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*Harrington*  
**Clinical Pediatric  
Dermatology**

A Textbook of Skin Disorders  
of Childhood and Adolescence  
Fifth Edition

*Hurwitz*  
Clinical  
Pediatric  
Dermatology

# Hurwitz Clinical Pediatric Dermatology

## A Textbook of Skin Disorders of Childhood and Adolescence

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FIFTH EDITION

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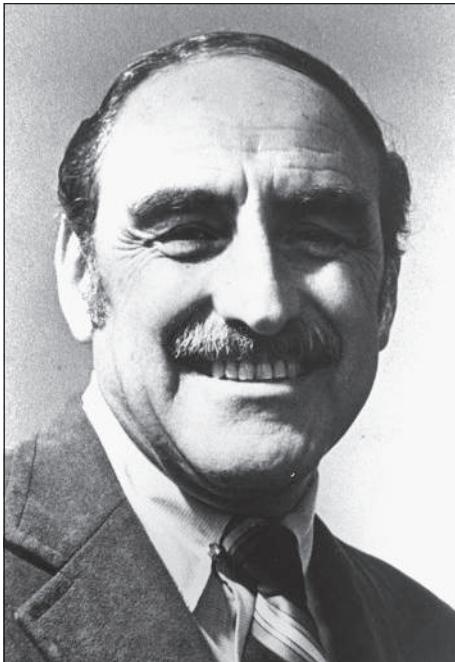
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# Foreword



Sidney Hurwitz, MD

After 15 years of practicing pediatrics and at 40 years of age, Dr. Sidney Hurwitz returned to Yale University School of Medicine to pursue a residency in dermatology and, subsequently, to embark on a career dedicated to the advancement of research, knowledge, and treatment of skin disorders in the young. During the next 25 years, Dr. Hurwitz became a legend in pediatric dermatology as Clinical Professor of Pediatrics and Dermatology at Yale University School of Medicine. He was a founder and President of both the Society for Pediatric Dermatology (U.S.) and the International Society of Pediatric Dermatology, and an author of more than 100 articles on childhood skin diseases and two single-authored textbooks, *The Skin and Systemic Disease in Children* and *Clinical Pediatric Dermatology*, first published in 1981. The first edition took 6 years of nights, weekends, and holidays, and the second edition 4 years. He dedicated the texts to his family: his wife, Teddy, and three daughters, Wendy, Laurie, and Alison. Dr.

Hurwitz died of overwhelming viral pneumonia at the age of 67 in November 1995, during his tenure as Honorary President of the International Society of Pediatric Dermatology. At the International Congress, Dr. Hurwitz's many contributions were recognized, including his textbook *Clinical Pediatric Dermatology*, recognized throughout the world as "the classic" in our field. He embraced us all with his ready smile, warmth, affection, and friendship. Sidney Hurwitz was a role model for all of us.

Drs. Amy S. Paller and Anthony J. Mancini share and embrace Dr. Hurwitz's vision of their specialty. As he did, they revel in providing clinical care to children of all ages, in the mentoring of future pediatric dermatologists, and in their love of learning, teaching, and collaborating with colleagues. True to the example set by Dr. Hurwitz, both Drs. Paller and Mancini have served the Society for Pediatric Dermatology in leadership roles.

Dr. Paller has contributed to the specialty as a National Institutes of Health-funded bench scientist and leading clinical investigator, in addition to her 30 years of practice in pediatric dermatology. She has a busy international and national lectureship schedule and has published more than 400 peer-reviewed papers and chapters, as well as four textbooks, among them *Clinical Pediatric Dermatology*. In common with Dr. Hurwitz, Dr. Paller relishes her years of working with young pediatric dermatologists. Dr. Paller served for 16 years as Head of the Division of Pediatric Dermatology at the former Children's Memorial Hospital in Chicago, following in the footsteps of her teacher and mentor, Dr. Nancy B. Esterly. She currently serves as the Walter J. Hamlin Professor and Chair of Dermatology and Professor of Pediatrics at Northwestern University. Dr. Paller has received several national and local awards for her mentorship and scholarship.

Dr. Mancini became Head of the Division of Pediatric Dermatology at Northwestern University and Children's Memorial Hospital (now Ann and Robert H. Lurie Children's Hospital of Chicago) in 2004 and is Professor of Pediatrics and Dermatology. Following in the footsteps of his mentors, he has dedicated his career to pediatric and dermatology education, as well as patient care and clinical research. He directs the pediatric dermatology fellowship program, established in 1983 as the first fellowship program in the country, and has published numerous scientific papers, chapters, and three textbooks. One of his greatest senses of accomplishment is that of mentoring his U.S.-trained and international pediatric dermatology fellows, as well as the pediatric residents at Children's Memorial Hospital, who have recognized Dr. Mancini with the Faculty Excellence in Education award for 13 years.

It is fitting that Drs. Paller and Mancini, authors of the third, fourth, and now fifth edition of *Clinical Pediatric Dermatology*, continue to immortalize Dr. Hurwitz's legacy.

# Preface



Amy S. Paller, MD



Anthony J. Mancini, MD

We were truly honored when initially asked to consider updating *Hurwitz Clinical Pediatric Dermatology*. Dr. Hurwitz was a true icon of our specialty and one of its founding fathers. Thanks to Dr. Hurwitz, the widely recognizable book sits on many a shelf and has educated and enlightened pediatricians, dermatologists, family practitioners, medical students, residents, nurses, and other allied pediatric care providers for decades. It is our hope that this tradition will continue, and we have made every effort to maintain the practicality, relevance, and usability of the text.

What lies between these covers will be familiar, but with many additions. The field of pediatric dermatology has continued to expand since our last edition. The molecular bases for many established skin diseases, as well as syndromes with cutaneous features, continue to be elucidated. Several new disease and syndrome associations have been recognized and described. The therapeutic armamentarium for cutaneous disease has broadened, with further elucidation of mechanisms of disease and, as a result, several newer classes of drugs available to the clinician. We have strived to maintain a text that is a marriage between cutting-edge review and practical clinical application, while maintaining the flavor of Dr. Hurwitz's first two editions and our third and fourth editions, each of them a balance between narrative text, useful tables, and vivid clinical photographs.

Several new features have been added to this fifth edition, including a downloadable ebook with the printed edition and over 350 new clinical images. We have updated the section on atopic dermatitis to reflect our growing understanding of underlying barrier defects and immune activation, which is starting to impact pediatric management. The numerous recent discoveries about the genetic basis underlying the ichthyoses, ectodermal defects, and mosaic gene disorders, many based on studies with whole exome sequencing, are now included. New directions, such as the use of stem cell and cell therapy, as well as recombinant protein, for treating epidermolysis bullosa are also touched on. Our discussion of treatment for pediatric head lice reflects the multitude of new therapy options, and we have expanded the discussion of viral exanthematous diseases, including the resurgence in measles infections and the broadened scope of manifestations related to enteroviral illnesses. The section on Epstein–Barr virus infections has been expanded, including an added section on acute

genital ulceration related to this and other organisms. In alignment with the explosive gains in knowledge about pediatric vascular lesions, there are expanded sections on oral and topical beta blocker therapy for infantile hemangioma and hemangioma syndrome associations, and an updated discussion of vascular malformations and several more recently elucidated syndrome associations. There is an updated discussion of the contemporary pediatric acne classification, acne presenting at various ages in childhood, and available acne therapies. Finally, our discussion of systemic disorders reflects the growing number of effective anti-inflammatory medications. The references have been extensively updated in our companion online edition, leaving only some excellent reviews and landmark articles to allow for more complete textual content for our readers of the print version.

We continue to be indebted to several individuals, without whom this work would not have been possible. First and foremost, we thank Dr. Sidney Hurwitz, whose vision, dedication, and enthusiasm for the specialty of pediatric dermatology lives on as a legacy in this text, initially published in 1981. We are indebted to Teddy Hurwitz, his wife, who entrusted to us the ongoing tradition of this awesome project; to Dr. Alvin Jacobs, a “father” of pediatric dermatology who kindled the flame of the specialty in both of us through his teaching at Stanford; to Dr. Nancy B. Esterly, the “mother” of pediatric dermatology, whose superb clinical acumen and patient care made her the perfect role model for another female physician who yearned to follow in her footsteps; and to Dr. Alfred T. Lane, who believed in a young pediatric intern and mentored him through the process of becoming a mentor himself.

We are also indebted to the staff at Elsevier, most notably Russell Gabbedy and Alex Mortimer, who worked tirelessly through this edition to again meet the many demands of two finicky academicians; to our patients, who continue to educate us on a daily basis and place their trust in us to provide them care; to the clinicians who referred many of the patients seen in these pages; to our pediatric dermatology fellows and nurses, who contribute enormously through assistance with taking and archiving our many clinical photographs; and to our families, whose understanding, sacrifice, support, and unconditional love made this entire endeavor possible.

# *Dedication*

Our Families:

Etahn	Nicki
Josh	Mallory
Max	Chris
&	Mack
Ben	&
	Alex

whose ongoing patience, understanding, support and  
personal sacrifice enabled us to  
complete this project.

And to the memory of

Sidney Hurwitz, MD,  
a role model par excellence

# An Overview of Dermatologic Diagnosis and Procedures

Accurate diagnosis of cutaneous disease in infants and children is a systematic process that requires careful inspection, evaluation, and some knowledge of dermatologic terminology and morphology to develop a prioritized differential diagnosis. The manifestations of skin disorders in infants and young children often vary from those of the same diseases in older children and adults. The diagnosis may be obscured, for example, by different reaction patterns or a tendency toward easier blister formation. In addition, therapeutic dosages and regimens often differ from those of adults, with medications prescribed on a “per kilogram” (/kg) basis and with liquid formulations.

Nevertheless, the same basic principles that are used to detect disorders affecting viscera apply to the detection of skin disorders. An adequate history should be obtained, a thorough physical examination performed, and, whenever possible the clinical impression verified by appropriate laboratory studies. The easy visibility of skin lesions all too often results in a cursory examination and hasty diagnosis. Instead, the entire skin should be examined routinely and carefully, including the hair, scalp, nails, oral mucosa, anogenital regions, palms, and soles, because visible findings often hold clues to the final diagnosis.

The examination should be conducted in a well-lit room. Initial viewing of the patient at a distance establishes the overall status of the patient and allows recognition of distribution patterns and clues to the appropriate final diagnosis. This initial evaluation is followed by careful scrutiny of primary and subsequent secondary lesions in an effort to discern the characteristic features of the disorder.

Although not always diagnostic, the morphology and configuration of cutaneous lesions are of considerable importance to the classification and diagnosis of cutaneous disease. A lack of understanding of dermatologic terminology commonly poses a barrier to the description of cutaneous disorders by clinicians who are not dermatologists. Accordingly, a review of dermatologic terms is included here (**Table 1-1**). The many examples to show primary and secondary skin lesions refer to specific figures in the text that follows.

## Configuration of Lesions

A number of dermatologic entities assume annular, circinate, or ring shapes and are interpreted as ringworm or superficial fungal infections. Although tinea is a common annular dermatosis of childhood, there are multiple other disorders that must be included in the differential diagnosis of ringed lesions including pityriasis rosea, seborrheic dermatitis, nummular eczema, lupus erythematosus, granuloma annulare, psoriasis, erythema multiforme, erythema annulare centrifugum, erythema migrans, secondary syphilis, sarcoidosis, urticaria, pityriasis alba, tinea versicolor, lupus vulgaris, drug eruptions, and cutaneous T-cell lymphoma.

The terms *arciform* and *arcuate* refer to lesions that assume arc-like configurations. Arciform lesions may be seen in erythema multiforme, urticaria, pityriasis rosea, and bullous dermatosis of childhood.

Lesions that tend to merge are said to be *confluent*. Confluence of lesions is seen, for example, in childhood exanthems, *Rhus* dermatitis, erythema multiforme, tinea versicolor and urticaria.

Lesions localized to a dermatome supplied by one or more dorsal ganglia are referred to as *dermatomal*. Herpes zoster classically occurs in a dermatomal distribution.

*Discoid* is used to describe lesions that are solid, moderately raised, and disc-shaped. The term has largely been applied to discoid lupus erythematosus, in which the discoid lesions usually show atrophy and dyspigmentation.

Discrete lesions are individual lesions that tend to remain separated and distinct. *Eczematoid* and *eczematous* are adjectives relating to eczema and suggest inflammation with a tendency to thickening, oozing, vesication, and/or crusting.

Grouping and clustering are characteristic of vesicles of herpes simplex or herpes zoster, insect bites, lymphangioma circumscriptum, contact dermatitis, and bullous dermatosis of childhood.

Guttate or drop-like lesions are characteristic of flares of psoriasis in children and adolescents that follow an acute upper respiratory tract infection, usually streptococcal.

*Gyrate* refers to twisted, coiled, or spiral-like lesions, as may be seen in patients with urticaria and erythema annulare centrifugum.

*Iris* or target-like lesions are concentric ringed lesions characteristic of erythema multiforme. The classic “targets” in this condition are composed of a central dusky erythematous papule or vesicle, a peripheral ring of pallor, and then an outer bright red ring.

*Keratosis* refers to circumscribed patches of horny thickening, as seen in seborrheic or actinic keratoses, keratosis pilaris, and keratosis follicularis (Darier disease). *Keratotic* is an adjective pertaining to keratosis and commonly refers to the epidermal thickening seen in chronic dermatitis and callus formation.

The *Koebner phenomenon* or *isomorphic response* refers to the appearance of lesions along a site of injury. The linear lesions of warts and molluscum contagiosum, for example, occur from autoinoculation of virus from scratching; those of *Rhus* dermatitis (poison ivy) result from the spread of the plant's oleoresin. Other examples of disorders that show a Koebner phenomenon are psoriasis, lichen planus, lichen nitidus, pityriasis rubra pilaris, and keratosis follicularis (Darier disease).

Lesions in a linear or band-like configuration appear in the form of a line or stripe and may be seen in epidermal nevi, Conradi syndrome, linear morphea, lichen striatus, striae, *Rhus* dermatitis, deep mycoses (sporotrichosis or coccidioidomycosis), incontinentia pigmenti, pigment mosaicism, porokeratosis of Mibelli, or factitial dermatitis. In certain genetic and inflammatory disorders, such linear configurations represent the lines of Blaschko, which trace various clones of embryonic cells and, as such, represent a form of cutaneous mosaicism. This configuration presents as a linear pattern on the extremities, wavy or S-shaped on the lateral trunk, V-shaped on the central trunk, and varied patterns on the face and scalp.

*Moniliform* refers to a banded or necklace-like appearance. This is seen in monilethrix, a hair deformity characterized by beaded nodularities along the hair shaft.

*Multiform* refers to disorders in which more than one variety or shape of cutaneous lesions occurs. This configuration is seen in patients with erythema multiforme, early Henoch–Schönlein purpura, and polymorphous light eruption.

*Nummular* means coin-shaped and is usually used to describe nummular dermatitis.

*Polyyclic* refers to oval lesions containing more than one ring, as commonly is seen in patients with urticaria.

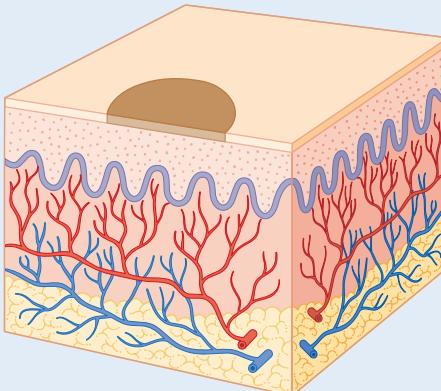
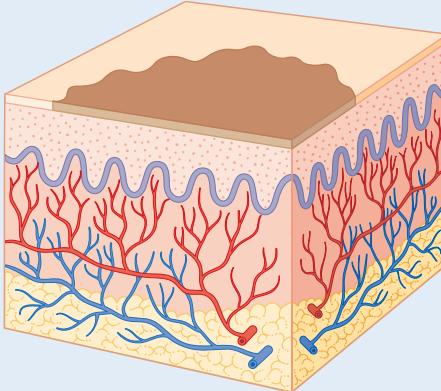
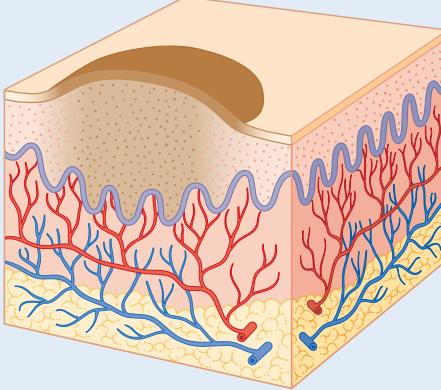
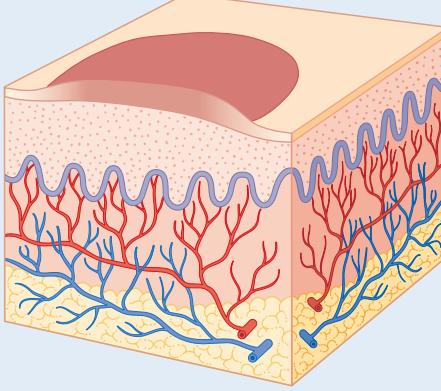
A reticulated or net-like pattern may be seen in erythema ab igne, livedo reticularis, cutis marmorata, cutis marmorata telangiectatica congenita, and lesions of confluent and reticularized papillomatosis.

*Serpiginous* describes the shape or spread of lesions in a serpentine or snake-like configuration, particularly those of cutaneous larva migrans (creeping eruption) and elastosis perforans serpiginosa.

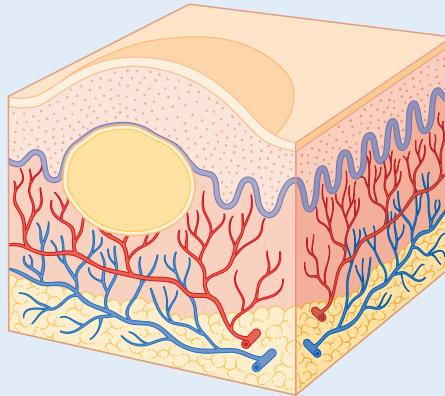
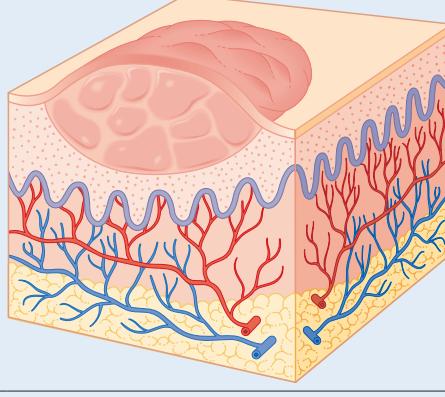
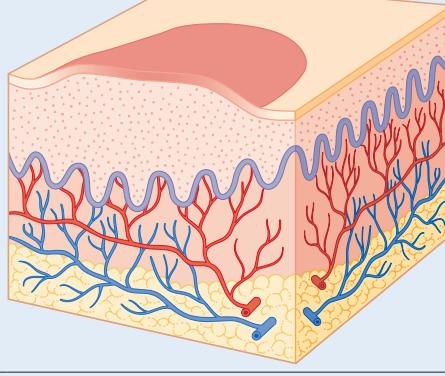
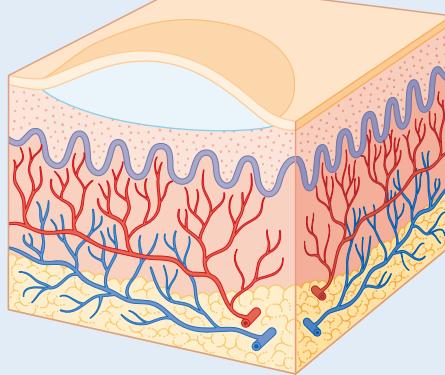
Umbilicated lesions are centrally depressed or shaped like an umbilicus or navel. Examples include lesions of molluscum contagiosum, varicella, vaccinia, variola, herpes zoster, and Kaposi varicelliform eruption.

*Text continued on p. 7*

**Table 1-1** Glossary of Dermatologic Terms

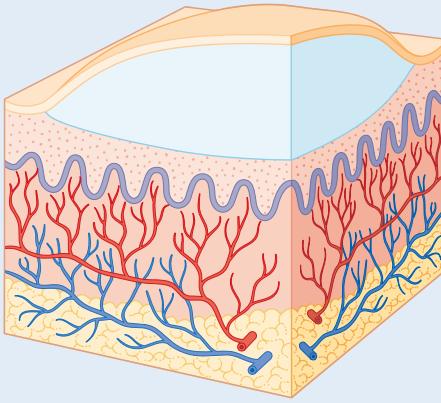
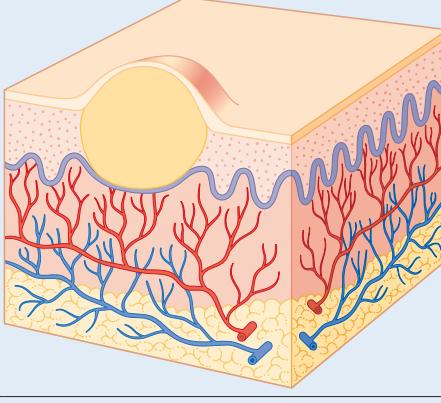
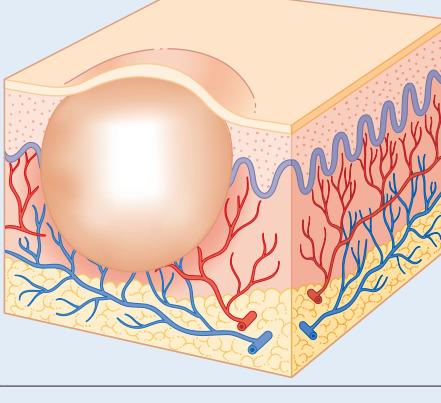
Lesion	Description	Illustration	Examples
<b>PRIMARY LESIONS</b>			
Macule	Flat, circumscribed change of the skin. It may be of any size, although this term is often used for lesions <1 cm. A macule may appear as an area of hypopigmentation or as an area of increased coloration, most commonly brown (hyperpigmented) or red (usually a vascular abnormality). It is usually round but may be oval or irregular; it may be distinct or may fade into the surrounding area.		Ephelides; lentigo (see Fig. 11-41); flat nevus (see Fig. 9-1); and tinea versicolor (see Fig. 17-35).
Patch	Flat, circumscribed lesion with color change that is >1 cm in size.		Mongolian spot (see Fig. 11-57); port wine stain (see Fig. 12-57); nevus depigmentosus (see Fig. 11-22); larger café-au-lait spot (see Fig. 11-43); and areas of vitiligo (see Figs. 11-1 through 11-10).
Papule	Circumscribed, nonvesicular, nonpustular, elevated lesion that measures <1 cm in diameter. The greatest mass is above the surface of the skin. When viewed in profile it may be flat-topped, dome-shaped, acuminate (tapering to a point), digitate (finger-like), smooth, eroded, or ulcerated. It may be covered by scales, crusts, or a combination of secondary features.		Elevated nevus (see Fig. 9-4); verruca (see Fig. 15-17); molluscum contagiosum (see Fig. 15-40); perioral dermatitis (see Fig. 8-20); and individual lesions of lichen planus (see Fig. 4-43).
Plaque	Broad, elevated, disk-shaped lesion that occupies an area of >1 cm. It is commonly formed by a confluence of papules.		Psoriasis (see Fig. 4-4); lichen simplex chronicus (neurodermatitis) (see Fig. 3-37); granuloma annulare (see Fig. 9-58); nevus sebaceus (see Figs. 9-41 through 9-44); and lesions of lichen planus (see Fig. 4-45).

**Table 1-1** Glossary of Dermatologic Terms (Continued)

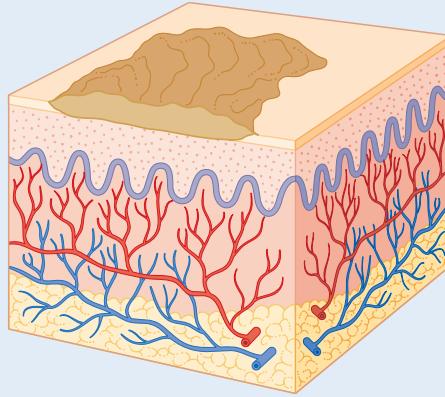
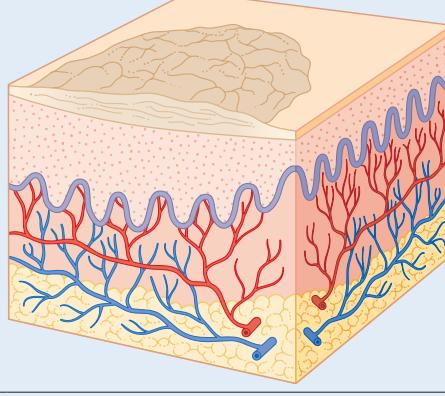
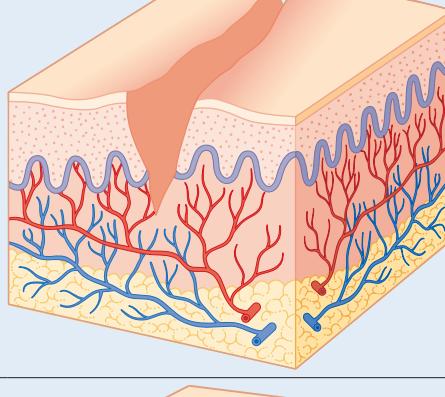
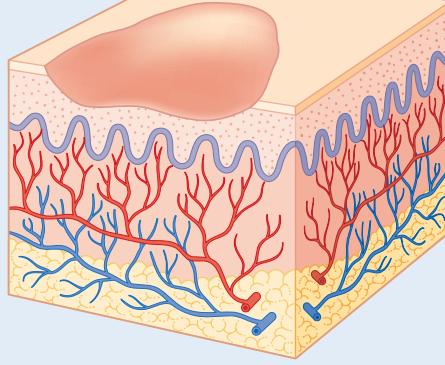
Lesion	Description	Illustration	Examples
Nodule	Circumscribed, elevated, usually solid lesion that measures 0.5 to 2 cm in diameter. It involves the dermis and may extend into the subcutaneous tissue with its greatest mass below the surface of the skin.		Erythema nodosum (see Figs. 20-44 and 20-45); pilomatrixoma (see Fig. 9-48); subcutaneous granuloma annulare (see Fig. 9-60); and nodular scabies (see Fig. 18-9).
Tumor	Deeper circumscribed solid lesion of the skin or subcutaneous tissue that measures >2 cm in diameter. It may be benign or malignant.		Deep hemangioma (see Fig. 12-7) and plexiform neurofibroma (Fig. 11-50).
Wheal	Distinctive type of elevated lesion characterized by local, superficial, transient edema. White to pink or pale red, compressible, and evanescent, they often disappear within a period of hours. They vary in size and shape.		Darier sign of mastocytosis (see Fig. 9-52); urticarial vasculitis (see Fig. 21-14); and various forms of urticaria (see Fig. 20-2).
Vesicle	Sharply circumscribed, elevated, fluid-containing lesion that measures ≤1 cm in diameter.		Herpes simplex (see Figs. 2-47, 15-10 and 15-11); hand-foot-and-mouth disease (see Fig. 16-30); pompholyx (see Fig. 3-41); varicella (see Fig. 16-1); and contact dermatitis (see Fig. 3-57).

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**Table 1-1** Glossary of Dermatologic Terms (Continued)

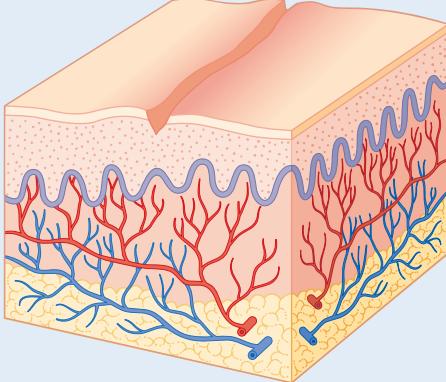
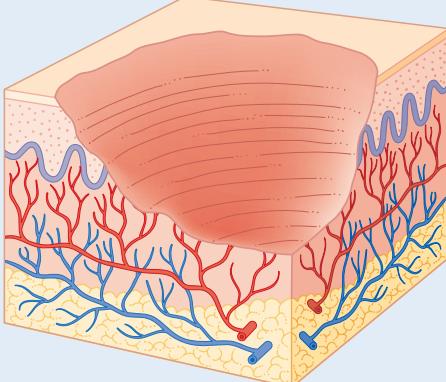
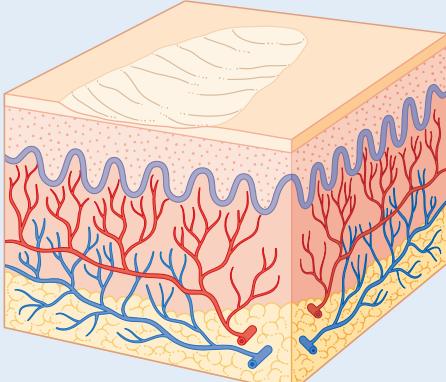
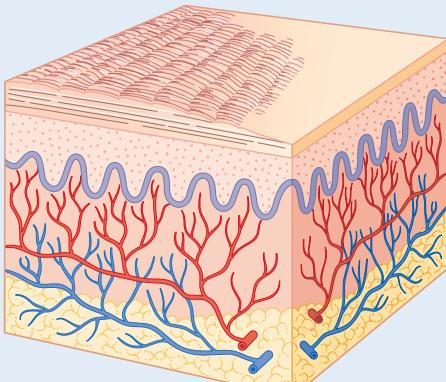
Lesion	Description	Illustration	Examples
Bulla	Larger, circumscribed, elevated, fluid-containing lesion that measures >1 cm in diameter.		Blistering distal dactylitis (see Fig. 14-21); bullous pemphigoid (see Fig. 13-26); chronic bullous disease of childhood (see Fig. 13-29); bullous systemic lupus erythematosus (see Fig. 13-32); and epidermolysis bullosa (see Fig. 13-4).
Pustule	Circumscribed elevation <1 cm in diameter that contains a purulent exudate. It may be infectious or sterile.		Folliculitis (see Fig. 14-11); transient neonatal pustular melanosis (see Fig. 2-17); pustular psoriasis (see Fig. 4-22); and infantile acropustulosis (see Fig. 2-19).
Abscess	Circumscribed, elevated lesion >1 cm in diameter, often with a deeper component and filled with purulent material.		Staphylococcal abscess (in a neonate, see Fig. 2-5; in a patient with hyperimmunoglobulinemia E, see Fig. 3-35).
<b>OTHER PRIMARY LESIONS</b>			
Comedone	Plugged secretion of horny material retained within a pilosebaceous follicle. It may be flesh colored (as in closed comedone or whitehead) or slightly raised brown or black (as in open comedone or blackhead). Closed comedones, in contrast to open comedones, may be difficult to visualize. They appear as pale, slightly elevated, small papules without a clinically visible orifice.		Acne comedones (see Figs. 8-3 and 8-4) and nevus comedonicus (see Fig. 9-45).
Burrow	Linear lesion produced by tunneling of an animal parasite in the stratum corneum.		Scabies (see Fig. 18-3) and cutaneous larva migrans (creeping eruption, see Fig. 18-39).
Telangiectasia	Persistent dilation of superficial venules, capillaries, or arterioles of the skin.		Spider angioma (see Fig. 12-86); periungual lesion of dermatomyositis (see Fig. 22-25); and Goltz syndrome (see Fig. 6-15).

**Table 1-1** Glossary of Dermatologic Terms (Continued)

Lesion	Description	Illustration	Examples
<b>SECONDARY LESIONS</b>			
Crust	Dried remains of serum, blood, pus, or exudate overlying areas of lost or damaged epidermis. Crust is yellow when formed by dried serum, green or yellowish-green when formed by purulent exudate, and dark red or brown when formed by bloody exudative serum.		Herpes simplex (see Fig. 15-4); weeping eczematous dermatitis (see Fig. 3-1); and dried honey-colored lesions of impetigo (see Fig. 14-2).
Scale	Formed by an accumulation of compact desquamating layers of stratum corneum as a result of abnormal keratinization and exfoliation of cornified keratinocytes.		Seborrheic dermatitis (greasy and yellowish, see Figs. 3-2 and 3-39); psoriasis (silvery and mica-like, see Fig. 4-1); pityriasis alba (fine and barely visible, see Fig. 3-33); and lamellar ichthyosis (large and adherent, see Fig. 5-10).
Fissure	Dry or moist, linear, often painful cleavage in the cutaneous surface that results from marked drying and long-standing inflammation, thickening, and loss of elasticity of the integument.		Angular cheilitis (see Fig. 17-40) and dermatitis on the plantar aspect of the foot (see Fig. 3-61).
Erosion	Moist, slightly depressed vesicular or bullous lesions in which part or all of the epidermis has been lost. Because erosions do not extend into the underlying dermis or subcutaneous tissue, healing occurs without subsequent scar formation.		Herpes simplex (see Figs. 3-28 and 15-1); epidermolytic ichthyosis in a neonate (see Fig. 5-4); and superficial forms of epidermolysis bullosa (see Fig. 13-7).

*Continued on following page*

**Table 1-1** Glossary of Dermatologic Terms (Continued)

Lesion	Description	Illustration	Examples
Excoriation	Traumatized or abraded (usually self-induced) superficial loss of skin caused by scratching, rubbing, or scrubbing of the cutaneous surface.		Atopic dermatitis (see Fig. 3-9) and acne excoriée (see Fig. 8-19).
Ulcer	Necrosis of the epidermis and part or all of the dermis and/or the underlying subcutaneous tissue.		Pyoderma gangrenosum (see Fig. 25-27) and ulcerated hemangioma of infancy (see Figs. 12-15 and 12-26).
Atrophy	Cutaneous changes that result in depression of the epidermis, dermis, or both. Epidermal atrophy is characterized by thin, almost translucent epidermis, a loss of the normal skin markings, and wrinkling when subjected to lateral pressure or pinching of the affected area. In dermal atrophy the skin is depressed.		Anetoderma (see Fig. 22-53); morphea (see Figs. 22-42 through 22-49); steroid-induced atrophy (see Fig. 3-32); and Goltz syndrome (see Fig. 6-17).
Lichenification	Thickening of the epidermis with associated exaggeration of skin markings. Lichenification results from chronic scratching or rubbing of a pruritic lesion.		Atopic dermatitis (see Fig. 3-8); chronic contact dermatitis (see Fig. 3-53); and lichen simplex chronicus (see Fig. 3-37).

**Table 1-1** Glossary of Dermatologic Terms (Continued)

Lesion	Description	Illustration	Examples
Scar	A permanent fibrotic skin change that develops after damage to the dermis. Initially pink or violaceous, scars are permanent, white, shiny, and sclerotic as the color fades. Although fresh scars often are hypertrophic, they usually contract during the subsequent 6 to 12 months and become less apparent. Hypertrophic scars must be differentiated from keloids, which represent an exaggerated response to skin injury. Keloids are pink, smooth, and rubbery and are often traversed by telangiectatic vessels. They tend to increase in size long after healing has taken place and can be differentiated from hypertrophic scars by the fact that the surface of a keloidal scar tends to extend beyond the area of the original wound.		Keloid (see Fig. 9-83); healed areas of recessive dystrophic epidermolysis bullosa (see Fig. 13-17); acne scarring (see Fig. 8-8), congenital erosive and vesicular dermatosis with reticulated supple scarring (see Fig. 2-21); and amniocentesis scars (see Fig. 2-4).

*Universal (universalis)* implies widespread disorders affecting the entire skin, as in alopecia universalis.

*Zosteriform* describes a linear arrangement along a nerve, as typified by lesions of herpes zoster, although herpes simplex infection can also manifest in a zosteriform distribution.

## Distribution and Morphologic Patterns of Common Skin Disorders

The regional distribution and morphologic configuration of cutaneous lesions are often helpful in dermatologic diagnosis.

Acneiform lesions are those having the form of acne, and *an acneiform distribution* refers to lesions primarily seen on the face, neck, chest, upper arms, shoulders, and back (see Figs. 8-3 through 8-13).

Sites of predilection of atopic dermatitis include the face, trunk, and extremities in young children; the antecubital and popliteal fossae are the most common sites in older children and adolescents (see Figs. 3-1 through 3-12).

The lesions of erythema multiforme may be widespread but have a distinct predilection for the hands and feet (particularly the palms and soles) (see Figs. 20-33 through 20-37).

Lesions of herpes simplex may appear anywhere on the body but have a distinct predisposition for the areas about the lips, face, and genitalia (see Figs. 15-1 through 15-12). Herpes zoster generally has a dermatomal or nerve-like distribution and is usually but not necessarily unilateral (see Figs. 15-13 and 15-14). More than 75% of cases occur between the second thoracic and second lumbar vertebrae. The fifth cranial nerve commonly is involved, and only rarely are lesions seen below the elbows or knees.

Lichen planus often affects the limbs (see Figs. 4-43 through 4-51). Favorite sites include the lower extremities, the flexor surface of the wrists, the buccal mucosa, the trunk, and the genitalia.

The lesions of lupus erythematosus most commonly localize to the bridge of the nose, malar eminences, scalp, and ears, although they may be widespread (see Figs. 22-3 and 22-6). Patches tend to spread at the border and clear in the center with atrophy, scarring, dyspigmentation, and telangiectases. The malar or butterfly rash is neither specific for nor the most common sign of lupus erythematosus; telangiectasia without the accompanying features of erythema, scaling, or atrophy is never a marker of this disorder other than in neonatal lupus.

Molluscum contagiosum is a common viral disorder characterized by dome-shaped skin-colored to erythematous papules, often with a central white core or umbilication (see Figs. 15-35 through 15-45). These papules most often localize to the trunk and axillary areas.

Although molluscum lesions can be found anywhere, the scalp, palms, and soles are rare sites of involvement.

Photodermatoses are cutaneous disorders caused or precipitated by exposure to light. Areas of predilection include the face, ears, anterior "V" of the neck and upper chest, the dorsal aspect of the forearms and hands, and exposed areas of the legs. The shaded regions of the upper eyelids, subnasal, and submental regions tend to be spared. The major photosensitivity disorders are lupus erythematosus, dermatomyositis, polymorphous light eruption, drug photosensitization, and porphyria (see Chapter 19).

Photosensitive reactions cannot be distinguished on a clinical basis from lesions of photocontact allergic conditions. They may reflect internal as well as external photoallergens and may simulate contact dermatitis from airborne sensitizers. Lupus erythematosus can be differentiated by the presence of atrophy, scarring, hyperpigmentation or hypopigmentation, and the presence of periungual telangiectases. Dermatomyositis with swelling and erythema of the cheeks and eyelids should be differentiated from allergic contact dermatitis by the heliotrope hue and other associated changes, particularly those of the fingers (periungual telangiectases and Gottron papules).

Pityriasis rosea begins as a solitary round or oval scaling lesion known as the *herald patch* in 70% to 80% of cases, which may be annular and is often misdiagnosed as tinea corporis (see Figs. 4-38 through 4-41). After an interval of days to 2 weeks, affected individuals develop a generalized symmetrical eruption that involves mainly the trunk and proximal limbs. The clue to diagnosis is the distribution of lesions, with the long axis of these oval lesions parallel to the lines of cleavage in what has been termed a *Christmas-tree pattern*. A common variant, inverse pityriasis rosea, often localizes in the inguinal region, but the parallel nature of the long axis of lesions remains characteristic.

Psoriasis classically consists of round, erythematous, well-margined plaques with a rich red hue covered by a characteristic grayish or silvery-white mica-like (micaceous) scale that on removal may result in pinpoint bleeding (Auspitz sign) (see Figs. 4-1 through 4-10). Although exceptions occur, lesions generally are seen in a bilaterally symmetric pattern with a predilection for the elbows, knees, scalp, and lumbosacral, perianal, and genital regions. Nail involvement, a valuable diagnostic sign, is characterized by pitting of the nail plate, discoloration, separation of the nail from the nailbed (onycholysis), and an accumulation of subungual scale (subungual hyperkeratosis). A characteristic feature of this disorder is the Koebner or isomorphic response in which new lesions appear at sites of local injury.

Scabies is an itchy disorder in which lesions are characteristically distributed on the wrists and hands (particularly the interdigital webs), forearms, genitalia, areolae, and buttocks in older children and

adolescents (see Figs. 18-1 through 18-11). Other family members may be similarly affected or complain of itching. In infants and young children, the diagnosis is often overlooked because the distribution typically involves the palms, soles, and often the head and neck. Obliteration of demonstrable primary lesions (burrows) because of vigorous hygienic measures, excoriation, crusting, eczematization, and secondary infection is particularly common in infants.

Seborrheic dermatitis is an erythematous, scaly or crusting eruption that characteristically occurs on the scalp, face, and postauricular, presternal, and intertriginous areas (see Figs. 3-38 and 3-39). The classic lesions are dull, pinkish-yellow, or salmon colored with fairly sharp borders and overlying yellowish greasy scale. Morphologic and topographic variants occur in many combinations and with varying degrees of severity from mild involvement of the scalp with occasional blepharitis to generalized, occasionally severe erythematous scaling eruptions. The differential diagnosis may include atopic dermatitis, psoriasis, various forms of diaper dermatitis, Langerhans cell histiocytosis, scabies, tinea corporis or capitis, pityriasis alba, contact dermatitis, Darier disease, and lupus erythematosus.

Warts are common viral cutaneous lesions characterized by the appearance of skin-colored small papules of several morphologic types (see Figs. 15-16 through 15-33). They may be elevated or flat lesions and tend to appear in areas of trauma, particularly the dorsal surface of the face, hands, periungual areas, elbows, knees, feet, and genital or perianal areas. Close examination may reveal capillaries appearing as punctate dots scattered on the surface.

## Changes in Skin Color

The color of skin lesions commonly assists in making the diagnosis. Common disorders of brown hyperpigmentation include postinflammatory hyperpigmentation, pigmented and epidermal nevi, café-au-lait spots, lentigines, incontinentia pigmenti, fixed drug eruption, photodermatitis and phytophotodermatitis, melasma, acanthosis nigricans, and Addison disease. Blue coloration is seen in mongolian spots, blue nevi, nevus of Ito and nevus of Ota, and cutaneous neuroblastomas. Cysts, deep hemangiomas, and pilomatricomas often show a subtle blue color, whereas the blue of venous malformations and glomuvenous malformations is often a more intense, dark blue. Yellowish discoloration of the skin is common in infants, related to the presence of carotene derived from excessive ingestion of foods, particularly yellow vegetables containing carotenoid pigments. Jaundice may be distinguished from carotenemia by scleral icterus. Localized yellow lesions may represent juvenile xanthogranulomas, nevus sebaceous, xanthomas, or mastocytomas. Red lesions are usually vascular in origin, such as superficial hemangiomas, spider telangiectases, and nevus flammeus (capillary malformations), or inflammatory, such as the scaling lesions of atopic dermatitis or psoriasis.

Localized lesions with decreased pigmentation may be hypopigmented (decreased pigmentation) or depigmented (totally devoid of pigmentation); Wood lamp examination may help to differentiate depigmented lesions, which fluoresce a bright white, from hypopigmented lesions. Localized depigmented lesions may be seen in vitiligo, Vogt-Koyanagi syndrome, halo nevi, chemical depigmentation, piebaldism, and Waardenburg syndrome. Hypopigmented lesions are more typical of postinflammatory hypopigmentation, pityriasis alba, tinea versicolor, leprosy, nevus achromicus, tuberous sclerosis, and the hypopigmented streaks of pigment mosaicism. A generalized decrease in pigmentation can be seen in patients with albinism, untreated phenylketonuria, and Menkes syndrome. The skin of patients with Chédiak-Higashi and Griscelli syndromes takes on a dull silvery sheen and may show decreased pigmentation.

## Racial Variations in the Skin and Hair

The skin of African-American and other darker-skinned children varies in several ways from that of lighter-skinned children based on genetic background and customs.<sup>1,2</sup> The erythema of inflamed black skin may be difficult to see and likely accounts for the purportedly decreased incidence of macular viral exanthems such as erythema

infectiosum. Erythema in African-American children commonly has a purplish tinge that can be confusing to unwary observers. The skin lesions in several inflammatory disorders such as atopic dermatitis, pityriasis rosea, and syphilis commonly show a follicular pattern in African-American children.

Postinflammatory hypopigmentation and hyperpigmentation occur readily and are more obvious in darker-skinned persons, regardless of racial origin. Pityriasis alba and tinea versicolor are more commonly reported in darker skin types, perhaps because of the easy visibility of the hypopigmented lesions in marked contrast to uninvolved surrounding skin. Lichen nitidus is more apparent and reportedly more common in African-American individuals; lichen planus is reported to be more severe, leaving dark postinflammatory hyperpigmentation. Vitiligo is particularly distressing to patients with darker skin types, whether African-American or Asian, because of the easy visibility in contrast with surrounding skin.

Although darker skin may burn, in general sunburn and chronic sun-induced diseases of adults such as actinic keratosis and carcinomas of the skin induced by ultraviolet light exposure (e.g., squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, and melanoma) have an extremely low incidence in African-Americans and Hispanics. Congenital melanocytic nevi also tend to have a lower tendency to transform to malignancy in darker-skinned individuals. Café-au-lait spots are more numerous and seen more often in African-Americans, although the presence of six or more should still raise suspicion about neurofibromatosis. Dermatoses papulosa nigra commonly develop in adolescents, especially female, of African descent. Mongolian spots occur more often in persons of African or Asian descent. Physiologic variants in children with darker skin include increased pigmentation of the gums and tongue, pigmented streaks in the nails, and Voight-Futcher lines, lines of pigmentary demarcation between the posterolateral and lighter anteromedial skin on the extremities.

Qualities of hair may also differ among individuals of different races. African-American hair tends to tangle when dry and becomes matted when wet. As a result of its naturally curly or spiral nature, pseudofolliculitis barbae is more common in African-Americans than in other groups. Tinea capitis is particularly common in prepubertal African-Americans; the tendency to use oils because of hair dryness and poor manageability may obscure the scaling of tinea capitis. Pediculosis capitis, in contrast, is relatively uncommon in this population, possibly related to the diameter and shape of the hair shaft. Prolonged continuous traction on hairs may result in traction alopecia, particularly with the common practice of making tight corn row braids. The use of other hair grooming techniques such as chemical straighteners, application of hot oils, and use of hot combs increases the risk of hair breakage and permanent alopecia. Frequent and liberal use of greasy lubricants and pomades produces a comedonal and sometimes papulopustular form of acne (pomade acne).

Keloids form more often in individuals of African descent, often as a complication of a form of inflammatory acne, including nodulocystic acne and acne keloidalis nuchae. Other skin disorders reportedly seen more commonly are transient neonatal pustular melanosis, infantile acropustulosis, impetigo, papular urticaria, sickle-cell ulcers, sarcoidosis, and dissecting cellulitis of the scalp. Atopic dermatitis and Kawasaki disease have both been reported most often in children of Asian descent.

## Procedures to Aid in Diagnosis

### BETTER VISUALIZATION

Although most lesions are diagnosed by clinical inspection, several techniques are used to aid in diagnosis. The Wood lamp (black light) is an ultraviolet A (UVA)-emitting device with a peak emission of 365 nm. With the room completely dark and the light held approximately 10 cm from the skin, the examiner can see: (1) more subtle differences in pigmentation and the bright whiteness of vitiligo lesions based on the strong absorbance of the light by melanin; and (2) characteristic fluorescence of organisms such as the pink-orange fluorescence of urine in porphyria (see Chapter 19), the coral red fluorescence of erythrasma, the yellow-orange fluorescence of tinea versicolor, the

green fluorescence of ectothrix types of tinea capitis (e.g., *Microsporum*) (see Chapter 17), and sometimes pseudomonas infection. False-positive assessments can result from detection of other fluorescent objects such as lint, threads, scales, and ointments.

Magnification using a lens or lighted devices such as the otoscope or ophthalmoscope can be used to more easily visualize lesions such as nailfold capillaries, especially after swabbing the skin with alcohol or applying a drop of oil. *Dermoscopy* (also known as *dermatoscopy* or *epiluminescence microscopy*) refers to examination of the skin with a dermatoscope, a handheld magnifier with an embedded light source. Dermoscopy provides more than just magnification, because it allows the viewer to visualize dermal diagnostic clues. In pediatric patients dermoscopy can be particularly useful for reassurance regarding the benign nature of pigmented nevi, visualization of vascular lesions, and hair disorders ranging from shaft defects to alopecia areata.<sup>1–3</sup> Finally, diascopy involves pressing a glass microscope slide firmly over a lesion and watching for changes in appearance. Purpura, which does not blanch with diascopy because the erythrocytes have leaked into tissue, can be distinguished from erythema from vasodilation, which blanches because the pressure from the slides forces the erythrocytes to move out of the compressed vessels. The yellow-brown (“apple jelly”) color of granulomatous lesions (e.g., granuloma annulare, sarcoidosis) persists during diascopy, and the constricted blood vessels of nevus anemicus do not refill when the slides are lifted after diascopy (as do the surrounding normal areas).

Several diagnostic techniques involve procedures to obtain scales or discharge (by scraping or swabbing) for analysis. Scraping can be performed with a sterile surgical or Fomon blade. A Cytobrush<sup>4</sup> or moistened swab<sup>5</sup> can be used for obtaining scales and broken hairs for fungal cultures and may be less frightening for young children (see Chapter 17). Vesicular lesions can be scraped for Tzanck smears and obtaining epidermal material for direct fluorescent analysis and viral (primarily herpes) cultures or to show the cellular content such as eosinophils in the vesicular lesions of incontinentia pigmenti. Potential scabies lesions, especially burrows, can be dotted with mineral oil and scraped vigorously for microscopic analysis, which may reveal live mites, eggs, or feces (see Chapter 18). When looking for superficial fungi, both potassium hydroxide (KOH) wet-mount preparations and cultures are often performed, although KOH examination should be performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved setting (see Chapter 17). For skin lesions the blade or Cytobrush should scrape the active lesional border. For possible tinea capitis it is important to obtain broken (infected) hairs and scales. The Cytobrush technique has been shown to be more effective than scraping,<sup>3</sup> and vigorously rubbing with a moistened cotton swab (either with tap water or the Culturette transport medium) before inoculation into fungal culture medium is well-tolerated, easy, and reliable.<sup>4</sup> Nail scrapings and subungual debris can also be obtained for evaluation; nail clippings can be sent for histopathologic evaluation with special stains to demonstrate fungal elements.

Hair plucks tend to be traumatic for children and often cause hair shaft distortion, but gentle-traction hair pulling yields hair that is appropriate for determining whether alopecia areata is still active (hair-pull test) and for microscopic evaluation of the telogen bulbs of telogen effluvium and the distorted bulb and ruffled cuticle of loose anagen syndrome (see Chapter 7). Cutting the hair shafts may suffice for seeking hair shaft abnormalities via a microscopic trichogram (which may require polarizing light such as to detect trichothiodystrophy) and detecting nits of pediculosis versus hair casts (see Chapter 18).

Patch testing is key to determining or confirming triggers of delayed-type hypersensitivity reactions in children with allergic contact dermatitis (see Chapter 3). Round aluminum (Finn) chambers are taped to the back for 48 hours, and reactions are detected immediately after removal and generally twice thereafter to capture late reactivity. Although a ready-to-apply system is available (TRUE test), expanded testing is often necessary to comprehensively evaluate possible triggers and is usually best performed by dermatologists who have expertise in patch testing more comprehensively.

Although swabs of mucosae and of purulent skin material are appropriate for microbial cultures, obtaining biopsy material for special stains and cultures of suspected deep fungal or mycobacterial

infections is better for pathogen detection (see Therapeutic Procedures section). Biopsies are also important for making a diagnosis based on routine histopathologic, immunofluorescent, and/or immunohistochemical evaluation. For example, immunofluorescent testing is used to delineate the level of cleavage and absent skin proteins in epidermolysis bullosa (see Chapter 13), as well as to define the immune deposits and patterning in immunobullous disorders (see Chapter 13) and Henoch–Schönlein purpura (see Chapter 21); in contrast, immunohistochemistry is important for confirming the diagnosis of Langhans cells in histiocytosis (see Chapter 10) and a variety of cutaneous lymphoproliferative disorders. Clinicopathologic correlation is important, however, and the pathologic result should be questioned (or repeated) if not consistent with clinical findings.

## Therapeutic Procedures

The most common therapeutic procedures in pediatric dermatology are: (1) treatment of warts with cryotherapy; (2) treatment of molluscum with cantharidin or curettage; (3) lesional biopsy or excision; and (4) laser therapy. These techniques should only be performed by trained, experienced practitioners. Phototherapy with ultraviolet B (UVB) light, narrow-band UVB, and UVA light is used occasionally in children and is discussed in Chapter 19.

Cryotherapy involves the application of liquid nitrogen to lesional skin, which causes direct injury. It is most commonly used for warts (see Chapter 15) but can be selectively applied to keloids and molluscum contagiosum. Although spray delivery is possible, application with a cotton swab that is adapted with extra cotton to fit the size of the lesion allows better retention of the liquid nitrogen, provides better avoidance of nonlesional skin, and is less frightening for young children. More pedunculated lesions (or filiform warts) can be treated by grasping the lesion with a forceps and freezing the forceps near the tip rather than the lesion directly. Generally freezing is performed until there is a white ring around the lesion, often with two to three freeze-thaw cycles. Cryotherapy is painful and as a result is generally reserved for children 8 years of age and older. Alternative cryotherapy agents that contain dimethyl ether or chlorodifluoromethane achieve temperatures considerably lower than liquid nitrogen and are not as effective. Potential complications include hypopigmentation and atrophic scarring.

Cantharidin is an extract from the blister beetle, *Cantharis vesicatoria*, that leads to epidermal vesication after application to molluscum contagiosum lesions (see Chapter 15). It is applied precisely to the lesion using a wooden applicator, should not subsequently be occluded, and is rinsed off after 2 to 6 hours. Because the extent of blistering cannot be controlled (with some children developing extensive blisters and others virtually none, even with the same bottle of cantharidin and applicator), lesions near the eyes, on mucosae, and in occluded areas should not be treated with cantharidin. Blistering occurs in 24 to 48 hours, and crusting clears within about a week.

Curettage is a scraping technique used most commonly after topical anesthetic application for physical removal of molluscum contagiosum, especially for larger lesions for which cantharidin is less effective. Curettage can also be used after electrodesiccation (with a hyfrecator) to remove the desiccated tissue, most commonly for removal of a pyogenic granuloma (see Chapter 12). Most pediatric dermatologists avoid use of curettage in younger patients given the associated discomfort.

Biopsies and excisions are performed in pediatric patients as intervention, not just for diagnosis. The decision to remove a lesion therapeutically should be based on the indication and urgency for removal, the age and maturity of the pediatric patient, the location, and the expected cosmetic result. Careful explanation of the procedure to the parent(s) and child is important to allay concerns and manage expectations. If possible, the area to be biopsied or excised can be treated initially with a topical anesthetic cream (such as 4% lidocaine or 2.5% lidocaine/2.5% prilocaine) under a clear occlusive film to minimize any discomfort associated with subsequent injection of deeper anesthesia. Buffering the lidocaine with sodium bicarbonate and use of a 30-gauge needle also help to decrease the pain of injection; once buffered, lidocaine with epinephrine must either be kept refrigerated or

discarded after a week because of accelerated epinephrine degradation. Regional nerve blocks can be used selectively for larger excisions or cryotherapy. Distraction techniques such as conversation, listening to music, or watching a video can also allay fear at almost any age. Punch biopsy is most useful for removing lesions under 6 mm in diameter. For larger lesions and in cosmetically sensitive areas, an elliptical excision is preferred. Elliptical excisions ideally have their long axis following skin lines to minimize tension on the wound and to optimize the ultimate cosmetic appearance of the scar. Shave biopsies are appropriate for the superficial removal of skin tags (acrochordons) and more protuberant small nevi that are cosmetically problematic but can be followed by lesional regrowth and should not be performed if there is any concern about lesional atypia or malignancy. Surgical wounds of 4 mm or larger in diameter should be closed with suture; wounds which are 3 mm or less can be left to heal via secondary intention after hemostasis, although suturing of any lesion often gives a better cosmetic result. Although octylcyanoacrylates such as Dermabond are appropriate for closure of lacerations, the cosmetic result of their use in elective procedures may be suboptimal and is generally not recommended. Deep sutures are often required to close the deeper space of larger/deeper wounds (e.g., >6 mm in diameter) using buried absorbable suture materials. Although a variety of methods are available for closing at the surface, interrupted or running subcuticular suturing with nonabsorbable suture material is most often used. Steri-Strips are often used to further protect the wound from dehiscence.

The most common complications of biopsies and surgical excisions are wound infection, dehiscence, postoperative bleeding or hematoma (especially on the scalp), and contact dermatitis, especially to adhesives and topical antibiotics. Parents should be given clear, written postoperative instructions about keeping dressings in place (and the wound completely dry) for the first 48 hours, appropriate wound care thereafter, limitation in physical activity (generally 4 weeks without sports or gym if an excision), managing potential complications, and when to have sutures removed (typically 7 days for the face and 10 to 14 days on the body and extremities).

Light amplifications by stimulated emission of radiation (lasers) produce intense light energy at a specific wavelength that can be emitted as a pulse or continuous wave to target tissue components for destruction. After absorption of the light, heat is generated and the target tissue is selectively destroyed. This process of selective destruction has been called *selective photothermolysis* and carries the benefit of destruction of the target chromophores (substances that absorb specific wavelengths of light) with minimal damage to surrounding tissues.<sup>5</sup>

By far the most common laser utilized in children is the pulsed-dye laser (PDL; wavelength 585 to 595 nm), which targets hemoglobin and is used for a variety of vascular lesions including capillary malformations (port wine stains, salmon patches), macular (flat) infantile hemangiomas, ulcerated hemangiomas (in which case it helps speed reepithelialization), spider telangiectasias, and even small pyogenic

granulomas.<sup>6</sup> PDL has also been utilized (with more variable response) for inflammatory linear verrucous epidermal nevus, erythematous striae, warts, and even some inflammatory dermatoses such as psoriasis and eczema.

The response of a port wine stain to PDL therapy is variable and may depend on the depth of the dermal capillaries, location of the stain (i.e., central facial stains classically respond less to PDL therapy than lesions on the forehead or peripheral face), size of the stain, and age at the time treatment is initiated. Sequential treatment sessions are often necessary (generally at 4- to 8-week intervals), and multiple treatments may be necessary to achieve significant improvement.<sup>7</sup> Port wine stains located on the extremities tend to require more treatments than those located elsewhere.<sup>8</sup>

Other lasers utilized in pediatric patients include neodymium:yttrium aluminum garnet (Nd:YAG; 1064 nm), alexandrite (755 nm), diode (810 nm), Q-switched ruby (694 nm), and intense pulsed light (555 to 950 nm) lasers, which have shown variable benefit in port wine stains, venous malformations, deeper hemangiomas, and pigmented lesions (mongolian spots, nevus of Ota, Becker melanosis).<sup>5,9</sup> The xenon-chloride excimer laser (308 nm) provides a wavelength similar to narrow-band UVB therapy, with the advantage of being able to selectively treat a more targeted area of the skin. It has been demonstrated useful in psoriasis, vitiligo, and pityriasis alba.<sup>10-12</sup>

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## Neonatal Skin

The skin of the infant differs from that of an adult in that it is thinner (40% to 60%), is less hairy, and has a weaker attachment between the epidermis and dermis.<sup>1</sup> In addition, the body surface area-to-weight ratio of an infant is up to five times that of an adult. The infant is therefore at a significantly increased risk for skin injury, percutaneous absorption, and skin-associated infection. Premature infants born before 32 to 34 weeks' estimated gestational age may have problems associated with an immature stratum corneum (the most superficial cell layer in the epidermis), including an increase in transepidermal water loss (TEWL). This increased TEWL may result in morbidity because of dehydration, electrolyte imbalance, and thermal instability. Interestingly, in the majority of premature infants an acceleration of skin maturation occurs after birth such that most develop intact barrier function by 2 to 3 weeks of life.<sup>2</sup> However, in extremely low-birthweight infants, this process may take up to 4 to 8 weeks.<sup>3</sup> In light of the elevated TEWL levels seen in premature infants, a variety of studies have evaluated the use of occlusive dressings or topical emollients in an effort to improve compromised barrier function.<sup>4-7</sup>

The risk of percutaneous toxicity from topically applied substances is increased in infants, especially those born prematurely.<sup>8,9</sup> Percutaneous absorption is known to occur through two major pathways: (1) through the cells of the stratum corneum and the epidermal malpighian layer (the transepidermal route) and (2) through the hair follicle-sebaceous gland component (the transappendageal route). Increased neonatal percutaneous absorption may be the result of the increased skin surface area-to-weight ratio as well as the stratum corneum immaturity seen in premature neonates. Although transdermal delivery methods may be distinctly advantageous in certain settings, extreme caution must be exercised in the application of topical substances to the skin of infants, given the risk of systemic absorption and potential toxicity. Table 2-1 lists some compounds reported in association with percutaneous toxicity in infants and children.

## SKIN CARE OF THE NEWBORN

The skin of the newborn is covered with a grayish-white, greasy material termed *vernix caseosa*. The vernix represents a physiologic protective covering derived partially from secretions of the sebaceous glands and in part as a decomposition product of the infant's epidermis. Vernix contains protein, lipids, and water and provides water-binding free amino acids that facilitate the adaptation from amniotic fluid immersion *in utero* to the dry ambient postnatal state.<sup>10</sup> Although its function is not completely understood, it may act as a natural protective cream to "waterproof" the fetus *in utero*, where it is submerged in the amniotic fluid.<sup>11</sup> Some studies suggest that vernix be left on as a protective coating for the newborn skin and that it be allowed to come off by itself with successive changes of clothing (generally within the first few weeks of life). It has been suggested that vernix-based topical creams may be effective in augmenting stratum corneum repair and maturation in infants and could play a role in the treatment of epidermal wounds.<sup>12</sup>

The skin acts as a protective organ. Any break in its integrity therefore affords an opportunity for initiation of infection. The importance of skin care in the newborn is compounded by several factors:

1. The infant does not have protective skin flora at birth.
2. The infant has at least one and possibly two open surgical wounds (the umbilicus and circumcision site).

3. The infant is exposed to fomites and personnel that potentially harbor a variety of infectious agents.

Skin care should involve gentle cleansing with a nontoxic, nonabrasive neutral material. During the 1950s, the use of hexachlorophene-containing compounds became routine for the skin care of newborns as prophylaxis against *Staphylococcus aureus* infection. In 1971 and 1972, however, the use of hexachlorophene preparations as skin cleansers for newborns was restricted because of studies demonstrating vacuolization in the central nervous system (CNS) of infants and laboratory animals after prolonged application of these preparations.<sup>13</sup> At the minimum, neonatal skin care should include gentle removal of blood from the face and head, and meconium from the perianal area, by gentle rinsing with water. Ideally, vernix caseosa should be removed from the face only, allowing the remaining vernix to come off by itself. However, the common standard of care is for gentle drying and wiping of the newborn's entire skin surface, which is most desirable from a thermoregulatory standpoint. For the remainder of the infant's stay in the hospital nursery, the buttocks and perianal regions should be cleansed with water and cotton or a gentle cloth. A mild soap with water rinsing may also be used at diaper changes if desired.

There is no single method of umbilical-cord care that has been proven to limit colonization and disease. Several methods include local application of isopropyl alcohol, triple dye (an aqueous solution of brilliant green, proflavine, and gentian violet), and antimicrobial agents such as bacitracin or silver-sulfadiazine cream. The routine use of povidone-iodine should be discouraged, given the risk of iodine absorption and transient hypothyroxinemia or hypothyroidism. A safer alternative is a chlorhexidine-containing product.<sup>14</sup>

## Physiologic Phenomena of the Newborn

Neonatal dermatology, by definition, encompasses the spectrum of cutaneous disorders that arise during the first 4 weeks of life. Many such conditions are transient, appearing in the first few days to weeks of life only to disappear shortly thereafter. The appreciation of normal phenomena and their differentiation from the more significant cutaneous disorders of the newborn is critical for the general physician, obstetrician, and pediatrician, as well as for the pediatric dermatologist.

At birth, the skin of the full-term infant is normally soft, smooth, and velvety. Desquamation of neonatal skin generally takes place 24 to 36 hours after delivery and may not be complete until the third week of life. Desquamation at birth is an abnormal phenomenon and is indicative of postmaturity, intrauterine anoxia, or congenital ichthyosis.

The skin at birth has a purplish-red color that is most pronounced over the extremities. Except for the hands, feet, and lips, where the transition is gradual, this quickly changes to a pink hue. In many infants, a purplish discoloration of the hands, feet, and lips occurs during periods of crying, breath holding, or chilling. This normal phenomenon, termed *acrocyanosis*, appears to be associated with an increased tone of peripheral arterioles, which in turn creates vasoconstriction, secondary dilation, and pooling of blood in the venous plexuses, resulting in a cyanotic appearance to the involved areas of the skin. The intensity of cyanosis depends on the degree of oxygen loss and the depth, size, and fullness of the involved venous plexus. Acrocyanosis, a normal physiologic phenomenon, should not be confused with true cyanosis.

**Table 2-1** Reported Hazards of Percutaneous Absorption in Infants and Children

Compound	Product	Toxicity
Alcohols	Skin antiseptic	Cutaneous hemorrhagic necrosis, elevated blood alcohol levels
Aniline	Dye used as laundry marker	Methemoglobinemia, death
Adhesive remover solvents	Skin preparations to aid in adhesive removal	Epidermal injury, hemorrhage, and necrosis
Benzocaine	Mucosal anesthetic (teething products)	Methemoglobinemia
Boric acid	Baby powder, diaper paste	Vomiting, diarrhea, erythroderma, seizures, death
Calcipotriol	Topical vitamin D <sub>3</sub> analog	Hypercalcemia, hypercalcemic crisis
Chlorhexidine	Topical antiseptic	Systemic absorption but no toxic effects
Corticosteroids	Topical anti-inflammatory	Skin atrophy, striae, adrenal suppression
Diphenhydramine	Topical antipruritic	Central anticholinergic syndrome
Lidocaine	Topical anesthetic	Petechiae, seizures
Lindane	Scabicide	Neurotoxicity
Mercuric chloride	Diaper rinses; teething powders	Acrodynia, hypotonia
Methylene blue	Amniotic fluid leak	Methemoglobinemia
N, N-dimethyl- <i>m</i> -toluamide (DEET)	Insect repellent	Neurotoxicity
Neomycin	Topical antibiotic	Neural deafness
Phenolic compounds (pentachlorophenol, hexachlorophene, resorcinol)	Laundry disinfectant, topical antiseptic	Neurotoxicity, tachycardia, metabolic acidosis, methemoglobinemia, death
Phenylephrine	Ophthalmic drops	Vasoconstriction, periorbital pallor
Povidone-iodine	Topical antiseptic	Hypothyroidism
Prilocaine	Topical anesthetic	Methemoglobinemia
Salicylic acid	Keratolytic emollient	Metabolic acidosis, salicylism
Silver sulfadiazine	Topical antibiotic	Kernicterus (sulfa component), agranulocytosis, argyria (silver component)
Tacrolimus	Topical immunomodulator	Elevated blood levels of immunosuppressive medication
Triple dye (brilliant green, gentian violet, proflavine hemisulfate)	Topical antiseptic for umbilical cord	Ulceration of mucous membranes, skin necrosis, vomiting, diarrhea
Urea	Keratolytic emollient	Uremia

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## CUTIS MARMORATA

Cutis marmorata is a normal reticulated bluish mottling of the skin seen on the trunk and extremities of infants and young children (Fig. 2-1). This phenomenon, a physiologic response to chilling with resultant dilation of capillaries and small venules, usually disappears as the infant is rewarmed. Although a tendency for cutis marmorata may persist for several weeks or months, this disorder bears no medical significance and treatment generally is unnecessary. In some children cutis marmorata may tend to recur until early childhood, and in patients with Down syndrome, trisomy 18, and the Cornelia de Lange syndrome, this reticulated marbling pattern may be persistent. When the changes are persistent (even with rewarming) and are deep violaceous in color, cutis marmorata telangiectatica congenita (Fig. 2-2; see also Chapter 12) should be considered. In some infants a white negative pattern of cutis marmorata (cutis marmorata alba) may be created by a transient hypertonia of the deep vasculature. Cutis marmorata alba is also a transitory disorder and appears to have no clinical significance.

## HARLEQUIN COLOR CHANGE

Harlequin color change, not to be confused with harlequin ichthyosis (see Chapter 5), is occasionally observed in full-term infants but usually occurs in premature infants. It occurs when the infant is lying on his or her side and consists of reddening of one-half of the body with simultaneous blanching of the other half. Attacks develop suddenly and may persist for 30 seconds to 20 minutes. The side that lies uppermost is paler, and a clear line of demarcation runs along the midline of the body. At times, this line of demarcation may be



**Figure 2-1** Cutis marmorata. Reticulate bluish mottling that resolves with rewarming.

incomplete; when attacks are mild, areas of the face and genitalia may not be involved.

This phenomenon appears to be related to immaturity of hypothalamic centers that control the tone of peripheral blood vessels and has been observed in infants with severe intracranial injury as well as in infants who appear to be otherwise perfectly normal. Although the peak frequency of attacks of harlequin color change generally occurs between the second and fifth days of life, attacks may occur anywhere



**Figure 2-2** Cutis marmorata telangiectatica congenita. Violaceous, reticulate patches with subtle atrophy. These changes did not resolve with rewarming and were associated with mild ipsilateral limb hypoplasia.

from the first few hours to as late as the second or the third week of life.<sup>15</sup>

### BRONZE BABY SYNDROME

*Bronze baby syndrome* is a term used to describe infants who develop a grayish-brown discoloration of the skin, serum, and urine while undergoing phototherapy for hyperbilirubinemia. Although the exact source of the pigment causing the discoloration is not clear, the syndrome usually begins 1 to 7 days after the initiation of phototherapy, resolves gradually over a period of several weeks after phototherapy is discontinued, and appears to be related to a combination of photoisomers of bilirubin or biliverdin or a photoproduct of copper-porphyrin metabolism.<sup>16–18</sup> Infants who develop bronze baby syndrome usually have modified liver function, particularly cholestasis, of various origins.<sup>19</sup> Although not all babies with cholestasis develop bronze baby syndrome during phototherapy, those that do should be investigated for underlying liver disease.<sup>20</sup> The disorder should be differentiated from neonatal jaundice, cyanosis associated with neonatal pulmonary disorders or congenital heart disease, an unusual progressive hyperpigmentation (universal-acquired melanosis, the “carbon baby” syndrome),<sup>21</sup> and chloramphenicol intoxication (the “gray baby” syndrome), which is a disorder in infants with immature liver function who are unable to conjugate chloramphenicol and is characterized by elevated serum chloramphenicol levels, progressive cyanosis, abdominal distention, hypothermia, vomiting, irregular respiration, and vasomotor collapse.<sup>22</sup> A distinctive purpuric eruption on exposed skin has also been described in newborns receiving phototherapy and is possibly related to a transient increase in circulating porphyrins.<sup>23</sup> This condition, however, is unlikely to be confused with bronze baby syndrome.

### Cephalohematoma

A cephalohematoma is a subperiosteal hematoma overlying the calvarium. These lesions are more common after prolonged labor,



**Figure 2-3** Cephalohematoma. Note the sharp demarcation at the midline.

instrument-assisted deliveries, and abnormal presentations. They usually develop over the first hours of life and present as subcutaneous swellings in the scalp. They do not cross the midline (Fig. 2-3), because they are limited to one cranial bone, which helps to distinguish them from caput succedaneum (see the next paragraph). Occasionally, a cephalohematoma may occur over a linear skull fracture. Other potentially associated complications include calcification (that may persist radiographically for years), hyperbilirubinemia, and infection. Although infected lesions (which are rare) may require aspiration,<sup>24</sup> most lesions require no therapy with spontaneous resorption and resolution occurring over several months.

### Caput Succedaneum

Caput succedaneum is a localized edema of the newborn scalp related to the mechanical forces involved in parturition. It is probably related to venous congestion and edema secondary to cervical and uterine pressure, and as such is more common with prolonged parturition and seen most often in primigravidae. Caput succedaneum presents as a boggy scalp mass and may result in varying degrees of bruising and necrosis in addition to the edema, at times with tissue loss. In distinction to cephalohematoma, caput succedaneum lesions often cross the midline. These lesions tend to resolve spontaneously over 48 hours, and treatment is generally unnecessary. One possible complication in cases of severe caput succedaneum is permanent alopecia. *Halo scalp ring* refers to an annular alopecia that presents in a circumferential ring around the scalp in infants with a history of caput.<sup>25</sup> It represents a pressure necrosis phenomenon, and the hair loss may be transient or, occasionally, permanent.

### Complications from Fetal and Neonatal Diagnostic Procedures

Fetal complications associated with invasive prenatal diagnostic procedures include cutaneous puncture marks, scars or lacerations, exsanguination, ocular trauma, blindness, subdural hemorrhage, pneumothorax, cardiac tamponade, splenic laceration, porencephalic cysts, arteriovenous or ileocutaneous fistulas, digital loss (in 1.7% of newborns whose mothers had undergone early chorionic villus

sampling), musculoskeletal trauma, disruption of tendons or ligaments, and occasionally gangrene. Cutaneous puncture marks, which occur in 1% to 3% of newborns whose mothers have undergone amniocentesis, may be seen as single or multiple 1- to 6-mm pits or dimples on any cutaneous surface of the newborn (Fig. 2-4).<sup>26,27</sup>

Fetal scalp monitoring can result in infection, bleeding, or fontanel puncture, and prenatal vacuum extraction can produce a localized area of edema, ecchymosis, or localized alopecia. The incidence of scalp electrode infection varies from 0.3% to 5.0%, and although local sterile abscesses account for the majority of adverse sequelae, *S. aureus* or Gram-negative infections, cellulitis, tissue necrosis, subgaleal abscess, osteomyelitis, necrotizing fasciitis, and neonatal herpes simplex infections may also occur as complications of this procedure (Fig. 2-5).<sup>28–30</sup> It is not unusual for new parents to be under the false impression that fetal scalp electrodes are the cause of aplasia cutis congenita (ACC; see later in this chapter).

Scalp injuries sustained during the birth process tend to be minor and include lacerations, erosions, and ecchymoses. Injuries of the scalp and face occur in approximately 16% of vacuum-assisted deliveries and in 17% of forceps-assisted deliveries.<sup>31</sup>

Transcutaneous oxygen monitoring (application of heated electrodes to the skin for continuous detection of tissue oxygenation) and pulse oximetry may also result in erythema, tissue necrosis, and first- or second-degree burns. Although lesions associated with transcutaneous oxygen monitoring generally resolve within 48 to 60 hours,



**Figure 2-4** Amniocentesis scars. Multiple depressed scars on the thigh of an infant born to a mother who had amniocentesis during pregnancy. (Courtesy of Lester Schwartz, MD.)



**Figure 2-5** Staphylococcal scalp abscess. Fluctuant, erythematous nodule on the scalp of this 9-day-old infant as a complication of intrauterine fetal monitoring.

persistent atrophic hyperpigmented craters may at times be seen as a complication. Frequent (every 2 to 4 hours) changing of electrode sites and reduction of the temperature of the electrodes to 43° C, however, can lessen the likelihood of this complication.<sup>32,33</sup>

*Anetoderma of prematurity* refers to macular depressions or outpouchings of skin associated with loss of dermal elastic tissue seen in premature infants. Reports suggest that these cutaneous lesions may correlate with placement of electrocardiographic or other monitoring electrodes or leads.<sup>34,35</sup>

Calcinosis cutis may occur on the scalp or chest of infants or children at sites of electroencephalograph or electrocardiograph electrode placement, as a result of diagnostic heel sticks performed during the neonatal period, or after intramuscular or intravenous administration of calcium chloride or calcium gluconate for the treatment of neonatal hypocalcemia. Seen primarily in high-risk infants who receive repeated heel sticks for blood chemistry determinations, calcified nodules usually begin as small depressions on the heels. With time, generally after 4 to 12 months, tiny yellow or white papules appear (Fig. 2-6), gradually enlarge to form nodular deposits, migrate to the cutaneous surface, extrude their contents, and generally disappear spontaneously by the time the child reaches 18 to 30 months of age. Although calcified heel nodules are usually asymptomatic, children may at times show signs of discomfort with standing or wearing shoes. In such instances, gentle cryosurgery and curettage can be both diagnostic and therapeutic. Calcinosis cutis after electroencephalography or electrocardiography is more likely to be seen in infants and young children or individuals where the skin has been abraded and usually disappears spontaneously within 2 to 6 months. It can be avoided by the use of an electrode paste that does not contain calcium chloride, and like calcified heel sticks, they may be treated by gentle cryosurgery and curettage.<sup>36,37</sup>

## Abnormalities of Subcutaneous Tissue

Skin turgor is generally normal during the first few hours of life. As normal physiologic dehydration occurs during the first 3 or 4 days of life (up to 10% of birth weight), the skin generally becomes loose and wrinkled. Subcutaneous fat is normally quite adequate at birth and increases until about 9 months of age, thus accounting for the traditional chubby appearance of the healthy newborn. A decrease or absence of this normal panniculus is abnormal and suggests the possibility of prematurity, postmaturity, or placental insufficiency.

Sclerema neonatorum and subcutaneous fat necrosis (SCFN) are two disorders that affect the subcutaneous fat of the newborn. Although there is considerable diagnostic confusion between these two entities, there are several distinguishing features that enable a clinical differentiation (Table 2-2). Sclerema neonatorum seems to occur significantly less often than SCFN.



**Figure 2-6** Heel stick calcinosis. Firm, pink to yellow papule on the medial plantar heel in an infant who had multiple heel sticks as a newborn.

**Table 2-2** Features of Sclerema Neonatorum and Subcutaneous Fat Necrosis

Sclerema Neonatorum	Subcutaneous Fat Necrosis
Premature infants	Full-term or postmature infants
Serious underlying disease (sepsis, cardiopulmonary disease, diarrhea, or dehydration)	Healthy newborns; may have history of perinatal asphyxia or difficult delivery
Wax-like hardening of skin and subcutaneous tissue	Circumscribed, indurated, erythematous nodules and plaques
Whole body except palms and soles	Buttocks, thighs, arms, face, shoulders
Poor prognosis; high mortality	Excellent prognosis; treat associated hypercalcemia, if present

**Figure 2-7** Subcutaneous fat necrosis. Indurated, erythematous plaques on the shoulders and back of this 1-week-old boy.

## SCLEREMA NEONATORUM

Sclerema neonatorum is a diffuse, rapidly spreading, wax-like hardening of the skin and subcutaneous tissue that occurs in premature or debilitated infants during the first few weeks of life. The disorder, usually associated with a serious underlying condition such as sepsis or other infection, congenital heart disease, respiratory distress, diarrhea, or dehydration, is characterized by a diffuse nonpitting woody induration of the involved tissues. The process is symmetrical, usually starting on the legs and buttocks, and may progress to involve all areas except the palms, soles, and genitalia.<sup>38</sup> As the disorder spreads, the skin becomes cold, yellowish-white, mottled, stony hard, and cadaver-like. The limbs become immobile, and the face acquires a fixed mask-like expression. Infants with this disorder become sluggish, feed poorly, show clinical signs of shock, and in a high percentage of cases die.

Although the etiology of this disorder is unknown, it appears to represent a nonspecific sign of severe illness rather than a primary disease. Infants with this disorder are characteristically small or premature, debilitated, weak, cyanotic, and lethargic. In 25% of cases the mothers are ill at the time of delivery. Exposure to cold, hypothermia, peripheral chilling with vascular collapse, and an increase in the ratio of saturated to unsaturated fatty acids in the triglyceride fraction of the subcutaneous tissue (because of a defect in fatty acid mobilization) have been hypothesized as possible causes for this disorder but lack confirmation.<sup>39</sup>

The histopathologic findings of sclerema neonatorum consist of edema and thickening of the connective tissue bands around the fat lobules. Although necrosis and crystallization of the subcutaneous tissue have been described, these findings are more characteristically seen in lesions of SCFN.

The prognosis of sclerema neonatorum is poor, and mortality occurs in 50% to 75% of affected infants. In a series of 51 infants with sclerema neonatorum in a special-care nursery within a Bangladeshi hospital, the fatality rate was 98%.<sup>40</sup> In infants who survive, the cutaneous findings resolve without residual sequelae. There is no specific therapy, although steroids and exchange transfusion have been used.<sup>38</sup>

## SUBCUTANEOUS FAT NECROSIS

Subcutaneous fat necrosis (SCFN) is a benign, self-limited disease that affects apparently healthy, full-term newborns and young infants. It is characterized by sharply circumscribed, indurated, and nodular areas of fat necrosis (Fig. 2-7). The etiology of this disorder remains unknown but appears to be related to perinatal trauma, asphyxia, hypothermia, and in some instances, hypercalcemia.<sup>41,42</sup> Although the mechanism of hypercalcemia in SCFN is not known, it has been attributed to aberrations in vitamin D or parathyroid homeostasis. Birth asphyxia and meconium aspiration seem to be commonly associated. In one large series, 10 out of 11 infants with SCFN had been delivered via emergency cesarean section for fetal distress, and nine of the 11 had meconium staining of the amniotic fluid.<sup>43</sup> The relation-

ship between SCFN, maternal diabetes, and cesarean section, if any, is unclear. SCFN after ice-bag application for treatment of supraventricular tachycardia has been reported,<sup>44</sup> and it has also been observed after selective head or generalized cooling for hypoxic-ischemic encephalopathy.<sup>45,46</sup>

The onset of SCFN is generally during the first few days to weeks of life. Lesions appear as single or multiple localized, sharply circumscribed, usually painless areas of induration. Occasionally the affected areas may be tender, and infants may be uncomfortable and cry vigorously when they are handled. Lesions vary from small erythematous, indurated nodules to large plaques, and sites of predilection include the cheeks, back, buttocks, arms, and thighs. Many lesions have an uneven lobulated surface with an elevated margin separating it from the surrounding normal tissue. Histologic examination of SCFN reveals larger-than-usual fat lobules and an extensive inflammatory infiltrate, needle-shaped clefts within fat cells, necrosis, and calcification. Magnetic resonance imaging (MRI) reveals decreased T1 and increased T2 signal intensity in affected areas.<sup>47</sup>

The prognosis for SCFN is excellent. Although lesions may develop extensive deposits of calcium, which may liquefy, drain, and heal with scarring, most areas undergo spontaneous resolution within several weeks to months. Hypercalcemia is a rare association, and infants with this finding may require low calcium intake, restriction of vitamin D, and/or systemic corticosteroid therapy. Etidronate therapy has been reported for treatment of recalcitrant SCFN-associated hypercalcemia.<sup>48</sup> Infants should be monitored for several months after delivery, because the onset of hypercalcemia can be delayed for several months.<sup>43,49</sup> Other rare systemic complications may include thrombocytopenia, hypoglycemia, and hypertriglyceridemia, all of which tend to be mild and/or self-limited.

