lithium, beta blockers, interferons, colchicine, and

amphetamines. Fortunately, spontaneous regrowth usually follows discontinuation of the offending agent. Less commonly, nonscarring alopecia is associated with lupus erythe matosus and secondary syphilis. In systemic lupus, there are two forms of alopecia—one is scarring secondary to discoid lesions (see below), and the other is nonscarring. The latter form coincides with flares of systemic disease and may involve the entire scalp or just the frontal scalp, with the appearance of multiple short hairs (“lupus hairs”) as a sign of initial regrowth. Scattered, poorly circumscribed patches of alopecia with a “moth-eaten” appearance are a manifestation of the sec ondary stage of syphilis. Diffuse thinning of the hair is also associated with hypothyroidism and hyperthyroidism (Table 61-4). Scarring alopecia is more frequently the result of a primary cutane ous disorder such as lichen planus, chronic cutaneous (discoid) lupus, central centrifugal cicatricial alopecia, folliculitis decalvans, or linear scleroderma (morphea) than it is a sign of systemic disease. Although the scarring lesions of discoid lupus can be seen in patients with sys temic lupus, in the majority of patients, the disease process is limited to the skin. Less common causes of scarring alopecia include sarcoidosis (see “Papulonodular Skin Lesions,” below), chemotherapeutic agents, and cutaneous metastases. In the early phases of discoid lupus, lichen planus, and folliculitis decalvans, there are circumscribed areas of alopecia. Fibrosis and subsequent loss of hair follicles are observed primarily in the center of these alopecic patches, whereas the inflammatory process is most prominent at the periphery. The areas of active inflammation in dis coid lupus are erythematous with scale, whereas the areas of previous inflammation are often hypopigmented with a rim of hyperpigmenta tion. In lichen planus, perifollicular macules at the periphery are usually violet-colored. A complete examination of the skin and oral mucosa combined with a biopsy and direct immunofluorescence microscopy of inflamed skin will aid in distinguishing these two entities. The periph eral active lesions in folliculitis decalvans are follicular pustules; these patients can develop a reactive arthritis. FIGURATE SKIN LESIONS (Table 61-6) In figurate eruptions, the lesions form rings and arcs that are usually erythematous but can be skin-colored to brown. Most commonly, they are due to primary cutaneous diseases such as tinea, urticaria, granuloma annulare, and erythema annulare centrifugum (Chaps. 60 and 62). An underlying systemic illness is found in a sec ond, less common group of migratory annular erythemas. It includes erythema migrans, erythema gyratum repens, erythema marginatum, and necrolytic migratory erythema. In erythema gyratum repens, one sees numerous mobile concentric arcs and wavefronts that resemble the grain in wood. A search for an underlying malignancy is mandatory in a patient with this eruption. Erythema migrans is the cutaneous manifestation of Lyme disease, which is caused by the spirochete Borrelia burgdorferi. In the initial stage (3–30 days after the tick bite, which may go unnoticed), a single annular lesion is usually seen that can expand to ≥10 cm in diameter. Primary EM, as defined by the CDC, has a diameter of ≥5 cm. Within several days, up to half of the patients develop multiple smaller ery thematous lesions at sites distant from the bite. Associated symptoms include fever, headache, photophobia, myalgias, arthralgias, and malar rash. Erythema marginatum is seen in patients with rheumatic fever, primarily on the trunk. Lesions are pink-red in color, flat to minimally elevated, and transient. There are additional cutaneous diseases that present as annular eruptions but lack an obvious migratory component. Examples include CTCL, subacute cutaneous lupus, secondary syphilis, and sarcoidosis (see “Papulonodular Skin Lesions,” below).

TABLE 61-5 Nonscarring Alopecia (Primary Cutaneous Disorders) CLINICAL CHARACTERISTICS PATHOGENESIS TREATMENT Telogen effluvium Diffuse shedding of normal hairs Follows major stress (high fever, severe infection) or change in hormone levels (postpartum) Reversible without

treatment Androgenetic alopecia (male pattern; female pattern) Miniaturization of hairs along the midline of the scalp Recession of the anterior scalp line in men and some women Alopecia areata Well-circumscribed, circular areas of hair loss, 2–5 cm in diameter In extensive cases, coalescence of lesions and/or involvement of other hair-bearing surfaces of the body Pitting or sandpapered appearance of the nails Tinea capitis Varies from scaling with minimal hair loss to discrete patches with “black dots” (sites of broken infected hairs) to boggy plaque with pustules (kerion)b Traumatic alopeciac Broken hairs, often of varying lengths Irregular outline in trichotillomania and traction alopecia Fringe sign in traction alopecia aTo date, Food and Drug Administration–approved for men. bScarring alopecia can occur at sites of kerions. cMay also be scarring, especially late-stage traction alopecia. ACNE (Table 61-7) In addition to acne vulgaris and acne rosacea, the two major forms of acne (Chap. 60), there are drugs and systemic diseases that can lead to acneiform eruptions. Patients with the carcinoid syndrome have episodes of flushing of the head, neck, and sometimes the trunk. Resultant skin changes of the TABLE 61-6 Causes of Figurate Skin Lesions I. Primary cutaneous disorders A. Tinea B. Urticaria (primary in ≥90% of patients) C. Granuloma annulare D. Erythema annulare centrifugum E. Psoriasis, annular pustular psoriasis F. Reactive granulomatous dermatitis, which includes interstitial granulomatous drug reaction II. Systemic diseases A. Migratory

1. Erythema migrans (CDC case definition is ≥5 cm in diameter)
2. Urticaria (≤10% of patients)
3. Erythema gyratum repens
4. Erythema marginatum
5. Pustular psoriasis (generalized and annular forms)
6. Necrolytic migratory erythema (glucagonoma syndrome)a B. Nonmigratory (may slowly expand)
7. Subacute cutaneous LE, LE tumidus
8. Sarcoidosis
9. Leprosy (borderline, tuberculoid)
10. Secondary syphilis (especially the face)
11. Cutaneous T-cell lymphoma (especially mycosis fungoides)
12. Interstitial granulomatous dermatitisb
13. Annular erythema of Sjögren’s syndrome aMigratory erythema with erosions; favors lower extremities and girdle area. bUnderlying diseases include rheumatoid arthritis, LE, granulomatosis with polyangiitis, and hematologic disorders, in particular myelodysplasia and chronic myelomonocytic leukemia. Abbreviations: CDC, Centers for Disease Control and Prevention; LE, lupus erythematosus.

Stress causes more of the asynchronous growth cycles of individual hairs to become synchronous; therefore, larger numbers of growing (anagen) hairs simultaneously enter the dying (telogen) phase Observation; discontinue any drugs that have alopecia as a side effect; must exclude underlying metabolic causes, e.g., hypothyroidism, hyperthyroidism Increased sensitivity of affected hairs to the effects of androgens—most common Increased levels of circulating androgens (ovarian or adrenal source in women)—less common If no evidence of hyperandrogenemia, then topical minoxidil; low-dose oral minoxidil; finasteridea; spironolactone (women); hair transplant Skin Manifestations of Internal Disease CHAPTER 61 The germinative zones of the hair follicles are surrounded by T lymphocytes Occasional associated diseases: hyperthyroidism, hypothyroidism,

vitiligo, Down syndrome Intralesional glucocorticoids; topical anthralin or tazarotene; topical contact sensitizers; JAK inhibitors; pulse prednisone (e.g., 300 mg orally once a month for 4–6 doses) Invasion of hairs by dermatophytes, most commonly Trichophyton tonsurans Oral griseofulvin or terbinafine plus 2.5% selenium sulfide or ketoconazole shampoo; examine family members Traction with curlers, rubber bands, tight braiding Exposure to heat or chemicals (e.g., hair straighteners) Mechanical pulling (trichotillomania) Discontinuation of offending hair style or chemical treatments; diagnosis of trichotillomania may require observation of shaved hairs (for growth) or biopsy, possibly followed by psychotherapy face, in particular telangiectasias, may mimic the clinical appearance of erythematotelangiectatic acne rosacea. PUSTULAR LESIONS Acneiform eruptions (see “Acne,” above) and folliculitis represent the most common pustular dermatoses. An important consideration in the evaluation of follicular pustules is a determination of the associated pathogen, for example, normal flora (culture-negative), Staphylococcus aureus, Pseudomonas aeruginosa (“hot tub” folliculitis), Malassezia, dermatophytes (Majocchi’s granuloma), and Demodex spp. Noninfec tious forms of folliculitis include HIV- or immunosuppression-associated eosinophilic folliculitis and folliculitis secondary to drugs such as glu cocorticoids, lithium, and epidermal growth factor receptor (EGFR) or MEK inhibitors. Administration of high-dose systemic glucocorticoids can result in a widespread eruption of follicular pustules on the trunk, characterized by lesions in the same stage of development. With regard to underlying systemic diseases, nonfollicular-based pustules are a characteristic component of pustular psoriasis (sterile) and can be seen in septic emboli of bacterial or fungal origin (see “Purpura,” below). In patients with acute generalized exanthematous pustulosis (AGEP) due primarily to medications (e.g., cephalosporins), there are large TABLE 61-7 Causes of Acneiform Eruptions I. Primary cutaneous disorders A. Acne vulgaris B. Acne rosacea II. Drugs, e.g., anabolic steroids, glucocorticoids, lithium, EGFR inhibitors, HER2 inhibitors, MEK inhibitors, iodides III. Systemic diseases A. Increased androgen production

1. Adrenal origin, e.g., Cushing’s disease, 21-hydroxylase deficiency
2. Ovarian origin, e.g., polycystic ovary syndrome, ovarian hyperthecosis B. Cryptococcosis, disseminated C. Dimorphic fungal infections D. Behçet’s disease Abbreviations: EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MEK, MAP (mitogen-activated protein) kinase.

areas of erythema studded with multiple sterile pustules in addition to neutrophilia.

TELANGIECTASIAS (Table 61-8) To distinguish the various types of telangiectasias, it is important to examine the shape and configuration of the dilated blood vessels. Linear telangiectasias are seen on the face of patients with actinically damaged skin and acne rosacea, and they are found on the legs of patients with venous hypertension and first appear on the legs in generalized essential telangiectasia. Patients with an unusual form of mastocytosis (telangiectasia macularis eruptiva perstans) and the carcinoid syndrome (see “Acne,” above) also have linear telangiectasias. Lastly, linear telangiectasias are found in areas of cutaneous inflam mation. For example, longstanding lesions of discoid lupus frequently have telangiectasias within them. PART 2 Cardinal Manifestations and Presentation of Diseases Poikiloderma is a term used to describe a patch of skin with: (1) reticulated hypo- and hyperpigmentation, (2) wrinkling secondary to epidermal atrophy, and (3) telangiectasias. Poikiloderma does not imply a single disease entity—although it is becoming less common, it is seen in skin damaged by ionizing radiation as well as in patients with

autoimmune connective tissue diseases, primarily dermatomyositis (DM), and rare genodermatoses (e.g., Kindler syndrome). In systemic sclerosis (scleroderma), the dilated blood vessels have a unique configuration and are known as mat telangiectasias. The lesions are broad macules that usually measure 2–7 mm in diameter but occasionally are larger. Mats have a polygonal or oval shape, and their erythematous color may appear uniform, but, upon closer inspection, TABLE 61-8 Causes of Telangiectasias I. Primary cutaneous disorders A. Linear/branching

1. Acne rosacea (face)
2. Actinically damaged skin (face, neck, V of chest)
3. Venous hypertension (legs)
4. Generalized essential telangiectasia
5. Cutaneous collagenous vasculopathy
6. Within basal cell carcinomas or cutaneous lymphoma B. Poikiloderma
7. Ionizing radiationa C. Spider angioma
8. Idiopathic
9. Pregnancy II. Systemic diseases A. Linear/branching
10. Carcinoid (head, neck, upper trunk)
11. Ataxia-telangiectasia (bulbar conjunctivae, head and neck)
12. Mastocytosis (within lesions) B. Poikiloderma
13. Dermatomyositis, lupus erythematosus
14. Mycosis fungoides, patch stage
15. Genodermatoses, e.g., xeroderma pigmentosum, Kindler syndrome C. Mat
16. Systemic sclerosis (scleroderma) D. Nailfold
17. Lupus erythematosus
18. Systemic sclerosis (scleroderma)
19. Dermatomyositis
20. Hereditary hemorrhagic telangiectasia E. Papular
21. Hereditary hemorrhagic telangiectasia F. Spider angioma
22. Cirrhosisb
23. Trastuzumab emtansine (may also involve mucosae) aBecoming less common. bDue to hyperestrogenic state.

