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- *Occupational Diseases and Injuries* [Update July 2016]
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View links to resources related to common dermatologic conditions.
— American Academy of Dermatology
   www.aad.org
— American College of Obstetricians and Gynecologists
   www.acog.org

See full text of past issues and any relevant changes or updates.
This monograph is designed to enable the obstetrician–gynecologist to do the following:

- Understand the pathophysiology and clinical manifestations of common dermatologic conditions
- Screen and evaluate patients who present with dermatologic problems
- Initiate management of common dermatologic disorders and make appropriate referrals of more complicated cases
- Counsel patients regarding the prevention of common disorders and best practices of skin, hair, and nail care

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Credit for *Clinical Updates in Women’s Health Care: Common Dermatologic Conditions*, Volume XVII, Number 1, January 2018, is initially available through December 2021. During that year, the unit will be re-evaluated. If the content remains current, credit is extended for an additional 3 years.

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Commonly, patients ask obstetrician–gynecologists about skin conditions at the time of annual health maintenance examinations or during pregnancy. The goal of this monograph is to provide a review of common skin lesions encountered in the office. Accordingly, the monograph guides the reader through initial evaluation, management, and indications for referral. The authors discuss basic care of the skin, hair, and nails and preventive strategies for dermatologic conditions. Readers should find the section on cutaneous manifestations of systemic disease to be particularly informative. Special attention is given to dermatologic changes that occur during pregnancy and dermatoses unique to pregnancy.

Russell R. Snyder, MD
Editor
ABSTRACT: The skin is the largest organ in the human body, and as such, cutaneous problems constitute a common component of visits to medical professionals. The skin functions as a physiologic barrier and a major organ of homeostasis. The practicing obstetrician–gynecologist can play an important role in identifying skin diseases and initiating management. Additionally, the skin often reflects internal disease states. An astute health care provider can identify systemic conditions early, with the goal of improving management. This monograph reviews common cutaneous conditions, both benign and malignant, hair and nail disorders, and skin conditions unique to the adult woman.

The skin holds a special position as the largest organ in the human body. Acting as a defender against the external world and a major organ of homeostasis, the skin plays roles in immunity, fluid conservation, temperature regulation, hormonal control, and sensation. Changes in the skin often are noted when systemic disease occurs, making observation of the skin an important factor in identifying internal disease. Aside from its biologic functions, the skin has a strong social function with ramifications to individuals who have skin diseases, which are visible to them and to the surrounding world. Because skin disease is visible to the patient and the health care provider, patients often take high levels of interest in their skin disease because any worsening or improvement of their condition is visually apparent.

Dermatologic problems make up a large portion of office visits. Studies show that more than one third of visits to a primary care provider concerned at least one skin problem (1). Obstetrician–gynecologists often act as the sole health care providers to women and, therefore, will see a large number of skin-related problems. Appropriate screening provided by obstetrician–gynecologists can detect disease at an early stage, reducing morbidity and mortality for their patients. Obstetrician–gynecologists have a unique role regarding the skin care of women, particularly the genital skin, an area often overlooked or avoided by other health care providers. Additionally, the unique cutaneous conditions that arise during pregnancy can be recognized early by obstetrician–gynecologists with early management leading to improved patient safety and comfort.

The goal of this monograph is to provide background information on the pathophysiology and clinical manifestations of commonly encountered dermatologic conditions to enable initial evaluation and screening of patients with these conditions, including guidelines on when referral to a specialist is appropriate. Preventive strategies and basic care of the skin, hair, and nails also will be discussed.
The following section will outline terminology commonly used when discussing and describing the skin. A basic review of skin anatomy and function follows, which forms a foundation for discussion of common conditions and their presentations.

The diagnosis of skin disease is based on examination and correct interpretation of cutaneous physical signs. Dermatologic examination should include assessment of the whole skin in addition to the area of involvement. Adequate illumination is important for a good assessment of the skin. Skin lesions can be divided into lesions of primary and secondary morphology and special lesions (Table 1).

### Table 1. Types of Skin Lesions

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macule</td>
<td>Flat, nonpalpable, and circumscribed skin discoloration less than 1 cm in size</td>
<td>Café-au-lait macule, vitiligo, lentigo, tinea versicolor, melasma, labial melanocytic macule, and vulvar melanosis</td>
</tr>
<tr>
<td>Patch</td>
<td>Flat, nonpalpable, and circumscribed skin discoloration 1 cm or greater in size</td>
<td>Vitiligo, leucoderma, nevus flammeus, and melasma</td>
</tr>
<tr>
<td>Papule</td>
<td>Solid elevation, less than 0.5 cm in diameter</td>
<td>Acrochordon (skin tag), acne, nevus, actinic keratosis, seborrheic keratosis, hyperkeratosis of the nipple and areola, melanoma, molluscum contagiosum, folliculitis, pilomatricoma, dermatofibroma, and angioma</td>
</tr>
<tr>
<td>Plaque</td>
<td>Broad papule or confluent papules, greater than 0.5 cm, without a deep component</td>
<td>Psoriasis, eczema, tinea corporis, mycosis fungoides, extramammary Paget disease, and Paget disease of the breast</td>
</tr>
<tr>
<td>Nodule</td>
<td>Large deep papule greater than 0.5 cm in diameter, with solid elevation</td>
<td>Rheumatoid nodule, xanthoma, lipoma, metastatic carcinoma, erythema nodosum, calcified hematoma, and neurofibroma</td>
</tr>
<tr>
<td>Tumor</td>
<td>Large nodule</td>
<td>Lipoma, Merkel cell carcinoma, plexiform neurofibroma, dermatofibrosarcoma protuberans, advanced basal cell carcinoma, and squamous cell carcinoma</td>
</tr>
<tr>
<td>Wheal</td>
<td>Evanescent, pruritic edematous, and plaque (a hive)</td>
<td>Urticaria, dermatographism, and urticaria pigmentosum</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Papule that contains clear fluid (a blister); epidermal; may be unilocular or multilocular; greater than 0.5 cm in diameter</td>
<td>Herpes simplex, herpes zoster, chicken pox, contact dermatitis, and poison ivy dermatitis</td>
</tr>
<tr>
<td>Bulla</td>
<td>Circumscribed collection of free fluid greater than 0.5 cm in diameter</td>
<td>Pemphigus vulgaris, bullous pemphigoid, bullous impetigo, and bullous fixed drug eruption</td>
</tr>
<tr>
<td>Pustule</td>
<td>Circumscribed collection of leukocytes and free fluid that vary in size</td>
<td>Acne, folliculitis, pustular psoriasis, impetigo, and folliculitis</td>
</tr>
<tr>
<td>Cyst</td>
<td>Nodule that contains fluid</td>
<td>Acne, epidermal inclusion cyst, Bartholin gland cyst, and proliferating trichilemmal cyst of the vulva</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scale (exfoliation)</td>
<td>Thick stratum corneum resulting from hyper-proliferation or increased</td>
<td>Psoriasis, toxic epidermal necrolysis, staphylococcal scalded skin</td>
</tr>
<tr>
<td></td>
<td>keratinocytes cohesion</td>
<td>syndrome, eczema, ichthyosis, and actinic keratosis</td>
</tr>
<tr>
<td>Crust (scab)</td>
<td>Collection of dry debris, dried sebum, pus, or blood</td>
<td>Impetigo and crust of genital herpes</td>
</tr>
<tr>
<td>Excoriation and</td>
<td>Linear erosions caused by mechanical means</td>
<td>Eczema and scabies</td>
</tr>
<tr>
<td>abrasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fissure</td>
<td>Linear cleft into the epidermis or dermis</td>
<td>Dry skin from soap or detergents and chapping (eg, hand dermatitis)</td>
</tr>
<tr>
<td>Erosion</td>
<td>Loss of all of the epidermis (heals without a scar)</td>
<td>Herpes zoster, herpes simplex, and impetigo</td>
</tr>
<tr>
<td>Ulcer</td>
<td>Loss of the epidermis and portions of the dermis (heals with scarring)</td>
<td>Basal cell carcinoma, decubitus ulcer, and dystrophic epidermolysis</td>
</tr>
<tr>
<td>Scars</td>
<td>New connective tissue replacing the lost dermal tissue (dermal–epidermal</td>
<td>Discoid lupus erythematosus, hypertrophic scars, keloids, and scarring</td>
</tr>
<tr>
<td></td>
<td>damage)</td>
<td>alopecia</td>
</tr>
<tr>
<td>Lichenification</td>
<td>Epidermal hyperplasia</td>
<td>Caused by chronic scratching or rubbing (eg, atopic dermatitis)</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Thinning of the epidermis, dermis, or both</td>
<td>Iatrogenic (corticosteroid injections), topical steroid overuse, morphea,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and lichen sclerosis (atrophic plaque)</td>
</tr>
<tr>
<td><strong>Special</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>Collection of purulent material in the dermis or subcutaneous fat</td>
<td>Infection</td>
</tr>
<tr>
<td>Burrow</td>
<td>Tunnel in the skin</td>
<td>Scabies</td>
</tr>
<tr>
<td>Comedone</td>
<td>Keratin, sebum, microorganisms, and epithelial debris within a dilated</td>
<td>Acne</td>
</tr>
<tr>
<td></td>
<td>follicular opening</td>
<td></td>
</tr>
<tr>
<td>Cyst</td>
<td>Nodule that contains fluid</td>
<td>Acne, epidermal inclusion cyst, Bartholin gland cyst, pilar cyst,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>steatocystadenoma, and eccrine or apocrine hydrocystoma</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>Deposition of blood in the extravascular tissue; larger than petechiae</td>
<td>Trauma</td>
</tr>
<tr>
<td>Fistula</td>
<td>Channel that communicates between two surfaces</td>
<td>Crohn disease, surgery, and hidradenitis suppurativa Hurley stage 3</td>
</tr>
<tr>
<td>Hematoma</td>
<td>Extravasations of blood, usually causing a swelling</td>
<td>Trauma or needle stick</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Pinpoint red lesion caused by blood in the extravascular tissue</td>
<td>Use of platelet inhibitors, such as acetyl salicylic acid or coumadin;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>infection (eg, endocarditis); and vitamin K deficiency</td>
</tr>
<tr>
<td>Sinus</td>
<td>Elongated tunnel, opening on one surface and having a blind pouch on the</td>
<td>Infection, foreign body, and hidradenitis suppurativa</td>
</tr>
<tr>
<td></td>
<td>other end</td>
<td></td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>Superficial cutaneous small vessels</td>
<td>Basal cell carcinoma and rosacea</td>
</tr>
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</table>
Skin Anatomy

In broad terms, the skin consists of the following three layers:

1. Epidermis
2. Dermis
3. Subcutaneous tissue

An illustration of basic skin anatomy is provided in Figure 1.

![Skin structure](image)

**Figure 1.** Skin structure. (Courtesy of Keshav G. Iyer and Mirra Chinta).

**Epidermis**

The epidermis is a stratified squamous epithelium, and it forms the tough, outer layer of the skin that is predominantly made up of keratinocytes that originate from cells in the deepest layer of the epidermis called the basal layer. These keratinocytes synthesize the protein keratin. Keratinocytes are connected to each other by protein bridges called desmosomes. These keratinocytes are in the constant transition from deeper layers to the superficial layer. Keratinocytes migrate slowly upward to the skin surface. Most of the skin has four layers of epidermis

1. The stratum basale (germinativum or basal cell layer)
2. Stratum spinosum (spinous or prickle cell layer)
3. Stratum granulosum (granular cell layer)
4. Stratum corneum (horny layer)

Furthermore, selected sites have a fifth layer called the stratum lucidum, which is a thin layer of translucent cells seen in thick epidermis.
Stratum basale is the innermost layer of the epidermis that mostly comprises dividing and nondividing keratinocytes that are attached to the basement membrane by hemidesmosomes. As keratinocytes divide, differentiate, and mature, they move from this deep layer to the surface. Additionally, the layer also has scattered cells producing pigment melanin (melanocytes) that are characterized by their dendritic processes that stretch between relatively large numbers of neighboring keratinocytes. Melanin produced by melanocytes accumulates in melanosomes and is transferred to the adjacent keratinocytes. Melanin pigment provides protection against ultraviolet (UV) radiation and is responsible for the skin discoloration. Merkel cells (touch receptors) also are found in the basal layer.

As keratinocytes mature, they move toward the outer layer of skin, initially forming the stratum spinosum. Intercellular protein bridges (desmosomes) connect these cells. This layer also contains dendritic cell population (Langerhans cells) that plays a significant role in immune reactions as antigen-presenting cells.

Keratinocytes continue to flatten losing their nuclei, and their cytoplasm appears granular at this level as they continue their upward migration through stratum granulosum. This layer typically is not seen in patients with psoriasis.

The outermost portion of the epidermis is called stratum corneum. This layer is relatively waterproof and prevents most bacteria, viruses, and other foreign substances from entering the body. This layer has increased thickness in areas that undergo more friction, such as palms and soles, and accounts for scale or hyperkeratosis noted under pathology.

**Dermis**

The dermis is a thick layer of fibrous and elastic tissue (made mostly of collagen, elastin, and fibrillin) that gives the skin its flexibility and strength. Furthermore, the dermis contains nerve endings, eccrine (sweat) glands and apocrine (sebaceous) glands, hair follicles, and blood vessels. Dermis is divided into two layers: 1) thin papillary layer and 2) thicker reticular layer.

**Subcutaneous Tissue**

Below the dermis lies subcutaneous tissue. It is a layer of adipose tissue that helps insulate the body from heat and cold, provides protective padding, and serves as an energy storage area.

**Functions of the Skin**

Skin has the following functions (Table 2):

- Providing a protective barrier against mechanical, thermal (including UV protection), and physical injury as well as noxious or harmful agents, including viruses and bacteria
- Preventing loss of moisture
• Immunologic surveillance
• Vitamin D synthesis
• Sensory organ function
• Temperature control

Table 2. Components of Skin and Their Functions

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
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<tbody>
<tr>
<td><strong>Structural</strong></td>
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<tr>
<td>Skin</td>
<td>Physical barrier</td>
</tr>
<tr>
<td>Blood and lymphatic vessels</td>
<td>Transport network for cellular defense</td>
</tr>
<tr>
<td><strong>Cellular</strong></td>
<td></td>
</tr>
<tr>
<td>Langerhans cells</td>
<td>Antigen presentation</td>
</tr>
<tr>
<td>T-lymphocytes</td>
<td>Facilitate immune reaction, self-regulatory mechanism through T-regulatory cells</td>
</tr>
<tr>
<td>Mast cells</td>
<td>Facilitate skin inflammatory reactions</td>
</tr>
<tr>
<td>Keratinocyte</td>
<td>Secretes inflammatory cytokines</td>
</tr>
<tr>
<td><strong>Immunologic</strong></td>
<td></td>
</tr>
<tr>
<td>Major histocompatibility complex</td>
<td>Enables antigen recognition by immune cells</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td>Cell-mediated chemicals produced by components of the cellular immune system</td>
</tr>
<tr>
<td>Eicosanoids</td>
<td>Nonspecific inflammatory mediators produced by mast cells, macrophages, and keratinocytes</td>
</tr>
<tr>
<td>Adhesion molecules</td>
<td>Cell surface molecules that facilitate intercellular binding and communication</td>
</tr>
<tr>
<td>Complement cascade</td>
<td>Triggers a host of destructive mechanisms, including opsonization, lysis, chemotaxis, and mast cell degranulation</td>
</tr>
</tbody>
</table>

The primary function of the skin is to act as a barrier to prevent microorganisms in the environment from invading the body and to prevent water loss. The integrity of the skin is critical for this function. The outermost part of the skin, the stratum corneum, is made of cornified keratinocytes with lamellar membrane (lipid) coating. These cornified keratinocytes that form the outermost layer of the skin are constantly shed and replaced. Structural proteins, such as filaggrin, keratin, enzymes (such as proteases), lipids, and antimicrobial peptides (such as defensins) play a role in maintaining the barrier function of the skin.

The pH of the skin is acidic (range 4–6), and acidic pH is unfavorable to the microbial growth. Fatty acids present in sebum also have an antimicrobial effect. As discussed earlier, the layers of keratin and the lipids and skin integrity help in preventing the loss of moisture.
Skin is the first line of defense for the body and is immunologically active. Langerhans cells present in the epidermis act as antigen-presenting cells. Skin is critical in preventing a vast array of microorganisms from invading the body. Mast cells, neutrophils, macrophages, natural killer cells, and eosinophils all form part of the innate immune response, whereas B-lymphocytes and T-lymphocytes play a key role in adaptive immunity and are stimulated by presentation of epitopes (proteins) by the antigen-presenting cells.

Skin is the initial site for vitamin D synthesis. Vitamin D is a fat-soluble vitamin that plays a significant role in calcium homeostasis and bone health. The first step to vitamin D₃ production is generation of 7-dehydrocholesterol, produced naturally in the skin, which is then converted (on UV light exposure) to calciferol or pre-vitamin D₃, which then undergoes isomerization to form vitamin D.

Skin also contains Merkel cells, which are tactile sensory receptors. They also contain lamellar (or Pacinian) corpuscles that act as receptors for pressure and vibration. The dermal layer of skin contains blood vessels, nerves, roots of hair follicles, eccrine glands, and apocrine glands. Cutaneous control of body temperature is maintained through the activity of eccrine (sweat) glands through the production of sweat and control of evaporation.

Establishing a Dialogue

Dermatologic History

Skin diseases can be marked by variable presentation. Obtaining an accurate dermatologic history and performing a physical examination are important as in any other field of medicine. Personal and family history related to a dermatologic condition may indicate or provide additional pointers about the patient’s presentation. For example, patients with a personal history and a family history of atopic diathesis, such as seasonal allergies or asthma, may have an increased risk of developing eczema. Family history and personal history also are important considering various types of skin cancer (eg, melanoma, non-melanomatous skin cancer, or a personal history of sunburns) and autoimmune disorders (eg, systemic lupus erythematosus [SLE]).

Regarding dermatologic history, it is important to elicit the timing of appearance; location of the rash or the lesion (dermatomal, mucosal, or genital); changes to the index lesion or lesions; associated symptoms, such as pruritus, pain, crusting, nonhealing wound, bleeding, joint pain, fatigue, or systemic symptoms; and determining how rapidly the lesion is changing. If the patient is concerned about a pigmented lesion, it is important to note if the lesion is changing color or has lost any pigment; examine the lesion for asymmetry, border, color, and diameter; and note whether the lesion is evolving. It is
important to know whether the patient has seen any health care provider for treatment and whether the treatment was initiated (either self-treatment or as recommended by a health care provider). When obtaining pharmacologic history, it may be important to ask directed questions to determine if the patient has taken any nonsteroidal antiinflammatory medications or any herbal supplements and whether she started any new personal hygiene products. Social history, occupational history, hobbies, and travel history often may reveal important details and may be useful in establishing a diagnosis.

Physical Examination

Skin evaluation must be performed under optimal lighting. Patients should be encouraged to wear a gown if a full skin evaluation is indicated. During the examination, the location of the lesion, its size, shape or configuration, color, consistency, and any overlying or underlying erythema, scale, crust, or ulcer should be recorded using dermatologic terminology (Table 1). Other techniques may aid in establishing the diagnosis. For example, a scale (if present) should be scraped, stained with 10% potassium hydroxide, and examined under the microscope for any fungal elements. The potassium hydroxide dissolves the epidermal keratinocytes, but it has no effect on the fungal elements. If there are grouped vesicles in a segmental or dermatomal pattern, viral culture and polymerase chain reaction (PCR), direct fluorescent antibody testing, or both for herpes simplex virus or varicella zoster virus should be performed. If the patient has honey colored crust, or if the lesions appear infected, bacterial culture and gram stain analysis should be performed. A Wood lamp examination may be performed to discern diagnosis of depigmented or hypopigmented lesions. Depigmented spots in patients with vitiligo appear as ivory or chalky white-colored lesions whereas erythrasma lesions appear coral red. The most poignant points regarding skin examination are listed in Box 1.

Box 1. Components of Skin Examination

- **History of the lesion in question:** location, size, shape, recent change in rash or lesion, associated symptoms, improving or worsening factors, and any treatments tried
- **Personal history:** history of excessive sun exposure, sunburns, skin cancer, radiation therapy, or chemotherapy
- **Social history:** occupation, hobbies, pets, recent camping, or travel
- **Family history:** skin cancer, including melanoma, and autoimmune diseases
- **Physical examination:** focused or full skin evaluation based on the lesion in question; lymph node examination if the patient is thought to have a drug rash, or if the patient has had history of skin cancer; oral mucosa examination; and examination of palms and soles
Common Dermatologic Conditions

Common Skin Conditions: Diagnosis, Evaluation, and Treatment

The following sections will describe common dermatologic conditions that may be encountered by the obstetrician–gynecologist in the office. Each section will briefly discuss the etiology of the condition, if known, the presentation of the disorder to enable recognition by the astute clinician, and basic steps of first-line treatment. Table 3 summarizes the typical sites of the most common skin conditions.