## Miscellaneous Cutaneous Disorders

### MILIARIA

Differentiation of the epidermis and its appendages, particularly in the premature infant, is often incomplete at birth. As a result of this immaturity, a high incidence of sweat-retention phenomena may be seen in the newborn. Miliaria, a common neonatal dermatosis caused by sweat retention, is characterized by a vesicular eruption with subsequent maceration and obstruction of the eccrine ducts. The pathophysiological events that lead to this disorder are keratinous plugging of eccrine ducts and the escape of eccrine sweat into the skin below the level of obstruction (see Chapter 8).

Virtually all infants develop miliaria under appropriate conditions. There are two principal forms of this disorder:

1. Miliaria crystallina (sudamina), which consists of clear superficial pinpoint vesicles without an inflammatory areola;



**Figure 2-8** Miliaria rubra. Multiple, erythematous, pinpoint macules and papules in an infant with atopic dermatitis who was being treated with overapplication of greasy emollients.



**Figure 2-9** Milia. Clustered, small, white papules on the lateral cheek.

2. Miliaria rubra (prickly heat), representing a deeper level of sweat gland obstruction and characterized by small discrete erythematous papules, vesicles, or papulovesicles (Fig. 2-8).

The incidence of miliaria is greatest in the first few weeks of life owing to the relative immaturity of the eccrine ducts, which favors poral closure and sweat retention. A pustular form of miliaria rubra has been observed in association with pseudohypoaldosteronism during salt-losing crises.<sup>50</sup>

Therapy for miliaria is directed toward avoidance of excessive heat and humidity. Light-weight cotton clothing, cool baths, and air conditioning are helpful in the management and prevention of this disorder. Avoidance of emollient overapplication (i.e., in infants with atopic dermatitis) should also be recommended, especially in warm, humid climates or in the winter when infants are bundled under heavy clothing.

## MILIA

Milia, small retention cysts, commonly occur on the face of newborns. Seen in 40% to 50% of infants, they result from retention of keratin within the dermis. They appear as tiny 1- to 2-mm pearly white or yellow papules. Particularly prominent on the cheeks, nose, chin, and forehead, they may be few or numerous and are often grouped (Fig. 2-9). Lesions may occasionally occur on the upper trunk, limbs, penis, or mucous membranes. Although milia of the newborn may persist into the second or third month, they usually disappear spontaneously during the first 3 or 4 weeks of life and accordingly require no therapy. Persistent milia in an unusual or widespread distribution, particularly when seen in association with other defects, may be a manifestation



**Figure 2-10** Sebaceous gland hyperplasia. Yellow-white, pinpoint papules on the nasal tip of this 2-day-old boy.

of hereditary trichodysplasia (Marie-Unna hypotrichosis), dystrophic forms of epidermolysis bullosa, Bazex or Rombo syndromes, or the oral-facial-digital syndrome, type I.

## BOHN NODULES AND EPSTEIN PEARLS

Discrete, 2- to 3-mm round, pearly white or yellow, freely movable elevations at the gum margins or midline of the hard palate (termed *Bohn nodules* and *Epstein pearls*, respectively) are seen in up to 85% of newborns. Clinically and histologically the counterpart of facial milia, they disappear spontaneously, usually within a few weeks of life, and require no therapy.

## SEBACEOUS GLAND HYPERPLASIA

Sebaceous gland hyperplasia represents a physiologic phenomenon of the newborn manifested as multiple, yellow to flesh-colored tiny papules that occur on the nose, cheeks, and upper lips of full-term infants (Fig. 2-10). A manifestation of maternal androgen stimulation, these papules represent a temporary disorder that resolves spontaneously, generally within the first few weeks of life.

## ACNE NEONATORUM

Occasionally infants develop a facial eruption that resembles acne vulgaris as seen in adolescents (Fig. 2-11). Although the etiology of this disorder is not clearly defined, it appears to develop as a result of hormonal stimulation of sebaceous glands that have not yet involuted to their childhood state of immaturity. In mild cases of acne neonatorum, therapy is often unnecessary; daily cleansing with soap and water may be all that is required. Occasionally, mild keratolytic agents or topical antibiotics may be helpful (see Chapter 8). Unusually severe or recalcitrant cases of acne neonatorum warrant investigation for underlying androgen excess.

A facial acneiform eruption in infants has been associated with the saprophytic *Malassezia* species and has been termed *neonatal cephalic pustulosis* (see Chapter 8). Lesions consist of pinpoint papules, papulopustules, or larger pustules, and they are located on the cheeks, chin, and forehead (Fig. 2-12). A correlation may exist between the clinical severity of lesions and the colonization with this fungal saprophyte.<sup>51,52</sup> In these infants, topical antifungal agents may lead to more rapid resolution of lesions.

## ERYTHEMA TOXICUM NEONATORUM

Erythema toxicum neonatorum (ETN), also known as *toxic erythema of the newborn*, is an idiopathic, asymptomatic, benign, self-limiting, cutaneous eruption in full-term newborns. Lesions consist of erythematous macules, papules, and pustules (Fig. 2-13), or a combination of these, and may occur anywhere on the body, especially the forehead, face, trunk, and extremities. The fact that these lesions



**Figure 2-11** Acne neonatorum. Erythematous papules and papulopustules on the cheek.



**Figure 2-12** Neonatal cephalic pustulosis. This 2-day-old male had numerous small and large pustules on the forehead, cheeks, and chin. They cleared rapidly over 1 week with ketoconazole cream.

(which histologically reveal follicular-centered eosinophils) often tend to spare the palms and soles may be explained by the absence of pilosebaceous follicles in these areas.

ETN often initially appears as a blotchy, macular erythema that then develops firm, 1- to 3-mm, pale yellow or white papules and pustules. The erythematous macules are irregular or splotchy in appearance, varying from a few millimeters to several centimeters in diameter. They may be seen in sharp contrast to the surrounding unaffected skin, may blend into a surrounding erythema, or may progress to a confluent eruption.

Although ETN appears most commonly during the first 3 to 4 days of life, it has been seen at birth and may be noted as late as 10 days of age.<sup>53</sup> Exacerbations and remissions may occur during the first 2 weeks of life, and the duration of individual lesions varies from a few hours to several days. The etiology of ETN remains obscure. One study suggested that it represents an immune response to microbial colonization of the skin at the hair follicle.<sup>54</sup> ETN incidence data are variable. Some authors report an incidence as low as 4.5%; others report incidences varying from 31% to 70% of newborns.<sup>55</sup> Two large prospective series of skin findings in newborns (one in the United States and



**Figure 2-13** Erythema toxicum neonatorum. Blotchy, erythematous macules and edematous papules.

one in Turkey) found incidences of 7% and 13.1%, respectively.<sup>56,57</sup> The incidence of ETN clearly appears to increase with increasing gestational age of the infant.<sup>58</sup> No sexual or racial predisposition has been noted.

ETN is usually diagnosed clinically. Skin biopsy, which is rarely necessary, reveals a characteristic accumulation of eosinophils within the pilosebaceous apparatus. The diagnosis can be rapidly differentiated from other newborn pustular conditions by cytologic examination of a pustule smear that with Wright or Giemsa staining reveals a predominance of eosinophils. Affected infants may have a peripheral eosinophilia. Although the eosinophilic response has led some observers to attribute the etiology of this disorder to a hypersensitivity reaction, specific allergens have never been implicated or confirmed.

Since erythema toxicum is a benign, self-limiting, asymptomatic disorder, no therapy is indicated. Occasionally, however, it may be confused with other pustular eruptions of the neonatal period, including transient neonatal pustular melanosis (TNPM), milia, miliaria, and congenital infections including candidiasis, herpes simplex, or bacterial processes. Of these, the congenital infections are the most important diagnostic considerations because of the implications for possible systemic involvement. Table 2-3 lists the differential diagnosis of the newborn with vesicles or pustules.

## EOSINOPHILIC PUSTULAR FOLLICULITIS

Eosinophilic pustular folliculitis (EPF) is an idiopathic dermatosis that occurs in both adults and infants. When it occurs in neonates or young infants, it may be clinically confused with other vesiculopustular disorders. Lesions consist of follicular pustules, most commonly occurring on the scalp and the extremities (Fig. 2-15). They tend to recur in crops, in a similar fashion to acropustulosis of infancy (see below), and some suggest that these conditions may be related.<sup>59,60</sup> As opposed to the adult form of EPF, the infancy-associated type does not reveal lesions grouped in an annular arrangement. EPF tends to present before 14 months of age in the majority of patients.<sup>61</sup> Histologic evaluation reveals an eosinophilic, follicular, inflammatory infiltrate, and peripheral eosinophilia may be present. EPF of infancy appears to be distinct from classic (adult) and human immunodeficiency virus (HIV)-associated EPF, although an infant with HIV and EPF has been reported.<sup>62</sup> Importantly, infantile EPF may occasionally be the presenting sign of hyperimmunoglobulinemia E syndrome (HIES) (see Chapter 3). Treatment for EPF is symptomatic, including topical corticosteroids and antihistamines, with eventual spontaneous resolution by 3 years of age in the majority of patients.<sup>61</sup> Topical tacrolimus may be useful in patients who are unresponsive to topical corticosteroids.<sup>63</sup>

## IMPETIGO NEONATORUM

Impetigo in newborns may occur as early as the second or third day or as late as the second week of life. It usually presents as a superficial

**Table 2-3** Differential Diagnosis of Vesicles or Pustules in a Newborn

Clinical Disorder	Comments
Acrodermatitis enteropathica	Periorificial erosive dermatitis common
Acropustulosis of infancy	Recurrent crops of acral pustules
Behçet syndrome	Oral and genital ulcers; may have cutaneous papules, vesicles, and pustules ( <b>Fig. 2-14</b> )
Eosinophilic folliculitis	Scalp and extremities most common sites
Epidermolysis bullosa	Trauma-induced blistering; bullae and erosions
Erythema toxicum neonatorum	Blotchy erythema, evanescent
Incontinentia pigmenti	XLD; linear and whorled patterns; may be vesicles, as well as warty lesions (hypopigmentation and hyperpigmentation occur later)
Infectious	
Bacterial	
Group A or B streptococci	
<i>Staphylococcus aureus</i>	Superficial blisters rupture easily
<i>Listeria monocytogenes</i>	
<i>Pseudomonas aeruginosa</i>	
Other Gram-negatives	
Fungal	
Candidiasis	Palms and soles involved; nail changes often present
Viral	
Herpes simplex	3 types: SEM, CNS, disseminated
Varicella zoster	
Cytomegalovirus	Blueberry muffin lesions more common
Spirochetal	
Syphilis	Red macules, papules; palm and sole scaling
Langerhans cell histiocytosis	Crusting, erosions, palms and soles, LAD
Miliaria	Especially intertriginous, occluded sites; crystallina type presents with clear vesicles without erythema; rubra type presents with red papules and papulopustules
Neonatal Behçet syndrome	
Neonatal cephalic pustulosis	Acneiform disorder, presenting with numerous pustules on the cheeks, forehead, chin; may respond to topical antifungal agents
Pustular psoriasis	
Scabies	Crusting, burrows; palms and soles usually involved
Transient neonatal pustular melanosis	Mainly affects black skin; peripheral collarettes; pigment persists for months
Urticaria pigmentosa	Stroking leads to urtication (Darier sign)
Vesiculopustular eruption of transient myeloproliferative disorder	Vesicles and pustules (face > elsewhere); usually in setting of trisomy 21

CNS, Central nervous system; LAD, lymphadenopathy; SEM, skin-eyes-mouth; XLD, X-linked dominant.



**Figure 2-14** Behçet syndrome. Shallow ulcerations on the scrotum, foreskin, and glans penis of an infant male with oral erosions and the human leukocyte antigen (HLA)-B51 group genotype. Note the associated papulopustular lesions on the medial thighs and buttocks, another characteristic feature of Behçet syndrome.



**Figure 2-15** Eosinophilic pustular folliculitis. Erythematous papules and pustules on the scalp of an infant female, who was subsequently diagnosed with hyperimmunoglobulinemia E syndrome.



**Figure 2-16** Neonatal *Staphylococcus aureus* pustulosis with multiple pustules in the diaper region. Note some superficial erosions with peripheral collarettes of scale. The culture was positive for *S. aureus*.

vesicular, pustular, or bullous lesion on an erythematous base. Vesicles and bullae are easily denuded, leaving a red, raw, and moist surface, usually without crust formation. Blisters are often wrinkled, contain some fluid, and are easily denuded. Lesions tend to occur on moist or opposing surfaces of the skin, as in the diaper area, groin, axillae, and neck folds. *S. aureus* pustulosis (or neonatal pustulosis) is a characteristic manifestation of cutaneous *S. aureus* infection in the neonate or infant. Patients have small pustules on an erythematous base (Fig. 2-16), often distributed in the diaper region. The lesions denude easily upon swabbing, and culture is positive for *S. aureus*. Streptococci may occasionally be causative. In term or late preterm neonates with localized involvement and without fever or systemic symptoms, evaluation for serious bacterial illness is generally not required, and treatment in the outpatient setting is often sufficient.<sup>64</sup> However, a complete blood cell count and blood culture is advisable given the rare association with bacteremia.

The term *pemphigus neonatorum* is an archaic misnomer occasionally applied to superficial bullous lesions of severe impetigo widely distributed over the surface of the body. However, a transient neonatal form of pemphigus vulgaris does exist and is caused by transplacental passage of antibodies from a mother with the same disease (see Chapter 13).

### SUCKING BLISTERS

Sucking blisters, presumed to be induced by vigorous sucking on the affected part *in utero*, are seen in up to 0.5% of normal newborns as 0.5- to 2-cm oval bullae or erosions on the dorsal aspect of the fingers, thumbs, wrists, lips, or radial aspect of the forearms. These lesions, which must be differentiated from bullous impetigo, epidermolysis bullosa, and herpes neonatorum, resolve rapidly and without sequelae.

### TRANSIENT NEONATAL PUSTULAR MELANOSIS

Transient neonatal pustular melanosis (TNPM) is a benign self-limiting disorder of unknown etiology characterized by superficial vesiculopustular lesions that rupture easily and evolve into hyperpigmented macules (Fig. 2-17). This disorder is seen in fewer than 1% of newborns<sup>65</sup> and occurs most commonly in infants with black skin. Lesions begin as superficial sterile pustules (Fig. 2-18) that rupture easily to leave a collarette of fine, white scale around a small hyperpigmented macule. Although the distribution may be diffuse, common areas of involvement include the inferior chin, forehead, neck, lower back, and shins. Rarely, vesicles that do not progress to pigmented macules may be detected on the scalp, palms, and soles.

Wright-stained smears of the pustules of TNPM, in contrast to lesions of ETN, demonstrate variable numbers of neutrophils, few or



**Figure 2-17** Transient neonatal pustular melanosis. Papules and papulopustules that rupture to leave a collarette of fine scales and eventual hyperpigmentation. (Courtesy of Nancy B. Esterly, MD.)



**Figure 2-18** Transient neonatal pustular melanosis. Tense pustules and collarettes of scale at sites of older lesions.

no eosinophils, and cellular debris. Histopathologic evaluation is usually unnecessary.

TNPM is a benign disorder without associated systemic manifestations, and therapy is unnecessary. The pustular lesions usually disappear within 24–48 h, leaving behind hyperpigmented macules that fade gradually, usually over several weeks to months. Occasionally, newborns may have solely the hyperpigmented macules, in which case it is presumed that the pustular phase occurred (and resolved) *in utero*.

### ACROPUSTULOSIS OF INFANCY

Acropustulosis of infancy, also known as *infantile acropustulosis* (IA), is an idiopathic pustular disorder with onset usually between birth and 2 years of age. It is characterized by recurrent, pruritic, vesiculopustular lesions that recur every few weeks to months. The lesions begin as pinpoint erythematous papules and enlarge into well-circumscribed discrete pustules.<sup>66</sup> They are concentrated on the palms (Fig. 2-19) and soles (Fig. 2-20) and appear in lesser numbers on the dorsal aspect of the hands, feet, wrists, and ankles. Occasional lesions may occur on the face and scalp.

The differential diagnosis of IA includes scabies, dyshidrotic eczema, pustular psoriasis, ETN, TNPM, impetigo, and subcorneal pustular dermatosis. However, the characteristic presentation and course of IA is usually distinctive enough to render a clinical diagnosis. A smear of pustule contents (or histologic evaluation) reveals large numbers of neutrophils and occasionally eosinophils.<sup>66–69</sup> Although the etiology of IA remains unclear, several authors have noted a possible



**Figure 2-19** Acropustulosis of infancy. Multiple tense erythematous papules and pustules on the palm of this 4-month-old girl.



**Figure 2-20** Acropustulosis of infancy. Tense pustules, some of which have ruptured, on the plantar and lateral surfaces of the foot of a 14-month-old female.

association with preceding scabies infestation.<sup>70-72</sup> IA appears to be common in internationally adopted children.<sup>73</sup>

Patients with IA experience fewer and less intense flares of their lesions with time, and the entire process usually subsides within 2 to 3 years. Pruritus, however, may be severe early in the course, making therapy desirable. Possible associations include irritability, sleeplessness, excoriation, and secondary bacterial infection. Systemic antihistamines, usually in high doses, may relieve pruritus. High-potency topical corticosteroids are quite effective for this condition,<sup>70</sup> and given the limited distribution of lesions, the epidermal thickness at affected (acral) sites, and the periodicity of flares, concerns regarding systemic absorption of these medications should be minimal. Dapsone has long been a recommended therapy for severe cases, but the risk-to-benefit ratio of this agent is not generally justified in patients with IA.

#### CONGENITAL EROSION AND VESICULAR DERMATOSIS

Congenital erosive and vesicular dermatosis healing with reticulated supple scarring is an uncommon disorder characterized by erosive and



**Figure 2-21** Congenital erosive and vesicular dermatosis healing with reticulated supple scarring. There is generalized, supple, reticulated scarring. Note also the associated scalp alopecia.

bullous lesions that, as the name implies, are present at birth and heal with characteristic scarring. Although its cause is unknown, it appears to represent a nonhereditary intrauterine event such as infection or amniotic adhesions, or perhaps an unusual healing defect of immature skin. The disorder generally involves skin of the trunk, extremities, scalp, face, and occasionally the tongue, with sparing of the palms and soles.

Congenital erosive and vesicular dermatosis occurs most often in premature infants and presents with extensive cutaneous ulcerations and intact vesicles that develop crusting and then heal during the first month of life. Occasionally, blistering may continue to occur beyond infancy.<sup>74,75</sup> Generalized, supple, reticulated scars occur with alternating elevated and depressed areas (Fig. 2-21). Up to 75% of the cutaneous surface may be involved, and the skin lesions have been described as having depressed hypopigmented regions alternating with normal to hyperpigmented zones.<sup>76,77</sup> Scars on the trunk and head, which often have a cobblestone-like appearance, may be oriented along the cutaneous lines of cleavage; on the limbs they tend to follow the long axes of the extremities.<sup>77-79</sup> Facial involvement was present in roughly 50% of published cases in one review.<sup>80</sup> Although the eyebrows are usually normal, alopecia may be noted on the scalp. Nails may be absent or hypoplastic, and affected areas on the tongue may manifest scarring and absence of papillae. Dentition is usually normal. Hyperthermia, especially in warm weather or after exertion, is common and although sweating is absent in scarred areas, compensatory hyperhidrosis in normal-appearing skin may be noted. Chronic conjunctivitis is a major continuing problem for these patients, and corneal scarring may occur.<sup>74,76</sup> Some patients have also been found to have neurologic defects, including mental and motor retardation, hemiparesis, microcephaly, pachygyria, cerebral palsy, and seizures.<sup>76,80</sup>

#### SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a common, self-limiting condition of the scalp, face, ears, trunk, and intertriginous areas characterized by greasy scaling, redness, fissuring, and occasional weeping. It appears to be related to the sebaceous glands and has a predilection for so-called "seborrheic" areas where the density of these glands is high. It usually presents in infants with a scaly dermatitis of the scalp termed *cradle cap* (Fig. 2-22) and may spread over the face, including the forehead, ears, eyebrows, and nose. Other areas of involvement include the intertriginous zones, umbilicus, and anogenital region



**Figure 2-22** Seborrheic dermatitis of the scalp (cradle cap). Erythema and greasy yellow scales involving the scalp of an infant male who also had similar changes in the eyebrows.



**Figure 2-23** Seborrheic dermatitis. Erythema of the medial thighs, suprapubic region and buttocks. This presentation can be difficult to distinguish from infantile psoriasis, but the scaling tends to be more mild and the response to topical anti-inflammatory therapy more brisk. The whitish debris in this child represents the barrier cream that his parents had applied rather than scaling.

(Fig. 2-23). (For a more detailed discussion of seborrheic dermatitis and its therapy, see Chapter 3.)

### LEINER DISEASE

The term *Leiner disease* refers to a shared phenotype for a number of nutritional and immunologic disorders characterized by severe seborrheic dermatitis with exfoliation, failure to thrive, and diarrhea. The disorder may occur during the first week of life but generally starts around 2 to 4 months of age. Patients are particularly prone to recurrent yeast and Gram-negative infections. Among disorders that may show this phenotype are: deficiency or dysfunction of complement, Bruton agammaglobulinemia, severe combined immunodeficiency, and HIES.<sup>81-85</sup>

### DIAPER DERMATITIS

Diaper dermatitis is perhaps the most common cutaneous disorder of infancy and early childhood. The term is used to describe an acute

### Box 2-1 Differential Diagnosis of Diaper Dermatitis

- Chafing dermatitis
- Irritant contact dermatitis
- Diaper candidiasis
- Seborrheic dermatitis
- Psoriasis
- Intertrigo
- Jacquet dermatitis
- Perianal pseudoverrucous papules and nodules
- Miliaria
- Folliculitis
- Impetigo
- Scabies
- Nutritional deficiency (i.e., acrodermatitis enteropathica, cystic fibrosis, biotin deficiency)
- Allergic contact dermatitis
- Atopic dermatitis
- Granuloma glutaeale infantum
- Langerhans cell histiocytosis
- Burns
- Child abuse
- Epidermolysis bullosa
- Congenital syphilis
- Varicella/herpes
- Tinea cruris
- Chronic bullous dermatosis of childhood
- Bullous mastocytosis

inflammatory skin reaction in the areas covered by the diaper. The incidence of diaper dermatitis is estimated to be between 7% and 35%, with a peak incidence at 9 to 12 months of age.<sup>86-88</sup>

The term *diaper rash* is commonly used as a diagnosis, as though the diverse dermatoses that may affect this region constitute a single clinical entity. In actuality, diaper dermatitis is not a specific diagnosis and is best viewed as a variable-symptom complex initiated by a combination of factors, the most significant being prolonged contact with urine and feces, skin maceration, and, in many cases, secondary infection with bacteria or *Candida albicans*. Although diaper dermatitis may often be no more than a minor nuisance, eruptions in this area may not only progress to secondary infection and ulceration but may become complicated by other superimposed cutaneous disorders or represent a manifestation of a more serious disease.

The three most common types of diaper dermatitis are chafing dermatitis, irritant contact dermatitis, and diaper candidiasis. However, the differential diagnosis of diaper dermatitis is broad (Box 2-1). In patients in whom a response to therapy is slow or absent, alternative diagnoses should be considered and appropriate diagnostic evaluations performed. The following sections contain a brief discussion of several potential causes of diaper dermatitis. Many of these entities are discussed in more detail in other chapters.

### Chafing Dermatitis

The most prevalent form of diaper dermatitis is the chafing or frictional dermatitis that affects most infants at some time. Generally present on areas where friction is the most pronounced (the inner surfaces of the thighs, the genitalia, buttocks, and the abdomen), the eruption presents as mild redness and scaling and tends to wax and wane quickly. This form responds quickly to frequent diaper changes and good diaper hygiene.

### Irritant Contact Dermatitis

Irritant contact diaper dermatitis usually involves the convex surfaces of the buttocks, the vulva, the perineal area, the lower abdomen, and the proximal thighs, with sparing of the intertriginous creases (Fig. 2-24). The disorder may be attributable to contact with proteolytic enzymes in stool and irritant chemicals such as soaps, detergents, and topical preparations. Other significant factors appear to be excessive heat, moisture, and sweat retention associated with the warm local environment produced by the diaper.



**Figure 2-24** Irritant contact diaper dermatitis. Erythema of the vulva, buttocks, and medial thighs. The inguinal creases were relatively spared.

The etiology of irritant contact diaper dermatitis is multifactorial, and past hypotheses have included potential roles for ammonia, bacteria and bacterial products, and urine pH. In 1921 when Cooke demonstrated that an aerobic Gram-positive bacillus (*Bacillus ammoniagenes*) was capable of liberating ammonia from urea, this organism was pinpointed as the etiologic agent of most diaper dermatoses.<sup>89</sup> More recent studies, however, have refuted the role of urea-splitting bacteria in the etiology of this disorder and incriminate a combination of wetness, frictional damage, impervious diaper coverings, and increase in skin pH. It is suggested that urinary wetness increases the permeability of the skin to irritants as well as the pH of the diaper environment, thus intensifying the activities of the fecal proteases and lipases, the major irritants responsible for this disorder.<sup>90,91</sup>

Several technological innovations in the design of disposable diapers and other diapering products have aimed to reduce moisture and irritancy in this environment, thus decreasing the risk of irritant dermatitis. The introduction of absorbent gelling materials into diaper technology was one such breakthrough and has been shown to result in less diaper dermatitis than conventional cellulose-core disposable diapers.<sup>92</sup> Other recent innovations include nonirritating disposable diaper wipes and diapers designed to deliver petrolatum-based formulations to the skin.<sup>93</sup>

A blistering, erosive contact dermatitis has been observed after oral ingestion (either intentional or accidental) of senna-containing laxatives.<sup>94,95</sup> Patients typically have well-demarcated, diamond-shaped eroded plaques with desquamation that in some cases initially could be mistaken for scalding burns. Prolonged contact with stool (i.e., via overnight wearing of the diaper) is often reported.

#### Allergic Contact Dermatitis

Although not traditionally considered a common cause for diaper dermatitis, allergic contact dermatitis has received increasing attention in the literature in recent years (see Chapter 3). Potential associations to consider include chemical constituents of the diaper (rubber additives, rubber accelerator compounds, adhesive resins), topically applied diaper products such as emollients and "butt balms" (emulsifiers), and baby wipes (fragrances and preservatives).<sup>96,97</sup> Disperse dyes, which are used to impart color to synthetic fabrics, can also be contact sensitizers and are found in some disposable diapers.

#### Diaper Candidiasis

Candidal (monilial) diaper dermatitis is a commonly overlooked disorder and should be suspected whenever a diaper rash fails to respond to usual therapeutic measures. Cutaneous candidiasis is a possible sequela of systemic antibiotic therapy and should be considered in any diaper dermatitis that develops during or shortly after antibiotic administration.<sup>98</sup>

Candidal diaper dermatitis presents as a widespread, beefy-red erythema on the buttocks, lower abdomen, and inner aspects of the



**Figure 2-25** Diaper candidiasis. Beefy-red, erythematous plaques with multiple red satellite papules and papulopustules.



**Figure 2-26** Oral candidiasis (thrush). Gray-white, cheesy patches and plaques of the buccal mucosa, tongue, and gingiva.

thighs. Characteristic features include a raised edge, sharp marginalization with white scales at the border, and pinpoint pustulovesicular satellite lesions (the diagnostic hallmark) (Fig. 2-25). Although cutaneous candidiasis commonly occurs in association with oral thrush (Fig. 2-26), the oral mucosa may be uninvolved. Infants harbor *C. albicans* in the lower intestine, and it is from this focus that infected feces present the primary source for candidal diaper eruptions.

If necessary, the diagnosis of candidal diaper dermatitis may be confirmed by microscopic examination of a potassium hydroxide preparation of skin scrapings, which reveals egg-shaped budding yeasts and hyphae or pseudohyphae. Growth of yeast on Sabouraud medium implanted with skin scrapings can also confirm the diagnosis, usually within 48 to 72 hours.

#### Seborrheic Dermatitis

Seborrheic dermatitis of the diaper area may be recognized by the characteristic salmon-colored, greasy plaques with a yellowish scale and a predilection for intertriginous areas (see above). Coincident involvement of the scalp, face, neck, and postauricular and flexural areas helps to establish the diagnosis. Seborrheic dermatitis of the diaper region may be difficult to distinguish from psoriasis.



**Figure 2-27** Psoriasis (diaper). Sharply demarcated, erythematous, scaly plaques involving the genitals and suprapubic region in this infant male.



**Figure 2-29** Acrodermatitis enteropathica. Eroded, erythematous patches and plaques in this 4-month-old boy with zinc deficiency. Note the associated balanoposthitis.



**Figure 2-28** Jacquet dermatitis. Severe diaper area erythema with ulcerated papules and islands of reepithelialization.

## Psoriasis

Psoriasis of the diaper area must also be considered in persistent diaper eruptions that fail to respond to otherwise seemingly adequate therapy (Fig. 2-27). The sharp demarcation of lesions suggests diaper area psoriasis, but the typical scaling of psoriasis may be obscured because of the moisture of the diaper region. The presence of nail changes and red, well-margined plaques with silvery mica-like scales on the trunk, face, axillae, umbilicus, or scalp may help confirm this diagnosis (see Chapter 4), although affected infants may have involvement limited to the diaper area.

## Intertrigo

Intertrigo (see Chapter 17) is a common skin eruption in the diaper area, particularly in hot weather or when infants are overdressed. It usually involves the inguinal creases, the intergluteal area, and the thigh creases (especially in chubby babies), and presents as bright red erythema often with a mild white-yellow exudate. Nondiapered areas of involvement include the anterior neck fold and the axillae.

## Jacquet Dermatitis

The term *Jacquet dermatitis* is used to describe a severe erosive diaper eruption with ulcerated papules or nodules (Fig. 2-28). In male infants, erosion and crusting of the glans penis and urinary meatus may result in painful or difficult urination.

## Perianal Pseudoverrucous Papules and Nodules

This is an eruption composed of verrucous (wart-like) papules has been observed to occur in children with incontinence of stool or urine. These patients have verrucous papules and nodules of the perianal and suprapubic regions, possibly representing a distinct reaction to severe irritant diaper dermatitis. Reported patients had a history of delayed ileoanal anastomosis for Hirschsprung disease, encopresis, or urinary incontinence.<sup>99–101</sup> The importance of this diagnosis lies in differentiating it from condylomata acuminata or other more serious dermatoses.

## Acrodermatitis Enteropathica

Acrodermatitis enteropathica, a disorder of zinc deficiency, may mimic a severe irritant contact dermatitis in the diaper area (see Chapter 24). Patients have a periorificial erosive dermatitis that is often most accentuated in the diaper region (Fig. 2-29) but also may involve the peri-oral face. Erythema and pustules may involve intertriginous or acral sites, and diarrhea, failure to thrive, and alopecia are commonly present.

## Langerhans Cell Histiocytosis

Lesions of Langerhans cell histiocytosis (LCH; see Chapter 10) may also have a predilection for the diaper area. This eruption, which often presents in a seborrheic dermatitis-like fashion, classically involves the groin, axillae, and retroauricular scalp. Palms and soles may also be involved. Characteristic lesions consist of yellowish to red-brown papules, often with concomitant erosive or purpuric qualities (Fig. 2-30). LCH should be considered in any infant with a recalcitrant or hemorrhagic seborrheic dermatitis-like eruption and/or flexural papules with discrete erosions. Lymphadenopathy is common, and multiorgan involvement (especially bones, liver, lung, mucosa, and middle ear) is possible. Skin biopsy with special stains for Langerhans cells is diagnostic.

## Treatment of Diaper Dermatitis

Before any consideration for therapy of diaper dermatitis, the appropriate etiology must be identified. Educating parents that diaper dermatitis is often recurrent is vital in an effort to prevent perceived management failure. The primary goals in preventing and treating diaper dermatitis include keeping the skin dry, protected, and infection-free.<sup>102</sup>

The primary goal in irritant or chafing dermatitis is to keep the area as clean and dry as possible. Frequent diaper changes, gentle cleansing with a moistened soft cloth or fragrance-free diaper wipe, exposure to air whenever possible, and the judicious use of topical therapy may be sufficient in most cases. Zinc oxide and petrolatum-based formulations tend to be most effective in forming a barrier to further skin contact with urine and feces. These products should be applied at every diaper



**Figure 2-30** Langerhans cell histiocytosis. Red-brown, purpuric eroded papules in a 3-month-old male. Note intertrigo-like erythema of the inguinal creases with superficial erosions.

change when acute dermatitis is present. Parents should be taught that cleansing the diaper area is necessary only when stool is present, as overwashing in itself can lead to irritation. A low-potency, nonfluorinated topical corticosteroid (i.e., 1% hydrocortisone) applied two to three times daily is appropriate until improvement is noted. Stronger steroids and combination antifungal-corticosteroid preparations should be avoided, given risks of local cutaneous side effects and, more importantly, systemic absorption because of increased skin penetration from occlusion effect.

Secondarily infected (bacterial) dermatitis should be treated with the appropriate systemic antibiotic. Candidal infection requires the use of a topical antifungal agent (i.e., nystatin, clotrimazole, econazole, miconazole). If there is evidence of *Candida* in the mouth (i.e., thrush) as well as the diaper area, topical therapy may be supplemented by oral nystatin. Oral fluconazole is useful for severe cutaneous candidiasis. Although gentian violet has been used for decades for the treatment of oral and diaper candidiasis, reports of bacterial infection and hemorrhagic cystitis in addition to the staining associated with its use suggest that gentian violet be avoided.<sup>103,104</sup> A combination product (0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum) is also available, has demonstrated efficacy, and offers the advantage of convenience.

### GRANULOMA GLUTEALE INFANTUM

Granuloma gluteale infantum is a benign disorder of infancy characterized by purple-red nodules in the skin of the groin, lower abdomen, and inner thighs (Fig. 2-31). Patients have usually received preceding therapy with topical corticosteroids. Although the appearance of these lesions may suggest a malignant process, granuloma gluteale infantum seems to represent a unique response to local inflammation, maceration, and possibly secondary infection (usually *C. albicans*). A similar eruption has been observed in elderly adults.<sup>105</sup> Histologic evaluation of biopsy tissue from granuloma gluteale infantum reveals a nonspecific inflammatory infiltrate, sometimes with giant cells.<sup>106,107</sup>

Lesions of granuloma gluteale infantum resolve completely and spontaneously within a period of several months after treatment of the initiating inflammatory process. Although intralesional corticosteroids or steroid-impregnated tape have been used, such therapy is not recommended.

## Developmental Abnormalities of the Newborn

### SKIN SIGNS OF OCCULT SPINAL DYSRAPHISM

Spinal dysraphism is a spectrum of disorders defined by absent or incomplete fusion of the midline bony elements and may include congenital spinal-cord anomalies.<sup>108</sup> Because occult spinal dys-



**Figure 2-31** Granuloma gluteale infantum. Erythematous to violaceous papulonodules on the labia majora of this infant with a history of potent topical corticosteroid use in the diaper region.



**Figure 2-32** Lumbosacral port wine stain associated with occult spinal dysraphism. Note the associated central depression in this boy who also had an underlying tethered spinal cord.

phism (OSD) can lead to irreversible neurologic complications, early recognition is desirable. Cutaneous or subcutaneous stigmata may be the presenting sign of OSD, and as such, a working knowledge of potentially associated lesions is vital. Lumbosacral skin lesions that may be associated with OSD and spinal cord defects include hypertrichosis (the classic "faun tail" or finer, lanugo hair), lipomas, vascular lesions (infantile hemangioma, port wine stain; Fig. 2-32), prominent sacral dimples, sinuses, appendages (skin tag, tail), ACC, and melanocytic nevi.<sup>109</sup> Gluteal cleft asymmetry or deviation is another useful finding. The presence of multiple findings increases the risk of OSD.<sup>110</sup> In one study, 11 of 18 patients with two or more congenital midline skin lesions had OSD, and the most common midline cutaneous lesions to be associated with OSD were lipomas (either isolated or in combination with other lesions).<sup>111</sup> In a prospective study of infants with lumbosacral infantile hemangiomas, the overall relative risk for spinal anomalies was 640; importantly, 35% of the infants with an isolated lumbosacral hemangioma (and no additional cutaneous findings) had spinal anomalies.<sup>112</sup>

The majority of simple midline dimples are not associated with OSD. Atypical dimples (>5 mm in size, further than 2.5 cm from the anus, associated with other lumbosacral lesions), on the other hand, have a significant risk of associated OSD.<sup>110</sup> The association of nevus simplex (small, dull-pink, vascular malformation, most commonly seen on the occipital scalp, glabella, or eyelids) of the sacrum and OSD is unclear, although most agree that these lesions, when occurring alone, do not predict an increased risk of underlying malformations. Cervical

OSD is significantly less common, and in those cases associated with cutaneous stigmata, more than one lesion is usually present.<sup>113</sup> It is important to remember that an isolated nevus simplex ("stork bite") of the posterior nuchal or occipital region is *not* an indicator of underlying OSD.

When OSD is being considered, radiographic imaging must be performed. MRI is the diagnostic modality of choice, especially with higher-risk cutaneous findings. Ultrasound screening may be considered in infants younger than 4 months (before ossification of the vertebral bodies is complete), with the advantages being that it is noninvasive and does not require sedation. However, ultrasonography is limited in that small cord lesions (i.e., lipomas or dermal sinus tracts) may be missed,<sup>110</sup> and the overall sensitivity is quite dependent on the experience of the ultrasonographer. In a study of 41 infants with lumbosacral infantile hemangioma, the sensitivity of ultrasound scanning in detecting spinal anomalies was only 50%, with a specificity of 77.8%.<sup>112</sup> In infants with low-risk lesions such as simple dimples or gluteal cleft deviation and without other high-risk findings (i.e., hypertrichosis, skin tags, lipoma, or other mass), the need for imaging is unclear. If it is performed, however, ultrasound may provide a reliable screening when interpreted by an experienced pediatric radiologist.<sup>114</sup> Early neurosurgical referral is indicated if underlying defects are diagnosed.

### DRUG-INDUCED FETAL SKIN MALFORMATIONS

There are numerous drugs, including alcohol, hydantoin, valproic acid, warfarin, aminopterin, and isotretinoic acid, that when taken by pregnant women produce an adverse effect on the fetus and newborn. Exposure to these drugs *in utero* may result in a variety of organ malformations, although specific skin malformations are rare. Teratogenic risks as they relate to skin have most commonly focused on antithyroid drugs, especially methimazole (MMI), and their possible role in causing ACC, (see below).

### CONGENITAL HEMIHYPERTROPHY

Idiopathic congenital hemihypertrophy is a developmental defect in which one side of the body is larger than the other. Although differences in symmetry are often detectable during the newborn period, they usually become more striking with growth of the child. The cutaneous findings most often associated with hemihypertrophy are hyperpigmentation, telangiectasia, abnormal nail growth, and hypertrichosis (Fig. 2-33). Body temperature and sweating differences have also been reported in patients with this disorder.<sup>115</sup>

Of particular significance is the fact that about 50% of persons with hemihypertrophy may have associated anomalies, including Wilms tumor, aniridia, cataracts, ear deformities, internal hemangiomas, genitourinary tract anomalies, adrenocortical neoplasms, and brain tumors. Therefore patients who exhibit congenital hemihypertrophy should be evaluated for potentially associated conditions. Associated tumors most commonly involve the kidney, adrenal gland, and liver.<sup>116</sup> In patients with hemihypertrophy combined with cutaneous vascular malformations (i.e., port wine stain), the possibility of Klippel-Trénaunay syndrome, Proteus syndrome, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal and spinal anomalies (CLOVES) syndrome, or another syndrome comprising a vascular anomaly with hypertrophy should be considered (see Chapter 12).

### APLASIA CUTIS CONGENITA

Aplasia cutis congenita (ACC) is a congenital defect of the skin characterized by localized absence of the epidermis, dermis, and at times, subcutaneous tissues. Although ACC generally occurs on the scalp, it may also involve the skin of the face, trunk, and extremities. The diagnosis of ACC is usually a clinical one, and the histologic picture varies. Although most cases appear to be sporadic, a variety of potential associations including teratogens, limb abnormalities, epidermal nevi, underlying embryologic malformations, epidermolysis bullosa, malformation syndromes, and infections have been proposed.<sup>117</sup>

ACC classically presents as solitary or multiple, sharply demarcated, weeping or granulating, oval to circular, stellate defects ranging from



**Figure 2-33** Congenital hemihypertrophy with hypertrichosis. (From Hurwitz S, Klaus SN. Congenital hemihypertrophy with hypertrichosis. Arch Dermatol 1971;103:98–100. ©1971 American Medical Association. All rights reserved.)



**Figure 2-34** Aplasia cutis congenita. Sharply demarcated ulceration on the scalp of an infant with this disorder.

1 to 3 cm in diameter. Some 70% of scalp lesions are isolated, 20% are double, and in 8% of patients three or more defects may be present.<sup>118</sup> The most common location for ACC is the scalp, and in those cases 80% occur in close proximity to the hair whorl.<sup>119</sup> Although aplasia cutis may also affect the occiput, the postauricular areas, and the face, involvement of these areas appears to be relatively uncommon. Whereas most scalp defects are small, larger lesions may occur and can extend to the dura or the meninges. Although treatment is generally unnecessary, large scalp lesions (i.e., >4 cm<sup>2</sup>) may require surgery with grafting to prevent the potential complications of hemorrhage, venous (sagittal sinus) thrombosis, and meningitis.

At birth, the skin defect may vary from an ulceration with a granulating base (Fig. 2-34) to a superficial erosion or even a well-formed scar. As healing of open lesions occurs, the defect is replaced by



**Figure 2-35** Aplasia cutis congenita. Healed scar with alopecia near the hair whorl in this 8-month-old girl.

smooth, hairless scar tissue (Fig. 2-35), although sometimes the tissue is raised and keloidal. Some lesions may present as a translucent, glistening membrane (membranous aplasia cutis) and when surrounded by a ring of long, dark hair (the “hair collar sign”) may represent a forme fruste of a neural tube defect.<sup>120</sup> This membranous form of ACC may have a recognizable appearance on prenatal sonography as a round hypoechoic defect.<sup>121</sup>

Although most infants with ACC are otherwise well, defects that may occasionally be present include cleft lip and palate, ophthalmologic defects, limb reduction defects, cardiac anomalies, gastrointestinal tract malformations, spinal dysraphism, hydrocephalus, defects of the underlying skull, congenital midline porencephaly, spastic paralysis, seizures, mental retardation, and vascular anomalies.<sup>117</sup> Adams–Oliver syndrome (AOS), an autosomal dominant or recessive malformation syndrome caused by mutations in the *ARHGAP31*, *DOCK6*, or *RBPJ* genes, is the association of ACC with transverse limb defects and cardiac and CNS abnormalities.<sup>122,123</sup> The cardiac malformations in AOS may include ventricular septal defects, tetralogy of Fallot, left-sided obstructive lesions, and truncus arteriosus.<sup>124</sup> Up to 50% of patients with trisomy 13 may have scalp ACC, and it may also occur at an increased rate in patients with 4p syndrome. Therefore any patient with signs of scalp ACC and congenital anomalies warrants chromosomal evaluation. Oculocerebrocutaneous (Delleman) syndrome is the association of orbital cysts, cerebral malformations, and focal skin defects including ACC-like lesions and skin tags.<sup>125,126</sup> Other findings in this syndrome include CNS malformations, clefting, and microphthalmia/anophthalmia. ACC in association with fetus papyraceus (vanishing twin syndrome) typically presents with bilateral symmetric buttock and lower extremity involvement as well as truncal lesions.<sup>127</sup>

The etiology of ACC remains unknown. Although most cases are sporadic, familial case reports have suggested autosomal dominant inheritance with reduced penetrance. Incomplete closure of the neural tube or an embryologic arrest of skin development has been suggested as an explanation for midline lesions. This hypothesis, however, fails to account for lesions of the trunk and limbs. In such instances, vascular abnormality of the placenta, with a degenerative rather than an aplastic or traumatic origin, has been postulated as the cause of the cutaneous defects.<sup>128</sup> Antithyroid drugs, most notably MMI, have long been hypothesized as causative teratogens in some cases of ACC. Although causality remains unproven, there are multiple reports of affected infants born to mothers treated with MMI during pregnancy, both as an isolated manifestation and as part of the presentation of “MMI embryopathy,” which includes dysmorphism, gastrointestinal tract malformations, and developmental delay.<sup>129</sup> Propylthiouracil has been recommended as the first-line agent in the management of hyperthyroidism during pregnancy, given its equal effectiveness and lack of reports of teratogenic ACC.<sup>130</sup> Recently a heterozygous missense mutation in *BMS1* (which affects ribosomal function) was identified in autosomal dominant ACC.<sup>131</sup>



**Figure 2-36** Setleis syndrome. A child with bilateral depressed oval areas on the temples, upwardly slanting eyebrows, narrowed palpebral fissures, and large lips. (Courtesy of Seth Orlow, MD.)

Recognition of ACC and differentiation of it from forceps or other birth injury will help prevent possible medicolegal complications occasionally encountered with this disorder. In patients with localized sporadic lesions, aside from cutaneous scarring, the prognosis of ACC is excellent. With conservative therapy to prevent further tissue damage and secondary infection, most small defects of the scalp heal well during the first few weeks to months of life. With aging of the child, most scars become relatively inconspicuous and require no correction. Those that are large and obvious can be treated with plastic surgical reconstruction.

### Setleis Syndrome

Setleis syndrome was initially described in 1963 by Setleis and colleagues, who described five children of three families, all of Puerto Rican ancestry, who had unique characteristic clinical defects confined to the face.<sup>132</sup> Patients have atrophic skin at the temples (historically likened to forceps marks), coarse facial appearance, absent or duplicated eyelashes of the upper eyelids (distichiasis), eyebrows that slant sharply upward and laterally, and periorbital puffiness (Fig. 2-36). Lips may be large with an inverted V contour. Although traditionally believed to have normal intelligence, patients with Setleis syndrome may have associated developmental delay.<sup>133</sup>

Reports of Setleis syndrome have suggested both autosomal recessive and autosomal dominant modes of inheritance,<sup>133,134</sup> and variable expressivity and reduced penetrance may be observed.<sup>135</sup> Setleis syndrome is considered by some to be a form of focal facial dermal dysplasia (see Chapter 6).<sup>136</sup> Recently, homozygous nonsense mutations in *TWIST2* have been confirmed in cohorts with the Setleis phenotype.<sup>137,138</sup>

### OTHER DEVELOPMENTAL DEFECTS

A congenital dermal sinus or dermoid cyst is a developmental epithelium-lined tract (or cyst) that extends inward from the surface of the skin. Since midline fusion of ectodermal and neuroectodermal tissue occurs at the cephalic and caudal ends of the neural tube, the majority of such defects are seen in the occipital and lumbosacral regions. Dermoids, however, can occur anywhere.

Dermal sinus openings may be difficult to visualize, particularly in the occipital scalp region where they may be hidden by hair. A



**Figure 2-37** Dermoid cyst. This mobile, nontender, subcutaneous nodule was present at birth in this 5-month-old girl. The lateral mid-forehead distribution is slightly higher than most dermoids, which present most often in the lateral eyebrow region.



**Figure 2-38** Dermoid sinus. Small sinus ostium at the superior nasal bridge. This patient had no intracranial extension.

localized thickening of the scalp, hypertrichosis, or dimpling in the midline of the neck or back should alert the physician to the possibility of such an anomaly. These sinuses are of clinical importance as portals for infection that may give rise to abscesses, osteomyelitis, or meningitis.

Dermoid cysts most commonly occur on the orbital ridge, presenting as a nontender, mobile subcutaneous nodule in the eyebrow/orbital ridge region (Fig. 2-37). In this location, there is no association with deep extension. About 3% of dermoids are located in the nasal midline<sup>109</sup> (including glabella, nasal dorsum, and columella), and recognition of these lesions is vital because of the potential for deep extension and CNS communication. Congenital midline nasal masses may represent not only dermoids but also cephaloceles, gliomas, hemangiomas, and a variety of less common neoplasms or malformations. It is vital to consider the diagnostic possibilities carefully when a child's parents seek treatment for a nasal midline mass, given the potential for intracranial connection seen with some of these disorders. Invasive diagnostic procedures should never be performed until radiologic evaluation has been completed.

In midline nasal dermoid cysts or dermal sinuses, an overlying sinus ostium may be present, sometimes with a white discharge or protruding hairs (Fig. 2-38). Presence of such a pit may indicate a higher likelihood of intracranial extension.<sup>139</sup> MRI or computed tomography (CT) of suspicious areas should be performed to evaluate for an underlying tract and CNS connection. Management of dermal sinuses and dermoid cysts consists of surgical excision, in an effort to prevent local infection and, in the case of intracranial extension, meningitis and/or abscess formation. Lesions of the lateral forehead or orbital ridge do not require radiographic imaging before surgical excision.

A cephalocele is a herniation of cranial contents through a defect in the skull. Cephaloceles develop as a result of faulty separation of neuroectoderm from surface ectoderm in early gestation and occur most commonly at the occiput, followed by the dorsal nose, orbits, and forehead. These lesions present as a compressible mass that transilluminates with light.<sup>109</sup> Occasionally, an overlying blue hue may be present, which at times can suggest the incorrect diagnosis of deep hemangioma. A useful diagnostic feature is the enlargement of the lesion that may be seen with any maneuver that results in increased intracranial pressure (such as crying or straining). This temporary change is caused by the patent connection between a cephalocele and the CNS. Hypertelorism, facial clefting, and brain malformations may be seen in conjunction with a cephalocele.<sup>140</sup> Surgical resection is the

treatment of choice, and multidisciplinary care (plastic surgery, neurosurgery) may be indicated.

A nasal glioma is an ectopic neuroectoderm from early development and may occur in extranasal (60%) or intranasal (30%) locations and less commonly in both extranasal and intranasal sites. This lesion presents as a firm, noncompressible, flesh-colored nodule, sometimes with a blue-red hue, and most often situated at the root of the nose. Hypertelorism may result, and no fluctuation in size is seen, because these lesions have no intracranial connection. An intranasal lesion presents as a protruding mass from the nose, simulating a nasal polyp. *Heterotopic brain tissue* is a term that has been used to similarly describe a rare developmental anomaly that occurs most often on the head and neck, especially in the nasal area, and usually without intracranial communication.<sup>141,142</sup> Surgical excision is the treatment of choice for these lesions.

Congenital fistulas of the lower lip (congenital lip pits) may be unilateral or bilateral and may be seen alone or in association with other anomalies of the face and extremities. They are characterized by single or paired, circular or slit-like depressions on either side of the midline of the lower lip at the edge of the vermillion border. These depressions represent blind sinuses that extend inward through the orbicularis oris muscle to a depth of 0.5 cm or greater. They may occasionally communicate with underlying salivary glands. Excision of lip pits is unnecessary unless mucous gland secretions are problematic.

Congenital lip pits may be inherited as an autosomal dominant disorder with penetrance estimated at 80%. They may be seen alone or, in 70% of patients, in association with cleft lip or cleft palate. Other associated anomalies include clubfoot, talipes equinovarus, syndactyly, and the popliteal pterygium syndrome (an autosomal dominant disorder with clefting, filiform eyelid adhesions, pterygium, genitourinary anomalies, and congenital heart disease).<sup>143</sup>

Skin dimpling defects (depressions, deep pits, or creases) in the sacral area and over bony prominences may be seen in normal children and infants with diastematomyelia (a fissure or cleft of the spinal cord), congenital rubella or congenital varicella-zoster syndromes, deletion of the long arm of chromosome 18, and Zellweger (cerebro-hepatorenal), Bloom, and Freeman-Sheldon (craniocarpotarsal dysplasia, "whistling face") syndromes.

Amniotic constriction bands may produce congenital constriction deformities, and congenital amputation of one or more digits or extremities of otherwise normal infants may occur. The deformities are believed to result from intrauterine rupture of amion with formation of fibrous bands that encircle fetal parts and produce permanent constriction of the underlying tissue.<sup>144</sup> Acquired raised bands of



**Figure 2-39** Acquired raised bands of infancy. Numerous linear raised bands on the back of an infant who had similar bands on the extremities. (Courtesy of Sarah L. Chamlin, MD.)



**Figure 2-40** Sock-line hyperpigmentation. Erythematous to hyperpigmented curvilinear streak on the lower leg of a 1-year-old female whose mother noted the changes shortly after dressing her in tight-fitting socks.

infancy (also known as *raised limb bands*) are linear skin-colored plaques that develop postnatally on the extremities of infants and involve no constrictive defects (Fig. 2-39). They may also occasionally occur on the trunk. Although some argue that these findings are distinct from amniotic constriction bands,<sup>145</sup> coexistence with congenital constriction bands<sup>146</sup> and prenatal ultrasound observation of amniotic bands<sup>147</sup> in reported patients suggests a potential overlap of these two conditions. Sock-line hyperpigmentation (also known as *sock-line bands*) has been described as circumferential, unilateral, or bilateral hyperpigmented streaks on the calf (Fig. 2-40) that are seen in otherwise-healthy children and acquired during infancy and may be related to the wearing of elastic socks or elastic pant legs.<sup>148</sup> It is believed to be distinct from acquired raised bands, must be differentiated from child abuse with a looped cord, and is usually self-limited.<sup>149</sup> These lesions have also been observed on the posterior heel of infants



**Figure 2-41** Preauricular sinus with ulceration. This lesion was prone to recurrent inflammation and infection and ultimately was surgically excised.

after wearing heel-length socks.<sup>150</sup> Damage to adipose tissue with inflammation and secondary postinflammatory changes have been hypothesized as the cause.

Preauricular pits and sinus tracts may develop as a result of imperfect fusion of the tubercles of the first two branchial arches. Unilateral or bilateral, these lesions present as small skin pits that may become infected or result in chronic preauricular ulcerations (Fig. 2-41), retention cysts, or both, necessitating surgical excision. Accessory tragi are fleshy papules, with or without a cartilaginous component, that contain epidermal adnexal structures. Usually seen in the preauricular area, they may also occur on the neck (anterior to the sternocleidomastoid muscle). Accessory tragi may be solitary or localized (Fig. 2-42, A) or multifocal, occurring along the embryologic migration line extending from the preauricular cheek to the mouth angle (Fig. 2-42, B). Although generally seen as an isolated congenital defect, they may be associated with other branchial arch syndromes (i.e., oculoauriculovertebral or Goldenhar syndrome). The prevalence of preauricular pits and tags is estimated at around 0.5% to 1.0%.<sup>151,152</sup>

An important consideration with preauricular pits and tags is that of potential associations, the most common concerns being those of hearing or genitourinary defects. Several studies have demonstrated an increased incidence of hearing impairment in the setting of isolated pits or tags, thus suggesting that hearing assessment should be performed in any newborn with these lesions.<sup>153,154</sup> The data regarding genitourinary malformations are more controversial, with studies both supporting and refuting an association with preauricular pits or tags.<sup>152,155</sup> It appears that when these preauricular lesions occur in the absence of other dysmorphic or syndromic features, such associations are less likely.

Branchial cleft cysts and sinuses, formed along the course of the first and second branchial clefts as a result of improper closure during embryonic development, are generally located along the lower third of the lateral aspect of the neck near the anterior border of the sternocleidomastoid muscle. Lesions may be unilateral or bilateral and may open onto the cutaneous surface or may drain into the pharynx. Although these lesions may present in childhood, they more commonly come to medical attention during adulthood because of recurrent inflammation. Treatment consists of complete surgical removal or marsupialization (exteriorization, resection of the anterior wall, and suturing of the cut edges of the remaining cyst to the adjacent edges of the skin).

Thyroglossal cysts and sinuses are located on or near the midline of the neck, and may open onto the skin surface, extend to the base of the tongue, or drain into the pharynx. Clinically, they present as a midline neck cyst that moves with swallowing (Fig. 2-43). These lesions represent persistence of the embryonic structure associated with normal thyroid descent, and occasionally may contain ectopic thyroid tissue. Although surgical excision is the treatment of choice, care must be exercised to preserve aberrant thyroid tissue in order to prevent postsurgical hypothyroidism.

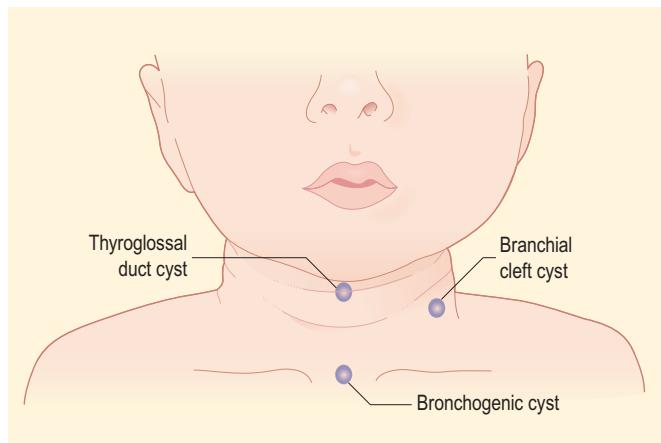


**Figure 2-42** Accessory tragi. These fleshy papules may present in a solitary/localized fashion (**A**) or in a multifocal form, occurring along the embryologic migration line extending from the preauricular cheek to the mouth angle (**B**).



**Figure 2-43** Thyroglossal duct cyst. This congenital nodule of the anterior midline neck was noted to move upward with swallowing.

Bronchogenic cysts present early, usually at birth, as a nodule or draining pit, usually over the suprasternal notch. These lesions may develop from ectopic elements of the tracheobronchial tree or may represent ectopic branchial cleft cysts. Surgical excision is the treatment of choice. **Figure 2-44** shows the locations of several types of congenital neck cysts.



**Figure 2-44** Congenital sinuses of the neck.

Congenital cartilaginous rests of the neck (also known as *wattles*) occur as small fleshy appendages on the anterior neck or over or near the lower half of the sternocleidomastoid muscle. Treatment consists of surgical excision with recognition of the fact that these cutaneous appendages may contain cartilage. Pterygium colli, congenital folds of skin extending from the mastoid region to the acromion on the lateral aspect of the neck, may be seen in individuals with Turner, Noonan, Down, lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, deafness (LEOPARD), or multiple pterygium syndromes; trisomy 18; short-limbed dwarfism; and combined immunodeficiency disease.

Supernumerary nipples (polythelia), present at times in males as well as females, are manifested as small brown or pink, concave, umbilicated, or elevated papules along or slightly medial to the embryologic milk line. They are most common on the chest or upper abdomen and occasionally are seen in other sites including the face, neck, shoulder, back, genitals, or thighs. Although much has been written about a relatively high incidence of renal malformation in patients with supernumerary nipples, current studies suggest that this anomaly in an otherwise apparently normal individual does not appear to be a marker of urinary tract malformation.<sup>156–158</sup>

There is a variety of developmental anomalies that may occur in the umbilical region. Urachal cyst or sinus is a lesion that represents persistence of the embryonic urachus, a fibrous cord that develops from the urogenital sinus. A midline nodule near the umbilicus may result, and at times urine drainage may be seen from a fistula connecting the umbilicus to the bladder. Vitelline (omphalomesenteric duct) remnant may present as an umbilical polyp or an umbilicoileal fistula that drains feces onto the skin surface. Complete excision is the treatment of choice for these anomalies.

## Congenital Infections of the Newborn

Viral, bacterial, and parasitic infections during pregnancy can be associated with widespread systemic involvement, serious permanent sequelae, and a variety of cutaneous manifestations in the newborn. This section discusses the most significant of these: congenital rubella, congenital varicella-zoster syndrome, neonatal varicella, neonatal herpes, congenital parvovirus B19 infection, congenital syphilis (CS), cytomegalic inclusion disease, congenital Epstein-Barr virus (EBV) syndrome, and congenital toxoplasmosis.

### CONGENITAL RUBELLA

Congenital rubella syndrome (CRS) was initially identified in 1941 by Norman Gregg, an Australian ophthalmologist who observed an unusual form of congenital cataracts in babies of mothers who had had rubella during pregnancy.<sup>159</sup> It occurs after a maternal rubella



**Figure 2-45** Congenital rubella with blueberry muffin lesions. Multiple violaceous, infiltrative papules and nodules in this newborn with congenital rubella.

infection during the first 16 weeks of pregnancy and only rarely when infection is acquired later in gestation. Earlier gestation directly correlates with the likelihood of CRS. Overall, the incidence of CRS in the United States has declined notably in parallel with the decline in rubella cases since licensure of the rubella vaccine in 1969. During 2004 through 2012, however, 79 cases of rubella and six cases of CRS were reported in the United States and were either import-associated or from unknown sources.<sup>160</sup> Occasional rubella outbreaks, such as those that occurred during the 1990s, have been related to a variety of factors, including occurrence in settings in which unvaccinated adults congregate, in unvaccinated foreign-born adults, and among children and adults in religious communities with low levels of vaccination coverage.<sup>161,162</sup> Studies suggest that young Hispanic women represent a population at elevated risk for delivering an infant affected by CRS, and thus this population needs to be targeted specifically for immunization.<sup>162,163</sup> Importantly, rubella virus continues to circulate in other parts of the world (i.e., Africa) where rubella vaccination programs are not established and increases the risk of imported rubella in the United States and subsequent CRS.<sup>160</sup>

Clinical manifestations of CRS are characterized by the classic triad of congenital cataracts, deafness, and cardiac defects (especially patent ductus arteriosus). *In utero* growth restriction may occur during the last trimester of pregnancy. CNS involvement may result in microcephaly, meningoencephalitis, and mental retardation. Other features include pigmentary retinopathy, hepatosplenomegaly, jaundice, radiolucent bone lesions in metaphyses, and thrombocytopenia.<sup>164</sup> Some infants with CRS may show few manifestations at birth or may be asymptomatic, but findings usually manifest over subsequent months. Occasionally, CRS findings may not become manifest until the second year of life.<sup>165</sup>

The most distinct cutaneous feature of CRS is a diffuse eruption composed of blue-red infiltrative papules and nodules and occasionally smaller purpuric macules, measuring 2 to 8 mm in diameter, representing so-called "blueberry muffin" lesions (Fig. 2-45). Blueberry muffin lesions are usually present at birth or within the first 24 hours, and new lesions rarely appear after 2 days of age. They may be observed in association with a variety of disorders, usually either infectious or neoplastic (Box 2-2). Histologic evaluation reveals extramedullary hematopoiesis, characteristic of viral infection of the fetus and not unique to infants with CRS but also seen in patients with congenital toxoplasmosis, cytomegalovirus (CMV) infection, erythroblastosis fetalis, congenital leukemia, and twin-twin transfusion syndrome. Other cutaneous manifestations in CRS may include a generalized nonspecific maculopapular eruption, reticular erythema of the face and extremities, hyperpigmentation, and recurrent urticaria. Vasomotor instability, manifested by poor peripheral circulation with generalized mottling and acral cyanosis, may also occur.

## Box 2-2 Differential Diagnosis of the Newborn with "Blueberry Muffin" Lesions

- Dermal (extramedullary) hematopoiesis
- Congenital infection
  - Toxoplasmosis
  - Rubella
  - Cytomegalovirus
  - Enterovirus
  - Parvovirus B19
- Erythroblastosis fetalis
- Inherited hemolytic diseases
- Twin-twin transfusion
- Neoplastic
  - Neuroblastoma
  - Leukemia
  - Histiocytosis
  - Alveolar rhabdomyosarcoma

The diagnosis of CRS should be suspected in infants with one or more characteristic findings including congenital cataracts, pigmentary retinopathy, cardiac defects, deafness, thrombocytopenia, hepatosplenomegaly microcephaly, or blueberry muffin lesions. The diagnosis may be confirmed by isolation of rubella virus from respiratory secretions, urine, cerebrospinal fluid (CSF), or tissue. Neonatal immunoglobulin (Ig) M rubella-specific antibodies or IgG antibodies that persist beyond the time expected for passively transferred immunity are also diagnostic. Real-time reverse transcription polymerase chain reaction (rRT-PCR) can also be performed on throat/nasopharyngeal swabs, serum and urine.

There is no specific therapy for CRS apart from supportive therapy and recognition of potential disabilities. Because of the high incidence of ophthalmic complications, regular ophthalmologic examinations are indicated. Infants who are congenitally infected may shed virus in urine and the nasopharynx for several months to 1 year and should be considered contagious until that time. The majority of infants who acquire CRS early in gestation will have permanent neurologic and audiologic sequelae, and long-term multidisciplinary care is indicated. A long-term follow-up study of 50 Australian patients with CRS revealed aortic valve disease in 68% and increased incidences of diabetes, thyroid disorders, early menopause, and osteoporosis compared with the general population.<sup>166</sup>

Congenital rubella can be effectively prevented by immunization with live rubella virus vaccine, and universal vaccination is recommended. Current efforts focus on immunizing high-risk populations with two doses of rubella vaccine, with a special effort to vaccinate populations at increased risk including college students, military recruits, and healthcare and daycare workers.<sup>165</sup> Because of the high risk of fetal damage, women known to have contracted maternal rubella during the early months of pregnancy may consider abortion. Although limited data suggest that administration of immunoglobulin to the mother may reduce the amount of viremia and damage when given as early as possible after exposure, it does not appear to prevent congenital infection.

## CONGENITAL VARICELLA SYNDROME

Congenital varicella syndrome, also known as *fetal varicella syndrome*, refers to a spectrum of congenital anomalies that may be seen in neonates born to women who contract varicella-zoster virus (VZV) infection during the first 20 weeks of gestation. Overall it is quite rare, probably because primary varicella infection during pregnancy is uncommon, since the majority of women have acquired immunity by child-bearing age.<sup>167</sup> The incidence of congenital varicella syndrome after maternal infection is estimated at around 0.4% to 1%, and the highest risk seems to be when infection is acquired between 13 and 20 weeks of gestation.<sup>168,169</sup> Primary VZV infection in a pregnant woman most often results in the birth of a normal newborn, related to either to lack of transmission to the fetus or self-limited fetal infection. Although there are rare reports of fetal sequelae in infants born

to mothers who develop herpes zoster infection (shingles) during pregnancy, this association is extremely rare.<sup>168,170</sup> Infants born to mothers with a history of maternal varicella during gestation appear to be at increased risk for infantile herpes zoster (shingles). Implementation of universal varicella vaccination programs has been demonstrated to result in reduction of both congenital varicella and neonatal varicella infections.<sup>171</sup>

Congenital varicella syndrome may present with various findings, including low birthweight, ophthalmologic defects (including microphthalmia, Horner syndrome, cataracts, and chorioretinitis), neurologic defects (including mental retardation, seizures, cortical atrophy, encephalomyelitis, and developmental delay), limb hypoplasia with flexion contractures and malformed digits, and gastrointestinal and genitourinary defects.<sup>167</sup> Cutaneous findings include vesicles and/or scarring (often depressed and pigmented) in a dermatomal distribution, although several affected newborns have been reported with cutis aplasia-like absence of skin.

Because the risk of fetal malformation in an infant born to a mother exposed to VZV during pregnancy is so slight, therapeutic abortion is not necessarily indicated. As noted, the majority of women who contract varicella during pregnancy have children with no evidence of the syndrome. Studies to date are inconclusive with regard to the utility of serologic or polymerase chain reaction (PCR)-based testing of fetal blood or amniotic fluid.<sup>172</sup> Prenatal ultrasound may reveal disseminated organ calcifications.<sup>173</sup> Studies suggest that the use of varicella-zoster immunoglobulin (VZIG) may clearly modify or prevent disease in the mother who has been exposed and is susceptible. Treatment of mothers with severe varicella with acyclovir or valacyclovir may be considered. Most important is screening of women of childbearing age without a history of varicella for antibody and offering vaccination when indicated. Susceptible females who are already pregnant should be counseled about avoiding contact with individuals who have chickenpox and about the availability of VZIG should it become necessary.

Neonatal varicella is a varicella infection of the newborn that occurs when a pregnant woman develops chickenpox during the last few weeks of pregnancy or the first few days postpartum. In such instances, the timing of the onset of disease in the mother and her newborn is critical. If the disease onset in the mother is 5 or more days before delivery or in the newborn during the first 4 days of life, the infection tends to be mild. In contrast, if the onset in the mother is within 5 days before delivery to 2 days after delivery or in the newborn between 5 and 10 days of birth, the infant's infection is often severe and disseminated (Fig. 2-46), with pneumonia, hepatitis, or meningoencephalitis and severe coagulopathy and a mortality rate of around 30%. In an effort to prevent neonatal varicella infection, VZIG (or intravenous immunoglobulin [IVIG] if the former is unavailable) should be given as soon as possible after delivery to all infants in whom the mother has the onset of varicella within 5 days before or within 48 hours after delivery, and these infants are also candidates for intravenous acyclovir therapy.<sup>174</sup>



**Figure 2-46** Neonatal varicella. Disseminated, erythematous papules, vesicles, and erosions.

## NEONATAL HERPES

Neonatal herpes simplex virus (HSV) infection may range from a mild, self-limited illness to one with devastating neurologic consequences or even death. The overall incidence in the United States is estimated at 9.6 per 100,000 births.<sup>175</sup> Up to 70% of neonatal HSV infections are caused by type 2 ("genital") HSV, and the disease is acquired either by ascending *in utero* infection or by spread during delivery through an infected birth canal (perinatal transmission). Infection of the newborn may also be acquired by intrauterine infection because of maternal viremia with transplacental spread or by postnatal hospital or household contact with other infants or persons with oral HSV infection.<sup>176-178</sup> Of infants with neonatal HSV, 85% acquire their infection during birth, 10% postnatally, and 5% from *in utero* exposure.<sup>179</sup> Congenital (intrauterine) HSV infection, which is not the focus of this section, is a rare disorder (approximately 5% of all neonatal HSV disease) resulting from intrauterine infection and is characterized by skin vesicles or scarring, chorioretinitis, microphthalmia, microcephaly, and abnormal brain CT findings.<sup>180</sup> Importantly, the majority of infants with cutaneous involvement have lesions at birth or within 12 hours of life (significantly earlier than infants with neonatal herpes).<sup>181</sup>

The risk of neonatal HSV infection in an infant born vaginally to a mother with primary genital infection is high (40% to 50%), whereas the risk to an infant born to a mother with recurrent infection is much lower, around 2% to 5%. The lower rate of transmission with recurrent maternal disease may reflect decreased viral load and partial protection of the fetus by transplacentally acquired antibodies.<sup>182</sup> Most babies with neonatal HSV become infected from mothers who are asymptomatic.

The clinical presentation of neonatal HSV has traditionally been divided into three separate patterns: skin, eyes, and/or mouth (SEM) disease; CNS disease; and disseminated disease. These presentations are summarized in Table 2-4. The exact frequency of the various forms is unclear, given partial overlap of patterns in some patients and potential delays in the appearance of CNS disease. Most infants affected with neonatal HSV become sick during the first 4 weeks of life, and in two-thirds, during the first week of life. SEM disease appears to be the least severe and associated with the most favorable prognosis. However, although most infants have SEM disease, 60% to 70% will progress to more diffuse involvement.<sup>183</sup>

Presenting features of neonatal HSV include skin lesions, fever, respiratory distress, and CNS dysfunction. The latter includes seizures, lethargy, poor feeding, irritability, and hypotonia. The skin eruption may vary from erythematous macules to individual or grouped vesicles (Fig. 2-47) or a widespread generalized vesicobullous eruption affecting the skin and buccal mucosa. The vesicles of neonatal HSV may become pustular after 24 to 48 hours and eventually becomes

**Table 2-4** Clinical Presentations of Neonatal Herpes

Type	Incidence* (%)	Skin Vesicles (%)	Comment
SEM disease	45	80-85	May progress to more severe infection, especially without early therapy
CNS disease	30	60-70	Clinical overlap with neonatal bacterial sepsis
Disseminated	25	75-80	Respiratory collapse, liver failure and DIC common

Adapted from Kimberlin DW. Herpes simplex virus infections in neonates and early childhood. *Semin Pediatr Infect Dis* 2005;16:271-81, and Kimberlin DW. Herpes simplex virus infections of the newborn. *Semin Perinatol* 2007;31:19-25.

CNS, Central nervous system; DIC, disseminated intravascular coagulopathy; SEM, skin, eyes, and/or mouth.

\*Approximate incidence out of all neonatal herpes patients.



**Figure 2-47** Neonatal herpes simplex infection. Clustered vesicles on an erythematous base in this newborn with congenital herpes simplex infection, skin, eyes, and/or mouth (SEM type).

crusted or ulcerated. Other skin findings may include purpuric, petechial, or zosteriform lesions, as well as large bullae with skin denudation similar to those seen in epidermolysis bullosa.<sup>184</sup> Skin lesions occur most often on the scalp and face, and in breech deliveries they have a predilection for the presenting part. Occasionally, the scalp of the infant may reveal diffuse edematous swelling resembling that seen in caput succedaneum. Rather than resolving spontaneously during the first week, this swelling may become necrotic with resultant drainage and eschar formation and irregularly grouped herpetic vesicles. Fetal scalp monitoring is a risk factor for HSV, because the virus more readily gains entry into the lacerated scalp. Eye involvement, seen only in around 5% of affected infants, may present with conjunctivitis or pathognomonic keratitis.

The disseminated form of neonatal HSV may affect several organs, especially the liver, adrenal glands, lungs, and the CNS. This form is associated with the highest mortality—up to 60%. In the absence of skin lesions or other pathognomonic features, disseminated disease may be difficult to diagnose and should always be considered in the neonate who has risk factors for HSV, possible sepsis (especially if a lack of response to antimicrobial therapy is noted), unexplained pneumonitis (especially in the first week of life), or unexplained nonspecific findings such as thrombocytopenia, coagulopathy, hepatitis, or fever.<sup>183</sup> In addition, infants with an unexplained CSF pleocytosis (usually lymphocytic) merit consideration for the diagnosis of HSV.

The diagnosis of HSV infection in the newborn can be confirmed in a variety of ways. In the presence of skin lesions, a Tzanck smear can be performed on scrapings from the base of an unroofed vesicle and microscopically reveals multinucleated cells and nuclear inclusions. The Tzanck smear, however, is highly operator-dependent and thus may have a relatively low sensitivity; it is also not specific. Direct fluorescent antibody study of skin lesion scrapings has a high sensitivity (80% to 90%), excellent specificity,<sup>185</sup> and readily available results. The gold standard for diagnosis of HSV infections remains viral culture, which can be taken from skin (especially vesicular fluid), eyes, mouth, CSF, rectum, urine, or blood.<sup>183</sup> Serologic studies generally are not useful in diagnosing neonatal HSV infection, because of the slow serologic response of the newborn and the potential confounding factor of transplacental antibody. PCR studies have been a major advance in the diagnosis of neonatal HSV infection and are especially useful for diagnosing CNS infection. Skin biopsy is rarely indicated, but if it is performed reveals characteristic intraepidermal vesicle formation with ballooning degeneration and multinucleation.

Other laboratory findings that may be suggestive of neonatal HSV infection include abnormal coagulation studies, thrombocytopenia, and elevated liver transaminases. Evaluation of CSF in those with CNS or disseminated disease often reveals a lymphocytic pleocytosis and elevated protein, although these findings may be absent in early disease and are not specific for HSV.<sup>186</sup> Electroencephalography and neuroimaging with MRI should also be performed.<sup>186</sup>

The outcome of neonatal HSV infection is quite variable. Prospective data on outcomes were gathered by the Collaborative Antiviral Study Group and revealed that the following were risk factors for mortality: CNS and disseminated disease, decreased level of consciousness at start of therapy, and prematurity. In those with disseminated disease, pneumonitis and disseminated intravascular coagulopathy were important risk factors.<sup>176</sup> Morbidity was greatest in infants with encephalitis, disseminated infection, seizures, or infection with HSV-2 (vs. HSV-1).

Education is vitally important in the prevention of HSV (and therefore neonatal HSV) during pregnancy. Studies have shown that women at greatest risk of acquiring the infection during pregnancy are those who are seronegative and whose partners are HSV-positive. It appears that acquisition of infection with seroconversion completed before labor does not affect the outcome of the pregnancy, whereas infection acquired near the time of labor is associated with neonatal HSV and perinatal morbidity.<sup>187</sup> Overall, 70% of infants with neonatal HSV are born to mothers who do not manifest any sign or symptom of genital infection at the time of delivery. Cesarean delivery should be offered to women with active HSV lesions at the time of labor, although not all cases of neonatal HSV can be prevented.<sup>180</sup> The use of acyclovir during pregnancy is controversial, although it may shorten the period of active lesions in the mother. In instances where there is a known history of maternal HSV, use of fetal scalp electrodes should be avoided whenever possible. Viral cultures in mothers with suspected genital HSV during the last few weeks before delivery and routine prophylactic cesarean section for asymptomatic women have not been demonstrated useful and are not routinely recommended.

Newborns with vesicular lesions or suspected HSV should be isolated (contact precautions), evaluated thoroughly for systemic infection, and treated with empiric antiviral therapy. Ophthalmologic evaluation should be performed, and prophylactic topical ophthalmic preparations such as idoxuridine, vidarabine, or trifluorothymidine solution should be initiated. In addition to antiviral therapy, supportive measures are often indicated, including management of seizures, respiratory distress, hemorrhage, and metabolic aberrations. Women with active HSV infection may handle and feed their infants provided they use careful hand-washing techniques and wear a disposable surgical mask or dressing to cover the lesions until they have crusted and dried. There is no unequivocal evidence that HSV is transmitted by breast milk or that breastfeeding by a mother with recurrent HSV infection poses a risk to the infant. It therefore appears that if all precautions are utilized, breastfeeding by a mother with recurrent HSV may be acceptable. After hospital discharge, affected infants should be monitored closely, because 5% to 10% will develop a recurrent infection requiring therapy within the first month of life.<sup>188</sup>

Both vidarabine and acyclovir have been demonstrated effective in the treatment of neonatal HSV. However, because of its safety profile, acyclovir is the treatment of choice.<sup>172</sup> Early studies suggested a dose range of 15 to 30 mg/kg per day for affected infants, but it was subsequently demonstrated that higher dosages are more effective. The survival rate for patients with disseminated HSV treated with high-dose acyclovir (60 mg/kg per day) was significantly higher, with a borderline significant decrease in morbidity.<sup>189</sup> Toxicity was limited to transient neutropenia during therapy, suggesting the importance of monitoring absolute neutrophil counts. Treatment recommendations are for 14 days for SEM disease and 21 days for CNS and disseminated disease.<sup>186,190</sup> Oral acyclovir suppression for 6 months after acute therapy is recommended for surviving infants with CNS disease, given the demonstrated improved neurodevelopmental outcomes.<sup>191</sup> Algorithmic guidelines on the management of asymptomatic neonates born to women with active genital herpes lesions have been published.<sup>192,193</sup>

## CONGENITAL PARVOVIRUS B19 INFECTION

Human parvovirus B19, the same virus that causes erythema infectiosum (fifth disease), may be transmitted by a gravid female to the fetus and may result in anemia, hydrops fetalis, and even intrauterine fetal demise. The cellular receptor for B19, a virus that lytically infects erythroid precursor cells, is globoside or P-antigen, which is found on erythroblasts and megakaryocytes.<sup>194</sup> Overall, up to 65% of pregnant

females are immune to B19 and therefore not at risk,<sup>195</sup> and the majority of infants born to mothers with B19 infection are delivered at term and asymptomatic. The greatest risk appears to be when infection is acquired before 20 weeks' gestation, and the overall incidence of fetal loss is between 1% and 9%.<sup>196–198</sup> Fetal B19 infection may result in severe anemia, high-output cardiac failure, generalized edema, pleural and pericardial effusions, and polyhydramnios. Although skin findings are not a major feature of congenital B19 infection, blueberry muffin lesions have been described.<sup>199</sup>

In infants who survive congenital B19 infection, there appears to be no increased risk of congenital anomalies or developmental aberrations. Pregnant women exposed to B19 should be reassured regarding the relatively low potential risk and offered serologic testing. Detection of B19 antigens in amniotic fluid or B19 deoxyribonucleic acid (DNA) via PCR are other methods available for diagnostic confirmation.<sup>200</sup> If acute B19 infection is confirmed, serial fetal ultrasonography should be performed to assess for signs of *in utero* infection. Management of severely afflicted fetuses includes fetal digitalization and *in utero* blood transfusions.

## CONGENITAL SYPHILIS

As a result of advances in the detection and treatment of syphilis during the years after the Second World War, the incidence of neonatal syphilis dropped to relatively insignificant levels by the mid-1950s. Since 1959, however, the incidence of primary and secondary syphilis has increased, with a resultant resurgence in the incidence of CS. Surveillance data reported to the Centers for Disease Control and Prevention (CDC) by 50 states and the District of Columbia from 1992 to 1998 revealed 942 deaths among 14,627 cases of CS, resulting primarily from untreated, inadequately treated, or undocumented treatment of syphilis during pregnancy.<sup>201</sup> In the United Kingdom, the number of babies reported with CS increased from two in 1996 to 14 in 2005.<sup>202</sup> A review of national surveillance data from 2003 through 2008 revealed an increase in the CS rate from 8.2 cases per 100,000 live births in 2005 to 10.1 cases per 100,000 live births in 2008. This increase paralleled the increase in primary and secondary syphilis among females from 2004 through 2007, and it was noted that the CS rates increased primarily in the South and among infants born to black mothers.<sup>203</sup> Such data reveal that CS still represents a public health problem and highlight the fact that early prenatal care via early detection and treatment of maternal syphilis is an essential component in CS prevention in neonates.

CS is a disorder in which the fetus becomes infected with the spirochete *Treponema pallidum*, usually after the 16th week of pregnancy. The risk of fetal transmission is estimated to be 70% to 100% for untreated early syphilis.<sup>204</sup> The widely varied manifestations of CS are determined in part by the stage of maternal syphilis, stage of the pregnancy at the time of infection, rapidity of maternal diagnosis, and treatment and immunologic reaction of the fetus.<sup>205</sup> Up to 40% of fetuses with CS are stillborn, and among affected live newborns, two-thirds are symptom-free at birth. Perinatal associations with CS include premature delivery, low birthweight, and small size for gestational age.<sup>206</sup>

The clinical manifestations of CS are divided into lesions of early CS (appearing before 2 years of age) and late CS (occurring after 2 years of age). Skin lesions of early CS are generally infectious, and because there is no primary stage, they may resemble those of acquired secondary syphilis. They differ from those of the second stage of syphilis in that the fetal lesions are generally more widely distributed, more severe, and of longer duration. Lesions of late CS represent either a hypersensitivity reaction on the part of the host or scars and deformities that are direct consequences of infection.

### Early Congenital Syphilis

Fetal infection with *T. pallidum* results in multisystem involvement with considerable variation in clinical expression. Although infants with CS commonly exhibit no external signs of disease at the time of birth, many experience clinical manifestations within the first month. Those with florid manifestations at birth appear to be more severely infected, are often premature, and usually have a poor prognosis. Recently, a retrospective review demonstrated that premature infants



**Figure 2-48** Congenital syphilis. Erythema, scaling, and fissuring of the plantar surfaces in early congenital syphilis.

are more likely to display characteristic features of early CS, including skin findings, hepatosplenomegaly, thrombocytopenia, and radiographic findings in long bones as neonates, as compared with full-term infants.<sup>207</sup>

The most common clinical manifestations of early CS are summarized in Table 2-5. Rhinitis (snuffles) is commonly the first sign of CS. Cutaneous lesions of CS are seen in one-third to one-half of affected infants and may be quite varied. Most common is a diffuse papulo-squamous eruption that includes the palms and soles, comparable with the rash seen in secondary syphilis in older patients. Vesiculobullous lesions are relatively rare, but when they involve the palms and soles are highly diagnostic of CS. The palms and soles are often fissured, erythematous, and indurated with a dull red, shiny appearance (Fig. 2-48). Concomitant with these changes, desquamation in large, dry flakes may occur over the entire body surface area. Flat, moist, wart-like lesions (condylomata lata) commonly appear in moist areas of skin in infants with CS and are extremely infectious. Intractable diaper dermatitis is occasionally present. Mucous patches, which present as fissures at mucocutaneous junctions, are among the most characteristic and most infectious of the early lesions seen in CS.