the erythema is the result of delicate telangiectasias. The most com mon locations for mat telangiectasias are the face, oral mucosa, and hands—peripheral sites that are prone to intermittent ischemia. The limited form of systemic sclerosis, also referred to as the CREST (cal cinosis cutis, Raynaud’s phenomenon, esophageal dysmotility, sclero dactyly, and telangiectasia) variant (Chap. 372), is associated with a chronic course and anticentromere antibodies. Mat telangiectasias are an important clue to the diagnosis of this variant as well as the diffuse form of systemic sclerosis because they may be the only cutaneous finding. Proximal nailfold telangiectasias are pathognomonic signs of the three major autoimmune connective tissue diseases: lupus erythemato sus, systemic sclerosis, and DM. They are easily visualized by the naked eye and occur in at least two-thirds of these patients. In both DM and lupus, there is associated nailfold erythema, and in DM, the erythema is often accompanied by “ragged” cuticles and fingertip tenderness. Under 10× magnification or by dermoscopy, the blood vessels in the nailfolds of lupus patients are tortuous and resemble “glomeruli,” whereas in systemic sclerosis

and DM, there is a loss of capillary loops and those that remain are markedly dilated. In hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber disease), the lesions usually appear during adolescence (mucosal) and adulthood (cutaneous) and are most commonly seen on the mucous membranes (nasal, orolabial), face, and distal extremities, including under the nails. They represent arteriovenous (AV) mal formations of the dermal microvasculature, are dark red in color, and are usually slightly elevated. When the skin is stretched over an individual lesion, an eccentric punctum with radiating legs is seen. Although the degree of systemic involvement varies in this auto somal dominant disease (due primarily to mutations in either the endoglin or activin receptor–like kinase gene), the major symptoms are recurrent epistaxis and gastrointestinal bleeding. The fact that these mucosal telangiectasias are actually AV communications helps to explain their tendency to bleed. HYPOPIGMENTATION (Table 61-9) Disorders of hypopigmentation are often classified as either diffuse or localized. The classic example of diffuse hypopigmen tation is oculocutaneous albinism (OCA). The most common forms are due to mutations in the tyrosinase gene (type I) or the OCA2 (previously P) gene (type II); patients with type IA OCA have a total lack of enzyme activity. At birth, different forms of OCA can appear similar—white hair, gray-blue eyes, and pink-white skin. However, the patients with no tyrosinase activity maintain this phenotype, whereas those with decreased activity will acquire some pigmentation of the eyes, hair, and skin as they age. The degree of pigment formation is also a function of racial background, and the pigmentary dilution is more readily apparent when patients are compared to their first-degree relatives. The ocular findings in OCA correlate with the degree of hypopigmen tation and include decreased visual acuity, nystagmus, photophobia, strabismus, and a lack of normal binocular vision. The differential diagnosis of localized hypomelanosis includes the following primary cutaneous disorders: postinflammatory hypopigmentation, idiopathic guttate hypomelanosis, pityriasis (tinea) versicolor, vitiligo, chemical- or drug-induced leukoderma, nevus depigmentosus (see below), progressive macular hypomelanosis, and piebaldism (Table 61-10). In this group of diseases, the areas of involvement are macules or patches with a decrease or absence of pigmentation. Patients with vitiligo also have an increased incidence of several autoimmune disorders, including Hashimoto’s thyroiditis, Graves’ disease, pernicious anemia, Addison’s disease, uveitis, alope cia areata, chronic mucocutaneous candidiasis, and the autoimmune polyendocrine syndromes (types I and II). Diseases of the thyroid gland are the most frequently associated disorders, occurring in up to 30% of patients with vitiligo. Circulating autoantibodies are often found, and the most common ones are antithyroglobulin, antimi crosomal, and antithyroid-stimulating hormone receptor antibodies. There are four systemic diseases that should be considered in a patient with skin findings suggestive of vitiligo—systemic sclerosis,

TABLE 61-9 Causes of Hypopigmentation I. Primary cutaneous disorders A. Diffuse

1. Generalized vitiligoa B. Localized
2. Postinflammatory
3. Idiopathic guttate hypomelanosis
4. Pityriasis (tinea) versicolor
5. Vitiligoa
6. Chemical- or drug-induced leukoderma, e.g., topical imiquimod, oral imatinib
7. Nevus depigmentosus and Blaschko-linear hypopigmentation (pigmentary mosaicism)b
8. Progressive macular hypomelanosis
9. Piebaldisma II. Systemic diseases A. Diffuse

10. Oculocutaneous albinismb
11. Hermansky-Pudlak syndromeb,c
12. Chédiak-Higashi syndromeb,d
13. Phenylketonuria B. Localized
14. Systemic sclerosis (scleroderma)e
15. Melanoma-associated vitiligo-like leukoderma, immunotherapyinduced or spontaneouse
16. Sarcoidosis
17. Cutaneous T-cell lymphoma (especially mycosis fungoides)
18. Tuberculoid and indeterminate leprosy
19. Onchocerciasise
20. Blaschko-linear hypopigmentation (pigmentary mosaicism)b,f
21. Incontinentia pigmenti (stage IV)
22. Tuberous sclerosis
23. Waardenburg syndrome and Shah-Waardenburg syndrome
24. Vogt-Koyanagi-Harada syndromee aAbsence of melanocytes in areas of leukoderma; congenital in piebaldism. bNormal number of melanocytes. cPlatelet storage defect and restrictive lung disease secondary to deposits of ceroid-like material or immunodeficiency; due to mutations in β or δ subunit of adaptor-related protein complex 3 as well as subunits of biogenesis of lysosome-related organelles complex (BLOC)-1, -2, and -3. dGiant lysosomal granules and recurrent infections. eCan resemble vitiligo due to acquired complete loss of pigment. fMinority of patients in a nonreferral setting have systemic abnormalities (musculoskeletal, central nervous system, ocular), previously referred to as hypomelanosis of Ito. melanoma-associated leukoderma, onchocerciasis, and Vogt-Koyanagi-

Harada syndrome. The vitiligo-like leukoderma seen in patients with systemic sclerosis has a clinical resemblance to idiopathic vitiligo that has begun to repigment as a result of treatment; that is, perifollicular macules of normal pigmentation are seen within areas of depigmenta tion. The basis of this leukoderma is unknown; there is no evidence of inflammation in areas of involvement, but it can resolve if the underlying connective tissue disease becomes inactive. In contrast to idiopathic vitiligo, melanoma-associated vitiligo-like leukoderma often begins on the upper trunk and extensor forearms, and its appearance, if spontaneous, should prompt a search for metastatic disease. It is also seen in patients undergoing immunotherapy for melanoma, including immune checkpoint-blocking antibodies (checkpoint inhibitors), with cytotoxic T lymphocytes presumably recognizing cell surface antigens common to melanoma cells and melanocytes, and is associated with a greater likelihood of a clinical response. A history of aseptic menin gitis, nontraumatic uveitis, tinnitus, hearing loss, and/or dysacousia points to the diagnosis of the Vogt-Koyanagi-Harada syndrome. In these patients, the face and scalp are the most common locations of pigment loss. There are two systemic disorders (neurocristopathies) that may have the cutaneous findings of piebaldism (Table 61-9). They are Shah-Waardenburg syndrome and Waardenburg syndrome. A possible

explanation for both disorders is an abnormal embryonic migration or survival of two neural crest–derived elements, one of them being melanocytes and the other myenteric ganglion cells (leading to Hirschsprung disease in Shah-Waardenburg syndrome) or auditory nerve cells (Waardenburg syndrome). The latter syndrome is charac terized by congenital sensorineural

hearing loss, dystopia canthorum (lateral displacement of the inner canthi but normal interpupillary distance), heterochromic irises, and a broad nasal root, in addition to the piebaldism. The facial dysmorphism can be explained by the neural crest origin of the connective tissues of the head and neck. Patients with Waardenburg syndrome have been shown to have muta tions in four genes, including PAX-3 and MITF, three of which encode transcription factors, whereas patients with Hirschsprung disease plus white spotting have mutations in one of three genes—endothelin 3, endothelin B receptor, and the transcription factor SOX10.

Skin Manifestations of Internal Disease CHAPTER 61 In tuberous sclerosis, the earliest cutaneous sign is macular hypomel anosis, referred to as an ash leaf spot. These lesions are often present at birth and are usually multiple; however, detection may require Wood's lamp examination, especially in lightly pigmented individu als. The pigment within them is reduced, but not absent. The average size is 1–3 cm, and the common shapes are polygonal and lance-ovate. Examination of the patient for additional cutaneous signs such as multiple angiofibromas of the face (adenoma sebaceum), ungual and intraoral fibromas, fibrous cephalic plaques, and connective tissue nevi (shagreen patches) is recommended. It is important to remember that an ash leaf spot on the scalp will result in a circumscribed patch of lightly pigmented hair. Internal manifestations include seizures, intel lectual impairment, central nervous system (CNS) and retinal ham artomas, pulmonary lymphangioleiomyomatosis (women), bilateral renal angiomyolipomas, and myocardial rhabdomyomas. The latter can be detected in up to 60% of children (<18 years) with tuberous sclerosis by echocardiography. Nevus depigmentosus is a stable, well-circumscribed hypomelanosis that is present at birth. There is usually a single oval or rectangular lesion, but when there are multiple lesions, the possibility of tuberous sclerosis needs to be considered. In Blaschko-linear hypopigmentation, also referred to as linear nevoid hypopigmentation and pigmentary mosaicism, streaks and swirls of hypopigmentation are observed; these terms have replaced hypomelanosis of Ito. Up to one-third of patients in a tertiary care setting had associated abnormalities involv ing the musculoskeletal system (asymmetry), the CNS (seizures and intellectual disability), and the eyes (strabismus and hypertelorism). Genetic mosaicism has been detected in these patients (e.g. activating mutations in MTOR), lending support to the hypothesis that the cuta neous pattern is the result of the migration of two clones of primordial melanocytes, each with a different pigment potential. Localized areas of decreased pigmentation are commonly seen as a result of cutaneous inflammation (Table 61-10) and have been observed in the skin overlying active lesions of sarcoidosis (see "Papu lonodular Skin Lesions," below) as well as in CTCL. Cutaneous infec tions also present as disorders of hypopigmentation, and in tuberculoid leprosy, there are a few asymmetric patches of hypomelanosis that have associated anesthesia, anhidrosis, and alopecia. Biopsy specimens of the palpable border show dermal granulomas that contain rare, if any, Mycobacterium leprae organisms. HYPERPIGMENTATION (Table 61-11) Disorders of hyperpigmentation are also divided into two major groups—localized and diffuse. The localized forms are due to an epidermal alteration, a proliferation of melanocytes, or an increase in pigment production. Both acanthosis nigricans and sebor rheic keratoses belong to the first group. Acanthosis nigricans can be a reflection of an internal malignancy, most commonly of the gastroin testinal tract, and it appears as velvety hyperpigmentation, primarily in flexural areas. However, in the majority of patients, acanthosis nigricans is associated with obesity and insulin resistance, although it may be a reflection of an endocrinopathy such as acromegaly, Cush ing's syndrome, polycystic ovary syndrome, or insulin-resistant dia betes mellitus (type A, type B, and lipodystrophic forms). Seborrheic

TABLE 61-10 Hypopigmentation (Primary Cutaneous Disorders, Localized) WOOD'S LAMP EXAMINATION (UV-A; PEAK = 365 NM) SKIN BIOPSY SPECIMEN PATHOGENESIS TREATMENT CLINICAL CHARACTERISTICS Postinflammatory hypopigmentation Can develop within active lesions, as in subacute cutaneous lupus, or after the lesion fades, as in atopic dermatitis Depends on particular disease Usually less enhancement than in vitiligo PART 2 Cardinal Manifestations and Presentation of Diseases Idiopathic guttate hypomelanosis Common; acquired; usually

2–4 mm in diameter Shins and extensor forearms Less enhancement than vitiligo Pityriasis (tinea) versicolora Common disorder Upper trunk and neck (shawl-like distribution), body folds Young adults Macules have fine white scale when scratched Golden fluorescence Hyphal forms and budding yeast in stratum corneum Vitiligo Acquired; progressive Symmetric areas of complete pigment loss Periorificial—around mouth, nose, eyes, nipples, umbilicus, anus Other areas—flexor wrists, extensor distal extremities Segmental form is less common—unilateral, dermatomal-like More apparent Chalk-white Chemical- or drug-induced leukoderma Similar appearance to vitiligo Often begins on hands when associated with chemical exposure Satellite lesions in areas not exposed to chemicals More apparent Chalk-white Piebaldism Autosomal dominant Congenital, stable White forelock Areas of amelanosis contain normally pigmented and hyperpigmented macules of various sizes Symmetric involvement of central forehead, ventral trunk, and mid regions of upper and lower extremities Enhancement of leukoderma and hyperpigmented macules alf potassium hydroxide (KOH) examination of scale is negative, consider the possibility of progressive macular hypomelanosis. Abbreviations: MBEH, monobenzylether of hydroquinone; PUVA, psoralens plus ultraviolet A irradiation; UV-B, ultraviolet B irradiation. keratoses are common lesions, but in one rare clinical setting, they are a sign of systemic disease, and that setting is the sudden appearance of multiple lesions, often with an inflammatory base and in association with acrochordons (skin tags) and acanthosis nigricans. This is termed the sign of Leser-Trélat and alerts the clinician to search for an internal malignancy. A proliferation of melanocytes results in the following pigmented lesions: lentigo, melanocytic nevus, and melanoma (Chap. 81). In an adult, the majority of lentigines are related to sun exposure, which explains their distribution. However, in the Peutz-Jeghers