### Table 3. Typical Locations of Skin Conditions

<table>
<thead>
<tr>
<th>Body Location</th>
<th>Common Skin Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp</td>
<td>Seborrheic dermatitis and lice</td>
</tr>
<tr>
<td>Groin folds</td>
<td>Seborrheic dermatitis and candidal infections</td>
</tr>
<tr>
<td>Elbows</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Genital area</td>
<td>Lichen sclerosis, hidradenitis suppurativa, and extramammary Paget disease</td>
</tr>
<tr>
<td>Breast</td>
<td>Paget disease</td>
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**Eczema**

Eczema, also known as atopic dermatitis, is a chronic condition characterized by relapsing and remitting symptoms. Often, the condition first occurs in childhood and can persist into adulthood. The underlying cause of eczema is a complex interplay between genetics and the environment (Box 2). Most patients with eczema have an underlying defect in filaggrin, which plays an important role in skin barrier function (2). This dysfunctional barrier allows environment factors to interact with the immune system and trigger inflammation. Patients with eczema were found to have an insufficiency of ceramides in the stratum corneum, which is another important layer responsible for water retention and proper barrier function (3). The Th2-type cytokines are strongly associated with eczema, and patients often have an imbalance favoring this cytokine profile (4). All individuals have *Staphylococcus* species residing on the skin, but those with eczema have higher rates of colonization with *Staphylococcus aureus*, which is

### Box 2. Causes of Eczema

- Dry skin → barrier dysfunction
- Filaggrin mutation → barrier dysfunction
- Th-type cytokine predominance → inflammation
- Staphylococcus superantigens
- Environmental triggers (stress and allergens)
thought to play a role in driving inflammation through secretion of superantigens (5). Diet rarely effects eczema incidence or severity. Individuals with eczema often exhibit other atopic tendencies, including food allergy or hypersensitivity, which are distinct and diagnosed with food challenge.

Eczema often first presents during childhood, but the condition can persist into adulthood. Generally, ill-defined erythematous, lichenified plaques that are intensely pruritic characterize active eczema. The location may depend on the age of the individual because the plaque tends to evolve over time even in the same individual. Infantile eczema is characterized by involvement of the cheeks, whereas in childhood and beyond often flexor folds (eg, antecubital and popliteal fossae; Fig. 2) are involved. Eczema in adulthood often involves the eyelids and hands (Fig. 3).

Eczema is a clinical diagnosis and rarely requires biopsy. The differential diagnosis includes contact dermatitis or irritant dermatitis, which can frequently coexist in patients with eczema. Other causes of itching should be excluded, such as infestations (eg, scabies). When the patient with eczema does not respond as expected to conventional therapy, rare entities should be considered, including immune deficiencies in children and vitamin deficiencies or malignancies (eg, cutaneous T cell lymphoma) in adults.

Etiologies of eczema should be addressed when planning treatment. A baseline for treating eczema should include regular use of an emollient to prevent dry skin and support a dysfunctional skin barrier. Ointments are more moisturizing than thick creams, and both are preferred over lotions. When inflammation is present, the use of topical corticosteroids or topical calcineurin inhibitors is a core component of therapy. Addressing itch with systemic antihistamines can be helpful. Identifying and treating infection, when present, can help in reducing flares and recalcitrance of disease.

Figure 2. Atopic dermatitis flexural.

Figure 3. Hand eczema with nail dystrophy. Chronic hand eczema presents with pruritic and painful dry scaly plaques on the hands.
CASE NO. 1. A teenager presents to the office with a chronic rash and itching behind her knees and in the creases of her elbows. The rash tends to be transient. She heard ingestion of gluten can be the cause of her rash, and she has eliminated it from her diet, but the rash has not changed. She uses coconut oil and cocoa butter as moisturizers. She is embarrassed about the rash, particularly during her practices on the swim team.

The differential diagnosis includes atopic dermatitis given the chronicity of the rash and the location. Consideration also should be given to contact dermatitis. The location would be atypical for psoriasis, and the rash is not clinically consistent with dermatitis herpetiformis, the rash related to celiac disease which presents with extremely pruritic papules or vesicles over the extensor arms. Biopsy often is not required, because the diagnosis can be established clinically.

Testing for allergies (including food allergies) should be performed only if there is a suspicious clinical history. Many patients will have a medical history positive for an atopic condition, including other environmental allergies and asthma. Patients with atopic dermatitis (eczema) have a defective skin barrier that results in increased loss of moisture from the skin. Patients should engage in a regular regimen of moisturization with a thick emollient preferably twice daily and always immediately after bathing. Avoidance of fragranced products, soap, and detergents is recommended. Topical corticosteroids often are required to manage inflammation when it is present. Atopic dermatitis cannot be cured, and patients should be counseled that the rash will likely recur over time. The goal of the treatment is to reduce symptom severity and duration and to prevent flares from occurring if possible. This patient has atopic dermatitis. She is counseled regarding gentle skin care, including moisturization with a thick emollient immediately after bathing and the use of fragrance-free and dye-free soap and detergents. She is prescribed a medium strength topical corticosteroid to use twice daily for 2 weeks on affected areas and then as needed for recurrence. She is counseled that the rash will likely recur. With the described treatment plan, her rash improves to the point that it is no longer symptomatic. She requires intermittent use of topical corticosteroid, and she moisturizes her skin daily.

Psoriasis

Psoriasis is a relatively common chronic inflammatory condition. There are multiple forms of psoriasis, including psoriasis vulgaris, pustular psoriasis, guttate psoriasis, erythrodermic psoriasis, inverse psoriasis, and palmoplantar psoriasis. Psoriasis also can be associated with a form of arthritis called psoriatic arthritis, which commonly involves the terminal interphalangeal joints. The most common presentation, psoriasis vulgaris, will be discussed in this section.

The pathogenesis of psoriasis continues to be elucidated, but significant progress in understanding this complex condition has occurred over the past decades. There is a genetic component to psoriasis, and certain genes, such as HLA-Cw6 and HLA-B27, are significantly associated with the development of psoriasis. The immune system, and particularly T cells, play an important role in the pathogenesis of the disease. In psoriatic plaques, the T-helper 1 (Th1) subsets of T cells prevail, and induce proinflammatory
cytokines, such as tumor necrosis factor alpha and interferon gamma. Tumor necrosis factor alpha and interferon gamma levels have been shown to be increased in patients with psoriatic plaques. Recent studies have begun to focus on a subset of CD4+ T cells called Th17 cells (6), the development of which is driven by interleukin-23. Th17 cells produce interleukin-17, which acts on keratinocytes. This leads to the production of pro-inflammatory cytokines, which are found at increased levels in patients with psoriasis. Many of these pathways are now important therapeutic targets used commonly in the treatment of psoriasis.

Psoriasis vulgaris (commonly referred to as plaque psoriasis) presents with well demarcated pink-to-red plaques with overlying silvery scale (Fig. 4 and Fig. 5), most often present on extensor surfaces, such as the elbows and knees. Scalp often is extensively involved. Involvement of the sacrum and navel is suggestive of plaque psoriasis. Nail involvement is common (Fig. 6) and is characterized by onycholysis, ridging, and nail pitting. Patients should be asked about joint symptoms because psoriatic arthritis can damage joints. The plaques of psoriasis can be itchy and, occasionally, painful.
Psoriasis can be distinctive clinically, but biopsy often is helpful in confirming the diagnosis, particularly before initiating systemic therapy. As mentioned previously, any joint symptoms should be elicited from the patient to identify early psoriatic arthritis, which, if untreated, can be destructive to joints. Recent research has identified a strong link between psoriasis and cardiovascular disease (7). Individuals with psoriasis should be considered to be at an increased risk of developing cardiovascular morbidity and mortality, and this risk increases proportionately with disease severity (8).

Treating psoriasis is based on different factors, including symptoms and extent of disease as well as comorbidities. For patients with relatively limited involvement and no joint disease, topical therapy remains first-line option. Initial topical therapeutic options include corticosteroids, vitamin D analogs, and calcineurin inhibitors (9). For patients with more extensive involvement, referral to light therapy can be beneficial. For patients with severe disease or joint disease, referral for consideration of systemic treatment is warranted. Courses of oral corticosteroids, such as prednisone, while resulting in short-term improvement, are well known to potentially cause severe flares when the regimen is stopped; therefore, oral corticosteroids are avoided in the management of psoriasis.

**Rosacea**

Rosacea is a chronic cutaneous condition primarily occurring on the face. Most often it occurs in fair-skinned individuals and affects up to 10% of the population (10). It is classified into four different types: 1) erythematotelangiectatic rosacea, 2) papulopustular rosacea, 3) phymatous rosacea, and 4) ocular rosacea. However, there is significant variability in presentations, patients often have features of more than one form, and the disease can progress from one form to another. For example, ocular rosacea can be seen in up to 50% of patients with cutaneous rosacea (11). The pathophysiology of rosacea is not completely understood, but studies in recent years have identified several etiologic factors at play. Rosacea is thought to occur due to a complex combination of genetic predisposition and exogenous triggers. Distinct genetic profiles have been identified for each subtype, with overlap (12). The progression of rosacea is thought to represent a type of inflammatory march, which proceeds from an inflammatory subtype to a fibrotic form in patients with advanced disease (12). In patients with rosacea, the inflammatory milieu is predominated by CD4+ type 1 T-helper cells, in addition to macrophages and mast cells. Recently, cathelicidin, an antimicrobial peptide, has been shown to play a role in inflammatory skin disease; specifically, it is believed to be upregulated in patients with rosacea (12). The active products of cathelicidin are formed by kallikrein proteases, which are in turn upregulated by increased expression of toll-like receptor 2. Increased expression of toll-like receptor 2 occurs in the setting of infestation with *Demodex* species, providing a link as to why *Demodex* infestation is associated with rosacea, in particular the papulopustular variant. *Demodex* is a small mite that lives within the human hair follicle and is found commonly on facial skin. Two species of *Demodex* mites live on
human skin, *Demodex folliculorum* and *Demodex brevis*. Cathelicidins are induced by the vitamin D pathway, which may explain why rosacea occurs predominantly on the face.

Considering the different subtypes can be helpful clinically when approaching a patient with a possible rosacea; however, it is important to recall that overlap and progression are possible. Erythematotelangiectatic rosacea presents predominantly as central facial erythema with associated telangiectasia, with increasing erythema during flares. Papulopustular rosacea is characterized by inflammatory lesions in the central face with associated erythema. Phymatous rosacea presents with sebaceous and fibrous proliferation most often on the distal nose, but also on the chin (11). Flares are precipitated by various exogenous factors, including strong emotions, alcohol consumption, heat, ingestion of spicy food, and UV exposure (13). During flares, papulopustular erythema is associated with burning and stinging sensations, edema, skin tension and itching, whereas erythematotelangiectatic rosacea is associated with dry facial skin (13).

Treatment of patients with rosacea ranges from avoidance of triggers to topical and oral medications. In one Cochrane review, topical brimonidine and topical azelaic acid have been associated with improvement of facial erythema (14). Over-the-counter oxy-metazoline also has been used with some success. Topical metronidazole also is associated with improvement. Topical ivermectin has been approved by the U.S. Food and Drug Administration (FDA) for use in patients with rosacea, and it has been shown to be superior to topical metronidazole. Oral doxycycline and oral tetracycline show improvement compared with placebo, and oral isotretinoin shows superior improvement compared with doxycycline (15). Response rates of patients to any therapy range from 33% to 80% (13). Ocular rosacea responds to topical cyclosporine. Laser therapy, notably the use of the pulsed dye laser or intense-pulsed light laser, can improve erythema and telangiectasia. Counseling patients to avoid triggers of flares, such as heat, alcohol, and spicy food, can be helpful, and advising consistent photoprotection will reduce UV-induced flares (11).

**Milia**

Milia are common benign lesions that present as small epidermoid cysts. Milia can occur in patients of any age but are most common in children. Milia can occur after other procedures involving the skin, including cosmetic procedures, such as chemical peels or laser therapy. Additionally, they can occur after burns or other trauma to the skin. Blistering diseases can heal with milia formation.

Milia present as small, superficial white papules most commonly in the head and neck region. They can be singular or multiple. Milia can occur elsewhere on the body, and in some locations (such as the hands) they may suggest an underlying blistering disease. The differential diagnosis for milia includes closed comedones of acne, sebaceous hyperplasia, and other benign adnexal neoplasms. Milia can be extracted through a small overlying incision with a needle or scalpel, with the assistance of a comedone extractor.
**Pityriasis Rosea**

Pityriasis rosea is a benign cutaneous condition occurring most often in young adults. It is characterized by a solitary “herald” patch followed by a more widespread eruption. It has an acute onset and persists for weeks before slowly resolving. Some physicians observe that pityriasis rosea occurs in seasonal clusters, whereas others observe year-round occurrences (16). The etiology of pityriasis rosea is contested, but is thought to be secondary to infectious causes given the occasional presence of prodromal symptoms. The roles of human herpesvirus 6 and human herpesvirus 7 in the eruption have been investigated, but it is currently unclear whether these subtypes play a causal role or if the ubiquitous virus is reactivated during presentation (16). Pityriasis rosea is slightly more common in pregnancy, and one case report has suggested possible fetal risk potentially secondary to human herpesvirus 6 (17).

Pityriasis rosea classically presents initially with a solitary, well demarcated, oval, pink, thin plaque with overlying fine scale on the trunk. This is called the “herald” patch of pityriasis rosea. Variants of the herald patch include edematous or vesicular plaques (16). A prodrome can include general malaise, nausea, loss of appetite, and gastrointestinal (GI) upset. Approximately 2 weeks after the appearance of the herald patch, a widespread eruption of smaller patches or thin plaques occurs. These lesions are similar to the initial presentation, but smaller, and appear classically in a “Christmas-tree” distribution along the skin cleavage lines of the trunk. The rash can be pruritic and can persist for weeks (classically 45 days) before fading slowly (17).

Few effective treatments alter the natural course of this benign condition. Erythromycin may possibly decrease the duration of the eruption and reduce itch. Other treatments, such as emollients, topical corticosteroids, and light therapy, were deemed to be ineffective (18). One study has examined the use of high-dose acyclovir, with some success (19).

**Seborrheic Dermatitis**

Seborrheic dermatitis is a common chronic skin condition affecting approximately 1–3% of adults with normal immune systems (20). Risk factors for severe involvement include immunosuppression, including HIV infection; neurologic disorders, such as Parkinson disease; psychiatric diseases; hepatitis C virus infection; and chronic pancreatitis. The pathogenesis of seborrheic dermatitis is not definitively known but is postulated to relate to *Malassezia* yeast (also known as *Pityrosporum ovale*) involvement because *Malassezia* is found in affected skin, and the infection is reduced by treatment (21). In susceptible individuals with defective epidermal barrier function, components of *Malassezia*, such as oleic acid, penetrate into the skin causing irritation and flaking. An association exists between seborrheic dermatitis and atopic dermatitis, suggesting that in some individuals, the disease may be part of the same clinical spectrum (22).
Seborrheic dermatitis most commonly affects the scalp, ears, face (especially the forehead and nasolabial folds, and groin) and also can involve the upper parts of the trunk. It is characterized by erythema and greasy scaling of affected areas (Fig. 7 and Fig. 8). Symptoms can include burning and itching, but the disease also can be asymptomatic. Pigmentary changes can occur particularly in individuals with darker skin types, but they do not tend to be permanent.

Management of seborrheic dermatitis is primarily topical and focuses on reducing yeast density, addressing inflammation, or both. Multiple over-the-counter shampoos are available to treat scalp seborrheic dermatitis, including 2% pyrithione zinc formulations. Prescription products include a 2% ketoconazole shampoo. All shampoos should be left on the scalp 5–10 minutes before rinsing the hair. To address inflammation, fluocinolone acetonide oil can be applied to scalp and left on overnight before washing, or patients may prefer the application of nonoily corticosteroid solutions or gels. Regarding the management of facial seborrheic dermatitis, short-term data indicate no difference between topical corticosteroid therapy and topical calcineurin inhibitor therapy in terms of total clearance, although topical corticosteroids have fewer adverse effects, such as burning or itching (23). Topical corticosteroids were found to be associated with less erythema and scaling than topical antifungal azoles. These two medications may be used in combination, which is generally highly effective. Long-term clearance is achieved more slowly with a mild topical corticosteroid than with a stronger formulation (23).

**Acne Vulgaris**

Acne vulgaris is a common condition that affects primarily adolescents but also is common in adults. The prevalence of acne in adult women is approximately 12% (24). The first etiologic factor in acne is early comedone formation, which occurs because of hyperkeratosis of the follicular infundibulum with increased adhesiveness of corneocytes leading to blockage of the follicle. Shed keratin and sebum then accumulate and *Propionibacterium acnes* proliferates. Often, the comedone wall ruptures and immuno-
genic contents are released into the surrounding dermis with subsequent inflammation, which can be marked and lead to scarring. Acne can be driven by the androgen effect on sebaceous glands; stimulation of androgen production leads to an increase in sebaceous gland size, number of eruptions, and sebum production. Generally, acne is unrelated to systemic conditions; however, rarely it can be associated with endocrine abnormalities, including polycystic ovary syndrome. Research into the effect of diet on acne has been inconclusive but suggests a possible link between dairy consumption (specifically skim milk) and acne severity in adolescents (25).

Generally, acne is classified as mild, moderate, or severe, but there is no current classification consensus. Commonly, acne is described as predominantly comedonal, inflammatory, or mixed. During an examination, postinflammatory hyperpigmentation and degree of erythema should be noted. The health care provider should look for evidence of scarring because this can be irreversible and warrants more treatment (26). In adult women, the appearance of acne in the week leading to menstruation is common and often manifests as involvement along the lower third of the face and jawline. This suggests hormonal influences that can be managed with hormonal therapy. In patients with signs of androgen excess, such as hirsutism or clitoromegaly, additional testing could be considered (ie, the measurement of free and total testosterone, dehydroepiandrosterone, androstenedione, luteinizing hormone, and follicle stimulating hormone levels) (27).

Published guidelines for the treatment of acne provide details of acne treatment stratified by the assessed severity (26, 27). Briefly, initial treatment for mild acne includes application of topical medications, such as benzoyl peroxide, topical antibiotics, and topical retinoids (eg, tretinoin cream or adapalene gel). If tolerated, benzoyl peroxide should be used as an adjunct to treatment with a topical antibiotic to help prevent the development of resistant bacteria. For moderate acne in women, additional use of oral antibiotics, combination hormonal therapy, or spironolactone can be considered. The U.S. Food and Drug Administration has approved the following combined oral contraceptive regimens for the treatment of moderate acne:

- Triphasic ethinyl estradiol plus norethindrone
- Triphasic ethinyl estradiol plus norgestimate
- Ethinyl estradiol plus drospirenone

For severe acne or recalcitrant acne especially with evidence of scarring, isotretinoin should be strongly considered. Isotretinoin use currently requires registration of the health care provider and the patient into the iPLEDGE system, with the goal of preventing teratogenic events. Isotretinoin use is strongly associated with birth defects, including hearing or vision impairment, facial dysmorphism, and cardiac or brain abnormalities. The iPLEDGE system is an FDA-mandated program instituted in 2006, intended to help reduce the risks associated with use of isotretinoin. Before prescribing isotretinoin, two negative pregnancy test results are required, and the use of two forms of birth control must be documented. Additionally, all reproductive-aged women taking isotretinoin must undergo monthly pregnancy testing.
Spirolonactone also should be avoided in pregnancy because of the risk of possible fetal antiandrogenic effects, and adequate contraception should be used. Patients should be informed that regardless of the treatment choice, improvement in acne can take months despite consistent use of medications, and persistence is warranted.

**CASE NO. 2.** A woman in her mid-twenties comes to the clinic. She is concerned about acne that flares around the times of her menses. She was told that individuals in their twenties do not get acne and is distressed by her appearance. Her acne lesions are most noticeable on the jawline and forehead, with scattered pustules, red papules, and open and closed comedones. She has some involvement of her chest and back. Currently, she is using a topical salicylic acid cleanser and used oral antibiotics in the past.

The most likely diagnosis is acne vulgaris given the presence of papules, pustules, and comedones. If comedones were absent, a diagnosis of rosacea could be considered. Additional variants of acne, including pomade acne or steroid acne, should be considered in the appropriate clinical scenario. Biopsy is not required for diagnosis. Laboratory workup for hormonal abnormalities is not required unless other signs of hyperandrogenism are present. The location of the acne can be a clue to an underlying etiology; for example, acne along the jawline is suggestive of a hormonal influence. Topical therapies are first line, and include topical retinoids, benzoyl peroxide, or topical antibiotics. If a hormonal influence is suspected, adding a combination oral contraceptive or spironolactone should be considered. If scarring is present or is a concern, referral to dermatologist for evaluation for isotretinoin therapy is warranted. This patient receives the diagnosis of acne vulgaris with a hormonal component. She is started on a topical tretinoin cream to be applied in the evenings, is instructed to use a benzoyl peroxide wash, and is additionally started on a combination oral contraceptive. The patient was counseled that acne can continue to occur in individuals through their 20’s or 30’s, and acne treatment takes time to have an effect. Indeed, her acne is slow to improve, but reduced involvement is noted at a 4-month follow-up.

**Perioral Dermatitis**

Perioral dermatitis is a common inflammatory skin condition that spontaneously resolves over a long time. Although the exact etiology is unclear, it is thought to be related to exposure to a topical corticosteroid, often used for the management of another facial dermatitis (28). Many other triggers have been reported, including fluorinated toothpaste, various moisturizers, sun exposure, temperature changes, use of hormonal contraceptives, and even chewing gum (29).