Necrotizing funisitis, spiral zones of red and blue umbilical cord discoloration interspersed with streaks of chalky white (hence the term *barber-pole umbilical cord*), has been described as a commonly overlooked, early diagnostic feature of CS. The external smooth surface of the umbilical cord without evidence of exudation apparently differentiates necrotizing funisitis from acute bacterial funisitis, an inflammation of the umbilical cord seen in newborns with acute bacterial infection.<sup>208</sup>

Hepatomegaly, when present, is often associated with icterus and occasionally ascites, splenomegaly, and generalized lymphadenopathy. The jaundice, together with anemia, edema, and cutaneous changes, produces a peculiar dirty, whitish brown (*café-au-lait*) appearance to the skin. Hemolytic anemia and occasional thrombocytopenia are common features of early CS. When occurring with hepatosplenomegaly, jaundice, and large numbers of nucleated erythrocytes in the peripheral circulation, an erroneous diagnosis of erythroblastosis fetalis may be made. Nephrotic syndrome and pneumonitis are occasionally present.

Although only 15% of infants with CS show clinical signs of osteochondritis at birth, 90% show radiologic evidence of osteochondritis and/or periostitis after the first month of life. Syphilitic osteochondritis may occur in any bone but is found most often in the long bones

**Table 2-5** Manifestations of Early Congenital Syphilis

System	Specific Features	Comment
Constitutional	Fever, wasting	
Nasal	Snuffles (nasal discharge)	Commonly the first sign 2–6 weeks of life Ulceration of nasal mucosa If deep, may involve cartilage and result in "saddle-nose deformity"
Hematologic	Hemolytic anemia Thrombocytopenia	
Lymphoid	Lymphadenopathy	Epitrochlear nodes highly suggestive
Visceral	Hepatosplenomegaly	50% to 75% of patients Icterus, jaundice, ascites associated
Mucocutaneous	Papulosquamous lesions  Condylomata lata Mucous patches	Diffuse eruption Palms and soles red, fissured ( <b>Fig. 2-42</b> ) Bright pink-red, fades to coppery brown Rare vesiculobullous lesions Eventual widespread desquamation Flat, wart-like lesions in moist areas (especially anogenital, nares, mouth angles) Present in 30% to 35% Weeping, fissuring at mucocutaneous junctions Extend out from lips in radiating fashion When deep, may leave scars (rhagades) of perioral region
Osseous	Osteochondritis  Periostitis  Dactylitis	15% of patients, especially long bones of extremities; often focal Usually asymptomatic, but severe involvement may lead to subepiphyseal fracture and painful pseudoparalysis of Parrot Most pronounced at 2–6 months of life Usually diffuse Calcification and thickening of cortex may lead to permanent deformity (i.e., frontal bossing, anterior bowing of tibia or saber shins) Affects small bones of hands/feet
CNS	CSF abnormalities	Increased protein, mononuclear pleocytosis, (+) CSF-VDRL

CNS, Central nervous system; CSF-VDRL, cerebrospinal fluid-Venereal Disease Research Laboratories test.

of the extremities. Radiographic findings consist of increased widening of the epiphyseal line with increased density of the shafts, spotty areas of translucency, and a resultant moth-eaten appearance. In most cases, the bony lesions are asymptomatic, but in some infants severe involvement may lead to subepiphyseal fracture with epiphyseal dislocation and extremely painful pseudoparalysis of one or more extremities (so-called "pseudoparalysis of Parrot"). Dactylitis, a rare form of osteochondritis of the small bones of the hands and feet that usually appears between 6 months and 2 years of age, may also occur.

Periosteal lesions are seldom present at birth. Periostitis of the frontal bones of the skull, when severe, may contribute to the flat overhanging forehead that persists as a stigma of children severely infected in infancy. The radiologic changes of periostitis are usually most pronounced between the second and sixth months of life and rarely persist beyond the age of 2 years. Lesions are usually diffuse (in contrast to the localized involvement characteristic of lesions of osteochondritis) and often extend the entire length of the involved bone. First seen as a thin, even line of calcification outside the cortex of the involved bone, the lesions progress and additional layers of opaque tissue are laid down, with the resulting "onion-peel" appearance of advanced periostitis. This eventually produces calcification and thickening of the cortex and, when severe, a permanent deformity. In the tibia, this results in an anterior bowing referred to as *saber shins*. In the skull it is seen (in 30% to 60% of patients) as frontal or parietal bossing.

Even though clinical evidence of CNS involvement is a relatively uncommon finding, CSF abnormalities may be detected in 40% to 50% of infants with CS. Recently IgM immunoblotting and PCR assay on serum or CSF were shown to be most predictive of CNS infection.<sup>209</sup> Clinical evidence of meningitis with a bulging fontanel, opisthotonos, and convulsions generally portends a poor prognosis. Low-grade syphilitic meningitis may result in a mild degree of hydrocephalus, and children with CNS involvement continuing beyond the period of

### Box 2-3 Signs of Late Congenital Syphilis

- Clutton joints (knee effusions)
- Eighth cranial nerve deafness\*
- Frontal bossing
- Gummas (skin, subcutaneous, and bone inflammation and ulceration)
- Higouménakis sign (thickening of inner third of clavicle)
- Hutchinson teeth\* (peg-shaped upper central incisors)
- Hydrocephalus
- Interstitial keratitis\*
- Mental retardation
- Mulberry molars
- Ocular changes (retinitis, optic nerve atrophy)
- Paroxysmal cold hemoglobinuria
- Rhagades (perioral fissuring)
- Saber shins
- Saddle nose
- Short maxillae

\*Hutchinson triad.

infancy may go on to demonstrate marked residua with varying degrees of physical and mental retardation.

### Late Congenital Syphilis

Late CS refers to the findings that persist beyond 2 years of age. It also includes varying signs and stigmata of CS in individuals in whom the diagnosis was overlooked or in those patients who were inadequately treated early in the course of the disease. Signs of late CS are summarized in **Box 2-3**, and a few are discussed in more detail here.

Perhaps the most pathognomonic signs of late CS are the dental changes. The deciduous teeth are prone to caries but show no specific abnormalities characteristic of this disorder. The term *Hutchinson*

incisors is applied to deformities of the permanent upper central incisors, and the condition is characterized by central notching with tapering of the lateral sides toward the biting edge (so-called "screwdriver teeth"). The simultaneous appearance of interstitial keratitis, Hutchinson incisors, and eighth nerve deafness is called the *Hutchinson triad*. Although described as a time-honored sign of CS, owing to the relative infrequency of eighth nerve deafness, this triad is actually extremely uncommon and rarely observed. The "mulberry molar" is a malformation of the lower first molars. The mulberry appearance is created by poorly developed cusps crowded together on the crown. Since these teeth are subject to rapid decay, mulberry molars are rarely seen past puberty. When present, however, they are pathognomonic of CS.

*Higouménakis sign* refers to unilateral thickening of the inner third of the clavicle and is commonly described as a manifestation of late CS. Because fracture of the middle third of the clavicle is the most common fracture occurring at birth, consequent healing and thickening of the involved bone often produces a clinical picture similar to that seen with Higouménakis abnormality. This finding should therefore not be considered a reliable stigma of late CS.

Paroxysmal cold hemoglobinuria is characterized by shaking chills and dark urine within 8 hours of cold exposure, and it may also occur as a manifestation of late CS. It is usually seen in patients with late CS who did not receive treatment, and although it is not pathognomonic, it is highly suggestive of late congenital or untreated acquired syphilis.

### Diagnosis and Treatment of Congenital Syphilis

Determination of the maternal serologic status for syphilis is standard of care in hospitals, and no newborn infant should be discharged without this information being known.<sup>210</sup> All infants born to mothers who are seropositive require a thorough clinical and laboratory examination, namely a quantitative nontreponemal syphilis test (i.e., Venereal Disease Research Laboratories [VDRL], rapid plasma reagent [RPR]), and preferably the same as that performed on the mother so that the titers can be compared. Further evaluation of the infant should occur if the mother received no therapy, inadequate therapy, therapy less than 1 month before delivery, therapy without the expected drop in antibody titer, or therapy before pregnancy with insufficient serologic follow-up examination.<sup>210</sup> Confirmation of a reactive nontreponemal test is accomplished with a specific treponemal test, such as the fluorescent treponemal antibody absorption (FTA-ABS) test and the microhemagglutination test for *T. pallidum* (MHA-TP). Placental changes may be a useful adjunct in the diagnosis of CS, and include necrotizing funisitis (see above in *Early Congenital Syphilis* section), villous enlargement, and acute villitis.<sup>211</sup> Diagnosis may be confirmed by positive darkfield examination from the umbilical vein or from moist lesions of the skin or mucous membranes.

Serologic tests in the newborn must be interpreted with caution, because their results may be caused by passive transfer of nontreponemal and treponemal antibodies from the mother and their antibody response may be delayed. A serologic titer in the newborn higher than that of the mother, however, is diagnostic. Additionally, since maternal IgM antibodies do not cross the placenta, detection of IgM in the infant indicates active infection.<sup>202</sup> If no other indications of active infection are evident, with serologic titers equal to or lower than the maternal titer, infants should be monitored closely, with repeated titers taken at appropriate intervals. In cases of passive transfer of antibody, the neonatal titer should not exceed that of the mother and should revert to negative within 4 to 6 months. In cases in which the mother is infected late in pregnancy, both mother and child may be nonreactive at delivery. In such instances, clinical signs and rising titers during the ensuing weeks will confirm the diagnosis.

Evaluation of the infant suspected of having CS should include a thorough physical examination, ophthalmologic evaluation, serologic studies, CSF-VDRL and cellular/protein analysis, long bone and chest radiographs, complete blood cell and platelet count, and liver function studies.<sup>210</sup>

Parenteral penicillin G is the treatment of choice for all forms of syphilis. Once the diagnosis of CS is confirmed, treatment should commence immediately with aqueous crystalline penicillin G in a dosage of 100,000 to 150,000 units/kg per day intravenously, divided every

12 hours during the first 7 days of life and every 8 hours thereafter, for a total of 10 days. Procaine penicillin G in a dosage of 50,000 units/kg per dose administered intramuscularly once daily for 10 days is an alternative. Treated infants should be monitored closely, with evaluations at 1, 2, 3, 6, and 12 months of age and nontreponemal tests at 2 to 4, 6, and 12 months after conclusion of treatment, until results become nonreactive, or the titer has decreased fourfold.<sup>210</sup>

Infants with evidence of CNS involvement should receive crystalline penicillin G at a dosage of 200,000 to 300,000 units/kg per day given every 4 to 6 hours for 10 to 14 days. Because studies with benzathine penicillin suggest inadequate penetration of the CNS of newborns when serum penicillin levels are low, its use for CS with CNS involvement is not recommended. However, some experts recommend a single intramuscular dose of benzathine penicillin G at 50,000 units/kg after the course of intravenous aqueous crystalline penicillin in children older than 2 years of age who have late and previously untreated CS.<sup>210</sup>

### CYTOMEGALIC INCLUSION DISEASE

Cytomegalic inclusion disease in the newborn is a generalized infection caused by the CMV, a DNA virus of the herpes virus group. It is the most common intrauterine infection in the United States.<sup>212</sup> CMV can be transmitted from person to person via urine, saliva, tears, and genital secretions, as well as via the transplacental route from mother to fetus. Congenital CMV infection occurs in 0.3% to 2.4% of all live births in developed countries,<sup>213</sup> and primary CMV infections are reported in 1% to 4% of seronegative pregnant women. The risk of viral transmission to the fetus is estimated at 30% to 40%.<sup>214</sup> CMV transmission has been reported far less often in association with nonprimary maternal infection.<sup>213</sup> In infants with congenital infection, around 5% to 18% are symptomatic at birth.<sup>215</sup> Although the majority of infected infants are asymptomatic, sequelae of congenital CMV infection in symptomatic patients may range from mild defects to severe or fatal disease. Infants of Native American and African-American descent have a disproportionately greater risk of mortality from congenital CMV infection compared to whites, Asians, and Hispanics.<sup>212</sup>

CMV is generally transmitted from a pregnant mother with inapparent infection across the placenta to the fetus late in gestation, although it can also be transmitted by passage through an infected maternal genital tract at the time of delivery or by postnatal CMV-positive blood transfusion. Postnatal transmission may also occur after consumption of infected breast milk, and low birthweight and early postnatal virus transmission are risk factors for symptomatic infection in this setting.<sup>216</sup> In the United States, the CMV seroprevalence is around 50%, leaving several women of reproductive age at risk for maternal infection.<sup>217</sup> Congenital infection is usually suspected based on fetal ultrasound findings including hydrops, intrauterine growth restriction, microcephaly, ventriculomegaly, and periventricular calcifications. Prematurity occurs in up to 34% of infants with symptomatic congenital CMV infection.<sup>218</sup> Although maternal immunity to CMV was once believed to protect the fetus from infection, it is now known that symptomatic congenital infection can occur after a recurrent maternal infection.<sup>219,220</sup> Because most congenital CMV infections are asymptomatic, diagnosis is most commonly made in infants who manifest several features of the syndrome.

Clinical findings of congenital CMV infection include jaundice, hepatosplenomegaly, anemia, thrombocytopenia, protracted interstitial pneumonia, chorioretinitis, deafness, microcephaly, hypotonia and eventual mental retardation. Cerebral calcifications (often paraventricular) may be noted on imaging studies. Cutaneous manifestations include jaundice, petechiae and purpura, a generalized maculopapular eruption, and a generalized blueberry muffin eruption similar to that seen in infants with congenital rubella and toxoplasmosis. Although extremely rare, vesicular lesions have also been reported in infants with this disorder. Most symptomatic cases of congenital CMV infection are fatal within the first 2 months of life. Those who survive often manifest severe neurologic defects including microcephaly, mental retardation, deafness, spastic diplegia, seizures, chorioretinitis, optic nerve atrophy, and blindness. In infants infected with CMV who do not manifest clinical symptoms at birth, 5% to 15%

develop late-onset sequelae such as hearing loss, chorioretinitis, mental retardation, and neurologic defects.<sup>221</sup>

The gold standard for diagnosis of congenital CMV infection remains the detection of virus in saliva, blood, or urine during the first few weeks of life.<sup>213</sup> Viral recovery or a strongly positive serum IgM anti-CMV antibody is considered diagnostic. PCR is becoming increasingly popular in the diagnosis of CMV disease and can be applied to urine, blood, saliva, and/or CSF. It offers more rapid results and increased sensitivity. Later in infancy, differentiation between intrauterine and perinatal infection is difficult unless signs of intrauterine infection such as chorioretinitis or ventriculitis are present. When the diagnosis remains in doubt, persistent or rising complement-fixation titers may provide confirmatory evidence. Electron microscopic examination for viral particles in urine samples is a rapid diagnostic technique that can also be used, if available. Quantitative PCR examinations on peripheral blood leukocytes can be used to monitor viral load in infected newborns who are infected with CMV.

Prenatal diagnosis should be reserved for pregnancies in which ultrasonographic findings suggest suspicion for CMV fetal infection.<sup>215</sup> Available methods include CMV isolation from amniotic fluid and identification of CMV DNA by PCR analysis. Demonstration of IgM anti-CMV antibody in percutaneous umbilical blood samples is also diagnostic, but this test is more difficult and has a lower sensitivity. Diagnosis of primary CMV infection in pregnant women is achieved with sensitive IgM and IgG avidity serologic assays, as well as conventional and molecular detection of virus in blood.<sup>222</sup>

There is no consistently effective therapy for congenital CMV infection, and prognosis for the patient with severe involvement is poor. Ganciclovir has been used, although large-scale studies are lacking, and its use is associated with significant toxicity. One phase II collaborative study of ganciclovir treatment in symptomatic congenital CMV revealed hearing improvement or stabilization in 16% of patients but only a temporary decrease in CMV excretion in the urine.<sup>223</sup> Intravenous ganciclovir therapy is recommended in the management of babies with symptomatic congenital CMV disease involving the CNS, and treatment should be initiated within the first month of life. Valganciclovir, the oral prodrug of ganciclovir, has been used as an alternative.<sup>224,225</sup>

## CONGENITAL EPSTEIN–BARR VIRUS SYNDROME

Because the majority of young adults are seropositive for EBV, primary infection during pregnancy is uncommon. Although features of congenital EBV infection such as micrognathia, cryptorchidism, cataracts, hypotonia, erythematous skin eruptions, hepatosplenomegaly, lymphadenopathy, and persistent atypical lymphocytosis have been reported, the low rate of EBV infection in pregnancy makes it difficult to assess the full extent of this risk. A recent prospective study comparing women with serologic evidence of primary, recurrent, or undefined infection to a control group found no differences in pregnancy outcome, birthweights, or incidence of congenital anomalies, suggesting that EBV infection during pregnancy does not represent a significant teratogenic risk.<sup>226</sup>

## CONGENITAL TOXOPLASMOSIS

Toxoplasmosis is a parasitic disorder caused by *Toxoplasma gondii*, an intracellular protozoan that may invade multiple tissues including muscle (including the heart), liver, spleen, lymph nodes, and the CNS. Although up to 23% of adolescents and adults may have laboratory evidence of *T. gondii* infection, most are asymptomatic or associated with self-limited symptoms.<sup>227</sup> However, infections in pregnant women may result in serious infantile sequelae if transmitted to the fetus, most notably mental retardation, seizures, and blindness. Toxoplasmosis is transmitted to the fetus transplacentally, and the greatest risk of transmission (60% to 90%) is when acute infection occurs during the third trimester. The severity of fetal infection tends to be greater when infection is acquired during the first trimester. Toxoplasmosis is postnatally transmitted to humans via consumption of raw or inadequately cooked meat (especially pork, lamb, mutton, and wild game)<sup>228</sup> or inadvertent ingestion of oocysts from cat feces in litter or soil.<sup>229</sup>

Most pregnant women with acute *T. gondii* infection are asymptomatic without any obvious signs.<sup>228</sup> The highest burdens of congenital toxoplasmosis are found in South America, parts of the Middle East, and some low-income countries in Africa.<sup>229</sup>

Fetal infection with *T. gondii* may result in stillbirth or prematurity. Signs and symptoms of congenital toxoplasmosis may be present immediately at birth or develop during the first few weeks of life and include fever, malaise, vomiting and diarrhea, lymphadenopathy, hepatosplenomegaly, microphthalmia, cataracts, microcephaly, pneumonitis, pericarditis, bleeding diathesis, and seizures. The classic triad of congenital toxoplasmosis consists of chorioretinitis, hydrocephalus, and intracranial calcifications. Up to 80% of patients develop visual or learning disabilities later in life. Hearing impairment, potentially resulting in deafness, may also occur.<sup>230</sup>

Cutaneous findings of congenital toxoplasmosis include a generalized rubella-like maculopapular eruption that generally spares the face, palms, and soles. Blueberry muffin-like lesions (representing extramedullary hematopoiesis) may be present, as may a scarlatiniform eruption or subcutaneous nodules. The skin eruption usually develops during the first weeks of illness, persists for up to 1 week, and may be followed by desquamation or hyperpigmentation.

Laboratory findings in patients with congenital toxoplasmosis are nonspecific and may reveal anemia, eosinophilia, thrombocytopenia, and at times severe leukopenia. The CSF may be xanthochromic and may contain leukocytes, erythrocytes, and an elevated level of protein. Skull radiographs of affected infants may reveal diffuse, punctate comma-shaped intracranial calcifications.

The diagnosis of congenital toxoplasmosis is made via the combination of clinical findings, serologic studies, DNA-based testing and, occasionally, parasite isolation. Identification of *T. gondii*-specific IgG and IgM antibodies are the most commonly used diagnostic modality, although the clinical significance of IgG antibodies is difficult to interpret during the first 6 months of life. Detection of *Toxoplasma*-specific IgA antibodies in the congenitally infected neonate may be more sensitive than IgM detection.<sup>231</sup> Peripheral blood, CSF, urine, and amniotic fluid specimens should be subjected to PCR testing for *T. gondii*.<sup>231</sup> Much attention has been focused on the prenatal diagnosis of toxoplasmosis, and in addition to maternal serologic studies other available methods include IgG avidity studies, the Sabin–Feldman dye test, and PCR analysis of amniotic fluid. Cordocentesis for evaluation of fetal blood serologies is rarely utilized in the current era.

Most newborns with toxoplasmosis are asymptomatic or have only mild symptomatology, although many may have learning disabilities later in life. Because of the serious sequelae that may develop, even in asymptomatic infants, congenital toxoplasmosis should be treated whether or not the infection is clinically apparent. If fetal infection is confirmed, recommended treatments for the mother have included various combinations of sulfadiazine, pyrimethamine, folic acid, and spiramycin.<sup>232,233</sup> Pyrimethamine combined with sulfadiazine, with folic acid supplementation, is recommended as initial therapy for congenital infection for up to one year. For mild disease, some experts recommend alternating this regimen monthly with spiramycin, during months 7 to 12 of treatment.<sup>231</sup>

The prognosis for infants with toxoplasmosis is variable, although infants who have predominantly CNS involvement have a uniformly poor prognosis. Affected infants may suffer from chorioretinitis with subsequent blindness, microcephaly, hydrocephaly, or mental retardation.

**The complete list of 233 references for this chapter is available online at <http://expertconsult.inkling.com>.**



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# 3

# Eczematous Eruptions in Childhood

Eczematous eruptions are characterized as inflamed papules and plaques, often in association with pruritus and serous discharge. The specific subtype of eczematous dermatitis is based upon the clinical morphology, distribution of lesions, and in many cases the history of exposure. Biopsy of the skin in these conditions is usually not helpful except to consider alternative diagnoses with distinct histopathologic features. In children, by far the most prevalent type of eczematous eruption is atopic dermatitis (AD).

## Atopic Dermatitis

AD, one of the most common skin disorders seen in infants and children, begins during the first 6 months of life in 45% of children, the first year of life in 60% of affected individuals, and before 5 years of age in at least 85% of affected individuals.<sup>1</sup> Although the term *eczema* is commonly used, AD is a more precise term to describe this subset of dermatitis or inflammation of skin. The concept of *atopy* (derived from the Greek *atopia*, meaning *different* or *out of place*) was originated by Coca and Cooke in 1923.<sup>2</sup> Although initially only asthma and allergic rhinitis were included in this category, Wise and Sulzberger in 1933 coined the term AD,<sup>3</sup> noting the association of this form of eczema with other atopic disorders.

### PREVALENCE AND ASSOCIATION WITH OTHER ATOPIC DISORDERS

The prevalence of AD in American children is 10% to 13%,<sup>4,5</sup> which is consistent with the prevalence in Scandinavia<sup>6,7</sup> and Japan<sup>8</sup> and represents a marked increase during the past several decades. Studies performed before 1960 estimated the prevalence to be up to 3%.<sup>9</sup> Of these, 67% have mild disease, 26% have moderate disease, and 7% have severe AD.<sup>5</sup> AD severity is increased in older children, the eldest child in the family, and in children with African-American or Hispanic race/ethnicity.<sup>5</sup> AD occurs more often in urban areas than in rural areas, in blacks, in smaller families, and in higher socioeconomic classes, suggesting that exposure to antigenic pollutants and lack of exposure to infectious agents or other antigenic triggers early in life may play a role in the development of the dermatitis. The subsequent steady increase has paralleled the increase seen in children with asthma, suggesting a shared mechanism or triggers. In fact, AD is often the first manifestation of the “atopic march,” with the later development of sensitization to foods and environmental allergens, asthma and allergic rhinitis. Children with AD overall have a threefold increased risk of developing asthma and a threefold increased risk of developing allergic rhinitis compared with children without AD. Greater severity, earlier onset, persistence of the AD, and parental history of allergic disease further increase the odds of developing other atopic disorders.<sup>7</sup> Overall, asthma occurs in up to 50% of children who develop AD during the first 2 years of life; allergic rhinitis develops in 43% to 80% of children with AD.<sup>10</sup> In addition to the higher prevalence of comorbid asthma, hay fever, and food allergies, severe AD in children is correlated with poorer overall health, impaired sleep, and increased healthcare utilization.<sup>11</sup> Some have classified AD into an immunoglobulin (Ig) E-associated form (“true” or “extrinsic” AD in 70% to 80% of patients) and a non-IgE-associated form (“non-atopic” or “intrinsic” AD). Although the significance of having high IgE levels is unclear, recent biomarker studies in adults have shown that individuals with intrinsic AD show similar activation of T helper (Th) 2 cytokines, but increased Th17 cytokines in comparison with adults with extrinsic AD.<sup>12</sup>

### GENETIC ALTERATIONS

A role for causative genetic alterations is suggested by the concordance of 77% in monozygotic twins<sup>13</sup> and the greater probability of having AD if one or, even more so, both parents have AD.<sup>14</sup> Loss-of-function mutations in profilaggrin (*FLG*) cause ichthyosis vulgaris, a common genetic disorder characterized by dry, scaling skin and hyperlinear palms (see Chapter 5) that has long been known to be associated with AD. Mutations in *FLG* occur in 10% to 30% of AD patients.<sup>15-19</sup> In addition to the tight linkage of AD with genes of the epidermal differentiation complex (particularly encoding filaggrin),<sup>20</sup> genome-wide association (GWA) studies have shown numerous other associated loci, primarily suggesting a role for epidermal barrier function and innate-adaptive immunity in the pathogenesis of AD.<sup>21</sup>

### UNDERSTANDING ATOPIC DERMATITIS PATHOMECHANISM AS A GUIDE TO THERAPY

The “inside-out” concept of AD pathogenesis focuses on immune abnormalities as being primary, whereas the “outside-in” theory considers the epidermal barrier dysfunction (a form of “innate immunity”) as primary. Nevertheless, AD results from the complex interaction between immune dysregulation, epidermal barrier dysfunction, and environmental interactions with skin.<sup>22,23</sup> Understanding these alterations have led to new therapies for AD (see the Management section).

In the acute phase of AD, environmental triggers including irritants, allergens, microbes, and mechanical injury (scratching or rubbing) activate the skin’s innate immune system, which includes epidermal Langerhans cells, keratinocytes, and local immune cells.<sup>24-25</sup> Expression of cytokines, particularly thymic stromal lymphopoietin (TSLP), interleukin (IL)-25 and IL-33, activate group 2 innate lymphoid cells (ILC2s), leading to Th2 cell activation.<sup>26</sup> Th2 cells express IL-4, -5, and -13, which promote eosinophilia and IgE production but suppress the expression of epidermal barrier proteins as well as antimicrobial peptides such as  $\beta$ -defensins and cathelicidin. This reduction in antimicrobial peptide production likely contributes to the propensity toward development of skin infection in AD patients.<sup>27</sup> TSLP and another Th2 cytokine, IL-31, are thought to mediate AD pruritus.<sup>28,29</sup> Systemic circulation of keratinocyte-derived TSLP has been suggested to promote the development of allergic sensitization in both the gastrointestinal (GI) tract and the lungs.<sup>30,31</sup>

Recent studies show that AD T cells also differentiate into Th22 cells, which produce IL-22 and thereby stimulate expression of keratinocyte S100As.<sup>32,33</sup> IL-22 has been implicated in the thickening of skin with lichenification. The role of Th17 cells in AD is not well understood, but increased levels of IL-17 are found (although not to the extent of Th2 cytokines and IL-22), particularly in patients with intrinsic (vs. extrinsic) AD.<sup>12</sup> With chronic AD, the Th2 and Th22 cytokine profiles are accentuated, and in addition, Th1 cytokines are detected (predominantly interferon- $\gamma$ ).<sup>32</sup>

Elevation of cytokines and chemokines in lesional and nonlesional skin, as well as in blood, are biomarkers of disease activity. In adult AD skin, the levels of IL-13, IL-22, CCL17 (TARC), and S100A biomarkers have been found to correlate with disease responses to cyclosporine A<sup>34</sup> and narrow-band ultraviolet light.<sup>35</sup> In the blood, levels of IL-33,<sup>36</sup> Th2 and Th22 cytokines/chemokines,<sup>37</sup> and periostin,<sup>38</sup> a Th2 cytokine-induced extracellular matrix protein, are increased in AD and correlate with disease severity.

The intact epidermis itself also plays a role in the skin’s innate immune system, because it functions as a barrier against water loss (preventing dry skin) and penetration of high molecular weight

### Box 3-1 Clinical Criteria for Atopic Dermatitis

#### Essential Feature

Pruritus (or parental reporting of itching or rubbing) in past 12 months

#### Plus Must Have at least Three of the Following

- History of generally dry skin in past year
- Personal history of allergic rhinitis or asthma (or history in first-degree family member if child <4 years old)
- Onset before 2 years of age (unless currently <4 years of age)
- History of skin crease involvement (antecubital or popliteal fossae; front of ankles; neck; periorbital)
- Visible flexural dermatitis (if child <4 years, include cheeks or forehead, and extensor surface of limbs)

Modified from Brenninkmeijer EE, Schram ME, Leeflang MM, et al. Diagnostic criteria for atopic dermatitis: a systematic review. *Br J Dermatol* 2008;158:754–65. © 2008 by John Wiley & Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

allergens such as dust mite antigens, foods, and microbes. This barrier can be altered by decreased expression of structural proteins (particularly filaggrin) and lipids (particularly ceramides) or by increased expression of proteases (especially kallikrein 5) that break down barrier proteins and increase TSLP.<sup>39–41</sup> Filaggrin is the major component of the stratum granulosum of epidermis and binds to keratin. Its precursor, profilaggrin, contains 10 to 12 monomers of filaggrin, and fewer monomers within the profilaggrin gene (i.e., 10 vs. 12) have been linked to an increased risk of developing AD,<sup>42</sup> which complements the known increased risk of developing AD with filaggrin insufficiency from null mutations in profilaggrin, as occurs in patients with ichthyosis vulgaris (see Chapter 5).<sup>43,44</sup> Filaggrin is also broken down into amino acids, such as urocanic acid, that promote skin hydration, providing another explanation for the dry skin of AD and ichthyosis vulgaris. AD in association with mutations in *FLG* has been shown to be more severe and more persistent.<sup>45</sup> Although little is known about epidermal lipids in AD, decreased content of long-chain ceramides<sup>46</sup> may also contribute to the defect, and many emollients now contain ceramides in an effort to correct the ceramide deficiency. One moisturizer contains both ceramides and filaggrin breakdown products (Cetaphil Restoraderm cream).<sup>47</sup>

## CLINICAL FEATURES

The cardinal features of AD are pruritus, chronicity, and the age-specific morphology and distribution of lesions (Box 3-1).<sup>48</sup> Extent of involvement may range from mild and limited, for example to flexural areas, to generalized and severe. AD has been divided into phases based on patient age and the distribution of lesions (infantile, childhood, and adult), but there is considerable overlap (e.g., infants may show the typical distribution of adult AD).

The infantile phase of AD reflects the manifestations of AD from birth to 6 months of age. It is characterized by intense itching, erythema, papules, vesicles, oozing, and crusting. In infants, it usually begins on the cheeks, forehead, or scalp (Figs. 3-1, 3-2, and 3-3) and then may extend to the trunk (Fig. 3-4) or particularly the extensor aspects of the extremities in scattered, ill-defined, often symmetrical patches. Generalized xerosis is common. Exacerbation of facial dermatitis on the medial cheeks and chin is often seen concomitant with teething and initiating foods. This localization likely reflects exposure to irritating saliva and foods, although contact dermatitis or urticaria may contribute. By 8 to 10 months of age the extensor surfaces of the arms and legs often show dermatitis (Fig. 3-5), perhaps because of the role of friction associated with crawling and the exposure of these sites to irritant and allergenic triggers such as those found in carpets. Although dermatitis of the antecubital and popliteal fossae, periorbital areas, and neck are more commonly involved in older children and adolescents, these sites may be affected in infants and young children as well (Fig. 3-6). Typically, lesions of AD spare the groin and diaper area during infancy (Fig. 3-7), which aids in the diagnosis. This sparing likely reflects the combination of increased hydration in the diaper area, protection from triggers by the diaper, and inaccessibility



**Figure 3-1** Acute atopic dermatitis (AD) on the cheek of an infant. Note the tremendous edema and exudation typical of infantile AD.



**Figure 3-2** Atopic dermatitis (AD) and seborrheic dermatitis. The seborrheic dermatitis of this 2-month-old boy with AD and severe combined immunodeficiency cleared within a few months, but the facial dermatitis persisted and required topical immunosuppressive therapy.



**Figure 3-3** Atopic dermatitis and the headlight sign. Note the relative sparing of the midface and immediate perioral area.



**Figure 3-4** Atopic dermatitis on the trunk and extremities of an infant.



**Figure 3-5** Involvement of the extensor surfaces of the legs and arms are commonly seen during the infantile phase of atopic dermatitis beginning at about 8 months of age, concomitant with crawling and exposure to irritant and allergenic triggers.



**Figure 3-7** Relative sparing of the diaper area is typical in infants with atopic dermatitis, likely owing to the occlusion of this site and protection from scratching and rubbing, as well as from allergenic triggers.



**Figure 3-8** Extensive lichenification on the legs of this affected toddler. Note the follicular accentuation and relative sparing of the popliteal areas.



**Figure 3-6** Although antecubital and popliteal fossa involvement is typical of the childhood and adult phases of atopic dermatitis, infants not uncommonly will show involvement at these fold areas. This infant is demonstrating his response to the pruritus.

to scratching and rubbing. The “headlight sign” has been used to describe the typical sparing of the nose and medial cheeks in AD, even when there is extensive facial involvement elsewhere (see Figs. 3-2 and 3-3).

Not uncommonly, infants initially show signs of seborrheic dermatitis, particularly during the first month or two of life. The associated pruritus and the dry (rather than greasier) scale suggest the combination of both disorders (see Fig. 3-3); the seborrheic component usually clears by 6 to 12 months, whereas the AD features persist. Alopecia may accompany the scalp involvement because of inflammation and chronic rubbing.

The childhood phase of AD usually occurs from 2 years of age to puberty. Affected persons in this age group are less likely to have exudative and crusted lesions and have a greater tendency toward chronicity and lichenification (Fig. 3-8). Eruptions are characteristically drier and more papular and often occur as circumscribed scaly patches. The classic areas of involvement in this group are the wrists, ankles, hands, feet, neck, and antecubital and popliteal regions (Figs. 3-9 and 3-10). Facial involvement switches from cheeks and chin to periorbital (Fig. 3-11) and perioral, the latter sometimes manifesting as “lip-licker’s dermatitis” (see Figs. 3-33 and 3-50). Dermatitis of



**Figure 3-9** Xerosis with erythema, fissuring, and crusting on the neck and periauricular area in this 10-year-old boy.



**Figure 3-12** Nipple eczema occasionally occurs in infants and children with AD and is exacerbated by the rubbing of clothes on the affected nipples.



**Figure 3-10** Atopic dermatitis with irritant dermatitis on the dorsal aspect of the hand. Note the fissuring, which can be quite uncomfortable.



**Figure 3-13** Papular atopic dermatitis (AD) is more commonly seen in African-American children with AD and can be difficult to distinguish from lichen nitidus (see Fig. 4-53) and juvenile frictional lichenoid dermatosis (see Fig. 3-44).



**Figure 3-11** Facial atopic dermatitis in children and adolescents typically affects the periorbital and perioral areas.

the nipples (Fig. 3-12) occurs in some infants and children and can be exacerbated by rubbing on clothing. Pruritus is often severe. Some children with AD show “nummular” or coin-shaped lesions with sharply defined oval scaly plaques on the face, trunk, and extremities (see **Nummular Dermatitis** section). In African-American children, the lesions of AD are often more papular and follicular-based (see Fig. 3-7; Fig. 3-13). Although localization at flexural areas is more common, some children show an inverse pattern with involvement primarily of extensor areas. Lymphadenopathy may be a prominent feature in affected children (Fig. 3-14), reflecting the role of lymph nodes in handling local infection and inflammation. Nail dystrophy may be seen when fingers are affected, indicating involvement of the nail matrix; children may show secondary staphylococcal or pseudomonadal paronychia.

The adult phase of AD begins later in childhood and often continues into adulthood. Predominant areas of involvement include the flexural folds (Fig. 3-15), the face and neck, the upper arms and back, and the dorsal aspect of the hands, feet, fingers, and toes. The eruption is characterized by dry, scaling erythematous papules and plaques and by the formation of large lichenified plaques from lesional chronicity. Weeping, crusting, and exudation may occur from the AD itself, but usually is the result of superimposed staphylococcal



**Figure 3-14** Lymphadenopathy is a common accompanying feature of severe atopic dermatitis (AD), especially when the AD is associated with infection.



**Figure 3-15** Involvement of popliteal and antecubital areas is characteristic in children and adolescents with atopic dermatitis. Note the patches of postinflammatory hypopigmentation on the legs.

infection or allergic contact dermatitis (ACD). Prurigo nodularis, well-circumscribed, usually hyperpigmented thickened papules, most common on the lower extremities, is most commonly seen during adolescence (Fig. 3-16).

Postinflammatory hypopigmentation may be seen at any age, especially in individuals with darker skin (see Fig. 3-15; Fig. 3-17). The pigmentary changes are transient and are reversible when the underlying inflammation is controlled; however, 6 months or more may be required for repigmentation, and sun exposure will accentuate the differences between uninvolved and hypopigmented skin areas. In contrast, hyperpigmentation is predominantly noted at sites of lichen-



**Figure 3-16** Prurigo nodularis. Well-circumscribed, usually hyperpigmented lichenified papules, most common on the lower extremities. Recurrent gouging of these intensely pruritic papules results in scarring.



**Figure 3-17** Postinflammatory hypopigmentation of atopic dermatitis (AD). Postinflammatory hypopigmentation occurs as a sequela of the inflammation of AD and is particularly prominent during summer months when the surrounding unaffected skin tans after exposure to ultraviolet light. The postinflammatory hypopigmentation is not scarring and tends to clear spontaneously after several months if further flares of dermatitis at the site are prevented.

ification, because the thickened epidermis accumulates epidermal melanin pigment, especially in darker skinned individuals. Children with lichenification show accentuation of skin markings (see Fig. 3-8; Figs. 3-18 and 3-19). Parents may mistake the postinflammatory pigment change seen in some children for scarring or a toxicity of topically applied medications and need reassurance. AD lesions are not usually scarring, but secondary infection and deep gouging of lesions can leave residual scarring and permanent depigmentation (see Fig. 3-19).

#### OTHER CLINICAL SIGNS

Several other clinical signs are seen with increased incidence in children with AD, although they may appear in children without AD as well. Dermographism, a manifestation of the triple response of Lewis that occurs in approximately 5% of the normal population, is characterized by a red line, flare, and wheal reaction. A red line



**Figure 3-18** Lichenification. Accentuation of skin markings are notable in thickened, lichenified skin of chronic atopic dermatitis. In darker-skinned individuals, hyperpigmentation tends to be associated with the lichenification.



**Figure 3-20** White dermographism is the paradoxical blanching of skin after stroking.



**Figure 3-19** Lichenification with mild crusting and depigmentation from gouging at the ankle.



**Figure 3-21** Lichen spinulosus is commonly seen in children with dry skin and sometimes with atopic dermatitis. The characteristic, usually round collections of tiny, discrete flat-topped papules are usually asymptomatic.

develops within 15 seconds at the exact site of stroking, followed within 15 to 45 seconds by an erythematous flare (because of an axon-reflex vasodilation of arterioles). The response finally eventuates in a wheal (because of transudation of fluid from the injured capillaries in the original stroke line) 1 to 3 minutes later. Individuals with AD often demonstrate a paradoxical blanching of the skin termed *white dermographism* (Fig. 3-20). The initial red line is replaced, generally within 10 seconds, by a white line without an associated wheal. Patients with AD may also show circumoral pallor, thought to relate to local edema and vasoconstriction.

Follicular hyperkeratosis or chicken-skin appearance, particularly on the lateral aspects of the face, buttocks, and outer aspects of the upper arms and thighs, is termed *keratosis pilaris* (see Figs. 7-24 and 7-25). Keratosis pilaris is not seen at birth but is common from early childhood onward and often persists into adulthood. Each lesion represents a large cornified plug in the upper part of the hair follicles, often with surrounding inflammation and vasodilation. Keratosis pilaris is more commonly associated with AD in children with ichthyosis vulgaris. Moisturizers alone tend to be insufficient as therapy for

keratosis pilaris, and keratolytic agents such as urea or  $\alpha$ -hydroxy acids are required. Their use is limited, however, by the increased potential for irritation in children with AD. Treatment should be discouraged unless of significant cosmetic importance, because keratosis pilaris is almost always asymptomatic.

Lichen spinulosus manifests as round collections of numerous tiny, skin-colored to hypopigmented dry spiny papules (Fig. 3-21).<sup>49</sup> More common in African-American children, lichen spinulosus usually occurs on the trunk or extremities. Lesions tend to be asymptomatic and may respond to application of emollients and mild topical corticosteroids. Children with AD also show an increased incidence of pityriasis alba, nummular dermatitis, dyshidrotic eczema, and juvenile plantar dermatosis (see related sections).



**Figure 3-22** Atopic pleats. Accentuated lines or grooves (Dennie-Morgan folds) are seen below the margin of the lower eyelids. This is a sign of the allergic diathesis and is not specific to atopic dermatitis. Note the mild periorbital dermatitis with hyperpigmentation and the lip-licker's dermatitis.



**Figure 3-23** Milia. Note that this child has numerous milia of the periorbital area, small inclusion cysts that are often a sign of chronic rubbing of the skin from periorbital dermatitis and/or allergic conjunctivitis. Milia clear spontaneously but after months to years.

Individuals with atopic disorders have a distinct tendency toward an extra line or groove of the lower eyelid, the so-called “atopic pleat” (Fig. 3-22). Seen just below the lower lid of both eyes, the atopic pleat may be present at birth or shortly thereafter and is often retained throughout life. This groove (commonly referred to as a *Dennie-Morgan fold*) may result from edema of the lower eyelids and skin thickening; it represents a feature of the atopic diathesis rather than a pathognomonic marker of AD. The atopic pleat has been found with increased incidence in African-American children.<sup>50</sup> Slate-gray to violaceous infraorbital discolorations (“allergic shiners”), with or without swelling, are also seen in patients with allergies and in patients with AD. Allergic shiners are thought to be a manifestation of vascular stasis induced by pressure on underlying venous plexuses by edema of the nasal and paranasal cavities; the swelling and discoloration become more prominent as a result of repeated rubbing of the eyes and postinflammatory pigment darkening. Another clinical feature, an exaggerated linear nasal crease, is caused by rubbing of the nasal tip (the so-called “allergic salute”) and occurs in 7% of schoolchildren.<sup>51</sup> Milia (tiny inclusion cysts; see Chapter 9) of the periorbital area are common in preadolescents (Fig. 3-23), may resemble acne, and are thought to result from the recurrent rubbing.

Many patients with atopic conditions exhibit an increased number of fine lines and accentuated markings of the palms (Fig. 3-24). These accentuated palmar markings often are a clue to the concurrent diagnosis of ichthyosis vulgaris (see the previous discussion of the pathomechanism and also Chapter 5), a relatively common



**Figure 3-24** Accentuated palmar creases. Hyperlinearity of the palms is a sign of concurrent ichthyosis vulgaris (see Chapter 5), a genetic disorder of skin associated with an increased risk of atopic dermatitis.

semi-dominant genetic disorder seen with increased incidence in children with AD. Although individuals with either AD or ichthyosis vulgaris may show accentuated markings on the palms and soles, the characteristic generalized scaling with larger and more severe scaling on the lower extremities, worsening during winter months, and often positive family history of patients with ichthyosis vulgaris further helps to distinguish these conditions.

Allergic keratoconjunctivitis (AKC) is a chronic noninfectious inflammatory condition and is one of the most severe ophthalmic complications associated with atopic dermatitis. AKC has been described in up to 30% of children with AD. It typically begins during late teenage years but has been described as early as 7 years of age.<sup>52</sup> Patients experience chronic itching and pain of the eyes, as well as tearing, redness, and blurred vision. It requires prompt and effective treatment to prevent permanent vision loss; moderate to severe eye irritation, increased redness, discharge, and any visual symptoms are features that require more urgent referral to an ophthalmologist. Complications of AKC include cataracts, keratoconus, infectious keratitis, blepharitis, tear dysfunction, and steroid-induced glaucoma. Treatment options include a combination of mast cell inhibitors, antihistamines, corticosteroids, and calcineurin inhibitors.

Posterior subcapsular cataracts have been described in up to 13% of adult patients with severe AD.<sup>53</sup> Rarely seen in children, these cataracts are usually asymptomatic. Keratoconus (elongation and thinning of the corneal surface) has been reported in about 1% of patients with AD and seems to develop independently of cataracts.<sup>53</sup> Keratoconus is exacerbated by continuous rubbing of the eyes and may require corneal transplantation.

## INFECTIOUS COMPLICATIONS

In contrast to a prevalence of a carrier state in 5% to 20% of individuals who have no atopic condition, *Staphylococcus aureus* is recovered in up to 90% of patients from lesions of AD—up to 76% from uninvolved (normal) skin and 50% to 60% from the anterior nares.<sup>54–56</sup> The increased adherence of *S. aureus* to the epidermal cells of individuals with AD<sup>57</sup> and a failure to produce endogenous antimicrobial peptides in the inflamed skin of patients with AD may account for the high rate of *S. aureus* colonization and infection. Although secondary infection in AD is usually from *S. aureus* (72%), 16% of cultures in infected patients with AD yield *S. pyogenes*, and 14% are mixed cultures.<sup>58</sup> Patients infected with group A streptococcus were more likely to be febrile, to have facial and periorbital involvement, have bacteremia and cellulitis, and to be hospitalized compared with those infected with *S. aureus* alone.<sup>58</sup>

The pyoderma associated with AD is usually manifested by erythema with exudation and crusting (Fig. 3-25), particularly at sites of scratching, and occasionally by small pustules at sites of dermatitis (Fig. 3-26). This complication must be considered whenever a flare of



**Figure 3-25** Staphylococcal infection in atopic dermatitis. Sites of excoriation on the dorsal aspects of the hand are oozing and crusted. Note the erythema and mild associated edema. Fissuring often occurs on the hands and feet, as seen on the right thumb. Both the dermatitis and the infection improved with oral administration of cephalaxin, and the use of daily baths with sodium hypochlorite helped to maintain control while minimizing crusting.



**Figure 3-27** Methicillin-resistant *S. aureus* (MRSA) infection in atopic dermatitis (AD). (A) Staphylococcal pustulosis on the knees in a girl with severe AD and recurrent MRSA infections. (B) Her father has an MRSA abscess on the arm. Decolonization of the entire family is important.



**Figure 3-26** Staphylococcal infection in atopic dermatitis (AD). Discrete nongrouped pustules and crusting overlying erythema and swelling of the periorbital area of a child with severe AD.

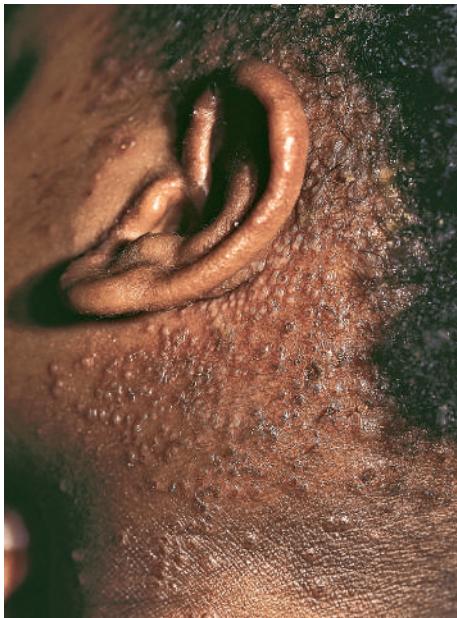
chronic AD develops or fails to respond to appropriate therapy. *S. aureus* exacerbates the AD through: (1) release of superantigen toxins, which enhance T-cell activation; (2) activation of superantigen-specific and allergen-specific T cells<sup>59</sup>; (3) expression of IgE antistaphylococcal antibodies<sup>60,61</sup>; and (4) increased expression of Th2 cytokines (including IL-31 and TSLP, which are known to cause pruritus directly) and increased expression of IL-22,<sup>62</sup> which is associated with epidermal thickening. Superantigen production also increases the expression of an alternative glucocorticoid receptor that does not bind to topical corticosteroids, leading to resistance.<sup>63</sup> Other factors produced by *S. aureus* are likely to exacerbate AD as well.<sup>64</sup> These observations emphasize the role of *S. aureus* as an important trigger of AD and endorse therapies that decrease the numbers of bacteria on the skin.

Although methicillin-resistant *S. aureus* (MRSA) colonization and superinfection of AD is increasing, the majority of children with AD harbor methicillin-sensitive *S. aureus* (MSSA).<sup>54,65</sup> MRSA infection may manifest as pustules (Fig. 3-27, A), abscesses (Fig. 3-27, B) or crusting that is indistinguishable clinically from MSSA infection but much more difficult to eradicate; suppression of MRSA often requires that the entire family (including pets, who can harbor MRSA) be treated initially or even on an intermittent basis to reduce colonization and familiar infections, such as with intranasal mupirocin ointment and once to twice weekly bleach baths or sodium hypochlorite-containing cleansers.

Greater cutaneous dissemination of certain viral infections has also been noted in children with AD and has been attributed to defects in the generation of antimicrobial peptide and the relative deficiency of Th1 cytokine generation and cytotoxic T-cell function. Molluscum

contagiosum is a cutaneous viral infection of childhood that most commonly affects the trunk, axillae, antecubital, popliteal fossae, and crural areas (see Chapter 15). Lesions are usually small, dome-shaped papules that often show central umbilication. The often-extensive molluscum lesions tend to be most numerous at sites of active dermatitis and can induce pruritus as well as dermatitis around the molluscum papules ("molluscum dermatitis").

Eczema herpeticum (EH, also termed Kaposi varicelliform eruption) describes the explosive development of a vesiculopustular eruption caused by herpes simplex virus in an individual with an atopic condition. Children with more severe AD and other atopic conditions are at greatest risk.<sup>66</sup> Herpes simplex virus has been associated with having fewer circulating and skin-resident T cells that express interferon- $\gamma$ .<sup>67</sup> The clustering and often umbilication of the vesicles is characteristic (Figs. 3-28 and 3-29), with sites of the dermatitis most commonly affected. The diagnosis can be verified by direct fluorescent assay and



**Figure 3-28** Eczema herpeticum (Kaposi varicelliform eruption). Grouped vesiculopustular lesions on the face, retroauricular, and neck areas. Several of the pustules are beginning to show umbilication.



**Figure 3-29** These small, round umbilicated vesicles and punched out erosions are typical lesions of herpes simplex infection.

viral culture. If these tests are not available, a Tzanck test can be performed by scraping the floor of vesicles and, after staining the smear with Giemsa or Wright stain, searching for multinuclear virus "giant cells" or balloon cells.

Hospitalization may be necessary, especially in infants under 1 year of age and in association with fever and/or systemic symptoms.<sup>68</sup> Early administration of acyclovir has been shown to lead to better outcomes for EH,<sup>69</sup> and use of topical corticosteroids or calcineurin inhibitors has not been associated with poorer outcomes in children hospitalized with EH.<sup>70</sup> Systemic antibiotics should be administered if secondary bacterial infection is strongly suspected but should not be used empirically.<sup>71</sup> Eczema vaccinatum was a problem when smallpox vaccinations were compulsory, most commonly contracted by accidental contact with a recently vaccinated individual. The global threat of bioterrorism and consideration of smallpox vaccinations has again brought to attention the risk of eczema vaccinatum for patients, particularly children, with AD.<sup>72</sup> Eczema vaccinatum is characterized by the widespread cutaneous dissemination of vaccinia viral lesions that manifest as firm, deep-seated vesicles or pustules that are all in the same stage of development (see Chapter 15). Lesions may become umbilicated or confluent. *Eczema coxsackium* is a recently coined term to describe the unusual cutaneous concentration in sites of previous or current AD of vesicles and erosions from Coxsackie A6 and, less commonly, Coxsackie A16 infection, which could be confused with EH.<sup>73,74</sup> Fever, oral erosions/ulcerations, and sore throat/mouth are among the most common associated symptoms. Lesions clear spontaneously in an average of 12 days but may persist for a month. Reactivity to *Malassezia* has been blamed for recalcitrant AD of the head and neck in adolescents. Although there are no documented differences in *Malassezia* species colonization, patients with head and neck AD are more likely to have positive skin-prick test results and *Malassezia*-specific IgE compared with healthy control subjects and patients with atopy without head and neck dermatitis. These patients may benefit from a 1- to 2-month course of daily itraconazole or fluconazole followed by long-term weekly treatment.<sup>75</sup>

## DIFFERENTIAL DIAGNOSIS

AD is a chronic fluctuating disease. The distribution and morphology of lesions vary with age, but itching is the cardinal symptom of this disorder. Although many skin conditions may occasionally resemble AD, certain characteristics assist in their differentiation.

Seborrheic dermatitis is characterized by a greasy yellow or salmon-colored scaly eruption that may involve the scalp, cheeks, trunk, extremities, and diaper area. The major differentiating features include a tendency toward earlier onset, characteristic greasy yellowish or salmon-colored lesions with a predisposition for intertriginous areas, a generally well-circumscribed eruption, and a relative absence of pruritus (see below). Infants may show both atopic and seborrheic dermatitis (see Fig. 3-2), with progression or persistence of the atopic lesions as the seborrheic dermatitis subsides.

Contact dermatitis can be divided into irritant contact dermatitis and ACD. Primary irritant dermatitis is commonly seen in infants and young children. It is most commonly seen on the cheeks and the chin (owing in part to the irritation of saliva), the extensor surfaces of the extremities (as a result of harsh soaps, detergents, or rough fabrics), and the diaper area (primarily from feces and vigorous cleansing). Primary irritant dermatitis is generally milder, less pruritic to asymptomatic, and not as eczematous and oozing as the eruptions seen in association with AD. Irritant dermatitis may also result from bubble baths, personal care products, and in handled materials such as modeling clays. Irritant contact dermatitis to saliva and to exposure to harsh soaps and fabrics occurs more often in children with concomitant AD. Although the diaper area in AD is typically normal, irritant diaper dermatitis can occur.

ACD, although relatively uncommon in the first few months of life, can mimic almost any type of eczematous eruption and is characterized by a well-circumscribed pruritic, erythematous, papular, and vesicular eruption. Although such eruptions involute spontaneously on identification and removal of the cause, this disorder often requires a carefully detailed history and prolonged observation before the true causative agent is identified. ACD to nickel occurs often in children

with AD<sup>76</sup> and may be misdiagnosed as recalcitrant periumbilical AD. Patients with recalcitrant AD may have concomitant allergic contact reactions, particularly to nickel and less often to topically applied medications and emollients, suggesting the role for patch testing.<sup>77</sup> Positive patch tests for potential allergens other than nickel have been described in up to 45% of children with AD,<sup>76,78,79</sup> and half of these are reactions to components in the emollients (avena extract; wheat protein; calendula; lanolin). Children with AD may react to fragrance, antiseptics (chlorhexidine), and even their topical steroid.<sup>78,80,81</sup>

Nummular dermatitis is a distinctive disorder characterized by coin-shaped lesions. Measuring 1 cm or more in diameter, lesions of nummular dermatitis develop on dry skin and are more often seen during dry winter months. The eruption is characterized by discrete erythematous round plaques formed by the confluence of papules and vesicles (Figs. 3-30 and 3-31). Nummular lesions tend to be more recalcitrant to topical therapy and, not uncommonly, become infected so that concomitant treatment of secondary staphylococcal infection and measures to limit staphylococcal overgrowth (such as dilute sodium hypochlorite baths) should be considered.

The lesions of psoriasis, another common skin disease of children, are bright red and topped with loosely adherent silvery micaceous

scale (see Chapter 4). Psoriatic lesions usually show a sharply delineated edge and have a predilection for the extensor surfaces (particularly the elbows and knees), the scalp, the buttock, and the genital regions. Approximately 5% of children with psoriasis also show dermatitis, either as typical psoriasis and atopic dermatitis lesions or a psoriasiform dermatitis; these children often have a family history of both atopy and psoriasis.

Scabies in infants and children is commonly complicated by eczematous changes because of scratching and rubbing of involved areas or the application of harsh topical therapeutic agents. The diagnosis of scabies is best made by the history of itching, a characteristic distribution of lesions, the recognition of primary lesions (particularly the pathognomonic burrow when present), positive identification of the mite on microscopic examination of skin scrapings, and the presence of infestation among the patient's family or associates (see Chapter 18).

Langerhans cell histiocytosis (LCH) most commonly occurs before 3 years of age (see Chapter 10). In affected neonates, reddish-brown, purpuric, crusted papules or vesiculopapules are typically present. In infants this skin eruption is often characterized as a scaly, erythematous seborrheic eruption on the scalp, behind the ears, and in the intertriginous regions. On close inspection the presence of reddish-brown, petechial or purpuric lichenoid papules or vesicular or crusted papules in infants is typical. Cutaneous biopsy and identification of CD1a+ Langerhans cells by immunostaining confirms the diagnosis of LCH.

Acrodermatitis enteropathica is an autosomal recessive disorder characterized by vesiculobullous eczematoid lesions of the acral and periorificial areas, failure to thrive, diarrhea, alopecia, nail dystrophy, and frequent secondary bacterial or candidal infection (see Chapters 2 and 24). The characteristic distribution of lesions accompanied by listlessness, diarrhea, failure to thrive, and low serum zinc levels differentiate lesions of acrodermatitis enteropathica from those of AD. Usually a disorder in formula-fed babies with the hereditary form, acrodermatitis enteropathica may also occur in breastfed babies owing to deficient zinc secretion into maternal breast milk.

Dermatitis during the neonatal or infantile periods is also seen in immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, which manifests with early onset intractable diarrhea and type 1 diabetes mellitus as well.<sup>82-84</sup> The disorder is often fatal during the first year of life. The cutaneous manifestations are seen in 70% of affected babies and tend to be the first sign.<sup>82</sup> Although an atopic-like dermatitis is most common, the eruption has also been described as psoriasiform or resembling ichthyosiform erythroderma. Lesions are often pruritic, secondarily infected by *S. aureus*, and resistant to treatment with topical corticosteroids. Other common cutaneous manifestations include severe cheilitis, onychodystrophy, and alopecia.

Infections of the upper and lower airways and GI tract are also common, and affected patients may succumb to sepsis. Food allergies and high levels of IgE and eosinophils are also associated. The autoimmune enteropathy is characterized by persistent, watery, and sometime mucoid or bloody diarrhea during the neonatal period, resulting in malabsorption and failure to thrive. The type 1 diabetes is difficult to control and results from lymphocytic infiltration of the pancreas. Other autoimmune symptoms, such as hypothyroidism, cytopenia, hepatitis, nephropathy, and arthritis can develop in patients who survive the initial acute phase.

IPEX syndrome results from mutations in *FOXP3*, leading to absent or dysfunctional regulatory T cells and self-reactive T-cell activation and proliferation. Detection of enterocyte autoantibodies helps to make the diagnosis.<sup>85</sup> Treatment generally includes supportive care and systemic immunosuppressive therapy (steroids, methotrexate, tacrolimus), although rapamycin has shown promise. Stem-cell transplantation is the curative treatment<sup>84</sup> if a suitable donor can be found.

Typical AD may be a feature of several forms of immunodeficiency, most notably in Wiskott–Aldrich syndrome (WAS) and the hyperimmunoglobulinemia E syndrome (HIES) (see related sections). These disorders are distinguished from AD by their recurrent noncutaneous infections and other characteristic features (e.g., thrombocytopenic purpura, bloody diarrhea, and purpuric lesions in WAS and facial and intertriginous staphylococcal abscesses in HIES).



**Figure 3-30** Nummular dermatitis. Characterized by well-defined, round (coin-shaped or nummular) plaques of vesiculopapules overlying erythema and edema. Oozing and secondary infection are common.



**Figure 3-31** Nummular dermatitis. Some patients show multiple nummular plaques.

## PROGNOSIS AND EFFECT ON QUALITY OF LIFE

Although studies in the past have shown that AD tends to clear in 43% of children by age 3 and in up to 70% by puberty,<sup>86,87</sup> recent studies have shown a 1-year prevalence of AD in adults of up to 10.2%<sup>88</sup> and that more than 80% of children with mild to moderate AD have recurrent symptoms or require medication use at least into the second decade of life.<sup>45</sup> Longitudinal studies are needed to verify data suggesting that most patients with AD have persistence of at least some form of their skin disease (often hand eczema) into adulthood.

The quality of life in infants, children, and adolescents with moderate to severe dermatitis is significantly reduced,<sup>89</sup> and having severe AD during childhood can have a great impact on psychosocial development.<sup>90</sup> Infants with AD have been shown to be excessively dependent and fearful. Sleep disturbance affects up to 60% of children with AD overall and 83% of children during flares. Neurocognitive function is impaired in children with sleep problems.<sup>91</sup> Even in clinical remission, children with AD show more sleep disturbance than healthy children,<sup>92</sup> including increased nocturnal wakefulness and a longer latency to rapid-eye-movement (REM) sleep.<sup>92</sup> Recent studies have also shown a strong association of AD with attention-deficit/hyperactivity disorder (ADHD)<sup>93–95</sup> that is associated with more severe disease and sleep deprivation,<sup>96</sup> reinforcing the impact of these factors on neurocognitive function. Disfigurement associated with moderate to severe AD, coupled with the reduction in sleep, restlessness, and fatigue at school, as well as limitations in participation in sports, isolates the affected child and strains relationships with peers and with teachers. AD is also associated with an increased odds ratio of depression, anxiety, conduct disorder, and learning delay.<sup>97</sup> Children with AD have a higher risk of injury requiring medical attention, related both to comorbid psychiatric and behavioral disorders and their atopy.<sup>97</sup>

As a chronic disorder that requires frequent attention, the family carries a high financial burden of parental missed days from work for doctor visits and home care, lost wages owing to interruption of employment, expensive medications, and the costs of special or additional bedding, clothes, and food. The socioeconomic impact of AD in the United States alone is estimated to be \$364 million to \$3.8 billion annually.<sup>98</sup> The demonstrated average reduction by 1 to 2 hours of parental sleep nightly also translates into increased parental stress<sup>99</sup> and the tendency of affected children to cosleep with parents affects family dynamics.<sup>100</sup> These stressful psychological factors often exacerbate the AD, as may concurrent infectious illness or the stress of assignments at school.

## MANAGEMENT

The management of AD requires patient and parent education,<sup>101</sup> avoidance of irritants and allergic triggers, good moisturization, and use of anti-inflammatory medications<sup>102</sup> (Table 3-1). Patient compliance is the main reason for poor outcome and is fueled by concerns about the use of topical corticosteroids and calcineurin inhibitors (see below). Aggressively but safely managing AD flares is important in preventing the exacerbation of disease by delayed or inadequate treatment. The National Eczema Association (NEA) offers a website for education and patient support ([www.nationaleczema.org](http://www.nationaleczema.org)). Age-specific structured educational programs have improved objective and

subjective severity scores,<sup>103</sup> and educational videos may improve severity beyond direct education.<sup>104</sup> Written action plans have been shown to improve adherence to therapy.<sup>105</sup> Several new reviews of AD management for children have been published.<sup>106–110</sup>

### Use of Emollients and Bathing

In general, dryness is worse during cold months when it is aggravated by heat in the house and low humidity. Key to maintaining hydration is the application of a good emollient, particularly within minutes after bathing. In general, the thicker and greasier the emollient, the higher the content of oil relative to water and the more effective the emollient (e.g., ointment is better than cream, which is better than lotion). Nevertheless, nonointment emollients, particularly ceramide-dominant creams, can be substituted when use of a greasy ointment is objectionable and may have inherent anti-inflammatory properties. Some patients, especially those with sensory issues and poor tolerance of ointments and creams, find oils to be helpful, although in general oils do not penetrate the skin as well as oil–water mixtures. Purified sunflower seed oil improves the AD skin barrier, whereas olive oil and mustard seed oil are detrimental to skin barrier recovery and can cause erythema,<sup>111,112</sup> emphasizing that oils are not interchangeable. Similarly, virgin coconut oil is superior to mineral oil in reducing AD severity<sup>113</sup> and to olive oil in decreasing *S. aureus*.<sup>114</sup> “Barrier repair” agents, such as N-palmitoyl ethanolamine (MimyX),<sup>115</sup> ceramide-dominant, physiological-lipid based cream (EPI Ceram),<sup>116</sup> and MASO63DP (Atopiclair),<sup>117</sup> also show mild anti-inflammatory properties and may be beneficial for children with mild to moderate AD but are much more costly than emollients.

### Preventing the Development of Atopic Dermatitis with Early Use of Emollients

Infants in at-risk families (i.e., with at least one parent or sibling who has AD) have a 30% to 50% chance of developing AD by 2 years of age.<sup>118</sup> Early evidence suggests that limiting the use of skin cleansers and applying an oil-in-water emollient at least once daily may lower the risk<sup>119–121</sup> or decrease the AD severity.<sup>122</sup>

Water hardness has been shown to be associated with an increased prevalence of AD,<sup>123,124</sup> and a preliminary analysis suggests that hard water also increases the development of AD in at-risk infants. Although ion-exchange water softeners do not lower the prevalence of AD,<sup>125</sup> other techniques to soften water without adding ions have yet to be tested. Several trials have shown no protective effect of maternal dietary avoidance during pregnancy and in most cases during lactation on the incidence of AD during the first 18 months of life.<sup>126</sup>

### Use of Bathing for Atopic Dermatitis

Although water exposure can increase xerosis through evaporative loss, daily baths hydrate the skin, especially if the water loss is prevented by emollient application within a few minutes after bathing. Baths are also fun for infants and children, contribute to parent–child bonding, and remove surface bacteria and desquamated scale. Whether to limit the duration of bathing is controversial, but many recommend limiting the bath to approximately 10 minutes. Older children and adolescents should be instructed to avoid excessively warm baths and showers. Only mild soaps with lower pH to suppress protease activation (such as Dove or Basis) or soapless cleansers (such

**Table 3-1** Management of Mild, Moderate, and Severe Forms of Atopic Dermatitis

Mild	Moderate	Severe
Bathing and barrier repair* Avoidance of irritant and allergic triggers Intermittent, short-term use of class VI or VII topical steroids (see Table 3-2) ± topical calcineurin inhibitors Treat superinfection	Bathing and barrier repair* Avoidance of irritant and allergic triggers Intermittent, short-term use of class III–V topical steroids (see Table 3-2) ± topical calcineurin inhibitors Treat superinfection Oral antihistamines	Bathing and barrier repair* Avoidance of irritant and allergic triggers Class II topical steroids for flares (see Table 3-2); class III–V topical steroids ± tacrolimus ointment for maintenance Treat superinfection Oral antihistamines Consider systemic anti-inflammatory agents, ultraviolet light therapy

\*Barrier repair may be accomplished by application of effective emollients or from barrier-repair agents.

as Cetaphil, CeraVe, or Aquanil) should be used if a cleanser is felt to be needed. Bubble baths are contraindicated in moderate to severe AD. Bath oils are only slightly beneficial and because they tend to make the tub slippery should be used sparingly and cautiously.

The addition of dilute sodium hypochlorite (bleach) to the bath (1 mL/L or  $\frac{1}{4}$  cup per half-tub of water) or use of a sodium hypochlorite wash is helpful in controlling the dermatitis of children who with a history of skin infection (see **Topical Anti-Inflammatory Medications** section).<sup>54</sup> Although the antibacterial effect has been implicated in AD improvement, the recently demonstrated anti-inflammatory effect of sodium hypochlorite<sup>127</sup> may also play a role (see **Treatment of Secondary Cutaneous Infections** section). Children may complain about sitting in a tub bath because of stinging, particularly during acute exacerbations with raw skin and crusting. In such instances, the addition of 1 cup of salt or baking soda may make the bath more tolerable until more aggressive therapy such as treatment of the secondary infection with oral antibiotics leads to improvement.

Wet wraps of plain water can be applied at night after bathing and emollient or after application of the topical anti-inflammatory agent to decrease pruritus and the sensation of burning at night.<sup>128-130</sup> Short-term use (up to 14 days) of wet wraps over topical corticosteroids is more efficacious than wraps over bland emollients alone but can be associated with transiently increased steroid absorption. Although wet gauze bandage wraps (such as Kerlix or Kling) are often used in a hospital setting, dressing the young child at home in moist pajamas and socks that cling to the skin and are topped by a dry layer to avoid excessive cooling can be very soothing and promote sleep. Unna boots can also be loosely applied to the legs or arms at night (under self-adherent wraps) to decrease pruritus and protect from scratching.

Open wet compresses may be useful in children with weeping, oozing, or crusted lesions. Aluminum acetate (as in Burow solution, 1:20 or 1:40) is germicidal and suppresses the weeping and oozing of acutely inflamed lesions. Burow solution 1:40 is prepared by dissolving one packet or effervescent tablet (Domeboro) in a pint of cool or tepid tap water. These compresses are applied with a soft cloth such as a man's handkerchief or strips of bed-sheeting two to three times daily for 10 to 15 minutes for up to 5 days. Washcloths and heavy toweling interfere with evaporation and therefore are not as effective. Compresses should be lukewarm, moderately wet (not dripping), and remoistened at intervals. After the compress, the topical anti-inflammatory agent may be applied.

### Avoidance of Irritant Triggers

Many patients have problems with eccrine sweating and sweat retention during the summer months, leading to increased pruritus, especially in the face of lichenification and significant dermal inflammation. The increased vasodilation of already inflamed skin from increased summer heat further contributes to pruritus and cutaneous warmth. Nevertheless, children with AD should be encouraged to participate as actively in sports as possible. Swimming is an excellent sport for children with AD if exposure to chlorinated pool water is tolerated. Children should be coated with an emollient (after sunscreen application) as a protectant against pool chemicals; rinsing immediately after swimming with application of emollient may decrease the risk of irritation. Children should also be kept cool after application of the thick emollient, or if sweating is anticipated, a less occlusive moisturizer should be applied. Air-conditioning is important during hot weather to decrease pruritus. The pruritus and erythematous papules of miliaria rubra, which can develop when sweating and are prevented by an occlusive moisturizer, can be confused by parents with exacerbation of the dermatitis, setting up a cycle of worsening involvement from repeated application of the occlusive emollient. Recognition and education in decreasing the frequency of emollient application are vital in this situation.

Overdressing children during winter months should also be avoided to prevent overheating. The low humidity of winter months and use of indoor heating also increases skin xerosis and may promote dermatitis; humidifiers maybe useful but may increase the exposure to mold allergens if they are not cleaned often. Saliva is a major irritant for infants with AD, and exposure to large amounts of saliva with teeth-ing and eating, including saliva mixed with food, exacerbates the

facial dermatitis. Protecting the face before meals or naptime with a thick, protective emollient may be helpful. Similarly, older children with AD are at risk for lip-licker's dermatitis because of the irritant effects of saliva.

Attention to clothing is also important. Soft cotton clothing is recommended over wool or other harsh materials, which tend to precipitate itching and scratching, and in one study fabric softener decreased skin dryness.<sup>131</sup> There is only low-quality evidence regarding AD improvement or decrease in bacterial colonization from use of special textiles, particularly silk and silver-coated cotton, but there is no evidence of harm.<sup>132</sup> Affected children should avoid use of harsh soaps and detergents, fabric softeners, products with fragrance, and bubble baths. Smoking of cigarettes in homes of children with AD should be avoided, because it can lead to an increase in irritation and pruritus and may also increase the tendency toward subsequent development of asthma.<sup>133</sup>

### Avoidance of Triggering Allergens

It may be possible to identify potential allergen triggers by taking a careful history and doing selective allergy tests.<sup>134</sup> However, triggers that can easily be avoided are difficult to find for most affected individuals, and without a documented or proven food allergy, avoiding potentially allergenic foods as a means of managing AD is not recommended. Testing for allergy to milk, egg, peanut, wheat, and soy is recommended in children younger than 5 years of age with moderate to severe AD who have persistent AD despite optimized management with topical therapy and/or have a reliable history of an immediate reaction after ingestion of a specific food.<sup>135,136</sup> Food antigen-specific IgE (sIgE) levels correlate better than a radioallergosorbent test (RAST) and prick tests,<sup>137</sup> but the level of sIgE is not clinically useful for predicting the development of clinically relevant food allergy. Negative skin-prick tests or serum allergen-specific IgE levels are highly predictive at eliminating potential allergens. However, at 6 months of age, 83% of patients with severe AD show IgE food sensitization to milk, eggs, and/or peanuts, and 65% of these children retain food sensitivity by 12 months of age. In comparison, 5% of 6-month-old infants and 11% of 12-month-old infants without atopy show IgE food sensitization.<sup>138</sup> Fewer than 40% of children with moderate to severe AD with food sensitization show reactivity during food challenges,<sup>139</sup> and many of these eruptions are urticarial. In a recent longitudinal study, 16% of more than 1000 infants with AD (all severities) developed food allergies, particularly to peanut (7%), milk (4%), and egg (4%) with the highest risk in infants with greater AD severity.<sup>140</sup> Foods may also induce extracutaneous manifestations in pediatric patients with AD, particularly involving the GI tract. Foods may also act as irritants, especially citrus foods, and that reactions to chemicals in foods, such as tartrazine or other colorings, may occur. For children in whom food allergies are suspected to be relevant, comangement with a pediatric allergist is recommended.

Despite the fact that maternal dietary antigens are known to cross the placenta, most studies have provided no evidence that avoidance of maternal dietary antigens during pregnancy or lactation has a protective effect during the first 18 months of life on the development of AD or on food sensitization by 7 years of age.<sup>126,141</sup> As a result, breastfeeding without restricting maternal diet as a strategy to prevent food allergy is recommended until 4 to 6 months unless contraindicated for medical reasons.<sup>136</sup> Despite earlier studies suggesting the opposite, more recent analyses have shown that peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children,<sup>142,143</sup> although reduction in developing AD only correlated with wheat consumption.<sup>143</sup> As a result, hydrolyzed infant formulas, rather than cow's-milk or soy-milk formulas can be given to at-risk infants who are not exclusively breastfed if available and affordable, but they may not affect the risk of AD. Solid foods, including potentially allergenic foods, should not be delayed beyond 4 to 6 months of age in at-risk infants.<sup>144,145</sup>

The most common food allergens often contaminate other foods and are difficult to avoid entirely. Restrictions in diet should not worsen the quality of the patient's and family's life more than the AD itself. Challenges of agents that may trigger IgE reactivity are best conducted under medical observation, because anaphylaxis has occasionally been reported. It should be remembered that excessively restrictive

diets in atopic children may lead to weight loss, calcium deficiency, hypovitaminosis, and kwashiorkor.<sup>146</sup> Proper nutritional counseling and supplementation should be included in management, including warning against the use of protein-poor rice and almond milk for cow's milk, hydrolyzed, and elemental formulas. After the first few years of life, the risk of significant reactivity to food diminishes (particularly with eggs, milk, soy, and wheat). Unless a careful dietary history suggests food sensitivity as a trigger, improvement through dietary manipulation in children older than 5 years is rarely noted.

In contrast to potential reactivity to foods, reactivity of children and adolescents with AD to aeroallergens increases with age. The most common aeroallergen triggers are house-dust mites (*Dermatophagoides pteronyssinus*), grass pollens, animal dander, and molds, particularly *Alternaria*. Plant pollens, particularly ragweed, also contain an oleoresin capable of producing sensitization and eczematous contact dermatitis. Air-borne dermatitis may involve the exposed surfaces of the face, neck, arms, legs, and "V" area of the chest but can be distinguished from photosensitivity, which results in sharper lines of demarcation between normal skin and eczematous skin. Exacerbation of facial dermatitis during pollen season or after children contact a pet should alert parents to the possibility of allergy to an aeroallergen or contact allergen (see [Allergic Contact Dermatitis](#) section). Cat exposure during infancy can increase the risk of developing AD,<sup>147</sup> especially in infants with an *FLG* mutation.<sup>148</sup> Cat exposure in children with AD has been shown to increase the risk of developing asthma, although dog exposure may be protective.<sup>149</sup> Epicutaneous application of aeroallergens by atopy patch test on unaffected atopic skin shows reactivity as an eczematoid patch in 30% to 50% of patients with AD but tends to be negative in patients with only respiratory allergy to these triggers or in healthy volunteers. However, patch tests have not been standardized, and their performance and interpretation vary widely. The value toward AD control of mite-allergen avoidance measures (encasing mattresses and pillows, washing bedding in hot water weekly, vacuuming living areas and bedrooms frequently, keeping only soft nonfurry toys, cleaning carpets regularly or removing them, and eliminating pets) is controversial, and a meta-analysis found no value in encasing mattresses to prevent allergic diseases or symptoms.<sup>150</sup> Immunotherapy for food allergies or aeroallergens has long been controversial as treatment for AD, unlike its efficacy for treating allergic rhinitis and extrinsic asthma; recent double-blind, placebo-controlled studies, however, suggest some value of specific oral and sublingual immunotherapy, including to peanuts.<sup>151,152</sup>

### Topical Anti-inflammatory Medications

Topical corticosteroids have been the mainstay of treatment for AD (see [Table 3-1](#)), and are available in a wide range of potencies from the weakest class VII corticosteroids (e.g., hydrocortisone acetate) to the ultrapotent class I steroids ([Table 3-2](#)). The use of more potent topical corticosteroids, particularly when applied to large surface areas, under occlusion, or for long periods may lead to adverse effects ([Box 3-2](#)), most commonly local atrophy. The face and intertriginous areas are the most susceptible sites and may show local effects, even when

weaker steroids are used for prolonged periods. Because of their increased body surface area-to-weight ratio, small children have the greatest risk of systemic absorption of topically applied steroids. Concern about the use of topical steroids has led to "steroid phobia" among families and even physicians.<sup>153</sup> As a result, compliance may be decreased and weak topical steroids insufficient for adequate control may be used. In a recent study, 81% of parents or adult patients with AD had fears about the use of topical steroids, and 36% admitted nonadherence as a result.<sup>154</sup> Recently, topical steroid addiction has been cited as an adverse effect of topical corticosteroids, but it is virtually never seen in children with AD who use topical steroids and should not discourage the use of topical steroids in pediatric patients. In older patients with AD, this disorder is characterized by a burning/stinging, sharply delineated erythematous eruption, primarily on the face and genital region, occurring days to weeks after discontinuation of prolonged, inappropriate, and frequent use of moderate-to-high-potency topical corticosteroids.<sup>155</sup> In general, group I corticosteroids are not recommended for patients younger than the age of 12 years, should not be used in intertriginous areas or under occlusion, and require a rest period after 14 days of use. Use of this group of ultrapotent steroids is usually reserved for lichenified plaques and recalcitrant dermatitis of the hands and feet and should be limited. Considering the widespread use of topical corticosteroids, few local adverse reactions occur when topical steroids are carefully chosen and used appropriately based on site of application and severity of the dermatitis ([Fig. 3-32](#)).<sup>156</sup> As such, even potent topical corticosteroids may safely be used in small areas for short periods.

The choice of treatment will depend on the severity and localization of the dermatitis, the age of the pediatric patient, and the history of use of topical anti-inflammatory agents. The least potent preparation that adequately controls the disease process should be used. For children with mild to moderate disease, intermittent use of a low-strength topical steroid with emollient application to maintain clearance usually suffices. However, children with moderate to severe disease often show a cycle of rapid recurrent flaring when topical anti-inflammatory suppression is discontinued. A commonly used regimen to maintain control in these children while minimizing the risk of chronic steroid application is to apply midpotency to potent topical steroids for acute flares (e.g., for a few days to up to 2 weeks twice daily) followed by intermittent therapy with topical steroid.<sup>157</sup> or to avoid continuing steroid altogether, with a topical calcineurin inhibitor. Studies have suggested that topical calcineurin inhibitors can be applied three times weekly to recurrently affected sites to retain control of the dermatitis once improved with the use of topical steroids.<sup>158,159</sup>

The potency of a topical corticosteroid is largely determined by vasoconstrictor assay and is related to its vehicle as well as to



**Figure 3-32** Steroid-induced atrophy. Although unusual, steroid-induced atrophy in this patient with atopic dermatitis resulted from the twice-daily application of a class III–IV topical steroid over 1 year. Note the excellent control of the dermatitis but the obvious striae and prominence of veins because of atrophy of overlying skin.

### Box 3-2 Potential Side Effects of Topical Corticosteroids

#### Local Cutaneous Side Effects

- Atrophy
- Striae
- Periorificial granulomatous dermatitis
- Acne
- Telangiectasia
- Erythema
- Hypopigmentation
- Ocular effects
- Cataracts
- Glaucoma

#### Systemic Side Effects

- Hypothalamic–pituitary–adrenal axis suppression

**Table 3-2** Relative Potencies of Topical Corticosteroids (From Most Potent to Weakest)

Class	Drug	Dosage Form(s)	Strength (%)
I. Very high potency	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, ointment, foam	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. High potency	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, ointment, foam, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, ointment, gel, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
III-IV. Medium potency	Betamethasone valerate	Cream, ointment, lotion, foam	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream	0.1
	Triamcinolone acetonide	Cream, ointment	0.1
V. Lower-medium potency	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone propritate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
VI. Low potency	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution, oil	0.01
VII. Lowest potency	Dexamethasone	Cream	0.1
	Hydrocortisone	Creams, ointments, lotions, solutions	0.25, 0.5, 1
	Hydrocortisone acetate	Creams, ointments	0.5–1

its chemical formulation. Vasoconstrictor assays reveal that generic formulations tend to vary in their clinical activity and their vehicles may at times contain agents differing from those of brand-name formulations. Thus care must be taken in considering substitution of generic formulations for brand-name corticosteroids. The concentration of each topical corticosteroid is only significant with respect to potency relative to other corticosteroids of the same chemical formulation. Accordingly, hydrocortisone acetate 2.5% is much weaker than triamcinolone acetonide 0.1%, which in turn is weaker than clobetasol propionate 0.05%, even though the concentrations would suggest the opposite. It also should be recognized that hydrocortisone acetate differs chemically from hydrocortisone butyrate, hydrocortisone propritate, and hydrocortisone valerate, which as midpotency steroids are stronger than hydrocortisone acetate. Halogenated steroids are usually stronger than nonhalogenated steroids.