Type of inflammatory infiltrate depends on specific disease Block in transfer of melanin from melanocytes to keratinocytes could be secondary to edema or decrease in contact time Destruction of melanocytes if inflammatory cells attack basal layer of epidermis Treat underlying inflammatory disease Abrupt decrease in epidermal melanin content Possible somatic mutations as a reflection of aging or UV exposure None Invasion of stratum corneum by the yeast Malassezia Yeast is lipophilic and produces C9 and C11 dicarboxylic acids, which

in vitro inhibit tyrosinase Selenium sulfide 2.5% shampoo; topical imidazoles; oral fluconazole Absence of melanocytes in well-developed lesions Mild inflammation Autoimmune phenomenon that results in destruction of melanocytes—primarily cellular (circulating skinhoming autoreactive T cells) Topical glucocorticoids, calcineurin inhibitors, JAK inhibitors; UV-B (narrowband) > PUVA; oral JAK inhibitors; transplants, if stable; depigmentation (topical MBEH), if widespread and treatment-resistant Decreased number or absence of melanocytes Exposure to chemicals that selectively destroy melanocytes, in particular phenols and catechols (germicides; rubber products) or ingestion of drugs such as imatinib Release of cellular antigens and activation of circulating lymphocytes may explain satellite phenomenon Possible inhibition of KIT receptor Avoid exposure

to offending agent, then treat as vitiligo Drug-induced variant may undergo repigmentation when medication is discontinued Amelanotic areas—few to no melanocytes Defect in migration of melanoblasts from neural crest to involved skin or failure of melanoblasts to survive or differentiate in these areas Mutations within the KIT protooncogene that encodes the tyrosine kinase receptor for stem cell growth factor (kit ligand) None; occasionally transplants and LEOPARD (lentigines; ECG abnormalities, primarily conduc tion defects; ocular hypertelorism; pulmonary stenosis and subaortic valvular stenosis; abnormal genitalia [cryptorchidism, hypospadias]; retardation of growth; and deafness [sensorineural]) syndromes, len tigines do serve as a clue to systemic disease. In LEOPARD/Noonan with multiple lentigines syndrome, hundreds of lentigines develop dur ing childhood and are scattered over the entire surface of the body. The lentigines in patients with Peutz-Jeghers syndrome (PJS) are located primarily around the nose and mouth, on the hands and feet, and within the oral cavity. While the pigmented macules on the face may

TABLE 61-11 Causes of Hyperpigmentation I. Primary cutaneous disorders A. Localized

1. Epidermal alteration a. Seborrheic keratosis b. Pigmented actinic keratosis
2. Proliferation of melanocytes a. Lentigo b. Melanocytic nevus (mole) c. Melanoma
3. Increased pigment production a. Ephelide (freckle) b. Café au lait macule c. Postinflammatory hyperpigmentation (also dermal) d. Melasma (also dermal)
4. Dermal pigmentation a. Fixed drug eruption B. Localized and diffuse
5. Drugs (e.g., minocycline, hydroxychloroquine, bleomycin) II. Systemic diseases A. Localized
6. Epidermal alteration a. Acanthosis nigricans (insulin resistance > other endocrine disorders, paraneoplastic) b. Seborrheic keratoses (sign of Leser-Trélat)
7. Proliferation of melanocytes a. Lentigines (Peutz-Jeghers and LEOPARD/Noonan with multiple lentigines syndromes; xeroderma pigmentosum) b. Melanocytic nevi (Carney complex [LAMB and NAME syndromes])a
8. Increased pigment production a. Café au lait macules (neurofibromatosis, Legius syndrome, McCune-Albright syndromeb) b. Urticaria pigmentosac
9. Dermal pigmentation a. Incontinentia pigmenti (stage III) b. Dyskeratosis congenita
10. Dermal deposits a. Exogenous ochronosis b. Localized argyria B. Diffuse
11. Endocrinopathies a. Addison’s disease b. Nelson’s syndrome c. Ectopic ACTH syndrome d. Hyperthyroidism
12. Metabolic a. Porphyria cutanea tarda b. Hemochromatosis c. Vitamin B12, folate deficiency d. Pellagra e. Malabsorption, including Whipple’s disease
13. Melanosis secondary to metastatic melanoma
14. Autoimmune a. Primary biliary cholangitis b. Systemic sclerosis (scleroderma) c. POEMS syndrome d. Eosinophilia-myalgia syndromed
15. Drugs (e.g., cyclophosphamide) and metals (e.g., silver) aAlso lentigines. bPolyostotic fibrous dysplasia. cSee also “Papulonodular Skin Lesions.” dLate 1980s. Abbreviations: ACTH, adrenocorticotropic hormone; LAMB, lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi; LEOPARD, lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis and subaortic valvular stenosis, abnormal genitalia, retardation of growth, and deafness (sensorineural); NAME, nevi, atrial myxoma, myxoid neurofibroma, and ephelides (freckles); POEMS, polyneuropathy, organomegaly, endocrinopathies, M-protein, and skin changes.

fade with age, the oral lesions persist. However, similar intraoral lesions are also seen in Addison's disease, in Laugier-Hunziker syndrome (no internal manifestations), and as a normal finding in darkly pigmented individuals. Patients with PJS, an autosomal dominant syndrome due to mutations in a novel serine threonine kinase gene, have multiple benign polyps of the gastrointestinal tract, testicular or ovarian tumors, and an increased risk of developing gastrointestinal (primarily colon) and pancreatic cancers.

In the Carney complex, numerous lentigines are also seen, but they are in association with cardiac myxomas. This autosomal dominant disorder is also known as the LAMB (lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi) syndrome or NAME (nevi, atrial myxoma, myxoid neurofibroma, and ephelides [freckles]) syn drome. These patients can also have evidence of endocrine overactivity in the form of Cushing's syndrome (primary pigmented nodular adre nocortical disease) and acromegaly. Skin Manifestations of Internal Disease CHAPTER 61 The third type of localized hyperpigmentation is due to a local increase in pigment production, and it includes ephelides and café au lait macules (CALMs). While a single CALM can be seen in up to 10% of the normal population, the presence of multiple or largesized CALMs raises the possibility of an associated genodermatosis, for example, neurofibromatosis (NF) or McCune-Albright syndrome. CALMs are flat, uniformly brown in color (usually two shades darker than uninvolved skin), and can vary in size from 0.5 to 12+ cm. More than 90% of adult patients with type I NF will have six or more CALMs measuring ≥1.5 cm in diameter. Additional findings are discussed in the section on neurofibromas (see "Papulonodular Skin Lesions," below). In comparison with NF, the CALMs in patients with McCuneAlbright syndrome (polyostotic fibrous dysplasia with precocious puberty in females due to mosaicism for an activating mutation in a G protein [Gsα] gene) are usually larger, are more irregular in outline, and tend to respect the midline. In incontinentia pigmenti, dyskeratosis congenita, and bleomycin pigmentation, the areas of localized hyperpigmentation form a pattern— swirls and streaks in the first, reticulated in the second, and flagellate in the third. In dyskeratosis congenita, atrophic reticulated hyperpig mentation is seen on the neck, trunk, and thighs and is accompanied by nail dystrophy, pancytopenia, and leukoplakia of the oral and anal mucosae. The latter often develops into squamous cell carcinoma. In addition to the flagellate pigmentation (linear streaks) on the trunk, patients receiving bleomycin often have hyperpigmentation overlying the elbows, knees, and small joints of the hand. Localized hyperpigmentation is seen as a side effect of several other systemic medications, including those that produce fixed drug reac tions (nonsteroidal anti-inflammatory drugs [NSAIDs], sulfonamides, and tetracyclines) and those that can complex with melanin or iron (antimalarials and minocycline). Fixed drug eruptions recur in the exact same location as circular areas of erythema that can become bul lous and then resolve as macular brown circles. The eruption usually appears within hours of readministration of the offending agent, and common locations include the genitalia, distal extremities, and perioral region. Chloroquine and hydroxychloroquine produce gray-brown to blue-black discoloration of the shins, hard palate, and face, while blue macules (often misdiagnosed as bruises) can be seen most commonly on the lower extremities and in sites of inflammation with prolonged minocycline administration. Estrogen in oral contraceptives can induce melasma—symmetric brown patches on the face, especially the cheeks, upper lip, and forehead. Similar changes are seen in pregnancy and in patients receiving phenytoin. In the diffuse forms of hyperpigmentation, the darkening of the skin may be of equal intensity over the entire body or may be accen tuated in sun-exposed areas. The causes of diffuse hyperpigmenta tion can be divided into four major groups—endocrine, metabolic, autoimmune, and drugs. The

endocrinopathies that frequently have associated hyperpigmentation include Addison’s disease, Nel son’s syndrome, and ectopic adrenocorticotropic hormone (ACTH) syndrome. In these diseases, the increased pigmentation is diffuse but is accentuated in sun-exposed areas, as well as in the palmar creases, sites of friction, and scars. An overproduction of the pituitary

hormones α-MSH (melanocyte-stimulating hormone) and ACTH can lead to an increase in melanocyte activity. These peptides are products of the proopiomelanocortin gene and exhibit homology; for example, α-MSH and ACTH share 13 amino acids. A minority of patients with Cushing’s disease or hyperthyroidism have generalized hyperpigmentation.

The metabolic causes of hyperpigmentation include porphyria cuta nea tarda (PCT), hemochromatosis, vitamin B12 deficiency, folic acid deficiency, pellagra, and malabsorption, including Whipple’s disease. In patients with PCT (see “Vesicles/Bullae,” below), the skin darkening is seen in sun-exposed areas and is a reflection of the photoreactive prop erties of porphyrins. The increased level of iron in the skin of patients with types 1 and 2 hemochromatosis stimulates melanin pigment production and leads to the classic bronze color. Patients with pellagra have a brown discoloration of the skin, especially in sun-exposed areas, as a result of nicotinic acid (niacin) deficiency. In the areas of increased pigmentation, there is a thin, varnish-like scale. These changes are also seen in patients who are vitamin B6 deficient, have functioning carcinoid tumors (increased consumption of niacin), or take isoniazid. Approximately 50% of the patients with Whipple’s disease have an associated generalized hyperpigmentation in association with diarrhea, weight loss, arthritis, and lymphadenopathy. A diffuse, slate-blue to gray-brown color is seen in patients with melanosis secondary to meta static melanoma. The color reflects widespread deposition of melanin within the dermis as a result of the high concentration of circulating melanin precursors. PART 2 Cardinal Manifestations and Presentation of Diseases Of the autoimmune diseases associated with diffuse hyperpigmen tation, primary biliary cholangitis and systemic sclerosis are the most common, and occasionally, both disorders are seen in the same patient. The skin is dark brown in color, especially in sun-exposed areas. In primary biliary cholangitis, the hyperpigmentation is accompanied by pruritus, jaundice, and xanthomas, whereas in systemic sclerosis, it is accompanied by sclerosis of the extremities, face, and, less commonly, the trunk. Additional clues to the diagnosis of systemic sclerosis are mat and cuticular telangiectasias, calcinosis cutis, Raynaud’s phe nomenon, and distal ulcerations (see “Telangiectasias,” above). The differential diagnosis of cutaneous sclerosis with hyperpigmentation includes POEMS (polyneuropathy; organomegaly [liver, spleen, lymph nodes]; endocrinopathies [impotence, gynecomastia]; M-protein; and skin changes) syndrome. The skin changes include hyperpigmentation, induration, hypertrichosis, angiomas, clubbing, and facial lipoatrophy. Diffuse hyperpigmentation that is due to drugs or metals can result from one of several mechanisms—induction of melanin pig ment formation, complexing of the drug or its metabolites to melanin, and deposits of the drug in the dermis. Busulfan, cyclophosphamide, 5-fluorouracil, and inorganic arsenic induce pigment production. Complexes containing melanin or iron plus the drug or its metabolites are seen in patients receiving minocycline, and a diffuse, brown-gray, muddy appearance within sun-exposed areas may develop, in addition to pigmentation of the mucous membranes, teeth, nails, bones, and thyroid. Administration of amiodarone can result in both a phototoxic eruption (exaggerated sunburn) and/or a slate-gray to violaceous dis coloration of sun-exposed skin. Biopsy specimens of the latter show yellow-brown granules in dermal macrophages, which represent intra lysosomal accumulations of lipids, amiodarone, and its metabolites. Actual

deposits of a particular drug or metal in the skin are seen with silver (argyria), where the skin appears blue-gray in color; gold (chrysi asis), where the skin has a brown to blue-gray color; and clofazimine, where the skin appears reddish brown. The associated pigmentation is accentuated in sun-exposed areas, and discoloration of the eye is seen with gold (sclerae) and clofazimine (conjunctivae). VESICLES/BULLAE (Table 61-12) Depending on their size, cutaneous blisters are referred to as vesicles (<1 cm) or bullae (>1 cm). The primary autoimmune blistering disorders include pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, bullous pemphigoid, gestational pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita, linear IgA bul lous dermatosis (LABD), and dermatitis herpetiformis (Chap. 62).