Perioral dermatitis presents with erythema, monomorphic papules, and occasionally pustules around the mouth, on the chin, and possibly on the nasolabial folds (Fig. 9). There is a characteristic clear zone around the vermillion border, which can be a clue for the diagnosis. Symptoms can include itching or burning. It is seen most commonly in adult women.
The primary treatment for perioral dermatitis is identification and avoidance of triggers, including the use of any topical corticosteroids. Management with topical corticosteroids is a common error, and a flare of the dermatitis often will occur upon discontinuation of the medication. For this reason, an option is to wean off topical corticosteroids slowly, which reduces the risk of a flare but extends the time to resolution. Stopping the medication completely will cause a flare but will result in a more rapid resolution (the time frame of 1–3 months) (29). Other medications that can be helpful include topical metronidazole (30), topical clindamycin, or topical erythromycin applied every 12 hours. For more severe cases, oral antibiotics have been used with a slow taper.

**Drug Reactions**

Reactions to systemic medications are a common occurrence and a common reason for patients to seek medical care. Drug eruptions vary broadly in clinical presentation. A precise etiology of drug eruptions often is unknown and may depend on the medication used. Drug eruptions also vary in severity. Most drug eruptions do not have systemic manifestations, but severe cutaneous adverse reactions can occur. Serious and potentially life-threatening drug reactions include Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug hypersensitivity syndrome (also known as drug reaction with eosinophilia and systemic symptoms or DRESS). An exhaustive discussion is beyond the scope of this monograph, but brief patterns of presentation will be discussed.

Drug eruptions often can be distinguished by their clinical presentation and timing of the onset of administration of suspected causal medications. Most drug eruptions are uncomplicated. Biopsy can be helpful in confirming the diagnosis, but it is not always diagnostic. Most drug eruptions present as morbilliform drug eruptions, so called because the erythematous macules and papules resemble the rash classically seen in measles infection. The rash usually is most prominent on the trunk and proximal extremities, although it can be widespread. Pruritus is common. Morbilliform drug eruptions (Fig. 10 and Fig. 11) often occur approximately 1–2 weeks after starting a medication. The second most common form of drug eruption is urticarial. Fixed drug eruptions are characterized by well demarcated red to brown patches occurring at the same body site within hours.
on reexposure of an offending medication and may require a high level of clinical sus-
picion to recognize (31). The most common area of involvement is the genitalia. Some-
times, patients can have a pustular rash (acute generalized exanthematous pustulosis; 
Fig. 12), which is characterized by superficial pustules.

Figure 10. Uncomplicated drug reaction: morbilliform drug eruption caused by cephalexin. Drug reactions typically are associated with pruritus.

Figure 11. Uncomplicated drug reaction: diffuse erythema resulting from a drug eruption caused by sulfamethoxazole–trimethoprim.

Figure 12. Acute generalized exanthematous pustulosis caused by vancomycin. These eruptions are characterized by abrupt development of superficial pustules.
Stevens–Johnson syndrome and toxic epidermal necrolysis (Fig. 13) are two conditions on a clinical spectrum, characterized by epidermal necrosis and resultant desquamation of the skin with mucosal involvement (32). Absent mucosal involvement makes this diagnosis less likely. The timing of medication administration usually is within 1–3 weeks of the symptom onset but can be longer. A patient with drug hypersensitivity syndrome, also known as drug hypersensitivity with eosinophilia and systemic symptoms (or DRESS) presents with nonspecific findings but sometimes has more prominent facial edema, occasional oral involvement, and no desquamative rash. Internal manifestations can occur, including abnormal blood counts and liver and renal involvement. Medication administration usually occurs up to 2 months before the onset of symptoms.

In uncomplicated drug eruptions, if clinically feasible, patients should be switched to an alternative medication while being treated for their symptoms. In cases of strong clinical need to continue the medication and difficulty switching to an alternative, patients can be treated symptomatically with the causal medication continued. Symptomatic management can include antihistamines for itch and topical corticosteroids (usually with medium potency) for rash. In patients with severe cutaneous adverse reactions, the offending medication always must be stopped and the patient counseled to avoid the medication completely in the future. Reexposure can result in faster onset and more severe reactions. If a severe cutaneous reaction, such as Stevens–Johnson syndrome or toxic epidermal necrolysis, has occurred, hospital admission may be required for supportive management.
Disorders of Skin Pigmentation

Skin color varies by individual, and the individual variations are controlled by numerous genes. The different skin color variations are caused by different sizes and numbers of melanosomes. Disorders of skin pigmentation can result from the following five causes: 1) abnormal melanocytic migration from the neural crest to the skin during embryogenesis, 2) impaired melanin pigment transfer from melanosomes to keratinocytes in the epidermis, 3) abnormal melanin synthesis, 4) defective melanin degradation, and 5) destruction of melanocytes. Pigmentary disorders are classified as hyperpigmentation disorders and hypopigmentation disorders. These can be either genetic or acquired and can be localized or generalized. The most commonly used system for identifying skin types is the Fitzpatrick system (33) (Table 4).

### Table 4. Fitzpatrick Skin Type Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>Tanning Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>White; very fair; red or blond hair; blue eyes; freckles</td>
<td>Always burns, never tans</td>
</tr>
<tr>
<td>II</td>
<td>White; fair; red or blond hair; blue, hazel, or green eyes</td>
<td>Usually burns, tans with difficulty</td>
</tr>
<tr>
<td>III</td>
<td>Cream white; fair with any eye or hair color; common</td>
<td>Sometimes mild burn, gradually tans</td>
</tr>
<tr>
<td>IV</td>
<td>Brown; typically, Mediterranean skin type</td>
<td>Rarely burns, tans with ease</td>
</tr>
<tr>
<td>V</td>
<td>Dark brown; Middle-Eastern skin type</td>
<td>Very rarely burns, tans very easily</td>
</tr>
<tr>
<td>VI</td>
<td>Black</td>
<td>Never burns, tans very easily</td>
</tr>
</tbody>
</table>


Several common causes of hyperpigmentation and hypopigmentation of skin exist; some are listed in Box 3 and discussed in the next sections. Certain disorders also cause diffuse hyperpigmentation, including Addison disease and hemochromatosis.

### Hyperpigmentation Disorders

**Postinflammatory Hyperpigmentation**

This is a common sequel of inflammation and is more prominent in patients with darker skin with a higher Fitzpatrick skin type (type IV to type VI) than in those with lighter skin types. Postinflammatory hyperpigmentation presents as irregular, darkly pigmented macules and patches at sites of previous injury or inflammation (Fig. 14). The hyperpigmented patches or macules typically persist for months or years. Sometimes, postinflammatory hyperpigmentation can occur after laser therapy and may be transient or long lasting.
### Box 3. Differential Diagnosis for Hyperpigmentation and Hypopigmentation of Skin

**Common Hyperpigmentation**
- Postinflammatory hyperpigmentation
- Melasma
- Solar lentigines
- Ephelides (freckles)
- Nevi
- Melanoma and precursors
- Café-au-lait macules
- Labial melanotic macules

**Hypopigmentation**
- Acquired
  - Postinflammatory hypopigmentation
  - Pityriasis alba
  - Vitiligo
  - Tinea versicolor
- Congenital (uncommon)
  - Albinism
  - Piebaldism
  - Hypomelanosis of Ito
  - Tuberous sclerosis

---

**Figure 14.** Postinflammatory hyperpigmentation: ill-defined hyperpigmented patch at the site of a previous inflammatory lesion.
Typically, these pigmentary changes resolve with time. Treatment of patients with postinflammatory hyperpigmentation includes hydroquinone cream, azelaic acid cream, salicylic or glycolic acid peels, and topical retinoids, such as tazarotene. Prolonged use of hydroquinone creams can cause exogenous cutaneous ochronosis that presents with hyperpigmentation of skin, which is difficult to treat. Various laser and light devices have been used for the treatment of cutaneous hyperpigmentation; however, efficacy data for postinflammatory hyperpigmentation are limited to case reports and small series. The role of pulsed dye laser in the treatment of melasma is controversial with studies showing conflicting results (34). Few reports describe improvement in postinflammatory hyperpigmentation after the treatment with a 1064 nm Q-switched neodymium-doped yttrium aluminum garnet (Nd:YAG) laser, a 532 nm Q-switched Nd:YAG laser (35–44), Q-switched ruby laser (45, 46), and 1550 nm erbium-doped fractional laser (47). However, it is to be noted that postinflammatory hyperpigmentation is a potential adverse effect of laser therapy, particularly in individuals with dark skin color. This risk is reduced with the use of long-wavelength lasers (eg, 1064 nm Q-switched Nd:YAG).

**Melasma**

Melasma is a progressive, asymptomatic, macular skin hyperpigmentation occurring in the sun-exposed areas, particularly on the face. Melasma can occur during pregnancy (called chloasma) and is associated with the use of oral contraceptives, or it may be idiopathic. Also, it has been associated with autoimmune thyroiditis. Oral contraceptive use carries a potential risk of development of melasma. One study showed an improvement of melasma after switching from a combined oral contraceptive to a levonorgestrel-releasing intrauterine device (IUD) (48). Another study showed that in vitro, progesterone and chlormadinone acetate can inhibit proliferation of human melanocytes and can counteract the stimulatory effects of estrogen on melanocytes (49). Thus, choosing a progesterone-only contraceptive method or a levonorgestrel-releasing IUD may prevent the development of melasma.

Women are more affected compared with men, and melasma is more prominent in patients with darker skin types than with those with lighter skin types. Typically, melasma presents in one of three patterns of distribution: 1) centrofacial (most common), 2) malar, and 3) mandibular. Melasma results from pigment deposition in the skin. These pigments may be located superficially in the epidermis or more deeply in the dermis or may be present in both epidermis and dermis. The location of the pigment is associated with important treatment considerations.

The first-line treatment options include topical hydroquinone cream, glycolic acid peel, azelaic acid cream, and retinoids (eg, tretinoin cream and adapalene gel). Combination products with hydroquinone and retinoids, glycolic acid, or topical corticosteroids or a triple-combination treatment of fluocinonide, hydroquinone, and tretinoin cream can be used. Patients with epidermal and mixed types of melasma typically do not respond well to laser therapies, and postinflammatory hyperpigmentation often can result. Deep dermal
melasma may respond to laser treatment. Patients must be advised to wear sunscreen regularly. Melasma that is induced by pregnancy or oral contraceptive use tends to fade within several months after pregnancy or after the cessation of oral contraceptives.

**Solar Lentigines**

Solar lentigines are macular, 1- to 3-cm, hyperpigmented, well-circumscribed lesions on sun-exposed surfaces of the skin. These mainly occur on face, hands, forearms, chest, back, and shins.

Solar lentigines result from a local proliferation of basal melanocytes. There are few systemic disorders that are associated with multiple lentigines, including Peutz–Jeghers syndrome (GI hamartomas and buccal, lip, perioral, or digital lentiginous macules that are present since birth or early childhood), LEOPARD syndrome (multiple lentigines, electrocardiogram abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retarded growth, and sensorineural deafness), and LAMB syndrome (multiple lentigines, atrial or mucocutaneous myxomas, myxoid neurofibromas, ephelides, and blue nevi). The differential diagnosis for solar lentigines includes pigmented seborrheic keratosis, actinic keratoses, or lentigo maligna. Pigmented lesions with rapid growth or evolution that appear atypical and are associated with itching, bleeding, pain, or erosions must be biopsied. Patients must be advised to adhere to UV protective measures, including regular use of sunscreen and UV protective clothing.

**Ephelides**

Ephelides (ie, freckles) are small, 1- to 2-mm, sharply defined asymptomatic macular lesions of uniform color, most often found on the face, neck, chest, and arms. Onset usually occurs in childhood after sun exposure. Treatment of these lesions usually is not necessary because they tend to fade during winter months.

**Café-au-Lait Macules**

Café-au-lait macules are asymptomatic tan or brown macules or patches ranging in size from 1 cm to 30 cm that are typically present at birth or may occur early in life. These are epidermal in origin and are caused by an increase in melanin pigment in melanocytes and basal keratinocytes. Typically, they are seen on the trunk, although they can be found in other areas as well. Approximately, 10–30 % of the population can have a solitary café-au-lait macule (50). Multiple café-au-lait macules are seen in patients with tuberous sclerosis, Albright syndrome, and Fanconi anemia. Also, they are an important diagnostic sign of neurofibromatosis. Diagnosis of neurofibromatosis requires the presence of two or more of the following criteria:

- Six or more café-au-lait macules larger than 5 mm in greatest diameter in prepubertal individuals and larger than 15 mm in greatest diameter in postpubertal individuals
- Two or more neurofibromas of any type or one plexiform neurofibroma
• Freckling in the axillary or inguinal region
• Optic glioma
• Two or more Lisch nodules (iris hamartomas)
• A distinctive osseous lesion, such as sphenoid dysplasia, or thinning of long bone cortex with or without pseudoarthrosis
• A first-degree relative (ie, parent, sibling, or child) with neurofibromatosis type 1 according to these criteria

**Labial Melanotic Macule**

A labial melanotic macule is a well-defined, asymptomatic, oval, brown to black, flat patch on the central third of the lower lip most commonly seen in women. Its etiology is likely associated with UV exposure. Similar lesions also can appear inside the mouth, on the vulva, and in periurethral area in women (sun-protected site). Benign vulvar melanosis or vulvar melanotic macule (also called genital lentigo) is an asymptomatic, even, brown to black macule with a smooth or jagged margin (Fig. 15). Usually, it is solitary and ranges from 1 mm to 8 mm in size.

Differential diagnosis for labial melanotic macule includes ephelides (freckles), lentigo simplex, solar lentigo, venous lake, amalgam tattoo, and lentigo maligna. These conditions can be differentiated from labial melanotic macule by a combination of clinical and histologic features. Multiple lesions may be a sign of a systemic conditions, such as Peutz–Jeghers syndrome, Addison disease, and Laugier–Hunziker syndrome.

No treatment is required for benign melanotic macules. It is important to visualize the entire vulva when examining these patients with vulvar melanosis. A lesion should be investigated if there is any progressive change or if it is symptomatic.

**Figure 15.** Vulvar melanosis. This patient was referred for evaluation of possible vulvar melanoma. Physical examination revealed several areas of macular hyperpigmentation. A biopsy of the darkest area revealed proliferative changes of benign melanocytes. Biopsy frequently is performed to rule out melanoma.
Hypopigmentation Disorders

Vitiligo

Vitiligo is one of the most common pigmentary skin disorders. It affects 0.1–2% of general population worldwide (51–54); however, certain regions of India have a prevalence of 8–10% (55). Vitiligo is an acquired pigmentary skin disorder that is characterized by well-circumscribed depigmented macules and patches surrounded by normal skin pigmentation (Fig. 16, Fig. 17, and Fig. 18). Occasionally, there may be intermediate tan or hypopigmented zone resulting in trichrome vitiligo. The hair in involved area may be normal or white in color. Vitiligo appears chalky white on visualization with a Wood lamp. Six types of vitiligo have been described based on the extent and distribution of the involved areas and include: 1) localized or focal, 2) segmental, 3) generalized, 4) universal, 5) acrofacial, and 6) mucosal. Vitiligo most commonly involves the face, upper part of the chest, dorsal aspects of the hands, axillae, and groin. Other areas involved include the eyes, nose, mouth, ears, nipples, umbilicus, penis, vulva, and anus. Vitiligo often is noted in areas of trauma (elbows and knees) and pressure (waist line). Focal vitiligo can affect dermatomal or nondermatomal areas. Isolated areas of involvement, including vitiligo of vulva and glans penis, can occur. The acrofacial type of vitiligo affects the distal fingers and facial orifices and is difficult to treat as is segmental vitiligo. Segmental vitiligo occurs in 5–16% of adult vitiligo cases (56, 57) and 15–20% of childhood vitiligo cases (58, 59) and often has a dermatomal distribution.

Figure 16. Vitiligo: depigmented patches on upper and mid back.

Figure 17. Vitiligo: diffuse depigmentation on the lower leg.

Figure 18. Erythema in vitiligo patches. Patients with vitiligo are sensitive to ultraviolet radiation because they do not have any melanin pigment in the depigmented patches.
Patients with vitiligo also can develop a local loss of melanin pigment around benign melanocytic nevi and melanomas. This is called the halo phenomenon. Melanoma-associated depigmentation occurs in 2–16% of patients with melanoma (60) and, more commonly, after the treatment (61). In patients with melanoma, this portends a likely metastatic spread. Patients with vitiligo caused by a lack of UV protective melanin pigment secondary to autoimmune destruction of melanocytes by CD8 T cells are sensitive to UV light and can have sunburns (62–64). Patients also may have other autoimmune disorders, such as autoimmune thyroid disease (more common association), type I diabetes mellitus, alopecia aerate, pernicious anemia, and autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy syndrome. A family history of vitiligo can be seen in up to 30% of cases and is thought to result from multifactorial genetic basis.

Differential diagnosis includes morphea and lichen sclerosus, ie, hypopigmented skin lesions that are associated with textural changes in the involved skin. Pityriasis alba is an ill-defined fine scaly papular lesion whereas tinea versicolor is a papule or macule with fine scale mainly located on the back and chest and demonstrates yeast and hyphal forms with 10% potassium hydroxide examination. Patients with severe chronic actinic damage may develop vitiligo-like depigmentation; however, these lesions are located in the areas of considerable solar or actinic damage. Chemical leukoderma may closely resemble vitiligo and, typically, is caused by exposure to aromatic or aliphatic derivatives of phenols and catechols, including paratertiary butylphenol (adhesive in shoes), amylphenol, butylcatechol, and alkyl phenols. However, other chemicals, such as sulphydryls, mercurials, arsenics, cinnamon, and p-phenylenediamine also have been implicated (65–67).

Vitiligo can be difficult to treat. Spontaneous repigmentation can occur in 15–25% of cases (68). Response typically is slow, taking weeks to months, and may be partial. Segmental vitiligo is the least responsive form. Treatment of vitiligo can be approached in three steps: 1) stopping progression of vitiliginous areas, 2) repigmentation of the depigmented areas, and 3) psychologic support for the patients. Many treatments may stop the progression, and patients may even have spontaneous repigmentation, but they may not have a durable repigmentation. The anatomic location of the lesion and acute or chronic nature of presentation predict the rate and likelihood of response. Facial vitiligo has an excellent prognosis whereas segmental and acrofacial vitiligo have a worse prognosis in terms of repigmentation.

Topical treatment is appropriate for limited skin area involvement (less than 10–20% of the body surface area). Topical potent corticosteroids are used for a 2-month trial. Treatment should be limited to 4–6 months, and the patient must be monitored for acne, atrophy, and telangiectasias. Topical pimecrolimus cream and tacrolimus ointment, 0.1%, have been particularly efficacious in treating facial vitiligo. Topical calcipotriene and other vitamin D analogs have had variable results (69). Use of a narrow-band UV B lamp two to three times weekly has become the preferred form of phototherapy to treat vitiligo; however, long treatment courses (100–200 treatments) may be required for
the full benefit. Psoralen and UV A therapy also can be used; however, it is less effective than the narrow-band UV B therapy. Excimer laser is shown to be as effective as or more effective than the narrow-band UV B lamp (70), and the response is more rapid. The addition of topical corticosteroid to excimer laser treatment can enhance efficacy. Anecdotal reports of vitiligo reversal with the use of tofacitinib (71), a JAK 1/3 inhibitor for alopecia, and ruxolitinib, a JAK 1 and JAK 2 inhibitor used for the management of polycythemia vera and high-risk myelofibrosis (72), have shown promise with repigmentation of vitiligo-affected areas; however, this effect was not durable.

The major problem for patients with vitiligo is appearance, and patients can be psychologically devastated. Nontreatment can be an option for fair-skinned individuals (Fitzpatrick type I and II patients) because their lesions may not be as discernible as those in patients with darker skin. However, these patients still need to follow strict photoprotective measures. Phototherapy may dramatically increase the risk of skin cancer in patients with lower Fitzpatrick phototypes; hence, alternative approaches to treatment should be strongly considered in these patients. Camouflage with liquid cosmetic concealers may be appropriate. In focal cases that are resistant to treatment, the involved areas can be camouflaged with a tattoo.

Surgical treatments, including minigrafts, suction blister graft, transplantation of autologous epidermal cell suspension, and ultrathin epidermal grafts, have been used. Surgery is recommended primarily in patients with treatment-resistant vitiligo. Patients must have stable disease for a surgical consideration.

If more than 50–80% of body surface area is affected by vitiligo, the patient can consider depigmentation with monobenzone. Monobenzone (monobenzyl ether of hydroquinone), 20%, is applied twice daily for 3–6 months to residual pigmented areas. It may take up to 10 months to complete the treatment. This form of treatment should be considered permanent, and the goal is total depigmentation.

**Postinflammatory Hypopigmentation**

Sometimes inflammation can result in an injury to the melanocytes causing decreased melanin production and, hence, hypopigmentation. This can take several months to resolve.

**Halo Nevus**

Patients may develop an area of depigmentation around an existing melanocytic nevus. This phenomenon is particularly common in children and young adults and is typically associated with vitiligo and other autoimmune disorders.

**Nevus Depigmentosus**

Nevus depigmentosus is a circumscribed area of depigmented skin that is present since birth. It is most commonly seen on the trunk.
**Idiopathic Guttate Hypomelanosis**

Idiopathic guttate hypomelanosis is a common acquired disorder that affects women more than men. It occurs mostly on the shins and forearms, suggesting UV exposure as a cause. Lesions are small (2–5 mm), numerous, hypopigmented, irregularly shaped, and sharply defined macules of hypoactive melanocytes.