Ointments are the most commonly chosen vehicle for treating AD. Corticosteroid ointments afford the advantage of occlusion, more effective penetration, and in general greater efficacy than equivalent cream or lotion formulations. Ointments are particularly effective in the management of dry, lichenified, or plaque-like areas of dermatitis. Ointment formulations, however, may occlude eccrine ducts, inducing sweat retention and pruritus, and hair follicles, leading to folliculitis. As with emollients, formulations in ointments may not be as well tolerated during the summer months of increased heat, perspiration, and high humidity. Creams often contain additives that may be irritating or sensitizing. Creams and lotions, however, are more cosmetically elegant and afford the advantages of greater convenience and accept-

ability during hot weather and in intertriginous areas. Traditional gels and foams are not well tolerated in individuals with AD, but they may be most effective in the management of acute weeping or vesicular lesions. Topical corticosteroids in emollient-based foam formulations and hydrocolloid gels (in contrast to the alcohol-containing foams and gels) are particularly useful for hairy areas, to avoid occlusion, and for cosmetics. Oil preparations are most commonly used for scalp dermatitis. Best applied to a wet scalp, oil formulations can be shampooed out after at least 1 hour to overnight. A fluocinolone acetonide oil preparation, however, has been shown to be helpful after the bath for children with extensive AD.<sup>160</sup>

Occlusion of treated areas with polyethylene film such as Saran wrap or the use of corticosteroid-impregnated polyethylene film (Cordran tape) enhances the penetration of corticosteroids up to 100-fold. This mode of therapy is particularly effective for short periods (8 to 12 hours a day on successive days) for patients with chronic lichenified or recalcitrant plaques of dermatitic skin. Occlusive techniques, however, are contraindicated for prolonged periods of time and are not recommended in infected or intertriginous areas. Given that the diaper is an occlusive dressing, application of steroids in the diaper area of infants should be avoided or limited to short-term use of low-strength topical steroids.

For sites of severely lichenified dermatitis, salicylic acid can be compounded into preparations with steroids to improve penetration. Tar (liquor carbonis detergens or crude coal tar) can be also be used as an adjunctive therapy in patients with chronic dermatitis in the form of tar baths (e.g., Cutar) or compounded with topical corticosteroids

(e.g., compounding triamcinolone 0.1% with 6% salicylic acid and 5% to 10% liquor carbonis detergents in Aquaphor ointment). The objectionable odor, staining properties, potential for irritation, risk of causing folliculitis, and low potential risk of later carcinogenesis make tar a choice only for only selected patients.

A variety of steroid-free topical anti-inflammatory agents have been introduced to allow patients to decrease their application of topical steroids and thus associated risks. Topical calcineurin inhibitors (tacrolimus ointment 0.03% and pimecrolimus cream 1%) have been approved for the past decade as an alternative therapy for AD in children older than 2 years of age.<sup>161,162</sup> Several studies and anecdotal reports have suggested good efficacy and safety for tacrolimus ointment 0.1% (above 2 years of age) and for tacrolimus 0.03% ointment and pimecrolimus cream in infants under 2 years of age, but their use is off-label.<sup>163,164</sup> Tacrolimus and pimecrolimus prevent the formation of a complex that includes calcineurin, a phosphatase.<sup>165</sup> Without this complex, the phosphate group from the nuclear factor of activated T cells (NF-AT) cannot be cleaved, the NF-AT transcription factor cannot be transported to the nucleus, and production of cytokines associated with T-cell activation is inhibited. Tacrolimus and pimecrolimus also inhibit mediator release from mast cells and basophils and decrease IgE receptor expression on cutaneous Langerhans cells.<sup>166</sup>

To date, the only confirmed safety issue associated with the use of calcineurin inhibitors in children is burning or pruritus with application, described in the minority of affected children, particularly those with active inflammation. This sensation has been shown to result from stimulation of TRPV1 receptors in skin with depletion of substance P.<sup>167</sup> Calcineurin inhibitors do not show the atrophogenic potential of the corticosteroids and can be safely used on the head, neck, and intertriginous areas. Furthermore, no adverse effects on the eyes have been found, allowing safe application in periorbital areas. No increase in cutaneous infections has been noted in children.<sup>168</sup> Tacrolimus ointment shows good efficacy in children with moderate to severe AD<sup>169</sup> the efficacy of the 0.1% ointment is comparable to a midpotency topical corticosteroid,<sup>170</sup> and that of the 0.03% ointment to a low-potency steroid. Pimecrolimus cream is also comparable to a low-potency steroid and is indicated for pediatric patients with mild to moderate AD.<sup>171,172</sup> Assays of systemic absorption of tacrolimus and pimecrolimus have shown transient low levels in the blood, if at all, and no adverse effects on systemic immunity have been demonstrated.<sup>169,173</sup>

In 2006, the US Food and Drug Administration placed a black box warning on the class of calcineurin inhibitors based on the theoretical potential for topical calcineurin inhibitors to cause skin carcinogenesis and lymphoma. This theoretical risk was based on the known risk of malignancy (posttransplant lymphoproliferative disease and non-melanoma skin cancer) in transplant patients who are profoundly immunosuppressed by systemically administered tacrolimus and in animal studies when treated with 26 to 47 times the maximum recommended dosage. However, the number of malignancies and lymphomas is very low in AD children in postmarketing registries,<sup>174</sup> and task forces of the American College of Allergy, Asthma, and Immunology; the American Academy of Allergy, Asthma, and Immunology; and the American Academy of Dermatology found no evidence to support the issuance of a black box warning.<sup>175-178</sup> Nevertheless, pimecrolimus and tacrolimus are best used intermittently in rotation with topical steroids, and patients need to be advised of these potential risks, as well as to practice sun protection while using these agents. Several new nonsteroidal anti-inflammatory medical devices (also known as "barrier-repair agents"; see related text) have also become available for mild to moderate dermatitis and may decrease the need for steroid application.<sup>179</sup> Phosphodiesterase 4 inhibitors (oral apremilast and topical crisaborole) are currently in trials as new nonsteroidal approaches for treating AD.<sup>180</sup>

### Role of Antihistamines

Reduction of the pruritus of AD is best achieved by application of topical anti-inflammatory medications. Sedating antihistamines, such as hydroxyzine, diphenhydramine, and doxepin, may help itchy children fall asleep, although they have little direct effect on the pruritus itself. Nonsedating antihistamines may be valuable as treatment for other atopic conditions such as allergic rhinitis and have been shown

to decrease the risk of urticaria, but their value in decreasing pruritus is unclear, because they are usually nonsedating.<sup>181</sup> Long-term use in young children has not led to behavioral, cognitive, or psychomotor developmental abnormalities.<sup>182</sup> Regardless, many pediatric dermatologists use both sedating and nonsedating antihistamines as part of an overall atopic dermatitis treatment program and attest to their clinical benefit.

### Treatment of Secondary Cutaneous Infections

Antistaphylococcal antibiotics are important in the management of patients with heavy *S. aureus* colonization or infection because of the role of *S. aureus* overgrowth in triggering dermatitis. Topical antibiotics, such as mupirocin, or fusidic acid (not currently available in the United States) can be used for localized impetiginized lesions, but systemic antibiotics are required for more extensive involvement. Despite the increase in community-acquired (CA) MRSA nationally, most atopics still harbor MSSA (84% to 93%).<sup>54,55</sup> As a result, cephalaxin is still used most commonly (and successfully) to empirically treat secondarily infected dermatitis and will cover both staphylococcal and streptococcal organisms.<sup>58</sup> The chronic administration of systemic antistaphylococcal therapy for AD should be avoided in an effort to minimize the risk of development of MRSA in the atopic population.

Dilute sodium hypochlorite (bleach) baths are now standard of care as a maintenance measure for decreasing flares in moderate to severe AD. The addition of ½ cup of 5% to 6% sodium hydroxide per full tub of water (1 mL/L or 4 mL per gallon) markedly reduces the severity and extent of the dermatitis in children with a history of staphylococcal infections.<sup>54,183,184</sup> Even daily maintenance dilute sodium hypochlorite baths are generally well tolerated and may be needed for more severe AD. A washcloth can be used to distribute the bleach-bath water to the head and neck, avoiding the eyes and mouth. If skin erosions from secondary infection make bathing uncomfortable, postponing bleach baths until after the first few days of treatment may be necessary. If a bath is not possible, a 5- to 10-minute wet compress with bleach solution or a shower using a sodium hypochlorite-containing wash (such as CLn) can be used.<sup>185</sup> Intermittent application of mupirocin ointment to the nares and hands of patients and caregivers twice daily for five sequential days each month, and use of gentle antibacterial soaps<sup>186</sup> may also decrease colonization.

Antiviral treatment of cutaneous herpes simplex infections is important in preventing widespread dissemination, which rarely is life-threatening. Administration of oral acyclovir (100 mg tid to qid for children under 6 years of age; 200 mg qid for older children) for a week usually controls the infection. More extensive involvement may require hospitalization and intravenous acyclovir treatment, especially in younger children. For children with recurrent EH, a course of prophylactic administration of oral acyclovir once daily for 6 months or longer effectively suppresses the recurrences. Adjunctive therapies include topical compresses and concurrent administration of topical or systemic antibiotics if bacterial infection is also suspected. In general, topical corticosteroids can be continued during the course of systemic acyclovir therapy without impacting clearance of the viral infection if the dermatitis is problematic. Molluscum infections (see Chapter 15) can be managed by curettage after application of topical anesthetics,<sup>187</sup> or if available, by cantharidin application.<sup>188</sup> Children with molluscum and AD (but not nonatopical) may show improvement in both their dermatitis and the molluscum lesions by treatment with high doses of oral cimetidine (40 mg/kg per day divided twice daily) for a 3-month course.<sup>189,190</sup> Imiquimod has not been found beneficial in double-blind, randomized trials.

### Other Considerations for Atopic Dermatitis that Fails to Respond: Adherence and Alternative Diagnoses

Moderate to severe AD may be recalcitrant to topical corticosteroid and calcineurin therapy. Although secondary staphylococcal infection is a common reason for recalcitrance, several other factors should be considered before initiating systemic immunosuppressive therapy or phototherapy. Poor adherence is a major reason for failure to respond. In one study with electronic-cap monitoring to detect opening of tubes, mean adherence of patients with mild to moderate atopic dermatitis was 32%, increasing on or near office visit days.<sup>191</sup> Shortening the time between prescription of the medication and the

follow-up office visit<sup>192</sup>; prescribing once-a-day treatment; using sticker charts to engage children<sup>193</sup>; providing adequate education about the disease, the use of treatment, and why it is needed; and adapting instruction on medication utilization to existing elements of the family routine (e.g., linking to bathing or brushing the teeth)<sup>194</sup> may be helpful.

Chronic, unresponsive dermatitis, especially involving the eyelids, hands, feet, or vulva may result from ACD,<sup>195</sup> and comprehensive patch testing should be undertaken (see [Contact Dermatitis](#) section). Several other alternative diagnoses that may require different intervention are described (see [Differential Diagnosis](#) section).

### Management of Children with Severe Atopic Dermatitis Requiring Systemic Immunosuppressive Therapy

Systemic immunosuppressive therapy<sup>196,197</sup> or ultraviolet light treatment can be considered for patients with recalcitrant moderate to severe disease. Narrow-band ultraviolet-B light therapy, which avoids intervention with systemic immunosuppressive therapy, has been reported to cause at least moderate improvement in 89% of children and complete clearance in 40% over a median of 3 months.<sup>198</sup> Nevertheless, the requirement for frequent treatments in a medical office (two to three times weekly) and holding still in a hot, enclosed box while wearing protective goggles, as well as the unknown risk of long-term cutaneous damage from ultraviolet light, complicate the use of this form of therapy for most pediatric patients.

Systemic corticosteroid therapy is effective for most patients with AD, but the rapid rebound after discontinuation of therapy and high risk of potential side effects make its use impractical for patients with AD. Systemic administration of nonsteroidal anti-inflammatory medications to children with AD has largely replaced the use of systemic corticosteroids by pediatric dermatologists in the management of more recalcitrant severe AD.

Cyclosporine has the most rapid onset of action and greatest efficacy but also the highest risk of potential side effects. Therapy is initiated with 3 to 5 mg/kg per day (microemulsion for preferred). Response may be seen within 1 to 3 months, but medication should be tapered once significant improvement is achieved; trough levels can be determined in patients without a sufficient response to determine if a higher dosage can be administered. Discontinuation of treatment usually leads to relapse flares, but low-dose continuing treatment or intermittent courses in children can be effective.<sup>199–201</sup> Several experts now recommend initial treatment with cyclosporine to rapidly suppress the severe AD (for 3 months) followed by continued treatment with ultraviolet light treatment or an alternative, safer immunosuppressant such as mycophenolate mofetil or methotrexate. Renal and hepatic function and blood pressure must be carefully monitored during cyclosporine therapy.

Azathioprine (2.5 to 3.5 mg/kg per day) has effectively suppressed severe, recalcitrant AD in 58% to 92% of children during a 3-month trial.<sup>202–204</sup> Pretreatment determination of thiopurine methyltransferase level can predict the risk of developing myelosuppression, and hepatic functions should also be monitored. In one study the thiopurine methyltransferase (TPMT) levels changed unpredictably during treatment in 25% of patients, suggesting that periodic assessment of TPMT levels is warranted to optimize clinical response.<sup>204</sup> Azathioprine should be used with caution, given its recent link of hepatosplenic T-cell lymphoma.

Mycophenolate mofetil has been found to cause at least 60% improvement in 91% of treated children with a dosage of 40 to 50 mg/kg per day for children and 30 to 40 mg/kg per day for adolescents with maximal effects at 8 to 12 weeks.<sup>205</sup> Complete blood counts and liver function testing should be performed.

Methotrexate was found to be effective or very effective in 75% of children with severe AD in a recent retrospective analysis. There were no serious adverse events noted, although 14% experienced minor nausea and 14% had slight elevation in hepatic transaminases. Low-dose therapy (0.3 to 0.5 mg/kg per week)<sup>206</sup> is administered with folate supplementation. The need for a small test dose of methotrexate has not been demonstrated. Complete blood counts should be followed weekly, and hepatic transaminases should be monitored at least monthly.

Interferon- $\gamma$  downregulates Th2 lymphocyte function, and treatment with recombinant interferon- $\gamma$  (50  $\mu$ g/m<sup>2</sup> daily or every other day) has led to improvement in some patients, including pediatric patients.<sup>207–209</sup> Clinical improvement correlates with decreases in peripheral eosinophilia but not IgE levels. Flu-like symptoms are particularly common early in the treatment course. The high price and benefit for only a subset of individuals also limit the use of interferon- $\gamma$  in children who are severely affected with AD.

Biologics to date have not been used for pediatric AD. However, weekly subcutaneous injection of IL-4 receptor antibody (dupilumab) shows very promising results in adult AD, consistent with the important role of Th2 cytokines in AD inflammation.<sup>210</sup> An alternative biologic approach may be treatment with ustekinumab to combat the impact of elevation of downstream Th22 cytokine activation, as has been shown effective in adults and an adolescent with severe AD.<sup>211–213</sup>

### Use of Experimental or Complementary Treatment Approaches

The impact of vitamin D3 levels and potential value of vitamin D3 supplementation remain controversial. Low levels of vitamin D3, including in cord blood,<sup>214,215</sup> have been associated with childhood AD,<sup>216,217</sup> although there is not a relationship with disease severity<sup>218</sup> unless there is allergic sensitization.<sup>219</sup> Vitamin D3 has been shown to upregulate the expression of cathelicidin, including in the skin of individuals with AD, but topically applied vitamin D3 irritates skin affected by AD. Although one small open-label study of oral vitamin D3 supplementation in children who were vitamin-D deficient with AD showed clinical improvement,<sup>220</sup> a small double-blind trial showed improved serum levels of vitamin D3 after 3 weeks but no clinical improvement in AD.<sup>221</sup> At this time there is insufficient evidence to recommend vitamin D3 supplementation for AD.<sup>222</sup>

Probiotics have recently received considerable attention as a means of prevention of AD. Evidence that reduced diversity in the gut microbiota is a risk factor in the development of AD<sup>223–226</sup> provides further rationale for probiotic use. Although there is some evidence of benefit prenatally in prevention (for reviews,<sup>227–230</sup>) there is insufficient evidence to recommend probiotics as part of standard management of infantile AD. Not all lactobacilli are effective, and *Lactobacillus rhamnosus* GG has shown the greatest efficacy; in fact, early administration of *L. acidophilus* did not prevent AD development<sup>230</sup> and increased atopic sensitization.<sup>231</sup> Although early studies suggest some benefit of prebiotics (fiber compounds that stimulate the growth of advantageous organisms) and fatty acids (such as the  $\gamma$ -linolenic acid [GLA] alone or in combination with  $\omega$ -3 fatty acids),<sup>230</sup> there is insufficient evidence to recommend these approaches for either reducing the risk of developing AD or treating AD.

Leukotriene antagonists such as montelukast, which are used extensively in asthma prophylaxis, have largely been ineffective.<sup>232</sup> The benefit from administration of traditional Chinese herbal therapy has been variable.<sup>233–235</sup> Regardless, the demonstration of hepatic toxicity, cardiac adverse events, and idiosyncratic reactions from this therapy has raised concerns; furthermore, the discovery of glucocorticoid contamination in some preparations warns that these alternative agents be used with caution.<sup>236</sup> Massage therapy has been advocated as a means to improve the clinical signs of atopic dermatitis in young children, in addition to improving the psychological well-being of the patients and family members.<sup>237</sup> Psychological counseling, behavioral modification, hypnotherapy, and biofeedback can also be helpful in decreasing scratching.<sup>104</sup> Psychological intervention for families can also be beneficial, because increased parental stress and depression correlate with higher levels of biological markers of inflammation.<sup>238</sup> A form of alternative medicine, particularly herbal remedies and homeopathy, is used in 42.5% to 63.5% of patients with AD.<sup>239,240</sup> More than half reported no improvement but tried the therapies based on recommendation from nonphysicians, concern about the potential risks of topical steroids, and dissatisfaction with conventional treatment. Of concern is that these complementary approaches have potential side effects, have not been adequately tested for safety and efficacy, and require time and effort that might otherwise be directed toward use of physician-prescribed treatment.

## Pityriasis Alba

Pityriasis alba is a common cutaneous disorder characterized by asymptomatic hypopigmented patches, usually on the face, neck, upper trunk, and proximal extremities.<sup>241</sup> Individual lesions vary from 1 cm or more in diameter and may show a fine scale (Fig. 3-33). This disorder is thought to represent a nonspecific dermatitis with residual postinflammatory hypopigmentation and occurs more often in individuals with darker skin types.<sup>242</sup> Histologic evaluation shows normal numbers of melanocytes but decreased epidermal melanosomes and melanocyte degeneration.<sup>243</sup> Most cases appear after sun exposure because of the contrast that results between areas that can show a pigmentary response to ultraviolet light and the pityriasis alba areas that do not.

The differential diagnosis of the hypopigmented macules of pityriasis alba includes tinea versicolor, vitiligo, the white macules seen in association with tuberous sclerosis; nevus depigmentosus; cutaneous T-cell lymphoma; leprosy; postinflammatory hypopigmentation secondary to atopic dermatitis, psoriasis, tinea corporis, or pityriasis rosea; and in light-skinned individuals, nevus anemicus. Application of mild topical corticosteroids or calcineurin inhibitors for a few weeks followed by frequent emollient and protection of the sites and surrounding area from sun exposure appears to diminish the dry skin and fine scaling, allowing repigmentation of involved areas. Patients and parents should be warned that, as with postinflammatory hypopigmentation, repigmentation may take several months to years. Effective moisturization during drier months may help prevent recurrence of the pityriasis alba in subsequent summers.

## Hyperimmunoglobulinemia E Syndrome

HIES is a rare immunodeficiency disorder characterized by very high levels of IgE in association with AD and recurrent cutaneous and sinopulmonary infections.<sup>244,245</sup> The AD is seen in 100% of patients, usually within the first 6 months, and is of variable severity (Fig. 3-34). Most patients have an autosomal dominant form (also called *Job syndrome*), which results from mutations in the gene encoding signal transducer and activator of transcription 3 (*STAT3*).<sup>246,247</sup>

Many neonates or infants with autosomal dominant HIES have pruritic papulopustules, especially on the face, which show eosinophilic folliculitis or eosinophilic dermatitis by biopsy of lesional skin.<sup>248</sup> Infections often begin during the first 3 months of life. Cutaneous candidiasis may also be an early clinical feature (83%). Cutaneous *S. aureus* infections may take the form of excoriated crusted plaques, pustules, furuncles, cellulitis, paronychia, lymphangitis, or abscesses, especially on the neck, scalp, periorbital areas, axillae, and groin (Fig. 3-35).



**Figure 3-33** Pityriasis alba. Circumscribed scaly hypopigmented lesions on the cheek. These patches are thought to represent postinflammatory hypopigmentation and are most easily visible in children with darker skin. Note the concomitant lip-licker's dermatitis.

**3-35). The abscesses are slightly erythematous and tender but not nearly to the degree expected for a normal individual. Although some patients demonstrate cutaneous manifestations only,<sup>249</sup> patients with HIES usually have recurrent bronchitis and pneumonias with resultant empyema, bronchiectasis, and in 77% of patients, pneumatocele formation. The pneumatoceles tend to persist and become the site of further infections with bacteria (*Pseudomonas*) or fungi (*Aspergillus*, *Candida*). Rarely, massive hemoptysis ensues. Other common sites of infection include the ears, oral mucosae, sinuses, and eyes. Visceral infections other than pneumonia are unusual.**

By late childhood and adolescence, patients with HIES begin to develop progressive facial coarseness,<sup>244</sup> perhaps reflecting bony abnormalities and recurrent facial abscesses. Osteopenia is usually detected by adolescence or early adulthood, and patients have an increased risk of bone fractures, often because of unrecognized or minor trauma.<sup>250</sup> Scoliosis occurs in 64% of patients 16 years of age or older, and hyperextensibility of joints has been reported in 70% of patients. Dental abnormalities associated with HIES syndrome include retention of primary teeth, lack of eruption of secondary teeth, and delayed resorption of the roots of primary teeth.<sup>251</sup> Focal brain hyperintensities and an increased incidence of lymphoma are other features. Patients with HIES of intermediate phenotypes that include



**Figure 3-34** HIES with AD of the antecubital area.



**Figure 3-35** Hyperimmunoglobulinemia E syndrome (HIES). In addition to atopic dermatitis, most infants and children with HIES show erythematous, slightly purulent cold abscesses, shown here on the forehead and scalp. (Reprinted with permission from Bologna JL, Jorizzo JL, Rapini RP. Dermatology. Elsevier, 2003.)

staphylococcal and mucocutaneous candidal infections may have STAT3 mosaicism.<sup>252</sup>

The abnormalities in STAT3 signaling impair Th17-cell development, leading to insufficient expression of IL-17 and IL-22, which drive expression of antimicrobial peptides, thus promoting *S. aureus* and candidal infections.<sup>253</sup> The diagnosis of HIES is largely based on clinical findings and the presence of very high levels of IgE. There are no specific tests to confirm the diagnosis other than the finding of HIES-related mutations. Patients have markedly elevated levels of polyclonal IgE. Although levels of more than 2000 IU/mL are needed to consider the diagnosis in older children and adults, the normal levels of IgE in infants (0 to 50 IU/mL) are considerably lower than those in older children. A 10-fold increase in IgE levels above normal levels for age should trigger consideration of HIES, although these levels of IgE are more common in AD without HIES.<sup>254</sup> Affected individuals tend to have IgE antibodies directed against *S. aureus* and candida. Levels of IgE are not related to clinical course and may decrease to normal in affected adults. Approximately 93% of patients have eosinophilia of the blood and sputum. Abnormal polymorphonuclear leukocyte and monocyte chemotaxis has been noted, but is intermittent and not correlated with infection. Cell-mediated immunity (Th1-driven) is often abnormal as well and may manifest as anergy to skin testing, altered responses in mixed leukocyte culture, and impaired blastogenic responses to specific antigens such as *Candida* and tetanus. The decrease in memory (CD27+) B cells is markedly decreased in 80% of patients, in contrast to individuals with AD and high levels of IgE.<sup>255</sup>

Autosomal recessive HIES usually results from loss-of-function mutations in DOCK8 (dedicator of cytokinesis), which regulates the actin cytoskeleton and is less common than the dominant form. Although patients share the cardinal features of high levels of IgE, AD, and infections, patients fail to show the bone, dental, and coarse facial features of the dominant form. Cardinal features that are not part of the STAT3-deficient form include severe viral infections (molluscum, herpes, and life-threatening cytomegalovirus [CMV] infections), early malignancy (cutaneous and mucosal squamous cell carcinomas), neurologic changes (aneurysms and strokes), and an increased risk of autoimmune issues (anemia, thrombocytopenia, and vasculitis).<sup>256,257</sup> One patient with autosomal recessive HIES and homozygous mutations in TYK2 (which activates STAT3) had nontuberculous mycobacterial infections.<sup>258,259</sup> The additional clinical features of recessive HIES have been ascribed to additional abnormalities in IL-12 and interferon- $\alpha/\beta$ -cytokine production.

HIES must be distinguished from a number of other disorders in which IgE levels may be elevated. Most common is AD, which shows similar inflammatory cutaneous features and often very high levels of IgE, especially if severe;<sup>254</sup> the concurrent presence of abscesses, coarse facies, noncutaneous infections, and dental and bony abnormalities in HIES may enable differentiation. WAS can be distinguished by thrombocytopenia with cutaneous petechiae and hemorrhagic episodes. Eosinophilia and elevations of IgE levels with dermatitis can also be seen in patients with DiGeorge syndrome, the Omenn syndrome type of severe combined immunodeficiency, graft-versus-host disease (GVHD), and selective IgA deficiency.

The mainstay of therapy for HIES is antistaphylococcal antibiotics, and patients are usually treated prophylactically with trimethoprim-sulfamethoxazole. When other bacterial or fungal infections develop, infections must be treated with appropriate alternative antibiotics. Recombinant interferon- $\gamma$  has shown inconsistent efficacy. The cutaneous and pulmonary abscesses often require incision and drainage. The pneumatoceles should be removed surgically, especially if present for longer than 6 months, to prevent microbial superinfection. Therapy for AD as discussed in previous sections is also useful for HIES; omalizumab has improved the severe dermatitis of a recalcitrant patient with a relatively low level of IgE.<sup>260</sup> Alendronate sodium may alleviate the osteopenia.<sup>250</sup>



**Figure 3-36** A bleeding diathesis owing to thrombocytopenia and platelet dysfunction, the most common manifestation of patients with Wiskott–Aldrich syndrome (WAS), may manifest as petechiae, ecchymoses, and purpuric patches. The dermatitis of patients with WAS is indistinguishable from atopic dermatitis.

microthrombocytopenia and platelet dysfunction, and recurrent severe pyogenic infections.<sup>261,262</sup> Bleeding is the most common manifestation, but the presence of mild to severe AD distinguishes WAS from X-linked thrombocytopenia and X-linked neutropenia with myelodysplasia, which are both allelic. The majority of patients are male, but full expression has been reported in girls.<sup>263</sup>

The dermatitis usually develops during the first few months of life and fulfills criteria for AD (Fig. 3-36). Excoriated areas commonly have serosanguineous crust and often show petechiae or purpura. IgE-mediated allergic problems such as urticaria, food allergies, and asthma are also seen with increased frequency.

The hemorrhagic diathesis results from both quantitative and qualitative defects in platelets. Platelets from patients with WAS are small and structurally abnormal with a reduced half-life, although megakaryocyte numbers are normal. Epistaxis and bloody diarrhea are often the initial manifestations. Mucocutaneous petechiae and ecchymoses (see Fig. 3-36), spontaneous bleeding from the oral cavity, hematemesis, melena, and hematuria are common, but the severity varies.

Recurrent bacterial infections begin in infancy as placentally transmitted maternal antibody levels diminish and include staphylococcal impetigo, furunculosis, otitis externa and media, pneumonia, pansinusitis, conjunctivitis, meningitis, and septicemia. Infections with encapsulated bacteria such as pneumococcus, *Haemophilus influenzae*, and *Neisseria meningitidis* predominate. With advancing age, T-cell function progressively deteriorates and patients become increasingly susceptible to infections caused by herpes and other viruses and to *Pneumocystis jiroveci*.

Additional clinical features may be hepatosplenomegaly, lymphadenopathy, and autoimmune complications. The most common autoimmune complication is hemolytic anemia, occurring in 36% of patients and usually before 5 years of age.<sup>264</sup> Other autoimmune disorders that clearly seem linked to WAS are autoimmune neutropenia (25%), arthritis (29%), IgA nephropathy, and painful cutaneous vasculitis (22%) that can appear as purplish induration of skin and soft tissues.

The clinical course of WAS is progressive, usually resulting in death by adolescence without transplantation. Overall, 40% of patients die of infection, 21% of hemorrhage (usually intracranial), and 25% of malignant neoplasia. Lymphoreticular malignancies occur overall in 13% to 22% of patients,<sup>265</sup> with an average age of onset of 9.5 years. Non-Hodgkin lymphoma<sup>265,266</sup> is the most common malignancy and is often linked to Epstein–Barr (EBV) infection, and extranodal and brain involvement predominate. Fewer than 5% who develop lymphoma survive more than 2 years.

## Wiskott–Aldrich Syndrome (WAS)

WAS is a rare X-linked recessive disorder, which in its classic form consists of dermatitis that meets criteria for AD, bleeding from

Individuals with WAS have mutations in the gene that encodes WAS protein (WASP), and the extent of WASP depletion correlates with disease severity. WASP, through complexing with other proteins, activates Arp2/3 and ultimately polymerizes the actin cytoskeleton to enable cell movement, dendrite formation, formation of immune synapses, T-cell activation, and B-cell homeostasis. Platelet abnormalities result from defective migration in proplatelet formation, inherent platelet defects increasing fragility, and autoimmunity against platelets. T-regulatory cell dysfunction has been blamed for the increased risk of autoimmune complications. The mechanism for the AD is not defined but could relate to T-cell activation defects and the abnormal interactions of WAS Langerhans cells with T cells after antigenic stimulation.

Laboratory studies show thrombocytopenia in 100% of patients, with platelets below about  $80,000/\text{mm}^3$  and often below  $20,000/\text{mm}^3$ . Platelets tend to be small, and aggregation is sometimes defective. Eosinophilia is common, but lymphopenia is not usually seen until after 6 to 8 years of age. Total serum  $\gamma$ -globulin is usually normal, but levels of IgM are often low, with variable IgG levels and increased levels of IgA, IgE, and IgD. The number of T lymphocytes and response *in vitro* to mitogens may be normal in early life but often decreases with advancing age. Delayed hypersensitivity skin-test reactions are usually absent, and antibody responses to polysaccharide antigens are markedly diminished.

Several conditions may be confused with WAS. Many other immunodeficiencies are characterized by dermatitis, increased susceptibility to infections, and the development of malignancy, but do not share the bleeding diathesis. The clinical findings of hemorrhage, petechiae, and recurrent sinopulmonary infections in WAS help to differentiate WAS from AD.

Bone marrow transplantation with human leukocyte antigen (HLA)-identical marrow is the treatment of choice. Full engraftment results in normal platelet numbers and functions, immunological status, and if T lymphocytes engraft, clearance of the dermatitis.<sup>267</sup> Optimal survival occurs with matched sibling donors and allogeneic transplantation below the age of 5 years (87%). Despite the good result of matched unrelated donors in young children (71%), there is a higher risk of acute GVHD after transplant (56%) versus matched siblings (16%).<sup>268</sup> Mixed chimerism (i.e., engraftment of T cells but not myeloid or B cells) increases greatly the risk of chronic GVHD. If a matched donor is unavailable, infusion of autologous stem cells modified *ex vivo* by gene therapy is an alternative approach.<sup>269</sup>

Appropriate antibiotics and transfusions of platelets and plasma decrease the risk of fatal infections and hemorrhage. Intravenous infusions of  $\gamma$ -globulin are also useful in patients. Topical corticosteroids may improve the dermatitis, and chronic administration of oral acyclovir is appropriate for patients with EH. Splenectomy has been used selectively for patients with severe platelet abnormalities; however, splenectomy increases the risk of infection by encapsulated organisms, markedly increasing the risk of mortality after transplantation. Children with WAS are unable to mount immune responses after administration of vaccines against encapsulated organisms. Rituximab has been used successfully in some children with EBV-induced lymphoma to prolong survival.<sup>270</sup>

## Lichen Simplex Chronicus

Lichen simplex chronicus (circumscribed neurodermatitis) is a localized, chronic pruritic disorder characterized by patches of dermatitis that result from repeated itching, scratching, and rubbing of the involved area. The pruritus may begin in an area of normal-appearing skin or may be initiated in a preexisting lesion of atopic, seborrheic, or contact dermatitis, lichen planus, or psoriasis.

Lesions of lichen simplex chronicus generally occur in adolescents or adults but may be seen in younger children. The disorder may develop at any location on the body, but the most common areas of involvement are those that are easily reached and may be scratched unobtrusively (particularly during periods of tension and concentration). These include the nape or sides of the neck, wrists, ankles, hands, and pretibial areas. Other common sites of involvement include the inner aspects of the thighs, vulva, scrotum, and perianal areas.



**Figure 3-37 (A) and (B)** Lichen simplex chronicus. Localized plaques of dermatitis that result from repeated scratching and rubbing of the involved area.

The clinical features of lichen simplex chronicus include single or multiple oval plaques with a long axis that usually measure up to 15 cm in diameter (Fig. 3-37). During the early stages, the skin is reddened and slightly edematous with exaggerated skin markings. Older, more typical lesions are characterized by well-circumscribed, dry, thickened, scaling, pruritic, often hyperpigmented plaques.

The diagnosis of lichen simplex chronicus is dependent on the presence of pruritic lichenified plaques in the characteristic sites of predilection. Lesions of tinea corporis may be differentiated by a lack of lichenification, by the presence of a scaly border (often with clearing in the center), by demonstration of hyphae on microscopic examination of skin scrapings, and by fungal culture. Psoriatic plaques generally may be differentiated by a characteristic thick, adherent white or silvery scale, their underlying deep red hue, and characteristic areas of involvement. Lesions of AD may be differentiated by history, more poorly demarcated lesions, the presence of atopic stigmata, and a tendency toward involvement in antecubital and popliteal areas.

The successful management of lichen simplex chronicus depends on an appreciation of the itch-scratch-itch cycle and the associated scratching and rubbing that accompany and perpetuate this disorder. Topical application of potent corticosteroids, under occlusion if necessary, and the administration of systemic antihistamines (such as diphenhydramine or hydroxyzine) usually induces remission of the pruritus and the eruption within a period of several weeks. Use of tap water compresses before application of the topical corticosteroid or compounding topical steroid with salicylic acid (e.g., 6% salicylic acid and 0.1% triamcinolone powder in hydrophilic ointment) may increase penetration of the topical anti-inflammatory agent. Other techniques include application overnight of flurandrenolide-impregnated tape, protection from scratching and rubbing by occluding with adhesive dressings, and injection of intralesional triamcinolone acetonide (e.g., 5–10 mg/mL) in tolerant adolescents.

## Seborrheic Dermatitis

*Seborrheic dermatitis* refers to a self-limiting erythematous, scaly, or crusting eruption that occurs primarily in the so-called “seborrheic areas” (those with the highest concentration of sebaceous glands), namely the scalp, face, and postauricular, presternal, and intertriginous areas. Seborrheic dermatitis in the pediatric population is most commonly seen in infants and adolescents. The cause of seborrheic dermatitis is not well understood. Its predilection for areas of high sebaceous gland density and the correlation of activity with increased hormonal levels during the first year of life<sup>271</sup> and adolescence suggests a relation to sebum and sebaceous glands. Seborrheic dermatitis of adolescence and adulthood has been attributed to *Pityrosporum ovale* (*Malassezia ovalis*), a lipophilic yeast normally found in abundance on the human scalp.<sup>272</sup> However, the relationship between seborrheic dermatitis in infants and that of adolescents and adults is controversial. It is unclear if this organism plays an etiologic role in infants.<sup>273,274</sup> Many infantile cases improve with topical ketoconazole, suggesting that overgrowth of yeast may, at least in some instances, play a role in the pathogenesis of this disorder.

Seborrheic dermatitis appears in infancy between the second and tenth week of life (usually the third or fourth) and peaks in incidence at 3 months of age.<sup>275</sup> Infantile seborrheic dermatitis often begins with a noneczematous, erythematous, scaly dermatitis of the scalp (termed *cradle cap*) or the diaper area and is manifested by thin dry scales or sharply defined round or oval patches covered by thick, yellowish brown, greasy crusts. Although the condition is limited to the scalp in most affected infants, it may progress to the forehead, ears, eyebrows, nose, and back of the head (see Figs. 3-2 and 2-22). Erythematous greasy, salmon-colored, sharply marginated scaly patches may also involve the intertriginous and flexural areas of the body, the postauricular areas, the trunk, umbilicus, anogenital areas, and groin (Fig. 3-38). Pruritus is slight or absent, and the lesions usually lack the dry, fine scaling character associated with AD. Overlap of seborrheic dermatitis and AD, however, may occur with the features of AD becoming more prominent as the seborrheic dermatitis subsides. In one study, 49% of infants with AD had a history of infantile seborrheic dermatitis, in contrast to 17% of controls.<sup>276</sup>

The differential diagnosis of seborrheic dermatitis during infancy includes AD, psoriasis, LCH, and immunodeficiency. Lesions of AD are almost always pruritic, are poorly defined, and show dry, fine scaling. In addition, the occluded diaper area is usually spared in AD, in contrast to the common diaper area involvement of seborrheic dermatitis. Psoriasis can be quite difficult to differentiate, because it can present in infants in a fashion very similar to that of seborrheic dermatitis, with sharply marginated, brightly erythematous scaling patches. Psoriasis tends to show a slower response to topical corticosteroid therapy and can be distinguished, if necessary, by skin biopsy. Although LCH



**Figure 3-38** Seborrheic dermatitis. A cause of diaper rash in young infants, seborrheic dermatitis is difficult to distinguish clinically from infantile psoriasis but tends to be less erythematous, to have thinner scaling, and to respond more quickly to topical anti-inflammatory medications.

can at times be mistaken for seborrheic dermatitis, the presence of discrete 1- to 3-mm yellowish to red-brown crusted or eroded papules, purpuric lesions, hepatosplenomegaly, or lymphadenopathy support the diagnosis of LCH; histopathologic and immunohistochemical examination of cutaneous lesions confirms the diagnosis of LCH. When the erythema and scaling of infantile seborrheic dermatitis becomes severe, generalized, and exfoliative, the diagnosis of immunodeficiency must be considered. The lack of constitutional findings (diarrhea, fever, weight loss), alopecia, associated infections, and the spontaneous clearance or rapid response to therapy of seborrheic dermatitis help to distinguish the conditions. Severe generalized seborrheic-like dermatitis in association with failure to thrive, recurrent skin and other infections, and chronic diarrhea (once called *Leiner syndrome*) can be seen in several immunodeficiency disorders, including C3 and C5 complement deficiencies, C5 dysfunction, hyperimmunoglobulinemia E syndrome, severe combined immunodeficiency (especially Omenn syndrome), and X-linked agammaglobulinemia.<sup>277</sup>

Between puberty and middle age, seborrheic dermatitis may appear on the scalp as a dry, fine, flaky desquamation, commonly known as *dandruff*. This seborrhea is an extreme form of normal desquamation in which scales of the scalp become abundant and visible, often overlying inflammation. Erythema and scaling of various degrees may also involve the supraorbital areas between the eyebrows and above the bridge of the nose, nasolabial crease (Fig. 3-39), lips, pinnae, retroauricular areas, and aural canals. Blepharitis is a form of seborrheic dermatitis in which the eyelid margins are red and covered with small, white scales. Seborrheic dermatitis may also involve the sideburns, beard, and mustache areas, with diffuse redness, greasy scaling, and pustulation. The severity and course of seborrheic eruptions of the eyelids and bearded areas are variable and have a tendency to chronicity and recurrence.



**Figure 3-39** Seborrheic dermatitis. (A) Facial seborrheic dermatitis in adolescents typically involves nasolabial folds and may result from overgrowth of lipophilic yeasts of the normal flora. In (B) tinea faciei was considered, but the distribution and bilaterality are atypical for tinea.

Occasionally an adolescent patient may have an eruption that has clinical features of both seborrheic dermatitis and psoriasis. Such eruptions may be termed *sebopsoriasis*. Lesions of seborrheic dermatitis can be differentiated from those of psoriasis by a lack of the characteristic vivid red hue or micaceous scale, a predisposition toward flexural rather than extensor aspects of the extremities, and the fact that lesions of seborrhea generally tend to remain within the confines of the hairline. Lesions of psoriasis (or sebopsoriasis) commonly extend beyond the hairline and in general are more resistant to standard antiseborrheic therapy.

The prognosis of infantile seborrheic dermatitis is excellent. In some patients, the disorder clears within 3 to 4 weeks even without treatment, and most cases clear spontaneously by 8 to 12 months of age. The condition generally does not recur until the onset of puberty, although mild scaling of the scalp, particularly at the vertex, can be seen in some affected children through preschool years. Treatment of infantile scalp seborrheic dermatitis is best managed by frequent shampooing.<sup>278</sup> Although antiseborrheic shampoos including ketoconazole shampoo<sup>279</sup> may be useful, in infants or young children, these products may be drying or irritating to the eyes. A gentle “no-tears” shampoo usually suffices. If the scales are thick and adherent, removal can be facilitated by the thin application of mineral or baby oil followed by gentle scalp massage with a soft toothbrush and then shampooing. Antiseborrheic shampoos are alternatives if therapy with no-tears shampoo is not effective. If there is a significant inflammatory component, a topical corticosteroid lotion, oil, or solution, with or without 3% to 5% precipitated sulfur or salicylic acid, may be applied once to twice daily. For involvement other than the scalp, a low-strength topical corticosteroid or topical antifungal agent is usually effective when applied once to twice daily.

Adolescents with seborrhea of the scalp may try a variety of antiseborrheic shampoos, tar shampoo, ketoconazole shampoo, or 5% tea tree-oil shampoo.<sup>278,280</sup> Antiseborrheic shampoos may contain selenium sulfide (e.g., Sebulex, Exsel, and Selsun), salicylic acid (e.g., T-sal), or zinc pyrithione (e.g., Head and Shoulders and DHS Zinc). If the scale is extremely thick and adherent, it can be loosened by warmed mineral oil massaged into the scalp or by the use of P&S Liquid (Baker Cummins), ideally left on overnight. Scales are then loosened by scrubbing gently with the fingers or a soft brush, and the scalp is shampooed. For patients with associated erythema or pruritus, topical corticosteroid lotions, gels, oils, or foams may be used. Seborrheic dermatitis of the face or intertriginous areas in adolescents usually responds quickly to the application of a mild corticosteroid, calcineurin inhibitor, or antifungal medication. If these are too greasy, a foam preparation of ketoconazole is available.<sup>281</sup>

Blepharitis may be managed by warm-water compresses, gentle cleansing with a dilute solution of a nonirritating or baby shampoo, and mechanical removal of scales when necessary. Topical corticosteroids on the eyelids or eyelid margins should be used with caution, although calcineurin inhibitors (e.g., tacrolimus or pimecrolimus) may be used safely in this area.

Seborrheic dermatitis of the intertriginous or diaper areas occasionally may be complicated by secondary candidal or bacterial infection. Candidal infection is usually seen in the diaper areas as discrete erythematous scaling papules and sometimes pustules, especially at the periphery of the affected area. Secondary bacterial infection is more commonly seen as oozing at the neck fold and other intertriginous sites. In such instances, topical anticandidal and/or antibacterial agents are generally helpful. For patients refractory to topical treatment or for those with significant secondary bacterial infection, bacterial cultures and appropriate systemic antibiotics are necessary.

## Intertrigo

Intertrigo is a superficial inflammatory dermatitis that occurs in areas where the skin is in apposition (Fig. 3-40; see also Fig. 17-38). As a result of friction, heat, and moisture, the affected areas become intensely erythematous in a well-demarcated pattern, macerated, and often secondarily infected by bacteria or *Candida*, or in adolescents by dermatophytes (see Chapter 17). Intertrigo with secondary streptococcal infection often presents with oozing and can be associated with



**Figure 3-40** Intertrigo is a superficial inflammatory dermatitis that occurs at sites of skin apposition. Secondary bacterial or yeast infection is common. Note the weeping of clear fluid.



**Figure 3-41** Pompholyx, or dyshidrotic eczema. An acute recurrent or chronic eruption of the palms, soles, and lateral aspects of the fingers with deep-seated tapioca-like vesicles to large, tense bullae.

bacteremia.<sup>282,283</sup> Treatment is directed toward elimination of the macerated skin. Open wet compresses, dusting powders (such as ZeaSORB), topical corticosteroid lotions, and when indicated, appropriate antibiotics or fungicidal agents may be used.

## Dyshidrotic Eczema

Dyshidrotic eczema (pompholyx) is an acute recurrent or chronic eczematous eruption of the palms, soles, and lateral aspects of the fingers, characterized by deep-seated, variably inflamed lesions that range from tapioca-like vesicles to large, tense bullae (Figs. 3-41 and 3-42).<sup>284</sup> The distribution of lesions generally is bilateral and somewhat symmetrical. Patients complain of considerable pruritus and/or burning. Hyperhidrosis is often associated. Attacks usually last a few weeks, but relapses are frequent, often several times per year.

Dyshidrotic eczema may be confused with contact dermatitis or tinea, disorders commonly unilateral or more localized. ACD (see **Allergic Contact Dermatitis** section) on the feet or hands most commonly results from exposure to potassium dichromate (for tanning leather) or rubber but occasionally is caused by paraphenylenediamine (PPD; in hair dyes and as an additive to henna), nickel, fragrance mix, colophony (in glues and also in violin rosin), and



**Figure 3-42** Pompholyx, or dyshidrotic eczema. Superficial crusting and desquamation often replace the ruptured tiny vesicles of dyshidrotic eczema.

potassium dichromate.<sup>285</sup> Fungal culture and patch testing can be performed to distinguish these disorders from tinea and contact dermatitis, respectively. “Id” reactions and pustular psoriasis must also be considered in the differential diagnosis of this disorder and are most commonly bilateral. Juvenile plantar dermatosis is limited to the feet and tends to be bilateral (Fig. 3-43). A reaction on the palms and soles resembling dyshidrotic eczema has also been described after intravenous immunoglobulin (IVIG), most commonly after the first IVIG treatment in adults with neurological disorders.<sup>286,287</sup> In a minority of these cases, eczematous lesions may be extensive. Severe dyshidrotic eczema may also occur after IVIG therapy for Kawasaki disease<sup>288</sup> or Stevens–Johnson syndrome.<sup>289</sup>

The natural course of dyshidrotic eczema is one of frequent recurrence. Open wet compresses tend to open the vesicles, and application of moderate to potent topical corticosteroids, although not curative, helps to relieve the manifestations of this disorder. Topical tacrolimus 0.1% ointment has been used successfully as an alternative that allows rotational therapy.<sup>289</sup> When infection is present, antibiotics may be administered topically or systemically. Although not a disorder of eccrine glands *per se*, the use of topical aluminum chloride in concentrations of 12% (e.g., Certain Dri) to 20% (e.g., Drysol) may decrease the associated hyperhidrosis and help to control the disorder if not too irritating. Hyperhidrosis can also be controlled by oral administration of glycopyrrolate if topical application of drying agents is ineffective. For adolescents with recalcitrant hyperhidrosis, intradermal injections of botulinum toxin might be considered.<sup>290</sup> Phototherapy with either narrow-band ultraviolet-B light or high doses of ultraviolet A1 light<sup>291</sup> and even short courses of oral corticosteroids with gradual tapering have been used.

## Juvenile Plantar Dermatoses

Juvenile plantar dermatosis (dermatitis plantaris sicca or “sweaty-sock dermatitis”) is a common dermatosis of infancy and childhood, most commonly localized to the distal aspect of the soles and toes, particularly the great toes, but sparing the interdigital spaces. Associated with hyperhidrosis and thought to represent a frictional irritant dermatitis, the disorder is manifested acutely by a symmetrical, smooth, red, glazed, and fine scaling (see Fig. 3-43, A) but can become lichenified with chronicity (see Fig. 3-43, B). Similar changes have also been reported on the fingertips in up to 5% of patients with excessive perspiration. Untreated juvenile plantar dermatosis generally tends to persist for several years, and although there is no seasonal pattern, some patients report slight worsening of the condition during the summer and in cold weather.

The differential diagnosis of juvenile plantar dermatosis includes tinea pedis, palmoplantar psoriasis, pityriasis rubra pilaris, and shoe-contact dermatitis. Tinea pedis can manifest as scaling and erythema



**Figure 3-43** Juvenile plantar dermatosis. (A) Characteristic smooth, glazed dermatosis with scaling on the skin of the toes and distal plantar surfaces of the feet of a child with juvenile plantar dermatosis (“sweaty sock dermatitis”). (B) Scaling, lichenification, and fissuring in association with chronic juvenile plantar dermatitis. This patient also has ichthyosis vulgaris, which explains the hyperlinear soles.

of the plantar foot but is more likely to involve the interdigital spaces. Associated pustulation of tinea may be mistaken for secondary staphylococcal infection. Potassium hydroxide scrapings and culture may be required to distinguish tinea pedis and juvenile plantar dermatosis. The plaques of psoriasis are often thicker and more erythematous. Pityriasis rubra pilaris may closely resemble psoriasis but often shows a salmon-orange coloration on the palms and soles. Both psoriasis and pityriasis rubra pilaris usually show lesions elsewhere. Contact dermatitis owing to a component of shoes is more commonly on the dorsum of the foot, but the plantar foot is occasionally involved (see *Shoe Dermatitis* section).

Although treatment is not always completely successful, children with hyperhidrosis of the feet should wear all-cotton socks and avoid occlusive footwear whenever possible, remove their shoes when indoors, change their socks whenever they are damp, dust an absorbent powder such as ZeaSORB into shoes and hosiery (to help lessen perspiration), and use an emollient cream as soon as the shoes and socks are removed. Use of a medium-strength to potent topical steroid is usually effective in diminishing the associated pruritus and inflammation. Low-strength topical steroids are often not effective, probably owing to the thick overlying stratum corneum of the plantar surface. Topical or systemically administered antistaphylococcal antibiotics

may be needed if patients show crusting or pustulation suggesting secondary infection. Careful application of a cyanoacrylate (Super Glue) to fissured areas often provides relief from the associated discomfort.

## Frictional Lichenoid Dermatitis

Frictional lichenoid dermatitis (frictional lichenoid eruption, juvenile papular dermatitis, recurrent summertime pityriasis of the elbows and knees) is a recurring cutaneous disorder affecting children, especially boys, between 4 and 12 years of age.<sup>292</sup> Most cases are seen in the spring and summer when outdoor activities are common, and many cases have been associated with playing in sandboxes (sandbox dermatitis) or on grass. Approximately half of the affected children have AD, allergic rhinitis, or asthma.<sup>293</sup> The eruption is characterized by aggregates of discrete lichenoid papules, 1 or 2 mm in diameter, which occur primarily on the elbows, knees, and backs of the hands of children in whom such areas are subject to minor frictional trauma without protection of clothing (Fig. 3-44). Lesions may be hypopigmented, and associated pruritus is often severe but may be absent. It tends to occur in children with a predisposition to atopy.

The differential diagnosis of this disorder includes psoriasis, AD, molluscum, flat warts, lichen nitidus, and the papular acrolocated syndrome (Gianotti-Crosti syndrome; see Chapter 16). The management of frictional lichenoid dermatitis includes avoidance of frictional trauma to the involved areas (as might occur with leaning on elbows and knees) and application of topical corticosteroids and emollient, especially to ease any associated pruritus.

## Nummular Dermatitis

Nummular dermatitis is characterized by discoid or coin-shaped plaques. The name is derived from the Latin word *nummulus* ("coin-like"), because of the shape and size of the lesions. The plaques of nummular dermatitis are composed of minute papules and vesicles, which enlarge by peripheral extension to form discrete, round or oval, erythematous, often lichenified and hyperpigmented plaques that measure 1 cm or more in diameter (see Figs. 3-30 and 3-31). They usually occur on the extensor surfaces of the hands, arms, and legs as single or multiple lesions on dry or asteatotic skin. Pruritus is usually associated and may be intense. Occasionally the face and trunk may be involved. The surrounding skin may be xerotic, particularly in children with AD and nummular dermatitis, but in many patients is normal. Secondary staphylococcal infection is common and manifests as crusting and exudation.

Nummular dermatitis must be differentiated from ACD, AD (which may be seen concurrently), psoriasis, and superficial dermatophyte infections of the skin. History of exposure, patch testing if appropriate, fungal culture, and biopsy of lesional skin can help to distinguish these conditions.

Effective therapy requires application of class II to IV topical corticosteroids, preferably in an ointment base or under occlusion. The combination of a refined tar preparation (liquor carbonis detergens 5% to 10%) in a strong corticosteroid used twice daily is an alternative means of treatment. Secondary staphylococcal infection should always be considered, especially in recalcitrant lesions, and commonly requires systemic administration of antibiotic (such as cephalexin). Therapy with a topical corticosteroid can be continued in the face of treated infection.

## Winter Eczema

Winter eczema, also known as asteatotic eczema, eczema craquelé, or xerotic eczema, is a subacute eczematous dermatitis characterized by pruritic scaly erythematous patches, usually associated with dryness and dehydration (asteatosis) of the epidermis. Generally seen on the extremities and occasionally on the trunk, these changes are most common during winter when the humidity is low, particularly in adults and adolescents who bathe or shower often with harsh or



**Figure 3-44** Frictional lichenoid dermatosis. Aggregates of lichenoid papules occur primarily on the elbows, knees (**A**), knuckles, and backs of the hands of children (**B**). Although the somewhat monomorphic appearance of the papules on the hand in this child is suggestive of lichen nitidus (see Chapter 4), the associated pruritus, localization, and concurrent presence of lichenoid papules of various sizes on the elbows allow the diagnosis to be made clinically.

drying soaps. Frequent bathing with incomplete drying and resultant evaporation of moisture causes dehydration of the epidermis, with redness, scaling, and fine cracking that may resemble cracked porcelain (hence the term *eczema craquelé*). Treatment of winter eczema is centered in the maintenance of proper hydration of the stratum corneum and is dependent on the routine use of emollients, limiting the time and temperature of showers, use of mild soaps, and topical therapy with corticosteroids (preferably those in an ointment base) for individual lesions.

## Lichen Striatus

Lichen striatus is a self-limiting inflammatory dermatosis that follows Blaschko lines, the path of ectodermal embryologic development of skin.<sup>294,295</sup> Although not considered contagious or inherited, lichen



**Figure 3-45 (A) and (B)** Lichen striatus. A self-limiting, usually unilateral linear or curvilinear collection of small, erythematous, flat-topped papules that follows one of the Blaschko lines, lines of the embryologic development of skin. Lines on the face tend to be particularly thin.

striatus has been described in more than one family member.<sup>296,297</sup> It has followed viral infections, vaccination (e.g., hepatitis B virus), and trauma, but its cause is unknown. The mean age of onset is 4 years of age, although older children may be affected. Girls appear to be affected two to three times more often than boys. In the largest series to date, 60 of 115 affected children were atopic.<sup>295</sup>

The eruption is usually asymptomatic and reaches its maximum extent within a few weeks to months. Only 6% of affected children show more than one band. Lesions begin as 2- to 4-mm erythematous to hypopigmented, slightly scaling, flat-topped papules that rapidly coalesce to form the curvilinear band. The line of involvement tends to be narrow but can range from several millimeters to 1 or 2 cm in width. Most commonly lichen striatus affects an extremity but occasionally the face (Fig. 3-45),<sup>298</sup> neck, trunk, or buttocks is affected. Nail involvement is seen, typically by extension of an extremity lesion.<sup>299</sup> In dark-skinned or tanned individuals the eruption may appear as slightly scaly (Fig. 3-46) or as a band-like area of hypopigmentation (Fig. 3-47). Although the band is usually continuous, it may occasionally be interrupted by or interspersed with coalescent plaques several centimeters in diameter along a line of Blaschko.

The differential diagnosis of lichen striatus most commonly includes inflammatory linear verrucous epidermal nevus (ILVEN), which tends to be more psoriasiform (Fig. 3-48; see also Chapter 9 and Fig. 9-38) and blaschkitis<sup>300</sup> (more eczematous) (Fig. 3-49). In contrast to lichen



**Figure 3-46** Lichen striatus. Linear collection of papules of lichen striatus, most commonly seen on the extremities. The erythema is more difficult to appreciate on darker skin, but the mild scaling may be more apparent.

striatus, blaschkitis is usually papulovesicular, pruritic, involves multiple bands, tends to last for about a month, recurs often, and tends to respond to topical anti-inflammatory medication. Biopsy of blaschkitis shows pure spongiosis without a lichenoid infiltrate. Other acquired inflammatory lesions distributed along lines of Blaschko can include linear forms of lichen planus, linear lichen nitidus, lichenoid drug eruptions,<sup>301</sup> lichenoid chronic GVHD, lupus erythematosus, AD, and linearly arranged ("Koebnerized") lesions of verruca plana. When the diagnosis remains in doubt, histopathologic examination of a cutaneous biopsy specimen will help exclude other possible linear eruptions.

Lichen striatus usually resolves spontaneously within 3 to 24 months (mean duration, 6 months)<sup>295</sup> but occasionally lasts longer (up to 3.5 years)<sup>302</sup> and often leaves an area of hypopigmentation that subsequently disappears. Recurrences occur in 2% of children. Therapy is generally unnecessary, and topical corticosteroids do not tend to hasten resolution. However, facial lesions have responded to tacrolimus,<sup>303</sup> and the combination of a topical tazarotene and topical steroid have been associated with lesional clearing.<sup>304</sup>

## Contact Dermatitis

*Contact dermatitis* may be defined as an eczematous eruption produced either by local exposure to a primary irritating substance (irritant contact dermatitis) or by an acquired allergic response to a clinically relevant sensitizing substance (allergic contact dermatitis, ACD).<sup>31</sup> A contact allergen can sensitize but does not cause a reaction on first exposure. With continued or repeated exposure, the allergen may trigger a contact dermatitis based on a type IV allergic reaction. An irritant, on the other hand, may be defined as a substance that produces an eczematous response on the basis of irritation rather than by immunologic means and can occur in anyone; allergens only can trigger contact dermatitis in susceptible individuals. Photocontact reactions (see Chapter 19) such as phytophotodermatitis after contact with the juice or rinds of certain lemons and limes occur only when the skin is exposed to ultraviolet light. ACD should be distinguished from contact urticaria, which can be distinguished by the morphology of the lesions (urticarial) and is best treated with antihistamines.<sup>305,306</sup>

### PRIMARY IRRITANT DERMATITIS

Common substances that produce primary irritant dermatitis include harsh soaps, bleaches, detergents, solvents, acids, alkalis, bubble baths, certain foods, saliva, urine, feces, and intestinal secretions. The severity of the dermatitis varies from person to person or from time to time in the same person as a result of the condition of the skin at the



**Figure 3-47 (A) and (B)** Lichen striatus. The streaks of lichen striatus may be hypopigmented macular streaks from onset, and are particularly prominent in children with darker skin types. The stripe of hypopigmentation can be a narrow stripe, but often is a collection of bands or a broad band.

time of exposure, the strength of the irritant, the location of the eruption, the cumulative effect of repeated exposures to the irritating substance, and local factors such as perspiration, maceration, and occlusion.

In children, the lips and adjacent skin commonly become dry and, as a result of a licking habit, inflamed and scaly (lip-licker's dermatitis) (Fig. 3-50). If extensive, lip-licker's dermatitis must be distinguished from ACD (see Fig. 3-54) and perioral granulomatous dermatitis (Fig. 3-51), which is characterized by small erythematous papules of the perioral, and often suborbital, areas and is exacerbated by application of topical corticosteroids (see Chapter 8). Contact dermatitis induced by mango (see *Poison Ivy (Rhus) Dermatitis* section; Fig. 3-55) can also resemble lip-licker's dermatitis. Saliva also commonly becomes trapped between the thumb and mouth of thumbsuckers, and a similar reaction is commonly seen in toddlers who continue to use pacifiers for long periods of time. In infants with AD, saliva is a significant irritant associated with the extensive drooling from teething and contributes to the dermatitis on the cheeks and chin. In the infant and young



**Figure 3-48** Inflammatory verrucous epidermal nevus (ILVEN). Lichen striatus must be differentiated from ILVEN, a persistent mosaic lesion that follows the lines of Blaschko (see Chapter 9). The papules of ILVEN tends to be more erythematous, less discrete, more scaly and more pruritic than those of lichen striatus, but biopsy or observation over 2 to 3 years may be necessary to determine the diagnosis.



**Figure 3-49** Blaschkkitis. Although distributed along a Blaschko line, lesions of blaschkkitis are eczematous, are often multiple, and last for just a few weeks in contrast to those of lichen striatus or ILVEN.

child, circumoral erythema may also represent a contact dermatitis in response to foods such as citrus foods, carrots, shrimp, and spinach. The dermatitis is caused by direct contact with the skin, not from ingestion of the offending food substances, although exposure is aggravated by regurgitation of food particles, dribbling of saliva, and rubbing of the involved areas.

Diaper dermatitis is the most common form of irritant contact dermatitis in infancy (see Chapter 2), with a peak age of incidence of 9



**Figure 3-50** Lip-licker's dermatitis. Chronic contact dermatitis with lichenification and hyperpigmentation in the shape of licking from the tongue and sometimes beyond.



**Figure 3-51** Periorificial granulomatous dermatitis. The discrete, tiny, noneczematous papules are usually seen in a perioral distribution but may be perinasal and/or infraorbital. The morphology and distribution help to distinguish periorificial granulomatous dermatitis from perioral irritant or allergic contact dermatitis.

to 12 months of age. ACD in the diaper area is rare. Irritant diaper dermatitis typically affects the exposed convex surfaces and spares the folds, which are protected. Toddlers and younger children who use “pull-up” diapers at night and children with enuresis not uncommonly show an irritant dermatitis of the buttocks region related to exposure to urine and limited absorbency of the pull-up. Perianal dermatitis is often irritant, related to exposure to stool, but must be distinguished from perianal psoriasis (see Chapter 4) and perianal streptococcal cellulitis (see Chapter 14). Juvenile plantar dermatosis has been linked to exposure to sweat and is more commonly seen in children with plantar hyperhidrosis (see previous discussion). Excessive handwashing, especially during winter months and in compulsive handwashers, is the most common cause of dermatitis on the dorsum of the hands. The increased attention to handwashing as a means to decrease the spread of infectious disease has markedly increased the risk of developing irritant hand dermatitis in school-aged children.

Soccer and hockey shin guards typically trap sweat and cause friction, leading to an irritant contact dermatitis on the anterior aspect of the lower legs of school-aged children that can become lichenified if chronic. Strategies to reduce friction, such as wearing a cotton sock under the guard and coating the area with absorbent powder or petrolatum before using the guards, together with topical

anti-inflammatory therapy for the dermatitis as needed, have been helpful.<sup>307</sup> Should the dermatitis persist or worsen, ACD should also be considered, particularly to the rubber compounds and neoprene components in sporting equipment (Table 3-3). Irritant reactions may also occur from exposure to fiberglass particles attached to clothes after exposure to fiberglass insulation panels or drapes.<sup>308</sup> Because clothes washed in a washing machine in which fiberglass materials have been washed are also capable of inducing this cutaneous reaction, children whose parents have been exposed may also be affected. Fiberglass dermatitis presents as a pruritic, patchy folliculitis or subacute dermatitis. Microscopic examination of skin scrapings from involved areas or suspected articles of clothing may reveal pale, greenish, granular rod-like fibers one to two times the width of a hair. The use of methylphenidate transdermal patches in children with ADHD often leads to irritant reactions confined to the site of patch application; ACD to the patch is rare.<sup>309</sup>

Avoidance of the irritant is key to improvement. Low-potency topical corticosteroids or calcineurin inhibitors are used to treat the dermatitis of face and intertriginous areas; medium-strength topical steroids, or even potent topical steroids for hands and feet, may be required. Moisturizing creams or ointments lubricate and protect the affected areas. The treatment of irritant diaper dermatitis is discussed in Chapter 2.

## ALLERGIC CONTACT DERMATITIS

ACD may account for up to 20% of all dermatitis in childhood and is likely to be underdiagnosed.<sup>80,81,310</sup> Key areas of involvement are the eyelids, neck, hands, axillae, anogenital area, and lower extremities. ACD represents a type IV immunologic (delayed hypersensitivity or cell-mediated) reaction in which antigenic contact with cutaneous Langerhans cells and T-lymphocyte activation are key. Despite their clinical similarity, nickel sensitization involves Th1/Th17 and Th22 lymphocytes, but fragrance allergy and, to a lesser extent, rubber allergy largely involve Th2 lymphocyte activation.<sup>311</sup> After sensitization to the offending allergen, ACD will develop upon reexposure to the sensitizing substance. Sensitization may occur after only a few exposures to the offending substance, or allergy may occur after years of contact. Once the area has become sensitized, however, reexposure to the offending allergen may result in an acute dermatitis within a relatively brief period (generally 8 to 12 hours after exposure to the sensitizing allergen).

Reactions to *Rhus* family of contact allergens (e.g., poison ivy) are the most common triggers in children. Other major sources of clinically relevant ACD in children are metals (especially nickel, chromates, cobalt, and occasionally gold), fragrances and balsam of Peru, lanolin/wool alcohols, topical antibiotics (neomycin and bacitracin), formaldehyde, and rubber products<sup>80,81</sup> (Table 3-3). Girls are at greater risk for developing contact allergy, especially during adolescence and on the face because of their greater exposure to ear piercing (nickel), cosmetics (preservatives and fragrances), and hair products. Initial sensitization to common allergens and occasionally ACD itself may occur during infancy.<sup>312</sup> Of tested children, 23% to 49% have AD, although it is unclear whether this high number represents a referral bias or truly increased risk<sup>77,313-315</sup>; the greatest relevant reactivity in this group is to allergens in the emollients.<sup>78</sup> More recently recognized triggers in children are PPD contaminating henna tattoos,<sup>316</sup> disperse dyes in clothing,<sup>317</sup> cocamidopropyl betaine (CAPB) in “no-tears” shampoos and cleansers,<sup>318</sup> and the preservatives methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI), which are in wet wipes. The diagnosis of ACD is based on the appearance and distribution of skin lesions and aided when possible by a history of contact with an appropriate allergen (Tables 3-3 and 3-4). Appearance on exposed areas only, linearity, and sharp edges are also clues to a reaction to a contactant, although ACD usually expands beyond the contact area in contrast to irritant contact dermatitis. For example, linearly distributed vesicles and bullae overlying erythema are typical of poison-ivy reactions. Dermatitis can appear at a distant site because of allergen transfer from one body site to another or by “recall reactions,” which are flares at sites of prior allergen exposure.

Dermatitis on the eyelids, hands, feet, and legs is most commonly associated with positive reactions on patch testing. Eyelid dermatitis

**Table 3-3** Most Common and/or Relevant Sensitizers in Children and Their Sources\*

Group	Allergen	Sources	Typical Distribution	Other Comments
Plant	Urushiol	Poison ivy, sumac, oak	Extremities in linear streaks; face, genitals	If aerosolized, can be extensive and on face resemble angioedema
Metal	Nickel	Jewelry, snaps, buckles, eyeglasses, keys, coins, cell phones, tablets, laptop computers, orthodontics	Subumbilical, face, eyelids, earlobes, neck, wrists	Detect with glyoxime on objects
Topical antibiotic	Neomycin	Antibiotic-containing ointments	Face, eyelids	Bacitracin can also sensitize
Fragrance and Balsam of Peru	Fragrance mix Balsam of Peru ( <i>Myroxylon pereirae</i> )	Cosmetics, perfumes, sunscreens, toothpaste, flavoring agents in food and drink, lozenges, lip balms, topical healing agents, insect repellents	Face, eyelids, mouth, lips, neck, hands	Cross reacts with eugenol/isoeugenol (essential oils from several spices, such as cloves and cinnamon); vanilla, tiger balm, benzoin, propolis, colophony, citrus peel
Preservative	Thimerosal	Creams, lotions, mascara, vaccines	Torso, face	Largely removed
Metal	Cobalt	Buttons, snaps, jewelry, cement, ceramics, vitamin B <sub>12</sub>	Umbilical, earlobes, neck, hands	Contaminant with nickel
Metal	Chromate	Leather (tanned), cement, paints, matches, green felt	Umbilical, hands, soles	
Metal	Gold	Jewelry, occupational exposure to jewelry, medicinal use; rarely dental gold	Face, eyelids, earlobes, neck wrists, fingers; rarely mucosal	Long-lasting patch reaction
Rubber accelerator	Thiuram	Elastic (waistband, socks), gloves, shoes (soles and insoles), pesticides	Waistline, feet, hands	Washing clothes with bleach causes release
Emollient	Lanolin/wool alcohols	Emollients, lip balms, soaps, aftershave, baby and bath oil, hand sanitizers	Hands, body	Sheep wool products
Preservative	Formaldehyde/formaldehyde releasing	Lotions, cosmetics, shampoo, newsprint, wrinkle-resistant clothes	Hands, face, ears, trunk (sparing axillae)	
Oxidative chemical	Paraphenylenediamine	Hair dyes, printer ink, contaminant in henna tattoos (black)	Hairline, ears, hands, sites of tattoos	
Preservative	Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI)	Many infant products, such as wet wipes, protective creams, liquid soaps, shampoos, household cleaners, paints	Especially hands; can be head and neck, feet, diaper region, generalized	
Surfactant	Cocamidopropyl betaine (CAPB)	Cleansing products for children (such as tear-free formulations)	Face, hands	
Dye	Disperse dyes	Diaper material, colored synthetic garments (school and athletic uniforms)	Areas of high friction, e.g., around the axillae sparing the vault, anterior thighs	
Rubber accelerator and antioxidant	Mixed dialkyl thiourea	Neoprene in computer mouse pads, wetsuits, shoes, athletic braces, shin guards, protective pads	Areas of friction and sweating under athletic equipment	
Adhesives	p-tert-butylphenol formaldehyde	Glues, surface coating and adhesives in shoes, ECG pads, leather goods, upholstery, hobbies	Hands, feet	

ECG, Electrocardiogram.

\*For additional information, see <https://www.truetest.com/global/patientinfo.htm> and choose the specific antigen.

**Table 3-4** Distribution of Dermatitis and Possible Triggers

Localization	Triggers
Eyelids	Cosmetics, emollients (hands), fragrances, hair dyes, metals, nail products
Hairline, postauricular, ear helix	Hair dyes, hair products
Earlobes, neck	Fragrance, metal jewelry
Periaxillary	Textile dyes, formaldehyde and formaldehyde releasers
Axillary vault	Deodorants
Subumbilical	Metal (snaps, belt buckles)
Extremities, linear streaks	Poison ivy and oak, phytophotodermatitis
Plantar aspect of feet	Adhesive, rubber in shoes
Dorsal aspect of feet	Leather (chromates, dyes), rubber, adhesive



**Figure 3-52** Toilet seat dermatitis. This boy's mother used wipes with iodopropynyl butylcarbamates and fragrance to clean the seat. The dermatitis cleared after a switch to dilute bleach water.

often results from preservatives in cosmetics, fragrances, or emollients applied to the hands. Shoe dermatitis (to the leather chromates, rubber, or dyes) should be suspected if lesions occur on the dorsum of the foot. Subumbilical or earlobe dermatitis is typical of nickel contact allergy, and axillary-vault dermatitis should lead to investigation of sensitivity to deodorant or fragrances, whereas axillary dermatitis sparing the vault may relate to clothing dyes. Toilet seat dermatitis (buttock and posterior thighs) could result from ACD to essential oils, lacquer, or paint in a wooden toilet seat but now more commonly is irritant contact dermatitis from detergents or allergic contact dermatitis to a cleansing component (Fig. 3-52) (and responds well to treatment of the dermatitis followed by prevention with the use of toilet seat covers).<sup>319</sup> Occasionally oral lichenoid reactions occur after ingestion of allergens. The histopathologic picture of ACD usually does not allow differentiation from primary irritant dermatitis or AD.

The acute lesions of ACD are characterized by intense erythema accompanied by edema, papules, vesiculation (sometimes bullae), oozing, and a sharp line of demarcation between involved and normal skin. In the subacute phase, vesiculation is less pronounced and is mixed with crusting, scaling, and thickening of the skin. Chronic lesions, conversely, are characterized by lichenification, fissuring, scaling, and little or no vesiculation.



**Figure 3-53** Nickel contact dermatitis with id. (A) Note the characteristic subumbilical (or periumbilical) hyperpigmented plaque of dermatitis in this patient with nickel contact dermatitis. (B) The lichenification and hyperpigmentation indicate a chronic dermatitis. The tiny discrete papules seen around the plaque extend across the entire trunk and represent an id reaction to the dermatitis.

### Autosensitization Dermatitis or Id Reaction

An id reaction (autosensitization dermatitis, autoeczematization) describes a hypersensitivity disorder characterized by the acute onset of small edematous papules or papulovesicles. Id reactions to nickel are found in up to 50% of patients<sup>320</sup> and may appear on the trunk (Fig. 3-53), forearms, flexor aspects of the upper arms, the extensor aspects of the upper arms and thighs, and less commonly, the face. The eruption is nearly always symmetrical but may demonstrate light sensitivity or an isomorphic response (the Koebner phenomenon), in which trauma elicits new lesions. Lesions are generally associated with moderate to severe pruritus. The disorder usually appears acutely over a few days and nearly always is preceded by an exacerbation of the preexisting dermatitis by infection, rubbing, or inappropriate therapy. The acute eruption may subside spontaneously in a few weeks if the primary dermatitis is controlled. Relapses, however, are common, particularly when the initial local lesion flares and is followed by a further disseminated eruption.

The diagnosis of id reaction is made clinically on the basis of a generalized papulovesicular eruption that develops in the wake of pre-existing eczematoid dermatitis. Treatment depends on the use of open wet compresses, antihistamines, and topical corticosteroid preparations. Control of the primary lesion is critical to prevent further or recurrent antigenic stimulation. Although seldom indicated, a 2- to 3-week course of systemic corticosteroids may at times be necessary in cases unresponsive to more conservative therapy.

Id reactions may also be seen in response to infectious agents, particularly in bacterial and dermatophyte infections. The tiny papules of

**Table 3-5** Allergen Components in the Commercially Available TRUE Test Kit

Panel 1.2	Panel 2.2	Panel 3.2
Nickel sulfate	p-tert-Butylphenol formaldehyde resin	Diazolidinyl urea
Wool alcohol (lanolin)	Epoxy resin	Quinoline mix
Neomycin sulfate	Carba mix	Tixocortol pivalate
Potassium dichromate	Black rubber mix	Gold sodium thiosulfate
Caine mix	Cl+ Me-isothiazolinone	Imidazolidinyl urea
Fragrance mix	Quaternium-15	Budesonide
Colophony	Methyldibromo glutaronitrile	Hydrocortisone 17-butrate
Paraben mix	p-Phenylenediamine	Mercaptobenzothiazole
Negative control	Formaldehyde	Bacitracin
Balsam of Peru	Mercapto mix	Parthenolide
Ethylenediamine dihydrochloride	Thimerosal	Disperse Blue 106
Cobalt dichloride	Thiuram mix	Bronopol

TRUE, Thin-Layer Rapid Use Epicutaneous.

the id reaction associated with tinea capitis most commonly are localized to the head and neck. Often, the id reaction of tinea capitis occurs after initiation of treatment with oral antifungal agents and is erroneously considered to be a drug reaction. Recognition of the underlying infection and continuing the antimicrobial treatment is critical for clearance.

### Patch Testing

Patch tests may be used to confirm the diagnosis of ACD if a specific agent is suspected, even in young children.<sup>321</sup> Different panels of antigens for patch testing are available in Europe, the United States, and Japan, which has led to efforts to standardize testing internationally. In the United States, the Thin-Layer Rapid Use Epicutaneous (TRUE) patch test kit (Allerderm; <http://www.truetest.com>) is commercially available and has been expanded to 35 allergens (Table 3-5). Of the most relevant allergens in children,<sup>322</sup> only dialkyl thioureas and CAPB are not found in the latest TRUE test kits. These kits test have allergens for reactivity against the most common contact allergens measured and preloaded onto hypoallergenic tape for easy use; however, the potential allergens are not inclusive and lack flexibility. The North American Contact Dermatitis Group (NACDG) and American Contact Dermatitis Society (ACDS) screening allergen series are more extensive sets of test substances.

When patch testing is performed, patches should be placed on grossly normal, nonhairy skin such as the back or volar forearm.<sup>323</sup> Distraction techniques such as having the child watch a video are very useful, particularly for testing smaller children.<sup>324</sup> Patch testing should be deferred in the presence of extensive active dermatitis; false-positive reactions may be obtained, and a strongly positive patch-test reaction may cause acute exacerbation of the dermatitis. Antihistamines affect type I reactions and not type IV reactions; thus their administration is not a contraindication to patch testing. Systemic corticosteroid and immunosuppressive therapy might mask weak patch-test responses, and it is preferable that oral steroids be discontinued at least 3 weeks before patch testing. Potent topical steroids have also been shown to suppress patch-test reactivity<sup>325</sup> and should be avoided at the site of testing for 1 week before patch testing.

Patch tests generally should be kept in place for 48 hours, and a reading can be made after an interval of 20 to 60 minutes after removal of the patch to allow the skin to recover from the effects of pressure and occlusion (Fig. 3-54). The patch or its removal may



**Figure 3-54** Patch testing. Positive patch test reaction to p-tert-butylphenol formaldehyde resin in a patient with shoe dermatitis because of reactivity to the glue (see Fig. 3-55).

produce mild transient erythema or a temporary blanching effect, resulting in false reactions.

Reactions are graded based on redness, induration, and presence of blistering. Unless testing for weak sensitizers (such as fabrics or cosmetics), a doubtful reaction (faint macular erythema only) is usually of no significance. A 1 plus (1+) reaction is characterized by erythema, infiltration, and possibly papules. The addition of vesicles to this response indicates a 2 plus (2+) reaction, and a bullous reaction is read as 3 plus (3+). A second reading of the patches should be performed at 72 to 96 hours after the patches are placed. This reading distinguishes irritant from allergic reactions, because irritant reactions often resolve after patches are removed, whereas allergic reactions increase in time. Delayed reading at 5 days or beyond may be needed for certain allergens (metals such as nickel, cobalt, potassium dichromate, and gold; topical antibiotics such as neomycin and bacitracin; topical corticosteroids; PPD). In a recent study, 66% of children had a positive reaction at 48 hours, 84% at 72 hours, and 50% between days 7 and 9; 13% only had delayed reactions to offending agents, stressing the need to include the late observation.<sup>326</sup>

Based on the results, families can learn more about specific allergens at <https://www.truetest.com/global/patientinfo.htm>; members of the ACDS have access to the ACDS Contact Allergen Management Program (CAMP), which provides detailed lists of products that patients are able to use. It may also be advisable for patients to test a product on a limited area on the upper inner arm twice a day for 1 week (the repeat open application test [ROAT]).

Occasionally, positive reactions may have no clinical significance. In that case, the reaction is termed *contact allergy* rather than ACD. Similarly, the offending material may not give rise to a positive reaction at the site of the test but may show a positive test if carried out on an area of skin closer to the point of the previously existing dermatitis. The value of patch tests is corroborative and should be used only as a guide in an attempt to confirm a suspected allergen. Scratch and intracutaneous tests are not useful in contact allergic dermatitis.

### Poison Ivy (*Rhus*) Dermatitis

In the United States, poison ivy, poison oak, and poison sumac produce more cases of ACD than all other contactants combined.<sup>327</sup> The plants causing poison ivy dermatitis are included under the botanical term *Rhus* and are *Toxicodendron* species. Poison ivy and poison oak are the principal causes of *Rhus* dermatitis in the United States. Regardless of the specific *Rhus* plant, the clinical appearance of the dermatitis may be identical. The *Rhus* group belongs to the family of plants known as Anacardiaceae, and cross reactions may occur. These include furniture lacquer derived from the Japanese lacquer tree, oil from the shell of the cashew or Brazil nut, the fruit pulp of the gingko tree, and the marking nut tree of India, from which a black "ink" used to mark wearing apparel is produced. The ACD to this ink is termed *dhobi itch*. The rind of the mango also cross reacts, and the possibility of contact dermatitis to *Rhus* should be considered in children with perioral dermatitis after eating mango or on the hands of mango pickers<sup>328</sup> (Fig. 3-55).



**Figure 3-55** Mango dermatitis. Individuals who react to *Rhus* family plants may demonstrate a perioral dermatitis after eating mango but only when in contact with the mango rind, not from the fruit itself.



**Figure 3-56** Poison ivy plant. A member of the *Rhus* family, showing three notched leaflets. (Courtesy of Dr Jon Dyer.)

The poison ivy plant (Fig. 3-56) characteristically shows three leaflets notched at the edge. It grows luxuriantly as a tall shrub or woody rope-like vine in vacant lots, among grasses, and on trees or fences throughout all sections of the United States except the extreme southwest. Poison sumac grows as a shrub or tree, never as a vine. It has 7 to 13 leaflets (arranged in pairs along a central stem), with a single leaflet at the end, is relatively uncommon, grows less abundantly, and is found only in woody or swampy areas primarily east of the Mississippi River. Poison oak, conversely, grows as an upright shrub, is most prominent on the West Coast, and is not a problem in the eastern United States. Although *Rhus* dermatitis is more common in the summer, the eruption may occur at any time of year by direct contact with the sensitizing allergen from the leaves, roots, or twigs of the plants.

The eruption produced by poison ivy and related plants is a delayed contact hypersensitivity reaction to an oleoresin (urushiol) of which the active sensitizing ingredient is a pentadecylcatechol. It is characterized by itching, redness, papules, vesicles, and bullae (Fig. 3-57). Although often irregular and spotty, a linear distribution is highly characteristic because of scratching and transfer of the urushiol oleoresin (Koebner phenomenon). When contact is indirect, such as from a pet that has the oleoresin on its fur, the dermatitis is often diffuse, thus making the diagnosis more difficult unless the true nature of



**Figure 3-57** (A) *Rhus* dermatitis with Koebner phenomenon. (B) A characteristic linear vesicular eruption on the forearms with poison ivy (*Rhus*) dermatitis.

exposure is suspected. In the fall, when brush and leaves are burned, it must be remembered that the sensitizing oil may be vaporized and transmitted by smoke to exposed cutaneous surfaces, often presenting as a diffuse facial dermatitis with periorbital swelling (Fig. 3-58).

*Rhus* dermatitis usually first appears in susceptible, sensitized individuals within 1 to 3 days after contact with the sensitizing oleoresin; in highly sensitive individuals it may occur within 8 hours of exposure. Such temporal differences are probably the result of the degree of exposure, individual susceptibility, and variation in cutaneous reactivity of different body regions.

About 70% of the population of the United States would acquire *Rhus* dermatitis if exposed to the plants or the sensitizing oleoresin contained in its leaves, stems, and roots. The result is an acute eczematous eruption that, barring complications or reexposure to the offending allergen, persists for 1 to 3 weeks. Since the undiluted sap from plants of the *Toxicodendron* species turns black when exposed to dry surfaces and skin, dramatic black lacquer- or enamel-like deposits on the skin ("black spot poison ivy") and clothing of individuals exposed



**Figure 3-58** *Rhus* dermatitis. The entire face may become swollen with *Rhus* dermatitis, especially if the patient was exposed through aerosolization. The fine vesication distinguishes contact dermatitis from angioedema.