TABLE 61-12 Causes of Vesicles/Bullae I. Primary mucocutaneous diseases A. Primary blistering diseases (autoimmune)

1. Pemphigus, foliaceus and vulgarisa
2. Bullous pemphigoidb
3. Gestational pemphigoidb
4. Cicatricial pemphigoidb
5. Dermatitis herpetiformisb,c
6. Linear IgA bullous dermatosisb
7. Epidermolysis bullosa acquisitab,d B. Secondary blistering diseases
8. Contact dermatitisa,b
9. Erythema multiformee
10. Stevens-Johnson syndromee
11. Toxic epidermal necrolysise
12. Bullous fixed drug eruption, including generalized variante
13. Pseudoporphyria, drug- or tanning booth–induced C. Infections
14. Varicella-zoster virusa,f
15. Herpes simplex virusa,f
16. Enteroviruses, e.g., hand-foot-and-mouth diseasef
17. SARS-CoV-2
18. Staphylococcal scalded-skin syndromea,g
19. Bullous impetigoa
20. Bullous tinea II. Systemic diseases A. Autoimmune
21. Paraneoplastic pemphigusa (bronchiolitis obliterans)
22. Bullous systemic lupus erythematosus B. Infections
23. Cutaneous embolib C. Metabolic
24. Diabetic bullaea,b
25. Porphyria cutanea tardab
26. Porphyria variegatab
27. Bullous dermatosis of hemodialysisb (less often associated with peritoneal dialysis and also referred to as pseudoporphyria) D. Ischemia
28. Coma bullae E. Secondary blistering diseases
29. Toxic epidermal necrolysise (respiratory and gastrointestinal tracts can be involved)
30. Edema bullae (venous hypertension, congestive heart failure) aIntraepidermal. bSubepidermal. cAssociated with gluten enteropathy. dAssociated with inflammatory bowel disease. eDegeneration of cells within the basal layer of the epidermis can give

impression split is subepidermal. fAlso systemic. gIn adults, associated with renal failure and immunocompromised state. Vesicles and bullae are also seen in contact dermatitis, both allergic and irritant forms (Chap. 60). When there is a linear arrangement of vesicular lesions, an exogenous cause or herpes zoster should be suspected. Bullous disease secondary to the ingestion of drugs can take one of several forms, including phototoxic eruptions, isolated bul lae, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) (Chap. 63). Clinically, phototoxic eruptions resemble an exag gerated sunburn with diffuse erythema and bullae in sun-exposed areas. The most commonly associated drugs are doxycycline, quino lones, voriconazole, thiazides, NSAIDs, vemurafenib, and psoralens. The development of a phototoxic eruption is dependent on the doses of both the drug and ultraviolet (UV)-A irradiation. Toxic epidermal necrolysis is characterized by bullae that arise on widespread areas of tender erythema and then slough. This results in large areas of denuded skin. The associated morbidity, such as sepsis, and mortality rates are relatively high and are a function of the extent of

epidermal necrosis. In addition, these patients may also have involve ment of the mucous membranes and respiratory and intestinal tracts. Drugs are the primary cause of TEN, and the most common offenders are aromatic anticonvulsants (phenytoin, barbiturates, carbamazepine), sulfonamides, aminopenicillins, allopurinol, and NSAIDs. Generalized bullous fixed drug eruption, severe acute graft-versus-host disease (grade 4), vancomycin-induced LABD, and flares of cutaneous lupus can also resemble TEN. In erythema multiforme (EM), the primary lesions are pink-red macules and edematous papules, the centers of which may become vesicular. In contrast to a morbilliform exanthem, the clue to the diag nosis of EM, and especially SJS, is the development of a “dusky” violet color in the center of the lesions. Target lesions are also characteristic of EM and arise as a result of active centers and borders in combination with centrifugal spread. However, target lesions need not be present to make the diagnosis of EM. EM has been subdivided into two major groups: (1) EM minor due to herpes simplex virus (HSV); and (2) EM major due to HSV, Mycoplasma pneumonia, or, occasionally, other viruses, Chlamydia, or drugs. Involvement of the mucous membranes (ocular, nasal, oral, and genital) is seen more commonly in the latter form, and in patients with Mycoplasma pneumoniae–induced rash and mucositis (MIRM)/reactive infectious mucocutaneous eruption (RIME), there may be minimal cutaneous involvement. Hemorrhagic crusts of the lips are characteris tic of EM major and SJS as well as herpes simplex, pemphigus vulgaris, and paraneoplastic pemphigus. Fever, malaise, myalgias, sore throat, and cough may precede or accompany the eruption. The lesions of EM usually resolve over 2–4 weeks but may be recurrent, especially when due to HSV. In addition to HSV (in which lesions usually appear 7–12 days after the viral eruption), EM can also follow vaccinations, radiation therapy, and exposure to environmental toxins, including the oleoresin in poison ivy. Induction of SJS is most often due to drugs, especially sulfonamides, aromatic anticonvulsants, lamotrigine, aminopenicillins, and nonnu cleoside reverse transcriptase inhibitors (e.g., nevirapine). Widespread dusky macules and significant mucosal involvement are characteristic of SJS, and the cutaneous lesions may or may not develop epidermal detachment. If the latter occurs, by definition, it is limited to <10% of the body surface area (BSA). Greater involvement leads to the diagno sis of SJS/TEN overlap (10–30% BSA) or TEN (>30% BSA). In addition to primary blistering disorders and hypersensitivity reactions, bacterial and viral infections can lead to vesicles and bullae. The most common infectious agents are HSV (Chap. 197), varicella-zoster virus (Chap. 198), and S. aureus (Chap. 152). Staphylococcal scalded-skin syndrome (SSSS) and bullous impetigo are two blistering

disorders associated with staphylococcal (phage group II) infection. In SSSS, the initial findings are redness and ten derness of the central face, neck, trunk, and intertriginous zones. This is followed by short-lived flaccid bullae and a slough or exfoliation of the superficial epidermis. Crusted areas then develop, characteristically around the mouth in a radial pattern. SSSS is distinguished from TEN by the following features: younger age group (primarily infants and toddlers), more superficial site of blister formation, no oral lesions, shorter course, lower morbidity and mortality rates, and an association with staphylococcal exfoliative toxin (“exfoliatin”), not drugs. A rapid diagnosis of SSSS versus TEN can be made by a frozen section of the blister roof or exfoliative cytology of the blister contents. In SSSS, the site of staphylococcal infection is usually extracutaneous (conjunctivi tis, rhinorrhea, otitis media, pharyngitis, tonsillitis), and the cutaneous lesions are sterile, whereas in bullous impetigo, the skin lesions are the site of infection. Impetigo is more localized than SSSS and usually presents with honey-colored crusts. Occasionally, superficial purulent blisters also form. Cutaneous emboli from gram-negative infections may present as isolated bullae, but the base of the lesion is purpuric or necrotic, and it may develop into an ulcer (see “Purpura,” below). Several metabolic disorders are associated with blister formation, including diabetes mellitus, renal failure, and porphyria. Local hypox emia secondary to decreased cutaneous blood flow can also produce blisters, which explains the presence of bullae over pressure points

in comatose patients (coma bullae). In diabetes mellitus, tense bullae with clear sterile viscous fluid arise on normal skin. The lesions can be as large as 6 cm in diameter and are located on the distal extremities. There are several types of porphyria, but the most common form with cutaneous findings is porphyria cutanea tarda (PCT). In sun-exposed areas (primarily the hands), the skin is very fragile, with trauma lead ing to erosions mixed with tense vesicles. These lesions then heal with scarring and formation of milia; the latter are firm, 1- to 2-mm white or yellow papules that represent epidermoid cysts. Associated findings can include hypertrichosis of the lateral malar region (men) or face (women) and, in sun-exposed areas, hyperpigmentation and firm scle rotic plaques. An elevated level of urinary uroporphyrins confirms the diagnosis and is due to a decrease in uroporphyrinogen decarboxylase activity. PCT can be exacerbated by alcohol, hemochromatosis and other forms of iron overload, chlorinated hydrocarbons, hepatitis C virus and HIV infections, and hepatomas.

Skin Manifestations of Internal Disease CHAPTER 61 The differential diagnosis of PCT includes (1) porphyria variegata— the skin signs of PCT plus the systemic findings of acute intermittent porphyria; it has a diagnostic plasma porphyrin fluorescence emission at 626 nm; (2) drug-induced pseudoporphyria—the clinical and histo logic findings are similar to PCT, but porphyrins are normal; etiologic agents include naproxen and other NSAIDs, furosemide, tetracycline, and voriconazole; (3) bullous dermatosis of hemodialysis—the same appearance as PCT, but porphyrins are usually normal or occasion ally borderline elevated; patients have chronic renal failure and are on hemodialysis; (4) PCT associated with hepatomas and hemodialysis; and (5) epidermolysis bullosa acquisita (Chap. 62). EXANTHEMS (Table 61-13) Exanthems are characterized by an acute generalized eruption. The most common presentation is erythematous macules and papules (morbilliform) and less often confluent blanching erythema (scarlatiniform). Morbilliform eruptions are usually due to either drugs or viral infections. For example, up to 5% of patients receiving penicil lins, sulfonamides, phenytoin, or nevirapine will develop a maculo papular eruption. Accompanying signs may include pruritus, fever, eosinophilia, transaminitis, and transient lymphadenopathy (Chap. 63).

TABLE 61-13 Causes of Exanthems I. Morbilliform A. Drugs B. Viral

1. Rubeola (measles)
2. Rubella
3. Erythema infectiosum (erythema of cheeks; reticulated on extremities)
4. Epstein-Barr virus, echovirus, coxsackievirus, CMV, adenovirus, HHV-6/HHV-7a, SARS-CoV-2, dengue, chikungunya, and West Nile virus infections
5. HIV seroconversion exanthem (plus mucosal ulcerations) C. Bacterial
6. Typhoid fever
7. Early secondary syphilis
8. Early Rickettsia infections
9. Early meningococcemia
10. Ehrlichiosis D. Acute graft-versus-host disease E. Kawasaki disease II. Scarlatiniform A. Scarlet fever B. Toxic shock syndrome C. Kawasaki disease D. Early staphylococcal scalded-skin syndrome aPrimary infection in infants and reactivation in the setting of immunosuppression. Abbreviations: CMV, cytomegalovirus; HHV, human herpesvirus; HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Similar maculopapular eruptions are seen in the classic childhood viral exanthems, including (1) rubeola (measles)—a prodrome of coryza, cough, and conjunctivitis followed by Koplik’s spots on the buccal mucosa; the eruption begins behind the ears, at the hairline, and on the forehead and then spreads down the body, often becoming confluent; (2) rubella—the eruption begins on the forehead and face and then spreads down the body; it resolves in the same order and is associated with retroauricular and suboccipital lymphadenopathy; and (3) erythema infectiosum (fifth disease)—erythema of the cheeks is fol lowed by a reticulated pattern on the extremities; it is secondary to a parvovirus B19 infection, and an associated arthritis is seen in adults.