**Hair Loss**

**Etiology**

Hair loss encompasses many clinical entities with varying etiologies, presentations, and outcomes. Several common causes of hair loss will be discussed in this section with guidance on when to suspect a scarring process, which should generate a referral and specialized care. Relatively common causes of hair loss in women include seborrheic dermatitis, androgenetic alopecia (Fig. 19), telogen effluvium, trichotillomania (Fig. 20), and alopecia areata (Fig. 21 and Fig. 22). Androgenetic alopecia, which occurs in women as well as in men, is very common. It is a result of androgen action on the hair follicles, causing miniaturization of terminal hair. Telogen effluvium occurs when a trigger, such as physical illness or extreme stress, causes an increased number of hairs to enter the telogen (resting) phase of hair growth, causing markedly increased shedding of hair, which generally occurs several months after the trigger. Trichotillomania is self-induced pulling of hair and is commonly associated with obsessive–compulsive personality disorder. Alopecia areata is an autoimmune condition in which the hair follicle is targeted by the immune system, causing patchy hair loss with varying degrees of involvement.

**Figure 19.** Androgenetic alopecia (female pattern alopecia). A widened part, as seen in this illustration, is one of the first abnormalities noted in female-pattern alopecia.

**Figure 20.** Trichotillomania. Unlike alopecia areata, trichotillomania appears as a patch of incomplete baldness with irregular jagged borders. The hair within this patch is shorter than the surrounding normal hair.
Presentation

A first step in the evaluation of a patient with hair loss is to determine whether the process is scarring or nonscarring. Scarring hair loss, by nature, causes permanent loss of hair and, therefore, early recognition, referral, and treatment are essential to minimizing the effect of the disease. On visual examination, loss of follicular ostia can indicate a scarring process. Biopsy may be necessary for definitive evaluation, and referral for further evaluation upon suspicion of a scarring alopecia is warranted.

Nonscarring alopecia can be suggested by history and physical examination. Androgenetic alopecia in women can present as diffuse loss of hair density or in a patterned fashion similar to that seen in male patients. When evaluating frontal hair loss of the temples, it is important to ensure that this is not a scarring process because frontal fibrosing alopecia can mimic frontal hair loss secondary to androgenic alopecia. Telogen effluvium presents as diffuse hair shedding resulting in decreased density and is common after childbirth. Patients with trichotillomania present with well circumscribed patches of hair loss with irregular borders and broken hair of varying length. In contrast, patients with alopecia areata present with round, smooth patches of hair loss with “exclamation point” hairs that have a tapered base and can be seen best under magnification. Alopecia areata can have a variable clinical course and occasionally can cause loss of all scalp hair (alopecia totalis) and even all hair on the body (alopecia universalis).

Management

Management of hair loss is based on the underlying condition. Therefore, confirming the diagnosis is an important first step. Treatment of female androgenic alopecia includes topical minoxidil (2% or 5% strength, twice or once daily, respectively) (73). In women with evidence of hyperandrogenism, systemic agents, such as spironolactone, could be...
considered. Telogen effluvium is a self-limited phenomenon and requires no treatment beyond reassurance. Normal hair regrowth should occur, but recurrences can happen. Trichotillomania is difficult to treat and likely will require assistance of a psychiatrist in managing concurrent psychiatric comorbidities. Alopecia areata can be self-limited but often is managed with topical or injected corticosteroids or alternative immunosuppressants that warrant referral to a dermatologist.

CASE NO. 3. A patient presents to the office 3 months after delivery of her first child. She is concerned because she noticed her hair has rapidly become thinner, and she is losing large amount of hair in the shower. She feels her hair is thinning particularly around the temporal regions.

Given the overall thinning of the hair and temporal relationship to delivery, telogen effluvium is the most likely diagnosis. Alternative possibilities include androgenetic alopecia, but this would be less likely to occur in an acute fashion. Alopecia areata would present as discrete patches rather than as diffuse thinning. Assessment of trichotillomania can be difficult but would clinically be notable for hair of variable length in odd geographic patches. A hair pull test was performed by gathering a group of hairs (approximately 50) and pulling firmly. Multiple hairs were removed, a sign of telogen effluvium. One to two pulled out hairs would constitute a negative test result. Other measures include assessment of new medications because they are a potential trigger and measurement of serum ferritin levels because low iron stores are a correctable cause of this disorder, and low iron stores may interfere with hair regrowth. If patients have other symptoms of thyroid disease, measurement of thyroid stimulating hormone levels should be considered. Low iron stores and thyroid abnormalities should be corrected, if they exist. The diagnosis of telogen effluvium was established. The patient was counseled that this condition is common after delivery, but it is self-limited. The patient was reminded that all individuals lose approximately 100 hairs daily. Hair regrowth will occur, but it may take months. The patient wishes to treat the telogen effluvium, and she is advised to use over-the-counter minoxidil. At a 6-month follow-up, her hair loss seems to have stabilized, and at a 12-month follow-up, she feels that her hair has regrown to its usual density.

Nail Disorders

Etiology

Nail disorders are varied both in presentation and in etiology. Nail conditions can be primary or caused by other cutaneous or systemic diseases. In this section, three nail conditions will be discussed in detail: 1) onychomycosis, 2) psoriasis, and 3) lichen planus.

Onychomycosis represents one of the most common nail disorders seen in all patient populations, with an estimated prevalence of 12% (74). The prevalence of onychomycosis increases with age. Most infections are caused by dermatophytes, most commonly Trichophyton rubrum, which is also a common fungus found in tinea pedis. Although this is a common problem, patients have an increased risk when they are immunosuppressed, have a family history (particularly in the same home), or have a history of trauma to the nails.
Psoriatic nail disease is a common finding in individuals with psoriasis with variable severity. The abnormal keratinization that drives skin findings also is found in the nail units.

Lichen planus with nail involvement is an unusual disorder. It is mentioned in this monograph because it can cause scarring that can cause permanent disfigurement of the nails. It is secondary to an autoimmune process where T lymphocytes attack the skin, mucous membranes, and nails.

**Presentation**

Patients with onychomycosis present with thickening and often yellowish discoloration of the nails. Multiple types of onychomycosis exist based on their location within the nail, the most common being distal lateral subungual onychomycosis. Subungual debris often is present. Occasionally, redness and swelling of the proximal nail fold may occur. Often, all nails are not affected. Psoriasis typically presents with pitting, splitting of the nail (onycholysis), and white spots within the nail (leukonychia), and it usually affects all nails. Diagnosis is definitively established by laboratory testing. A clipping of the nail is sent to a histopathology laboratory for fungal staining. Alternatively, fine scrapings from the underside of the nail plate may be obtained with a nail curette for a potassium hydroxide test or culture. The potassium hydroxide test includes the following steps:

1. Using a number 15 blade to gently scrape scale onto a clean glass slide
2. Adding one drop of 20% potassium hydroxide
3. Placing a cover glass on top of the slide
4. Gently warming the slide for approximately 5 seconds with a match or a lighter
5. Placing the slide on a microscope stage on low power to examine for fungal structures, such as hyphae or yeast

Histopathologic results can take weeks to return because fungal species grow slowly. Lichen planus presents initially with nonspecific changes, such as splitting of the nail, longitudinal ridging, and thickening of the nail. Over time, pterygium may occur at the proximal nail fold, which is a scarring process that can cause permanent changes to the nail.

**Management**

Effective treatment of onychomycosis is difficult. Oral treatments have cure rates of 60–70% (75). Therefore, the risks of treatment must be weighed against the benefits. First-line therapy typically involves a course of terbinafine for 12 weeks (if toenails are involved) or 6 weeks (if only fingernails are involved). Alternative therapies include pulsed itraconazole (76) or fluconazole, and both carry risks of medication interactions. Topical therapies usually are ineffective. Psoriatic nail disease can be difficult to treat, but it can improve with systemic therapies for psoriasis, which typically are managed by a dermatologist. Treatment of lichen planus nail disease, particularly if scarring is a concern, warrants referral to a dermatologist for management.
Vascular Lesions

Etiology
Common vascular lesions in women, specifically during pregnancy, include spider angio-
mas, cherry angiomas, and pyogenic granulomas. Discussion of all other forms of vascular
lesions is beyond the scope of this monograph. During pregnancy, vascular lesions are
thought to be proliferative in part because of the influence of estrogen on these lesions.
Increased estrogen levels also are thought to contribute to the presence of these lesions
in other disease processes, such as liver disease. The exact etiology of these entities
remains unknown. Spider angiomas are particularly common during pregnancy, with
approximately two thirds of Caucasian women developing lesions, which often resolve
in the postpartum period (77). Cherry angiomas are a proliferation of mature capillar-
ies most commonly on the trunk. They are not thought to have an increased incidence
during pregnancy. Pyogenic granulomas are common, friable papules that tend to bleed.
Often, they occur in the second and third decades of life, and the oral variant is common
during pregnancy (78).

Presentation
Spider angiomas present as a central feeding vessel with surrounding spider-like projec-
tions. The entire lesion will blanch with diascopy and refill from the central vessel.
Spider angiomas are most common on the head and neck. Cherry angiomas (also called
hemangiomas) present as well-demarcated, bright red dome-shaped papules that occa-
sonally can be fibrotic and are mostly found on the trunk. Pyogenic granulomas are
exophytic papules that often are friable and bleed easily. An important diagnostic consid-
eration for a pyogenic granuloma or cherry hemangioma includes an amelanotic mel-
noma, which should be considered if the progress is unusual with continued growth or
friability in the appropriate clinical context.

Management
Spider angiomas do not require treatment unless they are cosmetically bothersome.
Spider angiomas related to pregnancy often resolve after delivery. If treatment is desired,
laser therapy can be performed. Cherry hemangiomas also do not require treatment but
will tend to persist over time. Laser therapy can be performed if treatment is desired.
Pyogenic granuloma often will be treated because of the persistent bleeding that can be
irritating for patients. Treatment often consists of shave biopsy with cauterization of the
base that often contains a slightly larger feeding vessel. Pyogenic granuloma related to
pregnancy often will resolve in the postpartum period.

Malignancies
Skin cancer is the most common type of cancer in the United States (79). Most types of
skin cancer are caused by excessive exposure to UV rays, mostly from the sun or from
the use of indoor tanning beds and sun lamps. Research has shown that the number of skin cancer cases caused by tanning is higher than the number of lung cancer cases caused by smoking. In the United States alone, 419,254 cases of skin cancer can be attributed to indoor tanning; 6,199 of these cases are associated with melanoma (80, 81). The incidence of skin cancer is increasing steadily.

**Basal Cell Carcinoma**

Basal cell carcinoma is a slow growing, locally destructive tumor that results from proliferation of basal keratinocytes. Basal cell carcinoma is the most common type of skin cancer (82). Basal cell carcinoma occurs mostly in adults, especially in the elderly population with fair skin, blond or red hair, light eye color, poor tanning ability (Fitzpatrick skin type I), and sun-damaged skin. Patients with basal cell carcinoma typically present with lesions in the head and neck regions (85%) (Fig. 23). The most common site of basal cell carcinoma is the nose. The male-to-female ratio is 2:1 (83, 84). The main risk factor for the development of basal cell carcinoma is UV light exposure. Ultraviolet B radiation damages DNA and its repair system and alters the immune system. Basal cell carcinoma typically grows by direct extension and appears to require the surrounding stroma to support its growth. Patients who underwent organ transplantation and have profound immunosuppression have a 10-to-100-times higher risk than the general population of developing this type of cancer. Histologically, basal cell carcinoma has the following five major histologic patterns:

1. Nodular
2. Superficial
3. Micronodular
4. Infiltrative
5. Morpheaform

**Clinical Types**

Basal cell carcinoma occurs in many different clinical forms, which vary in appearance and malignant potential. Nodular basal cell carcinoma is the most common form of basal cell carcinoma. The lesion begins as a pearly white or pink, dome-shaped papule with prominent telangiectasia that expands peripherally. The lesion often ulcerates and bleeds.

Basal cell carcinoma may contain melanin that imparts a brown, black, or blue color through all or part of the lesion. This is known as pigmented basal cell carcinoma. Clinically, the lesion may resemble a melanoma or pigmented seborrheic keratosis. However, on close inspection, it may reveal an elevated, pearly white, translucent border. Pigmented basal cell carcinomas will not have a pigment network. Diagnosis is achieved by biopsy.
Another type of basal cell carcinoma is cystic basal cell carcinoma. This variant of nodular basal cell carcinoma has a characteristic smooth round cystic appearance.

Sclerosing or morpheaform basal cell carcinoma is an insidious tumor that may be innocuous in appearance. The tumor is waxy, firm, flat-to-slightly raised, and either pale white or yellowish with indistinct borders and may become depressed and have a scar-like feature. Treatment consists of wide excision or Mohs micrographic surgery.

Superficial basal cell carcinoma is the least aggressive form of basal cell carcinoma and typically occurs on the trunk and extremities and occasionally on the face. The tumor spreads peripherally and invades after considerable time. Lesions are well-circumscribed, red plaques with thin, raised, and pearly white border.

Nevoid basal cell carcinoma or Gorlin–Goltz syndrome is a rare condition inherited as an autosomal dominant trait with high penetrance and variable expression. This disease is characterized by multiple basal cell carcinomas early in life, numerous small pits on palms and soles (50% to 87%), epithelium-lined jaw cysts, lamellar calcification of falx cerebri (65% to 90%), and a variety of skeletal abnormalities, including those of ribs, skull, and spine (85). Often, patients have coarse facies, macrocephaly, hypertelorism, and frontal bossing. The gene associated with this disorder is located on chromosome 9q22.3–q31. The mean age of development of basal cell carcinoma is 23 years. Often, patients have dental problems, resulting from jaw cysts. The first dental cyst occurs...
in 80% of patients by the age of 20 years (85). The initial evaluation of patients sus-
pected of having Gorlin–Goltz syndrome should include the following:

- Family history
- Dental consultations
- Radiography of jaws, skull, chest, spinal column, and hands

**COMMON TREATMENT AND RISK OF RECURRENCE**

Treatment of basal cell carcinoma depends on clinical presentation, cell type, tumor size, and location. Nodular and superficial basal cell carcinomas are the least aggressive and can be completely removed by surgical excision or electrodessication and curettage or can be treated with imiquimod cream.

Basal cell carcinomas with micronodular, infiltrative, and morpheaform histologic forms are more aggressive and have a higher incidence of positive tumor margins after excision than nodular and superficial types. These forms have the greatest rates of recurrence; hence, these variants require more aggressive treatment with wide excision or Mohs microscopic surgery.

Mohs surgery is the treatment of choice for most sclerosing basal cell carcinomas and other basal cell carcinomas with poorly defined clinical margins; for tumors in areas of potentially high recurrence, such as the nose or eyelid; for large primary tumors; and for large, recurrent basal cell carcinomas. Basal cell carcinomas on the nose, ear, and eye require special consideration and are treated with Mohs surgery.

**RELATIVE RISK AND FOLLOW-UP**

Patients treated for basal cell carcinoma should be monitored annually for 5 years or longer. Patients with one diagnosis of basal cell carcinoma, often develop another basal cell carcinoma within 5 years after treatment (36–50%) (86, 87). Thus, patients with basal cell carcinoma may benefit from an annual skin evaluation.

**OTHER TREATMENT OPTIONS**

Additional treatment options for basal cell carcinoma include radiation therapy, imiqui-
mod, 5-fluoroacil, and vismodegib. Radiation therapy is useful for elderly patients who cannot tolerate minor surgical procedures.

Imiquimod is an immune response modifier that induces cytokines related to cell-
mediated immune responses. Imiquimod 5%-cream used five to seven times per week for a period of 6 weeks is effective in the treatment of superficial basal cell carcinomas. Local skin reactions are common but well tolerated. Although the initial clearance rate at 12 weeks after treatment is approximately 95%, the 2-year recurrence rate after treatment is approximately 20% (88).
Another treatment option is 5% fluorouracil cream. It is approved by the FDA for the treatment of superficial basal cell carcinomas and is used in rare cases.

Vismodegib and sonidegib are orally administered hedgehog-pathway inhibitors approved by the FDA for locally advanced and metastatic basal cell carcinomas. Advanced basal cell carcinomas are characterized as inoperable because of multiple postsurgical recurrences. The surgery is not effective and is associated with significant deformity or loss of function. These advanced lesions also can be metastatic. Vismodegib and sonidegib are alternatives to surgery; they have been classified as pregnancy category D medications by the FDA.

**Melanoma**

Incidence of melanoma has steadily increased in past several years. Typically, the lesion is characterized by a changing mole or an atypical or dysplastic mole (Fig. 24). Malignant melanoma is the sixth most common type of cancer in the United States and causes 1–2% of all deaths from cancer (89). Melanoma develops from proliferation of transformed melanocytes. Frequently, the lesions occur on the trunk in men and lower extremities in women. Patients with dark skin typically develop melanoma in the acral areas. Usually, melanoma is seen in adults, although it can be seen in children in the setting of giant congenital nevi or atypical or dysplastic nevus syndrome or xeroderma pigmentosum.

Risk factors for melanoma include Caucasian race with lighter skin, giant congenital nevus, atypical nevus syndrome, history of dysplastic or changing moles, family (first-degree relatives) and personal history of melanoma, immune suppression (patients with lymphoma, leukemia, or solid organ transplant recipients), nonmelanomatous skin cancer, sun sensitivity and history of sunburns, and the use of a tanning bed.

![Figure 24. Dysplastic nevus groin.](image)
**Clinical Types**

The following subtypes of melanomas have been identified:

- Lentigo maligna
- Superficial spreading
- Nodular melanoma
- Acral–lentiginous melanoma
- Amelanotic melanoma

Lentigo maligna represents approximately 5% of all cases of melanoma (90). It is associated with extensive sun exposure and occurs on sun-exposed areas of the skin in adults (Fig. 25). Typically, vertical growth and metastasis occur many years after exposure, often resulting in a pigment patch greater than 1 inch. Superficial spreading melanoma is the most common form of melanoma (70%) (90). It can exhibit a prolonged horizontal growth pattern over months to years before becoming invasive. Nodular melanoma represents 15–30% of all cases of melanoma (91). Typically, it is an invasive lesion. Acral–lentiginous melanoma represents 8% of all cases of melanoma and is most commonly seen in patients with darker skin types (90). Acral–lentiginous melanoma occurs on the palms, soles, nail beds, mucous membranes, and penis. Amelanotic melanoma, as the name suggests, is devoid of pigmentation. It may appear as a pink, red, purple, or skin-colored nodule or a papule often with an asymmetrical shape and irregular border.

![Figure 25. Chronic sun damage on the arm. Chronic sun damage results in dry, thin, wrinkled skin with scaly patches.](image-url)
**Screening and Diagnosis**

A list of criteria, called ABCDE criteria, is used to aid in the screening for melanoma (Fig. 26 and Fig. 27). These criteria include the following:

- Asymmetric shape
- Irregular borders
- Color variability or recent change in color
- Size 6 mm in diameter
- Evolving

Pruritus, ulceration, and bleeding in a mole are a concern. Women coming for annual examination and pregnant women with atypical nevus should be screened with the ABCDE criteria. Figure 28 represents a diagnostic algorithm for melanoma.

![Figure 26. Malignant melanoma. This malignant melanoma meets the “ABCD” criteria. It is asymmetric with notched borders and multiple colors and is approximately 1.2 cm in diameter.](image1)

![Figure 27. Another example of malignant melanoma.](image2)

![Figure 28. Algorithm for the diagnosis of melanoma.](image3)
Prognostic factors for melanoma include the following seven factors: 1) thickness or level of invasion of the melanoma, 2) mitotic index, 3) ulceration or bleeding at the primary site, 4) the number of regional lymph nodes involved, with distinction of macro-metastasis and micrometastasis, 5) systemic metastasis, 6) site of melanoma (nonvisceral versus lung versus other visceral sites), and 7) increased serum lactate dehydrogenase level. The risk of melanoma relapse decreases substantially over time; however, late relapses are not uncommon.

**Reproductive Considerations**

Melanocytic lesions of the genital area are rare. They can arise on the vulva and less frequently on the perineum, mons pubis, and male genitalia. These pigmented lesions include regular melanocytic nevi, lentigines, dysplastic melanocytic nevi, and melanomas with microscopic features similar to those seen elsewhere on the body. There is a small subset of benign nevi named atypical melanocytic nevi of the genital type that occur in young women. They have distinctive histologic features in some cases overlapping morphologically with those of melanoma. Atypical melanocytic nevi of the genital type are more common on the labia minora, whereas dysplastic nevi are more common in the region of labia majora. Atypical melanocytic nevi of genital type may present as a macule or papule. The macules on the labia minora and clitoris often are black and often have cytologic atypia on histologic examination that may raise the concern of a melanoma. However, a careful histologic analysis can distinguish these lesions. Concentric eosinophilic fibroplasia and lamellar fibroplasia are common in patients with dysplastic nevi whereas fibroplasia with a plaque-like lymphocytic infiltrate and diffuse eosinophilic fibroplasia are seen in patients with radial growth phase melanoma. Atypical melanocytic nevi of the genital type typically are associated with a nonspecific stromal pattern.