**Figure 3-59** *Rhus* dermatitis. The oleoresin may be transmitted by the fingers to other parts of the body, including the male genitalia.

to poison ivy or other urushiol-containing plants may rarely be seen.<sup>329,330</sup> These spots typically cannot be removed with soap and water and may precede the development of typical dermatitis.

The best prophylaxis, as with any type of ACD, is complete avoidance of the offending allergen. Patients should be instructed in how to recognize and avoid members of the poison *Rhus* group. When poison ivy is present in the garden or in children's play areas, chemical destruction or physical removal is indicated. Heavy-duty vinyl gloves should be used if the plants are uprooted, because the urushiol is soluble in rubber and can penetrate latex gloves.<sup>331</sup> No topical measure is totally effective in the prevention of poison ivy dermatitis, but certain commercially available barrier preparations with quaternium-18 bentonite (organoclay) have been shown to diminish reactivity significantly (IvyBlock, StokoGard, Hollister Moisture Barrier, Hydropel).<sup>332</sup> Desensitization to the oleoresin of poison ivy by systemic administration of *Rhus* antigen is unreliable and should be reserved only for extremely sensitive individuals who cannot avoid repeated exposure to the antigen. Systemic reactions are not uncommon with the use of hyposensitization procedures.

In an effort to minimize the degree of dermatitis, individuals with known exposure should wash thoroughly with soap and water as rapidly as possible so that removal of the oil is accomplished, preferably within 5 to 10 minutes of exposure. If the oleoresin is not carefully removed shortly after exposure, the allergen may be transmitted by the fingers to other parts of the body (particularly the face, forearms, or male genitalia) (Fig. 3-59). However, the fluid content of vesicles and bullae is not contagious and does not produce new lesions. Thus unless the sensitizing antigen is still on the skin, the disorder is neither able to be spread on an individual nor contagious from one person to another.

Complete change of clothing is advisable, and whenever possible, contaminated shoes and clothing should be washed with soap and water or cold water mixed with alcohol to remove the urushiol. Harsh soaps and vigorous scrubbing offer no advantage over simple soaking and cool water. Thorough washing may not prevent a severe dermatitis in highly sensitive persons. It may, however, reduce the reaction and prevent spread of the oleoresin. When early washing is not feasible, it is worthwhile to wash at the first opportunity in an effort to remove any oleoresin remaining on the skin or clothing and thus prevent its transfer to other parts of the body.

In the management of mild *Rhus* dermatitis, treatment with an antipruritic "shake" lotion such as calamine lotion is helpful. Topical preparations containing potential sensitizers such as diphenhydramine or benzocaine should be avoided. As in other acute eczematous eruptions, cool compresses with plain tap water or Burow solution are soothing, help remove crusts, and relieve pruritus. Administration of potent topical corticosteroids and systemic use of antihistamines and antipruritic agents are helpful. Because the acutely involved areas tend to be vesicular and weeping, creams and lotion forms of topical steroids are more commonly used than occlusive ointments.

In severe, more generalized cases of *Rhus* dermatitis, short-term systemic corticosteroid treatment may be indicated. Systemic corticosteroid therapy may be initiated with dosages of 1 mg/kg per day of prednisone or its equivalent. Steroids should be tapered gradually over 2 to 3 weeks. Premature termination of systemic corticosteroids may result in a rapid rebound, with return of the dermatitis to its original intensity.

### Metal and Metal Salt Dermatitis

Nickel dermatitis, the most common ACD to metal, is also by far the most common cause of contact allergy in children undergoing patch testing, with a prevalence of 10.3% to 40% in tested children worldwide.<sup>313,322,333</sup> Nickel may be added to other metals to increase metal strength (in chromium or cobalt) or as plating to increase attractiveness and durability (a variety of metals, including gold).

Earlobe dermatitis is a cardinal sign of nickel dermatitis. Ear piercing has repeatedly been shown to be a strong risk factor for both females<sup>334</sup> and males.<sup>335</sup> The current trend toward piercing of additional body areas in both males and females has increased the numbers of nickel-sensitive individuals. A positive family history of nickel ACD appears to be a risk factor.<sup>320</sup> Several studies have shown an increased risk of nickel sensitivity in girls (perhaps because of piercing).<sup>336</sup> Since piercing of ears or other sites is responsible for an increased tendency of sensitization to nickel and nickel products, piercing should be done with a stainless steel needle. Persons undergoing piercing should be advised to wear only stainless steel earrings or titanium earrings until the earlobes (or other sites) are completely healed, usually about 3 weeks. Although stainless steel contains up to 20% nickel, the nickel is bound tightly and usually causes no problems.

Prominent pruritic periumbilical and subumbilical papules should also trigger consideration of contact allergy to nickel from the nickel-containing buttons on pants and belt buckles (see Fig. 3-53) and may



**Figure 3-60** Nickel contact dermatitis. This dermatitis (**A**) represents a reaction to nickel-containing eyeglass frames (**B**).

present as recalcitrant lichenified plaques in children with AD.<sup>337</sup> Circular erythematous scaling patches on the midline trunk of infants may signal reactivity to the metal snaps in baby clothes, and at least 6% of the fasteners in children's clothing have been shown to release nickel ion.<sup>338</sup> Other potential triggers are zippers, clothing hooks, the dorsal eyelets on shoes, nickel-containing eyeglass rims (Fig. 3-60), shoe buckles, musical instruments,<sup>339</sup> razors,<sup>340</sup> gaming systems,<sup>341</sup> laptops,<sup>342</sup> tablets,<sup>343</sup> and cell phones/cell phone accessories.<sup>344,345</sup> Although the concentration of nickel in orthodontic appliances is low and has not been found to sensitize against nickel, patients who are already nickel sensitive, usually from exposure through ear piercing, may rarely show gingival reactions induced by the appliance<sup>346</sup>, the prevalence of reactions to orthodontic appliances is approximately 0.03%.<sup>347</sup> Students should be aware of the presence of nickel in seats with metal studs, which may lead to patches on the posterior thighs,<sup>348</sup> and metal ballet balance bars may lead to hand dermatitis. Hand dermatitis may also be associated with nickel allergy, because nickel may be present in the metal handles of scissors, keys, doorknobs, and the wheels of skateboards. Nickel coins in the United States no longer contain nickel, but small amounts are present in coins from other countries, and reactions to coin rolling or after coin ingestion by young children have been described.<sup>349</sup> Patch testing for nickel sensitivity can be performed, but false negatives are not uncommon, and repeated testing may be helpful. If a substance is suspected of containing free nickel, application of a test solution of dimethylglyoxine in a 10% aqueous solution of ammonia (Allerderm Ni kit) to the suspected item will usually cause the suspected metal to turn pink.

Once the presence of hypersensitivity to nickel has been established, the hypersensitivity usually lasts for years. Patients must therefore be taught how to avoid contact with nickel objects through the use of proper substitutes. If possible, wearing clothes with nickel should be avoided, and substitution of pants with elasticized waists for jeans

with metal snaps and leather for metal belt buckles should be considered. Periodic coating of the offending metal with clear nail polish (including after each washing if laundered) may prevent loss of nickel, but sewing cloth over the nickel snap is not effective because sweating encourages nickel to leach through the fabric into contact with skin. In general, watches with stainless steel backs should be worn; application of an adhesive moleskin on the back of a watch may be helpful. Sterling silver or platinum jewelry is usually tolerated. Nickel-free eyeglass frames are available. The majority of inexpensive earrings contain some nickel,<sup>350</sup> so that individuals with the allergy should wear only surgical stainless steel earrings, "hypoallergenic" earrings with titanium (which looks like platinum), or earrings with plastic casings (Blomdahl, Simply Whispers). Vinyl gloves can be worn by patients who are sensitive to nickel in order to avoid hand contact with nickel. Midstrength to potent topical steroids can be used to treat a reaction, but avoidance of nickel is required for full efficacy. Dietary avoidance of nickel is difficult but has been recommended by some authors in patients with severe nickel-induced hand ACD and those with systemic contact dermatitis who do not respond to avoidance. Foods with high nickel content include canned foods, chocolate, cocoa, soy beans, cashews, almonds, oatmeal, legumes, and several fish and shellfish.

Chromates are an ingredient in the manufacture of many products such as cement, mortar, leather, paints, and anticorrosives. They are used in the dye of the green felt fabric used for pool tables and the yellow-green pigment of tattoos and cosmetics. Dichromates are used to toughen the collagen in leather and allow it to resist wear, water, and changes because of heat. Most contact reactions in children that are caused by chromates manifest as shoe dermatitis (see *Shoe Dermatitis* section).

Cobalt blue pigment is found in glass and pottery and used in the blue and green of watercolor paints and crayons. It is inextricably linked to nickel in metal-plated objects and costume jewelry, and it can be found in cosmetics, joint replacements, and cement. Oral administration of vitamin B<sub>12</sub>, which also contains cobalt, can cause intractable hand eczema, and injection may lead to dermatitis at the injection site in individuals who are sensitive to cobalt.

Allergic reactions to aluminum are probably not rare and develop most often from vaccination with Al-adsorbed vaccines, including those for diphtheria, tetanus, and pertussis; *Haemophilus influenza*; pneumococcus; hepatitis A and B; and human papillomavirus.<sup>351,352</sup> Children most commonly present with intensely itchy subcutaneous nodules or indurations localized to the site on the anterolateral thigh from 3 weeks to 4 years after the vaccination. Exacerbation of the itching may occur with intercurrent upper respiratory or GI tract infections, sometimes as a prodromal sign. These itchy indurated areas persist for a median duration of 4.6 years. In one study patch testing with aluminum showed reactivity in 95% of those affected, and almost 20% of these reported ACD after exposure to Al-containing deodorants, cosmetics, sunscreens, emollients, and buttons.<sup>352</sup> Other contactants that contain aluminum are Al-precipitated pollen extracts used for allergen-specific immunotherapy, ear drops, and pigments used in tattooing. More than 90% of children with these reactive lesions had milder reactions after vaccines beyond infancy, suggesting that the value of continued vaccination outweighs the risk of avoidance of Al-adsorbed vaccines.

### Shoe Dermatitis

Shoe dermatitis is an extremely common form of contact dermatitis in childhood that usually results from rubber products, especially given the increasing trend for athletic shoes. It is commonly misdiagnosed as tinea pedis, a disorder that occurs uncommonly in children before puberty. In one study, more than 50% of children with foot dermatitis showed reactivity to suspected contact allergens.<sup>353</sup>

Shoe dermatitis usually begins on the dorsal surface of the base of the great toe. It may remain localized or spread to involve the dorsal surfaces of the feet and other toes. The thick skin of the plantar surfaces is generally more resistant but may demonstrate dermatitis over the sole, ventral surface of the toes, instep, or even the entire plantar surface that may be confused with juvenile plantar dermatosis or psoriasis. Erythema, lichenification, and in severe cases, weeping and crusting are typical, but the interdigital spaces usually are spared. In

contrast, maceration, scaling, and occasional vesiculation of the interdigital webs, particularly between the fourth and fifth toes, are usually seen with *tinea pedis*. Irritant dermatitis from friction and ill-fitting shoes may also sharply localize to the dorsal aspects of the toes.

Rubber components are the principal allergens<sup>354</sup>; these include accelerators (most commonly mercaptobenzothiazole but also thiuram, carbamate, and diphenylguanidine) and rubber antioxidants. Rubber accelerators facilitate the transformation of liquid rubber to solid. Several components of the approved patch-test kit in the United States test for rubber, including the carba mix, the black rubber mix, mercaptobenzothiazole, mercapto mix, and the thiuram mix (Table 3-5); however, additional testing should be performed if shoe dermatitis is suspected but an agent is not found in this standard kit, because it is not fully inclusive. Rubber is a common component of the insoles of shoes and particularly of box toes. Rubber cement may be used in joining show uppers, outer leather, and linings.

Individuals with rubber sensitivity may also react to exposure to pacifiers (perioral); wearing latex gloves or handling rubber bands or balloons (hand dermatitis); wearing underwear, swimwear and socks with elastic (especially if clothes are bleached; waist and inguinal areas); handling rubber handle grips (sweaty hands)<sup>355</sup>; wearing swim goggles (periorbital); using cosmetic applicators (face); and wearing adhesive bandages. In adolescent boys, penile contact dermatitis may result from wearing rubber condoms.

Neoprene is a form of rubber in which dialkyl thioureas are used to speed up vulcanization, making it tougher and more pliable for shaping. It is now widely used in sporting equipment, mouse pads and computer cases, wetsuits, athletic shoes, shin guards and other protective pads, orthopedic braces, leggings, and Halloween masks. Components of neoprene-containing items that cause ACD are diethyl thiourea (a dialkyl-thiourea that is not in the TRUE test) and p-tertiary (tert)-butylphenol formaldehyde resin in adhesive.<sup>356</sup>

Less commonly, chromates in leather and adhesives (colophony and p-tert-butylphenol formaldehyde resin) can cause foot dermatitis (Fig. 3-61). p-Tert-butylphenol formaldehyde resin has also recently been implicated in ACD from the foam padding of a bra.<sup>357</sup> The nickel in eyelets and arch supports should also be considered. Iatrogenic ACD also often occurs on the foot, particularly because of neomycin or bacitracin in topical antibiotics.<sup>358</sup> Hyperhidrosis and wearing of occlusive hosiery and shoes contribute to shoe-contact allergy by leaching out allergens and increasing their percutaneous penetration.

Patients with shoe sensitivity should avoid the offending allergen and control associated hyperhidrosis. Use of shoe substitutes depends on whether the reactivity is to rubber, chromates, or adhesives. Vegetable-tanned footwear is a substitute if reactivity is to chromates.



**Figure 3-61** Shoe dermatitis. The recalcitrance of this patient's dermatitis to potent topical steroids led to patch testing, which showed reactivity to p-tert-butylphenol formaldehyde resin (see Fig. 3-54), a component of the glue used in shoes. More commonly, shoe dermatitis is seen on the dorsal aspect of the feet and results from rubber products in shoes or chromates used to tan the leather.

Open sandals, unlined sewn leather moccasins (such as from L.L. Bean), wooden clogs, or plastic "jelly" sandals are other alternatives. In addition, polyvinyl shoes, although they increase the tendency to perspiration, commonly lack many of the potential sensitizers seen in regular shoes; Bass Weejuns loafers and vinyl tennis shoes may also be acceptable substitutes. Since the inner sole is a common source of contact sensitization, removal and replacement with cork insoles, Dr. Scholl's Air Foam pads, or Johnson's Odor-Eaters held in place with a non-rubber adhesive such as Elmer's glue, are often helpful.

The management of active shoe dermatitis, as in other eczematous disorders, is aided by the use of open wet compresses, topical corticosteroids, and antipruritic agents. Since hyperhidrosis is usually responsible for the "leaching" out of potential sensitizing agents, utilization of measures that minimize excessive perspiration of the feet is advisable. Athletic equipment can be lined with water-repellent canvas as an adjunct to the use of a protective sock or sleeve. The topical use of aluminum chloride, available as Drysol or Certain Dri, or tannic acid soaks (two teabags in 1 quart of water) once or twice weekly, often assist in the control of hyperhidrosis. Noncaking agents such as ZeaSORB powder dusted freely into shoes and hosiery not only tend to lessen perspiration but also may act as a mechanical barrier, thus limiting contact with potential allergens and irritants. When painful fissures are present, soaking the foot in water for 20 minutes at bedtime followed by the careful application of superglue or liquid adhesive into the fissured areas, the use of topical corticosteroids and emollient creams, and occlusion at night with plastic wrap or small plastic bags will hasten resolution and lessen discomfort. Barrier socks (Microair), which have three layers of fabric that provide a physical barrier and are breathable, have been helpful in decreasing reactions if exposure cannot be avoided.<sup>359</sup> Individuals with rubber allergy should wear vinyl rather than rubber gloves, and avoid bleaching clothes with elastic, and using rubber swim goggles, rubber headphones, and latex condoms.

### Dermatitis to Cosmetics and Topical Medications

The most common cosmetic agents causing ACD are lipsticks, antiperspirants, hair dyes with PPD, substances in commercial and home permanent wave formulations, lanolins, acrylics, nail lacquers, benzalkonium and ascorbic acid in contact-lens solutions, fragrances (perfumes), sunscreen components (particularly benzophenone and increasingly octocrylene), and a number of preservatives used in cosmetics and shampoos. These allergens are the most common triggers of ACD of the hands.<sup>360</sup> Because early use of cosmetics abets this problem, it is recommended that cosmetics be avoided in young children. Even "toy" cosmetics contain fragrance, particularly cinnamic aldehyde.<sup>361</sup> In many instances, the eyelids are affected not by cosmetics applied to the lids and lashes but by preparations applied to the scalp, face, and nails. Exposure to peppermint oil most commonly leads to perioral dermatitis.<sup>362</sup> Peppermint oil is found in cosmeceuticals, personal hygiene products (mouthwashes, toothpastes, and bath preparation), topical medications (cooling sensation), and food.

ACD is increasingly blamed on preservatives and vehicle components.<sup>363</sup> Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI; Kathon CG)<sup>364</sup> or MI alone<sup>364</sup> is a preservative in baby shampoos, soaps, wet wipes, and protective creams. The dermatitis usually manifests on the face, perianal/buttock area, and/or hands and resists topical and oral antibiotics and corticosteroids. One study found that MCI/MI ranked third in positive patch-testing results in pediatric patients.<sup>365,366</sup> Lesions from MCI/MI on the buttock may be confused with baboon syndrome, which is characterized by well-defined symmetric erythema on the buttocks and sometimes on the upper thighs and axillae and usually related to oral drug ingestion.<sup>367</sup> Recent studies found that testing to higher concentrations of MCI/MI as well as to MI alone is necessary to detect ACD to MCI or MI.<sup>368</sup> However, the TRUE test tests for only the MCI/MI mix at lower concentration.

Another common cause of fingertip and facial dermatitis is CAPB, a surfactant contained in many no-tears shampoos and soaps, contact-lens solutions, and moist baby and facial wipes. CAPB reactivity has been found in 11.3% children who have undergone patch testing.<sup>322,369</sup>

Formaldehyde and formaldehyde releasers (such as quaternium-15, diazolidinyl or imidazolidinyl urea, bromonitropropanediol/bronopol,

and dimethylol dimethyl [DMDM] hydantoin<sup>363</sup> are other preservatives that may trigger contact allergy. A reaction to tosylamide/formaldehyde resin in nail polish is seen largely in female patients who paint their nails<sup>370</sup> but has been described in boys, including from application to the nails as a deterrent to nail biting.<sup>371</sup> Dermatitis tends to occur on the eyelids, cheeks, lips, chin and neck, rather than on the nails themselves. Although the incidence of lanolin sensitivity from emollients is low, lanolin and its derivatives may be present under many different names (e.g., wool wax, wool grease, and wool fat). Lanolin sensitivity should be suspected in children with AD who tolerate application of petrolatum but not the application of lanolin-containing emollients, such as Aquaphor or Eucerin.

In the United States, parabens (compounds containing p-hydroxybenzoic acid) are often added in low concentrations to creams, lotions, and cosmetics in an attempt to retard microbial growth; although possible allergens, they are weaker than other preservatives such as MCI/MI, CAPB, and formaldehyde/formaldehyde releasers. Thimerosal is an organic mercurial compound used as a preservative. It has largely been removed from vaccines but can be found in cosmetics, eye drops, and contact-lens solutions. Although positive patch testing to thimerosal may occur, reactivity is unlikely to be clinically relevant, and rates of sensitization will likely decline with the removal of thimerosal from many vaccines.<sup>372</sup> Although still in the TRUE test kit, the NACDG has removed thimerosal from their standard testing trays because of its low clinical relevance.

More than 5000 different fragrances are in use today, and the ingredient "fragrance" on a label represents a mixture of many. Reactivity to fragrance has been shown to increase with age.<sup>373</sup> Use of perfumes in adolescent girls has been associated with the "atomizer sign," the presence of primary dermatitis at the Adam's apple where the perfume is sprayed.<sup>374</sup> Deodorants can be triggers for ACD in the axillary vault and generally cause an eczematous dermatitis (see **Metal and Metal Salt Dermatitis** section); antiperspirants containing zirconium may produce allergic granulomatous reactions. If near the axillary area but not in the vault clothing and disperse dye is the most like cause of the reactivity (see **Clothing Dermatitis** section). Even baby washes and shampoos have fragrance as a component. "Unscented" or "fragrance-free" means that the product has no perceptible odor but does not necessarily mean devoid of fragrance chemicals, because it may just reflect the addition of masking agents. Furthermore, manufacturers are not required in the United States to list specific fragrances and often do not list essential oils and fragrances used for reasons other than aroma (e.g., preservatives, bisabolol, citrus oil). Testing to both fragrance mix and balsam of Peru captures 70% to 80% of fragrance allergies. True fragrance-free products are available.<sup>375</sup>

The most common allergy-containing fragrances are cinnamic alcohol and cinnamic aldehyde, which are among the eight components of the fragrance mix used in contact allergy testing. Cinnamic alcohol and cinnamic aldehyde are components of chewing gums, toothpaste, mouthwash, flavored lip balms, chewable vitamins,<sup>376</sup> detergents, soaps, and deodorants.<sup>377</sup> Other fragrances are used in perfumes, aftershaves, colognes, and even food flavorings. Reactions to fragrance mix were noted in 18% of 500 children in a recent study in the United Kingdom.<sup>314</sup>

Balsam of Peru (*Myroxylon pereirae* tree extract) is an oleoresin that may contain some of the fragrances in the fragrance mix as well as a range of other components (such as citrus peel, tea tree oil, benzoic acid, and others). Individuals who react to balsam of Peru may react to beeswax, colophony, various spices, turpentine, and coumarin. Balsam of Peru is found in many body washes, shampoos, and diaper-area salves. Its presence as a flavoring in citrus peel and spices (e.g., cinnamon, cloves, vanilla, nutmeg, paprika, and curry) has led to systemic contact dermatitis reactions to citrus products, spices, pickles, chocolate, wine, and colas<sup>378</sup>; avoidance of ketchup in affected children can lead to marked clearance of widespread, recalcitrant dermatitis.<sup>379</sup>

A variety of topical prescription and over-the-counter formulations are capable of producing contact and (at times) systemic contact reactions. Of these, ethylenediamine, benzocaine and its derivatives, topical antibiotics, and topical preparations with diphenhydramine are the most common. Topical application of diphenhydramine (such as in Caladryl) is generally frowned upon, because it reportedly could

cause sensitization and lead to a generalized reaction after systemic administration of diphenhydramine, but occurrence is exceedingly rare. In addition, application of over-the-counter topical antibiotics may cause contact dermatitis and may lead to worsening of cutaneous inflammation despite appropriate use. Neomycin sulfate has long been considered the most allergenic of the topical antibiotics, but bacitracin allergy is increasing in prevalence, and anaphylactic reactions to topical application of bacitracin have been described<sup>380</sup>; both are ingredients in "triple antibiotic" formulations. Although neomycin and bacitracin are not chemically related, both bacitracin and neomycin cosensitization may occur concurrently when topical antibiotics with both are applied. Fusidic acid is an antibiotic used topically outside the United States that can cause both ACD and anaphylaxis after topical application.<sup>381</sup> Recently, ACD to potassium peroxymonosulfate, used as a chemical shock treatment for hot tubs and swimming pools to clear the water, has been described.<sup>382</sup>

Ethylenediamine, a compound stabilizer seen in various topical creams, including with nystatin cream, cross reacts with certain antihistamines, among them hydroxyzine and promethazine hydrochloride. Ingestion of a cross-reacting oral antihistamine in an ethylenediamine-sensitive individual can cause generalized dermatitis<sup>383</sup>; systemic contact dermatitis may also occur from administration of hydroxyzine but without reactivity to ethylenediamine.

The trend of adolescents to hair streaking and dyeing and to henna tattoos has increased the exposure to dyes containing PPD. In addition to typical contact allergic dermatitis, these reactions to PPD may resemble erythema multiforme or vesicular erythema multiforme.<sup>384</sup> Because of the tendency to use PPD in the mixture to darken and increase the precision of design of the temporary henna tattoo, children may show ACD to PPD at any site of henna tattooing.<sup>317,385</sup> Henna itself is rarely a sensitizer. Concentrations of PPD as high as 17.5% have been found in henna-tattoo preparations despite the limit of 6% PPD allowed in hair dyes. Once sensitized to PPD after a henna tattoo, children not only have a lifelong potential reactivity to permanent oxidative hair dye<sup>386</sup> but also may show systemic contact dermatitis to components that cross react with PPD such as hydrochlorothiazide, sulfonamide medications, and ester anesthetics such as benzocaine.<sup>387</sup> PPD may also be a component of fur dyes, dark-colored cosmetics, inks, rubber products, and photographic supplies. PPD reactions in children may also occur because of "connubial dermatitis," in which a child is sensitized through contact with the product on a parent.<sup>322</sup>

ACD from topical corticosteroids has been increasing in incidence and should be considered when patients with dermatitis are worsening despite the application of topical steroids.<sup>388</sup> Sensitization can also occur from ophthalmic solutions and aerosolized inhaled corticosteroids.<sup>389</sup> Reactions to topical steroids can be anywhere, but typically those from ophthalmic solutions involve the conjunctivae, eyelids, and periorbital areas whereas ACD to inhaled steroids is usually on the face, sometimes with extension. Generalized eruptions may occur after systemic exposure to a cross-reacting steroid. Five groups of corticosteroids have been classified based on their chemical structures (A, B, C, D1, and D2) (Table 3-6). Sensitization to group A steroids (in over-the-counter hydrocortisone and oral prednisone) is highest (overall 5.72%).<sup>390</sup> Topical steroids can be screened by the ROAT on the forearm. Tixocortol pivalate, budesonide, and hydrocortisone 17-butyrate are used to test for allergy to topical corticosteroids, although the combination of tixocortol pivalate and budesonide detect almost 90% of the patients with corticosteroid allergies. Positive reactions to topical steroids may not be detectable until 5 days or more after patching. The majority of individuals who test positive to topical steroids have other positive patch tests as well, and it should be remembered that ACD may result from the excipient (e.g., preservative or penetration enhancer) or even the nickel from the tube, rather than the steroid itself.

### Adhesive Tape Dermatitis

Although most cutaneous reactions related to the wearing of adhesive tape are of a mechanical rather than contact sensitivity type, allergic reactions may be caused by the rubber compounds (rubber accelerators or antioxidants) that have been incorporated into the adhesive or the vinyl backing of the adhesive (Fig. 3-62). Dermicel (Johnson

**Table 3-6** Classification of Topical Corticosteroids Based on Chemical Structure and Cross Reactivity

Group A	Group B	Group C	Group D1	Group D2
Hydrocortisone acetate	Amcinonide	Desoxymethasone	Alclometasone	Difluoprednate
Methylprednisolone	Budesonide*	Dexamethasone	Beclomethasone	Hydrocortisone 17-butyrate*
Prednisolone	Desonide	Diflucortolone	Betamethasone dipropionate	Prednicarbate
Tixocortal pivalate*	Fluocinolone Fluocinonide Halcinonide Triamcinolone	Fluocortolone Halometasone	Betamethasone 17-valerate Clobetasol Diflorasone Fluticasone Mometasone	

\*Used to test reactivity.



**Figure 3-62** Tape contact dermatitis. Note that this patient did not react to the cloth Band-Aid (left), but rather to the larger tape (right).

& Johnson), Steri-Strips, or Micropore surgical tape (3M Company), nonrubber acrylate, and spray-on Band-Aids are helpful for those individuals allergic to or irritated by ordinary adhesive tapes.

### Clothing Dermatitis

Although nonspecific irritation from fabrics, rubber, dyes, and cleaning solutions is not uncommon, ACD caused by true sensitization to fabrics is occasionally seen in childhood. Permanent press and crease-resistant fabrics have been responsible for many cases of contact dermatitis because of the use of formaldehydes and formaldehyde-releasing preservatives. Of textiles, blended cottons, corduroy, silk, and rayon have the highest concentrations of formaldehyde, whereas polyester has the least. In a recent survey of 65 children suspected of having contact dermatitis, 7.5% reacted to formaldehyde and 3.8% to each of the listed formaldehyde-releasing preservatives.<sup>322</sup> This type of dermatitis is more likely to occur in individuals whose clothes are tight-fitting and close to the skin. The inner thighs, axillary lines, and popliteal fossae are particularly susceptible.

Dermatitis attributable to dyes in wearing apparel such as school and athletic uniforms is increased from clothing dyed black or dark blue (because the concentration of dyes in dark clothing is much

higher than that of dyes in light-colored clothing, and dark colors tend to bleed more readily than dyes of lighter hue). Disperse dyes may be used in patch testing, but the garment can also be directly applied for patch testing. Children may also react to the epoxy resin in the adhesive holding a knee patch onto jeans and elastic or rubber waist bands in underwear in which the rubber components are leached out after exposure to bleach.

### Compositae Dermatitis

Compositae is one of the largest plant families (10% of the world's flowering plants) and includes among its members chrysanthemum, ragweed, artichoke, sunflower, lettuce, spinach, chamomile, gingko, feverfew, parthenium, and dandelions. Contact allergy to compositae is well recognized in florists, gardeners, and farmers but only occasionally occurs in children.<sup>391</sup> Bisabolol, a compositae derivative, is a component of moisturizers and has been implicated in pediatric ACD.<sup>392</sup>

The complete list of 392 references for this chapter is available online at <http://expertconsult.inkling.com>.

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# 4

# Papulosquamous and Related Disorders

## Childhood Psoriasis

Psoriasis is a relatively common immune-mediated disorder that accounts for 4% of all dermatoses seen in children under 16 years of age and occurs overall in 0.5% to 0.8% of pediatric patients with a linear increase in prevalence by age from 0.2% at 2 years to 1.2% at 18 years.<sup>1-5</sup> Psoriasis rarely is present at birth.<sup>6</sup> Approximately one-third of adults with psoriasis noted the onset during the first 2 decades of life. As in the adult population, psoriasis occurs most often in Caucasian children.<sup>4</sup> The severity of the condition may vary from a life-threatening neonatal pustular or exfoliative dermatosis to a mild, localized disorder that causes no distress. Psoriasis usually follows an irregularly chronic course marked by remissions and exacerbations of unpredictable onset and duration.

Both complex genetic and environmental factors participate in the risk of psoriasis. Approximately 30% of pediatric patients have an immediate family history of psoriasis,<sup>7</sup> and the risk of occurrence in monozygotic twins is two to three times that of dizygotic twins.<sup>8</sup> The major genetic determinant is *PSOR1* (35% to 50% of patients), which is within the major histocompatibility complex on chromosome 6.<sup>9</sup> Early-onset psoriasis has been linked to human leukocyte antigen (HLA) antigen Cw6, and 73.7% of patients with guttate psoriasis show HLA Cw6 antigen, in contrast to a rate of 7.4% in the general population. Autosomal dominant mutations in caspase recruitment domain family member 14 (*CARD14*) or *PSOR2* also lead to a psoriatic<sup>10</sup> (or pityriasis rubra pilaris [PRP]) phenotype. At least 35 additional susceptibility loci for psoriasis have subsequently been identified at other chromosomal locations, among them genes regulating T-cell function, especially interleukin (IL)-23 function, tumor necrosis factor (TNF) activation, nuclear factor (NF)-κB signaling, T-helper (Th) 2 cytokines, interferon (IFN)-mediated antiviral responses, and macrophage activation.<sup>11</sup>

Evidence that psoriasis is an immune-mediated disorder is also based on the success of targeted therapy, such as cyclosporine and inhibitors of TNF; IL-12, -23, and -17; and their receptors. The majority of T cells in psoriatic plaques are CD45RO+ memory-effector T cells that migrate into skin exposed to an antigenic trigger. Th1 and Th17 cytokines predominate, in contrast to the largely Th2 cytokine response of the acute lesions of atopic dermatitis.<sup>12</sup> The innate immune system plays a key role in psoriasis, initiating a cascade that involves activation of myeloid dendritic cells by TNF-α, IFN-γ, IL-6 and IL-1β. The activated dendritic cells express IL-12 and IL-23, leading to Th1 and Th17 cell expression of TNF-α/IFN-γ and of IL-17/IL-22, respectively. These cytokines stimulate the keratinocytes to produce more IL-1β and IL-6, TNF-α, chemokines, and antimicrobial peptides, further contributing to immune activation and cutaneous inflammation.<sup>13</sup> Skin injury and streptococcal infections<sup>14,15</sup> are well-known environmental triggers, but the occurrence of psoriasis has also been linked to *Staphylococcus aureus* infection<sup>16</sup> and Kawasaki disease,<sup>17</sup> suggesting a role for superantigens. Psoriasis has been triggered by administration of growth hormone therapy, IFN (e.g., for chronic hepatitis), and other drugs (particularly, lithium, β blockers, antimalarials, and sodium valproate).<sup>18</sup> Flares of psoriasis have also clearly been linked to psychological and physical stress.

## CLINICAL MANIFESTATIONS

Classic lesions of psoriasis consist of round, brightly erythematous, well-margined plaques covered by a characteristic grayish or

silvery-white (mica-like, or “micaceous”) scale.<sup>19-21</sup> Psoriatic papules coalesce to form plaques that measure 1 cm or more in diameter (Figs. 4-1, 4-2, and 4-3). The disorder may present as solitary lesions or countless plaques in a generalized distribution. Lesions are usually bilaterally symmetrical with a distinct predilection for the scalp, elbows, knees, and lumbosacral and anogenital regions. However, lesions may also be found in a flexural distribution with involvement of the axillae, groin, perineum, central chest, and umbilical region. This variant, termed *inverse psoriasis* (Figs. 4-4 and 4-5), may be seen without any extensor surface involvement in 2.8% to 6.0% of patients or in association with only regional involvement in 30% of patients. Lesions may also be limited to the palms (Fig. 4-6) and soles (Fig. 4-7, A).<sup>22</sup> A peripheral white ring is often the first sign of involution (termed a *Woronoff ring*). However, when the central portions of the plaques resolve, the involuting lesions may appear nummular (small circles), annular (central clearing) (Fig. 4-7, B), gyrate, or arcuate (semicircular). A linear variant that courses along the Blaschko lines has also been described<sup>23</sup> and may be associated with psoriatic arthritis.<sup>24</sup>

The hallmark of psoriasis is the micaceous scale that is generally attached at the center rather than the periphery of lesions. Removal of this scale results in fine punctate bleeding points. This phenomenon (termed the *Auspitz sign*) is highly characteristic and relates to rupture of capillaries high in the papillary dermis of lesions. The Koebner phenomenon (an isomorphic response) is commonly seen in psoriasis (Fig. 4-8) but also in verrucae, *Rhus* dermatitis, lichen planus, lichen nitidus, Darier disease, and PRP. This valuable diagnostic sign of psoriasis describes the occurrence of skin lesions at sites of local injury such as after irritation (a scratch or sunburn) (Fig. 4-9), a surgical scar, or a preexisting disease such as seborrheic or atopic dermatitis. The Koebner phenomenon likely is responsible for psoriasis of the diaper region and around enteral feeding tubes.<sup>25</sup>

## Facial Psoriasis

Facial psoriasis is more common in children than in adults and occurs without other involvement in 4% to 5% of patients. Involvement of the periorbital area is most typical (Fig. 4-10), and lesions may be subtle, leading to confusion with atopic dermatitis (Fig. 4-11). The plaques of psoriasis tend to be more clearly delineated than patches of atopic dermatitis, are less pruritic, and may show an annular configuration. It should be noted, however, that approximately 5% of pediatric patients show an eczema/psoriasis overlap, either showing typical lesions of both atopic dermatitis and psoriasis or lesions that are intermediate (e.g., nummular and psoriasisiform).<sup>26</sup> Almost all patients with the overlap have a family history of both atopic disease and psoriasis. Although mucosae do not tend to be affected in psoriasis, geographic tongue is an often unrecognized feature of psoriasis in many children (Fig. 4-12).

## Guttate Psoriasis

Seen in up to 44% of pediatric patients, guttate psoriasis generally occurs in children and young adults and is often the first manifestation of psoriasis.<sup>8</sup> Lesions are drop-like (guttate), round or oval, measure from 2 mm to 6 mm in diameter (Figs. 4-13 and 4-14), and generally occur in a symmetrical distribution over the trunk and proximal aspects of the extremities (occasionally the face, scalp, ears, and distal aspects of the extremities). Guttate psoriasis is often, but not necessarily, triggered by group A streptococcal infection of the oropharynx or perianal area.<sup>20,27</sup> Two-thirds of patients with guttate psoriasis give a history of an upper respiratory tract infection 1 to 3 weeks before the



**Figure 4-1** Psoriasis. Typical plaques of psoriasis with thick, micaceous scale overlying erythema.



**Figure 4-3** Psoriasis. Psoriasis often involves the forehead, particularly contiguous to the scalp. Note the eyelid and brow involvement. Given the yellowish scaling, this has been called "sebopsoriasis."



**Figure 4-2** Psoriasis. Variably sized erythematous plaques with moderately thick overlying scale.

onset of an acute flare of the disorder.<sup>28</sup> Although guttate psoriasis may clear spontaneously (Fig. 4-15), 40% of affected children progress to the plaque type,<sup>29</sup> which may ultimately be more severe psoriasis than in children with plaque disease initially.<sup>20</sup>

### Scalp Psoriasis

The scalp is commonly the initial site of psoriatic involvement (20% to 40%), and scalp psoriasis occurs more often in affected girls than boys,<sup>20</sup> perhaps because the Koebner phenomenon associated with combing, brushing, and vigorous shampooing. Most typical are well-demarcated erythematous plaques with thick, adherent silvery scales similar in appearance to those on other parts of the body (Fig. 4-16). However, psoriatic lesions of the scalp, eyebrows, and ears (the superior and postauricular folds and external auditory meatus) may instead be greasy and more salmon-colored, suggesting a diagnosis of seborrheic dermatitis. In this variant, often termed *sebopsoriasis*, lesions may present with features of both seborrhea and psoriasis. Whereas lesions of seborrheic dermatitis generally remain within the hairline, lesions of psoriasis often extend beyond the confines of the hairline onto the forehead (see Fig. 4-3), preauricular, postauricular, and nuchal regions. Rapid response to therapy further distinguishes seborrhea from psoriasis. Another scaling disorder of the scalp that may be a variant of psoriasis is pityriasis amiantacea (asbestos-like) (Fig. 4-17)<sup>30</sup>; the alternative term, *tinea amiantacea*, should be abandoned, because the disorder is unrelated to dermatophyte infection. The disorder more commonly occurs in pediatric patients without other signs of psoriasis and is characterized by large plates of scale



**Figure 4-4** Psoriasis. Discrete, brightly erythematous plaques of inverse psoriasis in a 3-year-old boy. Note that the scaling tends to be thinner in an intertriginous area.



**Figure 4-5** Psoriasis. In contrast to the relative sparing of the glans in the toddler in Figure 4-4, this boy's psoriasis of the genital region involved only the glans.



**Figure 4-6** Psoriasis. Annular plaques on the elbow. Note the central clearing, leaving hyperpigmentation.

firmly adherent to the hair and scalp. Focal hair loss and secondary infection may be associated. Pityriasis amiantacea usually begins in school-aged children and adolescents and progresses to more typical psoriasis in 2% to 15% of pediatric patients. Pretreatment of affected scalp areas with fluocinolone 0.01% oil daily and then shampooing with a keratolytic shampoo is usually effective.

### Diaper-Area Psoriasis

Psoriatic diaper rash (see Fig. 2-27) with or without dissemination is the presenting manifestation in 13% and 4% of patients, respectively.<sup>26</sup> This form of psoriasis must be differentiated from infantile seborrheic dermatitis (see Chapter 3) and, when localized to the diaper area, other forms of diaper dermatitis (see Chapter 2). The sharply defined plaques, bright-red coloration, shininess, and larger, drier scales of psoriasis help to differentiate it from seborrheic dermatitis. Many infants with diaper-area psoriasis also show psoriasisiform lesions elsewhere (Fig. 4-18). Because of the increased moisture of the occluded diaper region, scale may not be visible clinically but can be revealed by scraping the area gently. The incidence of psoriasis in the diaper area during infancy probably reflects the Koebner phenomenon, triggered by trauma from exposure to stool and urine, and resolves when toilet trained. Nevertheless, boys and girls out of diapers may also show genital area involvement. Of prepubertal girls with a genital region complaint, 17% had psoriasis<sup>31</sup> particularly involving the vulva, perineum, and natal cleft.

### Nail Involvement

Although statistics vary, the nails appear to be affected in 25% to 50% of pediatric patients with psoriasis, more commonly during the second decade of life and in males<sup>20</sup> (Figs. 4-19, 4-20, and 4-21). Pitting is most characteristic, manifesting as small, irregularly spaced depressions measuring less than 1 mm in diameter. Larger depressions or punched-out areas of the nail plate may also be noted. These pits are thought to represent small intermittent psoriatic lesions in the nail matrix region that forms the superficial layers of the nail plate. Psoriatic pitting may be indistinguishable from nail pitting seen in alopecia areata (see Chapter 7) and atopic dermatitis (see Chapter 3), although other features assist in differentiating these disorders. Discoloration, onycholysis (separation of the distal and lateral nail plate edges), and subungual hyperkeratosis (lifting of the nail plate with nail thickening) (see Fig. 4-21) are also commonly seen. Secondary bacterial, candidal, and occasionally dermatophyte infections occur with increased incidence.

### Other Forms of Psoriasis

Pustular psoriasis and erythrodermic (exfoliative) psoriasis are the most severe variants of childhood psoriasis<sup>32,33</sup> but occur in only approximately 1% of pediatric patients with the disease.<sup>8</sup> Pustular psoriasis has been described as early as the first week of life.<sup>34,35</sup> It usually occurs as generalized pustular psoriasis, but can be limited to the palms and soles (pustulosis palmaris et plantaris) or to fold areas.<sup>36</sup>



**Figure 4-7** Psoriasis. Involvement of the psoriasis on the palms (**A**) and soles (**B**).

On previously quiescent psoriatic plaques or normal skin, erythematous halos develop and rapidly become studded with superficial pinpoint-sized up to 2- or 3-mm pustules (Fig. 4-22). The lesions of generalized pustular psoriasis in children show an annular morphology in 60% of patients (Fig. 4-23).<sup>34,37</sup> Sheets of erythema and pustulation can involve the flexures, genital regions, webs of the fingers, and periungual areas.<sup>38</sup> The cutaneous inflammation typically progresses in an explosive manner from discrete sterile pustules to crusts and ultimately to generalized exfoliative dermatitis. More than 90% of the skin shows intense erythema, massive exfoliation, and associated abnormalities of temperature and cardiovascular regulation. The nails often become thickened or separated by subungual lakes of pus. Mucous membrane lesions in the mouth and tongue are not uncommon. Fever, malaise, and anorexia are typically associated with



**Figure 4-8** Psoriasis. This patient shows the Koebner phenomenon, with development of a linear plaque of psoriasis after trauma to the arm.



**Figure 4-9** Psoriasis. Sunburn on the upper chest and neck led to a flare in an adolescent previously in excellent control.



**Figure 4-10** Psoriasis. Eyelid involvement is often mistaken for atopic or contact dermatitis.

generalized pustular psoriasis. Affected children may show failure to thrive. Patients with extensive pustular or erythrodermic psoriasis usually require hospitalization, and courses are not uncommonly complicated by cutaneous infection and bacterial septicemia. The disease is cyclic and associated with complete clearance of the pustular phase and unexplained exacerbations that span decades. Relapses are common and become progressively more severe, often with a poor prognosis. In contrast to the occurrence of pustular psoriasis in adults known to have psoriasis, pustular psoriasis is often the first manifestation of psoriasis in affected infants and children. The predominant histologic feature on biopsy is the large intraepidermal unilocular pustule containing polymorphonuclear leukocytes (the spongiform



**Figure 4-11** Psoriasis. Facial psoriasis most commonly involves the periorbital area, but more extensive facial involvement can occur.



**Figure 4-12** Psoriasis. Geographic tongue can be seen as the most common mucosal manifestation of patients with psoriasis.



**Figure 4-13** Guttate psoriasis. Tiny guttate (tear-drop) plaques after a streptococcal infection.

pustules of Kogoj) with little if any surrounding spongiosis or inflammation. Although staphylococcal infection may at times occur as a secondary complication, lesions are usually sterile.

Pustular psoriasis with its onset during infancy may be localized to the neck fold.<sup>36</sup> The disorder is often misdiagnosed as dermatitis



**Figure 4-14** Guttate psoriasis. Erythematous, scaling plaques on the leg that measure less than 1 cm in diameter.



**Figure 4-16** Scalp psoriasis. Thick, discrete scaling overlying erythema on the scalp.



**Figure 4-15** Guttate psoriasis. These small hypopigmented macules are the postinflammatory residual lesions of guttate psoriasis.



**Figure 4-17** Pityriasis (tinea) amiantacea. In this severe form of psoriasis of the scalp the scales are strongly adherent (asbestos-like).



**Figure 4-18** Psoriasis in an infant. In addition to diaper area involvement, this infant showed disseminated plaques of typical psoriasis.

caused by bacterial or candidal infection (Fig. 4-24). Biopsy facilitates making the diagnosis, particularly given that many lesions clinically appear more papular than pustular. Other fold areas may be affected, and dissemination to generalized pustular psoriasis is not uncommon.

Pustulosis palmaris et plantaris (pustulosis of the palms and soles) is a bilaterally symmetric, chronic pustular eruption on the palms and soles characterized by deep-seated 2- to 4-mm sterile pustules that develop within areas of erythema and scaling. Plaque or pustular psoriasis may be seen elsewhere on the body. Within several days the pustules resolve and leave a yellow-brown scale that is generally shed



**Figure 4-19** Nail psoriasis. Several fingers show severe onycholysis with oil spots and nail pitting, accentuated where the pits trapped old nail polish. Having just a few nails involved is common.



**Figure 4-20** Nail psoriasis. Note the trachyonychia or rough longitudinal striations, sometimes called "sandpapered" nails (see Chapter 7).



**Figure 4-21** Nail psoriasis. Extensive subungual hyperkeratosis in a teenager. Note the isolated small plaque on one finger.

within 1 or 2 weeks. Phases of quiescence and exacerbation are characteristic, and exfoliating crusted lesions may be seen concurrently with newly developing pustules.

Psoriasis-like pustules during the neonatal period or in infancy, often in association with sterile multifocal osteomyelitis or periostitis,



**Figure 4-22** Pustular psoriasis. Collections of small pustules, some with an annular configuration, overlying bright erythema.



**Figure 4-23** Pustular psoriasis. Note the annular configuration of the pustules.



**Figure 4-24** Localized pustular psoriasis in an infant. In infants, pustular psoriasis may be localized to intertriginous areas, particularly the neck fold, and be confused with dermatitis or infection. This form is difficult to treat and may eventuate in generalized pustular psoriasis.

should raise the possibility of inappropriate activation of IL-1 family cytokines (IL-1 and IL-36) from biallelic mutations in IL-1 or IL-36 receptor antagonists. Pustules may be widespread or grouped and more localized. Deficiency of IL-1 receptor antagonist (DIRA) also may feature joint swelling and pain, oral stomatitis, and pyoderma

gangrenosum, especially during childhood.<sup>38–40</sup> Most neonates with DIRA are born prematurely. Deficiency of IL-36 receptor antagonist (DITRA) is the major cause of generalized pustular psoriasis in patients without common psoriasis.<sup>41–43</sup> DITRA has been described in babies and is characterized by irritability, tender skin, diarrhea, dysphagia, and failure to thrive in association with their pustular psoriasis and/or exfoliative erythroderma. Neutrophilia and thrombocytosis are common, but other organs are not involved.<sup>44</sup> The early onset, and poor response to standard therapy are clues to diagnosis. Skin biopsies in DIRA and DITRA show features similar to those seen in pustular psoriasis.<sup>45</sup> Pediatric patients often respond rapidly to subcutaneous administrations of anakinra 2 to 4 mg/kg per day.<sup>44</sup>

Pustules overlying erythroderma can also be a feature of patients with mutations in *CARD14*, which typically has its onset during infancy or early childhood. More commonly, however, patients with *CARD14* mutations often show signs of recalcitrant plaque-type psoriasis or PRP (see Pityriasis Rubra Pilaris section) and respond rapidly to ustekinumab.

Pustular psoriasis may also present after infancy in association with sterile lytic lesions of bone (sometimes called *chronic recurrent multifocal osteomyelitis* [CRMO]) as part of several syndromes.<sup>46</sup> CRMO in association with congenital dyserythropoietic anemia and neutrophilic dermatoses comprises Majeed syndrome, an autosomal recessive disorder caused by mutations in *LPIN2*.<sup>47</sup> Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome (see Chapter 8) describes the constellation of synovitis, acne, palmoplantar pustulosis and psoriasis, hyperostosis, and osteitis and usually affects the bones of the lower limb, pelvis, and clavicle.<sup>48,49</sup> The bone and joint lesions can severely impact quality of life but may respond to immunosuppressive medications such as methotrexate and aggressive intervention for the acne with isotretinoin.<sup>50</sup>

## Comorbidities

The most common comorbidity of pediatric psoriasis, as in affected adults, is obesity, which tends to precede the onset of psoriasis by at least 2 years in the majority of affected children.<sup>51,52</sup> Several studies have confirmed the association of pediatric psoriasis and obesity.<sup>53–56</sup> Being overweight (“excess adiposity,” between the 85th and 95th percentiles in body mass index [BMI]) or obese (95th percentile or greater BMI) occurs in pediatric psoriasis with an odds ratio (OR) of 2.65 (95% confidence interval [CI], 1.70 to 4.15) globally and OR of 4.22 (CI, 2.05 to 8.67) in the United States,<sup>7</sup> and the association with excess adiposity is seen regardless of psoriasis severity. However, waist circumference percentile and waist-to-height ratio, which are both better indicators of metabolic risk than BMI percentile, are only increased in children with moderate to severe psoriasis.<sup>7</sup> Early evidence suggests that aggressive therapy for psoriasis does not lead to weight or waist circumference reductions.<sup>7</sup>

Increasing evidence suggests an association with early cardiovascular disease in affected children, as has been noted in adult psoriasis. Pediatric psoriasis is associated with approximately two to four times the rate of comorbidity from hyperlipidemia, hypertension, and diabetes than unaffected children and adolescents.<sup>55</sup> In a study of 20 US children with psoriasis, metabolic syndrome (as defined by having at least three of the following: high triglycerides, high density lipoprotein cholesterol, fasting blood glucose, waist circumference percentile, and blood pressure) occurred in 30% with psoriasis but 5% of the control group ( $p < .05$ ).<sup>57,58</sup> These data suggest that early intervention with lifestyle modification and possibly systemic anti-inflammatory therapy may decrease the long-term metabolic risk for these children. Although results have been controversial, a recent study showed significant improvement in the psoriasis and quality of life in overweight adult psoriasis patients on a low-calorie weight loss diet for 8 weeks.<sup>59</sup>

Joint pain has been described in approximately 10% of US children with moderate to severe psoriasis,<sup>7,53</sup> suggesting that inquiry about pain, joint swelling, or limping, as well as examination of the joints for arthritis should be part of the routine evaluation. Psoriatic arthritis is now considered a form of juvenile idiopathic arthritis, and criteria have been established by the International League of Associations for Rheumatology (ILAR).<sup>60–63</sup> These include arthritis with psoriasis or arthritis and: (1) a family history of confirmed psoriasis in a parent or sibling; (2) dactylitis;<sup>64</sup> or (3) nail pitting or onycholysis.<sup>64</sup> The

diagnosis is excluded if the patient has a positive rheumatoid factor titer or signs of systemic disease (daily fever, evanescent erythematous eruption, generalized adenopathy, hepatomegaly or splenomegaly, or serositis). The occurrence of pediatric psoriatic arthritis is biphasic. Younger children affected by psoriatic arthritis tend to be female with dactylitis and small-joint involvement that is more likely to progress and persist. The swelling often includes the juxtaarticular tissue, resulting in a blunt “sausage-shaped” appearance of the involved fingers or toes. Progression to polyarthritis occurs in 30%, leading to flexure deformities and severe bone destruction (osteoporosis, shortening and tapering of the involved distal phalanx) with longstanding disease. On radiologic examination, this resembles a sharpened pencil (the so-called “pencil-in-cup” or “pencil-and-goblet” deformity) at the metatarsophalangeal and metacarpophalangeal joints. Arthritis in older children is characterized by more enthesitis and axial joint disease.<sup>60</sup> Psoriatic skin lesions occur in approximately 60% of children with psoriatic arthritis, are identical to those seen in patients who do not manifest joint disease, and are not related in severity to that of the joint disease. Either skin disease or arthritis may develop initially, and in most patients flares of joint and skin disease do not correlate.

Pediatric patients with moderate to severe plaque psoriasis have demonstrated significantly impaired physical, emotional, social, and school functioning in comparison to healthy children<sup>65</sup> on par with children who have arthritis or asthma and to a greater extent than children with diabetes.<sup>66</sup> In one study, 65% of children with psoriasis experienced stigmatization and 43% complained about fatigue.<sup>67</sup> Pediatric patients with psoriasis have a higher risk of developing psychiatric disorders, especially depression<sup>68</sup> and anxiety.<sup>69</sup>

The risk of developing Crohn disease (but not ulcerative colitis) is also higher in pediatric psoriasis.<sup>55</sup> Asymmetric anterior uveitis of psoriasis has been described in 14% to 17% of children with juvenile psoriatic arthritis. The cutaneous lesions of psoriasis may develop several years after the onset of persisting uveitis.<sup>70</sup>

## DIAGNOSIS OF PSORIASIS

The diagnosis of psoriasis can usually be made clinically, although biopsy can be performed if the diagnosis is in question. Biopsy sections show epidermal thickening (acanthosis with elongation of the rete ridges), retention of nuclei in the stratum corneum (parakeratosis), and a mononuclear infiltrate. Focal collections of neutrophils in the stratum corneum or subcorneal layer (Munro’s microabscesses) are an additional feature in biopsies from patients with pustular psoriasis.

## COURSE

Most patients have long-term mild to moderate disease, often with plaques confined to areas of frictional trauma such as the elbows, knees, buttocks, and scalp. The course of psoriasis, however, is unpredictable, ranging from spontaneous remissions to frequent exacerbations without an evident trigger. Although sunlight generally is beneficial and often leads to improvement during the summer, sunburns can elicit the Koebner phenomenon and lead to exacerbation. With appropriate therapy, satisfactory control of the disease is possible in a majority of patients.

## DIFFERENTIAL DIAGNOSIS

Guttate psoriasis and plaque psoriasis are most commonly confused with dermatitis as well as other papulosquamous disorders described in this chapter, especially pityriasis rosea or pityriasis lichenoides chronica (PLC) (Box 4-1). PRP is the hardest to differentiate, especially when involved areas are largely the palms, soles, elbows, and knees. The follicular accentuation, focal areas of sparing, and sometimes more salmon coloration of PRP can help to distinguish the conditions clinically; biopsy sections of PRP may show perifollicular inflammation. A plaque-type psoriasisform eruption and less often a generalized or annular pustular psoriatic eruption may follow Kawasaki disease (see Chapter 21).<sup>71–73</sup> Generalized and localized forms of pustular psoriasis can be differentiated from infectious causes of pustulosis by cultures and from noninfectious conditions such as eosinophilic

### Box 4-1 Differential Diagnosis of Psoriasis

#### Guttate and Plaque Psoriasis

Pityriasis rubra pilaris  
Pityriasis rosea  
Pityriasis lichenoides chronica  
Psoriasisform dermatitis  
Lichen planus  
Drug eruptions  
Widespread dermatophytosis

#### Facial Psoriasis

Discoid lupus erythematosus  
Seborrheic dermatitis

#### Scalp Psoriasis

Tinea capitis  
Seborrheic dermatitis

#### Nail Psoriasis

Trauma  
Onychomycosis  
Lichen planus

#### Diaper Area Psoriasis

Seborrheic dermatitis  
Irritant dermatitis  
Candidal diaper dermatitis

#### Pustular Psoriasis

Staphylococcal pustulosis  
Candidal pustulosis  
Herpes simplex infection  
Acute generalized exanthematous pustulosis (viral, drug)  
Extensive eosinophilic folliculitis  
Interleukin-1 receptor antagonist deficiency  
Palmpoplantar pustular psoriasis  
Candidiasis  
Infantile acropustulosis

#### Erythrodermic Psoriasis

Extensive pityriasis rubra pilaris  
Congenital ichthyosiform erythroderma  
Erythrokeratoderma variabilis

folliculitis or infantile acropustulosis by biopsy. Psoriasisform dermatitis may also be seen in boys with immune dysregulation, polyendocrinopathy, enteropathy, or X-linked (IPEX) syndrome (see Chapter 3). Atypical cases of psoriatic arthritis must be differentiated from other types of juvenile idiopathic arthritis or systemic lupus erythematosus.

### Therapy of Pediatric Psoriasis

Education is a key component of psoriasis therapy. Patients and parents must understand the chronicity of the disorder and the tendency in 38% of pediatric patients for spontaneous remissions lasting for variable periods.<sup>74</sup> Most patients respond well to available therapies, but the response is slower than with dermatitis.<sup>75-81</sup> The therapeutic approach should be simplified and tailored to the individual patient to optimize compliance, because therapy is time consuming. Patients and family members of the patient should understand the rationale for treatment and any potential risks. Older children and adolescents should be empowered to maintain their own therapeutic routine with parental guidance. The concept that injury to skin may exacerbate psoriasis (Koebner phenomenon or isomorphic response) should also be explained (Table 4-1). Removal of potential trigger factors, including medications and rapid intervention for streptococcal infection should be explored.

#### Topical Therapy

The topical therapies most commonly used in children include topical corticosteroids, topical calcineurin inhibitors, vitamin D<sub>3</sub> analogues

**Table 4-1** Prevention of Psoriasis in Pediatric Patients

Site of Potential Psoriasis	Preventative Behavior
Creases and folds	Minimize friction by maintaining appropriate weight Avoid irritating underarm deodorants
Face	Avoid irritating soaps and burning from exposure to ultraviolet light
Genital and perianal regions	Avoid irritation from tight garments and exposure to accumulated feces and urine
Hands and feet	Minimize excessive sweating and exposure to irritants such as harsh soaps Avoid tight shoes
Nails	Avoid long fingernails or toenails, trauma to nails in play situations, excessive use of nail polish and remover, and wearing tight shoes Hydrate nails before trimming and avoid manipulation of cuticles
Scalp	Avoid vigorous brushing, combing, or scratching of scalp

**Table 4-2** Topical Treatments for Psoriasis in Children

Medication	Use in Children	Potential Side Effects and Comments
Emollients	Useful in mild disease; adjunct	None
Topical steroids	First-line therapy	Local side effects: atrophy, striae Systemic side effects: impaired growth, adrenal suppression, cataracts, tachyphylaxis
Tar	Thicker plaques	Irritation, staining, folliculitis
Salicylic acid	Thicker plaques; usually compounded with steroids ± tar	Irritation
Anthralin	Short contact application	Irritation; less staining than tar
Calcitriol or calcipotriene	Usually adjunct with steroids	Irritation
Tazarotene gel	Usually adjunct with steroids	Irritation
Tacrolimus/pimecrolimus	Face, intertriginous areas	Burning with initial applications

(calcipotriene and calcitriol), tar preparations, and anthralin (also called *dithranol*; short-contact therapy) (Table 4-2). Emollients are important adjunctive measures to decrease associated scaling and dryness but do not replace medications that treat inflammation. The mainstay of treatment for plaque psoriasis remains topical corticosteroids (see Chapter 3, Table 3-2), which often produce dramatic resolution of lesions as monotherapy. Application up to twice daily of class II–IV (potent to midpotency) topical steroids is required to improve lesions on the trunk and extremities. Ointments tend to penetrate the psoriatic scale better and are preferred. If individual thick plaques fail to respond, a course of ultrapotent topical steroid ointment (such as clobetasol, halobetasol, or augmented betamethasone) can be initiated but should be restricted to 2 weeks of application because of the risk for developing striae (especially in the preadolescent/adolescent

population) and local atrophy with continued use. "Weekend therapy" regimens combine class I steroids (used on weekend days only) and topical calcipotriene/calcitriol and should be administered by a dermatologist familiar with the use of these regimens.<sup>82</sup> Keratolytic agents to enhance penetration, such as 6% salicylic acid, are often compounded into steroid ointment with or without tar. The keratolytic applied alone (e.g., Keralyt gel), occlusion, or steroid-impregnated tapes are alternative treatments for more hyperkeratotic, resistant lesions. Use of halogenated midpotent to potent steroids should be avoided in the diaper area, intertriginous areas, and on the face. Topical calcipotriene/calcitriol and tacrolimus ointment, combined or as monotherapy, are steroid-sparing alternatives. Once the acute lesions are under control, treatment can be tapered to lower potency steroids and/or emollients.

Tar is a time-honored and effective adjunct to the topical treatment of psoriasis that is both anti-inflammatory and antiproliferative. Tar (in the form of 1% to 10% crude coal tar or 5% to 10% liquor carbonis detergents) can be compounded into preparations with topical steroids and/or salicylic acid and applied overnight or before ultraviolet light exposure. Tar as a single agent is available in several over-the-counter preparations (e.g., Estar gel, Fototar). Tar preparations, however, stain skin and clothing, have an odor that is often objectionable to children and adolescents, and increase the risk of developing folliculitis. Tar may also be administered in the form of a tar bath (e.g., Cutar bath oil, Doak Oil Forte, Balnetar) or foam.

An alternative to tar therapy is short-contact anthralin therapy, formulated in a temperature-sensitive vehicle that releases the active medication at skin-surface temperature.<sup>83,84</sup> Anthralin, also called *dithranol*, is applied for 5 minutes initially with gradually increasing times of exposure as tolerated and needed for efficacy. Discoloration of skin or clothing is significantly less than that with tar therapy. Contact with the face, eyes, and mucous membranes should be avoided.

Calcipotriene (cream, ointment or solution) and calcitriol (ointment) are most effective when combined with topical steroids but serve as steroid-sparing agents that may be efficacious in children as monotherapy as well.<sup>85,86</sup> These vitamin-D<sub>3</sub> analogues are best applied twice daily, but the onset of action is slow (often 6 to 8 weeks). Combination therapy of betamethasone (0.064%) and calcipotriene (0.005%) ointment is also available.<sup>87</sup> Irritant dermatitis, particularly on the face and intertriginous areas, occurs in up to 20% of patients.

The topical retinoid tazarotene is available in 0.05% and 0.1% strength creams and gels. Tazarotene is best applied once a day in combination with once-daily application of a medium to potent topical steroid, but even with the topical steroid it is often too irritating for use in childhood psoriasis.

Calcinurin inhibitors, particularly tacrolimus ointment 0.1%, are useful with twice-daily application for 1 to 2 months for facial and intertriginous psoriasis.<sup>88</sup> Although not found to be useful outside of the facial and intertriginous areas in double-blind trials in adults, topical tacrolimus ointment is sometimes useful outside of these areas for childhood psoriasis.

### Treatment of Scalp Lesions

Psoriatic scalp lesions are a frustrating and sometimes recalcitrant component of psoriasis. Topical corticosteroids may be applied in the form of oils, solutions, or foams, and calcipotriene solution may be steroid-sparing. Clobetasol and fluocinolone shampoos are also available. Removal of scales can be facilitated by softening scales through application of oil-based medications. For example, fluocinolone 0.01% oil under shower cap occlusion can be applied for 1 hour to overnight to the wet, affected scalp and should be followed by washing with shampoos containing tar, steroid (0.01% fluocinolone or clobetasol), zinc, or keratolytic agents. Alternatively, a phenol and saline (Baker Cummins P&S) solution with a shower cap for occlusion can be applied overnight. In the morning, the patient can shampoo and then apply a steroid foam or solution if needed. Many patients will apply a second shampoo after the medicated shampoo and use a conditioner after shampooing.

### Treatment of Nail Psoriasis

Psoriatic nails are extremely distressing to the patient, respond slowly to therapy, and are difficult to treat topically because of the failure of

topical agents to penetrate the nail plate. Instillation of class-I steroid solutions into the subproximal nailfold area can be successful, especially applied under occlusive tape at night, but application nightly of flurandrenolide-impregnated tape (Cordran) to the base of the nail for approximately 6 months tends to yield better results. Injections of triamcinolone suspension (10 mg/mL) into the nailfold of the abnormal nail with a 30-gauge needle every 4 to 6 weeks is painful, even with the use of topical anesthetic creams and should be reserved for the motivated older child or adolescent who fails to respond to topical application. Nightly application of tazarotene 0.05% or 0.1% gel under occlusion, if tolerated, has been shown to cause improvement.<sup>89</sup> Use of topical indigo naturalis oil extract has recently been described.<sup>90</sup> Disfiguring nail psoriasis that is unresponsive to topical measures may respond to systemic intervention (generally methotrexate or a biologic medication), but the decision to start a systemic medication must be carefully weighed.

### Compresses for Pustular Psoriasis

Local applications of wet dressings with Burow solution 1:40 or potassium permanganate 1:5000 (one crushed 65 mg tablet into 250 mL of water) often help relieve acute flares of the pustular aspect of palmoplantar or generalized pustular psoriasis.

### Ultraviolet Light

Most patients with psoriasis benefit from exposure to sunlight and accordingly are often better during the summer months. However, sunburn precautions must be taken with sunscreens, avoidance during hours of most intense sunlight, and sun-protective clothing, because sudden overexposure may result in sufficient epidermal injury to cause exacerbation of the disorder. For those who can arrange exposure to sunlight on a regular basis, this can be an important aspect of therapy alone or in combination with topical therapies. Although natural sunlight is easier for children and less aggressive than artificial ultraviolet therapy, ultraviolet treatments under professional supervision may also be used as therapy,<sup>91-96</sup> especially when psoriasis involves more than 10% to 20% body-surface area, involves the palms and soles, and/or is recalcitrant to topical therapy.<sup>93</sup> Response to phototherapy is enhanced by preexposure application of oil or ointment.<sup>92</sup> Narrow-band ultraviolet B (nbUVB) ( $\approx$ 311 nm) has a higher ratio of therapeutic-to-toxic wavelengths than broadband UVB light (290 to 320 nm) and is considered at least as efficacious. More than 90% of children treated with nbUVB improve by more than 75%.<sup>97-99</sup>

The UVB light is best initiated in a light box at a dermatology office as outpatient therapy. Once patients and parents know how to increase the doses of ultraviolet light gradually, judge the effects of the daily treatment, and practice preventive eye care, home light-box therapy can be initiated. Home light boxes are ultimately less invasive to the mainstream activities of a family and may be more cost-effective than in-office therapy, although careful monitoring is required. In general, ultraviolet light therapy is started at 70% to 75% of the minimal erythema dose and increased by about 10% to 20% with each treatment as tolerated. A minimum of three treatments per week is required to clear psoriasis. Although rarely used in young children, phototherapy may be administered to young children who are accompanied by parents in the light unit. Tricks such as use of singing together or listening to a radio or compact disc (CD) player with earphones can be used to distract the child during treatment. Acutely, UVB therapy is associated with skin darkening, a chance of skin burning, and, not uncommonly, early pruritus. Although long-term data are lacking in children with psoriasis, recurrent exposure to UVB light could theoretically increase the long-term risk of the development of skin cancer and premature aging.

The excimer laser ( $\approx$ 308 nm) is fiber-optically targeted UVB light that can treat localized plaques of psoriasis without exposing normal skin to unnecessary radiation. Although its use in children has been limited,<sup>93,100</sup> it is painless and offers safety advantages over nbUVB therapy.<sup>101,102</sup> Psoralens and ultraviolet A (PUVA) light (320 to 400 nm) are used rarely in children because of the ocular toxicity, generalized photosensitivity, and the risk of later development of actinic changes and cutaneous carcinomas<sup>103</sup>; topical application of the psoriasis with UVA is a safer alternative but rarely needed.

Protective eyewear must be worn for 24 hours after each PUVA exposure because of the risk of cataract development. The use of topical PUVA light in a hand/foot box has proven effective in adolescents and older children with psoriasis of the hands and feet.

### Systemic Therapy

Oral medications for treating psoriasis have potentially harmful side effects and should be reserved for children with erythrodermic and pustular forms of psoriasis or for those with moderate to severe plaque-type psoriasis recalcitrant to topical therapies.<sup>104,105</sup> In general, systemic corticosteroids should be avoided. Although occasionally effective, steroids are often ineffective or lead to flares of psoriasis when withdrawn, including triggering of pustular psoriasis. Especially in guttate psoriasis, examination for the possibility of pharyngitis or perianal cellulitis should be performed, and culture for β-hemolytic streptococci obtained as appropriate. Antibiotics should be prescribed if the culture is positive, although recurrent positive cultures may signal a carrier state. Although important for treating streptococcal infections, trials of antibiotic therapy are usually not helpful.<sup>106</sup> Some pediatric patients with refractory psoriasis have been shown to improve after tonsillectomy for the treatment of chronic and recurring streptococcal infection.<sup>15,107–109</sup> A recent study showed that 86% of adult patients who underwent tonsillectomy showed sustained improvement (30% to 90%) 2 years after the procedure in contrast to the unchanged status of control patients. Clinical improvement correlated with reduction in circulating keratin peptide-reactive skin-homing (CLA+) T cells (which also recognize cross-reacting streptococcal M proteins), suggesting that the tonsils generate the T cells recognizing these determinants.<sup>15</sup>

The various systemic medications that are available for treating moderate to severe psoriasis are shown in Table 4-3. Methotrexate is indicated for severe unresponsive psoriasis, exfoliative erythrodermas, pustular psoriasis,<sup>93,110</sup> nail psoriasis, and psoriatic arthritis. It is occasionally used for nail psoriasis if nonsystemic agents are ineffective. Methotrexate has antimitotic, antichemotactic, and anti-inflammatory activities. After appropriate screening tests (blood

counts, hepatic testing, purified protein derivative [PPD] or Quantiferon gold for tuberculosis) and testing for pregnancy in female patients of childbearing age, oral methotrexate is initiated at an oral dosage of 0.3 mg/kg per week, and can be increased to 0.6 mg/kg per week if needed for efficacy.<sup>104,111,112</sup> The upper limit in children is usually 20 mg/week. If methotrexate is not efficacious orally, a trial of subcutaneous weekly administration can be undertaken, especially in obese children requiring higher dosing. Methotrexate assays can be performed to determine if a dosage increase is needed in children who respond inadequately after 12 weeks.<sup>113</sup>

The most common side effects are nausea, abdominal discomfort, fatigue, headaches, and anorexia. The most significant side effect is bone marrow suppression. Administration of folic acid diminishes the risk of nausea, mucosal ulcerations, and macrocytic anemia.<sup>114</sup> The dosage is 1 mg/day (may skip the day of methotrexate administration) or 5 mg/week (day after methotrexate). Switching to subcutaneous administration also reduces gastrointestinal complaints. In young children, one chewable multivitamin contains about 400 µg folic acid. Although optimal dosing of folic acid has not been determined, a common practice is to administer the folic acid on the 6 days when methotrexate is not given, because it antagonizes the efficacy of the methotrexate. Liver and bone marrow function should be monitored by blood testing, but testing should not be in the 72 hours after methotrexate administration when transaminases may be transiently elevated. Obese children may have hepatic steatosis and a higher risk of transaminase abnormalities. Liver biopsy is unnecessary in children, and overall hepatic toxicity is rare. Live vaccines such as measles, mumps, and rubella (MMR), poliovirus, and intranasal influenza vaccines may not be given to a child taking weekly methotrexate. Sulfa drugs, including trimethoprim/sulfamethoxazole (Bactrim), should be avoided while taking methotrexate. Improvement is sometimes seen by as little as 3 weeks after initiation of treatment but more commonly requires 10 weeks. Once clearing is achieved, the methotrexate should be gradually lowered (e.g., 2.5 mg/month) during the subsequent months.

Cyclosporine has been used in young patients with severe unresponsive psoriasis, exfoliative erythrodermas, or pustular psoriasis.<sup>104,115</sup> Its

**Table 4-3** Treatment of Pediatric Psoriasis with Phototherapy and Systemic Agents

Intervention	Baseline Labs	Dosing	Follow-Up Tests	Potential Side Effects and Comments*
Methotrexate	CBC, LFTs; TB testing	0.3–0.6 mg/kg/wk	Monthly CBCs, LFTs for first 6 months and then every 3 months; annual TB testing	GI toxicity, fatigue most common; bone marrow suppression and hepatotoxicity
Cyclosporine	CBC, LFTs, BUN, Cr, Mg <sup>++</sup> ; TB testing	3–5 mg/kg/d; can go higher based on drug trough levels	BP checks; monthly CBCs, LFTs for first 6 months and then every 3 months; annual TB testing	Renal and hepatic toxicity, hypertension, hypertrichosis, immunosuppression, UVB-induced skin cancer
Acitretin	CBC, LFTs, fasting lipids	0.5–1 mg/kg/d	CBC, LFTs, fasting lipid levels; pregnancy testing as appropriate	Cheilitis, hyperlipidemia, musculoskeletal pain, hair loss, skin fragility, bone toxicity if used long-term, teratogenicity
TNF inhibitor: etanercept	TB testing required; optional CBC, LFTs	0.8 mg/kg sc injection weekly (max 50 mg)	Annual TB testing; other testing controversial	Increased risk of mycobacterial infection and possibly lymphoma
TNF inhibitor: adalimumab	TB testing required; optional CBC, LFTs	24 mg/m <sup>2</sup> sc every 2 weeks	Annual TB testing; other testing controversial	Increased risk of mycobacterial infection and possibly lymphoma
TNF inhibitor: infliximab	TB testing required; LFTs; optional CBC	3.3–5 mg/kg IV at 0, 2, 6, then every 7–8 wks	Annual TB testing; LFTs every 3 months	Increased risk of mycobacterial infection and possibly lymphoma; rarely used for psoriasis unless need very rapid intervention
Ustekinumab	TB testing required; optional CBC, LFTs	0.75 mg/kg baseline, 4 wks, every 12 weeks; usually 45 or 90 mg	Annual TB testing; other testing controversial	Increased risk of mycobacterial/ <i>Salmonella</i> infection and possibly lymphoma

BP, Blood pressure; BUN, blood urea nitrogen; CBC, complete blood count; Cr, creatinine; GI, gastrointestinal; HIV, human immunodeficiency virus; IV, intravenous; LFTs, liver function tests; Mg, magnesium; MMR, measles, mumps, and rubella; sc, subcutaneous; TB, tuberculosis; TNF, tumor necrosis factor-alpha; UVB, ultraviolet B.

\*All interventions below other than phototherapy and acitretin are immunosuppressive. If suggested by history or examination, undertake baseline hepatitis A/B/C and/or HIV testing. Before starting any immunosuppressive agent, vaccinations should be up-to-date. Live and live attenuated vaccines should be avoided; among common ones are varicella, MMR, intranasal influenza. Systemic medications are all potential teratogens. See text for more details.

mechanism of action involves inhibition of cytokine production by T lymphocytes. Cyclosporine is usually initiated orally at a dosage of 4 to 5 mg/kg per day (and 3 mg/kg per day if microemulsion) and maintained for 3 to 4 months followed by gradual downward titration and discontinuation within a year of initiation. The dosing can be increased if trough cyclosporine levels prove to be low. The potential complications are hypertension, renal and hepatic toxicity, and hypertrichosis; however, concerns about future leukemias, lymphomas, cutaneous carcinomas, and other oncogenic risks are heightened with childhood use. Live vaccines (e.g., MMR and poliovirus) cannot be used in patients receiving cyclosporine therapy. Patients must also avoid macrolide family medications (e.g., azithromycin) because they can markedly increase cyclosporine levels.

Retinoids tend to be less effective than methotrexate or cyclosporine as a single agent for treating plaque-type psoriasis but can be quite effective for exfoliative erythrodermas and for pustular psoriasis that does not respond to compresses and topical corticosteroids alone.<sup>116</sup> Oral retinoids are often used more successfully in combination with topical ointments, ultraviolet light treatment, methotrexate, or cyclosporine. Acitretin normalizes epidermal differentiation and has an anti-inflammatory effect. The usual regimen is oral administration at a dosage of 0.5 to 1 mg/kg per day, although the dosage can be titrated depending on patient response and laboratory results.<sup>82</sup> Complications related to retinoid usage are most commonly dryness of the skin and mucous membranes and elevation of serum triglyceride levels. The potential for skeletal toxicity (premature epiphyseal closure and hyperostosis), although rare, must be monitored clinically and if appropriate radiographically during infancy, childhood, and puberty in patients who receive retinoids long term. Screening tests include blood counts, fasting lipid profiles, and hepatic studies. Retinoids cause severe teratogenicity and should be used with caution in adolescent girls. Isotretinoin may be an alternative retinoid for female adolescents with pustular psoriasis because of its much more rapid clearance but generally it is not as effective as acitretin.

Dimethylfumarate, a fumaric acid ester, is an immunosuppressant available outside of the United States for treating moderate to severe psoriasis. In a retrospective study of 14 pediatric patients (median age at onset, 15 years), only 36% of patients were nonresponders and 36% showed complete clearance.<sup>117</sup> Severe diarrhea and flushing were the causes of discontinuation in two patients, although transient mild elevation in liver function testing or leukopenia were noted in 36% of the children.

Biologic agents are highly effective, but as with all systemic immunosuppressant medications, are not currently approved by the US Food and Drug Administration (FDA) for pediatric psoriasis (although etanercept is approved for use in pediatric psoriasis in several other countries). Currently available biologic agents inhibit either TNF- $\alpha$  (adalimumab, etanercept, infliximab) or IL-12/IL-23 (ustekinumab).<sup>118</sup> Most of the use of biologic agents for psoriasis in pediatric patients has involved TNF inhibitors. Of the TNF inhibitors, etanercept has been used the most in children, including in infants.<sup>119–123</sup> Etanercept is also the only agent tested in a double-blind, randomized trial in US children.<sup>53,124</sup> In this trial of 211 pediatric patients with moderate to severe plaque type psoriasis, 57% achieved 75% improvement by 12 weeks of therapy with 0.8 mg/kg etanercept; only 11% of patients treated with the vehicle control achieved this degree of improvement. However, etanercept is given weekly, whereas adalimumab requires dosing every other week and has been shown to be more efficacious than etanercept in adults, leading to the pediatric use of adalimumab by many physicians, especially in adolescents. Ustekinumab administration has only been described in a few anecdotal reports for treating severe pediatric psoriasis<sup>125,126</sup> but may be the optimal therapy for CARD14-related psoriasis and PRP.

Weighted average psoriasis area and severity index (PASI)-75 scores in adults with moderate to severe psoriasis after 12 weeks of treatment in placebo-controlled studies were 78.6% for infliximab, 72.1% for ustekinumab, 70.5% for adalimumab, 48.1% for etanercept, and 21% for alefacept,<sup>127</sup> suggesting greater efficacy for adalimumab and ustekinumab than etanercept. Similarly, a meta-analysis showed adalimumab and ustekinumab to have similar efficacy and also greater efficacy than etanercept, cyclosporine, methotrexate, and fumaric acid.<sup>128</sup> Nevertheless, multiple factors need to be considered in making

the choice of systemic agent, including patient preference, cost, tolerance, adverse effects, dosing schedule, and mode of administration. Of importance, biologic agents are also considerably more costly than methotrexate, which is a major deterrent to their use. The mean annual cost for TNF inhibitors for adults in the United States is approximately \$15,000 for etanercept, \$18,000 for adalimumab, and \$24,000 for infliximab.<sup>129</sup> Although primarily used for plaque psoriasis, TNF inhibitors have led to improvement for recalcitrant palmoplantar pustulart<sup>130</sup> and erythrodermic<sup>131</sup> psoriasis. TNF inhibitors can show loss of efficacy with time; in adults the 4-year drug survival for etanercept or adalimumab is approximately 40%.<sup>132</sup> Should a TNF inhibitor lose its efficacy, switching to an alternative TNF inhibitor (or a different class of medication) can significantly improve psoriasis severity.<sup>133</sup>

The long-term risks of biologic therapy in children are unknown, although to date serious acute adverse events are rare. Patients may be at risk for mycobacterial and *Salmonella* infections<sup>134</sup> and baseline intermediate strength purified protein derivative (PPD) or quantiferon gold with annual reevaluation is recommended; the need to obtain baseline and follow-up levels of other laboratory tests (e.g., blood counts and liver function tests) in children is controversial. Adverse effects on the development of the immune system in young children and an increased risk of lymphoma are theoretical concerns.

### Development of Psoriasis and Psoriasiform Dermatitis During Administration of Tumor Necrosis Factor Inhibitors

Just as psoriatic arthritis can develop in children with psoriasis who are administered a TNF inhibitor, children taking biologic agents for indications other than psoriasis can develop psoriasis or psoriasiform dermatitis.<sup>135–137</sup> Occurring most often in children treated for Crohn disease, this seemingly paradoxical inflammatory cutaneous response has also been described in children with juvenile idiopathic arthritis, hidradenitis suppurativa, or Behcet syndrome. The psoriasis from TNF inhibitors favors the scalp, periorificial skin, nails, dorsal aspect of hands and feet (Fig. 4-25), and often the palms and soles, where it can be pustular. Lesions are not uncommonly secondarily infected with *S. aureus*. The eruptions are described after a wide range of duration of treatment, ranging from one dose to up to 63 months. Its occurrence in no way affects the response to the biologic agent for the original indication, and the risk of occurrence is not reduced by concurrent administration of methotrexate. The mechanism for the development of psoriasis despite suppression by TNF inhibition remains unclear. Cytokine imbalance with increased expression of IFN, known to increase risk of psoriasis in chronic active hepatitis, has been proposed.<sup>138</sup> Patients with Crohn disease who developed psoriasis on infliximab were more likely to have homozygous *IL-23R* polymorphisms, suggesting a genetic tendency.<sup>135</sup> An infectious trigger, particularly streptococcal or staphylococcal infection, has been suggested as well.



**Figure 4-25** Psoriasiform eruption induced by tumor necrosis factor (TNF) inhibitor on the dorsal aspect of the hands.

Optimal management has not been assessed for children. The literature largely describes affected adults, approximately half of whom respond to discontinuation of the original TNF inhibitor. However, the original indication is usually good control for children taking these TNF inhibitors, so families resist the idea of changing therapy. Trying topical therapy alone is warranted before considering an alternative systemic regimen. Initiation of methotrexate<sup>139</sup> or ustekinumab<sup>140</sup> are other therapeutic options.

### THERAPY FOR PSORIATIC ARTHRITIS

Many patients with psoriatic arthritis require only nonsteroidal anti-inflammatory drugs, maintenance of joint position, functional splinting, and physiotherapy. The combination of methotrexate and a biologic agent is now most commonly used for more recalcitrant cases. Occasionally arthroscopic synovectomy or joint replacement is required.

### PSYCHOSOCIAL AND EDUCATIONAL SUPPORT

Psoriasis affects the family as well as the child. Caregivers of the children often experience anxiety and/or depression related to the child's psoriasis.<sup>141</sup> The National Psoriasis Foundation ([www.psoriasis.org](http://www.psoriasis.org)) is available as a support group for patients and families of patients and provides superb educational material about psoriasis.