Both measles and rubella can occur in unvaccinated adults, and an atypical form of measles is seen in adults immunized with either killed measles vaccine or killed vaccine followed in time by live vaccine. In contrast to classic measles, the eruption of atypical measles begins on the palms, soles, wrists, and ankles, and the lesions may become pur puric. The patient with atypical measles can have pulmonary involve ment and be quite ill. Rubelliform and roseoliform eruptions are also associated with Epstein-Barr virus (5–15% of patients), echovirus, coxsackievirus, cytomegalovirus, adenovirus, SARS-CoV-2, dengue, chi kungunya, and West Nile virus infections. While detection of specific IgM antibodies or fourfold elevations in IgG antibodies often allows the proper diagnosis, polymerase chain reaction (PCR) has gradually replaced serologic assays. Occasionally, a maculopapular drug eruption is a reflection of an underlying viral infection. For example, ~95% of the patients with infectious mononucleosis who are given ampicillin will develop a rash. PART 2 Cardinal Manifestations and Presentation of Diseases Of note, early in the course of infections with Rickettsia and menin gococcus, prior to the development of petechiae and purpura, the lesions may be erythematous macules and papules. This is also the case in chickenpox prior to the development of vesicles. Maculopapu lar eruptions are associated with early HIV infection, early secondary syphilis, typhoid fever, and acute graft-versus-host disease. In the last, lesions frequently begin on the dorsal hands, forearms, and upper trunk; the macular rose spots of typhoid fever involve primarily the anterior trunk. The prototypic scarlatiniform eruption is seen in scarlet

fever and is due to an erythrogenic toxin produced by bacteriophage-containing group A β-hemolytic streptococci, most commonly in the setting of pharyngitis. This eruption is characterized by diffuse erythema, which begins on the neck and upper trunk, and red follicular puncta. Addi tional findings include a white strawberry tongue (white coating with red papillae) followed by a red strawberry tongue (red tongue with red papillae); petechiae of the palate; a facial flush with circumoral pallor; linear petechiae in the antecubital fossae; and desquamation of the involved skin, palms, and soles 5–20 days after onset of the eruption. A similar desquamation of the palms and soles is seen in toxic shock syndrome (TSS), in Kawasaki disease, and after severe febrile illnesses. Certain strains of staphylococci also produce an erythrotoxin that leads to the same clinical findings as in streptococcal scarlet fever, except that the anti-streptolysin O or DNase B titers are not elevated. In toxic shock syndrome, staphylococcal (phage group I) infections produce an exotoxin (TSST-1) that causes the fever and rash as well as enterotoxins. Initially, the majority of cases were reported in men struating women who were using tampons. However, other sites of infection, including wounds and nasal packing, can lead to TSS. The diagnosis of TSS is based on clinical criteria (Chap. 152), and three of these involve mucocutaneous sites (diffuse erythema of the skin, des quamation of the palms and soles 1–2 weeks after onset of illness, and involvement of the mucous membranes). The latter is characterized as hyperemia of the vagina, oropharynx, or conjunctivae. Similar systemic findings have been described in streptococcal toxic shock syndrome (Chap. 153), and although an exanthem is seen less often than in TSS due to a staphylococcal infection, the underlying infection is often in the soft tissue (e.g., cellulitis). The cutaneous eruption in Kawasaki disease (Chap. 375) is poly morphous, but the two most common forms are morbilliform and scarlatiniform. Additional mucocutaneous findings include bilateral conjunctival injection; erythema and edema of the hands and feet

followed by desquamation; and diffuse erythema of the oropharynx, red strawberry tongue, and dry fissured lips. This clinical picture can resemble TSS and scarlet fever, but clues to the diagnosis of Kawasaki disease are cervical lymphadenopathy, cheilitis, and thrombocyto sis. The most serious associated systemic finding in this disease is coronary aneurysms secondary to arteritis. Seen primarily in children, SARS-CoV-2–associated multisystem inflammatory syndrome must be distinguished from Kawasaki disease. Scarlatiniform eruptions are also seen in the early phase of SSSS (see “Vesicles/Bullae,” above), in young adults with Arcanobacterium haemolyticum infection, and as reactions to drugs. URTICARIA (Table 61-14) Urticaria (hives) are transient lesions that are com posed of a central wheal surrounded by an erythematous halo or flare. Individual lesions are round, oval, or figurate and are often pruritic. Acute and chronic urticarias have a wide variety of allergic etiologies and reflect edema in the dermis. Urticarial lesions can also be seen in patients with mastocytosis (urticaria pigmentosa), hypo- or hyperthy roidism, Schnitzler’s syndrome, and systemic-onset juvenile idiopathic arthritis (Still’s disease). In both juvenile- and adult-onset Still’s disease, the lesions coincide with the fever spike, are transient, and are due to dermal infiltrates of neutrophils; the latter is also referred to as neutro philic urticarial dermatosis. The common physical urticarias include dermographism, solar urti caria, cold urticaria, and cholinergic urticaria. Patients with dermogra phism exhibit linear wheals following minor pressure or scratching of the skin and may be a contributing factor to pruritic dermatoses. It is a common disorder, affecting ~5% of the population. Solar urticaria char acteristically occurs within minutes of sun exposure and is a skin sign of one systemic disease—erythropoietic protoporphyria. In addition to the urticaria, these patients have subtle pitted scarring of the nose and hands. Cold urticaria is precipitated by exposure to the cold, and therefore, exposed areas are usually affected. In occasional patients, the

disease is associated with abnormal circulating proteins—more com monly cryoglobulins and less commonly cryofibrinogens. Additional systemic symptoms include wheezing and syncope, thus explaining the need for these patients to avoid swimming in cold water. Autosomal dominantly inherited cold urticaria is associated with dysfunction of cryopyrin. Cholinergic urticaria is precipitated by heat, exercise, or emotion and is characterized by small wheals with relatively large flares. It is occasionally associated with wheezing. Whereas urticarias are the result of dermal edema, subcutaneous edema leads to the clinical picture of angioedema. Sites of involvement include the eyelids, lips, tongue, larynx, and gastrointestinal tract as well as the subcutaneous tissue. Angioedema occurs alone or in com bination with urticaria, including urticarial vasculitis and the physical urticarias. Both acquired and hereditary (autosomal dominant) forms TABLE 61-14 Causes of Urticaria and Angioedema I. Primary cutaneous disorders A. Acute and chronic urticariaa B. Physical urticaria

1. Dermographism
2. Solar urticariab
3. Cold urticariab
4. Cholinergic urticariab C. Angioedema (hereditary and acquired)b,c II. Systemic diseases A. Urticarial vasculitis B. Hepatitis B or C viral infection, SARS-CoV-2 infection C. Serum sickness D. Angioedema (hereditary and acquired) aA small minority develop anaphylaxis. bAlso systemic. cAcquired angioedema can be idiopathic, associated with a lymphoproliferative disorder, or due to a drug, e.g., angiotensin-converting enzyme (ACE) inhibitors. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

of angioedema occur (Chap. 366), and in the latter, urticaria is rarely, if ever, seen. Urticarial vasculitis is an immune complex disease that may be con fused with simple urticaria. In contrast to simple urticaria, individual lesions tend to last longer than 24 h and usually develop central pete chiae that can be observed even after the urticarial phase has resolved. The patient may also complain of burning rather than pruritus. On biopsy, there is a leukocytoclastic vasculitis of the small dermal blood vessels. Although urticarial vasculitis may be idiopathic in origin, it can be a reflection of an underlying systemic illness such as lupus ery thematosus, Sjögren’s syndrome, or hereditary complement deficiency. There is a spectrum of urticarial vasculitis that ranges from purely cutaneous to multisystem involvement. The most common systemic signs and symptoms are arthralgias and/or arthritis, nephritis, and crampy abdominal pain, with asthma and chronic obstructive lung disease seen less often. Hypocomplementemia occurs in one- to twothirds of patients, even in the idiopathic cases. Urticarial vasculitis can also be seen in patients with hepatitis B and hepatitis C infections and serum sickness but is usually not seen in serum sickness–like illnesses (e.g., due to cefaclor, minocycline). PAPULONODULAR SKIN LESIONS (Table 61-15) In the papulonodular diseases, the lesions are elevated above the surface of the skin and may coalesce to form larger plaques. The location, consistency, and color of the lesions are the keys to their diagnosis; this section is organized on the basis of color. ■ ■WHITE LESIONS In calcinosis cutis, there are firm white to white-yellow papules with an irregular surface. When the contents are expressed, a chalky white material is seen. Dystrophic calcification is seen at sites of previous inflammation or damage to the skin. It develops in acne scars as well as on the distal extremities of patients with systemic sclerosis and in the subcutaneous tissue and intermuscular fascial planes in DM. The latter is more extensive and is more commonly seen in children. A previous or current elevated calcium phosphate product, most commonly due to secondary

hyperparathyroidism in the setting of renal failure, can lead to nodules of metastatic calcinosis cutis, which tend to be subcu taneous and periarticular. These patients can also develop calcification of muscular arteries and subsequent ischemic necrosis (calciphylaxis). Osteoma cutis, in the form of small papules, most commonly occurs on the face of individuals with a history of acne vulgaris, whereas platelike lesions occur in rare genetic syndromes. ■ ■SKIN-COLORED LESIONS There are several types of skin-colored lesions, including epidermoid cysts, lipomas, rheumatoid nodules, neurofibromas, angiofibromas, neuromas, and adnexal tumors such as tricholemmomas. Both epi dermoid cysts and lipomas are very common mobile subcutaneous nodules—the former are rubbery and drain cheeselike material (sebum and keratin) if incised. Lipomas are also rubbery and somewhat lobu lated on palpation. When extensive facial epidermoid cysts develop during childhood or there is a family history of such lesions, the patient should be examined for other signs of Gardner syndrome, including osteomas and desmoid tumors. Rheumatoid nodules are firm 0.5- to 4-cm nodules that favor the extensor aspect of joints, especially the elbows. They are seen in ~20% of patients with rheumatoid arthritis and ~5% of patients with Still's disease. Biopsies of the nodules show palisading granulomas. Similar lesions that are smaller and shorterlived are seen in rheumatic fever. Subcutaneous granuloma annulare is sometimes misdiagnosed as rheumatoid nodules. Neurofibromas (benign Schwann cell tumors) are soft papules or nodules that exhibit the "button-hole" sign; that is, they invaginate into the skin with pressure in a manner similar to a hernia. Single lesions are seen in normal individuals, but multiple neurofibromas, usually in combination with six or more CALMs measuring >1.5 cm (see "Hyper pigmentation," above), axillary freckling, and multiple Lisch nodules, are seen in von Recklinghausen's disease (NF type I) (Chap. 95). In some patients, the neurofibromas are localized and unilateral due to somatic mosaicism.

TABLE 61-15 Papulonodular Skin Lesions According to Color Groups I. White A. Calcinosis cutis B. Osteoma cutis (also skin-colored or blue) II. Skin-colored A. Rheumatoid nodules B. Neurofibromas (von Recklinghausen's disease [NF1]) C. Angiofibromas (tuberous sclerosis, MEN syndrome, type 1; also pink-red) D. Neuromas (MEN syndrome, type 2b) E. Adnexal tumors

1. Basal cell carcinomas (basal cell nevus syndrome)
2. Tricholemmomas (Cowden disease)
3. Fibrofolliculomas (Birt-Hogg-Dubé syndrome) F. Osteomas (arise in skull and jaw in Gardner syndrome) G. Primary cutaneous disorders Skin Manifestations of Internal Disease CHAPTER 61
4. Epidermal inclusion cystsa
5. Lipomas III. Pink/translucentb A. Amyloidosis, primary systemic B. Papular mucinosis/scleromyxedema C. Multicentric reticulohistiocytosis IV. Yellow A. Xanthomas B. Tophi C. Necrobiosis lipoidica D. Pseudoxanthoma elasticum E. Sebaceous adenomas (Muir-Torre syndrome) V. Redb A. Papules
6. Angiokeratomas (Fabry disease and related lysosomal storage diseases)c
7. Bacillary angiomatosis (primarily in AIDS) B. Papules/plaques
8. Cutaneous lupus erythematosus
9. Lymphoma cutis
10. Leukemia cutis
11. Sweet syndrome C. Nodules
12. Panniculitis

13. Medium-sized vessel vasculitis (e.g., cutaneous polyarteritis nodosa/cutaneous arteritis) D. Primary cutaneous disorders
14. Arthropod bites
15. Cherry hemangiomas
16. Infections, e.g., streptococcal cellulitis, sporotrichosis
17. Polymorphous light eruption
18. Cutaneous lymphoid hyperplasia (lymphocytoma cutis, pseudolymphoma) VI. Red-brownb A. Sarcoidosis B. Urticaria pigmentosa C. Erythema elevatum diutinum (chronic leukocytoclastic vasculitis) D. Lupus vulgaris VII. Blueb A. Venous malformations (e.g., blue rubber bleb syndrome) B. Primary cutaneous disorders
19. Venous lake
20. Blue nevus VIII. Violaceous A. Lupus pernio (sarcoidosis) B. Lymphoma cutis C. Cutaneous lupus erythematosus IX. Purple A. Kaposi's sarcoma, acral angiodermatitis (pseudo-Kaposi's sarcoma) B. Angiosarcoma C. Palpable purpura (see Table 61-16) D. Primary cutaneous disorders
21. Angiokeratomas of the scrotum and vulva X. Brown-blackd XI. Any color A. Metastases aIf multiple with childhood onset, consider Gardner syndrome. bMay have darker hue in more darkly pigmented individuals. cMore widespread, especially lower trunk and girdle region, and often red-purple in color. dSee also "Hyperpigmentation." Abbreviations: MEN, multiple endocrine neoplasia; NF1, neurofibromatosis type 1.