Malignant melanoma is one of the most common types of malignancy that occurs during pregnancy. The incidence in pregnancy has been estimated to range from 0.14 to 2.8 per 1,000 live births, and melanoma accounts for approximately 8% of all malignant tumors arising during pregnancy (92). For many years, it was assumed that pregnancy-induced hormonal changes may cause a rapid melanoma progression and may result in poor maternal and fetal outcomes. However, the association of hormonal changes during pregnancy and melanoma is controversial. It is thought that immunologic changes during pregnancy may affect tumor surveillance, in that the immune cells may not be able to mount an effective surveillance allowing for escape of neoplastic cells. Although some studies have shown rare expression of hormone receptors on melanoma tumor surface, its clinical relevance remains unclear (93). Several studies have demonstrated that women who received the diagnosis of melanoma during pregnancy do not have thicker primary tumors, tumors located in poorer prognostic anatomic sites, or other characteristics that would favor a negative effect on survival. Thus, most existing literature does not support poor prognosis for pregnancy-associated melanoma (94). Furthermore, there is
no evidence to suggest any risk associated with oral contraceptives or hormone therapy use in poor melanoma prognosis.

Rarely, melanoma can metastasize to the placenta or the ovary. Male infants have a particularly high risk of developing melanoma from placental metastatic melanoma. Studies have shown an approximate 22–25% mortality risk to infants born to women with placental metastasis with death occurring within 3 months of diagnosis (95). Infants born to women with concomitant placental metastatic melanoma but without clinical evidence of the disease have a high risk of melanoma and should be periodically evaluated for the development of melanoma for at least 24 months after childbirth.

**Management**

Patients have a wide local excision. Margins of the excision are listed in Table 5.

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Recommended Clinical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>1 mm or less</td>
<td>1 cm</td>
</tr>
<tr>
<td>1.01–2 mm</td>
<td>1–2 cm</td>
</tr>
<tr>
<td>2.01–4 mm</td>
<td>2 cm</td>
</tr>
<tr>
<td>Greater than 4 mm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

Sentinel lymph node biopsy is performed to determine the microscopic nodal status and typically is used in patients with clinically negative nodes, tumors of intermediate thickness (0.76–4 mm), or thin tumors (less than 0.76 mm) with ulceration. The degree of involvement of regional lymph nodes helps in staging, prognosis, determining the adjuvant treatment regimen, and follow-up. Although sentinel lymph node biopsy (compared with observation of draining nodes) is not associated with increased or improved survival, the prognostic information obtained with the procedure is helpful in staging and in consideration of adjuvant therapy.

Complete lymph node dissection typically is performed in patients with clinically positive nodes. Elective nodal dissection is recommended for younger patients with lesions between 1.5–4 mm in thickness. Patients with thick tumors (greater than 4 mm) often already have widespread disease; the surgical removal of regional lymph nodes does not positively influence their prognosis.

Although surgical excision is the standard procedure for patients with in situ melanoma, it may not be feasible because of comorbidity. Topical imiquimod has emerged as an alternative treatment option for patients with lentigo maligna. Radiation therapy also has been used selectively for patients with lentigo maligna.
The National Comprehensive Cancer Network recommends antiprogrammed death ligand-1 monotherapy (pembrolizumab, nivolumab, or ipilimumab); targeted therapy, if the patient has a BRAF mutation; combination therapy of dabrafenib–trametinib, or vemurafenib–cobimetinib; single-agent therapy with vemurafenib and dabrafenib; and, when available, clinical trials for patients with metastatic melanoma (96). Other systemic therapies include the following:

- Cytotoxic chemotherapy (dacarbazine, temozolomide, paclitaxel, and carboplatin–paclitaxel)
- Biochemotherapy for metastatic disease (dacarbazine–temozolomide and cisplatin–carboplatin with or without vinblastine or nitrosourea and interleukin-2 and interferon alfa-2b)
- Biochemotherapy for adjuvant treatment of patients with high-risk disease

Follow-up for patients with melanoma is noted in Table 6.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 in situ</td>
<td>Annual skin check</td>
</tr>
<tr>
<td>Stage IA–IIB, no evidence of disease</td>
<td>Follow-up every 3–6 months for 2 years, then every 3–12 months for 3 years, then annual full skin evaluation as indicated</td>
</tr>
<tr>
<td>Follow-up every 6–12 months for 5 years, then annually; routine imaging</td>
<td></td>
</tr>
</tbody>
</table>

Squamous Cell Carcinoma

Etiology and Presentation

Squamous cell carcinoma of the skin accounts for 20% of cases of nonmelanomatous skin cancer and is the second most common type of skin cancer in the Caucasian population (97). Squamous cell carcinoma typically presents as a spectrum of subtypes with varying clinical behavior. It appears as an erythematous papule, plaque, or a nodule usually located in a sun-exposed area with overlying scaling, deep ulceration, crusting, and cutaneous horn (Fig. 29). In some cases, it can occur in sites not exposed to the sun, such as genitalia, suggesting a role of other factors in its development.

Actinic keratosis is a proliferation of atypical keratinocytes that are induced by UV exposure and are typically confined to epidermis. These precancerous lesions were long thought to exist in continuum with squamous cell carcinoma in situ. There is controversy in the rate of transformation of atypical keratinocytes to squamous cell carcinoma. One study noted that the rate of developing an invasive squamous cell carcinoma from a given actinic keratosis was approximately 0.075–0.096% per lesion per year (98).
Thus, for an individual with more than seven or eight actinic keratinocytes, if left untreated for 10 years, the chance of developing a squamous cell carcinoma is approximately 10.2%. Other studies have proposed a higher 10-year rate of transformation (13–20%) (99). There are several variants of actinic keratosis, including hypertrophic, pigmented, lichenoid, and atrophic. Hypertrophic actinic keratosis typically is seen as thickened hypertrophic plaques or papules that are clinically difficult to discern from squamous cell carcinoma.

Squamous cell carcinoma in situ (Bowen disease) represents an intraepidermal malignancy typically seen as a scaly plaque on sun-exposed skin in elderly individuals with considerable sun exposure. Risk factors for developing Bowen disease include UV exposure, light skin type, immune suppression, radiation or arsenic exposure, and human papillomavirus infection. The rate of transformation of Bowen disease to invasive squamous cell carcinoma is estimated to be 3–8%, and its metastatic potential after development of invasive squamous cell carcinoma is approximately 3–5% (100, 101). Bowen disease on sun-exposed sites is less aggressive compared with sun-protected sites. Erythroplasia of Queyrat is squamous cell carcinoma in situ, involving the vulva, oral mucosa, or glans. It is associated with factors, such as trauma, poor hygiene, friction, and syphilis. Bowenoid papulosis is another condition that is to be differentiated while considering Bowen disease. It is controversial whether Bowenoid papulosis is a true squamous cell carcinoma in situ versus a benign condition.

**Clinical Features**

Squamous cell carcinoma is characterized as a raised firm, erythematous keratotic scaly papule, plaque, or a nodule with more substance compared with actinic keratosis, occurring on actinically damaged sun-exposed skin. Actinic keratinocytes with rapid growth, ulceration, induration, erosion, bleeding, or associated pain must be biopsied to rule out
squamous cell carcinoma transformation. Although they are mostly keratotic, a few lesions also present as nodules without any epidermal change. Paresthesia and dysesthesia may reflect perineural spread of squamous cell carcinoma. Rapidly growing squamous cell carcinomas on the ear and lip are concerning. The lymphatics of the perichondrium could facilitate metastasis. The rate of squamous cell carcinoma metastasis from the lip and ear is approximately 10–14% and 11%, respectively (102). Squamous cell carcinoma occurring in the anogenital area also is thought to be high-risk and associated with human papillomavirus infection. Anogenital squamous cell carcinoma typically is associated with pain, erythema, irritation, pruritus, and bleeding. Maceration and lack of scale are common. Marjolin ulcer develops in patients with chronically damaged skin affected by long-standing ulcers, radiation dermatitis, osteomyelitis, or sinus tracts. Also, it is associated with significant rates of metastasis. There should be a low threshold to biopsy chronic ulcers that demonstrate acute changes in size and symptom. Verrucous carcinoma is a low-grade squamous cell carcinoma that has the propensity to become locally and deeply invasive. Clinically, it appears as a verrucous plaque. Buschke–Löwenstein tumor is a verrucous carcinoma found in the anogenital area. Keratoacanthoma is a variant of squamous cell carcinoma that is characterized by rapid growth phase. Clinically, it appears as a well-circumscribed papule or a nodule rapidly enlarging over several weeks. Lesions typically range between 1 cm and 3 cm in size and occur in the sun-exposed skin. Several variants of keratoacanthoma exist—solitary keratoacanthoma and keratoacanthoma centrifugum marginatum. It can also be seen in patients with multiple syndromes, such as Ferguson–Smith syndrome or Muir–Torre syndrome. The diagnosis is based on the clinical features and should be histopathologically confirmed to adequately address the prognosis and treatment.

**Management**

Squamous cell carcinoma is staged according to American Joint Committee on Cancer criteria based on primary tumor size, regional lymph node status, and presence of distant metastasis. Complete surgical excision with histopathologic control of excision margins is the key in the treatment of primary squamous cell carcinoma with a 4-mm margin around low-risk lesions and 6-mm margin around high-risk lesions. High-risk squamous cell carcinoma includes tumors that are larger than 2 cm, with subcutaneous or perineural invasion. They have a high risk of recurrence and are located in high-risk locations (ie, central face, ears, scalp, genitalia, hands, and feet). Sentinel lymph node biopsy can be considered in patients with squamous cell carcinoma with a tumor thickness greater than 6 mm; however, there is no evidence of prognostic and therapeutic benefit of nodal mapping. Radiation therapy can be used as an alternative to surgery for inoperable tumors or as adjuvant therapy in patients with a high risk of recurrence. In patients with squamous cell carcinoma with distant metastases, various chemotherapeutic agents are used; however, there is no standard regimen. The epidermal growth factor receptor inhibitors and immune checkpoint blockers can be considered.
Paget Disease of the Breast

Etiology and Presentation

Paget disease of the breast accounts for 0.6–3.2% of all cases of breast cancer. In 80–100% cases, the disease is associated with an underlying breast carcinoma (103). Clinically, patients with this disorder present with a chronic unilateral erythematous scaly plaque on the nipple or the areola. Commonly, ulceration, edema, nipple retraction, and bleeding are seen. Patients can have associated pain, itching, and burning sensation. Underlying palpable mass may be present in up to 50% of patients (104, 105). Differential diagnosis of Paget disease of the breast includes allergic contact dermatitis (Fig. 30), psoriasis, Bowen disease, and dermatophytosis. Histologically, the lesions appear as large cells with ample pale staining cytoplasm and large cytologically atypical nuclei that are distributed as single lesions or in aggregates. Paget cells stain positively for cytokeratin 7, cytokeratin 8, and cytokeratin 18 and carcinoembryonic antigen, epithelial membrane antigen, and high molecular weight glycoprotein mucin-1. Also, they stain positively for Her2/Neu receptor, estrogen receptor, and progesterone receptor in 88%, 30%, and 40% of cases, respectively (106, 107).

Management

Primary treatment for Paget disease of the breast is lumpectomy or complete mastectomy, often with axillary lymph node evaluation with or without radiation therapy. However, breast-conserving treatment also has been used for patients with Paget disease of the breast. No data are available regarding efficacy of tamoxifen or other adjuvant systemic therapy for Paget disease of the breast without associated ductal carcinoma in situ or invasive carcinoma. The prognosis depends on the presence of an underlying invasive ductal carcinoma or nodal metastases.

Figure 30. Allergic contact dermatitis of the perineum associated with Paget disease. This patient presented with a painful, itchy rash on the perineum. Evaluation revealed the cause to be an allergic reaction to a topical medicine. In older women, allergic contact dermatitis can be part of the differential diagnosis for Paget disease of the breast or extramammary Paget disease.
Extramammary Paget Disease

Extramammary Paget disease is an uncommon epidermal malignant neoplasm that typically involves the apocrine gland-bearing skin, including the skin of the vulva, perineal area, and axilla. Unlike Paget disease of the breast, extramammary Paget disease is more commonly limited to skin without an underlying malignancy. Extramammary Paget disease is estimated to have an incidence of 0.11 per 100,000 and it represents 14% of all cases of Paget disease. The mean age at diagnosis is between 72 years and 75 years. The male-to-female ratio is 1:3.2; however, in certain populations (eg, Asian race), the male-to-female ratio is 3:1, and the distribution is almost equal in the Caucasian population. Extramammary Paget disease of the vulva typically is a primary neoplasm (80%), whereas extramammary Paget disease involving the perianal area is associated with colorectal adenocarcinoma in 80% of cases (103).

Presentation

Extramammary Paget disease appears as an erythematous scaly plaque, often with crusting, maceration, or ulceration. Common sites of involvement include vulva, perineal area, and axilla (in women). These lesions may be associated with pain and pruritus. Biopsy of the lesion is the recommended diagnostic measure. The differential diagnosis includes Hailey–Hailey disease, hidradenitis, lichen sclerosis et atrophicans, and fungal infection. Skin biopsy confirms the diagnosis. In cases of noninvasive perianal extramammary Paget disease, four quadrant punch biopsies are recommended for mapping of lesions because Paget cells may extend beyond gross margins of the lesion. Biopsy demonstrating dermal invasion and lymphovascular invasion is associated with an increased risk of metastatic disease. Imaging studies (computed tomography and positron emission tomography) can be used to detect metastases. Serum carcinoembryonic antigen levels can be used to monitor for recurrence in patients with metastatic disease.

Management

The treatment of extramammary Paget disease depends on whether the lesion is primary or secondary. For a secondary lesion, the underlying malignancy must be managed in addition to local control of the disease. Patients with biopsy-confirmed Paget disease should undergo further evaluation of the breast, genitourinary tract, and GI tract (103).

Surgery is the therapeutic mainstay for patients with primary extramammary Paget disease; however, there is a high recurrence rate with wide local excision (approximately 20–44%) (99, 108, 109). After wide local excision, the edge of the resected margins is checked by frozen sections for residual disease. After confirmation of complete resection and no residual tumor, the defect is closed with split thickness skin graft. Extramammary Paget disease of the vulva is almost always noninvasive and can be managed conservatively with vulvectomy and split thickness skin grafting without loss of sexual function (110, 111). However, in the case of local invasion, abdominoperitoneal resection or
chemoradiation can be used. Tumors with an invasive component on histology have a higher recurrent rate compared with in-situ disease. Mohs micrographic surgery has emerged as a tissue-sparing therapy for patients with extramammary Paget disease. Studies have shown that patients with tumors treated with Mohs surgery have low recurrence rates compared with those treated with traditional wide local excision (108).

Other therapeutic regimens include 5-fluorouracil or docetaxel-based chemotherapy that also has demonstrated some efficacy in patients with metastatic disease. Mitomycin C or carboplatin with 5-fluorouracil, low-dose mitomycin, cisplatin, and etoposide have been used. A combination of 5-fluorouracil and photodynamic therapy also have been used (112). When used alone, these regimens induce only incomplete responses and may need to be followed by further surgical intervention. Ionophoresis may improve topical drug delivery. Photodynamic therapy also may be used to visualize the clinical margins of the lesion. Topical imiquimod therapy is promising for patients with contraindications to other forms of treatment (113–115). Radiation therapy has been used typically for patients who are poor surgical candidates.

Because of multifocality of this disease, regional recurrence is common even when the resected margins test negative histologically. In patients with perianal disease, complete physical examination, proctosigmoidoscopy, biopsy of new lesions, and random biopsy of edges of split-thickness skin graft are recommended. Thus, long-term follow-up typically is required for patients with extramammary Paget disease to monitor disease recurrence or development of associated cancer.

### Merkel Cell Carcinoma

#### Etiology

Merkel cell carcinoma is a neuroendocrine carcinoma that arises in the skin touch receptors called the Merkel cells. The disease has a higher mortality (33% at 3 years) than malignant melanoma, although it is approximately 40 times less common than melanoma. Reported incidence of Merkel cell carcinoma has almost quadrupled in the past 15 years likely because of the routine use of cytokeratin 20 immunohistochemistry for diagnosis and the improved recognition of this malignancy by dermatopathologists and increasing population older than 65 years with extensive sun-exposure history and prolonged immune suppression (99, 116). More than 80–90% of these tumors also contain the Merkel cell polyomavirus oncoproteins that drive the cancer (117). Patients with immune suppression, such as those with leukemia and lymphoma and solid organ transplantation recipients, have an increased risk of developing this type of cancer and also have a poor prognosis.

#### Presentation

Merkel cell tumors typically are painless and grow rapidly (Fig. 31). Merkel cell carcinoma has a propensity for lymphatic spread. Even a small-sized tumor is associated with a
high risk of nodal spread. Histologically, Merkel cell carcinoma appears as sheets of small basophilic cells with scant cytoplasm, fine chromatin, and a lack of nucleoli with numerous mitotic figures, and often it is associated with lymphovascular invasion. The cytokeratin 20 stain shows a typical perinuclear dot-like pattern. Patients with Merkel cell carcinoma have negative thyroid transcription factor-1 test and CK7 immunohistochemistry results. The thyroid transcription factor-1 test typically is associated with positive results in patients with small-cell lung cancer, another neuroendocrine cancer.

**Figure 31.** Merkel cell carcinoma presenting on the fifth digit of the left hand. (Courtesy of Dr. Paul Nghiem, www.merkelcell.org.)

**Diagnosis and Management**

Patients typically undergo imaging studies. Treatment includes wide local excision with a 2-cm margin with or without sentinel lymph node biopsy and subsequent lymph node dissection or radiation of the node bed in case of a positive lymph node biopsy result. Patients with distant metastasis previously underwent chemotherapy with the platinum group of chemotherapy and or palliative radiation. However, with recent immunologic advances, many immunotherapeutic drugs, such as antiprogrammed death-1 protein and antiprogrammed death-1 ligand blockers are now in clinical trials for metastatic Merkel cell carcinoma with promising results.

**Dermatofibrosarcoma Protuberans**

**Etiology**

Dermatofibrosarcoma protuberans is a rare tumor of the dermal layer of the skin, typically affecting individuals aged 30–50 years with a higher incidence in men than in women (a male-to-female ratio of 3:2). It accounts for approximately 0.1% of all skin neoplasms. Most cases are associated with chromosomal abnormalities, including reciprocal translocation t(17;22) (q22;q13). More than 90% of patients with dermatofibrosarcoma protuberans present with a translocation in different regions of chromosomes 17 and 22. In the
translocation t(17,22), an exon of the platelet-derived growth factor-B in chromosome 22 is fused with the collagen-1-alpha 1 in chromosome 17. This fused oncogene produces mature and fully functional platelet-derived growth factor subunit B protein.

**Presentation**

Dermatofibrosarcoma protuberans is characterized by a slow, infiltrative growth pattern. It has considerable morbidity because of its aggressive local invasiveness. It is typically located on the trunk, followed by extremities. Initially, it grows as an asymptomatic, reddish or skin colored indurated plaque with some surrounding telangiectasia that may slowly enlarge and become a firmer, multinodular lesion that may ulcerate, bleed, or become painful. In rare cases, dermatofibrosarcoma protuberans may undergo distant metastasis. Dermatofibrosarcoma protuberans typically is CD34 positive and factor XIIIa negative. Magnetic resonance imaging is useful to determine deep tumor invasion, especially recurrent lesions.

**Management**

Surgery is the mainstay of treatment for patients with dermatofibrosarcoma protuberans. However, dermatofibrosarcoma protuberans is characterized by an overall high recurrence rate after wide local excision. Accurate removal with the least recurrence requires careful and extensive evaluation of all the margins. Mohs micrographic surgery is an alternative to traditional surgery for patients with dermatofibrosarcoma protuberans. Adjuvant radiation therapy reduces local recurrence in patients who have close or positive margins and patients with unresectable macroscopic disease. Imatinib mesylate is a tyrosine kinase inhibitor currently approved by the FDA for adults with unresectable, recurrent, or metastatic dermatofibrosarcoma protuberans.

**Cutaneous Cell Lymphoma**

**Etiology and Presentation**

Primary cutaneous lymphomas represent a heterogeneous group of T cell and B cell lymphomas. Cutaneous lymphomas represent 3.9% of all non-Hodgkin lymphomas, and mycosis fungoides represents most of these cases. The incidence of cutaneous cell lymphomas has increased in the past several years. Age-adjusted incidence of cutaneous cell lymphomas is thought to be 6.4–9.6 cases per million individuals in the United States (118). Mycosis fungoides infection tends to favor older individuals, but also it can affect young children. Patients with mycosis fungoides and Sezary syndrome (ie, erythrodermic form of cutaneous T cell lymphoma) have a significantly increased risk of developing a second lymphoma, in particular Hodgkin lymphoma and the cutaneous cell lymphomas subtype lymphomatoid papulosis, as well as other nonhematologic malignancies. Mycosis fungoides typically has a slow indolent course whereas Sezary syndrome has an aggressive course.
There are several types of cutaneous cell lymphoma, including patch and plaque type, hypopigmented mycosis fungoides, pigmented purpuric type, granulomatous slack skin, pagetoid reticulosis, alopecia mucinosa, tumor stage mycosis fungoides, and erythrodermic variant.

**Diagnosis and Management**

Diagnosis is established with skin biopsy and flow studies from peripheral blood for T cell clonality. Treatments include topical corticosteroids; topical retinoids; or topical chemotherapy, such as nitrogen mustard or topical mechlorethamine; psoralen and UV A radiation therapy; UV B radiation therapy, extracorporeal photochemotherapy; DAB-IL-2 toxin and denileukin diftitox; systemic high-dose chemotherapy (adriamycin and cyclophosphamide–hydrodaunorubicin–Oncovin [vincristine]–prednisone [or prednisolone] therapy [also known as CHOP therapy]); and histone deacetylase inhibitors.