## Reactive Arthritis

Reactive arthritis (formerly called *Reiter syndrome*) most commonly occurs in young men between 20 and 40 years of age<sup>142</sup> but has been described in children as young as 9 months of age. It has been reported in almost 100 children, usually boys.<sup>143</sup> In affected adults, reactive arthritis usually occurs after sexually transmitted infection, particularly *Chlamydia*, or gastrointestinal infection and has been associated with human immunodeficiency virus (HIV) infection.<sup>142</sup> In children, it usually develops after an acute enteric infection, particularly one caused by *Shigella flexneri*, *Salmonella typhimurium*, or *Yersinia*. Diarrhea is initially present in 90% of affected children but in only one-third of adults with this disorder. Fever, anorexia, weight loss, and malaise may be other early signs. Several weeks may pass between the onset of fever and diarrhea and the clinical findings of reactive arthritis.

The classic triad of reactive arthritis includes nonbacterial conjunctivitis, urethritis, and arthritis. However, the complete triad is rarely seen at onset, may take several weeks to develop, and is incomplete in the majority of affected children. Conjunctivitis is the most common ocular manifestation and occurs overall in 50% of children. It tends to be bilateral, is self-limited with clearance in weeks, and ranges in severity from mild injection to mucopurulent inflammation. Acute, painful anterior uveitis, iritis, keratitis, corneal ulceration, and optic neuritis have rarely been described. The arthritis typically is asymmetric and involves more than one joint, most commonly large weight-bearing joints, such as the hip, knee, and ankle. However, other large or small joints can be affected, and involvement occasionally is symmetric. In contrast to the pattern in affected adults, the sacroiliac joint is rarely involved in pediatric cases. Many children also show enthesitis, a typical feature of reactive arthritis characterized by focal tenderness at sites where ligament and tendon insert into bone. The arthritis and enthesitis tend to resolve after a few months but occasionally persist or recur. The urethritis in children is usually asymptomatic, and detection of sterile pyuria may be the only evidence of urethral inflammation. Less commonly, inflammation of the meatus may be clinically detectable or urethral discharge may be noted.

The cutaneous manifestations of reactive arthritis may develop in association with, or independently of, the other features of the disorder. Most classic are the circinate balanitis/vulvitis and keratoderma blennorrhagica. The circinate balanitis/vulvitis occurs in 15% to 75% of affected children<sup>144,145</sup> and presents as well-defined erosions on the glans penis in uncircumcised males and on the vulva in females; circumcised male patients often show inflamed hyperkeratotic plaques on the shaft and scrotum. The keratoderma blennorrhagica occurs in



**Figure 4-26** Keratoderma blennorrhagicum, showing thickened, psoriasisiform papules and plaques on the foot of a patient with reactive arthritis. (Reprinted with permission from Schachner LA, Hansen RC, editors. Pediatric dermatology. Edinburgh: Mosby; 2003: Fig. 15.16.)

8% to 25% of children<sup>143,144</sup> and appears as psoriasisiform scaling, inflammatory papules, pustules, and plaques on pressure or weight-bearing areas of the palms and soles (Fig. 4-26).

Psoriasisiform papules and plaques have also been described on the extensor surfaces of the extremities and the dorsal aspects of the feet and hands. Oral lesions consist of painless erythema, shallow erosions, and small pustules that may occur on the buccal mucosa, gums, lips, palate, and tongue. Oral lesions generally resolve spontaneously after a period of several days. Lesions on the tongue, particularly when thickly coated, may simulate a geographic tongue. Nail changes resembling psoriasis have also been seen.<sup>146</sup>

Diagnosis of the disorder is made based on the constellation of clinical features and is supported by nonspecific laboratory findings. Rheumatoid factor is negative, but most affected children show HLA-B27 antigen. Sterile pyuria and significant elevation of erythrocyte sedimentation rate are usually found. Mild anemia with leukocytosis may be present as well. If performed early, stool cultures may yield the triggering bacterial organism. Although biopsy of the skin lesions may be helpful, it does not distinguish the cutaneous lesions of reactive arthritis from those of psoriasis. Reactive arthritis must be differentiated from other seronegative arthropathies, including psoriatic arthritis,<sup>147</sup> juvenile idiopathic arthritis, infectious arthropathies (especially gonococcal and Lyme disease), Kawasaki disease,<sup>148</sup> Behcet syndrome, and rheumatic fever.

Reactive arthritis is almost always self-limiting in children and clears without sequelae. A few children have died, but the prognosis in children is considered much better than that in adults.<sup>144</sup> A minority of children show recurrent or chronic arthritis. Treatment consists primarily of bed rest and administration of nonsteroidal anti-inflammatory drugs. The cutaneous lesions may respond to topical corticosteroids. Ophthalmologic consultation is appropriate for patients with ocular manifestations. Occasionally, intraarticular injection of corticosteroids or administration of systemic medication is required. Sulfasalazine, methotrexate, acitretin, cyclosporine, and infliximab<sup>149</sup> have been used for patients with severe, unresponsive disease.

## Pityriasis Rubra Pilaris

Pityriasis rubra pilaris (PRP) is a chronic skin disorder characterized by small follicular papules, disseminated yellowish-pink scaly plaques surrounding islands of normal skin, and hyperkeratosis of the palms and soles (Figs. 4-27 through 4-31). Small, follicular-based keratotic papules are an important diagnostic feature but are not always present. Although most pediatric cases are acquired without a family history of the disorder,<sup>150</sup> autosomal dominant PRP has been described in families<sup>151</sup> and is now known to result from activating mutations in *CARD14* (*PSORS2*), which encodes caspase recruitment domain family, member 14. *CARD14* is expressed by keratinocytes and activates NF- $\kappa$ B signaling.<sup>152</sup> Whereas the hereditary form tends to have an earlier onset and be persistent,<sup>151</sup> the sporadic forms of PRP show *CARD14* activation without mutation<sup>153</sup> and may be indistinguishable



**Figure 4-27** Pityriasis rubra pilaris. Symmetric, diffuse, well-circumscribed salmon-colored plaques representing the coalescence of follicular-based papules. The discrete papules can be seen at the borders. Note the “skip areas.”



**Figure 4-29** The keratodermic sandal of a patient with type IV pityriasis rubra pilaris.



**Figure 4-28** Pityriasis rubra pilaris. Note the well-circumscribed palmar erythema and keratoderma.



**Figure 4-30** Pityriasis rubra pilaris. Follicular scaling papules on the knee, a common site.

clinically and histologically from the hereditary form. Involvement of the cheeks and patterned lesions on the trunk are a feature sometimes seen with *CARD14* mutations (see Fig. 4-31).

PRP must be distinguished from psoriasis and disorders of cornification, especially the erythrokeratodermias; it is a rare manifestation of dermatomyositis.<sup>154</sup> Keratoderma of the palms and soles develops in the majority of affected children and can be present before or after the appearance of other features.<sup>155</sup> When seen on the soles, this has been referred to as a “keratodermic sandal” (see Fig. 4-29). The keratoderma shows a sharply demarcated border, sometimes extending to involve the dorsum of the hands and feet. The salmon color and associated edema help to distinguish the keratoderma from psoriasis, ichthyosis, hereditary palmoplantar keratoderma, and erythrokeratodermias (see Chapter 5). Thickening of the elbows, knees (see Fig. 4-30), ankles, and Achilles tendon (see Fig. 4-29) is seen in most

affected children.<sup>156</sup> The most characteristic clinical feature is the 1-mm follicular papule with a central keratotic plug that is often surrounded by salmon-colored erythema (see edges of coalescent scale, Fig. 4-27). Initially discrete, the papules usually coalesce into hyperkeratotic plaques with sharply marginated patches and thickened psoriasiform plaques with a coarse texture similar to the surface of a nutmeg grater. The plaques are generally symmetrical and diffuse and contrast sharply with islands of normal skin that occur within the affected areas. Despite their frequency in affected adults, the distinct follicular-based papules on the dorsal aspect of the fingers are found in a minority of affected children.<sup>155</sup>

More than 40% of pediatric patients show cephalic involvement, often extending from the face to the neck and onto the upper trunk in a cape-like configuration with sharp borders (see Fig. 4-27). Scalp

scaling may be extensive, with large, adhesive scales and underlying salmon-colored erythema. Although perioral and periorbital areas may show the keratotic papules and erythema, the mucosae are spared. Ectropion has been described in children with extensive PRP.

The nails are dystrophic in 13% of patients and can show thickening, onycholysis, transverse striations, and subungual debris (Fig. 4-32). The characteristic pitting of nails seen in psoriasis, however, is not a feature of this disorder. The Koebner phenomenon, a hallmark



**Figure 4-31** Individuals with mutations in *CARD14* may show changes of pityriasis rubra pilaris, sometimes with unusual patterning on the trunk.



**Figure 4-32** Unusual nail changes in a girl with extensive pityriasis rubra pilaris (PRP). Note the onycholysis and splinter hemorrhages. Her skin disease was more typical of PRP than psoriasis.

of psoriasis, has been described in approximately 10% of children with PRP. Pruritus is only occasionally a feature but may occur in children with diffuse disease.

The onset of PRP in children may be acute, as is more typical of adults, appearing and spreading during a few days. Alternatively, the eruption may begin on the scalp and forehead and extend gradually. Exfoliative, rapidly progressive dermatitis with associated malaise, chills, and fever is rarely described in children. Biopsy of a follicular-based papule can aid in diagnosis if it shows the characteristic follicular keratosis, as well as epidermal parakeratosis and dermal mononuclear infiltrates, particularly surrounding the hair follicle.

The disorder has been classified into five types based on the age of onset (types I and II in adults; types III–V in children) and clinical features (Table 4-4).<sup>157</sup> Of these, type IV PRP (juvenile circumscribed type) is the most common type in pediatric patients.<sup>158</sup> However, many pediatric cases cannot easily be fit into any of these classifications because of overlap. In addition, children may originally exhibit characteristics of one type that then evolve into another type. An alternative system of classification of five types has been proposed based on the presentation and courses in 104 children. This newer classification adds a new type I that shows only palmoplantar keratoderma without follicular plugging (20% of children), but combines Griffiths' types I and III into a single classification that includes all ages.<sup>155</sup>

The clinical course of PRP is variable. In a review of 29 pediatric cases, 52% showed clearance within 6 months (mean 2.7 months), and an additional 11% were symptom-free by 1 year after onset.<sup>158</sup> In another study of 30 children, 43% showed 90% to 100% clearing, an additional 23% showed at least 30% clearing, and 17% showed a poor outcome.<sup>159</sup> However, in a more recent study of 28 patients, two-thirds of patients with type III and IV juvenile PRP (i.e., most of the patients) had a protracted course lasting longer than 3 years.<sup>160</sup> The prognosis does not correlate with acute versus gradual onset or extent of involvement. The course at times is characterized by spontaneous remissions and exacerbations; some children have disease that evolves into a phenotype more typical of psoriasis than PRP.

Patients with PRP may respond to emollients, topical corticosteroids, tazarotene<sup>161</sup> and keratolytic agents (e.g., formulations containing urea, salicylic acids, or  $\alpha$ -hydroxy acid), particularly those with milder disease. Calcineurin inhibitor therapy may clear facial lesions.<sup>162</sup>

Nonresponders with more extensive disease are best treated with systemic retinoid therapy, which has been shown to be more effective in children than UVB light, methotrexate, cyclosporine, or azathioprine.<sup>159</sup> Adequate therapeutic trials of retinoids require at least 4 to 6 months and careful monitoring. Extensive extraspinal hyperostosis has been described in a child with PRP after long-term administration of oral retinoid therapy.<sup>163</sup> Given the self-limited nature of the disorder in many affected children, retinoids should be tapered and discontinued as tolerated after several months of continuous therapy. TNF inhibitors with or without retinoids have also been helpful in many patients.<sup>164,165</sup> Treatment with ustekinumab has also proven very effective for patients with recalcitrant PRP,<sup>166</sup> and given that IL-23 is an intermediate in the *CARD14*-induced NF- $\kappa$ B signaling pathway, may be the best choice for treatment of patients with *CARD14* activation.

**Table 4-4** Classification of Pityriasis Rubra Pilaris in Adults and Children

Type	Incidence	Clinical Features
I Classic adult	Most adults	Follicular keratotic papules, first on face and extending caudally; progresses to generalized keratoderma with islands of sparing; palms and soles usually involved; generally clears within 3 years
II Atypical adult	Rare	More ichthyosiform scaling; coarse palmoplantar keratoderma; long duration
III Classic juvenile	14% to 35% of children	Same as type I
IV Circumscribed juvenile	Most common type in children	Thick plaques on knees, elbows; palms, and soles involved
V Atypical juvenile	Rare, familial; onset in first years of life	"Sclerodermatos" changes on palms and soles; follicular hyperkeratosis



**Figure 4-33** Pityriasis lichenoides et varioliformis acuta. Symmetrical oval and round reddish brown macular, papular, necrotic, and crusted lesions on the chest of a 9-year-old boy.

## Pityriasis Lichenoides

Pityriasis lichenoides (formerly called *parapsoriasis*) is a spectrum of cutaneous eruptions that has been subdivided into two forms<sup>167</sup>: (1) an acute form, pityriasis lichenoides et varioliformis acuta (PLEVA, Mucha–Habermann disease); and (2) a chronic form, PLC. Overall, 19% to 38% of cases occur in pediatric patients,<sup>168,169</sup> occasionally during the first decade of life and even at birth.<sup>170</sup> Some children show clinical and/or histological features of both the acute and chronic forms, suggesting considerable overlap and confirming the concept that these groups represent a spectrum of disease. As a result, a newer classification is based on distribution into diffuse, central (neck, trunk, and extremities), and peripheral (acral) forms, rather than the morphology of lesions.<sup>171</sup> Acral involvement, including of the face, is more common in children than in adults, and the disorder persists longer before spontaneous remission in children as well.<sup>172</sup>

PLEVA is a polymorphous eruption that usually begins as asymptomatic to pruritic symmetrical 2- to 3-mm, oval or round, reddish-brown macules and papules. The papules occur in successive crops and rapidly evolve into vesicular, necrotic, and sometimes purpuric lesions (Fig. 4-33). These develop a fine crust and gradually resolve with or without a varioliform scar. Lesions may involve the entire body but are often most pronounced on the trunk, proximal thighs, and upper arms, especially the flexor surfaces. The face, scalp, mucous membranes, palms, and soles are often spared or may be involved to a lesser degree. Transient hypopigmentation or hyperpigmentation may result. The course usually lasts for periods of a few weeks to several months. Patients occasionally have associated fever and constitutional symptoms. A rare variant, the febrile ulceronecrotic form, is characterized by large, coalescing, ulceronecrotic nodules and plaques associated with high fever and arthralgias<sup>173,174</sup>; 50% of reported cases have been in children.<sup>175</sup> Febrile ulceronecrotic PLEVA may be associated with gastrointestinal, pulmonary,<sup>176</sup> and central nervous system<sup>177</sup> involvement.

PLC may begin *de novo* or may evolve from PLEVA; overall it affects 37.5% of pediatric patients with pityriasis lichenoides. The course of PLC is variable and may last for 6 months to several years. Lesions characteristically appear as scaling papules and plaques (Figs. 4-34 and 4-35) that resolve with dyspigmentation but no scarring.

In the early stages, pityriasis lichenoides may be mistaken for chickenpox, arthropod bites, impetigo, vesicular pityriasis rosea, vasculitis, or scabies; chronic forms may be confused with psoriasis, lichen planus, pityriasis rosea, and secondary syphilis. The duration of the eruption (often in crops), the presence of macules and papules interspersed with vesicular, crusted, or hemorrhagic lesions with or without varioliform scarring, and subsequent hypopigmentation or hyperpigmentation help to differentiate pityriasis lichenoides from other conditions. When the diagnosis remains in doubt, histopatho-



**Figure 4-34** Pityriasis lichenoides chronica. Small, erythematous papules with numerous residual macules of postinflammatory hypopigmentation.



**Figure 4-35** Pityriasis lichenoides chronica. Annular scaling plaques with associated hyperpigmentation in an African-American patient.

logic examination of a skin biopsy specimen will often substantiate the proper diagnosis, showing heavy mononuclear cell perivascular infiltration and, in more acute lesions, erythrocyte extravasation into the dermis, intraepidermal vesicle formation, and epidermal necrosis.

The cause of pityriasis lichenoides is unknown. However, studies demonstrating T-cell clonality<sup>178,179</sup> suggest that pityriasis lichenoides is a benign lymphoproliferative process in which a vigorous host immune reaction prevents the condition from evolving into lymphoma. The common temporal association of preceding exposure to viral infection, especially to parvovirus or human herpesvirus (HHV)-8,<sup>174,180,181</sup> or immunization, especially to MMR,<sup>182</sup> implicates an abnormal immune response to a viral antigenic trigger. These results

are consistent with rare reports of cutaneous T-cell lymphoma occurring in patients with clinical manifestations or a history of PLEVA or PLC.<sup>183–185</sup> CD30+ T cells in the biopsy specimens of a few patients with pityriasis lichenoides<sup>186</sup> shows overlap with lymphomatoid papulosis (see Lymphomatoid Papulosis section)<sup>180</sup> and suggests a spectrum of lymphoproliferative disorders from benign (PLEVA, PLC) to lymphomatoid papulosis to T-cell lymphoma.

Pityriasis lichenoides does not tend to improve with topical corticosteroids or oral antihistamines, although the associated pruritus may decrease. Children often show a partial to full response to administration of systemic antibiotics,<sup>168</sup> particularly erythromycin, azithromycin,<sup>187</sup> or tetracyclines. A recent study found a good response in 64% of children after 1 month but in 73% of patients by 2 months and 83% in 3 months, suggesting that a 3-month trial is appropriate.<sup>188</sup> If successful, antibiotics can be tapered, but continued administration at low to full dosage may be required for sustained clearance. Tetracyclines should not be administered to children younger than 8 years of age (depending on the status of eruption of secondary teeth) or to pregnant women. Ultraviolet light is the most effective therapy,<sup>189</sup> and most children show clearance in sun-exposed areas.<sup>190</sup> The improvement from exposure to ultraviolet light may also explain the common onset during autumn or winter months. Narrow-band ultraviolet light exposure is highly effective for pediatric patients who are unresponsive to antibiotics, do not have exposure to natural sunlight, and are significantly bothered by the pityriasis lichenoides.<sup>191,192</sup> Methotrexate,<sup>193</sup> cyclosporine,<sup>194</sup> and cyclophosphamide<sup>177</sup> have resulted in improvement in persistent cases but are only appropriate to consider for severely affected children such as those with the febrile ulcerocro-necrotic form.

## Lymphomatoid Papulosis

Lymphomatoid papulosis is a benign, recurrent, self-healing dermatosis with histologic features suggesting lymphoma.<sup>195–197</sup> It is considered to be within the spectrum of lymphoproliferative disorders that ranges from pityriasis lichenoides to cutaneous T-cell lymphoma and has been included as a separate group in classifications of lymphomas.<sup>198</sup>

The disorder is manifested by numerous reddish-brown papules or, less commonly, vesiculopustules that are most often noted on the trunk and proximal extremities but occasionally on the hands and feet, scalp, and genitalia (Fig. 4-36).<sup>199</sup> Regional distribution has been described in children, although more generalized spread may occur after several years.<sup>200</sup> Lesions characteristically develop hemorrhagic necrotic centers and crusting and gradually involute with residual hyperpigmentation or hypopigmentation. Occasionally, varioliform scars or large ulcerating nodules (Fig. 4-37), plaques, or nonulcerating papules occur. Although individual lesions evolve over a period of several weeks to 1 month or more, tend to appear in crops, and sometimes disappear spontaneously within a few weeks to months, the entire course of the disorder may be prolonged and last for years. The disorder is generally asymptomatic.

Lymphomatoid papulosis must be distinguished clinically and histopathologically from arthropod bites, PLEVA, pseudolymphoma, and lymphoma.<sup>201</sup>

The classic histopathologic picture of lymphomatoid papulosis in children is characterized by a heavy infiltrate of scattered large CD30+ CD15- cells that resembles Hodgkin disease in a background of inflammatory cells (type A), although variants resembling mycosis fungoides (type B), anaplastic large T-cell lymphoma (type C), and mixtures of these lymphomas have been described.

In 10% to 20% of adult patients, malignant lymphoma develops, and adults with lymphomatoid papulosis are also at increased risk for developing nonlymphoid malignancies.<sup>202,203</sup> In a report of 35 pediatric patients with lymphomatoid papulosis, 9% of them developed non-Hodgkin lymphoma during a mean follow-up period of 9 years,<sup>197</sup> emphasizing the need for long-term surveillance. Treatment is generally unnecessary except for cosmetic reasons because of the asymptomatic nature and tendency toward spontaneous clearance. The sometimes aggressive nature of lymphomatoid papulosis may lead to the misdiagnosis of lymphoma and chemotherapeutic treatment.<sup>198</sup>



**Figure 4-36** Lymphomatoid papulosis. Reddish-brown papules, most commonly noted on the proximal extremities and trunk. This picture shows lesions in different stages of evolution from development of necrotic centers and crusting to resolution.



**Figure 4-37** Lymphomatoid papulosis. Ulcerating nodule.

Application of ultrapotent topical corticosteroids twice daily for 2 to 3 weeks followed by weekly pulses has resulted in near clearance.<sup>204</sup> Other described therapies in children have included systemic steroids, systemic antibiotics, and PUVA and UVB light, although none have led to sustained complete remission.

## Pityriasis Rosea

Pityriasis rosea is an acute, benign, self-limiting disorder that affects male and female patients equally.<sup>205,206</sup> Approximately 50% of cases occur before 20 years of age, especially in adolescents. Only 4% of cases occur before 4 years of age. Most patients are otherwise well; however, a prodrome of headache, malaise, pharyngitis, lymphadenopathy and mild constitutional symptoms is present in approximately 5% of affected patients, particularly in association with more florid involvement. The etiology of pityriasis rosea remains controversial. A viral disorder is suggested by the occasional presence of prodromal symptoms, the course of the disease, epidemics with seasonal cluster, occasional reports of simultaneous occurrence in closely associated individuals, and a tendency to lifelong immunity in 98% of



**Figure 4-38** Herald patch (pityriasis rosea). Oval lesion with finely scaled elevated border, occasionally misdiagnosed as tinea corporis.



**Figure 4-39** Pityriasis rosea. The collarette of scale can be subtle.

cases. There is evidence both to support and refute the idea that pityriasis rosea is a reaction to HHV-6 and/or -7.<sup>207</sup>

Some 70% of cases start with a single isolated lesion, the so-called “herald patch” (Fig. 4-38), which is found most commonly on the trunk, upper arm, neck, or thigh. This characteristic initial lesion presents as a sharply defined oval area of scaly dermatitis (2 to 5 cm in diameter) with a finely scaled, slightly elevated border that gradually expands. After an interval of 2 to 21 days, a secondary generalized eruption of smaller papules (0.2 to 1 cm) appears in crops, characteristically sparing the face (in 85% of individuals), scalp, and distal extremities. In about 25% of cases, itching, particularly of secondary lesions, may be noted. The orientation of the long axis of these lesions is most characteristic. The typically ovoid lesions run parallel to the lines of skin cleavage, leading to a pattern resembling a “Christmas tree” on the back, wrapping around the trunk horizontally at the axillary area and suprapubic areas, and following inguinal folds. The smaller lesions also show a “collarette of scale” that surrounds the lesions (Figs. 4-38 and 4-39). Although the truncal distribution is most common, some patients, particularly children, show an inverse distribution of lesions on the face, axillae, and groin (Figs. 4-40 and 4-41). This atypical form of pityriasis rosea may be particularly difficult to diagnose if there is no history of a herald patch and if the characteristic morphology of lesions goes unrecognized. The face and neck are more often involved in children than in adults, particularly in African-American children. Pityriasis rosea has also been found to be more extensive, more often papular (34%), and associated with residual dyspigmentation in affected African-American children.<sup>208</sup>

Occasionally, lesions may be predominantly round and papular, particularly in young children and African-Americans (Fig. 4-42). Vesicular, pustular, urticarial, and hemorrhagic variants have also been described. The herald patch occasionally is the only manifestation.



**Figure 4-40** Pityriasis rosea. Inverse pattern showing the distribution along skin lines. Scaling may be more difficult to appreciate in intertriginous areas.



**Figure 4-41** Pityriasis rosea. The axillary area is a good site to look for orientation along skin lines that facilitates the diagnosis.

Involvement of the oral mucous membranes occurs in up to 16% of patients as asymptomatic erythematous patches that rarely appear erosive, hemorrhagic, or bullous.

The secondary eruption peaks within a few days to a week. Clearance usually occurs within 6 weeks, initially in the lesions that appeared earliest, but may require as long as 5 months. The disorder is rarely recurrent.<sup>207</sup> Postinflammatory hypopigmentation or hyperpigmentation may commonly be noted, particularly in dark-skinned individuals, and may persist for weeks to months after clearance of the pityriasis rosea.



**Figure 4-42** Pityriasis rosea. Truncal involvement with larger plaques and predominantly round papular lesions, most commonly seen in young children and African-Americans. Note the peripheral scale and distribution along skin lines.

The diagnosis of pityriasis rosea depends on recognition of the distribution of lesions and the characteristic appearance of the oval lesions with their fine peripheral or collarette scales. The histologic features of pityriasis rosea are not diagnostic and resemble those of a subacute or chronic dermatitis. The herald patch may be mistaken for tinea corporis, and the full-blown eruption must be differentiated from widespread tinea infection, drug eruption, PLEVA, seborrheic dermatitis, nummular eczema, psoriasis (particularly the guttate variety), and importantly, secondary syphilis. The latter must be considered in sexually active individuals who show involvement of the palms and soles, an unusual (but occasional) site for lesions of pityriasis rosea. The hemorrhagic form of pityriasis rosea must also be distinguished from vasculitis, including Henoch-Schönlein purpura, and viral disorders with thrombocytopenia.

Most patients require no treatment beyond reassurance as to the nature and prognosis of the disorder. Pruritus, if present, usually responds to topical antipruritics (calamine lotion, lotions containing menthol and/or camphor, lotions with pramoxine), oral antihistamines, colloidal starch or oatmeal baths, and mild topical corticosteroid formulations. Exposure to ultraviolet light or sunshine tends to hasten resolution of lesions, and in the summertime it is not uncommon to see patients with pityriasis rosea under covered areas with little to no evidence of the eruption on sun-exposed regions.<sup>209</sup>

## Lichen Planus

Lichen planus is a disorder primarily of adults, but 2% to 11% of reported cases occur in children and adolescents,<sup>210</sup> including as those young as 3 weeks of age. The etiology of lichen planus is unknown, but evidence suggests a cell-mediated autoimmune response. Familial cases are rare<sup>211</sup> but have an earlier age at onset, increased severity, a greater likelihood of chronicity, and an increased incidence of erosive, linear, ulcerative, and hypertrophic forms. Several cases in children have been described after hepatitis B vaccination.<sup>212-214</sup> The association of lichen planus with hepatitis C, as seen in adults,<sup>215</sup> has not been noted in children.<sup>212,216</sup> Lesions resembling lichen planus are a common manifestation of chronic graft-versus-host disease (see Chapter 25).

The primary lesion is a small, shiny, flat-topped polygonal, reddish or violaceous papule (Figs. 4-43 and 4-44).<sup>217</sup> Individual papules vary from 2 mm to 1 cm or more and may be closely aggregated or widely dispersed. Lichen planus is generally mildly to intensely pruritic in adults but is not uncommonly asymptomatic in affected children.<sup>210</sup>



**Figure 4-43** Lichen planus. The shiny flat-topped polygonal violaceous papules of lichen planus may be linear in orientation, suggesting the Koebner phenomenon after scratching. Note the intense residual hyperpigmentation and subtle overlying reticulated scaling.



**Figure 4-44** Typical violaceous lesions of lichen planus on the penile shaft, a common site.

The disorder is usually limited to a few areas with the lower legs the most common site<sup>212</sup>; lichen planus also often affects the flexural surfaces of the ankles and wrists, the genitalia (Fig. 4-45), and the lower back. Involvement of the face (Fig. 4-46), palms, and soles is unusual.<sup>203</sup>

At times, one may detect characteristic small grayish puncta or streaks that form a network over the surface of papules. These delicate white lines, termed *Wickham striae*, become more visible under magnification with a hand lens or by wetting the lesion with an alcohol swab or a drop of oil, which renders the horny layers of lesions more



**Figure 4-45** The shiny flat-topped polygonal violaceous papules of lichen planus. Note the Wickham striae (linear whitish-gray streaks) on the surface.



**Figure 4-48** Oral lichen planus. Wickham striae on the buccal mucosa.



**Figure 4-46** Mildly pruritic violaceous lesions on the eyelids with postinflammatory intense hyperpigmentation; biopsy confirmed lichen planus.



**Figure 4-49** Lichen planus of the nails. Anonychia and pterygium formation.



**Figure 4-47** Lichen planus. Note the linearity of lesions from scratching and the Koebner phenomenon.

transparent. Occasionally, lesions may coalesce to form plaques or a linear configuration (the Koebner phenomenon) at sites of minor trauma, such as scratch marks (Fig. 4-47).

Mucous membrane involvement is seen in up to 40% of pediatric patients<sup>218</sup> and is much less common than in adult patients (50% to 70% of adult patients).<sup>210,213</sup> When present, lesions usually appear as pinhead-sized white papules forming annular or linear lace-like patterns on the inner aspects of the cheeks (Fig. 4-48).<sup>219,220</sup> Lesions on

the palate, lips, and tongue are less characteristic and except for their reticulated appearance may easily be mistaken for areas of leukoplakia. On the lips the papules are more often annular, sometimes with adherent scaling reminiscent of that seen in lupus erythematosus. Although the typical reticulated mucosal lesions of lichen planus are asymptomatic, painful ulcerative lesions have been found on the tongue, oral mucous membranes, and mucosal surfaces of the pharynx, esophagus, gastrointestinal tract, vulva, and vagina.

Up to 10% of adult patients with lichen planus demonstrate involvement of one to all nails, but nail involvement appears to be less common in affected children; one study, however, noted nail involvement in 19% of 100 children.<sup>210,212</sup> Violaceous lines or papules in the nailbed may occasionally be seen through the nail plate. The nail dystrophy consists of loss of luster, thinning of the nail plate, longitudinal ridging or striation, splitting or nicking of the nail margin, atrophy, overlapping skin folds (pterygia), marked subungual hyperkeratosis, lifting of the distal nail plate, red or brown discoloration, and at times complete and permanent loss of the nail (Fig. 4-49).<sup>221</sup> Some children with 20-nail dystrophy (trachyonychia, see Chapter 7) may have lichen planus, but biopsy of the nail matrix would be needed to confirm the diagnosis in the absence of cutaneous changes.<sup>222</sup>

Although lichen planus is considered to be papulosquamous, many variations in morphology and configuration may be noted. These

variations include vesicular, bullous, actinic, annular, hypertrophic (Fig. 4-50), atrophic, linear,<sup>223</sup> erythematous, and follicular forms (Table 4-5).<sup>223-225</sup> Lichen planus pemphigoides is a rare autoimmune blistering disease in which the typical lichen planus lesions evolve into bullous lesions with a mean lag time of 8 weeks (see Chapter 13).<sup>224</sup> The extremities are most commonly involved, and approximately half



**Figure 4-50** Lichen planus. The plaques of lichen planus may be hypertrophic but show the characteristic violaceous coloration and intense hyperpigmentation.

**Table 4-5** Variants of Lichen Planus

Variant Type	Characteristics
Bullous <sup>225</sup>	Bullae develop on existent LP lesions
LP pemphigoides <sup>224</sup>	LP + bullous pemphigoid with autoimmune reactivity, usually against type XVII collagen (bullous pemphigoid 180 antigen)
Actinic	Onset during spring, summer; primarily sun-exposed surfaces (face, neck, dorsum of arms and hands); often annular configuration; most commonly in children and young adults
Annular	Occur in 10% of patients, often scattered amid typical lesions of LP
Hypertrophic	Pruritic, thick hyperkeratotic plaques, especially on the legs and dorsal regions of the feet; persistent
Atrophic	May represent a resolving phase in which larger plaques become centrally depressed with residual hyperpigmentation
Hemorrhagic/purpuric	Shows nonblanching component on diascopy
Linear <sup>223</sup>	LP occurring spontaneously along the lines of Blaschko; presumably reflects somatic mosaicism
Erosive/ulcerative	Intensely painful ulcerations on the palms and soles; chronic lesions may evolve into squamous cell carcinoma; erosive lesions may occur on mucosal surfaces
LP/lupus erythematosus	Overlapping features of lupus and LP; lesions are usually acral and patients may show high titers of ANA
Lichen planopilaris	Follicular LP; keratotic plugs surrounded by violaceous erythema, especially on scalp but can affect any hair-bearing area; usually results in cicatricial alopecia

ANA, Anti-nuclear antibodies; LP, lichen planus.

of the affected children show palmoplantar lesions. Direct and indirect immunofluorescence shows the presence of circulating antibodies, and patients often respond to topical corticosteroid and oral dapsone therapy, but systemically administered steroid may be required.

Many drugs may produce an eruption that resembles lichen planus (lichenoid drug eruption). Most commonly implicated are antihypertensives (captopril, enalapril, labetalol, and propranolol), diuretics (especially hydrochlorothiazide), antimicrobials (especially hydroxychloroquine and quinidine), metals (especially gold salts), and penicillamine. Among other agents rarely implicated but used often in children and adolescents, are griseofulvin, tetracycline, carbamazepine, phenytoin, and nonsteroidal anti-inflammatory drugs. In contrast to other drug eruptions, in which the latent period between introduction of the drug and the reaction is within 1 month, the latent period with lichenoid drug eruptions is typically several months to years after initiation of a medication. Similarly, the time to clearance after discontinuation of the medication is also prolonged and can take several weeks to months. The lichenoid lesions of lichenoid drug eruptions tend to be more eczematous, psoriasiform, or pityriasis rosea-like than the typical papules of lichen planus. Lesions occur much less commonly on oral mucosae than on skin.<sup>226</sup> In addition, they uncommonly show Wickham striae and are often photodistributed, particularly on the extensor forearms. The histologic picture resembles lichen planus, but shows more eosinophils.

The diagnosis of lichen planus depends on the recognition of the typical purple, polygonal, pruritic papules and plaques. When the diagnosis is in doubt, histopathologic examination of a cutaneous lesion can confirm the proper diagnosis. Characteristic changes are destruction of the basal cell layer (liquefactive degeneration), saw-toothing of the rete pegs, and a band-like lymphocytic infiltrate that hugs and invades the lower epidermis. Although cases of lichen planus occasionally clear in a few weeks, two-thirds of affected individuals with acute forms display spontaneous resolution within 8 to 15 months. In most patients, the lesions tend to flatten but are often replaced by an area of intense hyperpigmentation that may persist for months or years (Fig. 4-51). Occasionally, lichen planus itself may persist for years, and 10% to 20% of patients suffer one or more recurrences of their disorder.

The standard therapy for lichen planus in pediatric patients involves administration of class II–IV topical steroids and oral antihistamines.



**Figure 4-51** Lichen planus. Intense residual postinflammatory hyperpigmentation.



**Figure 4-52** Lichen nitidus. Sharply demarcated, pinpoint- to pinhead-sized monomorphic, round, usually flesh-colored lesions. Lesions may be distributed in a linear configuration after trauma to the site (Koebner phenomenon).



**Figure 4-53** Lichen nitidus. Note the even distribution of these pinpoint- to pinhead-sized round lesions on the dorsal aspect of the hand.

Pruritus may require 3 weeks of therapy to subside and the lesions themselves 6 weeks to begin to flatten.<sup>212</sup> Topical tacrolimus has been effective in cases recalcitrant to topical steroids.<sup>227</sup> For more extensive or recalcitrant cases, the addition of a 2- to 6-week course of systemic corticosteroids (1 mg/kg per day) is usually helpful in ameliorating the associated pruritus and hastening clearance.<sup>228</sup> Acitretin has also been effective for lichen planus, especially if hypertrophic.<sup>229</sup> Hypertrophic lichen planus lesions may also respond to application of class I topical steroids under occlusion, flurandrenolide-impregnated tape, or intralesional injections of triamcinolone. When traditional forms of therapy fail, metronidazole,<sup>230</sup> griseofulvin,<sup>231</sup> dapsone,<sup>210</sup> PUVA or UVB light therapy,<sup>210</sup> oral retinoids,<sup>228</sup> cyclosporine,<sup>232</sup> and thalidomide<sup>233</sup> have been shown to be effective in selected cases.

If drug-induced lichen planus is considered, medications should be discontinued whenever possible. Mucous-membrane lesions should be treated if symptomatic, eroded, or ulcerated. Topical anesthetics such as diphenhydramine elixir, viscous lidocaine, topical corticosteroids (such as Kenalog in Orabase), or topical tacrolimus ointment<sup>234</sup> may be beneficial. Since erosive forms of oral lichen planus may have an increased risk of malignant transformation, patients with oral lesions should avoid carcinogenic factors (such as tobacco) and receive periodic follow-up examinations and biopsy of suspicious lesions.<sup>235</sup> Nails may respond to administration of systemic corticosteroids, but local application of potent steroids under occlusion or flurandrenolide-impregnated tape at the nail base can be used if the disorder is largely limited to the nail.<sup>221</sup>

## Lichen Nitidus

Lichen nitidus is a relatively uncommon benign dermatosis that affects individuals of all ages but is most commonly seen in children of preschool and school age. Although the etiology remains unknown, association with lichen planus has been reported,<sup>236</sup> and some authorities consider lichen nitidus to be a variant of lichen planus. Familial cases have rarely been described.<sup>237,238</sup> Lichen nitidus has been seen in association with Down syndrome,<sup>239</sup> Niemann–Pick disease<sup>240</sup> and Russell–Silver syndrome.<sup>241</sup>

The individual papules of lichen nitidus are sharply demarcated, pinpoint to pinhead sized, round or polygonal, and usually flesh-colored (Figs. 4-52 and 4-53). The surface of each lesion is flat, shiny, and slightly elevated, sometimes with a central depression. The eruption is arranged in groups, primarily located on the trunk, genitalia, abdomen, and forearms of affected individuals but may be generalized.<sup>242</sup> Linear lesions in lines of trauma (Koebner reaction) are common. Minute, grayish, flat papules on the buccal mucous membrane and nail changes (thickening, ridging, pitting, onycholysis) have

occasionally been noted.<sup>243</sup> A rare variant is spinous follicular lichen nitidus, which may be localized or generalized and is often associated with perifollicular granulomas.<sup>244</sup> Lichen nitidus occasionally clears spontaneously after a period of several weeks to months but more often lasts much longer (occasionally years) with little or no response to treatment. As with lichen planus, significant postinflammatory pigmentary changes may persist.

Biopsy can confirm the diagnosis and characteristically shows claw-like projections of the rete ridges encircling an inflammatory infiltrate of lymphocytes, histiocytes, and occasionally giant cells, resembling a hand clutching a ball. Topical corticosteroids or calcineurin inhibitors occasionally clear the lesions but more often are not effective. Narrow-band UVB phototherapy has cleared generalized lichen nitidus.<sup>245</sup> The usually asymptomatic nature and tendency for spontaneous healing, however, make intervention less critical.

## Keratosis Lichenoides Chronica

Keratosis lichenoides chronica is a rare, chronic, progressive dermatosis that is much more common in adults than in pediatric patients.<sup>246–248</sup> Lesions may be present from birth or appear during infancy and are sometimes pruritic in children.<sup>249</sup> Familial occurrence (probably autosomal recessive) is more common in pediatric cases than in adults. The characteristic erythematous lichenoid papules and scaling verrucous lesions show a linear or reticulated pattern. The eruption tends to be symmetric, particularly on the limbs and less commonly the abdomen and buttock. Pediatric patients often have facial involvement, with well-defined scaling erythematous papules that may appear purpuric or resemble seborrheic dermatitis. Alopecia of the anterior scalp (receding frontal hairline), eyebrows and eyelashes may be noted. The palms and soles may show keratoderma, and nails may be discolored with thickening and longitudinal ridging. Occasionally, mucosae are affected; painful ulcerations or keratoses of the oropharyngeal or genital mucosae, hoarseness, and keratoconjunctivitis have been described. Biopsy sections resemble those of lichen planus.

Keratosis lichenoides chronica may persist for decades and is unresponsive to topical corticosteroid therapy, although one reported patient improved with the application of topical tacrolimus ointment.<sup>250</sup> Ultraviolet light exposure, PUVA therapy, and oral administration of retinoids, alone or in combination, may at times be beneficial.

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The hereditary disorders of cornification, or the ichthyoses, are characterized by impairment in desquamation with hyperkeratosis and/or scaling.<sup>1,2</sup> The ichthyoses are largely distinguished by their clinical and in some cases, histologic and ultrastructural features. The discovery of the underlying molecular basis of most of the forms of ichthyosis has not only further refined classification,<sup>2</sup> but has also facilitated understanding of the interactions among epidermal proteins and the role of epidermal lipids in normal epidermal function. Desquamation is the end result of proteolytic degradation of corneodesmosomes (the intercellular junctions within the stratum corneum) and is abetted by friction and cell hydration. Desquamation requires normal epidermal differentiation and depends on a gradient of pH, the presence of protease inhibitors, and the generation of hygroscopic molecules within the stratum corneum cells. Abnormalities in desquamation and differentiation usually result from abnormal corneocyte shedding (retention hyperkeratosis) or from increased epidermal cell proliferation (epidermal hyperplasia).

The epidermal barrier consists of stacked corneocytes (cells of the stratum corneum) and surrounding highly hydrophobic lipid layers (lamellae) formed by the secretion of lamellar body contents at the interface of the stratum granulosum and the stratum corneum. Most of the mutations that lead to ichthyosis affect lipid metabolism or epidermal proteins, leading to barrier dysfunction and resulting in increased transepidermal water loss and decreased water-holding capacity.<sup>3,4</sup> Many of the features of ichthyosis are thought to be continuous compensatory attempts to restore the barrier (e.g., upregulated epidermal lipid synthesis, epidermal hyperproliferation, and inflammation). This homeostatic response likely allows survival of affected individuals.

## Nonsyndromic Forms of Ichthyosis

Four major forms of nonsyndromic ichthyosis<sup>5</sup> have been delineated, based largely on clinical and genetic characteristics. These are the most common forms of ichthyosis:

1. Ichthyosis vulgaris, the most common ichthyosis, transmitted as an autosomal semi-dominant trait
2. Recessive X-linked ichthyosis (RXLI), expressed only in males and transmitted as an X-linked recessive trait
3. Keratinopathic ichthyosis, an autosomal dominant trait (most common is epidermolytic ichthyosis [EI])
4. Autosomal recessive congenital ichthyosis (ARCI) (most collodion babies; the lamellar ichthyosis [LI]/congenital ichthyosiform erythroderma [CIE] spectrum).

## ICHTHYOSIS VULGARIS

Ichthyosis vulgaris is by far the most common genetic form of ichthyosis, and the majority of individuals affected by the disorder are undiagnosed (Table 5-1) either because of the minimal clinical manifestations or because the condition is dismissed as dry skin. This disorder, which is not present at birth, may be noted after the first 2 to 3 months of life and often not until later in childhood. Ichthyosis vulgaris generally improves with age, in summer, and in warm moist environments. Scales are most prominent on the extensor surfaces of the extremities and are most severe in cold and dry weather. Scales on the pretibial and lateral aspects of the lower leg are large and plate-like, resembling fish scales (Fig. 5-1, A); the flexural areas are characteristically spared. In other areas, small, white, bran-like scales may

be seen. Scales tend to be darker on dark-skinned individuals. Scaling of the forehead and cheeks, common during childhood, generally diminishes and clears with age, but hyperlinearity and mild to moderate thickening of the palms and soles is characteristic (Fig. 5-1, B). Discrete hyperkeratosis may occur on the elbows, knees, and ankles.

Patients with ichthyosis vulgaris often reveal an atopic background with a tendency toward atopic dermatitis, asthma, and/or allergic rhinitis.<sup>6</sup> The diagnosis of ichthyosis vulgaris should be considered in patients with atopic dermatitis who show large scales, particularly on the extensor aspects of the extremities; examination of the palms and soles shows the hyperlinearity. The presence in a parent of hyperlinear palms and dry skin, especially on the lower extremities, may be helpful in confirming this diagnosis. Keratosis pilaris, which is commonly associated with ichthyosis vulgaris and atopy<sup>7</sup> (see Chapter 3, and Chapter 7, Figs. 7-24 and 7-25), is most predominant on the upper arms, buttocks, and thighs.

A reduced or absent granular layer in skin sections may help to differentiate ichthyosis vulgaris from other forms of ichthyosis. Given that filaggrin is the major protein of the granular layer, it is not surprising that mutations in the gene encoding for profilaggrin, the precursor of filaggrin, are responsible.<sup>8</sup> In fact, *FLG* mutations are observed in 7.7% of Europeans and 3.0% of Asians, although not all manifest with ichthyosis vulgaris, given the dependence on environmental factors of its phenotype.<sup>7-9</sup> *FLG* mutations are uncommon in darker-skinned populations, even with ichthyosis vulgaris.<sup>10</sup> Ichthyosis vulgaris is now known to be a semi-dominant condition, in contrast to the previous assumption of dominant inheritance (i.e., manifestations are seen with a mutation on one allele in 1:12 Europeans but are worse if null mutations are on both alleles (probability, 1:576). The cleaved product of profilaggrin, filaggrin, plays an important role in linking a protein (involucrin) and lipids (ceramides) in the corneocyte envelope (see Chapter 3). In addition, filaggrin breaks down to amino acid metabolites that increase skin hydration (natural moisturizing factor). Without filaggrin, the epidermis cannot provide normal barrier function; transepidermal water loss is increased, leading to xerosis; and the ingress of foreign substances (such as allergens and pathogens) occurs more readily, thereby increasing the risk of exposure to triggers of atopy. In fact, mutations in profilaggrin are strongly linked to the risk of atopic dermatitis and secondary asthma, regardless of the ethnicity or specific profilaggrin mutation. The risk is highest in individuals with two mutated alleles. Overall up to 30% of patients of a Northern European background with atopic dermatitis and more than 20% of Japanese with atopic dermatitis<sup>11,12</sup> have *FLG* mutations. Signs of atopic dermatitis may be seen before other clinical signs of ichthyosis vulgaris, and most individuals with ichthyosis vulgaris never show evidence of atopic dermatitis. However, reduction of filaggrin expression, including in absence of *FLG* mutation, is a feature of autosomal dominance, because the inflammation itself and exogenous stressors suppress the expression of *FLG* and other important differentiation proteins, even in nonlesional skin.<sup>13,14</sup> Emollients may improve dry skin but do not normalize the epidermal gene expression profile of filaggrin.<sup>15</sup>

Individuals with *FLG* mutations have a generally altered risk of developing common diseases, even beyond atopic disorders. Mechanistic studies have shown increased penetration of allergens and chemicals in filaggrin-deficient skin, and epidemiological studies have found higher levels of hand eczema, irritant contact dermatitis, nickel sensitization, and serum vitamin-D levels.

Excessive exposure to factors that decrease skin barrier functions and increase the risk of atopic dermatitis should be avoided. Individuals with ichthyosis vulgaris should be protected against neonatal

**Table 5-1** Comparison of the Most Common Types of Ichthyosis

	<b>Ichthyosis Vulgaris</b>	<b>X-Linked Recessive Ichthyosis</b>	<b>Keratinopathic Ichthyosis,* Epidermolytic Ichthyosis</b>	<b>ARCI: Classic Lamellar Ichthyosis</b>	<b>ARCI: Classic Congenital Ichthyosiform Erythroderma</b>
Prevalence	1:100	1:4000 males	1:300,000	1:300,000	1:300,000
Inheritance	Autosomal semi-dominant	X-linked recessive	Usually autosomal dominant	Usually autosomal recessive	Autosomal recessive
Onset	2 months and beyond	17% at birth; 83% by 1 year	Birth, with superficial blistering	Birth, as collodion baby	Birth, as collodion baby
Character of scales	Fine, white to larger scales, esp. on legs	Large, brown	Verrucous scale, superficial blisters	Large, plate-like scales	Fine white scaling overlying erythema
Localization	Can be generalized; relative sparing of flexures; hyperlinear palms	Accentuation at neck and behind ears; relative sparing of flexures	Generalized; especially at flexures and overlying joints	Generalized; ectropion, occasional alopecia, nail dystrophy	Generalized; ectropion; occasional alopecia
Distinct histologic features	Often shows decreased granular layer	None	Epidermolytic hyperkeratosis	Massive orthokeratosis; moderate acanthosis	More acanthosis
Molecular basis	Mutations in profilaggrin ( <i>FLG</i> ); worse if both alleles	Deletions in <i>ARSC1</i> (arylsulfatase C)	Mutations in <i>KRT1</i> and <i>KRT10</i> ; superficial form with mutations in <i>KRT2</i>	Most commonly mutations in <i>TGM1</i> ; rarely other types (see CIE)	Mutations in <i>TGM1</i> ; <i>ALOXE3</i> ; <i>ALOX12B</i> ; <i>NIPAL4</i> ; <i>ABCA12</i> ; <i>CYP4F22</i> ; <i>PNPLA1</i> ; <i>LIPN</i> ; <i>CerS3</i>
Comments	Increased risk of atopic dermatitis and keratosis pilaris	Accumulation of cholesterol sulfate; FISH analysis to detect deletion; genital abnormalities rare; asymptomatic corneal opacities; contiguous gene deletion: with retardation, anosmia (Kallman syndrome) and/or chondrodysplasia punctata	Superficial form shows more superficial blistering and much less thickening; secondary <i>Staphylococcus aureus</i> infection	Transglutaminase activity can be measured in skin samples	May be associated with neurologic abnormalities

ARCI, Autosomal recessive congenital ichthyosis; CIE, congenital ichthyosiform erythroderma; FISH, fluorescent *in situ* hybridization analysis.

\*Previously known as epidermolytic hyperkeratosis, bullous congenital ichthyosiform erythroderma, and ichthyosis bullosa of Siemens (superficial form).

exposure to cats to prevent atopic dermatitis and should abstain from smoking to prevent asthma.<sup>9</sup>

Although rare in children, “acquired” ichthyotic scaling has been described in patients with nutritional disorders such as hypovitaminosis or hypervitaminosis A, hypothyroidism, sarcoidosis, dermatomyositis, leprosy, tuberculosis, human immunodeficiency virus (HIV) infection, and neoplastic disorders, particularly lymphomas. It should be noted that these forms were described before the availability of testing for profilaggrin mutations; given the many undiagnosed patients, it is possible that the underlying condition served as a trigger for increased cutaneous inflammation or dryness that led to increased expressivity of the gene mutation. Pityriasis rotunda, a rare variant of acquired ichthyosis, is characterized by asymptomatic, circular or oval, brown scaly patches on the trunk or extremities. Seen primarily in individuals of Japanese, African, and West Indian origin, its occurrence in Caucasians is extremely rare. The condition may at times be associated with an underlying disorder, may follow pregnancy, or may be familial. In contrast to ichthyosis vulgaris, pityriasis rotunda is chronic, is resistant to treatment, and tends to improve only when the underlying disorder is treated.

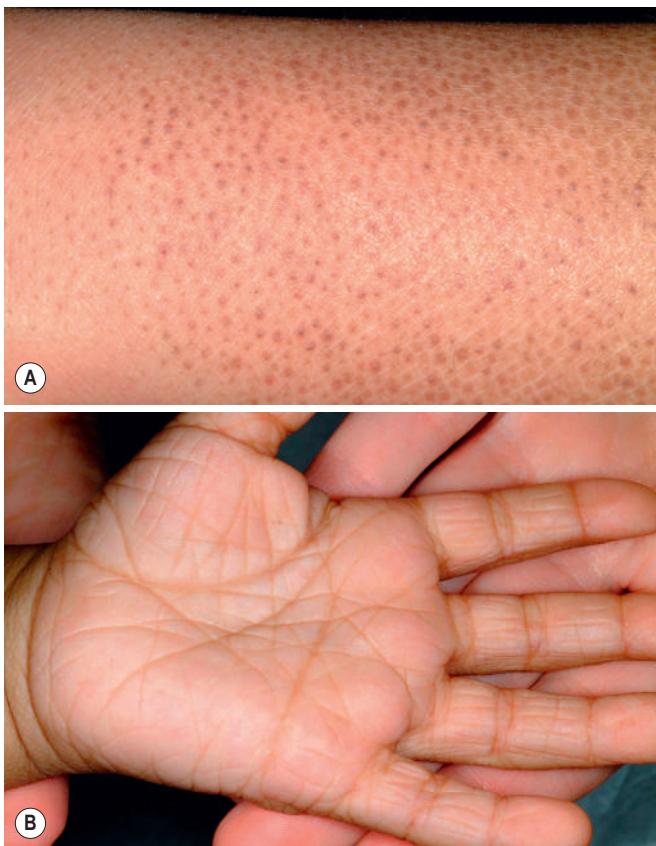
### RECESSIVE X-LINKED ICHTHYOSIS

Recessive X-linked ichthyosis (RXLI) occurs in 1:2500 to 5000 males and results from mutation (and usually a complete deletion) in the *ARSC1* gene that encodes steroid sulfatase (STS), also known as *arylsulfatase C* (see Table 5-1). The disorder has rarely been described in

females who have Turner syndrome or carry the mutation on both alleles. Female carriers do not tend to show ichthyosis, because the affected gene is located at the distal tip of the X chromosome, a location that escapes X-inactivation. Thus rather than having random inactivation of one of the X chromosomes as dictated by the Lyon hypothesis, both of the alleles are expressed in every cell, providing sufficient enzyme. STS normally is concentrated in lamellar bodies and secreted into the spaces between stratum corneum cells. It degrades cholesterol sulfate, generating cholesterol for the epidermal barrier. Cholesterol sulfate itself is an epidermal protease inhibitor, so STS deficiency prevents normal degradation of the stratum corneum desmosomes and leads to corneocyte retention.<sup>16,17</sup>

Low placental production of estrogens and elevated sulfated steroid levels have been described in the urine of mothers of boys with RXLI, associated with a difficult or prolonged labor and failure to have cervical dilation. Deletion of both *ARSC1* and a contiguous gene (up to 10% of patients) results features of ichthyosis and Kallmann syndrome (associated with mental retardation, hypogonadism, and anosmia) and/or X-linked recessive chondrodysplasia punctata (bone dysplasia with stippled epiphyses).<sup>18</sup>

RXLI usually manifests within the first 3 months of life. Approximately 17% of affected individuals show scaling at birth, often in the form of a mild collodion-like membrane. Most develop scaling during the first 6 months of life (Fig. 5-2). The severity of the scaling can range from mild to severe. This form of ichthyosis generally involves the entire body with accentuation on the scalp, neck, abdomen, back, front of the legs, and feet, but sparing the palms, soles, central face,



**Figure 5-1** Ichthyosis vulgaris. **(A)** Scales are most prominent on the extensor surfaces of the extremities, especially the lower extremities. **(B)** The palms and soles are thickened with increased palmar markings.



**Figure 5-2** Recessive X-linked ichthyosis. Scaling may be subtle, particularly in younger infants. This 6-month-old boy was diagnosed *in utero* by increased maternal estradiol levels and then FISH analysis of chorionic villus samples. Note the fine scaling on the trunk (**A**) and the large scales on the scalp (**B**).

and flexural areas (Fig. 5-3, A). Scales may be small to large and tend to be brown in coloration and darker in darker-skinned patients. The sides of the neck often appear dark and unwashed (Fig. 5-3, B). Patients may shed or molt their scales episodically, particularly in the spring and fall.

Boys with X-linked ichthyosis rarely have hypogonadism and/or cryptorchidism; testicular cancer has been described in one patient.<sup>19</sup> Deep corneal opacities may be found in approximately 50% of affected adult males and less often in female carriers of this disorder. The opacities, easily detectable by slit-lamp examination, are discrete and diffusely located near the Descemet membrane or deep in the corneal stroma. Although they are a marker for the disorder in older patients, these opacities do not affect vision.

X-linked ichthyosis is often suspected prenatally, because fetal STS deficiency leads to low maternal serum and urinary estriol levels.<sup>20</sup> Fluorescent *in situ* hybridization analysis (FISH) for the STS gene shows deletion of the gene found in 90% of patients. RXLI can also be confirmed by reduced arylsulfatase C activity in leukocytes. Elevated blood levels of cholesterol sulfate and increased mobility of  $\beta$ -lipoproteins have also been seen.<sup>21</sup>

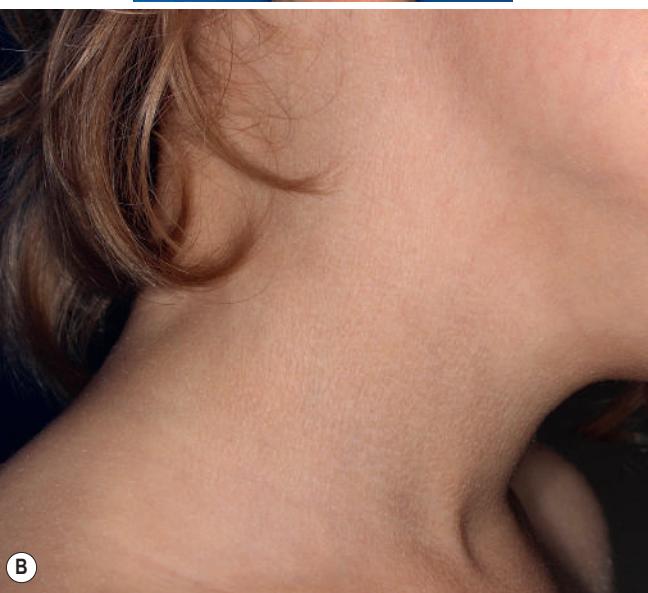
The features of RXLI may be seen in patients with autosomal recessive multiple sulfatase deficiency, a syndromic form of ichthyosis characterized by features of mucopolysaccharidoses, metachromatic leukodystrophy, X-linked recessive chondrodysplasia punctata, and RXLI. The disorder results from mutations in sulfatase-modifying factor 1 (*SUMF1*), which encodes  $\alpha$ -formylglycine generating enzyme required for posttranslational modification of sulfatases.<sup>22,23</sup> Progressive neurologic deterioration, a feature of the metachromatic leukodystrophy, usually leads to death during infancy.

## KERATINOPATHIC ICHTHYOSSES

The new classification of the ichthyoses has renamed the group of epidermolytic forms of ichthyosis associated with keratin gene mutations as *keratinopathic*. The major subgroups are epidermolytic ichthyosis (EI) (formerly called *bullous CIE, Brocq type*)<sup>24</sup> and superficial EI (formerly called *ichthyosis bullosa of Siemens*). The designation *epidermolytic hyperkeratosis* is a histologic description that is not specific to this group of disorders, although it traditionally referred to EI.

Mutations are usually point mutations that lead to an abnormal but full-length keratin that incorporates into the keratin filament. The resultant keratin network functions poorly, leading to skin cell collapse and clinical blistering, especially in response to trauma. The thickening of skin is thought to be compensatory to protect against blistering but has also been linked to abnormal lamellar-body secretion.<sup>25</sup> Virtually all forms are inherited in an autosomal dominant manner, although EI may rarely be autosomal recessive.<sup>26,27</sup> EI results from mutations in *KRT1* or its partner in intermediate filament formation, *KRT10*; both are expressed throughout the suprabasal layers of epidermis. Superficial EI is caused by mutations in *KRT2*, which is only expressed in more superficial epidermis and also partners with keratin 10.<sup>28-30</sup>

EI affects approximately 1 in 300,000 individuals, and 50% of patients have new mutations. The skin is red and may be tender at birth. Superficial bullae generally appear within the first week of life (often within a few hours after delivery; Fig. 5-4) and may be confused with those of epidermolysis bullosa (see Chapter 13) or with staphylococcal scalded skin syndrome (see Chapter 14). Skin thickening often appears from the third month on, but subtle thickening may be



**Figure 5-3** Recessive X-linked ichthyosis. **(A)** Scales may be large and hyperpigmented, especially in darker-skinned individuals. The popliteal and antecubital areas are typically spared. **(B)** The neck is typically affected with darker scaling that can appear as a dirty neck.

detectable during the first month of life, especially over the elbows and knees, and may be useful in suggesting the diagnosis. The blisters occur in crops and vary from 0.5 cm to several centimeters in diameter. They tend to heal quickly, consistent with their superficial location. When ruptured, they discharge clear fluid and leave raw denuded areas. Secondary bacterial infection, especially with *Staphylococcus aureus*, is commonly associated with this disorder.

Verruciform grayish-brown scales eventually cover most of the skin surface; the flexural creases and intertriginous areas show particularly marked involvement (Fig. 5-5).<sup>31</sup> Palms and soles have varying degrees of thickening and scaling (Fig. 5-6), but more



**Figure 5-4** Epidermolytic ichthyosis. In the neonate superficial blisters predominate and may be mistaken for epidermolysis bullosa.

marked involvement often occurs in individuals with mutations in *KRT1*, because keratin 9 expression in the palms and soles can compensate for abnormal keratin 10 expression, but expression of *KRT1* (which is the partner for both keratins 9 and 10) remains critical.<sup>31</sup> Facial involvement may occur, but ectropion does not; although scalp involvement may result in nit-like encasement of hair shafts, the hair, eyes, teeth, and nails are normal. A disagreeable body odor is commonly associated with severe forms of this disorder owing to the thick, macerated scale and overgrowth of bacteria and, less often, candida. Skin-biopsy specimens show marked hyperkeratosis with lysis of the epidermal cells above the basal cell layer (epidermolytic hyperkeratosis) leading to the bullae.<sup>32</sup> Keratolytic agents are often poorly tolerated in keratinopathic forms of ichthyosis and can increase skin fragility.

Mutations in *KRT1* and *KRT10* can lead to other ichthyotic phenotypes as well. Mutations in either can lead to an annular variant (annular EI).<sup>33</sup> Annular erythematous polycyclic scaling plaques on the trunk and extremities slowly enlarge, resolve, and later recur.

Ichthyosis Curth–Macklin (formerly called *ichthyosis hystrix*) has its onset of manifestations during early childhood as progressively worsening diffuse or striate palmoplantar keratoderma (PPK) that can be associated with deep fissuring, flexural contracture, and digital constriction. Affected individuals develop characteristic “porcupine quill-like” verrucous yellow-brown scaling especially on the hands and feet and overlying the large joints. Binuclear cells and pathognomonic concentric perinuclear “shells” of aberrant keratin are characteristic ultrastructural findings.<sup>34</sup> Keratin 1 mutations have been described in some<sup>35,36</sup> but not all affected patients.

The epidermolytic hyperkeratotic form of epidermal nevus shows a histologic appearance identical to that of epidermolytic hyperkeratosis (see Chapter 9). This form of nevus represents a mosaic condition in which the affected skin but not the normal intervening skin carries a mutation in *KRT1* or *KRT10*.<sup>37</sup> Individuals with more extensive forms of the epidermolytic hyperkeratotic form of epidermal nevus can have offspring with generalized epidermolytic hyperkeratosis, reflecting germline mutations. Prenatal diagnosis can be performed in at-risk families.<sup>38</sup>

Superficial EI shows milder thickening and more superficial blistering. Palms and soles are minimally thickened if at all. Although large, tense bullae can occur intermittently (Fig. 5-7, A), in general the appearance of blisters has been likened to molting (Mauserung phenomenon) (Fig. 5-7, B) because of the superficial location of the cleavage plane. Accordingly, less hyperkeratosis is seen in sections of skin biopsies, and the lysed areas of epidermis only begin halfway up the stratum spinosum. Affected individuals may be misdiagnosed as mild EI clinically, but the limited localization of the epidermolysis histologically and the finding of mutations in *KRT2* by molecular genetic testing can distinguish the disorders.<sup>39,40</sup>

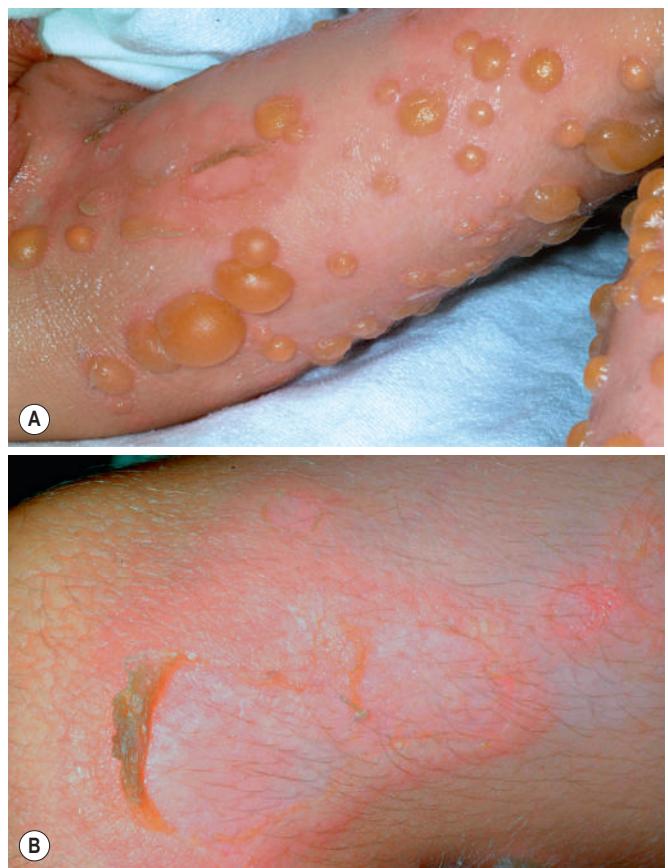


**Figure 5-5** Epidermolytic ichthyosis. (A) Thick verrucous scale on the legs of a 6-year-old boy. Note the intensification of scaling over the knees and ankles and the areas of blistering on the legs. (B) The scaling can take on a corrugated appearance.

Ichthyosis *en confetti*, also called *congenital reticular ichthyosiform erythroderma* or *ichthyosis variegata*, is a rare autosomal recessive keratinopathy that resembles nonbullous CIE but progressively shows reversion to normal-appearing skin in a “confetti” pattern of macules.<sup>41,42</sup> Mutations occur in the sixth or seventh exon of *KRT1* or *KRT10*, which seem to be predisposed to postzygotic translocations that allow protein expression of the mutated allele and correct the phenotype. The keratin is produced but stays intracellular and is not able to function normally. In some patients this reversion starts during the first years of life and is progressive, especially with keratin 1 mutations,<sup>41</sup> whereas in others the onset is later during childhood or even young adulthood, especially with keratin 10 mutation.<sup>43</sup> Other major



**Figure 5-6** Epidermolytic ichthyosis. The marked hyperkeratotic sole in this child virtually assures that the underlying gene defect involves *KRT1*.



**Figure 5-7** Superficial epidermolytic ichthyosis. (A) Occasionally, affected individuals may show tense bullae that resemble bullous pemphigoid (see Chapter 13). The bullae on this patient arose when he developed a viral exanthema. (B) Note the milder hyperkeratosis and the “molting” appearance of desquamation of superficial scale.

features include malformation of ears, hypoplasia of mammae, and dorsal acral hypertrichosis.<sup>44</sup>

### COLLODION BABY

*Collodion baby* is a descriptive term for an infant who is born with membrane-like covering resembling collodion (Fig. 5-8).<sup>45,46</sup> The



**Figure 5-8** Collodion baby. Note the shiny thickened skin, mild ectropion, mild eclabium, and ear deformity. In this 5-day-old baby, the “membrane” is starting to crack and desquamate.

collodion baby is not a disease entity but is a phenotype common to several forms of ichthyosis. At least 65% of collodion babies have ARCI (see [Autosomal Recessive Congenital Ichthyosis](#) section), a group of genetically distinct forms of ichthyosis with overlapping clinical features<sup>47</sup>; some infants in this group (5% to 6%) shed their collodion membranes and show apparently normal skin (self-healing collodion baby [SHCB]).<sup>48,49</sup> Less often, collodion babies shed their membranes and show features of syndromic forms of ichthyosis (Conradi-Hünermann–Happle syndrome, trichothiodystrophy [see Chapter 7], or RXLI). Using a new severity score for newborns with a collodion membrane, classic nonsyndromic ichthyoses were found to have higher severity scores.<sup>47</sup> Recently, a collodion baby was born to a mother who received infliximab before and throughout the course of the pregnancy; although the collodion membrane shed and the skin appeared normal 1 year after birth, genotype analysis was not reported to distinguish a drug effect versus a gene mutation to cause the ichthyosis.<sup>50</sup>

Collodion babies are often born prematurely. At birth they are completely covered by a cellophane or oiled parchment-like “membrane” that, owing to its tautness, may distort the facial features and extremities. Thus peripheral edema with digital constriction, flattened ears, and bilateral eversion of the eyelids, lips, and at times the vulva often cause affected infants to resemble one another during the first few days of life. Among the problems facing these infants are an inability to suck properly, respiratory difficulty because of restriction of chest expansion by the thick membrane, cutaneous and systemic infection, and aspiration pneumonia. Despite the thickening of the stratum corneum, this membrane is a poor barrier, leading to excessive transcutaneous fluid and electrolyte loss,<sup>51</sup> hypernatremic dehydration, increased metabolic requirements, and temperature instability.

Supportive care is of primary importance in the management of collodion babies.<sup>45,52,53</sup> They are best managed in a humidified incubator with special attention given to the prevention of temperature instability, sepsis, and fluid and electrolyte imbalance. Systemic antibiotic therapy should be initiated if infection is detected but not prophylactically. Desquamation is encouraged by the application of emollients rather than manual debridement; given the poor cutaneous barrier and potential toxicity, use of keratolytic agents should be avoided during the first several months of life.

## AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSIS

Autosomal recessive congenital ichthyosis (ARCI) encompasses a wide range of clinical phenotypes that range from classic harlequin ichthyosis (HI) and nonbulloous CIE to classic LI.<sup>54</sup> The same individual may show a range of overlapping clinical features; for example, retinoid treatment may decrease the lamellar scaling but increase erythroderma.<sup>55</sup> Failure to thrive is a feature of ARCI, especially if severe, and short stature may ensue.<sup>56</sup> Overall, ARCI occurs in approximately 1 in 100,000 to 300,000 live births. The diagnosis is based on clinical findings; biopsy is not helpful unless needed to exclude alternative



**Figure 5-9** Lamellar ichthyosis phenotype of autosomal recessive congenital ichthyosis (ARCI). Large plate-like scaling on the forehead and cheeks. This patient shows moderate ectropion.

diagnoses. The features of the ARCI group of disorders usually persist throughout the affected individual’s lifetime. Many affected individuals complain of associated pruritus. Owing to the obstruction of eccrine glands by the overlying hyperkeratosis, severely affected patients tend to experience hyperpyrexia, heat intolerance, difficulty with perspiration, and heat exhaustion during periods of warm or hot, humid weather and vigorous physical exercise. Squamous cell carcinomas have been reported at a younger age.<sup>57</sup>

Mutations in nine known genes have been shown to result in the ARCI phenotype, and most of these mutated genes have been related to both LI and CIE phenotypes (see [Table 5-1](#)). A few cases of autosomal dominant LI have been described.<sup>58</sup> The discovery of the underlying genetic basis in families with ARCI has facilitated the prenatal diagnosis based on genotyping rather than the riskier diagnosis by fetal skin biopsy.<sup>59</sup> Up to 55% of individuals with ARCI have mutations in the gene encoding transglutaminase 1 (*TGM1*), particularly patients with the LI phenotype.<sup>60</sup> *TGM1* crosslinks several proteins to form the cornified envelope surrounding corneocytes. In patients missing transglutaminase, transglutaminase activity is undetectable in frozen skin specimens.<sup>61</sup> HI has been shown to result from nonsense mutations in the gene encoding the ABCA12 transporter.<sup>62,63</sup> Deficiency of ABCA12 leads to perturbation of lipid transport, which then leads to a paucity of lamellar bodies, the upper epidermal lamellar structures that provide intracellular lipids to the stratum corneum,<sup>63</sup> and to premature terminal differentiation of keratinocytes. ABCA12 has also been shown to be important for protease function.<sup>64,65</sup> Mutations in *ABCA12* that lead to the LI or more commonly CIE phenotype tend to be missense mutations,<sup>66</sup> so that some gene product is present for function, leading to the milder phenotype. Other genes found to be mutated in ARCI encoding include lipoxygenase-3 (*ALOX3*), 12(R)-lipoxygenase (*ALOX12B*),<sup>67,68</sup> ichthyin (*NIPAL4*)<sup>69–71</sup> *CYP4F22*, lipase N (*LIPN*),<sup>72</sup> *PNPLA1*,<sup>73</sup> and ceramide synthase 3 (*CERS3*).<sup>74,75</sup> Some of these encode proteins of the hepxolin pathway (*ALOX12B*, *ALOX3*, and *NIPAL4*). In addition to their disruption of stratum corneum lipid synthesis, these enzymes (or the ichthyin receptor) within the lipoxygenase pathway may also disrupt the processing of profilaggrin.<sup>76</sup>

The clinical features of the classic LI phenotype may range from very mild to severe. Individuals who show the greatest severity of LI have large lamellar plate-like scales with relatively mild underlying erythroderma, ectropion (eversion of an edge or margin of the eyelid resulting in exposure of the palpebral conjunctiva) (Fig. 5-9), and mild eclabium (eversion of the lips) (see [Table 5-1](#)). Lamellar scales are large, quadrangular, yellow to brown-black, often thick, and centrally adherent with raised edges resembling armor plates (hence the term LI) (Fig. 5-10). Scales are most prominent over the face, trunk, and extremities, with a predilection for the flexor areas. Cheeks are often red, taut, and shiny; more scales appear on the forehead than on the lower portion of the face. The palms and soles are almost always affected in LI; severity varies from increased palmar markings to a thick keratoderma with fissuring. The scalp is often scaly with scarring



**Figure 5-10** Lamellar ichthyosis phenotype of autosomal recessive congenital ichthyosis (ARCI). Large plate-like scaling on the legs.



**Figure 5-12** Congenital ichthyosiform erythroderma phenotype of autosomal recessive congenital ichthyosis (ARCI). Marked erythroderma underlying fine white scaling.



**Figure 5-11** Bathing suit distribution, lamellar ichthyosis phenotype of autosomal recessive congenital ichthyosis (ARCI). This distribution of the ichthyosis, largely involving the trunk and intertriginous areas with sparing of the face and limbs, signals a temperature-sensitive mutation in *TGM1*, encoding transglutaminase 1. This baby was born with a full collodion membrane.



**Figure 5-13** Harlequin ichthyosis. Profoundly thickened, armor-like skin with fissuring, leading to the polygonal, triangular, or diamond-shaped plaques that simulate the costume of a harlequin. Note the severe ectropion, ecbium, and digital infarction. (Courtesy of Sylvia Suarez, MD.)

partial hair loss (especially with *TGM1* mutations). Involvement of the nails is variable. They may be stippled, pitted, ridged, or thickened, often with marked subungual hyperkeratosis.

Variant forms of LI from mutations in *TGM1* manifest in a more limited distribution of lesional skin. Patients with bathing suit ichthyosis (BSI) are born with a full collodion membrane and transition to LI, but within the first months of life the scaling on the extremities clears (Fig. 5-11). The residual LI on warmer skin areas (axillae, trunk, scalp, neck) has been linked to temperature-sensitive mutations in *TGM1*.<sup>77</sup> Mutations in *TGM1* that encode proteins sensitive to hydrostatic pressure can result in the SHCB. Affected neonates show either a generalized or acral<sup>78</sup> collodion membrane at birth that clears entirely as the baby transitions to the dry environment postnatally.<sup>48</sup> The *TGM1* mutations in both BSI and SHCB phenotypes are missense mutations that are predominantly in the catalytic core domains.<sup>79</sup> *ALOX12B* and *ALOX3B* mutations have also been described with SHCB.<sup>49,80</sup>

Classic nonbulloous CIE is characterized by a much more prominent erythrodermic component that may first become apparent as the colloidion membrane is shed; some patients show CIE at birth without a classic collodion membrane. Affected individuals show fine white scales on the face, scalp, and trunk, although scaling may be more plate-like scales on the extensor surfaces of the legs (Fig. 5-12). The degree of ectropion is variable but often milder than with LI, and there is less PPK. Cicatricial alopecia is possible, and nails may show

thickening and ridging. Some patients with CIE show intrauterine growth retardation and/or failure to thrive, although nutritional deficiency and gastrointestinal abnormalities are uncommon.<sup>81</sup> Patients with CIE may have associated neurologic abnormalities.

HI is the most severe form of ARCI. At birth, the disorder manifests as profoundly thickened, armor-like skin that is fissured into polygonal, triangular, or diamond-shaped plaques that simulate the traditional costume of a harlequin (Fig. 5-13).<sup>82</sup> Rigidity of the skin results in marked ectropion; everted O-shaped lips with a gaping fishmouth deformity; and a distorted, flattened, and undeveloped appearance to the nose and ears. The skin rigidity can restrict respiratory movements, sucking, and swallowing. The hands and feet are ischemic, hard, and waxy, often with poorly developed digits and an associated rigid and claw-like appearance. Flexion deformity of the limb joints is common, and the nails may be hypoplastic or absent. Restrictive dermopathy (see Chapter 6) shows congenital contractures, tight skin, ectropion, and intrauterine growth retardation and can thus sometimes be confused with HI, but it shows no hyperkeratosis or scaling.

Death is usually associated with prematurity, pulmonary infection (in part associated with hypoventilation caused by thoracic rigidity), poor feeding, excessive fluid loss, poor temperature regulation, or sepsis as a result of cutaneous infection. The severity may be variable, however, and prolonged survival has been achieved by intensive supportive measures, emollients and, in some cases, oral administration of systemic retinoids.<sup>83-86</sup> Initiation of aggressive intervention for



**Figure 5-14** Harlequin ichthyosis. This boy survived the neonatal period without retinoid intervention and is thriving with severe erythroderma and residual deformation (now 5 years of age). Note the severe erythroderma with scaling, persistent eclabium, and residual deformities of the fingers after the harlequin scaling is shed.



**Figure 5-15** Erythrokeratoderma variabilis. This girl shows well-demarcated plaques that sometimes are migratory.

babies with HI is controversial. Even with administration of systemic retinoids or spontaneous clearance of the armor-like scaling, the optimal outcome resembles that of severe CIE (Fig. 5-14). Physicians often reserve initiation for babies who survive the first few weeks, because most infants are stillborn or die during the neonatal period (usually during the first few hours or days of life); however, it is unclear whether use of systemic retinoids leads to a better outcome than excellent supportive care, especially during the neonatal period therapy.<sup>87</sup> Pulmonary issues can be ongoing in infants and young children. Prenatal diagnosis of HI has been suspected based on ultrasound-based discovery of distal arthrogryposis<sup>88</sup> and can be performed definitively by molecular analysis.<sup>89</sup>

## OTHER FORMS OF NONSYNDROMIC ICHTHYOSIS

### Loricrin Keratoderma

Loricrin keratoderma (also called *Camisa disease*, a variant of Vohwinkel keratoderma) is an autosomal dominant disorder with ichthyosis and PPK. <sup>90,91</sup> Mutations occur in the gene encoding loricrin, a protein that is linked by transglutaminase-1 to involucrin and other proteins of the corneocyte envelope, thereby participating in barrier function and normal epidermal maturation.<sup>92,93</sup> Affected individuals may be born with a collodion membrane and later show a mild, nonerythrodermic generalized ichthyosis with flexural accentuation. The PPK is initially noted during the first weeks of age, is often transgrediens, and may show a honeycomb pattern that resembles that of Vohwinkel syndrome (connexin defect). Pseudoainhum (constricting bands of the digits) may occur but usually not until adolescence or even adulthood; the starfish-shaped keratoses of Vohwinkel syndrome are not seen with loricrin keratoderma. Alopecia is occasionally seen but not other ectodermal abnormalities or hearing impairment. Parakeratosis on routine skin biopsy is a characteristic histologic feature, but termination mutations in the C-terminus have been linked to milder PPK without pseudoainhum and without parakeratosis on affected skin biopsy.<sup>94</sup>

### Erythrokeratoderma Variabilis and Progressive Symmetric Erythrokeratoderma

Erythrokeratoderma variabilis (EKV) is a dominantly inherited ichthyosis characterized by two distinct types of lesions: (1) sharply marginated, pruritic, or burning areas of erythema with finer scaling that are often figurate in configuration and undergo changes in size, shape, and distribution during a period of days to weeks; and (2) hyperkeratotic plaques with thick, yellow-brown scales that usually overlie erythema (Fig. 5-15). Lesions are most often symmetrically distributed on the limbs, trunk, and buttock with relative sparing of the face, scalp, and flexures. In contrast to the chronic but remitting appearance of these plaques and figurate lesions, plaques on the knees, elbows,

Achilles tendons, and soles of the feet are often persistent. PPK has been described in 50% of affected families.

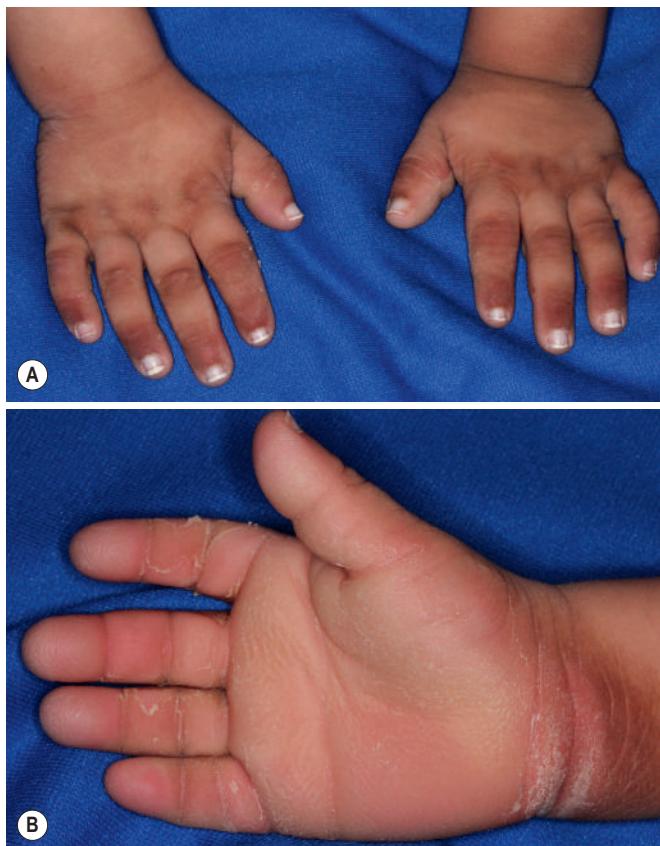
Although lesions are usually noted at birth or shortly thereafter during the first year of life, in a few individuals the onset has been noted during late childhood or early adulthood. The disorder may partially regress at puberty and tends to improve in summer. Patients usually tend to respond well to systemically administered retinoids.<sup>95</sup>

EKV has been known to result from mutations in genes that both map to chromosome 1p35.1 and encode interacting connexins: *GJB3* encoding connexin 31<sup>96</sup> and *GJB4* gene encoding connexin 30.3.<sup>97,98</sup> Most recently, EKV with hyperpigmented, well-delineated keratotic plaques was shown to result from mutations in *GJA1* encoding connexin 43 (Fig. 5-16).<sup>99</sup> Individuals with symmetrical EKV lesions during early infancy that clear by 25 years of age may develop progressive spinocerebellar ataxia in adulthood in association with heterozygous mutations in *ELOVL4*.<sup>100</sup> *ELOVL4* encodes an elongase needed for synthesis of very long-chain fatty acids in skin, eyes, and the neurologic system. When *ELOVL4* mutations affect both alleles, ichthyosis can occur in association with spastic diplegia and severe neurodevelopmental delay.<sup>101</sup> Homozygous *ELOVL4* mutations must be distinguished from Sjögren–Larsson syndrome (see *Sjögren–Larsson Syndrome* section).