Angiofibromas are firm pink-red to skin-colored papules that mea sure from 3 mm to 1.5 cm in diameter. When multiple lesions are located on the central cheeks (adenoma sebaceum), the patient should be evaluated for tuberous sclerosis or multiple endocrine neoplasia (MEN) syndrome, type 1. The former is an autosomal disorder due to mutations in two different genes, and the associated findings are dis cussed in the section on ash leaf spots as well as in Chap. 95.

Neuromas (benign proliferations of nerve fibers) are also firm, skin-colored papules. They are more commonly found at sites of amputations and in rudimentary polydactyly. However, when there are multiple neuromas on the eyelids, lips, distal tongue, and/or oral mucosa, the patient should be investigated for other signs of MEN syndrome, type 2b. Associated findings include marfanoid habitus, protuberant lips, intestinal ganglioneuromas, and medullary thyroid carcinoma (>75% of patients; Chap. 400). PART 2 Cardinal Manifestations and Presentation of Diseases Adnexal tumors are derived from pluripotent cells of the epider mis that can differentiate toward hair, sebaceous, apocrine or eccrine glands, or remain undifferentiated. Basal cell carcinomas (BCCs) are examples of adnexal tumors that have little or no evidence of differenti ation. Clinically, they are translucent papules with rolled borders, telan giectasias, and central erosion. BCCs commonly arise in sun-damaged skin of the head and neck as well as the upper trunk. When a patient has multiple BCCs, especially prior to age 30, the possibility of the basal cell nevus syndrome should be raised. It is inherited as an autosomal dominant trait and is associated with jaw cysts, palmar and plantar pits, frontal bossing, medulloblastomas, and calcification of the falx cerebri and diaphragma sellae. Tricholemmomas are also skin-colored adnexal tumors but differentiate toward hair follicles and can have a wartlike appearance. The presence of multiple tricholemmomas on the face and cobblestoning of the oral mucosa points to the diagnosis of Cowden disease (PTEN hamartoma tumor syndrome) due to mutations in the phosphatase and tensin homolog (PTEN) gene. Internal organ involve ment (in decreasing order of frequency) includes fibrocystic disease and carcinoma

of the breast, adenomas and carcinomas of the thyroid, genitourinary carcinomas, and gastrointestinal polyposis. Keratoses of the palms, soles, and dorsal aspect of the hands are also seen. Fibrofol liculomas are skin-colored to white, smooth papules that favor the face, ears, and neck and, when multiple, are associated with Birt-Hogg-Dubé syndrome, which is associated with renal lesions including cancer as well as pulmonary cysts (Chap. 90). ■ ■PINK LESIONS The cutaneous lesions associated with primary systemic amyloidosis are often pink to pink-orange in color and translucent. Common locations are the face, especially the periorbital and perioral regions, and flexural areas. On biopsy, homogeneous deposits of amyloid are seen in the dermis and in the walls of blood vessels; the latter lead to an increase in vessel wall fragility. As a result, petechiae and purpura develop in clini cally normal skin as well as in lesional skin following minor trauma, hence the term pinch purpura. Amyloid deposits are also seen in the striated muscle of the tongue and result in macroglossia. Even though specific mucocutaneous lesions are present in only ~30% of the patients with primary systemic (AL) amyloidosis, the diagnosis can be made via histologic examination of abdominal sub cutaneous fat, in conjunction with a serum free light chain assay. By special staining, amyloid deposits can be seen around blood vessels or individual fat cells. There are also three forms of amyloidosis that are limited to the skin and that should not be construed as cutaneous lesions of systemic amyloidosis. They are macular amyloidosis (upper back), lichen amyloidosis (usually lower extremities), and nodular amyloidosis. In macular and lichen amyloidosis, lesions are hyperpig mented and the deposits are composed of altered epidermal keratin. Early-onset macular and lichen amyloidosis have been associated with MEN syndrome, type 2a. Patients with multicentric reticulohistiocytosis also have pink-colored papules and nodules on the face and mucous membranes as well as on the extensor surface of the hands and forearms. They have a poly arthritis that can mimic rheumatoid arthritis clinically. On histologic examination, the papules have characteristic giant cells that are not

seen in biopsies of rheumatoid nodules. Pink to skin-colored papules that are firm, 2–5 mm in diameter, and often in a linear arrangement are seen in patients with papular mucinosis. This disease is also referred to as scleromyxedema. The latter name comes from the induration of the face and extremities that may accompany the papular eruption. Biopsy specimens of the papules show localized mucin deposition, and serum protein electrophoresis plus immunofixation electrophoresis demonstrates a monoclonal spike of IgG, usually with a λ light chain. ■ ■YELLOW LESIONS Several systemic disorders are characterized by yellow-colored cutane ous papules or plaques—hyperlipidemia (xanthomas), gout (tophi), diabetes (necrobiosis lipoidica), pseudoxanthoma elasticum, and MuirTorre syndrome (sebaceous tumors). Eruptive xanthomas are the most common form of xanthomas and are associated with hypertriglyceride mia (primarily hyperlipoproteinemia types I, IV, and V). Crops of yel low papules with erythematous halos occur primarily on the extensor surfaces of the extremities and the buttocks, and they spontaneously involute with a fall in serum triglycerides. Types II and III result in one or more of the following types of xanthoma: xanthelasma, tendon xan thomas, and plane xanthomas. Xanthelasma are found on the eyelids, whereas tendon xanthomas are frequently associated with the Achilles and extensor finger tendons; plane xanthomas are flat and favor the palmar creases and flexural folds. Tuberous xanthomas are frequently associated with hypercholesterolemia; however, they are also seen in patients with hypertriglyceridemia and are found most frequently over the large joints or hand. Biopsy specimens of xanthomas show collec tions of lipid-containing macrophages (foam cells). Patients with several disorders, including biliary cirrhosis, can have a secondary form of hyperlipidemia with associated tuberous and plane xanthomas. However, patients with plasma cell

dyscrasias have nor molipemic plane xanthomas. This latter form of xanthoma may be ≥12 cm in diameter and is most frequently seen on the neck, upper trunk, and flexural folds. It is important to note that the most common set ting for eruptive xanthomas is uncontrolled diabetes mellitus. The least specific sign for hyperlipidemia is xanthelasma, because at least 50% of the patients with this finding have normal lipid profiles. In tophaceous gout, there are deposits of monosodium urate in the skin around the joints, particularly those of the hands and feet. Addi tional sites of tophi formation include the helix of the ear and the olec ranon and prepatellar bursae. The lesions are firm, yellow to yellow-white in color, and occasionally discharge a chalky material. Their size varies from 1 mm to 7 cm, and the diagnosis can be established by polarized light microscopy of the aspirated contents of a tophus. Lesions of nec robiosis lipoidica are found primarily on the shins (90%), and patients can have diabetes mellitus or develop it subsequently. Characteristic findings include a central yellow color, atrophy (transparency), telan giectasias, and a red to red-brown border. Ulcerations can also develop within the plaques. Biopsy specimens show necrobiosis of collagen and granulomatous inflammation. In pseudoxanthoma elasticum (PXE), due to mutations in the gene ABCC6, there is an abnormal deposition of calcium on the elastic fibers of the skin, eye, and blood vessels. In the skin, the flexural areas such as the neck, axillae, antecubital fossae, and inguinal area are the pri mary sites of involvement. Yellow papules coalesce to form reticulated plaques that have an appearance similar to that of plucked chicken skin. In severely affected skin, hanging, redundant folds develop. Biopsy specimens of involved skin show swollen and irregularly clumped elastic fibers with deposits of calcium. In the eye, the calcium deposits in Bruch’s membrane lead to angioid streaks and choroiditis; in the arteries of the heart, kidney, gastrointestinal tract, and extremities, the deposits lead to angina, hypertension, gastrointestinal bleeding, and claudication, respectively. Adnexal tumors that have differentiated toward sebaceous glands include sebaceous adenoma, sebaceous carcinoma, and sebaceous hyperplasia. Except for sebaceous hyperplasia, which is commonly seen on the face, these tumors are fairly rare. Patients with Muir-Torre syndrome have one or more sebaceous adenoma(s), and they can also have sebaceous carcinomas and sebaceous hyperplasia as well

as keratoacanthomas. As a variant of Lynch syndrome, the internal manifestations of Muir-Torre syndrome include multiple carcinomas of the gastrointestinal tract (primarily colon) as well as cancers of the genitourinary tract. ■ ■RED LESIONS Cutaneous lesions that are red in color have a wide variety of etiologies; in an attempt to simplify their identification, they will be subdivided into papules, papules/plaques, and subcutaneous nodules. Common red papules include arthropod bites and cherry hemangiomas; the latter are small, bright-red, dome-shaped papules that represent a benign proliferation of capillaries. In patients with AIDS (Chap. 208), the development of multiple red hemangioma-like lesions points to bacil lary angiomatosis, and biopsy specimens show clusters of bacilli that stain positively with the Warthin-Starry stain; the pathogens have been identified as Bartonella henselae and Bartonella quintana. Dissemi nated visceral disease is seen primarily in immunocompromised hosts but can occur in immunocompetent individuals. Multiple angiokeratomas are seen in Fabry disease, an X-linked recessive lysosomal storage disease that is due to a deficiency of α-galactosidase A. The lesions are red to red-purple in color and can be quite small in size (1–3 mm), with the most common location being the lower trunk. Associated findings include chronic renal disease, peripheral neuropathy, and corneal opacities (cornea verticillata). While electron photomicrographs demonstrate lamellar lipid depos its in dermal fibroblasts, pericytes, and endothelial cells, nowadays, genetic analysis is more frequently performed for diagnosis. Wide spread acute eruptions of erythematous papules are discussed in the section on

exanthems. There are several infectious diseases that present as erythematous papules or nodules in a lymphocutaneous or sporotrichoid pattern, that is, in a linear arrangement along the lymphatic channels. The two most common etiologies are Sporothrix schenckii (sporotrichosis) and the atypical mycobacterium Mycobacterium marinum. The organisms are introduced as a result of trauma, and a primary inoculation site is often seen in addition to the lymphatic nodules. Additional causes include Nocardia, Leishmania, and other atypical mycobacteria and dimorphic fungi; culture or PCR of lesional tissue will aid in the diagnosis. The diseases that are characterized by erythematous plaques with scale are reviewed in the papulosquamous section, and the various forms of dermatitis are discussed in the section on erythroderma. Additional disorders in the differential diagnosis of red papules/ plaques include cellulitis, polymorphous light eruption (PMLE), cuta neous lymphoid hyperplasia (lymphocytoma cutis), cutaneous lupus, lymphoma cutis, and leukemia cutis. The first three diseases represent primary cutaneous disorders, although cellulitis may be accompanied by a bacteremia. PMLE is characterized by erythematous papules and plaques in a primarily sun-exposed distribution—dorsum of the hand, extensor forearm, and upper trunk. Lesions follow exposure to UV-B and/or UV-A, and in higher latitudes, PMLE is most severe in the late spring and early summer. A process referred to as “hardening” occurs with continued UV exposure, and the eruption fades spontaneously, but in temperate climates, it recurs the next spring. PMLE must be differentiated from cutaneous lupus, and this is accomplished by observation of the natural history, histologic examination, and some times direct immunofluorescence of the lesions. Cutaneous lymphoid hyperplasia (pseudolymphoma) is a benign polyclonal proliferation of lymphocytes within the skin that presents as infiltrated pink-red to red-purple papules and plaques; it must be distinguished from lym phoma cutis. Several types of red plaques are seen in patients with systemic lupus, including (1) erythematous urticarial plaques across the cheeks and nose in the classic butterfly rash; (2) erythematous discoid lesions with fine or “carpet-tack” scale, telangiectasias, central hypopigmentation, peripheral hyperpigmentation, follicular plugging, and atrophy located on the scalp, face, external ears, arms, and upper trunk; and (3) psoria siform or annular lesions of subacute cutaneous lupus with hypopig mented centers located primarily on the extensor arms and upper

trunk. Additional mucocutaneous findings include (1) a violaceous flush on the face and V of the neck; (2) photosensitivity; (3) urticarial vasculitis (see “Urticaria,” above); (4) lupus panniculitis (see below); (5) diffuse alopecia; (6) alopecia secondary to discoid lesions; (7) proximal nailfold telangiectasias and erythema; (8) EM- or TEN-like lesions that may become bullous; (9) oral or nasal ulcers; (10) livedo reticularis; and (11) distal ulcerations secondary to Raynaud’s phenomenon, vasculitis, or livedoid vasculopathy. Patients with only discoid lesions usually have the form of lupus that is limited to the skin. However, up to 10–15% of these patients eventually develop systemic lupus. Direct immunofluorescence of involved skin, in particular discoid lesions, shows deposits of IgG or IgM and C3 in a granular distribution along the dermal-epidermal junction.