**CASE NO. 4.** A woman in her early 60s comes to the clinic with a spot on her cheek that has been present for several months and is not healing. She thought it was an insect bite at first, but it does not seem to be improving and has grown slowly over the past month. On examination, an erythematous papule with a small amount of erosion is present just lateral to nasolabial fold. The patient would like a cream to help this spot resolve.

The differential diagnosis for a nonhealing lesion on a sun-exposed area in an adult patient includes basal cell carcinoma, squamous cell carcinoma, and other malignancies, including amelanotic melanoma. Occasionally, nonhealing lesions can occur secondary to patient continued manipulation (picking or scratching), but malignancy should be ruled out. For a nonhealing lesion with continued growth, biopsy is recommended to rule out malignancy. This may require a referral to dermatology. The patient should be counseled that most types of skin cancer grow slowly over time. Any nonhealing skin lesion should be evaluated for malignancy. Sun protection can help prevent additional lesions from developing. Out of concern for malignancy, the patient is referred to a dermatologist. A shave biopsy is performed, and the lesion is found to represent a basal cell carcinoma. The patient is then referred for Mohs micrographic surgery to completely excise the malignancy.

**Cutaneous Manifestations of Systemic Disease**

**Acanthosis Nigricans**

Acanthosis nigricans is characterized by hyperpigmented, velvety plaques with accentuated skin markings, involving the neck and flexural surfaces of the body (Fig. 32). It is thought to result from stimulation of growth factor signaling pathways on the epidermis. Acanthosis nigricans can occur in patients with insulin-resistant diabetes mellitus, secondary to increased stimulation of insulin-like growth factor receptors. Approximately 22–44% patients with polycystic ovary syndrome have associated acanthosis nigricans,
Benign acanthosis nigricans is typically characterized by insidious onset of thick hyperpigmented velvety papillomatous skin involving the nape of the neck, axilla, and less commonly anogenital area and groin. Rapid onset of acanthosis nigricans with involvement of extraflexural sites, mucous membrane or vermillion border, associated palmar keratodermas, and nail changes can be suggestive of underlying malignancy, and appropriate investigation to elucidate the underlying cause is necessary. Acanthosis nigricans can be classified into five different categories based on the underlying etiology:

1. Hereditary: benign autosomal dominant
2. Benign: seen in patients with diseases, such as acromegaly, diabetes mellitus, Addison disease, and Cushing disease
3. Drug-induced: associated with the use of stilbesterol and nicotinic acid
4. Pseudoacanthosis nigricans: seen in obese Asian or Hispanic individuals
5. Malignant: seen in patients with adenocarcinoma of the GI tract, ovary, and uterus

Differential diagnosis includes lichen amyloidosis, confluent and reticulate papilomatosis, and chronic lichenified eczema. Treatment of the underlying cause may help improve this condition.

Granuloma Annulare

Granuloma annulare is a relatively common condition that is characterized by degeneration of dermal collagen and associated necrobiotic granuloma formation. The lesions are asymptomatic and appear as flesh-colored annular rings mostly located on the dorsal aspect of hands and feet in children or young adults. These lesions can persist from months to years and may resolve by themselves. Generalized granuloma annulare can present as smaller papules that may be widespread on the trunk and limbs. The association between diabetes mellitus and granuloma annulare is controversial.
Differential diagnosis includes erythema annulare centrifugum, annular lichen planus, and annular sarcoidosis. Differential diagnosis for an isolated granuloma annulare lesion could include tinea corporis.

**Rheumatoid Arthritis**

Patients with rheumatoid arthritis (RA) can develop multiple cutaneous findings, including rheumatoid nodules, vascular reactions, neutrophilic dermatoses, and cutaneous adverse reactions from medications. Rheumatoid nodules are characterized as nontender subcutaneous nodules, occurring particularly over the ulnar border of the forearm, dorsum of the hands, extensor aspect of the knees, and other sites in patients with seropositive RA. Patients with RA can develop pigmented purpuric lesions caused by capillaritis and purpuric papules of distal digits caused by small vessel vasculitis. Also, they can develop erythematous indurated papules in a reticular pattern over the swollen joints, mostly over the elbow.

Neutrophilic dermatoses, such as Sweet syndrome, pyoderma gangrenosum, rheumatoid neutrophilic dermatitis, and neutrophilic lobular panniculitis also can be seen in patients with RA. Medications used to treat patients with RA also can have cutaneous adverse effects as listed in Table 7.

<table>
<thead>
<tr>
<th>Medications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsteroidal antiinflammatory drugs</td>
<td>Pseudoporphyria and toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Pemphigus, lichenoid drug reaction, changes akin to pseudoxanthoma elasticum, and elastosis perforans serpiginosa</td>
</tr>
<tr>
<td>Gold</td>
<td>Eruption akin to pityriasis rosea and lichenoid drug reaction</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Accelerated nodulosis and papular eruptions in extremities</td>
</tr>
<tr>
<td>Tumor necrosis factor-alpha inhibitor</td>
<td>Local injection site reaction, urticarial effects, anaphylaxis, angioedema, vasculitis, interstitial granulomatous dermatitis, lupus erythematosus, psoriasiform eruption and palmarplantar pustulosis, accelerated nodulosis, and dermatomyositis</td>
</tr>
</tbody>
</table>


**Systemic Lupus Erythematosus**

Lupus erythematosus is a group of diverse persistent autoimmune inflammatory diseases manifesting a wide range of symptoms and signs, mostly affecting young to middle-aged women. Systemic lupus erythematosus affects several organs, such as skin, joints, and kidneys, and blood test results reveal circulating autoantibodies. The clinical features of SLE are highly variable and may overlap with other diseases and conditions. Cutaneous involvement is noted in 80% of patients with SLE (122) (Box 4, Fig. 33, and Fig. 34).
Box 4. Features of Cutaneous Lupus

Acute Cutaneous Lupus
- Butterfly rash that resolves without scarring
- Bullous lupus: blisters or bulla; if severe, it may resemble toxic epidermal necrolysis; maculopapular rash; mucosal erosions and ulcerations; and photosensitivity
- Lupus rashes mainly on sun-exposed sites
- Diffuse hair loss (nonscarring alopecia) with brittle hair shafts

Subacute Lupus
- Flat scaly patches often in network pattern
- Annular or arculate polycyclic (overlapping circular) lesions
- Minimal scarring
- Affects trunk and arms
- Flares on exposure to sun, but usually spares face and hands

Chronic Cutaneous Lupus
- Affects 15–20% of patients with systemic lupus erythematosus
- Indurated hyperpigmented plaques
- Lesions may be localized (above neck in 80% of patients) or generalized (above and below the neck in 20% of patients)
- Hypertrophic (warty) lupus
- Tumid lupus or lupus panniculitis
- Mucous membrane involvement (lips, nose, mouth, and genitalia)
- Chilblain lupus
- Lupus panniculitis or lupus profundus


Figure 33. Malar rash of systemic lupus erythematosus. This patient with systemic lupus erythematosus has the classic “butterfly” rash over both cheeks as a manifestation of her photosensitivity.

Figure 34. Chronic cutaneous lupus. This patient has a scarring alopecia caused by discoid lupus. Areas of hair loss have an inflammatory erythema with a surrounding hyperpigmented border.
**Sjögren Syndrome**

Sjögren syndrome is characterized by keratoconjunctivitis sicca and xerostomia in association with an autoimmune disorder. Patients with Sjögren syndrome can develop vasculitis.

**Sarcoidosis**

Sarcoidosis is a systemic disease characterized by the formation of noncaseating granulomas in various tissues. Cutaneous involvement occurs in 20–35% of the patients and may be the initial manifestation of the disease (123). Sarcoidosis can involve the lungs, mediastinal and peripheral lymph nodes, skin, liver, spleen, eyes, and parotid glands. Less frequent but, usually, severe manifestations also occur in the central nervous system, heart, upper respiratory tract, and bones. Cutaneous involvement in patients with sarcoidosis may occur at any stage of the disease. Skin lesions of sarcoidosis can include lupus pernio, infiltrated plaques, maculopapular eruptions, subcutaneous nodules, and scars. Erythema nodosum is the most frequent nonspecific skin lesion in patients with sarcoidosis.

**Scurvy**

Patients with significant vitamin C deficiency will demonstrate perifollicular purpura, corkscrew hair, and spongy gingiva with bleeding and erosions. Severe vitamin C deficiency can result in subperiosteal hemorrhage with pseudoparalysis. Arthralgia, joint swelling, edema, loose teeth, weakness, and vasomotor instability also are possible.

**Pellagra**

Pellagra is a condition caused by niacin deficiency. It is characterized by photosensitivity, dermatitis (Fig. 35), diarrhea, and death. Pellagra is observed in malnourished individuals and as a complication of isoniazid therapy.

The skin may reflect signs of systemic disease. Skin manifestations of systemic disease are numerous and varied and may be helpful in establishing a diagnosis. Several conditions have been described in this section. Skin manifestations may be a presenting feature for underlying carcinomas and are listed in Table 8.

![Figure 35. Pellagra. This illustration shows a patient with dermatitis in the photo-distributed area. (Courtesy of Dr. Y.S. Marfatia, Baroda Medical College, India.)](image)
# Table 8. Diseases Commonly Associated With Cancer and Their Dermatologic Manifestations

<table>
<thead>
<tr>
<th>Type of Dermatosis</th>
<th>Clinical Description</th>
<th>Associated Type of Cancer</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Almost Always Associated With Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired hypertrichosis lanuginosa</td>
<td>Generalized lanugo; fine hair</td>
<td>Lung, colon, and breast carcinoma</td>
<td>None</td>
</tr>
<tr>
<td>Bazex syndrome (also called acrokeratosis paraneoplastica)</td>
<td>Thick hyperkeratotic plaques and longitudinal and horizontal nail ridging in 75% patients</td>
<td>Pharynx, larynx, or esophagus carcinoma</td>
<td>Acrally located, typically involving nose and helices</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>Flushing or erythema of head, neck, and upper trunk; diarrhea; intermittent bronchospasm; pellagra-like dermatitis; and sclerodermoid changes seen in patients with advanced disease</td>
<td>Gastric and bronchial carcinoid; neoplastic transformation of argentaffin cells</td>
<td>Patients should undergo a test for increased 5- hydroxyindole-acetic acid and computed tomography. Medical treatment includes somatostatin, methylsergide, cyproheptadine, beta-blockers, and phenothiazine derivatives.</td>
</tr>
<tr>
<td>Erythema gyratum repens</td>
<td>Concentric erythematous lesions</td>
<td>Internal malignancy in approximately 70–80% cases (most commonly bronchogenic carcinoma and less commonly esophageal or breast cancer)*</td>
<td>Morphology similar to wood grains</td>
</tr>
<tr>
<td>Glucogonoma syndrome (necrolytic migratory erythema)</td>
<td>Erythema, vesicles, pustules, and erosions in periorificial, acral, and flexural areas; lesions have circinate pattern because of peripheral spread, angular cheilitis, and glossitis</td>
<td>Alpha 2 glucagon-secreting tumors of islets of Langerhans</td>
<td>Weight loss, and diabetes mellitus associated with skin lesions</td>
</tr>
<tr>
<td>Leser–Trélat sign</td>
<td>Rapid appearance of multiple seborrheic keratosis; associated with acanthosis nigricans and pruritus</td>
<td>Adenocarcinoma in the stomach or colon</td>
<td>None</td>
</tr>
<tr>
<td>Paraneoplastic pemphigus</td>
<td>Erosive mucus membrane disease; erythema multiforme akin to bullous pemphigoid lesions</td>
<td>Non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Castleman disease</td>
<td>None</td>
</tr>
<tr>
<td>Tripe palms (acanthosis palmaris)</td>
<td>Ridged velvety lesions on palms</td>
<td>Stomach and lung cancer</td>
<td>May or may not be associated with acanthosis nigricans</td>
</tr>
<tr>
<td><strong>Strongly Associated With Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>Rapid onset of hyperpigmented velvety plaques in flexural areas</td>
<td>Adenocarcinoma of the stomach; gastrointestinal or genitourinary cancer; lung, breast, and ovarian cancer; lymphoma; and mycosis fungoides</td>
<td>Glositis, association with insulin resistance; may be seen in patients with tripe palms and florid oral papillomatosis</td>
</tr>
<tr>
<td>Antiepiligrin cicatricial pemphigoid</td>
<td>Tense skin blisters or erosions, oral ulcers, and conjunctival erosions or scarring</td>
<td>Advanced adenocarcinoma</td>
<td>None</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Heliotrope, Gottron papules, photo-distributed poikiloderma, dilated capillary loops in nailbed, and diffuse scaly scalp alopecia with pruritus</td>
<td>Ovarian, lung, colorectal, and pancreatic cancer and non-Hodgkin lymphoma</td>
<td>None</td>
</tr>
<tr>
<td>Neutrophilic dermatosis</td>
<td>Sweets syndrome— mostly atypical bullous presentation and pyoderma gangrenosum</td>
<td>Acute myelogenous leukemia or plasma cell dyscrasia (immuno-globulin A)—10–20% association; rarely solid tumors</td>
<td>None</td>
</tr>
<tr>
<td><strong>Potentially Associated With Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired angioedema</td>
<td>Angioedema</td>
<td>Lymphoproliferative disorders and B cell malignancies (most often non-Hodgkin lymphomas and indolent lymphomas)*</td>
<td>C1 esterase inhibitor dysfunction; no urticaria</td>
</tr>
<tr>
<td>Acquired ichthyosis</td>
<td>Scaly ichthyosis plaques on legs</td>
<td>Hairy cell leukemia and chronic lymphocytic leukemia</td>
<td>None</td>
</tr>
</tbody>
</table>
### Table 8. Diseases Commonly Associated With Cancer and Their Dermatologic Manifestations (continued)

<table>
<thead>
<tr>
<th>Type of Dermatosis</th>
<th>Clinical Description</th>
<th>Associated Type of Cancer</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small vessel vasculitis</td>
<td>Palpable purpura</td>
<td>Possible association with lymphoproliferative disorders</td>
<td>None</td>
</tr>
<tr>
<td>Primary systemic amyloidosis</td>
<td>Waxy, pruritic papules; peri-orbital purpura; and macroglossia</td>
<td>Plasma cell dyscrasia and multiple myeloma</td>
<td>None</td>
</tr>
<tr>
<td>Necrobiotic xanthogranuloma</td>
<td>Asymptomatic yellowish indurated plaque in a periorbital area</td>
<td>Possible association with monoclonal gammopathy of undefined significance (59%), and multiple myeloma (17%); other hematologic conditions reportedly associated with necrobiotic xanthogranuloma: B cell lymphoma chronic lymphocytic leukemia, Waldenström macroglobulinemia, non-Hodgkin lymphoma, and lymphoplasmacytic lymphoma.</td>
<td>None</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>Atrophic patch or plaque with fine scale or nodular lesions akin to cigarette paper</td>
<td>Paraproteinemia</td>
<td>None</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Retiform purpura, arthritis, acrocyanosis, arterial thrombosis, and Raynaud syndrome</td>
<td>Waldenström macroglobulinemia, chronic lymphocytic leukemia, and hepatitis C</td>
<td>None</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Pruritic erosions, and blisters in extensor surface, scalp, or buttocks</td>
<td>Enteropathy associated with T cell lymphoma</td>
<td>None</td>
</tr>
<tr>
<td>Exfoliative erythroderma</td>
<td>Diffuse scaly erythematous skin</td>
<td>Cutaneous T cell lymphoma and lymphoma or leukemia</td>
<td>None</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Increased photosensitivity; erosions, vesicles, or bullae in the dorsal side of the hands or other sun-exposed sites</td>
<td>Primary hepatocellular cancer</td>
<td>None</td>
</tr>
</tbody>
</table>

Certain diseases of the GI tract are frequently associated with skin manifestations. For example, both patients with ulcerative colitis and Crohn disease may develop erythema nodosum, vasculitis, bowel-associated dermatosis–arthritis syndrome-like lesions, pyoderma gangrenosum, Sweets syndrome, panniculitis, aphthosis, angular cheilitis, pyostomatitis vegetans, and perianal and abdominal fistulae. Many liver diseases and renal and endocrine disorders, including diabetes mellitus, also are noted to have cutaneous manifestations and they are listed in Table 9, Table 10, Table 11, and Table 12, respectively.

### Table 9. Cutaneous Manifestations Associated With Liver Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dermatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>Spider angioma, telangiectasia, palmar erythema, caput medusa, white nail bed and transverse white bands, jaundice, pruritus, sparse axillary and pubic hair, gynecomastia, and parotid enlargement</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Jaundice, diffuse hyperpigmentation, xanthomas, and pruritus</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Generalized hyperpigmentation</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Golden brown or greenish circle of pigment in corneal periphery (Kayser–Fleischer ring), blue lunula, and pretilial hyperpigmentation</td>
</tr>
<tr>
<td>Hepatitis B and hepatitis C</td>
<td>Cutaneous small vessel vasculitis, cryoglobulinemic vasculitis urticarial vasculitis, polyarteritis nodosa, necrotizing livedo reticularis, urticaria, porphyria cutanea tarda lichen planus (a particularly erosive oral disease), necrotic acral erythema, erythema multiforme, and erythema nodosum</td>
</tr>
</tbody>
</table>


### Table 10. Cutaneous Manifestations Associated With Kidney Diseases

<table>
<thead>
<tr>
<th>Dermatosis</th>
<th>Clinical Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calciphylaxis</td>
<td>Condition involving vascular calcification and cutaneous necrosis mostly in the lower extremity and characterized by painful necrotic skin lesions</td>
<td>Seen in patients with renal failure, occasionally can be seen in patients without any kidney problems, particularly in patients who use warfarin</td>
</tr>
<tr>
<td>Perforating disorders</td>
<td>Keratotic follicular papules in the extensor surface caused by transepidermal elimination of altered keratin or dermal connective tissue material</td>
<td>Kyrie disease, elastosis perforans serpiginosa, reactive perforating collagenosis, and perforating dermatosis</td>
</tr>
<tr>
<td>Diffuse cutaneous xerosis</td>
<td>Generalized dryness of skin</td>
<td>None</td>
</tr>
<tr>
<td>Nephrogenic systemic sclerosis</td>
<td>Woody indurated plaques on the extremities (or, to a lesser degree, on a trunk), limiting joint mobility</td>
<td>Occurs in patients with renal failure who have received gadolinium containing contrast media</td>
</tr>
</tbody>
</table>

### Table 11. Cutaneous Manifestations Associated With Endocrine Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dermatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing disease</td>
<td>Rounded facies; dorsal cervical vertebral fat deposition (“buffalo hump”); pelvic girdle fat deposition; reduced fat in the arms and legs; global skin atrophy; multiple striae on abdomen, flanks, arms and thighs; skin fragility; prolonged wound healing; purpura with minor trauma; steroid acne; and hirsutism</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Dry, rough, coarse, cold, and pale skin; edematous skin in myxedema; yellow skin color, easy bruising from capillary fragility; acquired ichthyosis; increased incidence of vitiligo and alopecia areata; dull, coarse, brittle, slowly growing hair; madarosis, and onycholysis</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Fine, velvety, warm, moist skin; localized or generalized hyperpigmentation; pruritus; pretibial myxedema; thyroid acropathy; urticaria; dermatographism; increased incidence of vitiligo and alopecia areata; onycholysis; and clubbing koilonychias</td>
</tr>
<tr>
<td>Addison disease</td>
<td>Hyperpigmentation prominent at sites of trauma and in axillae, perineum, nipples, and palmar creases and a loss of ambisexual hair in postpubertal women</td>
</tr>
</tbody>
</table>


### Table 12. Cutaneous Manifestations Associated With Diabetes Mellitus

<table>
<thead>
<tr>
<th>Dermatosis</th>
<th>Clinical Description</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthosis nigricans</td>
<td>Velvety hyperpigmentation of flexural surfaces</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Acral dry gangrene</td>
<td>Fingertip or toe necrosis</td>
<td>Large vessel vascular disease</td>
</tr>
<tr>
<td>Acral erythema</td>
<td>Erythema of hands or feet</td>
<td>Compensatory hyperemia in patients with small-vessel disease</td>
</tr>
<tr>
<td>Carotenemia</td>
<td>Yellowish skin discoloration</td>
<td>Increased serum carotene</td>
</tr>
<tr>
<td>Bullous diabeticorum</td>
<td>Noninflammatory bulla</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Diabetic cheiroarthropathy</td>
<td>Flexural contractures</td>
<td>Increased collagen glycosylation in the skin</td>
</tr>
<tr>
<td>Diabetic dermopathy</td>
<td>Brown atrophic macules or patches on lower extremities</td>
<td>Diabetic microangiopathy may contribute to many of the diabetic skin conditions, including diabetic dermopathy, even if it is not primarily causal.</td>
</tr>
<tr>
<td>Disseminated granuloma annulare</td>
<td>Annular lesions</td>
<td>Controversial association</td>
</tr>
<tr>
<td>Eruptive xanthoma</td>
<td>Yellow papules</td>
<td>Hypertriglyceridemia associated with poor glycemic control</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Skin bronzing or pigmentation</td>
<td>Iron overload associated with cirrhosis, cardiac dysfunction, and diabetes mellitus; mutation mostly in C282Y</td>
</tr>
<tr>
<td>Neuropathic ulcers</td>
<td>Nonpainful pressure ulcers mostly on the foot</td>
<td>Sensory neuropathy</td>
</tr>
<tr>
<td>Acquired perforating disorders</td>
<td>Keratotic papules on the extremities</td>
<td>Pathogenesis unknown; the condition may be seen in patients with diabetes mellitus and end-stage renal disease</td>
</tr>
<tr>
<td>Rubeosis</td>
<td>Chronic flushed appearance of face, neck, and upper extremities; improved with good glycemic control</td>
<td>Thought to be caused by neovascularization in patients with diabetes mellitus</td>
</tr>
<tr>
<td>Scleredema adultorum (of Buschke)</td>
<td>Erythematous or woody induration of upper back and nape of neck</td>
<td>Sclerotic skin disease typically associated with diabetes mellitus (called scleredema diabeticorum); affects mostly middle-aged obese individuals with diabetes mellitus; the pathogenesis mostly is unknown (in patients with diabetes mellitus, irreversible glycosylation of collagen and alterations in collagenase activity are thought to cause excessive accumulation of collagen and mucin leading to this condition)</td>
</tr>
</tbody>
</table>

Prevention and Health Care Maintenance

Ultraviolet Radiation and Damage Prevention

Skin cancer is the most common cancer in the United States (79). Most cases of skin cancer are caused by excessive exposure to UV rays, mostly from sun, but also from the use of tanning beds and lamps. Protective measures, including limiting the exposure, wearing protective clothing, and using sunscreen on exposed areas should be followed. Details are listed in Box 5.