Progressive symmetric erythrokeratoderma (PSEK; Darier–Gottron syndrome) is a dominant disorder that tends to have its onset during infancy, tends to stabilize after 1 or 2 years, and may partially regress at puberty. PSEK has been distinguished from EKV by the absence of the migrating red patches, the typical sparing of the chest and abdomen with scaling plaques limited to the extremities, buttocks, and face, and a higher incidence of PPK (~50% of cases); however, the conditions overlap phenotypically, and patients have been described with features of both,<sup>102</sup> suggesting that PSEK and EKV are a single disorder with variable manifestations. In fact, a *G12D* missense mutation in connexin 30.3 has been shown to cause both PSEK and EKV.<sup>103</sup>

### Peeling Skin Syndrome

Peeling skin syndrome (PSS), or keratolysis exfoliativa congenita, is an unusual autosomal recessive disease characterized by life-long, spontaneous superficial peeling of the skin that may be persistent or periodic.<sup>104–106</sup> The Nikolsky sign tends to be positive. The desquamation has been associated with increased stratum corneum and serum kallikrein levels. Two generalized types have been described. Desquamation is generalized, other than the palms and soles, which may be mildly thickened. Seasonal variation with worsening during summer months has been described.



**Figure 5-16** Erythrokeratoderma variabilis (EKV). A newly discovered underlying cause of EKV is mutations in *GJA1*, encoding connexin 43. One distinguishing feature of these patients is the marked hyperpigmentation of skin that progressively appears starting in infancy or childhood. (A) Note the hyperpigmentation and skin thickening on the dorsal aspects of the hands, the white nails, and (B) the keratoderma of the palm with typical “honeycombing” as is often seen with connexin gene defects.

In type A, the onset may be at birth but commonly begins in early childhood (by 6 years of age). These patients are asymptomatic. Skin biopsy shows a thickened stratum corneum with an intracorneal or subcorneal separation. Type A is caused by mutations in *CHST8*, which encodes a Golgi transmembrane N-acetylgalactosamine-4-O-sulfotransferase (GalNAc4-ST1).<sup>107</sup> In type B, the condition always begins at birth. Patients show erythematous migratory peeling patches and complain of associated pruritis or burning. Patients with the type B form may show short stature and easily removable anagen hairs.<sup>104</sup> Biopsy specimens reveal psoriasiform thickening of the epidermis and a subcorneal or intracorneal split. Type B results from loss of corneodesmin,<sup>108</sup> found in the stratum corneum and hair follicle.

An acral form of hereditary PSS is characterized by life-long painless peeling of predominantly the dorsal aspect of the hands and feet in superficial sheets<sup>109</sup> and exacerbation during summer months with increased sweating.<sup>107,110</sup> A facial variant has been described.<sup>111</sup> This acral form is caused by mutations in *TGM5* encoding transglutaminase-5,<sup>112,113</sup> which crosslinks epidermal proteins. Acral PSS in association with plantar keratoderma and peeling can be associated with mutations in encoding cystatin A (*CSTA*), a protease of the cornified cell envelope.<sup>114</sup> Cystatin A mutations can also be associated with generalized mild scaling and exfoliation.<sup>115</sup> Acral PSS may be misdiagnosed as localized epidermolysis bullosa simplex.

#### Keratosis Linearis-Ichthyosis Congenital-Keratoderma

Keratosis linearis-ichthyosis congenital-keratoderma (KLICK) is a rare, autosomal recessive disorder characterized by distinctive striate hyperkeratosis in the flexures (perpendicular to the fold) and PPK.<sup>116,117</sup>

It results from a single-nucleotide deletion in the 5' untranslated regions (UTRs) of the proteasome maturation protein (*POMP*) gene, which reduces levels of *POMP* and leads to proteasome insufficiency, increased endoplasmic reticulum (ER) stress, and perturbed processing of profilaggrin in differentiating keratinocytes.<sup>118,119</sup>

#### Syndromic Forms of Ichthyosis

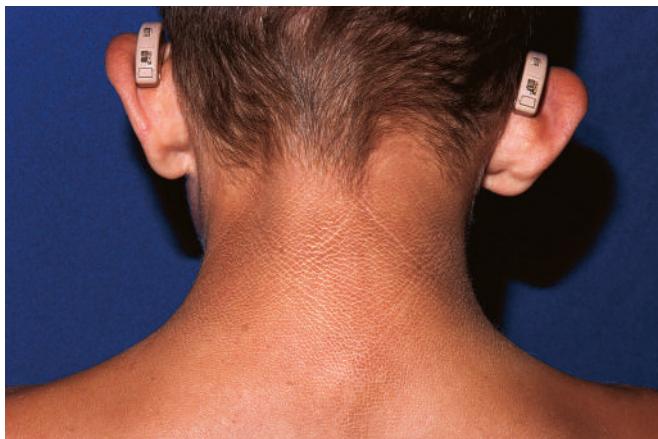
Syndromic forms of ichthyosis may be associated with a variety of extracutaneous abnormalities, most commonly involving the hair (e.g., Netherton; ichthyosis follicularis, alopecia, and photophobia [IFAP] and ichthyosis, hypotrichosis, and sclerosing cholangitis [IHSC] syndromes and ichthyosis with hypotrichosis; trichothiodystrophy) and neurologic system (e.g., Sjögren-Larsson; Refsum; dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma [CEDNIK]; and mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratoderma [MEDNIK] syndromes). Some syndromic disorders are lethal in the neonate (e.g., Neu-Laxova syndrome), infant (e.g., Gaucher disease type 2; arthrogryposis, renal dysfunction, and cholestasis [ARC] syndrome; multiple sulfatase deficiency) or child (e.g., CEDNIK syndrome).

#### NEUTRAL LIPID STORAGE DISEASE WITH ICHTHYOSIS

Neutral lipid storage disease with ichthyosis, or Chanarin-Dorfman syndrome, is a rare autosomal recessive disorder seen primarily in individuals of Middle Eastern or Mediterranean descent.<sup>120</sup> The clinical phenotype can variably include liver steatosis with hepatomegaly, muscle weakness/myopathy, ataxia, neurosensory hearing loss, subcapsular cataracts, nystagmus, strabismus, and mental retardation, but ichthyosis of the CIE phenotype is an almost constant finding. Patients are often born as collodion babies, occasionally with ectropion and eclabium. Skin biopsies show skin thickening with foamy keratinocyte cytoplasm owing to prominent neutral lipid droplets in the basal cells and eccrine glands seen best on oil-red O-stained frozen sections. Serum lipids are normal, although the triglyceride content of lymphocytes, macrophages, and fibroblasts in culture is two to 20 times that of normal cells. Muscle and liver enzymes may be elevated twofold to threefold. The diagnosis is confirmed by a peripheral blood smear, which shows lipid droplets in granulocytes (Jordan anomaly) that are also seen in the leukocytes of heterozygous carriers of Chanarin-Dorfman syndrome. Mutations have been identified in *ABHD5* or *CGI-58*,<sup>121</sup> a gene that encodes an enzyme expressed during differentiation in lipid transporting lamellar granules of epidermis<sup>122</sup> that is required for triglyceride degradation and normal barrier function.<sup>123,124</sup> A diet of moderate amounts of carbohydrates and medium-chain triglycerides, together with oral acitretin 0.5 mg/kg per day, has been shown to improve both the CIE and liver function tests.<sup>125</sup>

#### CHIME SYNDROME

Individuals with CHIME syndrome (also called *Zunich neuroectodermal syndrome*) show a combination of coloboma, heart defects, ichthyosis-form dermatosis, mental retardation, and ear anomalies, including conductive hearing loss.<sup>126,127</sup> The disorder is caused by mutations in *PIGL*,<sup>128</sup> a de-N-acetylase required to make glycosylphosphatidylinositol (GPI) anchors, which are membrane glycolipids that anchor the C-terminus of proteins during posttranslational modification.<sup>129</sup> The skin is notably thickened and dry at birth, with pruritis often developing during the first months of life (Fig. 5-17). The colobomas are usually retinal, although choroidal colobomas have been described. Several heart defects, including pulmonic stenosis, ventricular septal defect, transposition of the great vessels, and tetralogy of Fallot, have been associated. Patients show a typical facies with hypertelorism; a broad, flat nasal root; upslanting palpebral fissures; epicanthic folds; a long columella but short philtrum; macrostomia; full lips; and cupped ears with rolled helices. All patients show brachydactyly. The hair may be fine and sparse, and trichorrhexis nodosa has occasionally been described. Some patients have renal or urologic anomalies, and cleft palate has been described in association.



**Figure 5-17** CHIME syndrome. Thickened skin on the back of the neck. Note the hearing aids because of conductive hearing loss.



**Figure 5-18** KID syndrome. Note the fine, stippled papules studding the dorsal aspect of the fingers and the subungual hyperkeratosis.

## KID SYNDROME

KID syndrome is a rare autosomal dominant disorder characterized by keratitis, congenital ichthyosis, and neurosensory deafness.<sup>130,131</sup> Patients are usually born with erythematous skin that progressively becomes more thickened and leathery during the first months of life. Generalized tiny stippled papules are characteristic (Fig. 5-18), and 90% of patients develop well-defined verrucous plaques, especially on the face and limbs. Alopecia may be congenital (25%) and ranges from sparse hair to total alopecia (Fig. 5-19); a thick yellow scale may cover the scalp at birth. Most patients show PPK with a stippled or leathery pattern. Nails tend to be dystrophic, and sweating may be diminished.

The hearing loss is congenital, neurosensory, and nonprogressive; it can be detected by brainstem auditory-evoked potential testing. In contrast, ocular features are rarely seen at birth but progress and become evident by childhood or early adolescence. Photophobia may be the earliest sign, and the characteristic corneal vascularization and keratoconjunctivitis sicca lead to pannus formation and marked reduction in visual acuity.<sup>132</sup> KID syndrome must be distinguished from IFAP syndrome (see Chapter 7), an ichthyotic condition in which patients have total alopecia, thickened skin with spiny projections, PPK, and photophobia with decreased visual acuity.

Almost half of patients with KID syndrome have recurrent bacterial and candidal infections of the skin, eyes, and ear canals.<sup>130,133</sup> Some patients have demonstrated abnormal chemotaxis and impaired lymphocyte proliferative responses to *Candida albicans*. The follicular occlusion syndrome (including hidradenitis suppurativa) has been described in some patients, may lead to scarring alopecia, and may require surgical intervention.<sup>134</sup> More than 10% of patients develop squamous cell carcinoma of the skin, especially acral, or



**Figure 5-19** (A) KID syndrome. Markedly thickened skin with fine stippling on the cheeks and perioral skin. Note the total alopecia in this patient who was found to have a mutation in *GJB2*, which encodes connexin 26. (B) Note the fine projections, including between the thick scales, in this newborn. (A Courtesy of Amy Theos, MD. B Courtesy of Sapna Vaghani, MD and Daniela Russi, MD.)

tongue<sup>130,135</sup> occasionally during childhood, and trichilemmal tumors have also been described.<sup>136–139</sup> Dandy–Walker malformation has been described in several affected individuals.<sup>140</sup>

The disorder results from mutations in one of *GJB2* or *GJB6*, encoding connexins (proteins that create channels critical in intercellular communication) 26<sup>141</sup> and 30,<sup>142</sup> respectively. The latter connexin is also mutated in patients with Clouston syndrome, which shares the alopecia, nail dystrophy, PPK, and sometimes photophobia of KID syndrome (see Chapter 7). A baby with KID syndrome from a connexin 26 mutation has recently been described whose unaffected mother had the same point mutation but had an additional, more distal null mutation in the same allele that protected her from having phenotypic manifestations; the second mutation was lost in the baby, presumably by prezygotic reversion during meiosis of the maternal gamete.<sup>143</sup>

Therapy of KID syndrome is largely supportive. Chronic administration of fluconazole has improved the verrucous plaques of cutaneous candidiasis.<sup>144</sup> Cochlear implants<sup>145</sup> and corneal transplants have been used to correct the sensorineural hearing loss and corneal vascularization, respectively.<sup>132,146–148</sup> Recent research has suggested that mefloquine, a US Food and Drug Administration (FDA)-approved antimalarial drug, inhibits the aberrant connexin 26 hemichannels in keratinocytes from a mouse model of KID syndrome and may be a future intervention.<sup>149</sup>

## NETHERTON SYNDROME

Netherton syndrome (NS) is an autosomal recessive condition that combines ichthyosis, atopy, and hair shaft deformities. NS presents during the neonatal or early infantile period with generalized scaling

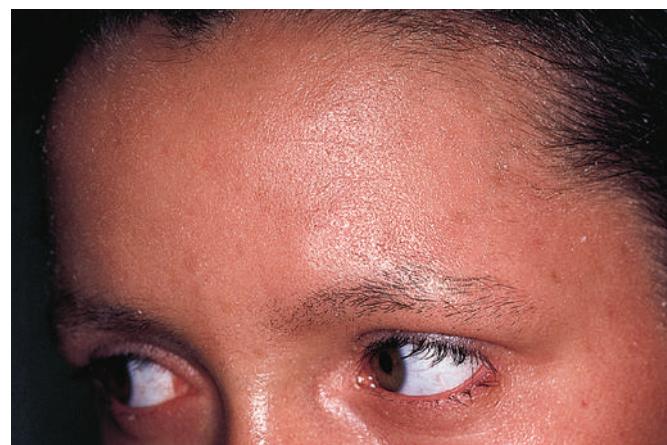


**Figure 5-20** Netherton syndrome. Polycyclic scaling lesions, many showing the scale edge. (A) Note the underlying erythroderma, scalp involvement, and short hair. (B) Sometimes there is more global erythroderma and larger desquamative scaling.

erythroderma but not a true collodion-baby phenotype. Neonates with NS are usually born prematurely and develop the eruption *in utero* or during the first weeks of life. Failure to thrive is often profound, requiring hospitalization for nutritional support and correction of the hypernatremic dehydration that may be associated.<sup>150</sup>

Patients may have diarrhea associated with intestinal villus atrophy, and the majority experience sepsis, upper and lower respiratory infections, and cutaneous *S. aureus* infection.<sup>151</sup> Adults with NS are also at risk for extensive papillomavirus infection,<sup>152</sup> usually involving the genital region, and may develop squamous cell carcinoma.<sup>57</sup> A variety of immunologic abnormalities have been described, suggesting that NS should be considered a primary immunodeficiency disorder. These include reduced memory B cells, defective response to vaccination, impaired antibody amplification and class switching, decreased natural killer (NK)-cell cytotoxicity, a skewed T-helper (Th) 1 phenotype, and increased proinflammatory cytokine levels.<sup>151</sup> Treatment with intravenous immunoglobulin may cause an increase in NK cell cytotoxicity and clinical improvement.<sup>151</sup>

Ichthyosis linearis circumflexa, the characteristic skin change associated with NS, is characterized by migratory, polycyclic scaly lesions with a peripheral double-edged scale (Fig. 5-20). Although most commonly seen in association with NS, patients may show only the ichthyosis linearis circumflexa without the hair shaft abnormalities or other features of NS. Ichthyosis linearis circumflexa is not generally seen before 2 years of age and occurs eventually in only 70% of patients. The ichthyosiform erythroderma that is the typical



**Figure 5-21** Netherton syndrome. Dry, lusterless hair that breaks and thus remains short and unmanageable. Note the eyebrow alopecia and facial erythroderma.

manifestation in the neonatal and infantile periods tends to improve with increasing age. Partial remissions have been noted and spontaneous fluctuation is common, but there is little tendency to spontaneous resolution. Routine histologic examination of skin-biopsy sections is not helpful, but immunohistochemical studies show absent or reduced expression of *LETKI*,<sup>153–155</sup> and electron microscopic studies have revealed features that are specific to NS.<sup>156,157</sup>

The classic hair shaft abnormality, trichorrhexis invaginata ("bamboo hairs," "ball-and-socket deformity"), is thought to result from a defect in keratinization of the internal root sheath. The hair defect results in easy hair breakage and hair that is poorly manageable, dry, and lusterless (Fig. 5-21) (see Chapter 7, Fig. 7-5). Multiple hairs from different areas should be examined, because only 20% to 50% of hairs may be affected. Examination of hairs from the eyebrow region often is most fruitful, and dermoscopy facilitates visualization of the "matchstick" hair defect.<sup>158,159</sup> Finding the hair shaft disorder is particularly difficult in the affected neonate.

NS results from loss-of-function mutations in *SPINK5*, which encodes lymphoepithelial Kazal-type-related inhibitor (*LETKI*), a serine protease inhibitor.<sup>160</sup> The increase in serine protease activity (kallikrein 5) leads to decreases in desmosomal proteins (desmoglein 1 and desmocollin 1) with premature degradation of corneocyte desmosomes and excessive desquamation.<sup>161–163</sup> Approximately two-thirds of patients show pruritic atopic-like dermatitis, food allergies, urticaria, angioedema, asthma, and/or anaphylaxis. In addition, most patients have increased levels of circulating eosinophils and immunoglobulin (Ig) E. These atopic manifestations likely result from the unregulated kallikrein 5 activity, which activates *PAR2* and *TSLP* (as in atopic dermatitis, see Chapter 3) as well as other cytokines<sup>164</sup> and contributes to both the very poor skin barrier and the cutaneous inflammation. The marked impairment in barrier function can lead to significant absorption of topically applied medication, necessitating careful monitoring of serum levels or adrenal suppression. Application of hydrocortisone 1% ointment caused Cushing syndrome in an 11-year-old boy, and immunosuppressive serum levels may be detectable after application of tacrolimus ointment.<sup>165</sup> Nevertheless, several patients have responded well to application of topical calcineurin inhibitors without detectable absorption.<sup>166,167</sup>

NS should be distinguished from other forms of ichthyosis, especially with abnormal hair, barrier defects, and early failure to thrive (Table 5-2). These include severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome<sup>168</sup>; epidermal growth factor receptor (EGFR) deficiency<sup>169</sup>; and ADAM17 deficiency.<sup>170–177</sup> Alopecia with ichthyosis is also a feature of trichothiodystrophy<sup>170</sup> (see Chapter 7), ichthyosis hypotrichosis syndrome,<sup>173–176</sup> and IHSC syndrome<sup>171,172</sup> (see Table 5-2).

Treatment of NS is largely supportive, although administration of infliximab led to sustained improvement and decreased thymic stromal lymphopoitietin levels,<sup>178</sup> and narrow-band ultraviolet B (UVB) light

**Table 5-2** Differential Diagnosis of Netherton Syndrome: Disorders with Ichthyosis and Alopecia (Hereditary Disorders Only)\*

Disorder	Inheritance	Gene	Features Resembling Netherton Syndrome	Differentiation from Netherton Syndrome
SAM syndrome	AR Loss-of-function mutations	<i>DSG1</i>	CIE with PPK, no collodion membrane; failure to thrive; hypernatremia; barrier defect; dermatitis; high IgE; malabsorption; eosinophilic esophagitis; multiple food allergies; recurrent infections; hypotrichosis; hypoalbuminemia	May have microcephaly, growth hormone deficiency, developmental delay, cardiac defects; psoriasisiform dermatitis with acantholysis in skin sections; absence of desmoglein
ADAM17 deficiency	AR Loss-of-function mutations	<i>ADAM17</i>	Psoriasisiform erythroderma/widespread pustules; failure to thrive; malabsorption; short, broken hair; recurrent infections	Bloody diarrhea; cardiomyopathy/cardiomyositis
EGFR deficiency	AR Loss-of-function mutations	<i>EGFR</i>	Erythema, scaling, and widespread pustules; alopecia; failure to thrive, watery diarrhea, high IgE and eosinophils, hypernatremia, hypoalbuminemia; recurrent bronchiolitis	Cardiovascular issues
Trichothiodystrophy	AR Loss-of-function mutations	<i>ERCC2, ERCC3, GTF2H5, C7orf11</i> (see Chapter 7)	CIE-like ichthyosis; short, brittle hair; "tiger tail" hair shaft defect under polarized microscopy	May have impaired intelligence, decreased fertility, short stature, and photosensitivity
IHS (also called autosomal recessive ichthyosis with hypotrichosis [ARIH] syndrome)	AR Loss-of-function mutations	<i>ST14</i> (encodes matriptase); abnormal filaggrin processing	Generalized, congenital ichthyosis with sparing of face, palms, and soles; diffuse nonscarring alopecia of scalp, eyelashes, and eyebrows from birth, but improves to sparse, unruly hair during adolescence and merely recession of the frontal hair line by adulthood	May have patchy follicular atrophoderma and hypohidrosis; photophobia from corneal abnormalities; blepharitis; dental abnormalities; hair microscopy may show pili torti or pili bifurcati
IHSC (or NISCH) syndrome	AR Loss-of-function mutations	<i>CLDN1</i> (encodes claudin 1, structural protein of tight junctions)	Congenital generalized scaling, predominantly on the limbs and abdomen and sparing skinfolds, palms and soles; coarse, curly hair with frontotemporal cicatricial alopecia	Congenital paucity of bile ducts or sclerosing cholangitis leads to neonatal jaundice with hepatomegaly; oligodontia, and enamel dysplasia; blood smears show small eosinophils and keratinocyte vacuoles without lipid contents

AR, Autosomal recessive; CIE, congenital ichthyosiform erythroderma; Ig, immunoglobulin; IHS, ichthyosis hypotrichosis syndrome; IHSC, ichthyosis-hypotrichosis-sclerosing cholangitis; NISCH, neonatal ichthyosis sclerosing cholangitis; SAM, severe dermatitis, multiple allergies, and metabolic wasting; PPK, palmoplantar keratoderma.

\*Netherton syndrome must also be distinguished from severe atopic dermatitis and immunodeficiency disorders.

has led to marked cutaneous improvement within a few months.<sup>179,180</sup> A Phase 1 *ex vivo* gene therapy trial is underway in the United Kingdom, with the normal *SPINK5* gene introduced by lentivirus into the grafted patient keratinocytes.<sup>155</sup>

### REFSUM DISEASE

Refsum disease is an autosomal recessive neurocutaneous disorder caused by deficiency in oxidation of phytanic acid, a branched, long-chain fatty acid derived from dietary chlorophyll.<sup>181–183</sup> The clinical features usually develop in late childhood or early adult life and progress slowly during months to several years. Neurologic manifestations are most prominent and include sensorineural deafness, anosmia, failing vision, night blindness owing to retinitis pigmentosa and a progressive weakness, foot drop, and loss of balance caused by a mixed sensorimotor neuropathy and cerebellar involvement. Delayed diagnosis may result in severe neurologic impairment, wasting, and depression. The associated ichthyosis, which can either coincide with or postdate the neurologic features, resembles ichthyosis vulgaris or in severe untreated cases, LI. Accentuated palmoplantar markings are associated.

Refsum disease results from mutations in one of two genes, either *PHYH* (also named *PAHX*), which encodes the peroxisomal enzyme phytanoyl-CoA hydroxylase, or *PEX7*, which encodes the PTS2

(peroxisomal targeting signal 2) receptor.<sup>184</sup> Phytanic acid cannot be synthesized by humans and is mainly derived from plant chlorophyll. Normally serum levels are undetectably low but in Refsum disease may account for up to 30% of serum lipids. The accumulation of phytanic acid disturbs the cholesterol balance and may alter lipid degradation.<sup>185</sup> Histology shows variably sized vacuoles in the epidermal basal and suprabasal cells, corresponding to the lipid accumulation seen with lipid stains of frozen sections. The diagnosis is based on the demonstration of increased levels of phytanic acid in the patient's serum, tissue, or urine. Therapy consists of a chlorophyll-free diet and avoidance of phytanic acid-containing foods.

### SJÖGREN–LARSSON SYNDROME

The ichthyosis of the autosomal recessive disorder, Sjögren–Larsson syndrome (SLS), usually manifests in the neonatal period as fine, white scaling, accentuated in flexural areas.<sup>186</sup> Erythema is occasionally present at birth but clears within months. Presentation as a collodion baby is rare. By 1 year of age, the ichthyosis of SLS is not erythrodermic but shows generalized velvety lamellar thickening (often with a yellowish hue) particularly on the trunk and neck with minimal desquamation (Fig. 5-22), PPK, and relative sparing of the face.<sup>187,188</sup> The skin is characteristically pruritic, and most patients are hypohidrotic. The degree of scaling varies from mild to severe (Fig. 5-23) and does



**Figure 5-22** Sjögren–Larsson syndrome. The skin shows velvety lamellar thickening with a yellowish hue and minimal desquamation.



**Figure 5-23** Sjögren–Larsson syndrome. Thick, lamellar scaling in an adolescent with severe retardation.

not change with increasing age.<sup>189,190</sup> Hair and nails are normal. The neurologic disease usually presents within the first year with failure to reach normal developmental milestones and the onset of spasticity. Phenotypic variability is seen, and some patients have been described with mild neurologic features of SLS without associated skin disease.<sup>191</sup> Spasticity and muscle paresis is most pronounced in the legs,<sup>189</sup> and most affected persons become dependent on a wheelchair for mobility. Most patients have a learning disability to a variable degree and a speech disorder, and some show seizures, short stature, kyphosis, and enamel hypoplasia. The pathognomonic retinal “glistening dots” are not present in all patients, but photophobia is common.

SLS results from mutations in the fatty aldehyde dehydrogenase gene (*FALDH* or *ALDH3A2*), a component of fatty alcohol, fatty alcohol oxidoreductase (FAO), which converts fatty alcohol to fatty acid.<sup>192</sup> Epidermal cells in affected individuals show abnormal lamellar bodies and lipid droplets, consistent with defective lipid metabolism.<sup>193</sup> Prenatal diagnosis of SLS is possible by measurement of FAO activity

in cultured amniocytes or chorionic cells, histologic analysis, and/or analysis of fetal deoxyribonucleic acid (DNA) if the gene defect is known. The ichthyosis is treated with topical keratolytic agents and retinoids<sup>189</sup>; dietary supplementation with medium-chain fatty acids is generally not helpful.<sup>187</sup> The leukotriene inhibitor zileuton may decrease the associated pruritus,<sup>194</sup> but no therapy to date has been found to slow the progressive neurologic deterioration. Ichthyosis with more severe neurologic changes than SLS (spastic diplegia, seizures, and intellectual disability) can also result from biallelic mutations in *ELOVL4*, a fatty acid elongase that catalyzes the first and rate-limiting step in very long chain fatty acid synthesis (see *Erythrokeratoderma Variabilis* and *Progressive Symmetric Erythrokeratoderma* section).<sup>101</sup>

### ICHTHYOSIS PREMATURITY SYNDROME

Ichthyosis prematurity syndrome (IPS) is an autosomal recessive disorder in which affected babies are born more than 6 weeks prematurely in association with polyhydramnios and opaque amniotic fluid because of the extensive shedding of epidermal cells.<sup>195,196</sup> Neonates often have perinatal respiratory distress and sometimes life-threatening neonatal asphyxia of amniotic keratin debris. Typically babies are born with generalized thick spongy desquamating skin that resembles vernix caseosa, accentuated on the scalp and eyebrows.<sup>197</sup> During the neonatal period the scaling may resemble cobblestones overlying moderate erythroderma. Although the marked thickening clears in survivors, xerosis with follicular keratosis and pruritus persists, and patients often show atopic dermatitis, dermatographism, asthma, and eosinophilia. More than 70% develop respiratory and/or food allergy.<sup>198</sup> Mutations have been identified in *SLC27A4*, the fatty-acid transport protein 4 (*FATP4*) gene, which encodes a fatty-acid transporter and leads to defective stratum corneum lipid homeostasis. *FATP4* may associate with ichthyin and transglutaminase 1 in lipid processing essential for maintaining the epidermal barrier function.<sup>199</sup>

### NEU–LAXOVA SYNDROME

Another autosomal recessive form of congenital ichthyosis associated with a high risk of early death is Neu–Laxova syndrome, characterized by severe intrauterine growth retardation, an edematous appearance, lung hypoplasia, microcephaly, and abnormal brain development with lissencephaly and agenesis of the corpus callosum.<sup>200–203</sup> The ichthyosis tends to be present at birth but ranges in severity from mild ichthyosis to an HI appearance. Patients tend to show typical facies, including protuberant eyes with a flattened nose, slanted forehead, micrognathia, deformed ears, and a short neck. Some affected neonates show microphthalmia or cleft palate. Syndactyly, limb or digital hypoplasia, and limb contractures are common, and X-rays often show poor bone mineralization. Mutations occur in one of three genes of the L-serine biosynthesis pathway, phosphoglycerate dehydrogenase (*PHGDH*),<sup>204</sup> phosphoserine aminotransferase (*PSAT1*) and phosphoserine phosphatase (*PSPH*).<sup>205</sup> Neu–Laxova represents the severe end of the spectrum of disorders caused by mutations in these genes (others have variable neurologic manifestations). Craniofacial and limb defects have been seen in a variety of syndromes with reduced intrauterine movement (fetal akinesia/hypokinesis sequence).

### GAUCHER SYNDROME TYPE 2

Gaucher syndrome type 2 results from an absence of lysosomal β-glucocerebrosidase, which hydrolyzes glucosylceramide to ceramide. The neonate with Gaucher syndrome type 2 (acute infantile cerebral form) may be a collodion baby<sup>206,207</sup> with the onset during infancy of neurologic signs and hepatosplenomegaly.<sup>208</sup> Glucosylceramide and ceramide are critical components of the intercellular bilayers of the stratum corneum and play a role in epidermal barrier function.<sup>4</sup> The absence of glucocerebrosidase leads to abnormal skin thickening and increased transepidermal water loss. Even when the skin appears normal clinically in affected patients, ultrastructural abnormalities in lamellar membranes may be seen.<sup>209</sup> Despite enzyme replacement therapy, nonneurologic manifestations of Gaucher disease may progress.<sup>210</sup>

### CEDNIK SYNDROME

CEDNIK syndrome first manifests between 5 and 11 months of age with progressive neurologic deterioration.<sup>211</sup> Affected infants show a generalized mild LI phenotype with sparing of skin folds but palmo-plantar thickening. The hair tends to be fine and sparse. Microcephaly, neuropathy, cerebral dysgenesis, sensorineural deafness, optic nerve atrophy, neurogenic muscle atrophy, and cachexia are associated, and affected individuals usually die within the first decade of life. Patients with CEDNIK syndrome have mutations in *SNAP29*, a component of the secretory (SNARE [soluble NSF attachment protein receptor]) pathway that is important for vesicle fusion and lamellar granule maturation and secretion. In CEDNIK syndrome, glucosylceramide and kallikrein-containing granules are abnormally retained in the stratum corneum, leading to retention hyperkeratosis and an abnormal epidermal barrier.

### MEDNIK SYNDROME

MEDNIK syndrome is an autosomal recessive disorder that shows manifestations at birth or within the first weeks of life.<sup>212,213</sup> Among the ichthyoses, it most closely resembles EKV and in fact has also been called *EKV3*. Nail thickening and mucosal involvement may be associated. Patients show congenital sensorineural deafness, psychomotor and growth retardation, mental retardation, and peripheral neuropathy. The severe, congenital, chronic diarrhea is life-threatening. MEDNIK syndrome results from mutations in *AP1S1*, encoding a subunit (1A) of an adapter protein complex (AP-1) that is involved in

the organization and transport of proteins during skin and spinal-cord development.<sup>214</sup>

### ARC SYNDROME

ARC syndrome presents with generalized desquamative lamellar scaling within the first days to weeks of life but not at birth.<sup>215–217</sup> Ectropion and mild scarring alopecia may be present. The distinguishing features are the associated arthrogryposis (contractures of the limbs, particularly of the knee, hip and wrist; rocker bottom feet; talipes equinovarus), renal tubular degeneration with metabolic acidosis, and intrahepatic bile-duct hypoplasia with cholestasis. Patients may also show cerebral malformations, hypothyroidism, deafness, dysmorphic features, and large, dysfunctional platelets. Death ensues during the first year of life. ARC syndrome results from mutations in *VPS33B*, which regulates SNARE protein-mediated fusion of membrane vesicles required for lamellar body secretion.<sup>218</sup> Incomplete ARC syndrome has been described without the arthrogryposis.<sup>219</sup>

### CONRADI–HÜNERMANN–HAPPLE SYNDROME

The key clinical features of Conradi–Hünermann–Happle (CHH) syndrome (also called *X-linked dominant chondrodysplasia punctata type II*) are linear ichthyosis, chondrodysplasia punctata, cataracts, and short stature.<sup>220</sup> Neonates tend to show severe ichthyosiform erythroderma with patterned yellowish markedly hyperkeratotic plaques (Fig. 5-24, A). After the first 3 to 6 months of life the erythroderma and scaling resolve, leaving erythema and later follicular atrophoderma in



**Figure 5-24** Conradi–Hünermann–Happle syndrome. Congenital scaling (A) and residual hyperpigmentation during infancy after scale clearance (B) and later during childhood (C) in a distribution that follows Blaschko lines.



**Figure 5-25** Conradi–Hünermann–Happle syndrome. Cicatricial alopecia of the eyebrows. Approximately half of this patient's scalp hair was replaced by cicatricial alopecia as well. Note the deformity of the nose.



**Figure 5-27** CHILD syndrome. Unilateral congenital ichthyosiform erythroderma with marked deformity of the arm. This girl's ipsilateral leg was also markedly shortened and required amputation.



**Figure 5-26** Conradi–Hünermann–Happle syndrome. Bilateral ptychotropism with psoriasiform plaques.

a distribution that follows Blaschko lines, hypopigmentation and hyperpigmented streaks particularly on the trunk (Fig. 5-24, B and C), and circumscribed cicatricial alopecia of the scalp and eyebrows (Fig. 5-25). Patients may show persistent psoriasiform lesions in intertriginous areas (ptychotropism) (Fig. 5-26). In addition to the cutaneous findings, patients with CHH show asymmetric skeletal involvement with punctate calcification of the epiphyseal regions that usually results in an asymmetric shortening of the long bones (especially the humeri and femora) and sometimes in severe kyphoscoliosis, facial dysplasia, and hip dislocation. Unilateral or bilateral sectorial cataracts; patchy, coarse, lusterless hair; nasal bone dysplasia with saddle-nose deformity (see Fig. 5-25), and a high-arched palate further characterize the disease. The bony abnormalities but not the skin lesions of CHH syndrome have been described in association with teratogenic exposures to medications and infections and maternal autoimmune diseases.<sup>221</sup>

X-chromosomal inactivation explains the distribution of skin lesions along Blaschko lines, the sectorial cataracts, and the asymmetric skeletal abnormalities. Abnormal cholesterol synthesis/metabolism has been detected in patients with CHH, and mutations

have been identified in emopamil binding protein (EBP), which encodes 3 $\beta$ -hydroxysteroid- $\Delta$ 8,  $\Delta$ 7-isomerase, a key component in cholesterol biosynthesis. Abnormal lamellar granules and malformed intercellular lipid layers have been detected ultrastructurally,<sup>222</sup> and plasma sterol analysis shows markedly elevated levels of 8(9)-cholesterol and 8-dehydrocholesterol.<sup>223</sup>

## CHILD SYNDROME

The CHILD syndrome is a congenital disorder characterized by congenital hemidysplasia, ichthyosiform erythroderma, and limb defects.<sup>224</sup> Also known as *unilateral CIE*, the hallmark of the disorder is the sharp midline demarcation and its largely unilateral cutaneous and skeletal features (Fig. 5-27). This X-linked dominant condition occurs almost exclusively in girls and is presumed to be lethal in affected males. The only case in a boy is thought to represent early postzygotic mosaicism.<sup>225</sup> The inflammatory ichthyosiform skin lesions of CHILD syndrome may be present at birth or develop during the first few months of life. They are characterized by yellow and waxy scaling and/or streaks of inflammation and scaling that is often patchy but may follow Blaschko lines. Similarly, streaks of normal skin may be interspersed within the area of the CHILD nevus. Unilateral alopecia and severe nail dystrophy with claw-like nails have been described. The face is typically spared. With increasing age, lesions may improve or even clear spontaneously, but lesions in intertriginous areas (ptychotropism) tend to persist and be the most severely affected sites.<sup>226</sup> Rarely a localized hyperkeratotic plaque with a sharp demarcation at the midline is the sole manifestation of the CHILD syndrome (CHILD nevus) (Fig. 5-28). A mild form of CHILD syndrome has been described in three generations,<sup>227</sup> suggesting genetic control of the skewing of X inactivation.<sup>228</sup>

Ipsilateral skeletal hypoplasia, ranging in severity from hypoplasia of the fingers to complete agenesis of an extremity, is an important feature of CHILD syndrome. As with the skin changes, unilaterality is not absolute, and slight changes may be present on the contralateral side. The molecular basis for the unilaterality is not understood, but the epidermal changes correlate with mutant gene expression in the epidermis; leukocytes show skewing of X-chromosome inactivation, and virtually all circulating cells express the normal gene.<sup>229</sup> Punctate epiphyseal calcifications may be demonstrable by radiography but tend to disappear after the first few years of life. Cardiovascular and renal abnormalities are the major visceral manifestations of CHILD syndrome, although anomalies of other viscera have been described. Biopsy of skin lesions shows epidermal thickening with characteristic infiltration of the papillary dermis of histiocytes showing foamy cytoplasm (verruciform xanthoma). Inactivating mutations have been identified in the NSDHL gene encoding a 3 $\beta$ -hydroxysteroid dehydrogenase,<sup>230</sup> which functions upstream of EBP in the cholesterol synthesis pathway. Treatment with keratolytic agents and retinoids is poorly



**Figure 5-28** CHILD nevus. The ptychotropism of a sharply demarcated thickened plaque of the inguinal area that ends abruptly at the midline. This girl showed mild thickening and hyperpigmentation involving only the right side of her body but no limb deformities or hemidysplasia.

tolerated, but topical application of compounded 2% lovastatin/2% cholesterol leads to dramatic improvement.<sup>229</sup>

#### TREATMENT OF LESIONAL SKIN OF NONSYNDROMIC AND SYNDROMIC ICHTHYOSSES

Treatment of patients with most forms of ichthyosis involves topical application of keratolytic agents and topical or systemic administration of retinoids.<sup>1,231</sup> The Foundation for Ichthyosis and Related Skin Types (FIRST; [www.firstskinfoundation.org](http://www.firstskinfoundation.org)) is a support group for patients and families with disorders of cornification. In addition to educational materials, FIRST provides information about commercially available treatment options. Several other foundations worldwide support families with ichthyosis and have educational websites as well (e.g., [www.ichthyosis.org.uk](http://www.ichthyosis.org.uk) and [www.ictiosis.org](http://www.ictiosis.org)).

The management of all types of ichthyosis consists of retardation of water loss, rehydration and softening of the stratum corneum, and alleviation of scaliness and associated pruritus. Daily to twice-daily baths using a superfatted soap or a soapless cleanser followed immediately by application of the emollient to moist skin can be helpful for all forms. Shorter baths are preferred for patients with ichthyosis vulgaris, especially with associated atopic dermatitis. However, many patients with LI or EI have found long baths to be particularly helpful. Ichthyosis vulgaris and RXLI can be managed quite well by topical application of emollients and the use of keratolytic agents to facilitate removal of scales from the skin surface.  $\alpha$ -Hydroxy acid preparations such as lactic and glycolic acids are the most commonly used as agents to desquamate excessive scale and increase hydration.<sup>231,232</sup> Urea in concentrations of 10% to 20% has a softening and moisturizing effect on the stratum corneum and is helpful in the control of dry skin and pruritus. Salicylic acid is another effective keratolytic agent and can be compounded into petrolatum at concentrations between 3% and 6% to promote shedding of scales and softening of the stratum corneum. When it is used to cover large surface areas for prolonged periods, however, patients should be monitored for salicylate toxicity, most commonly complaints of tinnitus. The combination of 6% salicylic acid in propylene glycol may be particularly helpful for



**Figure 5-29 (A)** and **(B)** Clearance of the lamellar phenotype of ichthyosis with topically applied tazarotene. After 2 months of nightly application of tazarotene 0.1% cream, this girl experienced remarkable improvement in her ichthyosis.

keratoderma of the palms and soles, especially when used under occlusive wraps. The LI phenotype of ARCI generally requires more potent keratolytic agents; individuals with milder forms of LI often respond well to the topical application of tazarotene (Fig. 5-29).<sup>233,234</sup> As the skin normalizes, the risk of irritation from tazarotene increases, sometimes leading to dermatitis and then requiring therapy to be intermittent. Topical N-acetylcysteine with or without urea (e.g., 10% N-acetylcysteine in 5% urea) has also been used for LI.<sup>235,236</sup> Recombinant transglutaminase-1 enzyme encapsulated in liposomes reversed the ichthyosis phenotype and barrier function in a skin-humanized mouse model of LI.<sup>237</sup>

The skin of EI is quite fragile, and patients generally will tolerate only intermittent, short-term use of keratolytic agents, if at all. Similarly, individuals with NS and CHILD syndrome tolerate topically applied keratolytic agents poorly. It should be remembered that individuals with ichthyosis usually have a barrier abnormality that can lead to increased percutaneous absorption. Although topical anti-inflammatory medications may be used for associated dermatitis or to decrease intense pruritus, the risk of detectable levels of corticosteroids or calcineurin inhibitors must be kept in mind. For example, topical tacrolimus ointment has been found to be helpful for individuals with NS, but toxic levels have sometimes been detected,<sup>165</sup> emphasizing the need for careful monitoring.<sup>167</sup>

Oral retinoids (isotretinoin, acitretin) have led to dramatic improvement in some pediatric patients with the ichthyoses but should be used with caution because of their many potential side effects that limit long-term therapy, particularly bone toxicity.<sup>238,239</sup> Liarazole, a retinoic acid-metabolism blocking agent (RAMBA),<sup>240</sup> has shown the efficacy of acitretin with fewer retinoic acid-related adverse events.<sup>241–243</sup> These systemic agents are generally reserved for use in adolescents and adults with more severe ichthyotic disorders that do not show a satisfactory response to topical agents.

Patients with the ichthyoses tend to be more susceptible to cutaneous infection, particularly dermatophyte and staphylococcal infections. Secondary infection should be considered when patients with ichthyosis (particularly ARCI and EI) develop a new eruption. The accumulation of scale predisposes to overgrowth of bacteria and an odor, which in addition to the significant cosmetic ramifications of these disorders, may lead to additional problems in social acceptance by peers. Patients with thick scale may benefit from use of mild antibacterial soaps (e.g., Lever 2000 or Cetaphil antibacterial soap) or use of antibacterial washes if not too irritating. Many patients benefit from the addition of bleach (4 cc per gallon or 1 cc per L;  $\frac{1}{2}$  cup per full standard tub) or baking soda (1 cup) into the bath water. Dermatophyte infections often require administration of systemic antifungal medications.<sup>244</sup>

Sweating is often inadequate in patients with ichthyosis owing to the occlusion of eccrine ducts. Affected individuals should be guarded against overheating during winter months and kept in air-conditioning during warmer months, with frequent wetting of the skin or even cooling suits (see Chapter 7) during sports activities. The ectropion of patients with ARCI exposes the conjunctivae and cornea, resulting in irritation.<sup>245</sup> Bland moisturizing drops can be administered several times daily to provide protective moisture, and patients may benefit from wearing eye patches at night if the eyes cannot close entirely. Some physicians recommend plastic surgery to correct the ectropion, because damage to the cornea may impair vision; however, this surgery is complex and often unsuccessful. Periorbital application of tazarotene (0.05% cream)<sup>246</sup> and N-acetylcysteine have decreased ectropion when used sparingly. Ichthyosis of the ear canal can lead to accumulation of skin debris and conductive hearing loss. In a recent survey, 80% with ichthyosis reported ear pruritus, 66% had trouble hearing, and 29% reported ear pain.<sup>247</sup> Regular professional ear cleaning and use of ear softeners can decrease the risk of hearing loss and recurrent ear infections.

In countries without significant dietary supplementation with vitamin D<sub>3</sub>, ichthyosis, particularly the epidermolytic and lamellar forms (Fig. 5-30), has been associated with an increased risk of the development of rickets in association with increased levels of parathyroid hormone and alkaline phosphatase.<sup>248–251</sup> Serum levels of parathyroid hormone at 75 pg/mL or less and 25(OH)D<sub>3</sub> at 8 ng/mL or less significantly increase the risk of developing rickets.<sup>252</sup> The increased risk may relate to decreased ultraviolet light exposure, failure of UVB light to penetrate the thickened scale, and/or an abnormality in processing of vitamin D<sub>3</sub> in response to UVB light. Nevertheless, vitamin D<sub>3</sub> supplementation should be considered.

## Other Disorders of Differentiation

### DARIER DISEASE

Darier disease (keratosis follicularis, Darier–White disease; acral form, acrokeratosis verruciformis of Hopf) is an autosomal dominant disorder that most commonly first manifests between 8 and 15 years of age as flesh-colored papules that become covered with a yellow, waxy scaling crust (Figs. 5-31 and 5-32).<sup>253</sup> Lesions often coalesce to form thickened, warty plaques that are malodorous. Sites most often affected include the forehead, temples, ears, nasolabial folds, scalp, upper chest and back, in the so-called “seborrheic” distribution. Isolated scalp involvement has been reported and may be the presenting sign.<sup>254</sup> Linear streaks of Darier disease along Blaschko lines have been attributed to gene mosaicism.<sup>255</sup> Localized congenital Darier disease has been described and may represent type 2 mosaicism,<sup>256</sup> but Darier disease can be bilateral and present during infancy (Fig. 5-33). Lesions of Darier disease are often worsened by exposure to ultraviolet



**Figure 5-30** Patients with ichthyosis are at increased risk for the development of rickets, as shown in this boy from Nigeria.



**Figure 5-31** Darier disease. Thickened, warty plaques on the forehead and temples are characteristic and tend to be symmetrically distributed.

radiation, heat,<sup>257</sup> friction, and other forms of trauma. Secondary bacterial or herpes simplex virus infection is common.<sup>258</sup> *S. aureus* has been isolated from almost 70% of lesional skin areas, and colonization is correlated with more severe disease.<sup>259</sup>

Punctate keratoses on the palms and soles, either raised or with a central pit, occur in most patients. Keratoses resembling flat warts may be found on the dorsal aspects of the hands (acrokeratosis verruciformis). In some patients, these acral keratotic lesions are the only manifestation. The nails are easily broken and often show a



**Figure 5-32** Darier disease. The discrete keratotic papules of Darier disease have led to the alternative name of *keratosis follicularis*.



**Figure 5-33** Darier disease. This infant showed erosive plaques of the genital region and histology that was suggestive of Darier disease in the first months of life. Genotyping confirmed the *ATP2A2* mutation.

characteristic V-shaped scalloping of the free edge (see Chapter 7, Fig. 7-65). Subungual thickening with streaks of discoloration and subungual hemorrhage may be seen. White, centrally depressed papules or verrucous white plaques simulating leukoplakia are often seen on the mucosae of the cheeks, palate, and gums,<sup>260</sup> and may involve the rectum and vulva. Neuropsychiatric problems including learning disability (in more than 40% of patients),<sup>261</sup> schizophrenia, bipolar disorder, and/or seizures are seen in approximately 5% of patients,<sup>262</sup> and bone cysts may be associated with Darier disease as well.<sup>263</sup>

The characteristic histopathologic changes of Darier disease include intraepidermal suprabasal clefts or lacunae and the formation of acantholytic “corps ronds” (cells with a basophilic nucleus surrounded by a clear halo) and “grains” (small, dark cells with a pyknotic nucleus) in the stratum corneum. Mutations responsible for Darier disease involve *ATP2A2*, which encodes the sarcoplasmic/endoplasmic reticulum calcium ATPase type 2 (SERCA2).<sup>264</sup> Epidermal differentiation requires elevations in calcium levels for intercellular junction assembly, and the affected enzyme participates in the calcium pump system.<sup>265-271</sup> Systemic<sup>272,273</sup> administration of retinoids has resulted in significant improvement in most affected individuals.<sup>274</sup> Infection control is of paramount importance for some



**Figure 5-34** Hailey–Hailey disease. Crusted, erosive plaques that are symmetrically distributed, especially at fold areas.

individuals. Topical application of 5-fluorouracil,<sup>275,276</sup> tacrolimus ointment,<sup>277</sup> and diclofenac gel<sup>278</sup> have been reported to be helpful. Recalcitrant areas have been treated successfully with carbon dioxide, erbium:yttrium-aluminum-garnet (YAG) and pulsed-dye lasers.<sup>279-281</sup> Miglustat, a commercially available inhibitor of sphingolipid synthesis, corrects the defect in differentiation and adhesion of Darier keratinocytes *in vitro* and may be a future systemic treatment.<sup>270</sup> Cyclooxygenase-2 inhibition has been shown to restore the UVB-induced downregulation of SERCA2 expression in keratinocytes, suggesting the possibility that celecoxib could be another therapeutic modality for Darier disease.<sup>282</sup>

#### HAILEY–HAILEY DISEASE (FAMILIAL BENIGN PEMPHIGUS)

Hailey–Hailey disease is an autosomal dominant genodermatosis characterized by recurrent vesicles and erosions that most commonly appear on the sides and back of the neck, in the axillae, in the groin, and in the perianal regions (Fig. 5-34).<sup>283</sup> The disorder usually has its onset in the late teens or early 20s but has been reported in a 5-month-old infant.<sup>284</sup> Most cases have a fairly constant course. The primary lesions are small vesicles that occur in groups on normal or erythematous skin. The vesicles may enlarge to form bullae and rupture easily, leaving an eroded base; they exude serum and develop crusts resembling impetigo. The Nikolsky sign may be present. Lesions tend to spread peripherally with an active, often serpiginous, border, and central resolution with peripheral extension often results in circinate lesions. In the intertriginous area lesions tend to form erythematous plaques with dry crusting and soft, flat, and moist granular vegetations. Burning or pruritus is common, and particularly in the intertriginous areas lesions tend to become irritating, painful, and exceedingly uncomfortable. Mucosal involvement is uncommon, but papular lesions of the oral mucosa, esophagus, vagina, and conjunctivae have been described. As with Darier disease, mosaic forms of Hailey–Hailey disease have been described and course along lines of Blaschko<sup>285</sup>; streaks of Hailey–Hailey disease may present during childhood in individuals with genomic *ATP2C1* mutations who develop a second mutation in the normal allele (type 2 mosaicism).<sup>286</sup>

Skin sections from the advancing border of a lesion show a suprabasal vesicle with acantholysis of epidermal cells that resembles a dilapidated brick wall. Mutations have been identified in *ATP2C1*, encoding a secretory calcium ( $\text{Ca}^{++}$ )/manganese ( $\text{Mn}^{++}$ )-adenosine triphosphatase (ATPase) pump of the Golgi apparatus.<sup>287</sup>

The cutaneous lesions of Hailey–Hailey disease are induced by several external stimuli, particularly heat, humidity, friction from ill-fitting clothing, exposure to ultraviolet light, and bacterial or candidal infection. Intervention includes avoidance of these precipitating factors through wearing lightweight clothing, avoidance of friction and overheating, and treatment with topical or systemic antimicrobials as required for colonization or infection. Patients may experience spontaneous improvement with exacerbations and remissions. Topical



**Figure 5-35** Porokeratosis. Multiple erythematous annular lesions surrounded by a wall-like ridge of scaling.



**Figure 5-36** Porokeratosis. Annular lesions with a hyperkeratotic peripheral wall-like ridge.

application of corticosteroids or calcineurin inhibitors<sup>288</sup> has been the mainstay of treatment for most patients; topical calcitriol has led to improvement as well.<sup>289</sup> Topical application of gentamicin led to lesional clearance in a patient with an *ATP2C1* premature stop mutation, attributed both to the antibacterial effect and to the ability of aminoglycoside therapy to induce readthrough of a pathogenic non-sense mutation<sup>290</sup>; oral antibiotics are used for recurrent secondary infections. Because of the role of sweating as an exacerbation, botulinum toxin type A injections have been useful for selected patients.<sup>291</sup> In persistent and disabling cases, oral retinoids,<sup>292</sup> photodynamic therapy,<sup>293</sup> ablative laser therapy, dermabrasion, or excision of involved regions followed by split-thickness skin grafts have been used.

## Porokeratoses

The porokeratoses are a group of hyperkeratotic disorders characterized by a thread-like raised hyperkeratotic border that shows a typical thin column of parakeratosis, or cornoid lamella, on histologic examination of lesional tissue.<sup>294,295</sup> The cornoid lamella can be more easily seen clinically by dermoscopy.<sup>296</sup> Porokeratosis is thought to be a disorder of dysregulated keratinization with epidermal cell hyperproliferation and premature apoptosis of keratinocytes.<sup>297</sup>

The porokeratoses may appear in several forms:

1. Classic porokeratosis of Mibelli
2. Linear porokeratosis
3. Porokeratotic eccrine ostial and dermal duct nevus (PEODDN)
4. Punctate porokeratosis
5. Porokeratosis palmaris et plantaris disseminata (PPPD)
6. Disseminated superficial actinic porokeratosis (DSAP).

Porokeratosis of Mibelli may manifest as one, a few, or many annular lesions that usually appear during childhood, enlarge over years, and persist indefinitely (Figs. 5-35 and 5-36).<sup>298</sup> Boys are affected more commonly than girls. The disorder has a predilection for the face, neck, forearms, and hands but also may affect the feet, ankles, buccal mucosa, and glans penis. Porokeratosis on the scalp may be associated with alopecia. The initial lesion begins as a crateriform hyperkeratotic papule that gradually expands to a plaque of circinate or irregular

contour measuring from a few millimeters to several centimeters in diameter. If several lesions are present, they are usually unilateral. The diagnostic feature of this disorder is the raised hyperkeratotic peripheral ridge, which has been compared to the Great Wall of China. Lesions are commonly mistaken for tinea corporis, warts, or granuloma annulare.

Linear porokeratosis presents in infancy or childhood as one to several collections of porokeratotic lesions that resemble porokeratosis of Mibelli but follow the lines of Blaschko, similar to epidermal nevi.<sup>299,300</sup> Ulcerated forms of linear porokeratosis have been described.<sup>301</sup>

PEODDN could be considered a form of linear porokeratosis, except that the porokeratosis involves adnexal structures, specifically the eccrine ostia and ducts and hair follicles.<sup>302-304</sup> PEODDN includes the previously termed *porokeratotic eccrine and hair follicle nevus* and *porokeratotic adnexal ostial nevus*. The nevus may be present at birth and if not, usually appears during the first years of life and occasionally during adulthood. Lesions present as multiple asymptomatic hyperkeratotic sometimes spiny papules and plaques, and punctate pits, often filled with a comedo-like keratin plug.<sup>305,306</sup>

The collections of papules tend to be distributed along Blaschko lines, particularly on the distal extremities, although lesions have been described on the face, proximal extremities, and trunk, including associated with unilateral breast hypoplasia. Lesions may be erythematous and eroded, especially during the neonatal period. Biopsy sections show a dilated eccrine acrosyringium and, in some cases, hair follicle with an overlying cornoid lamella. In most patients, the lesions are static, but progressive extension has been described. Spontaneous improvement of lesions on the extremities has been noted, whereas lesions on the palms and soles tend to persist. The association of spiky hyperkeratotic papules with deafness<sup>307</sup> and KID syndrome<sup>308</sup> have suggested that PEODDN results from a *GJB2* mutation (encoding connexin 26), which has now been demonstrated.<sup>309</sup>

Punctate porokeratosis presents as 1- to 2-mm punctate papules of the palms and soles during adolescence or adulthood. The peripheral raised rim may be difficult to appreciate, and differentiation from keraoderma punctata, Darier disease, and Cowden disease may require biopsy.

PPPD is an autosomal dominant variant of punctuate porokeratosis that occurs more often in males. Small “seed-like” keratotic papules

with a slightly elevated peripheral rim first develop during childhood or adolescence on the palms and soles. Lesions subsequently disseminate to other areas of the body, including parts not exposed to sunlight and the mucous membranes. Lesions may be asymptomatic to pruritic.

DSAP is the most common form of porokeratosis but rarely presents in its disseminated form during childhood<sup>310–312</sup> and only occasionally during late adolescence. Women are more often affected than men. An autosomal dominant disorder, most cases are sporadic and first show manifestations during the third or fourth decade of life. Lesions appear on sun-exposed areas of the skin, particularly on the lower legs and forearms, and are usually multiple, with most patients having more than 50 lesions. Most lesions measure 0.5 to 1 cm, with a range from 0.1 to 4.5 cm in diameter, and are asymptomatic to mildly pruritic. In contrast to the borders of the lesions of porokeratosis of Mibelli, the ridges are only slightly elevated above the cutaneous surface. Several individuals have been described with both DSAP and linear porokeratosis. Linear porokeratosis may be present during childhood in patients with DSAP as type 2 mosaicism with mutation in the normal allele (loss of heterozygosity), leading to an earlier and more severe lesion distributed along a line of Blaschko with DSAP appearing later, especially after ultraviolet light exposure.<sup>310,312–314</sup> Disseminated superficial porokeratosis is also autosomal dominant and has its onset during the third or fourth decade of life. Lesions primarily occur on the extremities and are bilaterally symmetric but do not spare sun-protected areas, as occurs in DSAP.

DSAP is a genetically heterogeneous disorder that has been shown to result most often from mutations in *MVK*, the gene encoding mevalonate kinase, which plays a role in regulating calcium-induced keratinocyte differentiation and could protect keratinocytes from apoptosis induced by UV light, a known trigger.<sup>315</sup> Immunosuppression (e.g., HIV infection or organ transplantation<sup>311</sup>) can also trigger the appearance of disseminated porokeratotic lesions.<sup>316</sup> *SLC17A9* (Solute carrier family 17, member 9) mutations also result in DSAP,<sup>317</sup> and other gene loci have been linked.<sup>318–320</sup>

Porokeratosis is a feature of CDAGS syndrome, an autosomal recessive disorder characterized by craniostenosis and clavicular hypoplasia, delayed closure of the fontanel and deafness, imperforate or anteriorly displaced anus, genitourinary malformations (especially hypospadias and urethrorectal fistula), and the porokeratotic skin eruption.<sup>321,322</sup> Other features include hearing loss and nonscarring alopecia.<sup>322</sup> The lesions typically affect the face (especially cheeks and chin) and extremities (elbows, knees, dorsal aspect of hands). The disorder has been mapped to chromosome 22q12-13,<sup>323</sup> but the underlying molecular defect is unknown.

Lesions of porokeratosis are slowly progressive and relatively asymptomatic but may require intervention for cosmesis. The development of squamous cell carcinoma or Bowen disease within lesions has occasionally been reported with all forms except the punctuate form, but the risk is highest with long-standing lesions. A variety of therapies have been used, many unsuccessfully, to destroy the abnormal clone of keratinocytes. Among these are keratolytics, diclofenac gel,<sup>324</sup> topical and oral retinoids,<sup>325,326</sup> topical imiquimod,<sup>327</sup> topical 5-fluorouracil, cantharidin,<sup>328</sup> cryotherapy, electrode desiccation, laser ablation,<sup>329,330</sup> photodynamic therapy with methyl aminolevulinate cream,<sup>331–333</sup> dermabrasion, curettage, and excision.

## Palmoplantar Keratodermas

Palmoplantar keratodermas (PPK; palmar and plantar hyperkeratosis, keratoderma of the palms and soles) describes a diffuse or localized thickening of the palms and soles that may occur as part of a genetic disorder or as an inflammatory disorder such as pityriasis rubra pilaris, psoriasis, or reactive arthritis (see Chapter 4).<sup>334,335</sup> Genetic forms of PPK may appear alone or as part of a more generalized disorder such as epidermolysis bullosa simplex and Kindler syndrome (see Chapter 13), LI, EI, Sjögren-Larsson syndrome, Conradi syndrome (see **Conradi-Hünermann-Happle Syndrome** section), pachyonychia congenita (PC), or hidrotic ectodermal dysplasia (see Chapter 7). Several classification systems have been proposed for the inherited forms of PPK, the simplest of which is diffuse, focal, or punctate PPK. The identification of the underlying molecular defect allows further

classification. Finally, a classification by functional subgroup has also been proposed and includes abnormalities in structural proteins (keratins), cornified envelopes (loricrin), cell-cell communication (connexins), cohesion (desmoplakin 1, desmoglein 1, plakophilin), and transmembrane signaling (cathepsin C).<sup>336</sup> Hereditary forms of PPK often first manifest when the affected child starts to walk and are usually symmetrical. Diffuse forms may initially appear focal, but the more extensive involvement is notable within the first few years of life.

In general, the treatment of all forms of hyperkeratosis of the palms and soles is palliative and consists of application of keratolytic formulations, such as 10% to 20% salicylic acid in a thick emollient cream (under occlusion at night if tolerated), intermittent use of Keralyt gel or 40% salicylic acid (Mediplast) plasters, periodic soaking of the affected area in water, and gentle removal of excessive keratinous material by a pumice stone, scalpel, or single-edged razor blade. Painful fissures can be treated by a formulation of 30% tincture of benzoin in zinc oxide or cyanoacrylate (Superglue) before the application of a keratolytic formulation. Patients should wear comfortable shoes and avoid pressure or friction to affected areas. Although oral retinoids are helpful, they are recommended only for short-term use for the temporary relief of individuals with significant disability; topical retinoids may be helpful for more limited keratoderma. Surgical excision and grafting has been used with variable results.<sup>337</sup> Specific therapeutic recommendations are noted below for certain forms of PPK.

## DIFFUSE KERATODERMAS

Epidermolytic PPK (EPPK; Vörner type) is an autosomal dominant disorder characterized by sharply circumscribed congenital thickening of the palms and soles (Fig. 5-37). Most patients have hyperhidrosis, which may lead to maceration and fissuring. The waxy hyperkeratosis, limited to the palms and soles, is surrounded by an erythematous border. Transgrediens (to the dorsal surface) may be seen, and some patients show thickened skin over the joints (knuckle pads).<sup>338,339</sup> Mild thickening over the elbows and knees may occur. An associated odor suggests secondary bacterial or fungal infection. Biopsy sections often show epidermolytic hyperkeratosis similar to that seen in EI, although more than one sample may be required to demonstrate the epidermolysis. Blistering, however, is not usually seen except the increased fragility that can occur with retinoid therapy. The disorder results from mutations in keratin 9, a form of keratin protein expressed only in the palms and soles.<sup>340</sup> Personalized ribonucleic-acid interference (RNAi)-based therapy has been developed in a *KRT9*-mutated mouse model of EPPK.<sup>341</sup>

Diffuse nonepidermolytic PPK (NEPPK; Unna type) is an autosomal dominant genodermatosis that clinically is indistinguishable from EPPK other than tending to be milder, but it does not show epidermolysis in biopsy sections. This form of PPK has been attributed largely to mutations in noncritical regions of the gene that encodes



**Figure 5-37** Epidermolytic palmoplantar keratoderma. Waxy thickening is limited to the palms and soles and usually surrounded by an erythematous border. This is an autosomal dominant disorder, as shown in mother and daughter.



**Figure 5-38** Knuckle pads. These hyperkeratotic plaques can be seen as an isolated entity but may be associated with palmoplantar keratoderma.

keratin 1 and to mutations in *KRT6a* or *16* (without the nail changes of PC, also caused by mutations in these genes).<sup>342</sup> Greither syndrome, with transgrediens involvement in a glove-and-sock distribution, is considered a more severe form of diffuse NEPPK, and mutations have been found in *KRT1*.<sup>343</sup> Diffuse NEPPK is a component of Naegeli-Franceschetti-Jadassohn syndrome and dermatopathia pigmentosa reticularis, allelic disorders resulting from mutations in *KRT14* that are also characterized by abnormal sweating, reticulate hyperpigmentation, absence of dermatoglyphics, and other ectodermal anomalies (see Chapter 7).<sup>344,345</sup>

PPK associated with hearing loss occurs in individuals with Vohwinkel syndrome, an autosomal dominant mutilating keratoderma characterized by extensive PPK with a distinct “honeycomb” pattern and constrictions (pseudoainhum) that may lead to amputation of distal digits.<sup>346</sup> In some cases, distinctive hyperkeratotic starfish-like plaques are present over the elbows, knees, and sometimes the knuckles. Sensorineural deafness is a common accompanying feature. Mutations in the *GJB2* gene encoding connexin 26 underlie Vohwinkel syndrome with deafness and are also responsible for KID syndrome, nonmutilating PPK with deafness, knuckle pads, and leukonychia (Bart–Pumphrey syndrome).<sup>347,348</sup> Knuckle pads can also be a feature of other forms of PPK<sup>336,338,349</sup> and occur as an isolated entity (Fig. 5-38).<sup>350</sup> The ichthyotic variant of Vohwinkel syndrome also shows PPK with a honeycomb appearance and pseudoainhum but has associated ichthyosis and no deafness (see *Loricrin Keratoderma* section, above).

Clouston syndrome (hidrotic ectodermal dysplasia) is an autosomal dominant condition that results from mutations in the *GJB6* gene encoding connexin 30 (see Chapter 7).<sup>351</sup> Keratoderma (hyperkeratosis) of the palms and soles is common and may be diffuse or focal. It occasionally extends to involve the sides and dorsal aspects of affected hands and feet. Nails grow slowly and may appear thickened or thinned, striated, discolored, brittle, or hypoplastic. The tips of the digits show pseudoclubbing (see Chapter 7, Fig. 7-22), and hyperpigmentation may overlie digital joints. Paronychial infections are common and may result in partial to complete destruction of the nail matrix. Body hair may be sparse, eyebrows and eyelashes may be thinned or absent, and the skin has a smooth texture. Scalp hair, generally normal during infancy and childhood, may become thin, fragile, or sparse to absent after puberty.

Mal de Meleda (keratosis palmoplantaris transgrediens) is an autosomal recessive form of diffuse PPK associated with inflammatory keratotic plaques that extend to the dorsal aspects of the hands and feet and may overlie joints (Fig. 5-39).<sup>352</sup> Hyperhidrosis, superinfection, and occasionally perioral erythema, brachydactyly, and nail abnormalities may be associated. Female carriers may show mild PPK with interdigital fissures and keratotic papules.<sup>353</sup> Flexion contractures and spontaneous amputation of the digits occurs in severe cases. Mal de Meleda is the result of mutations in *ARS* component B, which encodes *SLURP-1*.<sup>354,355</sup> The role of *SLURP-1* in epidermal homeostasis and tumor necrosis factor (TNF)  $\alpha$  inhibition explains the hyperproliferative and inflammatory phenotype.



**Figure 5-39** Mal de Meleda palmoplantar keratoderma. Diffuse plantar keratoderma overlying erythema that extends to the dorsal aspects of the feet and hands. The Mal de Meleda type is one of the few autosomal recessive forms of hereditary palmoplantar keratoderma.



**Figure 5-40** Olmsted syndrome. Mutilating, painful plaques of keratoderma on the palms and soles begin during infancy to early childhood.

Olmsted syndrome (mutilating PPK with periorificial plaques) is a rare autosomal dominant disorder characterized by the progressive development of mutilating, painful plaques of keratoderma on the palms and soles that begins during infancy to early childhood (Fig. 5-40).<sup>356,357</sup> The borders of the keratoderma tend to be erythematous, and hyperkeratotic plaques may affect intertriginous folds. Contractures and autoamputation from progressive constriction of the digits are common. Periorificial areas become thickened and fissured to varying degrees. Patients often show alopecia, corneal defects, and nail dystrophy. The risk of cutaneous squamous cell carcinoma is increased. Olmsted syndrome results from mutations in *TRPV3* (transient receptor potential cation channel, subfamily V, member 3),<sup>358,359</sup> which encodes a cation channel in the skin and brain that senses temperature and regulates vasoconstriction; this channel also plays a role in regulation of calcium-ion transport and hair cycling, which may explain the PPK and alopecia of Olmsted syndrome. Oral retinoids can be helpful in decreasing the keratoderma and the intense



**Figure 5-41** Huriez syndrome. Palmoplantar keratoderma is associated with sclerodactyly. Affected individuals have a high risk of developing local squamous cell carcinoma.

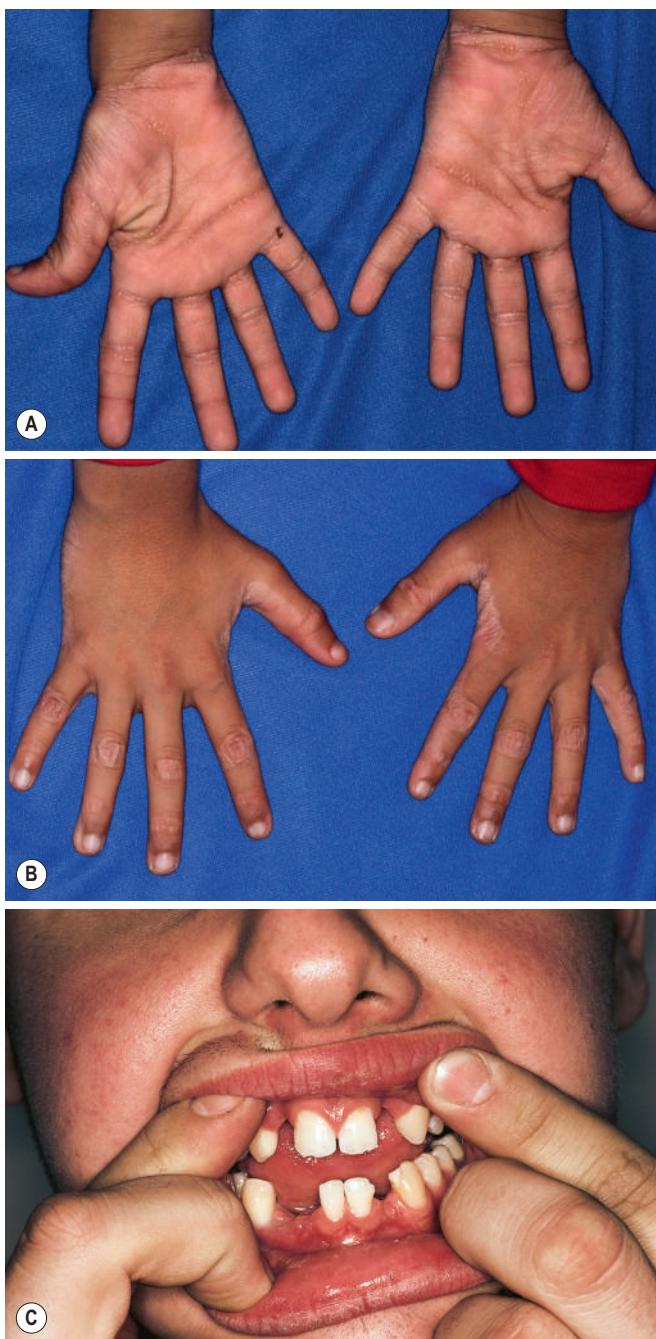
associated discomfort.<sup>360</sup> In addition to oral retinoids, EGFR inhibitors have been shown to improve the PPK.<sup>361</sup> Full-thickness excision of plaques with skin grafting has been successful in several patients.<sup>362</sup>

X-linked Olmsted syndrome has been linked to mutations in *MBTPS2*, and is allelic with IFAP and keratosis follicularis spinulosa decalvans (KFSD) syndrome (see Chapter 7).<sup>363</sup> The alopecia and mutilating keratoderma can also be seen in PPK-congenital alopecia syndrome, which can be autosomal dominant and milder or autosomal recessive and associated with pseudo-ainhum, sclerodactyly (which must be distinguished from Huriez syndrome, see next paragraph), contractures, and sometimes cataracts; the underlying cause is unclear.<sup>364</sup>

Sclerotylosis (Huriez syndrome, PPK with scleroatrophy) is an autosomal dominant PPK that presents at birth with a diffuse, symmetric keratoderma of the palms and soles. The fingers have a pseudosclerodermatous appearance with scleroatrophy (Fig. 5-41),<sup>365</sup> often with contractures and sometimes with reticulate erythema on the dorsal surface. Raynaud phenomenon is not associated. Nail abnormalities including longitudinal ridging, hypoplasia, and clubbing have been reported. Patients show an increased risk of developing squamous cell carcinoma of the palms or soles during the third and fourth decades,<sup>366</sup> and bowel cancer has been described. The gene has not yet been identified but is mapped to 4q23.<sup>367</sup> Sclerodactyly and PPK with an increased risk of squamous cell carcinoma are also features of Micali syndrome,<sup>368,369</sup> an autosomal recessive disorder that results from mutations in *RSPO1*, mapped to 1q34 and encoding R-spondin 1.<sup>370,371</sup> Variable features include chronic periodontal disease with early loss of teeth, bilateral cataracts and optic-nerve colobomata, and hypertriglyceridemia.

Deficiency of R-spondin 1 in males results in PPK and the risk of squamous cell carcinoma alone, but in female individuals with 46XX leads to sex reversal with the development of ambiguous genitalia, hypospadias, hypoplastic testes, and low testosterone levels.

Naxos disease and Carvajal syndrome (PPK with arrhythmogenic cardiomyopathy) are autosomal recessive forms of PPK associated with an early risk of sudden death from cardiac arrhythmia.<sup>372–375</sup> The keratoderma, which develops during infancy, tends to be more diffuse in Naxos disease and more striate in Carvajal syndrome. Patients with Carvajal syndrome also progressively develop striated lichenoid keratoses of the flexural areas and follicular keratoses of the knees and elbows. Both are associated with woolly hair from birth. The prominent cardiac abnormalities including electrocardiograph (ECG) changes, ventricular arrhythmias, and ventricular structural alterations may not become clinically apparent until the middle of the second decade of life. In general, right ventriculopathy has been associated with Naxos disease and left ventriculopathy with Carvajal



**Figure 5-42** Papillon-Lefèvre syndrome. Focal plaques of palmoplantar keratoderma (**A**) with transgrediens extension (**B**) are associated with the progressive periodontitis (**C**) and periosteal changes of the alveolar bone that begins during infancy or early childhood and result in loss of both deciduous and permanent teeth.

syndrome, but some patients have abnormalities of both ventricles.<sup>374</sup> The disorders result from mutations in *JUP*, which encodes the desmosomal component plakoglobin,<sup>376</sup> or in *DSP*, which encodes desmoplakin. Keratoderma and woolly hair but not cardiomyopathy can occur in individuals with mutations in *KANK2*, which encodes a non-desmosomal protein that controls activation of steroid receptors including the vitamin D receptor.<sup>377</sup>

The Papillon-Lefèvre syndrome and its variant, Haim-Munk syndrome, are autosomal recessive disorders that usually first show erythema and diffuse to localized psoriasiform hyperkeratosis of the palms (Fig. 5-42, A) and especially the soles during infancy or early childhood, coinciding with the timing of eruption of the primary

teeth.<sup>378–380</sup> The keratoderma often extends to the dorsal aspects of the hands and feet (Fig. 5-42, B). Psoriasisiform lesions occur on the knees and elbows. Rapidly progressive periodontitis and periosteal changes of the alveolar bone result in loss of both deciduous and permanent teeth (Fig. 5-42, C). Gingival involvement may manifest as early as 1 year of age and tends to be present by 5 years of age. Patients are usually edentulous by 15 years. Late-onset periodontitis after several years of PPK has also been described.<sup>381</sup>

Although an increased risk of acral lentiginous melanoma has been suggested, the reports are primarily in the Japanese population, which has a high incidence of this melanoma.<sup>382</sup> Haim–Munk syndrome (in individuals descended from Cochin, India) has the additional features of arachnodactyly, acroosteolysis, and onychogryphosis but not the calcification of the falk cerebri or susceptibility for bacterial infection described in some patients with Papillon–Lefèvre syndrome.<sup>383</sup>

Both disorders result from mutations in the *CTSC* gene, encoding cathepsin C, leading to impaired innate immune responses and desquamation from activation of serine proteases.<sup>384,385</sup> Diffuse NEPPK and chronic periodontal disease with loss of teeth are also a feature of Micali syndrome (see below). Papillon–Lefèvre syndrome responds well to topical tazarotene 0.1% cream or low-dose acitretin therapy.<sup>386</sup>

## FOCAL KERATODERMAS

PC describes a group of autosomal dominant conditions characterized most prominently by a characteristic nail dystrophy in association with painful plantar keratoderma that has a great impact on quality of life (see Chapter 7; Figs. 7-60 and 7-61). Mutations occur in one of five keratins: *KRT6a*, *KRT6b*, *KRT6c*, *KRT16*, and *KRT17*.<sup>387,388</sup> Presentation with focal PPK alone with minimal or no nail changes occasionally is caused by mutations in *KRT16* but is typical with mutations in *KRT6c*.<sup>389</sup> High-frequency ultrasound has shown bullae underlying the plantar keratoderma, which likely contribute to the pain.<sup>390</sup> Treatment is difficult, and only mechanical treatments, topical retinoids, and topical steroids have shown significant therapeutic efficacy.<sup>391</sup>

Striate PPK is an autosomal dominant condition characterized by focal keratoderma on the soles that often develops during infancy. Focal or characteristic streaks of keratoderma may develop on the palmar surface, especially if traumatized. Plantar involvement is nummular, not linear. The condition results from mutations in the gene encoding either desmoplakin or desmoglein-1<sup>392–396</sup> and affects the ability of keratin filaments to attach to the cell membrane. Striate PPK can be a feature of Carvajal syndrome and children with Costello syndrome.<sup>397</sup>

PPK and deafness due to mutations in the mitochondrial genome occur in the mitochondrial transfer RNA (tRNA) encoding the *MTTS1* gene. The focal PPK is typically first seen at 5 to 15 years of age.<sup>398</sup> Most prevalent over the plantar surface, keratotic plaques may also develop on the palm and at other pressure sites including the knees and elbows, Achilles tendons, and the dorsal surface of the toes. Palmar involvement is most pronounced in adults who are manual workers. Hearing loss occurs in approximately 60% of patients, and the PPK occurs in approximately 30%.

Richner–Hanhart syndrome (tyrosinemia type II) is an autosomal recessive disorder caused by a deficiency of hepatic tyrosine aminotransferase (mutations in the *TAT* gene)<sup>399</sup> and resulting in accumulation of tyrosine.<sup>400</sup> The early cutaneous lesions may be seen during childhood as sharply demarcated, yellowish keratotic papules of the palmar and plantar surfaces and sometimes occur during the late teenage years. The lesions become more erythematous, erosive, and painful with time. Nail dystrophy may be associated. Photophobia and bilateral tearing commonly occur within the first 3 months of life and progress to corneal erosions; herpetic ulceration is often erroneously diagnosed. Mildly affected individuals have been described, and may have just focal PPK with mild or no ocular manifestations.<sup>401,402</sup> The treatment of choice is dietary restriction of tyrosine with a low phenylalanine, low tyrosine diet.

Howel–Evans syndrome (tylosis with esophageal cancer) is a late-onset form of autosomal dominant focal PPK associated with the development of mucosal squamous cell carcinoma in 95% of affected patients by the age of 65 years, particularly of the esophageal mucosa

(38-fold increased risk).<sup>403</sup> The PPK is most prominent on pressure areas on the soles and is usually fully penetrant with the onset between 6 and 12 years of age. Palmar involvement is most prominent in manual laborers. Frictional hyperkeratosis may occur at other areas of trauma such as the elbows and knees, and oral leukokeratosis is often seen. Follicular hyperkeratoses are common and may be the initial manifestation in younger patients. The condition results from mutations in *RHBDF2*, which encodes the inactive rhomboid protease iRhom2 and results in dysregulation of EGFR signaling.<sup>404</sup>

Keratosis punctata palmaris et plantaris is an autosomal dominant disorder characterized by discrete keratoses of the palms and soles.<sup>405–407</sup>

Confined to the palmoplantar creases and volar aspects of the fingers, the central keratinous plug may be lost or can be picked out, leaving a shallow depressed pit with a keratotic base. Lesions can be particularly painful when walking or from pressure on the hands in persons who perform manual labor. The disorder results from mutations in one of two genes: heterozygous mutations in *AAGAB*,<sup>408,409</sup> which encodes a protein that participates in membrane trafficking of EGFR and other proteins, and *COL14A1*, which encodes collagen 14.<sup>410</sup> Oral retinoids have been used as treatment.<sup>411</sup> Punctate papules of the palms and soles are also a feature of porokeratosis punctata palmaris et plantaris, Cole disease (in association with guttate hypopigmentation),<sup>412,413</sup> keratosis punctata of the palmar creases, Darier disease, and Cowden syndrome (see Chapter 9).<sup>414</sup>

Aquagenic wrinkling of the palms (also called *acquired aquagenic PPK*, *aquagenic syringeal acrokeratoderma*, and *transient aquagenic palmar hyperwrinkling*) is a transient and recurrent keratoderma of the palms and lateral fingers induced by exposure to water.<sup>415–417</sup> Exposure to water elicits a whitening of the wet palm within a few minutes and visible thickening ("hand in the bucket sign"), often associated with a tight, tingling, pruritic, or even painful sensation (Fig. 5-43). The cause is thought to be influx of water across an osmotic gradient into eccrine ducts. Aquagenic wrinkling of the palms was originally described in patients with cystic fibrosis,<sup>418,419</sup> is most obvious in patients with the *DeltaF508* mutation,<sup>420</sup> and may be a cutaneous sign of carriers of cystic fibrosis.<sup>421,422</sup> Aquagenic wrinkling can also be seen in individuals with increased sweat chloride levels but without cystic fibrosis.<sup>423</sup> Unilateral involvement has been described in a child.<sup>424</sup> Tobramycin can induce aquagenic wrinkling without exposure to water.<sup>425</sup> Palmar injection of botulinum toxin has been used for symptomatic patients.<sup>426</sup> The lesions must be distinguished from hereditary papulotranslucent acrokeratoderma, an autosomal dominant disorder with onset during childhood with persistent palmar papules,<sup>427</sup> although exposure to water may lead to worsening. This condition also often begins at puberty and is often accompanied by palmar hyperhidrosis.