Skin Manifestations of Internal Disease CHAPTER 61 In lymphoma cutis, there is a clonal proliferation of malignant lym phocytes within the skin, and the clinical appearance resembles that of cutaneous lymphoid hyperplasia—infiltrated pink-red to red-purple papules and plaques. Lymphoma cutis can occur anywhere on the surface of the skin, whereas the sites of predilection for lymphocy tomas include the malar ridge, tip of the nose, and earlobes. Patients with non-Hodgkin’s lymphomas have specific cutaneous lesions more often than those with Hodgkin’s lymphoma, and, occasionally, the skin nodules precede the development of extracutaneous non-

Hodgkin’s lymphoma or represent the only site of involvement (e.g., primary cutaneous B-cell lymphoma). Arcuate lesions are sometimes seen in lymphoma and lymphocytoma cutis as well as in CTCL. Adult T-cell leukemia/lymphoma that develops in association with HTLV-1 infection is characterized by cutaneous plaques, hypercalcemia, and circulating CD25+ lymphocytes. Leukemia cutis has the same appear ance as lymphoma cutis, and specific lesions are seen more commonly in monocytic leukemias than in lymphocytic or granulocytic leuke mias. Cutaneous chloromas (granulocytic sarcomas) may precede the appearance of circulating blasts in acute myelogenous leukemia and, as such, represent a form of aleukemic leukemia cutis. Sweet syndrome is characterized by pink-red to red-brown edema tous plaques that are frequently painful and occur primarily on the head, neck, and upper extremities. The patients also have fever, neu trophilia, and a dense dermal infiltrate of neutrophils in the lesions. In ~10% of the patients, there is an associated malignancy, most com monly acute myelogenous leukemia. Sweet syndrome has also been reported with myelodysplasia, inflammatory bowel disease, systemic lupus erythematosus, and solid tumors (primarily of the genitourinary tract) as well as drugs (e.g., granulocyte colony-stimulating factor [G-CSF], hypomethylating agents, all-trans-retinoic acid). The dif ferential diagnosis includes neutrophilic eccrine hidradenitis; bullous forms of pyoderma gangrenosum; and, occasionally, cellulitis. Extra cutaneous sites of involvement include joints, muscles, eyes, kidneys (proteinuria, occasionally glomerulonephritis), and lungs (neutrophilic infiltrates). The idiopathic form of Sweet syndrome is seen more often in women, following a respiratory tract infection. Common causes of erythematous subcutaneous nodules include inflamed epidermoid cysts, acne cysts, and furuncles. Panniculitis, an inflammation of the fat, also presents as subcutaneous nodules and is frequently a sign of systemic disease. There are several forms of pan niculitis, including erythema nodosum, erythema induratum/nodu lar vasculitis, lupus panniculitis, lipodermatosclerosis, α1-antitrypsin deficiency, factitial, and fat necrosis secondary to pancreatic disease. Except for erythema nodosum, these lesions may break down and ulcerate or heal with a scar. The shin is the most common location for the nodules of erythema nodosum, whereas the calf is the most common location for lesions of erythema induratum. In erythema nodosum, the nodules are initially red but then develop a blue bruiselike color as they resolve. Patients with erythema nodosum but no underlying systemic illness can still have fever, malaise, leukocytosis, arthralgias, and/or arthritis. However, the possibility of an underlying illness should be excluded, and the most common associations are streptococcal infections, upper respiratory viral infections, sarcoidosis, and inflammatory bowel disease, in addition to drugs (oral contracep tives, sulfonamides, penicillins, bromides, iodides, BRAF inhibitors). Less common associations include bacterial gastroenteritis (Yersinia,

Salmonella) and coccidioidomycosis followed by pregnancy, Sweet syndrome, tuberculosis, histoplasmosis, brucellosis, and infections with Chlamydophilia pneumoniae, Chlamydia trachomatis, Mycoplasma pneumoniae, or hepatitis B virus.

Erythema induratum and nodular vasculitis have overlapping fea tures clinically and histologically, and whether they represent two sepa rate entities or the ends of a single disease spectrum is a point of debate; in general, the latter is usually idiopathic and the former is associated with the presence of Mycobacterium tuberculosis DNA by PCR within skin lesions. The lesions of lupus panniculitis are found primarily on the cheeks, upper arms, and buttocks (sites of abundant fat) and are seen in both the cutaneous and systemic forms of lupus. The overly ing skin may be normal, erythematous, or have the changes of discoid lupus. The subcutaneous fat necrosis that is

associated with pancreatic disease is presumably secondary to circulating lipases and is seen in patients with pancreatic carcinoma as well as in patients with acute and chronic pancreatitis. In this disorder, there may be an associated arthritis, fever, and inflammation of visceral fat. Histologic examina tion of deep incisional biopsy specimens will aid in the diagnosis of the particular type of panniculitis. PART 2 Cardinal Manifestations and Presentation of Diseases Subcutaneous erythematous nodules are also seen in cutaneous polyarteritis nodosa and as a manifestation of systemic vasculitis when there is involvement of medium-sized vessels, for example, systemic polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis, or granulomatosis with polyangiitis (Chap. 375). Cutaneous polyarteritis nodosa, more recently referred to as cutaneous arteritis, presents with painful subcutaneous nodules and ulcers within a red-purple, netlike pattern of livedo reticularis. The latter is due to slowed blood flow through the superficial horizontal venous plexus. The majority of lesions are found on the lower extremities, and while arthralgias and myalgias may accompany cutaneous polyarteritis nodosa, there is no evidence of systemic involvement. In both the cutaneous and systemic forms of vasculitis, skin biopsy specimens of the associated nodules will show the changes characteristic of a necrotizing vasculitis and/or granulomatous inflammation. ■ ■RED-BROWN LESIONS The cutaneous lesions in sarcoidosis (Chap. 379) are classically red to red-brown in color, and with diascopy (pressure with a glass slide), a yellow-brown residual color is observed that is secondary to the granulomatous infiltrate. The waxy papules and plaques may be found anywhere on the skin, but the face is the most common location. Usu ally there are no surface changes, but occasionally, the lesions will have scale. Biopsy specimens of the papules show “naked” granulomas in the dermis, that is, granulomas surrounded by a minimal number of lymphocytes. Other cutaneous findings in sarcoidosis include annular lesions with an atrophic or scaly center, papules within scars, hypopig mented papules and plaques, subcutaneous plaques, alopecia, acquired ichthyosis, erythema nodosum, and lupus pernio (see below). The differential diagnosis of sarcoidosis includes foreign-body granulomas produced by chemicals such as beryllium and zirconium, late secondary syphilis, reactive granulomatous dermatitis, and lupus vulgaris. Lupus vulgaris is a form of cutaneous tuberculosis that is seen in previously infected and sensitized individuals. There is often underlying active tuberculosis elsewhere, usually in the lungs or lymph nodes. Lesions occur primarily in the head and neck region and are red-brown plaques with a yellow-brown color on diascopy. Secondary scarring can develop within the central portion of the plaques. Cultures or PCR analysis of the lesions should be performed, along with an interferon γ release assay of peripheral blood, because it is rare for the acid-fast stain to show bacilli within the dermal granulomas. A generalized distribution of red-brown macules and papules is seen in the maculopapular form of mastocytosis, also known as urticaria pigmentosa (Chap. 366). Each lesion represents a collection of mast cells in the dermis, with hyperpigmentation of the overlying epidermis. Stimuli such as rubbing cause these mast cells to degranulate, and this leads to the formation of localized urticaria (Darier’s sign). Additional symptoms can result from mast cell degranulation and include head ache, flushing, diarrhea, and pruritus. Mast cells also infiltrate various

organs such as the liver, spleen, and gastrointestinal tract, and accu mulations of mast cells in the bones may produce either osteosclerotic or osteolytic lesions on radiographs. In the majority of these patients, however, the internal involvement remains indolent. A subtype of chronic cutaneous small-vessel vasculitis, erythema elevatum diutinum (EED), also presents with papules that are red-brown in color. The papules coalesce into plaques on the extensor surfaces of knees, elbows, and the small joints of the hand. Flares of EED have been associated with streptococcal

infections. ■ ■BLUE LESIONS Lesions that are blue in color are the result of vascular ectasias, hyper plasias, and tumors or melanin pigment within the dermis. Venous lakes (ectasias) are compressible dark-blue lesions that are found com monly in the head and neck region. Venous malformations are also compressible blue papulonodules and plaques that can occur anywhere on the body, including the oral mucosa. When there are multiple papu lonodules rather than a single congenital lesion, the patient may have the blue rubber bleb syndrome or Maffucci's syndrome due to muta tions in TEK or IDH1, respectively. Patients with the blue rubber bleb syndrome also have vascular anomalies of the gastrointestinal tract that may bleed, whereas patients with Maffucci's syndrome have associated osteochondromas. Blue nevi (moles) are seen when there are collec tions of pigment-producing nevus cells in the dermis. These benign papular lesions are dome-shaped and occur most commonly on the dorsum of the hand or foot or in the head and neck or presacral region. ■ ■VIOLACEOUS LESIONS Violaceous papules and plaques are seen in lupus pernio, lymphoma cutis, and cutaneous lupus. Lupus pernio is a particular type of sarcoid osis that involves the tip and alar rim of the nose as well as the earlobes, with lesions that are violaceous in color rather than red-brown. This form of sarcoidosis is associated with involvement of the upper respira tory tract. The plaques of lymphoma cutis and cutaneous lupus may be red or violaceous in color and were discussed above. ■ ■PURPLE LESIONS Purple-colored papules and plaques are seen in vascular tumors, such as Kaposi's sarcoma (Chap. 208) and angiosarcoma, and when there is extravasation of red blood cells into the skin in association with inflammation, as in palpable purpura (see "Purpura," below). Patients with congenital or acquired AV fistulas and venous hypertension can develop purple papules on the lower extremities that can resemble Kaposi's sarcoma clinically and histologically; this condition is referred to as pseudo-Kaposi's sarcoma (acral angiodermatitis). Angiosarcoma is found most commonly on the scalp and face of elderly patients or within areas of chronic lymphedema and presents as purple papules and plaques. In the head and neck region, the tumor often extends beyond the clinically defined borders and may be accompanied by facial edema. ■ ■BROWN AND BLACK LESIONS Brown- and black-colored papules are reviewed in "Hyperpigmenta tion," above. ■ ■CUTANEOUS METASTASES These are discussed last because they can have a wide range of colors. Most commonly, they present as either firm, skin-colored subcuta neous nodules or firm, red to red-brown papulonodules, whereas metastatic melanoma can be pink, blue, or black in color. Cutaneous metastases develop from hematogenous or lymphatic spread and are most often due to the following primary carcinomas: in men, mela noma, oropharynx, lung, and colon; and in women, breast, melanoma, and ovary. These metastatic lesions may be the initial presentation of the carcinoma, especially when the primary site is the lung. PURPURA (Table 61-16) Purpura are seen when there is an extravasation of red blood cells into the dermis and, as a result, the lesions do not blanch with pressure. This is in contrast to those erythematous or violet-colored

TABLE 61-16 Causes of Purpura I. Primary cutaneous disorders A. Nonpalpable

1. Trauma
2. Solar (actinic, senile) purpura
3. Steroid purpura
4. Stasis purpura due to venous hypertension
5. Capillaritis
6. Livedoid vasculopathy in the setting of venous hypertensiona II. Drugs (e.g., antiplatelet agents, anticoagulants) III. Systemic diseases A. Nonpalpable