**Box 5. Ultraviolet Protection**

- Limit exposure to ultraviolet (UV) rays
- Stay in shade when possible
- Wear protective clothing
  - Tightly woven clothing that covers all exposed skin acts almost as a total shield from UV radiation.
  - Sun-protective clothing is designated with an ultraviolet protection factor [UPF] rating.
- Wear hats (select hats with a 3–4-inch brim)
- Wear sunscreen with a sun protection factor (SPF) of 30 or higher
- Wear wrap-around sunglasses; they block 99% of UV A and UV B rays
- Use contact lenses that offer protection from UV rays
- Avoid excessive outdoor exposure to direct sunlight, particularly between 10 AM and 4 PM, when UV B radiation is the strongest; if your shadow is shorter than you are, the sun’s rays are strong
- Use caution on the beach, water, and snow because these surfaces reflect sunlight and increase UV exposure

The choice of sunscreen product ultimately is a matter of personal choice. Ideally, it should contain a broad-spectrum water-resistant sunscreen with UV A and UV B protection, with a sun protection factor of 30 or higher that is gentle to wear every day. Sunscreen should be used consistently for best protection.

Some individuals note that certain types of sunscreens are too oily; may cause acne flares, allergic reactions, or dry skin; and may contain harmful substances. Broad-spectrum sunscreens are classified as chemical or physical. Physical sunscreens contain zinc oxide, titanium dioxide, and mexoryl and are typically recommended when patients are active outdoors. Patients with sensitive skin should look for light oil-free lotions that are noncomedogenic. Patients who have an active outdoor lifestyle should use water-resistant or waterproof broad-spectrum sunscreen. Patients with rosacea should avoid sunscreens that contain octyl methoxycinnamate, octyl salicylate, and paraaminobenzoic
acid. Products that contain zinc oxide or titanium dioxide are recommended for those patients. General guidelines for correct sunscreen application are listed in Box 6.

**Box 6. Guidelines for Sunscreen Application**

- Choose appropriate sunscreen:
  - Sunscreens with a sun protection factor of 30 or higher are recommended.
  - Water-resistant sunscreens lose their efficacy after 40 minutes in the water.
  - Very water-resistant sunscreens lose their efficacy after 80 minutes in the water.
- Apply 1 oz of sunscreen (sun protection factor 30 or higher) 30 minutes before sun exposure when using chemical sunscreen (physical sunscreens are preferred because of their immediate ultraviolet blocking properties*)
- Cover all exposed areas, including tops of ears, scalp with thinning or no hair, nose, and bony surfaces
- Apply lip balm containing sunscreen to lips
- Reapply sunscreen every 2 hours when exposed to sun, immediately after toweling off, and every 40–80 minutes when sweating or being in water (when using a water resistant sunscreen)
- Replace sunscreens annually; sunscreens have an expiration date

*There are two general types of sunscreens: 1) physical, containing zinc oxide or titanium dioxide, and 2) chemical, containing one or more active ingredients, including oxybenzone or avobenzone. Physical sunscreens protect skin from the sun by deflecting or blocking the sun’s rays. They are quite photostable and don’t degrade easily in sunlight. Physical sunscreens typically protect the skin immediately after application. Physical sunscreens tend to be better tolerated by most skin types. Physical sunscreens can leave white streaks after application. Chemical sunscreens protect the skin by absorbing the sun’s rays. Chemical filters used in chemical sunscreens can be irritating and occasionally can cause allergic reaction. Chemical sunscreens need to be applied 30 minutes before exposure to sun to give the skin adequate time for absorption. Many sunscreens contain both physical and chemical ultraviolet (UV) filter. Most sunscreens are labeled as broad-spectrum sunscreen because they filter both UV A and UV B ray spectrum.

**Routine Skin Evaluation**

Patients with multiple nevi should monitor them and perform self-evaluations periodically. Any changes in the nevi (ie, shape, color, diameter, and symmetry or associated symptoms, such as itching and bleeding) must be brought to the attention of the physician and must be thoroughly evaluated. Patients with history of dysplastic nevi must be evaluated annually by a dermatologist or their primary care provider annually. Patients should be advised to adhere to follow-up schedules for nonmelanomatous types of skin cancer and melanoma.
Dry Skin Management

Dry skin can be caused by several causes, including low-humidity indoor heat, cold winter air, air conditioning, exposure to external elements, such as sun or wind, harsh soaps, or detergents, natural aging process, or underlying atopic dermatitis (Box 7). Although water moisturizes the skin during a bath, the water, heat, and soap remove protective oils from the skin. Individuals with extensive xerosis can decrease the frequency of their baths and take short showers with lukewarm or cold water and use fragrance-free or hypoallergenic soap sparingly (and only in areas covered with body hair). The patient should be advised to avoid rubbing with a towel and instead use a patting motion and use a moisturizer immediately after drying herself. Lotions are the mildest treatment for dry skin. Creams are greasy, but they are usually more effective than lotions for treating dry skin. Ointments are greasier than creams and generally are more effective than creams.

Box 7. Dry and Sensitive Skin Management Summary

- Limit bath time, do not use hot water for showers, and avoid heaters
- Avoid needless use of soaps; use fragrance-free, dye-free soaps; and limit use of soap to soiled or hair bearing areas (groin and axillae)
- Avoid scrubbing skin
- Thick emollients (creams and ointments) are better at hydrating the skin than thin lotions
- Always moisturize immediately after bathing or showering

Eczema Care

Patients with atopic dermatitis should follow the dry skin management rules described in the previous section. They must use fragrance-free or hypoallergenic detergents, dishwasher liquid, and hypoallergenic soaps. Patients with eczema with recurrent staphylococcal infection can use bleach baths to decrease the frequency of infection (Box 8).

Hand Dermatitis

Hand dermatitis is common and occurs as a result of contact with substance that one is allergic to, such as soaps, detergents, raw food, solvents, paint, oil, grease, acid, glue, and other irritating substances at work or at home. Preventive measures to improve or prevent worsening of hand dermatitis include the following:

- Use of waterproof heavy-duty appropriately sized vinyl gloves to protect hands from irritants; white cotton gloves can be worn under the vinyl gloves
• Dishes or clothes should be washed by hand only while wearing heavy-duty waterproof gloves, and direct contact with household products that contain solvents should be avoided.

• Limited use of soap and number of hand washes; hands should be lubricated after washing.

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**Box 8. Bleach Bath Preparation**

Follow these steps to prepare a bleach bath:

- Add lukewarm water to fill the tub as you would for a normal bath.
- Add one quarter to one half cup of common liquid bleach (with a concentration of 6% sodium hypochlorite).
- Stir the water, making sure to mix the bleach in well; this will create a solution of diluted bleach (approximately 0.005%), which is just a little stronger than swimming pool water.
- Soak in the bleach bath for approximately 15 minutes and rinse off the bleach well.
- Pat skin dry and apply prescribed medication or moisturizer.
- Use the bleach bath two to three times per week.

Bleach must not be used undiluted on skin and must not be used if there are open wounds or cuts because it can cause irritation. Bleach baths can increase dryness or xerosis of the skin. Bleach can change the color of the fabric upon contact.

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**Reproductive Considerations**

**Contraception**

Patients often wonder whether their contraception plays a role in common skin conditions; most frequently acne. A brief discussion of the effects of various contraceptive methods on acne is provided in this section. Common forms of contraception include combination oral contraceptives, combination patch and vaginal ring, IUDs, and progesterone-only injections, pills, or implants. Combined oral contraceptives often are used to treat acne because they have been found to reduce free testosterone levels (124). Three combined oral contraceptive regimens have been approved by the FDA for the treatment of moderate acne and are listed in the section “Acne Vulgaris.” Progesterone-only contraceptives may worsen acne (125). The patch and vaginal ring contain estrogen and progestin, similar to combined oral contraceptives. However, they have a less profound effect on acne and hirsutism than their oral counterparts. Depot medroxyprogesterone acetate may worsen acne and can be associated with weight gain (126). Intrauterine devices are available in hormonal or nonhormonal (copper) varieties. The hormonal IUD, which contains...
Contraception additionally plays an important role in dermatology because effective contraception is a requirement for numerous systemic dermatologic medications that are known teratogens. Examples include isotretinoin, methotrexate, mycophenolate mofetil, ketoconazole, and spironolactone. The section on “Acne Vulgaris” provides a brief discussion of the role of contraception in the treatment of acne, particularly regarding regulations for the use of isotretinoin.

**Pregnancy Changes and Dermatoses**

Pregnancy induces several skin changes. These can be divided into three categories, including the following:

1. Hormone-related benign skin changes
2. Preexisting skin conditions that change during pregnancy
3. Pregnancy-specific skin changes

Some of the common conditions will be discussed in the following sections.

**Striae Gravidarum**

Striae distensae, also called striae gravidarum or “stretch marks” when they occur in pregnancy, are a common skin problem. Clinically, they develop as erythematous to violaceous linear atrophic lines or bands on the abdomen after the 24th week of gestation and fade after pregnancy to become skin-colored or hypopigmented atrophic lines. Striae gravidarum also can occur on the breasts, buttocks, hips, and thighs. They are more common in younger women, women with large infants, and women with a high body mass index. Nonwhite populations and women with a history of breast or thigh striae or a family history of striae gravidarum are at an increased risk of developing striae. The cause of striae is multifactorial and includes physical factors (mechanical distention of the skin during pregnancy) and hormonal factors (eg, effects of adrenocortical steroids, estrogen, and relaxin on the elastic fibers of the skin). Striae may form as a result of structural connective tissue changes that include realignment and reduced elastin and fibrillin in the dermis. It is estimated that up to 90% of pregnant women develop striae gravidarum by the third trimester (128, 129). There are two clinical presentations of striae distensae, namely, striae rubra and striae alba. Striae rubra precedes striae alba and is characterized by an erythematous to violaceous color and evolves into a hypopigmented, scar-like, atrophic plaques known as striae alba.

Numerous creams, emollients, and oils (eg, vitamin E cream, cocoa butter, aloe vera lotion, and olive oil) have been used to prevent striae; however, there is no evidence...
that these treatments are effective. Most striae fade to pale- or flesh-colored lines and shrink postpartum, although they usually do not disappear completely. For patients with striae rubra who desire treatment, topical retinoid therapy or pulsed-dye laser therapy is an option. Striae alba typically do not respond to topical retinoids. Fractional laser therapy may improve striae alba lesions. The lasers may induce modest textural improvement.

**HYPERPIGMENTATION**

Nearly all women experience some degree of hyperpigmentation during pregnancy. These changes usually are more pronounced in women with a darker complexion. The areolae, axillae, and genitals are most commonly affected, although scars and nevi also may darken. The linea nigra is the line that often forms when the abdominal linea alba darkens during pregnancy.

**MELASMA**

Melasma (chloasma or mask of pregnancy) is a common acquired condition characterized by symmetric light to dark brown patches occurring primarily on the face. There are three classic patterns of melasma: 1) centrofacial, involving the forehead, cheeks, nose, upper lip (sparing the philtrum), and chin; 2) malar, affecting the cheeks and nose; and 3) mandibular, along the jawline. The condition occurs in 45–75% of pregnant women (130–134) and also may occur in women taking oral contraceptives. It can be exacerbated by sun exposure. It is most prevalent in young women of Hispanic, Asian, African, or Middle Eastern descent (135). After pregnancy, melasma may resolve or may fade in light-pigmented individuals but often persists in patients with dark skin.

The most common topical regimen to treat melasma is a combination of hydroquinone (2–4%), tretinoin (0.05–0.1%), and a corticosteroid (class V–VII). Prolonged use of hydroquinone can result in exogenous ochronosis and postinflammatory hyperpigmentation. Topical tretinoin as a monotherapy can be helpful, but the required treatment period often is 24 weeks or longer. Other topical agents noted to lighten melasma include glycolic acid, kojic acid, and azelaic acid. Cosmetic camouflage is helpful for patients with recalcitrant melasma. Patients must be advised to follow strict UV protective measures, including the use of a broad-spectrum sunscreen, sun avoidance, and the use of protective clothing, including broad-brimmed hats.

**HAIR AND NAIL CHANGES**

An increase or decrease in growth and production of hair is common during pregnancy. Women may develop hirsutism on the face, limbs, and back as a consequence of hormonal effects of pregnancy, most of which resolve in the postpartum period. Pregnant women also may notice mild thickening of scalp hair. This is caused by a prolonged active (anagen) phase of hair growth. Postpartum, scalp hair enters a prolonged resting (telogen) phase of hair growth, causing increased shedding (telogen effluvium), which
may last for several months or more than 1 year after pregnancy. A few women with a tendency toward androgenetic alopecia may notice frontoparietal hair loss, which sometimes may not resolve after pregnancy.

Nails usually grow faster during pregnancy. Pregnant women may experience increased brittleness, transverse grooves, distal onycholysis, and subungual hyperkeratosis.

**GLANDULAR CHANGES**

The effect of pregnancy on glandular function is contradictory and not well understood. Eccrine function seems to increase (except on the palms). However, the effect on apocrine function and sebaceous gland activity is incompletely understood.

**VASCULAR CHANGES**

Normal changes in estrogen production during pregnancy can cause dilation, instability, vascular proliferation, and congestion of blood vessels. Most of these vascular changes regress after delivery. Spider telangiectasia (spider nevi or spider angiomas) and palmar erythema are commonly seen in pregnant women. Many pregnant women also can develop varicosities and hemorrhoids.

Vascular changes coupled with increased blood volume can cause increased leakage, which leads to nonpitting edema of the face, eyelids, and extremities. Increased blood flow and instability of pelvic vessels may cause vaginal erythema (Chadwick sign) and a bluish discoloration of the cervix (Goodell sign). Vasomotor instability can cause facial flushing, dermatographism, hot and cold sensations, and marbling or mottled skin appearance. Pregnant women also develop gingival hyperemia and edema, which may be associated with gingivitis and bleeding, especially in the last trimester of pregnancy. Pyogenic granulomas can appear late in the first trimester or in the second trimester as deep red or purple nodules on the gingivae or, less commonly, on other skin surfaces. **Table 13** summarizes the physiologic changes during pregnancy.

<table>
<thead>
<tr>
<th>Changes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmentary</td>
<td>Melasma, linea nigra, and increased areolar pigmentation</td>
</tr>
<tr>
<td>Hair</td>
<td>Postpartum telogen effluvium resulting in hair loss, hirsutism, and frontal alopecia</td>
</tr>
<tr>
<td>Nail</td>
<td>Brittle nails, subungual hyperkeratosis, transverse grooving, and distal onycholysis</td>
</tr>
<tr>
<td>Glandular</td>
<td>Increased eccrine function except in palms; increased sebaceous function</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>Striae distensae</td>
</tr>
<tr>
<td>Vascular</td>
<td>Spider angiomas, palmar erythema, varicosities, gingival hyperplasia, pyogenic granuloma, nonpitting edema, vasmotor instability, hemorrhoids, and purpura</td>
</tr>
</tbody>
</table>
Preexisting skin conditions (eg, atopic dermatitis, psoriasis, candidal and other fungal infections, and cutaneous tumors, including malignant melanoma) may change during pregnancy. Atopic dermatitis and psoriasis may worsen or improve during pregnancy. Psoriasis is more likely to improve than worsen. Soft-tissue fibromas (skin tags) can occur on the face, neck, upper chest, and beneath the breasts during late pregnancy. These fibromas generally disappear in the postpartum period. The effects of pregnancy on the development and prognosis of malignant melanoma have been extensively researched; however, currently, pregnancy is not believed to affect survival.

**Pregnancy-Specific Dermatologic Disorders**

Pregnancy-specific dermatoses include polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy, and pemphigoid gestationis. These conditions are summarized in Table 14 and details are provided in the following sections.

<table>
<thead>
<tr>
<th>Dermatosis</th>
<th>Rash Presentation</th>
<th>Maternal and Fetal Risks</th>
<th>Newborn Skin Involvement</th>
<th>Risk of Recurrence</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphic eruption</td>
<td>Intensely pruritic urticarial plaques and papules; rash first appears on the abdomen, often along striae and occasionally involves extremities; face usually is not affected</td>
<td>None</td>
<td>None</td>
<td>Usually does not recur</td>
<td>Oral antihistamine and topical corticosteroid for pruritus and mild disease; severe cases may require systemic corticosteroids</td>
</tr>
<tr>
<td>Pemphigoid gestationis</td>
<td>Pruritic papules, plaques, and vesicles evolving into generalized vesicles or bullae; initial periumbilical lesions may spread, although the face, scalp, and mucous membranes usually are not affected</td>
<td>Increased risk of prematurity and small-for-gestational age status; risk correlates with severity of disease</td>
<td>Mild, transient lesions of pemphigoid gestationis in approximately 10% of neonates</td>
<td>Often recurs (a subsequent pregnancy is unaffected in 5–8% of women); flares can be associated with the use of oral contraceptives in 25–50% women during a menstrual period</td>
<td>Oral antihistamine and topical corticosteroid for pruritus and mild disease; severe cases may require systemic corticosteroids</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>Excoriations from scratching; distribution is nonspecific</td>
<td>An increased risk of premature labor in 20–60% patients, intrapartum fetal distress in 20–30% of patients, and risk of stillbirth in 1–2% of patients</td>
<td>None</td>
<td>40–70% recurrence risk with subsequent pregnancies; can be triggered by oral contraceptives</td>
<td>Oral antihistamines for mild pruritus and ursodeoxycholic acid (ursodiol) for severe cases</td>
</tr>
</tbody>
</table>


**Polymorphic Eruption of Pregnancy.** Polymorphic eruption of pregnancy is a common skin condition seen in pregnancy with an incidence of approximately 1 in 160 deliveries (136). It is seen predominantly in primiparous women and typically does not to recur in subsequent pregnancies.
The cause of polymorphic eruption of pregnancy is unknown. Typically, it presents as urticarial papules and plaques that usually appear within striae distensae during the latter portion of the third trimester or in the postpartum period with periumbilical sparing (Fig. 36). Typically, it resolves over 4 weeks and is not associated with any maternal or fetal morbidities. Typically, recurrences are unusual except in women with subsequent multiple gestations. Differential diagnosis includes pemphigoid gestationis, urticaria, contact dermatitis, drug eruption, and viral exanthema. Most patients benefit from the use of topical corticosteroids and oral antihistamines. Severe cases may require a short course of systemic corticosteroids.

**Intrahepatic Cholestasis of Pregnancy.** Intrahepatic cholestasis of pregnancy, historically known as pruritus gravidarum, is a genetically linked, hormone-dependent reversible cholestasis that typically presents as an intensely pruritic rash during late pregnancy and is associated with significant fetal risk.

Incidence of intrahepatic cholestasis of pregnancy varies among various ethnic groups (more prevalent in South America and among Araucanian Indian women) (137). Intrahepatic cholestasis of pregnancy also is seen in pregnant women with multiple gestations, possibly because of high hormonal levels in these patients.

Intrahepatic cholestasis of pregnancy results from diminished excretion of bile acids, which leads to increased serum bile acid levels. Some patients have ABCB4 gene mutation that encodes bile transporter proteins. Contributing factors for intrahepatic cholestasis of pregnancy include high levels of estrogen and progesterone (causing cholestatic effect) and hepatitis C viral infection.

Intrahepatic cholestasis of pregnancy is characterized by intense, generalized pruritus, most notably starting with palms and soles during the last trimester of pregnancy. Primary lesions are not identified and typically one can see excoriations (or in advanced cases,
Prurigo nodules (caused by scratching in the areas of intense pruritus. Most common areas of involvement include extensor surfaces of the extremities, buttocks, and abdomen. Only 10% of patients have associated jaundice, which typically results from severe and prolonged intrahepatic cholestasis of pregnancy (135). Additionally, these patients may have steatorrhea and vitamin K deficiency that may result in intrapartum and postpartum hemorrhage.