7. Clotting disturbances a. Thrombocytopenia (including ITP) b. Abnormal platelet function c. Clotting factor defects
8. Vascular fragility a. Amyloidosis (within normal-appearing skin) b. Ehlers-Danlos syndrome c. Scurvy
9. Thrombi a. Disseminated intravascular coagulation, purpura fulminans b. Warfarin (Coumadin□)-induced necrosis c. Heparin-induced thrombocytopenia and thrombosis d. Antiphospholipid antibody syndrome e. Monoclonal cryoglobulinemia f. Vasculopathy induced by levamisole-adulterated cocaineb g. SARS-CoV-2 infection h. Thrombotic thrombocytopenic purpura i. Thrombocytosis j. Homozygous protein C or protein S deficiency
10. Emboli a. Cholesterol b. Fat
11. Possible immune complex a. Gardner-Diamond syndrome (autoerythrocyte sensitivity) b. Waldenström's hypergammaglobulinemic purpura
12. Calciphylaxis B. Palpable
13. Vasculitis a. Cutaneous small-vessel vasculitis, including in the setting of systemic vasculitides
14. Embolic a. Acute meningococcemia b. Disseminated gonococcal infection c. Rocky Mountain spotted fever d. Ecthyma gangrenosum aAlso associated with underlying disorders that lead to hypercoagulability/ thrombophilia, e.g., factor V Leiden, protein C dysfunction/deficiency. bCombined vasculopathy/vasculitis can be seen. cBacterial (including rickettsial), fungal, or parasitic. Abbreviations: ITP, idiopathic thrombocytopenic purpura; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. lesions that are due to localized vasodilatation—they do blanch with pressure. Purpura (≥3 mm) and petechiae (≤2 mm) are divided into two major groups: palpable and nonpalpable (macular). The most fre quent causes of nonpalpable purpura and petechiae are primary cuta neous disorders such as trauma, solar (actinic) purpura, stasis purpura, and capillaritis. Less common causes are steroid purpura and livedoid vasculopathy (see "Ulcers," below). Solar purpura are seen primarily on the extensor forearms, whereas steroid purpura secondary to potent topical glucocorticoids or endogenous or exogenous Cushing's syn drome can be more widespread. In both cases, there is alteration of the

supporting connective tissue that surrounds the dermal blood vessels. In contrast, the petechiae that result from capillaritis are found primar ily on the lower extremities. In capillaritis, there is an extravasation of erythrocytes as a result of perivascular lymphocytic inflammation. The petechiae are bright red, 1–2 mm in size, and scattered within yellow-

brown patches. The yellow-brown color is caused by hemosiderin deposits within the dermis.

Systemic causes of nonpalpable purpura fall into several categories, and those secondary to clotting disturbances and vascular fragility will be discussed first. The former group includes thrombocytopenia (Chap. 120), abnormal platelet function as is seen in uremia, and clot ting factor defects. The initial site of presentation for thrombocytope nia-induced petechiae is the distal lower extremity. Capillary fragility leads to nonpalpable purpura in patients with systemic amyloidosis (see "Papulonodular Skin Lesions," above), disorders of collagen produc tion such as Ehlers-Danlos syndrome, and scurvy. In scurvy, there are flattened corkscrew hairs with surrounding perifollicular hemorrhage on the lower extremities, in addition to gingivitis. Vitamin C is a cofac tor for lysyl

hydroxylase, an enzyme involved in the posttranslational modification of procollagen that is necessary for cross-link formation. Skin Manifestations of Internal Disease CHAPTER 61 In contrast to the previous group of disorders, the noninflammatory purpura seen in the following group of diseases are associated with thrombi formation within vessels and have a retiform configuration. It is important to note that these thrombi are demonstrable in skin biopsy specimens. This group of disorders includes disseminated intravascu lar coagulation (DIC), monoclonal cryoglobulinemia, thrombocytosis, thrombotic thrombocytopenic purpura, antiphospholipid antibody syndrome, and reactions to warfarin and heparin (heparin-induced thrombocytopenia and thrombosis). DIC is triggered by several types of infection (gram-negative, gram-positive, viral, and rickettsial) as well as by tissue injury and neoplasms. Widespread purpura and hem orrhagic infarcts of the distal extremities are seen. Similar lesions are found in purpura fulminans, which is a form of DIC associated with fever and hypotension that occurs more commonly in children fol lowing an infectious illness such as varicella, scarlet fever, or an upper respiratory tract infection. In both disorders, hemorrhagic bullae can develop in involved skin. Monoclonal cryoglobulinemia is associated with plasma cell dyscra sias, chronic lymphocytic leukemia, and lymphoma. Purpura, primar ily of the lower extremities, and hemorrhagic infarcts of the fingers, toes, nose, and ears are seen in these patients. Exacerbations of disease activity can follow cold exposure or an increase in serum viscosity. Biopsy specimens show precipitates of the cryoglobulin within dermal vessels. Similar deposits have been found in the lung, brain, and renal glomeruli. Patients with thrombotic thrombocytopenic purpura can also have hemorrhagic infarcts as a result of intravascular thromboses. Additional signs include microangiopathic hemolytic anemia and fluc tuating neurologic abnormalities, especially headaches and confusion. Administration of warfarin can result in painful areas of erythema that become purpuric and then necrotic with an adherent black eschar; the condition is also referred to as Coumadin -induced necrosis. This reaction is seen more often in women and in areas with abundant subcutaneous fat—breasts, abdomen, buttocks, thighs, and calves. The erythema and purpura develop between the third and tenth day of therapy, most likely as a result of a transient imbalance in the levels of anticoagulant and procoagulant vitamin K–dependent factors. Contin ued therapy does not exacerbate preexisting lesions, and patients with an inherited or acquired deficiency of protein C are at increased risk for this particular reaction as well as for purpura fulminans and calciphy laxis. The latter can have a similar clinical appearance. Purpura secondary to cholesterol emboli are usually seen on the lower extremities of patients with atherosclerotic vascular disease. They often follow anticoagulant therapy or an invasive vascular proce dure such as an arteriogram but also occur spontaneously from disin tegration of atheromatous plaques. Associated findings include livedo reticularis, gangrene, cyanosis, ischemic ulcerations, and peripheral eosinophilia. Multiple step sections of the biopsy specimen may be necessary to demonstrate the cholesterol clefts within the vessels. Pete chiae are also an important sign of fat embolism and occur primarily on

the upper body 2–3 days after a major injury. By using special fixatives, the emboli can be demonstrated in biopsy specimens of the petechiae. Rarely, emboli of tumor or thrombus are seen in patients with atrial myxomas and marantic endocarditis.

In the Gardner-Diamond syndrome (autoerythrocyte sensitivity), female patients develop large ecchymoses within areas of painful, warm erythema. Intradermal injections of autologous erythrocytes or phos phatidyl serine derived from the red cell membrane can reproduce the lesions in some patients; however, there are instances where a reaction is seen at an injection site of the

forearm but not in the midback region. The latter has led some observers to view Gardner-Diamond syndrome as a cutaneous manifestation of severe emotional stress. More recently, the possibility of platelet dysfunction (as assessed via aggregation stud ies) has been raised. Waldenström's hypergammaglobulinemic purpura, more recently referred to as recurrent macular vasculitis in hypergam maglobulinemia, is a chronic disorder characterized by recurrent crops of petechiae and larger purpuric macules on the lower extremities. There are circulating complexes of IgG or IgA rheumatoid factor, and exacerbations are associated with prolonged standing or walking. Patients may have an underlying autoimmune connective tissue dis ease, e.g., Sjögren's syndrome. PART 2 Cardinal Manifestations and Presentation of Diseases Palpable purpura are further subdivided into vasculitic and embolic. In the group of vasculitic disorders, cutaneous small-vessel vasculitis, also known as leukocytoclastic vasculitis (LCV), is the one most com monly associated with palpable purpura (Chap. 375). Underlying etiologies include drugs (e.g., antibiotics), infections (e.g., hepatitis C virus), and autoimmune connective tissue diseases (e.g., rheumatoid arthritis, Sjögren's syndrome, lupus). Henoch-Schönlein purpura (HSP) is a subtype of acute LCV that is seen more commonly in children and adolescents following an upper respiratory infection. The majority of lesions are found on the lower extremities and buttocks. Systemic manifestations include fever, arthralgias (primarily of the knees and ankles), abdominal pain, gastrointestinal bleeding, and nephritis. Direct immunofluorescence examination shows deposits of IgA within dermal blood vessel walls. Renal disease is of particular concern in adults with IgA vasculitis. Several types of infectious emboli can give rise to palpable purpura. These embolic lesions are usually irregular in outline as opposed to the lesions of LCV, which are circular in outline. The irregular outline is indicative of a cutaneous infarct, and the size corresponds to the area of skin that received its blood supply from that particular arteriole or artery. The palpable purpura in LCV are circular because the eryth rocytes simply diffuse out evenly from the postcapillary venules as a result of inflammation. Infectious emboli are most commonly due to gram-negative cocci (meningococcus, gonococcus), gram-negative rods (Enterobacteriaceae), and gram-positive cocci (Staphylococcus). Additional causes include Rickettsia and, in immunocompromised patients, Aspergillus and other opportunistic fungi. The embolic lesions in acute meningococcemia are found primarily on the trunk, lower extremities, and sites of pressure, and a gunmetal-gray color often develops within them. Their size varies from a few millime ters to several centimeters, and the organisms can be cultured from the lesions. Associated findings include a preceding upper respiratory tract infection; fever; meningitis; DIC; and, in some patients, a deficiency of the terminal components of complement. In disseminated gonococcal infection (arthritis-dermatitis syndrome), a small number of inflam matory papules and vesicopustules, often with central purpura or hemorrhagic necrosis, are found on the distal extremities. Additional symptoms include arthralgias, tenosynovitis, and fever. To establish the diagnosis, a Gram stain of these lesions should be performed. Rocky Mountain spotted fever is a tick-borne disease that is caused by Rickettsia rickettsii. A several-day history of fever, chills, severe head ache, and photophobia precedes the onset of the cutaneous eruption. The initial lesions are erythematous macules and papules on the wrists, ankles, palms, and soles. With time, the lesions spread centripetally and become purpuric. Lesions of ecthyma gangrenosum begin as edematous, erythematous papules or plaques and then develop central purpura and necrosis. Bullae formation also occurs in these lesions, and they are frequently

found in the girdle region. The organism that is classically associated with ecthyma gangrenosum is Pseudomonas aeruginosa, but other gram-negative rods such as Klebsiella, Escherichia coli, and Serratia can produce similar lesions. In immunocompromised hosts, the list of potential pathogens

is expanded to include Candida and other oppor tunistic fungi (e.g., Aspergillus, Fusarium). ULCERS The approach to the patient with a cutaneous ulcer is outlined in Table 61-17. Peripheral vascular diseases of the extremities are reviewed in Chap. 292, as is Raynaud's phenomenon. Livedoid vasculopathy (livedoid vasculitis; atrophie blanche) repre sents a combination of a vasculopathy plus intravascular thrombosis. Purpuric lesions and livedo reticularis are found in association with painful ulcerations of the lower extremities. These ulcers are often TABLE 61-17 Causes of Mucocutaneous Ulcers I. Primary cutaneous disorders A. Peripheral vascular disease (Chap. 292)

1. Venous
2. Arteriala B. Livedoid vasculopathy in the setting of venous hypertensionb C. Squamous cell carcinoma (e.g., within scars), basal cell carcinomas D. Infections, e.g., ecthyma caused by Streptococcus (Chap. 153) E. Physical, e.g., trauma, pressure F. Drugs, e.g., hydroxyurea II. Systemic diseases A. Lower legs
3. Small-vessel and medium-vessel vasculitisc
4. Hemoglobinopathies (Chap. 103)
5. Cryoglobulinemia,c cryofibrinogenemia
6. Cholesterol embolia,c
7. Necrobiosis lipoidicad
8. Antiphospholipid syndrome (Chap. 121)
9. Neuropathice (Chap. 415)
10. Panniculitis
11. Kaposi's sarcoma, acral angiodermatitis (pseudo-Kaposi's sarcoma)
12. Diffuse dermal angiomatosis B. Hands and feet
13. Raynaud's phenomenon (Chap. 292)
14. Buerger disease C. Generalized
15. Pyoderma gangrenosum, but most commonly legs
16. Calciphylaxis (Chap. 422)
17. Infections, e.g., dimorphic fungi, leishmaniasis
18. Lymphoma D. Face, especially perioral, and anogenital
19. Chronic herpes simplexf III. Mucosal A. Aphthae B. Drug-induced mucositis C. Behçet's disease (Chap. 376) D. Erythema multiforme major, Stevens-Johnson syndrome, TEN E. Primary blistering disorders (Chap. 62) F. Lupus erythematosus, lichen planus, lichenoid GVHD G. Inflammatory bowel disease H. Acute HIV infection I. Reactive arthritis aUnderlying atherosclerosis. bAlso associated with underlying disorders that lead to hypercoagulability/thrombophilia, e.g., factor V Leiden, protein C dysfunction/ deficiency, antiphospholipid antibodies. cReviewed in section on purpura. dReviewed in section on papulonodular skin lesions. eFavors plantar surface of the foot. fSign of immunosuppression. Abbreviations: GVHD, graft versus host disease; HIV, human immunodeficiency virus; TEN, toxic epidermal necrolysis.

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