Pruritus typically persists until delivery and then it resolves spontaneously within days. Intrahepatic cholestasis of pregnancy is associated with significant fetal risk, including increase in premature birth (20–60%), intrapartum fetal distress (20–30%), and fetal loss (1–2%) (138). Fetal risk correlates with the increase in serum bile acid levels, especially when levels exceed 40 micromol per liter. Thus, prompt diagnosis and treatment are essential, as is close obstetric surveillance. The diagnosis is confirmed by an increase in total serum bile acid levels (greater than 11 micromol per liter in a pregnant woman).

Mild pruritus in patients can be treated with oral antihistamines. Patients with high bile acid levels typically are treated with ursodeoxycholic acid (ursodiol) to relieve pruritus and improve cholestasis while reducing adverse fetal outcomes. Patients should receive increased antenatal surveillance at the time of diagnosis. Delivery by 36–38 weeks of gestation is thought to likely reduce the perinatal mortality risk (139–143).

Pemphigoid gestationis. Pemphigoid gestationis (previously called herpes gestationis) is a rare autoimmune vesiculobullous eruption occurring during late pregnancy or immediately postpartum. It is associated with HLA-DR3 and HLA-DR4 and is rarely associated with hydatiform mole and choriocarcinoma. Patients with a history of the condition have an increased risk of other autoimmune diseases (eg, Graves disease).

Patients typically have abrupt onset of skin lesions on the trunk, particularly involving the abdomen and often adjacent to the umbilicus, that can progress rapidly to a generalized eruption with clustered vesicles and tense bullae on erythematous base. Patients can have spontaneous improvement during late gestation; however, these patients typically have a flare at the time of delivery. Most lesions start to resolve within weeks to months after delivery; however, some patients can have a protracted course. Patients may even have flare with menstruation or with the use of oral contraceptives. Pemphigoid gestationis often recurs with subsequent pregnancies with earlier involvement and a more severe course. Approximately 5–10% of neonates can have mild skin lesions resulting from passive transfer of maternal antibodies (144). These lesions typically resolve in few weeks. There is an increased risk of chronic placental insufficiency in patients with severe pemphigoid gestationis that can result in intrauterine growth restriction and increased risk of prematurity. Patients with mild pemphigoid gestationis may respond to oral antihistamines and topical corticosteroids, whereas patients with more severe symptoms may need oral corticosteroids.
**CASE NO. 6.** A primigravid woman at 33 weeks of gestation presents to her obstetrician–gynecologist with a pruritic eruption of red papules and plaques, which have worsened over the past few days. The rash began in stretch marks and spread to the buttocks and upper thighs. The rash is itchy, and the patient is having trouble sleeping at night. Her face, palms, and soles are uninvolved.

For a pregnant patient with a pruritic eruption in the third trimester, the differential diagnosis includes polymorphic eruption of pregnancy (previously known as pruritic urticarial papules and plaques of pregnancy), pemphigoid gestationis, contact dermatitis, or intrahepatic cholestasis of pregnancy. Polymorphic eruption of pregnancy does not have specific laboratory abnormalities and skin biopsy is not always specific; therefore, the diagnosis often is clinical. Excluding intrahepatic cholestasis of pregnancy by checking serum bile acid levels is important, given that this entity has implications for the health of the fetus. The patient receives the diagnosis of polymorphic eruption of pregnancy. She should be reassured that there are no maternal or fetal risks associated with polymorphic eruption of pregnancy. Cool soaks and emollients can provide some relief, and oral antihistamines can be helpful in controlling itch. Topical corticosteroids may be helpful but often are not particularly effective in addressing itch. The condition usually resolves around the time of delivery. The patient chooses to use emollients that help alleviate the condition a little. She gives birth at 39 weeks of gestation and has a complete resolution of both the rash and itch after delivery.

**Postmenopausal and Geriatric Care**

Dermatologic care of the female patient in the postmenopausal time period should focus on the management of common skin concerns and preventive screening for common malignancies. Numerous cutaneous conditions increase in prevalence with age. Some of the most common also can be the most irritating to patients, including difficulty with dry and fragile skin. Also, itch can become a bothersome symptom, and finding an underlying cause may be difficult or impossible. There are several preventive measures that can be helpful in addressing dry skin (Box 7). Skin fragility is a difficult problem to address because often it is a result of long-term sun exposure with resultant breakdown of collagen and elastin in skin. This leads to decreased support of the superficial layers of the skin and the blood vessels, which reside there, making skin tearing and skin bruising more likely. Patients should be counseled regarding sun protection as the most effective way to prevent these changes from occurring. Once the UV radiation damage has occurred, it is permanent and cannot be reversed. Patients should be counseled to maintain regular moisturization to maintain pliability of the skin and to use sun protection to prevent further damage from occurring. Dark spots on the skin also are commonly related to sun exposure and may be benign, but careful monitoring to rule out changes suspicious for melanoma or melanoma in-situ of sun-damaged skin (lentigo maligna) is warranted.

All health care providers should be aware of the increased rates of skin malignancies in this age group. Nonmelanomatous types of skin cancer are the most common malignancy, with recent estimates of 3.5 million cases each year in the United States (145).
Although nonmelanomatous skin cancer has a low mortality, morbidity and cost can be significant. The risk of melanoma also increases with age and carries a high mortality if not caught early. All health care providers should ask patients about changing or symptomatic lesions.

Other cutaneous conditions that are more commonly seen in older women than in other populations include vulvar disorders. This topic is covered in great detail in another Clinical Updates monograph (see the section “Resources”), but the mention of lichen sclerosus is warranted because this condition can cause permanent structural changes. Evidence of flat, white lesions in the vulvar area surrounded by red or violet discoloration should raise concern for lichen sclerosus. Eventually, the lesions will become atrophic, with a shiny appearance or wrinkling of the skin. Ulcerations can occur, and obliteration of normal anatomic structures can be an end result of the inflammation and scarring. Early recognition of this disorder can prevent morbidity associated with lichen sclerosus and may play a role in the prevention of squamous cell carcinoma within the lesions (146).

Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) comprises numerous topics not traditionally incorporated into allopathic medicine. Approximately 38% of adults in the United States used CAM in 2007 (147). Worldwide, this number is even higher. For this reason, an understanding of common CAM practices is helpful for the health care provider. In dermatology, CAM practices are more common than almost any other subspecialty, and most dermatologic patients will try CAM methods during their lives. However, CAM is diverse, and comprises botanicals and other dietary supplements, traditional Chinese medicine, homeopathy, and aromatherapy. These will be discussed here briefly; a detailed discussion of CAM is provided in another Clinical Updates monograph (see the section “Resources”).

Botanicals have been used for centuries to affect health, and modern medicine has roots in this practice. Today, botanical and dietary supplements aim to improve the body’s ability to heal. Some common botanical therapies are included in Table 15.

Traditional Chinese medicine has been practiced in China for the past 4,000 years. It incorporates numerous other entities, including herbal medicine, acupuncture, massage, and other lifestyle practices. Acupuncture has been used for dermatologic conditions but has more evidence regarding its use for pain and itching. It is thought to increase the release of endorphins, modulates release of other neuroactive substances, and may have antiinflammatory effects.
Homeopathy is a practice that started in the 19th century and is based on the “principle of similars” and the “principle of infinitesimals.” The “principle of similars” states that induced symptoms will cure those same symptoms. The “principle of infinitesimals” states that the higher the dilution, the greater the effect. Skin problems are a common reason patients use homeopathy, but evidence regarding its efficacy is lacking. The FDA does not regulate or endorse homeopathy.

### Direct-to-Consumer Marketing

Direct-to-consumer marketing occurs when pharmaceuticals are marketed directly to patients rather than physicians. This can include print, television, and internet advertisements. Direct-to-consumer marketing first began in the early 1980s and has expanded exponentially since that time. In 2005, direct-to-consumer marketing represented 18.2% of industry spending (148). The United States and New Zealand are some of the only industrialized countries that allow companies to include product claims in their advertising. The U.S. Food and Drug Administration’s regulation of advertisements has continued to relax since an initial ban on the practice was lifted in 1985 (149). Advocates of direct-to-consumer marketing argue that it empowers and informs patients regarding their own health. It can encourage patient–physician contact and promotes a dialogue.

### Table 15. Botanical Therapies

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Dermatologic Uses</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe vera</td>
<td>Reduces burning, itching, and scarring; has been shown to be effective in treating psoriasis, seborrheic dermatitis, and irritant dermatitis</td>
<td>Possible association with allergic contact dermatitis</td>
</tr>
<tr>
<td>Honey</td>
<td>Enhances healing, viral infections, antibacterial action</td>
<td>Rare contact dermatitis</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Postherpetic neuralgia, pruritus, diabetic neuropathy, and notalgia paresthetica</td>
<td>Temporary burning</td>
</tr>
<tr>
<td>Gingko</td>
<td>Antioxidant properties, photoaging, and vitiligo</td>
<td>Increases bleeding risk, gastrointestinal upset, vomiting, dizziness, and headache</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Decreases damage caused by ultraviolet B radiation</td>
<td>Slows wound healing and inhibits platelet function</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Photoprotection, photoaging, melasma, and acne</td>
<td>Diarrhea, nausea, and vomiting, mild contact dermatitis if topical vitamin C is used</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Atopic dermatitis and antioxidant properties</td>
<td>Increased risk of cardiovascular disease and hemorrhagic stroke</td>
</tr>
<tr>
<td>Witch hazel</td>
<td>Acne, eczema, bruises, and hemorrhoids</td>
<td>Nausea, vomiting, and hepatotoxic and nephrotoxic effects</td>
</tr>
<tr>
<td>Garlic</td>
<td>Antibacterial, antifungal, and antiviral properties</td>
<td>Topical contact dermatitis and anticoagulant effects</td>
</tr>
</tbody>
</table>

*Note: The table above lists some common botanical therapies used for dermatologic conditions, along with their potential adverse effects. Additional research is needed to determine their efficacy and safety.*
regarding treatment. Additionally, it is thought that patients who view direct-to-consumer marketing advertisements may have better treatment adherence rates. Conversely, direct-to-consumer marketing may overemphasize benefits, causing patients to underestimate risk. Current online direct-to-consumer marketing also raises concerns regarding illegal online pharmacies using direct-to-consumer marketing to enable patients to purchase medications without appropriate oversight (150).

New avenues for direct-to-consumer marketing are on the rise, such as genomic profiling and direct-to-consumer teledermatology websites. Navigating and supporting patients who use these resources will likely become an increasingly important role for the health care provider.

**Referral**

Referral to a dermatologist is necessary in some circumstances. The clinical situations that require a referral are listed as follows, although this list is not exhaustive, and referral is recommended for any recalcitrant cutaneous condition or diagnostic uncertainty:

- The first-line management of a common condition, such as eczema, psoriasis, seborrheic dermatitis, rosacea, or acne, is ineffective.
- Cutaneous malignancy of any form is suspected, and biopsy is recommended for diagnostic confirmation and management.
- A severe adverse cutaneous reaction is suspected.
- A patient has a blistering skin condition that requires specialized biopsy for diagnostic confirmation and immunosuppression.
- Scarring alopecia is suspected, which requires biopsy for confirmation.
- If a provider is considering the use of a systemic corticosteroid or immunosuppressant to manage a cutaneous condition, referral to a dermatologist is recommended if feasible.
Key Points

This monograph has extensively reviewed common cutaneous diagnoses that may be identified by the practicing obstetrician–gynecologist. Following are several key points to recall when providing care to the patient with a cutaneous condition:

- The skin consists of three main layers: 1) the epidermis, 2) dermis, and 3) subcutaneous tissue. It acts as a protective barrier, sensory organ, temperature regulator, and immune surveillance.

- Eczema is a common chronic condition characterized by a dysfunctional barrier.

- Acne vulgaris can occur in adulthood and is treated with anticomedonal, antibacterial, and antiinflammatory regimens.

- Drug reactions can either be uncomplicated or complicated; complicated drug reactions involve mucosal surfaces, internal organs, or both and can be life threatening.

- Hyperpigmentation disorders include postinflammatory hyperpigmentation, melasma, lentigines, café-au-lait macules, and labial melanotic macules.

- Hypopigmentation disorders include vitiligo, postinflammatory hypopigmentation, and rare entities, such as halo nevi, nevus depigmentosus, or idiopathic hypomelanosis.

- Hair loss can be caused by numerous entities, the most common of which in women include telogen effluvium, androgenetic alopecia, and alopecia areata.

- The nails can be involved in numerous skin diseases, but onychomycosis is one of the most common diseases that can be diagnosed in the clinic. Management is difficult, cure rates range from 60% to 70% (151), and oral treatment carries risks.

- Spider angiomas and cherry angiomas are common vascular lesions seen in women that tend to persist without treatment. They can be treated with pulsed-dye laser.

- Skin cancer is the most common type of cancer in the United States (79). Basal cell carcinoma and squamous cell carcinoma are the most common, but melanoma, Merkel cell carcinoma, and other rare cutaneous malignancies carry significant morbidity and mortality. If there is a concern for a skin malignancy, referral to dermatology is recommended.

- Many systemic diseases have cutaneous manifestations. Awareness of these cutaneous signs can lead to improved management or earlier identification of an underlying disorder.

- The practicing obstetrician–gynecologist will see dermatoses of pregnancy, including common changes, such as striae gravidarum and melasma, and more unusual conditions, such as pemphigoid gestationis. Certain conditions carry risk to either the woman or the fetus (intrahepatic cholestasis of pregnancy and pemphigoid gestationis).
<table>
<thead>
<tr>
<th><strong>American College of Obstetricians and Gynecologists</strong></th>
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</table>

*The following list is for information purposes only. Referral to these sources and websites does not imply the endorsement of the American College of Obstetricians and Gynecologists. This list is not meant to be comprehensive. The exclusion of a source or website does not reflect the quality of that source or website. Please note that websites are subject to change without notice.*

<table>
<thead>
<tr>
<th><strong>Other Resources</strong></th>
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Test Your Clinical Skills

Complete the answer sheet at www.clinicalupdates.org under “Test Your Clinical Skills” and receive 5 continuing medical education credits. The answers appear on page 84.

Directions: Select the one best answer or completion.

1. Temperature regulation by the skin occurs in which layer?
   A. Dermis
   B. Epidermis
   C. Subcutaneous
   D. All three layers

2. The most commonly involved joints in patients with psoriatic arthritis are
   A. proximal interphalangeal
   B. sacroiliac
   C. terminal interphalangeal
   D. vertebral

3. The most common site of acne eruption in adult women in the week before menstruation is
   A. back
   B. forehead
   C. the lower third of the face
   D. neck

4. The rash of a drug reaction is most prominent on the
   A. face
   B. genitals
   C. hands
   D. trunk

5. Superficial melasma caused by oral contraceptives does not respond to therapy with
   A. azelaic acid cream
   B. glycolic acid peel
   C. hydroquinone cream
   D. laser

6. Which type of vitiligo is least responsive to treatment?
   A. Acrofacial
   B. Mucosal
   C. Segmental
   D. Universal

7. Which of the following drugs is not effective in patients with onychomycosis?
   A. Fluconazole
   B. Itraconazole
   C. Ketoconazole
   D. Terbinafine
8. The most common type of malignant melanoma is
   A. acral–lentiginous
   B. lentigo maligna
   C. nodular
   D. superficial spreading

9. If a patient has eight lesions of actinic keratosis left untreated for 10 years, the chance of developing squamous cell carcinoma is
   A. 0%
   B. 5%
   C. 10%
   D. 20%

10. After a single biopsy showing noninvasive extramammary Paget disease, four quadrant biopsies of the lesion should be obtained if the lesion is located on the
    A. axilla
    B. perianal area
    C. perineum
    D. vulva

11. In patients with rheumatoid arthritis, erythematous indurated papules in a reticular pattern are most often seen in which anatomic location?
    A. Cervical spine
    B. Dorsum of hands
    C. Elbow
    D. Extensor aspect of knees

12. The best type of moisturizer to treat dry skin is
    A. cream
    B. gel
    C. lotion
    D. ointment

13. Recommended topical treatment for patients who desire treatment of striae gravidarum of the rubra type is
    A. aloe vera lotion
    B. cocoa butter
    C. retinoid
    D. vitamin E

14. The most common location for pemphigoid gestationis is
    A. extremities
    B. face
    C. genitals
    D. umbilicus


75. Hay RJ, Baran R. Why should we care if onychomycosis is truly onychomycosis [comment]? Br J Dermatol 2015;172:316–7. (Level III)


120. Gowri BV, Chandravathi PL, Sindhu PS, Naidu KS. Correlation of skin changes with hormonal changes in polycystic ovarian syndrome: a cross-sectional study clinical study. Indian J Dermatol 2015;60:419,515.160505. (Level II-3) 


125. Dawson AL, Dellavalle RP. Acne vulgaris. BMJ 2013;346:f2634. (Level III) 


Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I  Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III  Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Answers

Forthcoming and Current Titles

Each monograph in *Clinical Updates in Women’s Health Care* is an overview of a topic of importance to obstetrician–gynecologists in practice. Upcoming titles include the following:

- **Arthritis and Joint Disorders**

If not previously completed, earn CME credits for back issues of *Clinical Updates in Women’s Health Care*. Listed are recent titles, updates, and all current titles by publication date. Online access to a complete title list is available at [www.clinicalupdates.org](http://www.clinicalupdates.org).

- **Liver Disease: Reproductive Considerations** (Volume XVI, No. 1, January 2017)
- **Structural Heart Disease** (Volume XVI, No. 2, March 2017)
- **Arrhythmias** (Volume XVI, May 2017)
- **Gynecologic and Obstetric Care for Breast Cancer Survivors** (Volume XI, July 2017)
- **Mood and Anxiety Disorders** (Volume XVI, September 2017)
- **Ischemic Heart Disease** (Volume XVI, November 2017)

**Updates**

Also available at [www.clinicalupdates.org](http://www.clinicalupdates.org) are the following content updates:

- **Anorectal Disorders** (May 2015)
- **Care of Aging Women** (April 2015)
- **Complementary and Alternative Medicine** (June 2015)
- **Dermatoses** (April 2015)
- **Obesity** (August 2017)
- **Occupational Diseases and Injuries** (July 2016)
- **Sleep Disorders** (September 2015)
- **Upper Gastrointestinal Tract, Biliary, and Pancreatic Disorders** (May 2017)
List of Titles

2018
Common Dermatologic Conditions (Vol. XVII, No. 1, January 2018)

2017
Liver Disease: Reproductive Considerations (Vol. XVI, No. 1, January 2017)
Structural Heart Disease (Volume XVI, No. 2, March 2017)
Arrhythmias (Volume XVI, May 2017)
Gynecologic and Obstetric Care for Breast Cancer Survivors (Vol. XVI, No. 4, July 2017)
Mood and Anxiety Disorders (Vol. XVI, No. 5, September 2017)
Ischemic Heart Disease (Vol. XVI, No. 6, November 2017)

2016
Hypertension (Vol. XV, No. 1, January 2016)
Genetics: Counseling, Testing, and Diagnosis (Vol. XV, No. 2, March 2016)
Thrombosis, Thrombophilia, and Thromboembolism (Vol. XV, No. 3, May 2016)
Polycystic Ovary Syndrome (Vol. XV, No. 4, July 2016)
Challenging Patient Encounters (Vol. XV, No. 5, September 2016)
Liver Disease: General Pathophysiology, Diagnosis, and Management
(Vol. XV, No. 6, November 2016)
Liver Disease: General Pathophysiology, Diagnosis, and Management Supplement
(Vol. XV, No. 6, November 2016)

2015
Office Emergencies (Vol. XIV, No. 1, January 2015)
Metabolic Bone Disease (Vol. XIV, No. 2, April 2015)
Benign Breast Disease (Vol. XIV, No. 3, July 2015)
Hormone Therapy and Alternative Therapies for Menopause (Vol. XIV, No. 4, October 2015)
Lower Gastrointestinal Tract Disorders (Vol. XIV, No. 5, November 2015)

2014
Autoimmune Disorders (Vol. XIII, No. 1, January 2014)
Sexuality and Sexual Disorders (Vol. XIII, No. 2, April 2014)
Nutrition (Vol. XIII, No. 3, July 2014)
Adverse Drug Reactions (Vol. XIII, No. 4, October 2014)
Memory Loss and Dementia (Vol. XIII, No. 5, November 2014)

2013
Obesity (Vol. XII, No. 1, January 2013)
Exercise (Vol. XII, No. 2, April 2013)
Allergies (Vol. XII, No. 4, October 2013)
Thyroid Disorders (Vol. XII, No. 5, November 2013)

2012
Sleep Disorders (Vol. XI, No. 3, July 2012)
Upper Gastrointestinal Tract, Biliary, and Pancreatic Disorders (Vol. XI, No. 4, October 2012)
Anemia (Vol. XI, No. 5, November 2012)

2011
Renal Disease (Vol. X, No. 1, January 2011)
Complementary and Alternative Medicine (Vol. X, No. 4, October 2011)
2010
Anorectal Disorders (Vol. IX, No. 1, January 2010)
Anorectal Disorders Supplement (Vol. IX, No. 1, January 2010)
Occupational Diseases and Injuries (Vol. IX, No. 3, July 2010)
Perioperative Considerations for Coexisting Medical Conditions (Vol. IX, No. 4, October 2010)

2009
Vulvar Disorders (Vol. VIII, No. 2, April 2009)
Care of Aging Women (Vol. VIII, No. 4, October 2009)

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