Exposure to water can also lead to a white, spongy appearance in autosomal dominant diffuse nonepidermolytic PPK in individuals with mutations in *AQP5*, encoding water-channel protein aquaporin-5.<sup>428</sup> This white, spongy reactivity to water exposure is also



**Figure 5-43** Aquagenic wrinkling of the palms. The palm becomes whitened and thickened within a few minutes after exposure to water.

seen in "Nagashima-type" palmoplantar keratosis, an autosomal recessive diffuse PPK in individuals of Japanese and Chinese descent. The PPK is well demarcated and erythematous with transgrediens extension to the dorsal surfaces of the hands and feet and the Achilles tendon but is mild and nonprogressive, in contrast with Mal de Meleda PPK. Nagashima-type PPK results from loss-of-function mutations in *SERPINB7*, which encodes a serine protease inhibitor, suggesting that the enhanced water permeation is caused by activation of proteases.<sup>429–431</sup>

Hereditary acrokeratoelastoidosis (of Costa) is a rare autosomal dominant disorder characterized by persistent, asymptomatic, whitish papules and plaques that are most prevalent at the margins of the hands (especially thenar and hypothenar areas) and pressure areas on the palms and soles (border of ventral and dorsal areas).<sup>432</sup> Lesions are sometimes found on the knuckles and nailfolds. The condition can begin during infancy but usually begins during adolescence. Biopsy of acrokeratoelastoidosis shows hyperkeratosis, acanthosis, and decreased numbers of coarsely fragmented elastic fibers in the dermis. Aquagenic PPK can be associated.<sup>433</sup> Although generally bilateral, unilateral involvement has been described.<sup>434</sup> The underlying genetic basis is unknown.



The complete list of 434 references for this chapter is available online at <http://expertconsult.inkling.com>.

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# 6

# Heredity Disorders of the Dermis

Several hereditary disorders of the skin primarily manifest as disorders of the dermis. Clinical manifestations range from laxity of skin to infiltrated papules and from rigidity to thinning of dermis. Disorders of mucopolysaccharides are reviewed in Chapter 24.

## Ehlers–Danlos Syndrome

Ehlers–Danlos syndrome (EDS) consists of a group of six inherited disorders of collagen characterized by increased cutaneous elasticity, hyperextensibility of the joints, and fragility of the skin, sometimes with the formation of pseudotumors and large gaping scars.<sup>1,2</sup> The 1997 Villefranche classification<sup>3</sup> is still used with some refinements and includes autosomal dominant (AD) and autosomal recessive (AR) forms; the genetic and clinical characteristics of the major subtypes of EDS are reviewed in Table 6-1. Most forms of EDS are linked to mutations in genes encoding fibrillar collagens, enzymes involved in posttranslational modification of these proteins, and extracellular matrix proteins. Mutations in type V and type III collagen cause classic or vascular EDS, respectively, whereas mutations involving the processing of type I collagen are involved in the kyphoscoliosis, arthrochalasis, and dermatosparaxis type of EDS.

The prevalence of EDS, including the mild forms, may be as high as 1:5000 individuals. The spectrum of severity of EDS ranges from almost imperceptible findings to severe, debilitating disease. Most common is the classical type (Box 6-1). The vascular type tends to be most devastating. The kyphoscoliosis, arthrochalasis, and dermatosparaxis types are considerably less common than other forms. The effect on quality of life can be considerable, and three-quarters of affected individuals report fatigue that may be impacted by pain, sleep disturbance, difficulty with concentration, and diminished social functioning.<sup>4</sup>

The skin of individuals with the classic type is velvety, soft, and has a doughy consistency. After being stretched, it returns to its normal position as soon as released, in contrast to the lax skin of cutis laxa. Skin hyperextensibility should be tested at a site not subjected to mechanical forces or scarring, such as the volar surface of the forearm (Fig. 6-1). In contrast to 10% of apparently normal individuals, approximately 50% of patients with EDS can touch the tip of their nose with their tongue (Gorlin sign) (Fig. 6-2). In addition, the skin of the hands, feet, and at times the elbows tends to be lax and redundant, thus resulting in a loose-fitting glove- or moccasin-like appearance. A number of patients have pressure-induced herniation of subcutaneous fat on the wrists or on the medial or lateral aspect of the heels, evident when the patient is standing (piezogenic pedal papules) (Fig. 6-3).<sup>5</sup> In addition to abnormal elasticity, the skin of patients with the classical (but not the hypermobile) form of EDS is extremely fragile, and minor trauma may produce gaping “fishmouth” wounds (Fig. 6-4). It has poor tensile strength and cannot hold sutures properly. This leads to dehiscence, poor healing, and the formation of wide, papyraceous, wrinkled hernia-like scars, particularly over areas of trauma (such as the forehead, elbows, knees, and shins). Blood vessels are fragile, resulting in hematomas and a chronic bruise-like appearance, particularly on the anterior aspect of the lower extremities (Fig. 6-5). The resolution of hematomas is accompanied by fibrosis, which produces soft subcutaneous nodules (pseudotumors) and calcified subcutaneous nodules, especially on the shins and forearms (spheroids). Hyperextensible joints may result in “double-jointed” fingers or subluxation of larger joints (Fig. 6-6). This may occur spontaneously or follow slight trauma. Generalized hypermobility is determined by a score of 5 or higher in the 9-point scale established by Beighton and colleagues<sup>3</sup> (Fig. 6-7; Table 6-2). Sprains, dislocations or subluxations, and pes planus occur as complications, and patients complain of

chronic joint and limb pain despite normal skeletal radiographs.<sup>6</sup> Muscle hypotonia and delayed gross motor development have been described. Hiatal hernia, postoperative hernias, and anal prolapse have been noted as manifestations of the tissue hyperextensibility and fragility.<sup>7</sup> Anomalies of the heart and dissecting aortic aneurysms have rarely been described in the classical form<sup>8</sup> in contrast to the arterial form. Mitral valve prolapse is a common manifestation, but aortic root dilation is uncommon; both can be assessed by echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI) examinations.<sup>7</sup>

The diagnosis of classical EDS is primarily clinical. Routine histopathologic examination of skin from patients with EDS is usually normal but may show loose collagen and irregular fibroblasts<sup>9</sup>; electron microscopy demonstrates disorganized collagen fibers and fibrils with variable cross-sectional diameters. Studies of platelet function and coagulation are usually normal despite a tendency for bruising and increased bleeding, further implicating the defective structural integrity of skin and blood vessels.

The underlying molecular defect for 93% of patients with the classical form of EDS is mutations in the  $\alpha 1$  or  $\alpha 2$  chain of type V collagen, often leading to haploinsufficiency.<sup>10,11</sup> Type V collagen is a minor fibrillar collagen that regulates collagen fibril diameter. Patients with mutations in *COL1A1* at a nonglycine site (mutations at glycine sites lead to osteogenesis imperfecta [OI]) may exhibit features of classic EDS alone or with subtle features of OI (blue sclera, relatively short stature, osteopenia, or fractures).<sup>12</sup> Some children with nonglycine substitutions in type I collagen have classic EDS but develop spontaneous arterial rupture during adulthood.<sup>13</sup>

Several variants resemble classical EDS (see Table 6-1). A “classic-like” autosomal recessive form of EDS, caused by deficiency of the extracellular matrix protein tenascin-X, shows typical EDS but normal wound healing.<sup>14,15</sup> Heterozygous carriers may exhibit only joint hypermobility. A contiguous gene syndrome caused by a 6p deletion can present with tenascin-X deficiency as well as congenital adrenal hyperplasia (deletion in *CYP21A2*) with or without ovarian failure (deletion in *MSH5*).<sup>16,17</sup> The periodontal type (formerly type VIII EDS) is a variant of the classic type of EDS and shows variable inter- and intrafamilial clinical manifestations (including patients without skin or joint abnormalities).<sup>18</sup> The periodontal type is associated with periodontitis, a marfanoid body habitus, prominent eyes, and a short philtrum.<sup>19,20</sup> Patients with progeroid EDS (PEDS) exhibit loose, wrinkled facial skin; fine, curly hair; sparse eyebrows and eyelashes; downslanting palpebral fissures; developmental delay; skeletal abnormalities (spondyloepiphyseal dysplasia with bone fragility and severe kyphoscoliosis); and cutaneous and joint findings of classical EDS.<sup>21,22</sup> This variant is caused by biallelic mutations in either galactosyltransferase I ( $\beta 4GALT7$ ) or II ( $\beta 3GalT6$ ), key enzymes in initiating glycosaminoglycan (GAG) synthesis.<sup>22-24</sup>

Patients with the hypermobile type show extensive joint hypermobility and dislocations, particularly of the shoulder, patella, and temporomandibular joints. The skin is often soft and velvety but heals well and only occasionally shows hyperextensibility. Given that up to 40% of school-age children may show a score of 5 or higher using the 9-point Beighton criteria, the diagnosis of hypermobility-type EDS may be difficult.<sup>25</sup> It is also hard to distinguish from benign joint hypermobility syndrome,<sup>26</sup> and the term *joint hypermobility syndrome* has been suggested to encompass any child with symptomatic joint hypermobility,<sup>25,27</sup> including those with hypermobility-type EDS. The autonomic burden of hypermobility-type EDS is as high as in fibromyalgia and is primarily characterized by orthostatic issues (dizziness or even transient loss of consciousness with postural change or standing), palpitations, shortness of breath, and gastrointestinal (GI) complaints.<sup>28</sup>

**Table 6-1** Classification of Ehlers–Danlos Syndrome

Type	Mutations	Skin Findings	Joint Changes	Inheritance	Other Comments
Classic*	<i>COL5A1</i> , <i>COL5A2</i> (usually haploinsufficiency)	Hyperextensibility, bruising, velvety skin, widened atrophic scars, molluscoid pseudotumors, spheroids	Hypermobility and its complications, joint dislocations	AD	Mitral valve prolapse Hernias
<b>CLASSIC VARIANTS</b>					
EDS/OI overlap	<i>COL1A1</i>	Classic EDS features		AD	Blue sclerae, short stature, osteopenia/fractures May have late arterial rupture
Cardiac valvular	<i>COL1A2</i>	Classic EDS features		AR	Severe cardiac valve issues as adult
Periodontal	Unknown	Can have classic EDS features	Can have hypermobility	AD	Periodontitis Marfanoid habitus Prominent eyes Short philtrum
Progeroid	$\beta 4GALT7$ or $\beta 3GalT6$ , encoding galactosyltransferase I or II, key enzymes in GAG synthesis	Classic EDS features	Hypermobility	AR	Loose facial skin, curly hair, alopecia, developmental delay, spondyloepimetaphyseal dysplasia with bone fragility, and severe kyphoscoliosis
Classic-like	<i>TNXB</i>	Hyperextensibility, marked hypermobility, severe bruising, velvety skin, no scarring tendency	Hypermobility	AR	Parents (especially mothers) with one <i>TNXB</i> mutation can have joint hypermobility
Hypermobility*	Unknown; some may have <i>COL5A1</i> mutations	Mild hyperextensibility, scarring, textural change	Hypermobility, chronic joint pain, recurrent dislocations	AD	Sometimes confused with joint hypermobility syndrome
Vascular*	<i>COL3A1</i>	Thin, translucent skin; bruising; early varicosities; acrogeria	Small joint hypermobility	AD	Abnormal type III collagen secretion; rupture of bowel, uterus, arteries; typical facies; pneumothorax
Kyphoscoliosis*	<i>PLOD</i> (deficient lysyl hydroxylase)	Soft, hyperextensible, bruising, atrophic scars	Hypermobility	AR	Severe muscle hypotonia, congenital kyphoscoliosis, scleral fragility and rupture, marfanoid habitus, osteopenia
<b>VARIANTS WITH KYPHOSCOLIOSIS</b>					
Spondylocheirodysplastic form	<i>SLC39A13</i> , which encodes the ZIP13 zinc transporter	Similar to kyphoscoliotic form		AR	Bone abnormalities but without congenital hypotonia and progressive kyphoscoliosis Moderate short stature, wrinkled palms with thenar and hypothenar atrophy, blue sclerae
Brittle cornea syndrome	<i>ZNF469</i> or <i>PRDM5</i>	Skin hypermobility	Joint hypermobility	AR	Kyphoscoliosis Characteristic thin, brittle cornea, ocular fragility, blue sclera, and keratoconus
FKBP14 deficient	<i>FKBP14</i>	Features of kyphoscoliotic EDS		AR	Sensorineural hearing loss Severe congenital generalized hypotonia improved by childhood
Musculocontractural	<i>CHST14</i> (encoding dermatan 4-O-sulfotransferase) or <i>DSE</i> (encoding dermatan sulfate epimerase)	Fragile, hyperextensible skin with atrophic scars and delayed wound healing	Hypermobility	AR	Progressive kyphoscoliosis, adducted thumbs in infancy, clubfoot, arachnodactyly, contractures, characteristic facial features, hemorrhagic diathesis
Arthrochalasis*	Exon 6 deletion of <i>COL1A1</i> or <i>COL1A2</i>	Hyperextensible, soft skin with or without abnormal scarring	Marked hypermobility with recurrent subluxations	AD	Congenital hip dislocation Arthrochalasis multiplex congenita Short stature
Dermatosparaxis*	Type I collagen N-peptidase <i>ADAMTS-2</i>	Severe fragility Sagging, redundant skin		AR	Also occurs in cattle

AD, Autosomal dominant; AR, autosomal recessive; EDS, Ehlers–Danlos syndrome; GAG, glycosaminoglycan; OI, osteogenesis imperfecta.

\*In original Villefranche classification.

### Box 6-1 Most Common Features of Classic Ehlers–Danlos Syndrome

- Autosomal dominant
- Skin
  - Hyperextensible
  - Velvety, doughy skin
  - Fragile, thin, poor tensile strength, gaping scars after wounding
  - Easy bruising
  - Pseudotumors and spheroids
  - Piezogenic papules
- Joints/extremities
  - Hypermobility
  - Sprains, dislocations
  - Pes planus
  - Chronic joint and limb pain
  - Muscle hypotonia, delayed motor development
- Hiatal hernia, anal prolapse
- Mitral valve prolapse



**Figure 6-1** Ehlers–Danlos syndrome (EDS). Skin hyperextensibility on the arm.



**Figure 6-2** Ehlers–Danlos syndrome (EDS). Gorlin sign is five times more common in EDS than in normal individuals. Note the scars on the forehead.



**Figure 6-3** Ehlers–Danlos syndrome. Piezogenic pedal papules are caused by pressure-induced herniation of subcutaneous fat, seen here on the lateral aspect of the heel.

The vascular type of EDS is characterized by extensive bruising and often thin, translucent skin that is not hyperextensible.<sup>7,29,30</sup> Joint hypermobility is usually limited to the digits, and only 17% of patients meet Beighton criteria.<sup>31</sup> The facial appearance is often typical, with sunken eyes, a thin upper lip, and decreased facial fat. Spontaneous rupture of arteries, particularly midsized arteries, may occur during childhood, although its peak age of incidence is the third or fourth decade of life.<sup>32,33</sup> Arterial or intestinal rupture often presents as acute abdominal or flank pain (including from GI bleeding or bowel perforation), and intracranial aneurysms may be associated with cerebrovascular accidents.<sup>34</sup> Arterial rupture is the most common cause of death. Pregnancies may be complicated by prepartum and postpartum arterial bleeding and by intrapartum uterine rupture. Vaginal and perineal tears from the delivery heal poorly, and pneumothorax occurs in 11% of affected individuals. In one series, 94% of patients with vascular EDS showed blue sclerae.<sup>31</sup>

The vascular form of EDS has been associated with mutations in type III collagen (*COL3A1*), resulting in a reduced amount of type III collagen in dermis, vessels, and viscera. The prognosis for individuals with null mutations in *COL3A1* is better than with missense or exonskipping mutations.<sup>35</sup>

Vascular EDS may be confused with periodontal EDS and Loeys–Dietz syndrome. The latter is an autosomal dominant disorder characterized by joint hypermobility with dislocations; soft velvety skin; arterial tortuosity; widespread vascular aneurysm and dissection<sup>36</sup>; and an increased risk of atopy.<sup>37</sup> The disorder has been divided into Loeys–Dietz syndrome type 1 and type 2. Patients with type 1 disease have a marfanoid habitus (but do not fulfill Ghent criteria for Marfan syndrome [MFS]), craniofacial abnormalities, and mutations in *TGFB1* (transforming growth factor [TGF]- $\beta$ 1 receptor), whereas patients with type 2 have mutations in *TGFB2R* and no craniofacial or skeletal anomalies.<sup>36</sup>

The kyphoscoliotic type of EDS is characterized by generalized joint laxity with severe muscle hypotonia at birth, which leads to gross motor delay and congenital progressive scoliosis.<sup>38</sup> Severe hypotonia is predominant during infancy, and patients are thought to have congenital muscular dystrophy or myopathies. By the second or third decade of life, patients tend to lose the ability to ambulate. The skin may be fragile and heals with atrophic scars. Easy bruising and arterial rupture have been described.<sup>39</sup> Patients often show a marfanoid habitus, osteopenia, and scleral fragility with rupture of the ocular globe. Because of *PLOD1* mutations, this form shows a deficiency of collagen lysyl hydroxylase. The diagnosis can be confirmed by finding a high ratio of lysyl pyridinoline (LP) to hydroxylysyl pyridinoline (HP) crosslinks (LP/HP) in the urine by high-performance liquid chromatography (HPLC).<sup>38,40</sup>

**A****B**

**Figure 6-4** Ehlers–Danlos syndrome. (A) Minor trauma results in a large wound on the shin. The wound dehisced despite placement of several sutures. (B) Healed wound seen in (A). Note the old discoloration and scarring on the affected leg.

The spondylocheiropathic form of EDS resembles the kyphoscoliotic form but lacks the severe muscular hypotonia from birth and progressive kyphoscoliosis. In contrast to the kyphoscoliotic form, the spondylocheiropathic form shows moderate short stature, wrinkled palms with thenar and hypothenar atrophy, blue sclerae but no other eye abnormalities, and a variety of bone abnormalities.<sup>41</sup> Biallelic mutations in *SLC39A13*, which encodes the zinc transporter protein ZIP13, important for intracellular zinc homeostasis, are causative.<sup>42,43</sup>



**Figure 6-5** Ehlers–Danlos syndrome. Blood vessels are fragile, resulting in hematomas and chronic discoloration of the anterior aspect of the lower extremities of this adolescent girl.



**Figure 6-6** Ehlers–Danlos syndrome. Hyperextensible joints may result in double-jointed fingers, as seen in this girl.

Musculocontractural EDS is a variant with characteristic facial features, multiple contractures, a hemorrhagic diathesis with large subcutaneous hematomas, and several other systemic complications; this variant has been linked to dysfunction of dermatan sulfate from mutations in both alleles of genes encoding dermatan 4-O-sulfotransferase (*CHST14*)<sup>44,45</sup> or dermatan sulfate epimerase (DSE).<sup>46</sup> Another variant with progressive kyphoscoliosis, congenital hypotonia, joint hypermobility, and hyperelastic skin results from mutations in *FK506*-binding peptidylprolyl cis-transisomerasases (*FKBP14*)<sup>47</sup>; the presence of sensorineural hearing loss aids in diagnosis. The brittle cornea syndrome (BCS), an autosomal recessive condition caused by mutations in either *ZNF469* or *PRDM5*, is characterized by thin, brittle cornea; ocular fragility; blue sclera; and keratoconus; as well as associated skin and joint hypermobility and kyphoscoliosis.<sup>48–50</sup> Lysyl hydroxylase production and urinary pyridinoline excretion are normal in these variants.

Patients with the arthrochalasis type show generalized joint hypermobility with severe recurrent subluxations and congenital bilateral hip dislocation. The skin may be hyperextensible, fragile, and easy to bruise. Early and significant muscle hypotonia, kyphoscoliosis, and mild osteopenia have been described. Mutations in *COL1A1* or *COL1A2* that result in skipping of exon 6 lead to defective collagen synthesis.<sup>51</sup>



**Figure 6-7** Marfan syndrome (MFS). The long arm span and decreased upper-to-lower body ratio are characteristic of the “marfanoid habitus.”

**Table 6-2** Brighton Scale for Generalized Joint Hypermobility ( $\geq 5/9$  Meets Criteria\*)

Finding	Negative	One Side	Both Sides
Passive flexion of thumb to forearm	0	1	2
Passive dorsiflexion of fifth finger >90 degrees	0	1	2
Hyperextension of elbows >10 degrees	0	1	2
Hyperextension of knees <sup>†</sup> >10 degrees	0	1	2

\*Present = 1.

<sup>†</sup>Touching the floor with palms open and knees fully extended.

The dermatosparaxis form of EDS is characterized by severe skin fragility with sagging, redundant skin<sup>52</sup>; wound healing leads to wide atrophic scars, especially past infancy.<sup>53</sup> The skin may be soft and doughy in texture with easy bruising. Characteristic facies, gingival hyperplasia, large umbilical and inguinal hernias, delayed closure of the fontanelles, postnatal growth failure, and premature rupture of the fetal membranes may be seen. Electrophoretic demonstration of pro-collagen  $\alpha 1(I)$  or  $\alpha 2(I)$  chains from collagen or cultured fibroblasts is seen with the arthrochalasis and dermatosparaxis forms.

## MANAGEMENT OF EHLERS–DANLOS SYNDROME

Management is mainly supportive, but cardiovascular work-up, physiotherapy, pain management, and psychological and genetic counseling may be important. Wearing a medical bracelet warning of EDS and carrying information for teachers and healthcare workers can be helpful. The Ehlers–Danlos National Foundation ([www.ednf.org](http://www.ednf.org)) is a national support group. Children with skin fragility should use protective pads on the shins, knees, and forehead to decrease the risk of laceration and bruising. Low-impact sports (such as swimming) are preferable to contact sports and weight training in patients with

hypermobility. Physical and occupational therapists or rheumatologists can suggest devices (such as splints and braces) to make movement more comfortable. Children with significant hypotonia or motor developmental delay should be referred for appropriate physical therapy to improve muscular strength and coordination. Pain medication should be tailored to individual needs. Psychological counseling to help develop coping strategies and treat depression can be important, especially in patients with hypermobility and chronic pain.

A baseline echocardiogram should be performed in all patients with EDS in order to evaluate aortic root diameter and cardiac valves. Echocardiograms should be repeated in children and adolescents approximately every 3 years if the results are normal and annually if results are abnormal. Patients who have mitral valve prolapse and regurgitation should be given prophylactic antibiotics to prevent bacterial endocarditis.

Surgical procedures present problems, because tissues are friable and difficult to suture. Therefore edges of wounds should be approximated without tension by closely spaced sutures in two layers (absorbable and retained), adhesive reinforcement (e.g., Steri-Strips) to minimize scar spread, and pressure bandages to aid healing, diminish scarring, and lower the risk of hematoma and pseudotumor formation. Sutures should be kept in place for at least twice as long as for normal skin, and use of absorbable suture material without removal has been proposed. Prophylactic antibiotics after injury and close monitoring for postoperative infection are important to minimize post-operative complications. Ascorbate is a cofactor that stimulates prolyl hydroxylase and lysyl hydroxylase, enzymes that catalyze the formation of hydroxyproline and hydroxylysine to promote collagen deposition. Doses of 2 to 4 g/day have been administered to patients with the kyphoscoliosis type to improve wound healing and decrease the bleeding tendency.<sup>54</sup> Ascorbic acid sometimes decreases the bleeding tendency in other types. Anti-inflammatory drugs may improve the musculoskeletal pain associated with EDS, but those interfering with platelet function and prolonging bleeding (acetylsalicylic acids, non-steroidal anti-inflammatory drugs [NSAIDs] other than celecoxib family) should be avoided in patients with significant bruising. Dental procedures require extra precautions as well, because of increased bleeding.<sup>55</sup> More than half of patients who undergo posterior spinal fusion for scoliosis develop various complications.<sup>56</sup>

In patients with the vascular type of EDS, invasive vascular procedures (such as arteriography and catheterization) increase the risk of vascular rupture and should be replaced by ultrasound and/or subtraction angiography. Surgery should be avoided if possible but may be required for arterial or bowel complications.<sup>57</sup> Manipulation of vascular and other tissues should be minimized if surgery is required. Celiprolol, a long-acting  $\beta_1$  antagonist and partial  $\beta_2$  agonist, decreased by threefold the incidence of arterial rupture or dissection in patients with vascular EDS.<sup>58</sup> Pregnancy for women with the vascular type of EDS is high risk (up to 12% die from uterine rupture or peripartum arterial rupture). Planned caesarean section may be preferable to vaginal delivery.<sup>59</sup> Infants with EDS are prone to premature birth because of early rupture of membranes.<sup>60</sup> Preterm delivery occurs in 40% of pregnancies with affected neonates and 21% of pregnancies of affected mothers.<sup>61–64</sup>

## Marfan Syndrome

MFS is an AD disorder that occurs in approximately 1 : 5000 persons<sup>65</sup> and affects primarily the skeletal, ocular, and cardiovascular systems.<sup>66–72</sup> Mutations primarily occur in the *FBN1* gene that encodes fibrillin-1 (66% to 91%) and rarely in *TGFBR1* or *TGFBR2*, the genes also associated with Loey–Dietz syndrome (see *Ehlers–Danlos Syndrome* section). Fibrillin-1 is secreted into the extracellular matrix and polymerizes to form microfibrils of the zonular fibers of the lens and are associated with elastic fibers in the aorta and skin.<sup>73,74</sup> The microfibrils stabilize latent TGF- $\beta$ -binding proteins (LTBPs), which bind to and maintain TGF- $\beta$  in an inactive state.<sup>68</sup> Deficiency of fibrillin-1 thus leads to TGF- $\beta$  activation. About 27% of cases occur by spontaneous mutation; recurrence as a result of parental germline mosaicism has been described.<sup>75,76</sup>

Diagnosis is best made by clinical examination (including careful cardiac evaluation and measurement of body proportions) (Box 6-2),

## Box 6-2 Most Common Features of Marfan Syndrome

- Autosomal dominant disorder
- Present in ≥75% of individuals with Marfan syndrome (MFS):
  - Positive wrist and thumb sign
- Present in ≥50% and <75% of individuals with MFS:
  - Dolichostenomelia\*
  - Pes planus
  - Joint hypermobility
  - Aortic root dilation
  - Mitral valve prolapse
  - High arched palate with crowded dentition
  - Typical facial features
  - Lens displacement (ectopia lentis)
- Present in ≥25% and <50% of individuals with MFS:
  - Pectus excavatum or carinatum requiring surgery
  - Myopia
  - Scoliosis
  - Striae

\*Dolichostenomelia refers to a habitus in which the limbs are unusually long, as is typical of MFS (*dolichos*, long; *steno*, narrow or close; *melia*, of the limbs).

echocardiography, slit-lamp ophthalmologic examination, and radiographs or imaging as needed to find criteria. Cardiac examinations should be repeated every year until adulthood.<sup>67,72</sup> Early diagnosis is critical because of the potentially fatal complications, but the clinical features evolve with advancing age and diagnosis is difficult. Family history is also important, but manifestations may not be evident until adolescence and expressivity is variable, so that generations appear to be skipped. The Ghent diagnostic criteria (Box 6-3) were simplified in 2010, eliminating major and minor criteria and giving more weight to ectopia lentis and aortic root aneurysm/dissection.<sup>77</sup> Other organ involvement contributes to a systemic score to guide diagnosis if aortic disease, but not ectopia lentis, is present. A more important role is assigned to genotyping *FBN1* and other relevant genes. Criteria now enable diagnosis of ectopia lentis; mitral valve prolapse and myopia, mild and nonprogressive aortic root dilation, marfanoid skeletal changes, and skin features (MASS); and mitral valve prolapse syndrome. Criteria are still less reliable in children, especially since several of the more specific features are age-dependent (e.g., aortic dilation, ectopia lentis, dural ectasia, protrusion acetabuli),<sup>66,67,78</sup> and care should still be made to avoid branding children unnecessarily with MFS, given the potential stigma and lifestyle restrictions.

Patients are often tall with long extremities ("marfanoid habitus"; see Fig. 6-7). The arm span characteristically is greater than the height, and after puberty the upper segment (vertex to pubis)-to-lower segment (pubis to sole) ratio is less than 0.86. Arachnodactyly, kyphoscoliosis, pectus carinatum or excavatum, and a hindfoot deformity or flat feet are commonly seen in patients with this disorder. Joint laxity from capsular, ligamentous, and tendinous involvement may cause hyperextensibility and/or dislocation. Patellar dislocation is not uncommon; dislocation of the hip, often detected during the newborn period, may be the first sign of MFS. The thumb sign (thumb extends well beyond the ulnar border of the hand when overlapped by fingers) and wrist sign (thumb overlaps the fifth finger as they grasp the opposite wrist) are screening tests for the joint hypermobility of MFS.<sup>79</sup> Dural ectasia is occasionally seen in children, and imaging is performed largely to consider an additional Ghent criterion for diagnosis, but its presence is nonspecific. Specific facial features and pneumothorax are additional criteria (see Box 6-3).

Lack of subcutaneous fat and the presence of striae, most prominent on the upper chest, arms, thighs, and abdomen, are the most common cutaneous manifestations of MFS. In addition, elastosis perforans serpiginosa (see *Elastosis Perforans Serpiginosa section*) occurs with increased incidence in patients with MFS.

The most common ocular abnormalities are lens displacement (ectopia lentis; the hallmark of ocular involvement, seen in at least 55% of affected children) and myopia (almost half of children). Retinal detachment, cataracts, or glaucoma may impair vision and cause blindness. Cardiovascular abnormalities occur in almost 70% of children with MFS. Dilatation of the aorta is the most common defect

## Box 6-3 Revised Ghent Criteria for Marfan Syndrome

Without a family history of Marfan syndrome (MFS), any of these combinations allow diagnosis:

1. Aortic diameter (Z score\* ≥2) AND ectopia lentis
2. Aortic diameter (Z ≥ 2) AND fibrillin-1 (*FBN1*) mutation
3. Aortic diameter (Z ≥ 2) AND systemic criteria (≥7 points; see criteria below)
4. Ectopia lentis AND fibrillin-1 (*FBN1*) mutation with known aortic diameter (Z ≥ 2)

With a positive family history, these features allow the diagnosis:

1. Ectopia lentis
2. Systemic criteria (≥7 points) (see criteria below)
3. Aortic diameter (Z ≥ 2 above 20 years old, ≥3 below 20 years old)

Alternative diagnoses (no family history of MFS):

Ectopia lentis syndrome: ectopia lentis with or without systemic criteria  
AND: (1) with an *FBN1* mutation but one not known to be associated with aortic diameter (Z ≥ 2) OR (2) no *FBN1* mutation  
MASS: aortic diameter (Z < 2) AND systemic criteria (≥5 with at least one skeletal feature) but without ectopia lentis  
MVP syndrome: MVP AND aortic diameter (Z < 2) AND systemic criteria (<5) without ectopia lentis

Systemic criteria (maximum total: 20 points; score >7 indicates systemic involvement):

Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)  
Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)  
Hindfoot deformity = 2 (plain pes planus = 1)  
Pneumothorax = 2  
Dural ectasia = 2  
Protrusio acetabuli = 2  
Reduced US/LS AND increased arm/height AND no severe scoliosis = 1  
Scoliosis or thoracolumbar kyphosis = 1  
Reduced elbow extension = 1  
Facial features (3/5) = 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)  
Skin striae = 1  
Myopia >3 diopters = 1  
MVP (all types) = 1

MASS, Mitral valve prolapsed and myopia, mild and nonprogressive aortic root dilation, marfanoid skeletal changes, and skin features; MVP, mitral valve prolapse; US/LS, upper segment/lower segment ratio.

\*Z score is the standard deviation from normal means of the inner to inner-edge diameter of the aortic root at the sinus of Valsalva, normalized for the subject's body surface area and age.

and is generally greatest at the sinuses of Valsalva, and diffuse dilation of the proximal segment of the ascending aorta with aortic regurgitation often occurs. Mitral valve prolapse occurs in approximately 60% of affected children and adolescents.<sup>80</sup> Left ventricular dilation may predispose to patients to alterations of repolarization and fatal ventricular arrhythmias.<sup>81</sup> The most severely affected children, those with neonatal MFS, almost always have aortic dilation and severely impaired valves, leading to congestive heart failure, pulmonary hypertension, and a risk of early death.<sup>76</sup> In a child diagnosed with MFS, serial echocardiography at 6- to 12-month intervals is recommended, the frequency depending on the aortic diameter in relation to the body surface area and the rate of increase. Pregnancy has been associated with significant cardiac complications (aortic dissection, arrhythmia), postpartum hemorrhage, thromboembolism, and premature and babies who are small for gestational age.<sup>82-84</sup>

Conditions most often considered when patients have cutaneous and other system concerns are vascular-type EDS (aortic root dilation or dissection), Loeys–Dietz syndrome (aortic root dilation or dissection), homocystinuria, and MASS. Patients with MFS do not have the translucent and velvety skin or easy bruising of EDS or Loeys–Dietz syndrome. Neither type I nor type II Loeys–Dietz syndrome includes myopia or ectopia lentis, and craniosynostosis, hypertelorism, and bifid uvula, features of Loeys–Dietz syndrome, are not features of MFS.<sup>68</sup> Homocystinuria is an autosomal recessive disorder caused by mutations cystathionine β-synthase in which patients also show ectopia lentis and a marfanoid habitus; the presence of mental

retardation in patients with homocystinuria is a distinguishing feature. A defect in cobalamin C, an essential cofactor for cystathione  $\beta$ -synthase, similarly presents with marfanoid features, arachnodactyly, joint laxity, and scoliosis, in addition to macrocytic anemia and developmental delay.<sup>85</sup>

Perhaps hardest to distinguish is MASS, a marfan-like disorder caused by *FBN1* mutations but with a better prognosis. Striae are a prominent feature, and atrophic skin patches with abnormal elastic fibers may be present.<sup>86</sup> Pectus excavatum and marfanoid skeletal features are most common.<sup>87</sup> Among the distinguishing features are a stable and mild aortic root dilation and lack of ectopia lentis.

The prognosis of MFS depends on the extent and severity of cardiovascular defects. Death usually occurs in adulthood, but occasionally during childhood, as a result of cardiovascular sequelae, especially owing to complications related to dilation of the aortic root.<sup>88,89</sup> A rare neonatal form of MFS features the marfanoid body disproportion, lax skin, emphysema, ocular abnormalities, joint contractures, kyphoscoliosis, adducted thumbs, crumpled ears, micrognathia, muscle hypoplasia, and deficient subcutaneous fat over joints.<sup>90</sup> Severe cardiac valve insufficiency and aortic dilation result in death during the first 2 years of life. A neonatal progeroid variant of MFS with prematurity, congenital lipodystrophy, and frameshift mutations at the 3' end of *FBN1* has been described. In the differential diagnosis of progeria, the marfanoid habitus with accelerated linear growth, severe myopia, and dilation of the aortic bulb allow correct diagnosis.<sup>91,92</sup>

Children with MFS but without serious cardiac issues can participation in some sports but should avoid potentially harmful exertion, particularly contact sports (to protect the aorta and lens), sports with bursts of activity (such as sprinting), and isometric exercises (such as weightlifting), which might lead to further aortic root dilation, aortic rupture, or congestive heart failure.<sup>72</sup> Scuba diving should be avoided because of the risk of pneumothorax. Long-term propranolol therapy may decrease myocardial contractility,<sup>93</sup> thus decreasing the risk of aortic dilation, but the relative value of  $\beta$ -blockers versus the angiotensin receptor blocker losartan (or the combination of the two) is undergoing testing.<sup>94–96</sup> In one study, long-term treatment with doxycycline was shown to be more effective than a  $\beta$ -blocker in preventing thoracic aortic aneurysm through its inhibition of matrix metalloproteinases-2 and -9.<sup>97</sup> Aneurysmal and valvular heart defects may require prosthetic replacement, but this should be postponed as long as possible to avoid recurrent prosthesis replacement, particularly in growing children. Prophylactic replacement of the aortic root to prevent aortic dissection has led to increased life expectancy; in one recent study striae together with elevated TGF- $\beta$  and matrix metalloproteinase (MMP)-3 serum levels correlated with a higher risk of aortic dissection.<sup>98</sup> Early and regular ophthalmologic examinations are required to detect correctable amblyopia and retinal detachment. Ectopia lentis and even complete luxation may be tolerated for decades, but lens extraction may be required to treat diplopia, glaucoma, cataracts, or retinal detachment. Repair of the pectus excavatum is indicated if cardiopulmonary compromise occurs but should be delayed until skeletal maturation is nearly complete to prevent recurrence and should employ internal stabilization. Scoliosis may be lessened in adolescent girls by estrogen therapy, but this therapy may also produce an overall decrease in height. Bracing, physical therapy, and vertebral fusion may all be necessary to prevent severe scoliosis. The website for the National Marfan Foundation is [www.marfan.org](http://www.marfan.org).

## Osteogenesis Imperfecta

OI refers to a group of inherited disorders of bone fragility in which the skin may be thin, atrophic, and somewhat translucent.<sup>99–101</sup> The easy bruising and bone fractures may raise the possibility of child abuse. Wound healing may be normal, but scars are commonly atrophic or hypertrophic. Patients often show hyperlaxity of ligaments and hypermobility of joints, but joint dislocation does not occur. Blue sclerae are distinctive features in approximately 90% of patients but can also be seen in MFS and EDS; increased electron-dense granular material between scleral fibers permits scattering of light by normal pigment within the orbit. Otosclerosis with hearing loss may begin during adolescence (50% of the common type I by adulthood), and

fragile, discolored teeth are particularly common in the more unusual forms (dentinogenesis imperfecta [DI]). Patients may show mitral and aortic valve dilation and regurgitation and cystic medionecrosis of the aorta.

More than one classification scheme has recently been proposed; the newer Sillence classification<sup>101</sup> includes types 1 through 5 and the more-newly recognized, less common, and largely autosomal recessive forms based on clinical features. The classification described by Marini et al.<sup>102</sup> separates types of OI based on genetics and extends the five Sillence classification subtypes to 12 subtypes (I through XII) and an unclassified/other category (Table 6-3). OI has also been classified by severity of clinical features (mild to extremely severe), fracture frequency, bone densitometry, and level of mobility.<sup>101</sup> Changes in 16 genes may be classified under OI,<sup>101</sup> presenting variable clinical features, severity, and prognosis.<sup>102</sup> More than 85% of affected individuals have AD OI, of which most are type I OI, which is by far the mildest form.

Patients with AD OI almost all have mutations in type I collagen, which is composed of two  $\alpha 1$  (*COLA1*) and one  $\alpha 2$  (*COLA2*) polypeptide chains, forming a triple helical structure. Dominant OI can also result from mutations in *IFITM5*, leading to abnormalities in matrix mineralization. Overall, 10% to 15% of cases are autosomal recessive and result from mutation in one of at least 11 genes involved in posttranslational processing of type I collagen and bone formation (see Table 6-3). Some of these encode proteins involved in a complex required for proline (P986) hydroxylation of type I collagen (*CRTAP*, *P3H1*, *CYPB*).<sup>103–105</sup> Others are involved in collagen mineralization (*BRIL* and *PEDF*), collagen crosslinking, folding and chaperoning (*FKBP65* and *HSP47*), and osteoblast development (*osterix*, *OASIS*, *TRICB* and *WNT1*) (see Table 6-3).

Supportive orthopedic therapy includes physical therapy to prevent contractures and immobility-induced bone loss, orthoses to protect the lower limbs,<sup>106</sup> and in more severe cases bisphosphonates.<sup>107</sup> Cyclical treatment with intravenous bisphosphonates is the mainstay of medical therapy for children with moderate to severe OI and has been shown to increase bone mass density, improve muscle strength and mobility, and decrease fractures and bone pain.<sup>99,108</sup>

## Cutis Laxa

Cutis laxa (generalized elastolysis) results from mutations in one of 11 genes that disrupt the elastic tissue network in skin<sup>74,109–114</sup> (Box 6-4; Table 6-4). In general, the products of these genes are either: (1) proteins involved in the assembly of elastic fibers and upregulation of TGF- $\beta$  signaling (e.g., *ELN*, *FBLN4*, *FBLN5*, and *LTBP4*); (2) Golgi proteins that facilitate secretion of elastic network components (e.g., *ATP6V0A2*, *RIN2*, and *GORAB*); or (3) mitochondrial proteins (e.g., *PYCR1*, *ALDH18A1*, and *SLC2A10*).<sup>110</sup>

Cutis laxa can be acquired or congenital, with the genetic forms inherited as AD or autosomal recessive forms, the latter usually being more severe. An X-linked form (X-linked cutis laxa, or occipital

### Box 6-4 Most Common Features of Cutis Laxa

- Autosomal dominant or autosomal recessive forms
- Autosomal recessive forms subdivided into those with cardiovascular features (ARCL-1), those with developmental delay (ARCL-2), and those with developmental delay, athetosis, and corneal clouding (ARCL-3). A variety of underlying molecular bases for each group have been discovered (see Table 6-4)
- Skin
  - Loose, inelastic skin
  - Most common other features:
    - Facial dysmorphisms
    - Aortic dilation
    - Pulmonary artery stenosis
    - Pulmonary emphysema
    - Diverticulae: gastrointestinal, genitourinary
    - Uterine or rectal prolapse
    - Ventral, hial, inguinal hernias

ARCL, Autosomal recessive cutis laxa.

**Table 6-3** Classification of Osteogenesis Imperfecta

Type	Frequency/ Inheritance	Gene; Protein	Clinical Features	Effect of Gene Alteration
I	AD (>50%)	<i>COL1A1</i> , <i>COL1A2</i> ; type I collagen	Also called <i>nondeforming OI with blue sclerae</i> Fractures (90% to 95%), blue sclerae (100%), hearing loss (begins in adolescence and is in >50% by 40 years), vertigo, normal stature, rarely DI	Collagen I quantity
II	AD*	<i>COL1A1</i> , <i>COL1A2</i> glycine substitutions; type I collagen	Also called <i>perinatal lethal OI</i> Multiple fractures, severe rib (beading) and long bone (crumpled, accordion-like) deformities, frog leg positioning, blue-gray sclerae, small for gestational age 20% stillborn and 40% die by 1 month	Collagen I structure
III	AD	<i>COL1A1</i> , <i>COL1A2</i> glycine substitutions; type I collagen	Also called <i>progressive deforming OI</i> Severe deformities; multiple fractures with progressive deformities, short stature (<3rd %) with severe progressive scoliosis, marked osteopenia, nonambulatory Triangular face, hearing loss in adults, may have DI Progressive whitening of sclerae Majority now survive into adulthood and have normal growth velocity/decreased fractures with cyclic IV bisphosphonates	Collagen I structure
IV	AD	<i>COL1A1</i> , <i>COL1A2</i> glycine substitutions; type I collagen	Also called <i>common variable OI</i> ; milder than OI III Moderately short, mild to moderate scoliosis, recurrent fractures with variable deformity, osteoporosis Typically ambulatory DI common, adult-onset hearing loss, usually normal sclerae	Collagen I structure
V	AD (4% to 5%)	<i>IFITM5</i> ; BRIL	Also called <i>OI with calcification in interosseous membranes</i> Mild to moderate fractures (especially forearms, legs affected) and short stature, dislocation of radial head White sclerae, no DI Rarely, painful hyperplastic callus	Matrix mineralization
VI	AR	<i>SERPINF1</i> ; PEDF	Similar to type III, moderately short, scoliosis, white sclerae, no DI Abnormal bone mineralization	Matrix mineralization
VII	AR	<i>CRTAP</i> ; cartilage-associated protein	Moderately deforming Clinically types II and III, but milder forms documented Rhizomelic shortening of humerus and femur, coxa vara, "popcorn epiphyses" White sclerae, no DI	3-hydroxylation of collagen
VIII	AR	<i>LEPRE1</i> ; prolyl-3-hydroxylase-1/P3H1	Moderately deforming Clinically types II and III, but milder forms documented Rhizomelic shortening of humerus and femur, coxa vara, "popcorn epiphyses" White sclerae, no DI	3-hydroxylation of collagen
IX	AR	<i>PPIB</i> ; peptidyl-prolyl isomerase B/CyPB	Clinically types II and IV Fractures with generalized osteopenia, wide anterior fontanel Moderate growth deficiency, gross motor delay No rhizomelia or DI, white sclerae	3-hydroxylation of collagen
X	AR	<i>SERPINH1</i> ; HSP47	Clinically type III	Collagen chaperone
XI	AR	<i>FKBP10</i> ; FKBP10 (also called FKBP65)	Clinically type III Can have joint contractures	Telopeptide hydroxylation for crosslinking
XII	AR	<i>BMP1</i> ; BMP1/mTLD	Clinically type III	Collagen processing (cleaves C-propeptidase)
<b>OTHERS</b>				
	AR	<i>CREB3L1</i> ; OASIS	Clinically type III	Osteoblast development
	AR	<i>SP7</i> / <i>OSX</i> ; <i>SP7</i> / <i>osterix</i>	Clinically type II	Osteoblast development
	AR	<i>TMEM38B</i> ; TRIC-B	Clinically type III	Osteoblast development
AD/AR		<i>WNT1</i> ; <i>WNT1</i>	Clinically type II (AD) or type III (AR)	Osteoblast development
	AR	<i>PLOD2</i> ; PLOD2	Clinically type III; can have congenital joint contractures	Telopeptide hydroxylation
XLR		<i>PLS3</i> ; plastin 3	Clinically closest to type IV; no features beyond childhood fractures; manifests in hemizygous males and variable in heterozygote females	Bone formation and remodeling

AD, Autosomal dominant; AR, autosomal recessive; DI, dentinogenesis imperfecta; OI, osteogenesis imperfecta; XLR, X-linked recessive.

\*Usually new mutation; parental germline mosaicism in 2% to 6% of cases.

**Table 6-4** Cutis Laxa and Related Disorders

Disorder	ADCL	ARCL-1A	ARCL-1B	ARCL1C/ URDS	ARCL-2A	ARCL-2B	ARCL-3/ De Barys	GO	XLCL	MACS	ATS
Gene	<i>ELN</i>	<i>FBLN4</i>	<i>FBLN5</i>	<i>LTBP4</i>	<i>ATP6V0A2</i>	<i>PYCR1</i>	<i>ALDH18A1;</i> <i>PYCR1</i>	<i>GORAB</i>	<i>ATP7A</i>	<i>RIN2</i>	<i>SLC2A10</i>
Protein	Elastin	Fibulin-4	Fibulin-5	LTBP4	ATP6V0A2	PYCR1	P5CS; PYCR1	GORAB	ATP7A	RIN2	GLUT10
Lax skin	+++*	++	+++	+++	+++	+++	+++	++	+++	++	+++
Facial features											
Prominent ears	+++	+	+++	+	—	—	—	—	++	—	+
Hypertelorism	—	+++	—	+++	—	—	—	—	—	—	++
Retrognathia	—	+++	—	+++	+++	+++	—	—	—	—	+++
Other dysmorphism	—	++	—	++	—	++	++	+++	++	—	++
Emphysema	++	++	+++	+++	—	—	—	—	—	—	—
Supravalvular aortic stenosis	—	—	+++	—	—	—	—	—	—	—	—
Aortic aneurysm	++	+++	—	—	+	—	—	—	—	—	++
Arterial tortuosity	—	+++	+	—	—	—	++	—	++	—	+++
Hernias	++	+++	+++	+++	+++	++	++	++	+++	+	++
Bladder diverticula	—	—	+	+++	+	—	—	—	+++	—	—
Delayed motor development	—	+	+	—	+++	—	+++	+++	+++	—	—
Mental retardation	—	—	—	—	+++	+++	+++	++	+++	—	—
Growth delay	—	++	+	+++	+++	+++	+++	+++	+	—	—
IUGR	—	—	—	+	+++	+++	+++	+++	—	—	—
Lax joints	—	+	—	++	+++	+++	++	+++	++	+++	+++
Hypotonia	—	+	—	+++	+++	—	++	++	++	—	—
Congenital hip dislocation	—	+	—	—	+	+++	++	++	—	—	—
Patent anterior fontanel	—	—	—	++	+++	—	++	++	++	—	—
Occipital horns	—	—	—	—	—	—	—	—	+++	—	—
Osteoporosis	—	—	—	—	—	++	—	+++	++	+	—
Scoliosis	—	—	—	—	++	+	++	+++	++	+++	++
Macrocephaly	—	—	—	—	—	—	—	—	—	+++	—
Microcephaly	—	—	—	—	—	+	++	++	—	—	—
Gingival hyperplasia	—	—	—	—	—	—	—	—	—	+++	—
Corneal opacity	—	—	—	—	—	+	+++	—	—	—	—
Athetoid motion	—	—	—	—	—	+	+++	—	—	—	—
Alopecia	—	—	—	—	—	—	—	—	—	+++	—

ADCL, Autosomal dominant cutis laxa; ARCL, autosomal recessive cutis laxa; ATS, arterial tortuosity syndrome; GO, geroderma osteodysplastica; GORAB, golgin-  
RAB6-interacting; IUGR, intrauterine growth retardation; LTBP4, latent transforming growth factor  $\beta$ -binding protein 4; MACS, macrocephaly alopecia cutis  
laxa scoliosis syndrome; URDS, Urban–Rifkin–Davis syndrome; P5CS,  $\Delta^1$ -pyrroline-5-carboxylate synthase; URCS, Urban–Rifkin–Davis syndrome; XLCL, X-linked  
cutis laxa.

\*Incidence of finding range: —, not reported to ++++, common.

horn syndrome; formerly Ehlers–Danlos syndrome type IX) is now classified as a copper transport disease caused by a mutation in the copper transporting adenosinetriphosphatase (ATPase),  $\alpha$ -polypeptide ATP7A.

Patients with cutis laxa present a striking picture of loose, inelastic, redundant skin that sags and hangs in pendulous folds, as if it were too large for the body. The drooping and ectropion of the eyelids, together with the sagging facial skin and accentuation of the nasal, labial, and other facial folds, help produce the “bloodhound” or aged appearance (Fig. 6-8).

Most dominant cases result from heterozygous frameshift mutations in the gene encoding elastin.<sup>115</sup> The AD form may appear at any age and presents as a cosmetic problem with few systemic changes.<sup>116</sup> The skin in cutis laxa is extensible, but, in contrast to that of EDS does not spring back to place on release of tension. Special stains for elastic tissue (Verhoeff–van Gieson stain) of skin biopsy specimens demonstrate significantly decreased or absent dermal elastic fibers.

Systemic manifestations caused by weakened supportive tissue include aortic root dilation (55%), hernias (51%; ventral, hiatal, or inguinal), pulmonary emphysema (37%), pulmonary artery stenosis, diverticulae of the GI tract or urinary bladder, and uterine or rectal



Figure 6-8 Cutis laxa. Sagging skin in an affected 8-year-old child.



**Figure 6-9** Cutis laxa. This 2-year-old girl with fibulin-4 deficiency shows the sagging infraorbital and cheek skin of cutis laxa.

prolapse.<sup>115</sup> In patients with the severe autosomal recessively inherited disease, the disorder is gradually progressive, and death from pulmonary complications related to emphysema may occur early in infancy or in many instances in the second to fourth decades of life.

The autosomal recessive forms have traditionally been divided into three subgroups based on clinical characteristics, autosomal recessive cutis laxa (ARCL)-1, -2, and -3 (see Table 6-4).<sup>117-129</sup> Most genes mutated in ARCL have been identified, and the group is quite heterogeneous. All patients tend to have cutis laxa with hernias (umbilical, inguinal, diaphragmatic) and facial dysmorphisms. ARCL-1 is characterized by severe cardiopulmonary lesions, including infantile emphysema and cardiac defects, and bladder diverticulae.<sup>130</sup> Fibulin-5 deficiency has been associated with supravalvular aortic stenosis. Fibulin-4 deficiency (mutations in *FBLN4*, also called *EFEMP2*) may be associated with mild to moderate cutis laxa and has been linked to arachnodactyly, tortuous vessels with aneurysm, joint laxity, microcephaly, bone fractures, and pulmonary artery occlusion<sup>131</sup> (Fig. 6-9). Fibulins-4 and -5 are critical in elastic fiber assembly in the skin and other elastic tissues. More recently, *LTBP4* mutations (ARCL type 1C) have been found in patients with emphysema and severe GI and genitourinary (GU) tract involvement but no vascular abnormalities.

Patients with ARCL-2 (which includes “wrinkly skin syndrome”) have mild cutis laxa with growth, distinct facial features, and developmental delay without prominent vascular lesions or emphysema, in contrast to ARCL-1. Patients with ARCL-2A may show pretibial pseudoeccymotic skin lesions that resemble those found in EDS.<sup>132</sup> ARCL-3 or De Barsy syndrome<sup>126</sup> can be distinguished from ARCL-2 by athetoid movements and corneal opacities, but otherwise there is overlap between ARCL-2 and ARCL-3.<sup>126,127,133,134</sup> Geroderma osteodysplastica, resulting from mutations in *GORAB*, shows features of ARCL-2A and ARCL-3 (De Barsy syndrome) but has no associated corneal opacities or athetoid movement and characteristically has osteopenia with fractures.

Cutis laxa is also a component of several additional syndromes (Box 6-5). Cutis laxa is a component of macrocephaly, alopecia, cutis laxa, and scoliosis (MACS) syndrome, an autosomal recessive disorder that results from deficiency of *RIN2*, leading to decreased fibulin-5 and microfibrils.<sup>141</sup> Arterial tortuosity syndrome (ATS) features facial dysmorphism, vessel tortuosity, and joint laxity with scoliosis. Costello syndrome is an AD disorder characterized by soft, loose skin of the neck, hands, and feet with excessive wrinkling and deep creases resembling cutis laxa.<sup>135,142,143</sup> The digits tend to be hyperextensible with loose skin and characteristic ulnar deviation at the wrist (Fig. 6-10). Affected children develop papillomata around the nares, mouth (Fig. 6-11), and anal areas; acanthosis nigricans; and sometimes striate palmoplantar keratoderma. Although prenatal overgrowth and polyhydramnios occur, patients tend to have postnatal failure to thrive and a distinctive appearance with craniofacial findings that resemble those of lysosomal storage disorders. The facies are coarse with thick lips, macroglossia, and relative macrocephaly. Severe short stature, mental retardation, curly hair, palmoplantar keratoderma



**Figure 6-10** Costello syndrome. Note the loose, hyperextensible skin of the digits.

#### Box 6-5 Other Rare Genetic Disorders with Wrinkled or Lax Skin (not in Table 6-4)

- Ablepharon-macrostomia syndrome
- Barber-Say syndrome
- Cantú syndrome
- Costello syndrome
- GAPO syndrome
- Kabuki makeup syndrome
- Lens-Majewski syndrome
- Menkes syndrome
- Progeria
- Patterson pseudoleprechanism
- SCARF syndrome
- Transaldolase deficiency
- Williams syndrome

GAPO, Growth retardation, alopecia, pseudoanodontia and optic atrophy; SCARF, skeletal abnormalities, cutis laxa, craniostenosis, psychomotor retardation, and facial abnormalities.

#### Box 6-6 Associations with Acquired Cutis Laxa

- Infections: *Toxocara canis* (cat scratch); *Treponema pallidum* (syphilis); *Borrelia burgdorferi* (Lyme disease); *Onchocerca volvulus* (onchocerciasis)
- Medications: isoniazid; penicillins; D-penicillamine
- Inflammatory diseases: celiac disease; sarcoidosis; dermatitis herpetiformis
- Rheumatic disorders: systemic lupus erythematosus; rheumatoid arthritis
- Others:  $\alpha$ 1-antitrypsin deficiency; mastocytosis; nephrotic syndrome; amyloidosis; malignancy

(sometimes striate), and hypertrophic cardiomyopathy are other associated manifestations. Costello syndrome results from activating mutations in *HRAS*<sup>146-148</sup> and is associated with a 15% lifetime risk for malignancy, most commonly rhabdomyosarcoma.<sup>149</sup> Cutis laxa has also been described in children with Lenz-Majewski syndrome in association with generalized hyperostosis, proximal symphalangism, syndactyly, brachydactyly, mental retardation, hypertelorism, and enamel hypoplasia.<sup>136</sup> Lenz-Majewski syndrome has recently been linked to gain-of-function mutations in phosphatidylserine synthase 1 (*PTDSS1*).<sup>144</sup> Deficiency of transaldolase (TALDO) presents with hepatosplenomegaly, liver failure, and cirrhosis in association with dysmorphic features, hypertrichosis, cutis laxa, congenital heart disease, hemolytic anemia, thrombocytopenia and GU malformations<sup>145,150</sup>; patients may die *in utero* with hydrops fetalis. Cutis laxa has also been described in a child with typical Kabuki makeup syndrome.<sup>140</sup>

Cutis laxa can be an acquired condition (Box 6-6), although it occurs less commonly in children than in adults.<sup>151</sup> It can be localized, but in its generalized form ill-defined areas of loose skin appear insidiously but progressively, usually first on the face and then



**Figure 6-11** Costello syndrome. In addition to their hyperextensible joints and loose skin, affected children develop papillomata on the face, including around the nares and mouth. Note the coarse, curled eyelashes.

progressing in a cephalocaudad direction. The development of cutis laxa is often preceded by an urticarial eruption. Emphysema, aortic aneurysms with subsequent rupture, and GI and GU diverticulae have been associated. Although most affected children have not had systemic evidence of acquired cutis laxa, aortic dilation, emphysema, and severe tracheobronchomegaly have led to the demise of children with acquired cutis laxa. Children may develop cutis laxa after drug exposure to penicillin, D-penicillamine,<sup>152</sup> or isoniazid. Elastosis perforans serpiginosa may be related<sup>153</sup> (see *Elastosis Perforans Serpiginosa* section). Marshall syndrome (also called *type II acquired cutis laxa*) is a postinflammatory elastolysis characterized by well-demarcated, non-pruritic erythematous plaques that appear in crops during a period of days to weeks, often in association with fever, malaise, and peripheral eosinophilia.<sup>154</sup> Several children have developed the cutis laxa after Sweet syndrome,<sup>155</sup> with areas of cutis laxa occurring at sites of previous inflammation.<sup>156</sup> Acquired cutis laxa has recently been described in a child with extensive cutaneous mastocytosis.<sup>157</sup> Systemic involvement is rare, but fatal aortitis has been described. Interestingly, a child with acquired cutis laxa after *Toxocara* infestation was found to have compound heterozygous mutations in elastin and a fibulin-5 mutation on one allele, suggesting that environmental factors may trigger acquired cutis laxa in genetically predisposed individual.<sup>158</sup>

Therapy for cutis laxa is limited. Surgery can correct diverticulae, rectal prolapse, or hernias, and plastic surgery can make a dramatic improvement in patients, inevitably with important psychological benefit.<sup>159</sup> Unlike patients with EDS, patients with cutis laxa have no vascular fragility and heal well, enabling repeated facelift procedures. Pulmonary function studies may aid in the early detection of emphysema.

## Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum (PXE) is a genetic disorder of the elastic tissue that involves the skin, eyes, and cardiovascular system (Box 6-7).<sup>160</sup> Approximately 1 : 60,000 individuals are affected.<sup>161</sup> PXE has been linked to mutations in the adenosine triphosphate (ATP)-binding cassette (ABC) subfamily C member 6 (*ABCC6*) gene, which encodes a transmembrane ABC transporter.<sup>162,163</sup> PXE is now recognized to be a metabolic disease rather than a primary disease of elastic tissue.<sup>164,165</sup> *ABCC6* is expressed primarily in the liver and kidneys and at low levels if at all in tissues affected by PXE. Cells expressing *ABCC6* excrete nucleoside triphosphates, which are the precursors of inorganic



**Figure 6-12** Pseudoxanthoma elasticum. Xanthoma-like papules and plaques on the neck have been likened to plucked chicken skin.

### Box 6-7 Most Common Features of Pseudoxanthoma Elasticum

- Autosomal recessive
- Skin
  - Yellow papules and plaques (*peau d'orange*, "plucked chicken skin")
- Ocular
  - Angioid streaks
  - Retinal epithelial mottling (*peau d'orange*)
  - Loss of central vision
- Vascular calcifications, hemorrhage
  - Gastrointestinal bleeding
  - Hypertension
  - Cerebrovascular accidents
  - Claudication, myocardial infarction

pyrophosphate (PPi), the circulating factor that inhibits mineralization and thus prevents PXE.<sup>166</sup>

Most of the demonstrated gene mutations would be predicted to lead to autosomal recessive inheritance patterns, although pseudodominant inheritance owing to familial consanguinity has been described. PXE demonstrates marked phenotypic heterogeneity even among patients from the same family,<sup>167</sup> suggesting an important role for genetic and environmental factors.<sup>168</sup>

Lesions often develop prepubertally, especially on the lateral aspects of the neck, but may be overlooked because they are small and asymptomatic.<sup>169–171</sup> Most commonly, the diagnosis becomes apparent when the patient reaches the second or third decade of life. The severity may range from extensive flexural cutaneous elastic tissue involvement with severe retinal and cardiovascular complications, often resulting in early blindness and coronary artery disease, to primarily skin changes, milder eye findings, and rarely vascular disease. Earlier onset of cutaneous signs has not been associated with a worse prognosis. The cutaneous lesions are characterized by soft, yellowish (xanthoma-like) papules and polygonal plaques on the neck (Fig. 6-12), below the clavicles, in the axillae, and on antecubital fossae, perumbilical areas, and the perineum and thighs. They vary from several papules to linear plaques resembling plucked chicken skin, morocco leather, or orange skin (*peau d'orange*). The skin becomes more redundant with advancing age and tends to show progressive calcification at affected sites. Oral, anal, and vaginal mucosal lesions may occur, most commonly infiltration of the lip mucosa. Skin lesions that are similar clinically and ultrastructurally to PXE have been described in patients with β-thalassemia<sup>172</sup> or sickle cell anemia<sup>173</sup> or as a complication of D-penicillamine use,<sup>174</sup> but these are rare in children.

The characteristic angioid streaks are slate-gray to reddish-brown linear bands, resembling vasculature radiating from the optic papilla. Seen ultimately in 94% of patients,<sup>175</sup> angioid streaks represent

visualization of the choroid through tears in the calcified and brittle elastic lamina of the Bruch membrane.<sup>176</sup> Angiod streaks usually do not appear until the third decade of life but have been described in children as young as 10 years of age. Characteristic irregular retinal epithelial mottling (*peau d'orange*), resulting from degenerated elastic tissue, is commonly detected in children with PXE and usually precedes angiod streaks.<sup>170</sup> Loss of central vision (because of retinal hemorrhage and choroidal neovascularization with scarring, not to the angiod streaks *per se*) is the most common disability and may develop in more than 70% of patients with this complication.<sup>177</sup> These retinal changes are not pathognomonic, because they may also be found in patients with thalassemia,<sup>178</sup> sickle cell anemia, Paget disease of the bone, idiopathic thrombocytopenic purpura, acromegaly, EDS, and lead poisoning.<sup>179</sup> Carriers uncommonly may experience ophthalmologic complications.<sup>180</sup>

Calcification of degenerated elastic tissue of the internal lamina of blood vessels with subsequent hemorrhage is a common and potentially serious complication of PXE. The midsized arteries of the extremities, GI tract, and renal vasculature are sites of early manifestations of this degenerative damage. Both hypertension from resultant renal artery stenosis and GI bleeding may occur during adolescence. Late vascular sequelae in PXE include cerebrovascular accidents, intermittent claudication, and myocardial infarction. Severe coronary artery disease has been noted in adolescents with PXE and may respond to bypass surgery, and cardiovascular manifestations may be present during the first decade of life.<sup>181</sup> In addition, an infant with ABCC6 mutations and a brother with typical manifestations of PXE since adolescence died of generalized arterial calcification, leading to extensive arterial stenosis and myocardial ischemia.<sup>182</sup> Early evidence suggests that carriers of ABCC6 loss-of-function mutations have an increased risk of coronary artery disease, so parents should be counseled about preventive intervention.<sup>183</sup> Recent studies in mice suggest that statins can prevent but not reverse aberrant mineralization in mouse models of PXE.<sup>184</sup>

The diagnosis of PXE is based on the clinical findings and on histopathologic evidence of calcification in elastic tissue and basophilic degeneration of the elastic tissue in the middle and deeper zones of the dermis. Elastic tissue degeneration also affects connective tissue elements of the aorta and medium-sized muscular arteries in the heart, kidneys, GI tract, and other organs.

ABCC6 is thought to distribute to the dermis a reduced form of vitamin K. The form of vitamin K is a cofactor of matrix Gla-protein, an inhibitor of ectopic calcification, suggesting a reason for the dermal calcification.<sup>161</sup> Interestingly, a disorder that resembles severe PXE (with pendulous PXE-like skin changes that usually start during adolescence and only spares the face, hands, and feet) results from deficiency of an enzyme that activates matrix Gla-protein. This matrix Gla-protein activator ( $\gamma$ -glutamyl carboxylase or GGCX) is also important for vitamin K-dependent clotting, leading to cerebral aneurysms and a bleeding diathesis in addition to PXE-like changes.<sup>185–189</sup> Generalized arterial calcification of infancy (GACI) with extensive tissue mineralization and PXE skin involvement is allelic with PXE<sup>190</sup> but more commonly is caused by mutations in ENPP,<sup>191</sup> which only occasionally lead to PXE.

Because of the risk of progressive visual loss, patients under 40 years of age are advised to have fundus examination every other year and self-monitor visual acuity with the Amsler grid.<sup>175</sup> Patients with PXE should be advised to protect their eyes from even mild trauma and about the potential for future visual loss. Intravitreal injection of vascular endothelial growth-factor antagonists prevent neovascularization and thereby reduce the loss of visual acuity<sup>192</sup> with or without laser and photodynamic therapeutic options.<sup>176,189,193,194</sup> Because of the potential risk to eyes and calcified vessels when traumatized, contact sports and high-intensity cardiovascular exercise should be prohibited for persons with PXE. Avoidance of high-cholesterol foods and smoking, control of blood pressure, and safe aerobic exercises are always appropriate because of the vascular risks. Serial cardiac evaluation (careful auscultation and echocardiographic monitoring) to detect mitral valve prolapse and ophthalmologic examinations are important. Ultrasound studies have shown impaired left ventricular function, impaired aortic elastic properties, and a high prevalence of peripheral artery disease in patients with PXE; in these studies carriers

also showed a milder cardiovascular phenotype, suggesting the need to identify and monitor carrier of PXE.<sup>195</sup>

Early studies suggested that patients who extensively ingested dairy products rich in calcium and phosphate had more severe later disease. In addition, clinical and histologic improvement in skin lesions has been described in 50% of patients treated systemically with aluminum hydroxide.<sup>196</sup> The demonstration in a mouse model of PXE that increased dietary intake of magnesium prevents connective tissue mineralization suggests a new dietary manipulation for affected patients.<sup>197,198</sup> Warfarin has been shown to accelerate the ectopic mineralization<sup>199</sup> and should be avoided if possible. Plastic surgery may improve the appearance of sagging skin, although extrusion of calcium particles through the surgical wound may result in delayed healing and unsightly scars.<sup>200</sup> GI bleeding can usually be managed conservatively. Two support groups, the National Association for Pseudoxanthoma Elasticum and PXE International (at [www.pxe.org](http://www.pxe.org)), are available.

## Elastosis Perforans Serpiginosa

Elastosis perforans serpiginosa (EPS; also termed perforating elastoma) is a disorder of elastic tissue characterized by an annular, arciform, or linear arrangement of keratotic papules.<sup>201</sup> The individual papules measure 2 to 4 mm in diameter but collectively can lead to lesions as long as 15 to 20 cm in overall length. The papules are generally capped by a distinctive keratotic plug, which when forcibly dislodged reveals a bleeding crateriform lesion. Biopsy shows elongated tortuous channels within the epidermis that are perforated by abnormal and degenerated elastic tissue extruded from the dermis. Lesions show a predilection for distribution on the posterolateral aspects of the neck (Fig. 6-13) and occasionally the chin, cheeks, mandibular areas of the face, antecubital fossae, elbows, and knees.<sup>202</sup>

This cutaneous disorder primarily affects young persons, especially those in the second decade of life, and generally disappears spontaneously within 5 to 10 years. Up to 44% of reported cases have been seen in association with Down syndrome, OI, EDS, PXE, cutis laxa, Rothmund-Thomson syndrome, acrogeria, morphea, or MFS or as a complication of penicillamine therapy.<sup>203–206</sup> Thorough history and physical examination should suffice to consider underlying causes.<sup>206</sup> Treatment with stripping of the surface keratinous material by repeated application of Scotch tape, cryosurgery, laser, and use of keratolytic agents or imiquimod<sup>207</sup> may result in improvement of some lesions, but recurrences are common if therapy is effective.

EPS must be distinguished from three other perforating disorders of the skin that feature transepidermal elimination of altered dermal substances: reactive perforating collagenosis (Fig. 6-14), perforating folliculitis, and Kyrie disease. These perforating disorders occur more commonly in adults, especially in association with chronic



**Figure 6-13** Elastosis perforans serpiginosa. Annular, arcuate, and linear arrangement of erythematous keratotic papules on the posterolateral aspects of the neck. (Courtesy of Annette Wagner, MD.)



**Figure 6-14** Reactive perforating collagenosis. Pruritic papules with keratotic plugs stud the legs of this otherwise normal girl; biopsy is helpful in distinguishing among the perforating disorders.



**Figure 6-15** Goltz syndrome (focal dermal hypoplasia). Linear streaks of dermal hypoplasia with visible telangiectasia in an affected boy. The condition is presumed to be lethal in male individuals, suggesting that this boy's manifestation reflects postzygotic mosaicism.

#### Box 6-8 Most Prominent Features of Focal Dermal Hypoplasia (Goltz Syndrome)

- X-linked dominant, 10% of patients are male
- Linear or reticular patterns of:
  - Thinned dermis
  - Focal fat herniation
  - Hyperpigmentation or hypopigmentation
  - Papillomas
  - Ulcerations
- Ectodermal abnormalities
  - Sparse hair
  - Thin nails
  - Hypodontia, enamel hypoplasia
- Skeletal abnormalities, especially digital anomalies
- Ocular colobomas, strabismus, microphthalmia
- Diagnosis
  - Clinical features
  - Osteopathia striata (plain radiography)

renal disease and diabetes,<sup>208</sup> but can occur in children, including siblings. The underlying basis for the perforation and extrusion of dermal material is poorly understood, but skin biopsy can distinguish among them. As with EPS, treatment can be difficult. Topical retinoids and topical and intralesional corticosteroids often provide no relief; narrow-band ultraviolet B (UVB) light has been shown to decrease the pruritis and promote resolution of reactive perforating collagenosis.<sup>209</sup>

## Focal Dermal Hypoplasia

Focal dermal hypoplasia (Goltz syndrome) is characterized by linear streaks of dermal hypoplasia (Box 6-8). The condition is X-linked dominant and thought to be lethal in homozygous males; 90% of patients are female. The disorder results from mutations in *PORCN*, which encodes a protein that is critical for the secretion of Wnt, an important protein for skin and bone development.<sup>210–212</sup> Although the disorder in male individuals usually reflects postzygotic mosaicism

of the mutated *PORCN* gene<sup>213,214</sup> (Fig. 6-15), classic features of Goltz syndrome have also been described in a male with Klinefelter syndrome.<sup>215</sup>

Many of the cutaneous manifestations of focal dermal hypoplasia are present from birth.<sup>216,217</sup> These include the widely distributed linear areas of hypoplasia of the skin often with associated telangiectasia (Fig. 6-16); soft, yellow, reddish-yellow, or yellow-brown nodular outpouchings, often in a linear distribution (caused by herniation of the subcutaneous fat through the thinned dermis); and sometimes large cutaneous ulcers (caused by congenital absence of skin) that gradually heal with atrophy. Patients often show streaky hyperpigmentation or hypopigmentation, and erythematous papillomas of the affected skin or mucosae of the oral, anal, or genital region may develop. Paper-thin nails, sparseness of hair, and hypodontia with enamel hypoplasia have been described. Skeletal abnormalities are most commonly digital abnormalities (adactyly, syndactyly, and “lobster claw” deformities) (Fig. 6-17). Associated ocular abnormalities include colobomas, strabismus, and microphthalmia of the eyes. Eye, hair, teeth, and limb abnormalities without cutaneous features may also occur.<sup>218</sup> Other associated abnormalities may include umbilical or inguinal hernia, cleft lip and/or cleft palate, central nervous system abnormalities (microcephaly, mental retardation, myelomeningocele, and hydrocephalus,<sup>219</sup> giant cell tumor of bone,<sup>220</sup> and multiple basal cell carcinomas.<sup>221</sup>

Virtually all cases of focal dermal hypoplasia reveal fine parallel linear striations in the metaphyses of long bones at or near epiphyseal junctions on radiographs. Although striations can be seen with other bony abnormalities, this linear change in the metaphyseal regions of the long bones (termed *osteopathia striata*) is a very useful index for the diagnosis of this disorder. Although rarely necessary to confirm the diagnosis, biopsy of an affected area of skin can be performed and shows hypoplasia of dermal connective tissue with upward extension of the subcutaneous fat tissue almost to the normal epidermis. Even mildly affected females (from mosaicism or skewed X-inactivation) or



**Figure 6-16** Goltz syndrome. Streaks of dermal hypoplasia with visible telangiectasia that follow Blaschko lines. This girl underwent a series of pulsed-dye laser treatments, which reduced the visibility of telangiectasia and improved cosmesis on her face, arms and legs.



**Figure 6-17** Goltz syndrome. Skeletal deformities are common, especially involving the hand.

males (mosaicism) require genetic counseling because of the risk of having severely affected offspring.<sup>216,222</sup> Surgical intervention can ameliorate the developmental defects such as syndactyly or polydactyly and remove papillomas of the skin or mucous membranes. Pulsed-dye laser therapy can reduce telangiectasia, and dental care

can dramatically improve the hypodontia and enamel dysplasia.<sup>223</sup> Families can find support resources internationally through the National Foundation for Ectodermal Dysplasias (see: [www.nfed.org](http://www.nfed.org)).

Focal dermal hypoplasia should not be confused with focal facial dermal dysplasia (FFDD), which is characterized by bitemporal, round, scar-like lesions that resemble forceps marks. Thought to result from incomplete fusion of the ectodermal groove between the maxillary and mandibular prominences,<sup>224</sup> FFDD is currently classified into four subtypes. Patients with type I FFDD (autosomal dominant Brauer syndrome) have additional facial characteristics (flattened nasal tip, sparse lateral eyebrows, distichiasis [double row of eyelashes]), that are mild. FFDD type II (autosomal dominant Brauer–Setleis syndrome) is characterized by the addition of thin and puckered periorbital skin, absent eyelashes and/or distichiasis, upslanting palpebral fissures, a broad nasal tip and flat nasal bridge, and large lips.<sup>116,225</sup> Individuals with type III FFDD (autosomal recessive Setleis syndrome, see also Chapter 2) show the bitemporal lesions of focal facial dermal hypoplasia in association with a coarse facial appearance, anomalies of the eyelashes and lateral eyebrows,<sup>226,227</sup> dysplastic low-set ears, and a characteristic mouth with large lips and an inverted V contour with downturned corners. Setleis syndrome results from mutations in *TWIST2*, a transcription factor important for development.<sup>228</sup> Heterozygotes for *TWIST2* mutations may show partial features such as distichiasis and partial absence of the lower eyelashes.<sup>229</sup> Patients with type IV FFDD (autosomal recessive) usually have no other associated anomalies but may have buccal mucosal polyps<sup>230,231</sup>; type IV FFDD results from homozygous loss of function mutations in *CYP26C1*, a retinoic acid-degrading enzyme.<sup>230</sup>

Focal dermal hypoplasia must also be distinguished from microphthalmia with linear skin defects (MLS) syndrome (also called *MDAS* for *microphthalmia, dermal aplasia, and sclerocornea syndrome*).<sup>232</sup> This X-linked dominant developmental defect is characterized by microphthalmia and other eye abnormalities, in association with linear, jagged skin defects typically involving the face, scalp, neck and occasionally the upper trunk.<sup>233</sup> Other features can include short stature, developmental delay, structural brain abnormalities,<sup>234</sup> seizures, dia-phragmatic hernia, congenital heart defects, and even pseudotail,<sup>235</sup> although there is wide phenotypic variability. Mutations in mitochondrial holocytochrome C-type synthase (*HCCS*) at chromosome Xp22.2 are responsible.<sup>236</sup> *HCCS* encodes a holocytochrome C-type synthase involved in mitochondrial oxidative activity.

## Werner Syndrome

Werner syndrome (progeria of the adult) is a rare autosomal recessive disorder that results from mutations in the *WRN* gene, which encodes Werner protein, a deoxyribonucleic-acid (DNA) helicase enzyme that maintains genomic stability.<sup>237–240</sup> Patients usually develop and appear normal until adolescence when they lack the pubertal growth spurt. Premature graying of hair at the temples may be seen then, and patients develop progressive alopecia, short stature, bird-like facies, and an apparent aged appearance. Cutaneous features include sclerodermod changes of the skin of the extremities and to a lesser degree the face and neck, telangiectasias, mottled or diffuse pigmentation, keratoses, and indolent ulcers over pressure points, particularly on the soles and ankles.

Patients with Werner syndrome develop severe, often generalized vascular disease; diabetes mellitus (71%); hypogonadism (80%); osteoporosis (91%); cataracts (100%); loss of subcutaneous tissue and severe muscle wasting in the legs, arms, feet, and hands with large abdominal fat deposits (leading to a body habitus of a stocky trunk with spindly extremities)<sup>241</sup>; soft-tissue calcification; a high-pitched voice or hoarseness; and a predisposition to neoplastic disease (hepatoma, thyroid adenocarcinoma, ovarian carcinoma, melanoma, meningioma, leukemia, fibrosarcoma, osteogenic sarcoma, and carcinoma of the breast).<sup>242,243</sup> Patients may be thought to have insulin resistance with lipodystrophy<sup>241</sup> or scleroderma.<sup>244</sup> The mean age of death is 54 years. “Atypical” Werner syndrome affects about 15% of patients clinically diagnosed with Werner syndrome but results from mutations in *LMNA* (see *Progeria* section) rather than *WRN*.<sup>245</sup> Affected individuals start to show aging as young adults but at an

accelerated rate compared with patients who have Werner syndrome and usually have no diabetes or cataracts. Therapy for Werner syndrome is supportive, but a recent study in a mouse model of Werner syndrome suggests that vitamin C supplementation may reverse aging abnormalities and lengthen the life span.<sup>246</sup>

## Progeria

Progeria (Hutchinson–Gilford syndrome [HGPS]) is a rare disease that most often results from a specific mutation (1824C→T; G608G) on one allele of *LMNA*, which encodes lamin A, a component of the nuclear lamina.<sup>247–249</sup> Although this common mutation does not even change an amino acid, it does activate a cryptic splice site so that mutant lamin A precursor, or progerin, lacks a series of 50 missing amino acids and is thus permanently modified by lipid farnesylation. Farnesylation of progerin prevents its proper insertion into the nuclear lamina and leads to progressive deformities in the nuclei of patients with HGPS. It is unclear if nonfarnesylated progerin also has toxicity.<sup>250</sup> Interestingly progerin has also been shown to accumulate with aging in normal cells<sup>251</sup> and is induced in adult cells exposed to ultraviolet A (UVA) but not UVB light.<sup>252</sup>

Although the mutations in HGPS are dominant negative, an autosomal recessive form with homozygous *LMNA* mutations (R527C) has been described.<sup>253</sup> Affected children show features of HGPS but have additional GI and skeletal abnormalities, and carrier parents are asymptomatic. Atypical progeroid syndrome may result from missense *LMNA* mutations other than G608G that lead to nuclear abnormalities but are not rescued by farnesyltransferase inhibitors.<sup>254</sup>

HGPS first manifests by 24 months of age with cutaneous alterations (mean age is <12 months).<sup>255</sup> The most reported early skin feature is sclerodermod change, which most commonly involves the abdomen and bilateral lower extremities.<sup>255</sup> Other early changes are perioral and nasolabial cyanosis, prominent superficial veins of the scalp and body (Fig. 6-18), hypopigmentation and hyperpigmentation at sites of sclerodermatos change, and scalp alopecia, which progresses in a predictable pattern with midscalp and vertex area loss after other areas.<sup>255–257</sup> Patients progressively develop additional signs of premature aging including early skin wrinkling, osteopenia with fractures, and atherosclerosis.<sup>258</sup> Other characteristics are reduced birthweight with postnatal growth retardation<sup>259</sup>; profound midfacial hypoplasia and micrognathia but the appearance of hydrocephalus because upper head size is minimally reduced; and generalized atrophy of muscle and subcutaneous tissue with a beaked nose and a bird-like appearance. The teeth become crowded, irregular in form, or deficient in number, and deciduous dentition is often retained.<sup>260</sup> Speech

becomes high-pitched and squeaky, and intelligence is generally normal. The chest becomes narrow and the abdomen protuberant; owing to a mild flexion of the knees, a “horse-riding” stance becomes apparent.

Cardiac murmurs commonly occur after the age of 5 years and are soon followed by atherosclerosis-induced hypertension, cardiomegaly, angina, myocardial infarction, and congestive heart failure. Without intervention, death usually occurs at a mean age of 13.4 years, usually owing to the coronary artery disease.<sup>261</sup> Progeria should be distinguished from scleroderma and from atypical Werner, Hallermann–Streiff, Cockayne, Bloom, and Rothmund–Thomson syndromes.

Growth hormone treatment increases weight by approximately 50% and linear growth by only about 10%. In preclinical models, treatment with three medications have been found to reverse the nuclear distortion in progeric cells: farnesyltransferase inhibitors, the combination of a bisphosphonate and a statin, and rapamycin, although all three have different effects on the many abnormalities in progeric cells.<sup>262,263</sup> Farnesyltransferase inhibitor treatment for at least 2 years has led to some type of improvement in all treated patients involving weight, cardiovascular flexibility, bone structure, and/or sensorineural hearing.<sup>264</sup> Farnesyltransferase inhibitor therapy also increased mean survival by 1.6 years<sup>265</sup> and decreased the rate of clinical strokes, headaches, and seizures.<sup>266,267</sup> A trial of statin and bisphosphonate<sup>268</sup> is ongoing.

## Restrictive Dermopathy

Restrictive dermopathy is a rare, fatal autosomal recessive disorder characterized by taut, translucent, thin skin with erosions and fissures.<sup>269,270</sup> The intrauterine course is characterized by polyhydramnios with reduced fetal movements beginning at about 31 weeks' gestational age.<sup>271,272</sup> Clavicular hypoplasia is a consistent *in utero* characteristic.<sup>273</sup> Affected neonates show a dysmorphic facies (fixed round open mouth with micrognathia, a small pinched nose, hypertelorism, enlarged fontanelles, and widened sutures) and flexion contractures. Death usually occurs shortly after birth<sup>274,275</sup> owing to pulmonary atelectasis, but affected babies have survived as long as months with respiratory and nutritional support. Biopsy sections show a flat epidermal junction and a thin dermis with compact collagen fibers, sparse elastic fibers, and rudimentary skin appendages. Restrictive dermopathy most commonly results from loss of function mutations in both alleles of *ZMPSTE24* (*FACE1*), and occasionally from dominant negative mutations in *LMNA*.<sup>276–280</sup> *ZMPSTE24* is an important metalloproteinase that processes lamin A; in the face of *ZMPSTE24* deficiency, prelamin A accumulates and leads to nuclear membrane toxicity.

## Stiff Skin Syndrome

Stiff skin syndrome (SSS) is a highly heterogeneous condition with scleroderma-like changes and associated contractures. Characterized by cutaneous and subcutaneous induration that first develops between the neonatal period and early childhood, SSS is most severe on the legs, thighs, buttocks, and overlying joints.<sup>281–286</sup> Congenital fascial dystrophy is considered a subset in which the involvement exclusively involves the fascia. Contractures primarily involve the lower extremities with characteristic demarcation at the inguinal canal, although the shoulder girdle may also be affected.<sup>287</sup> Joint stiffness begins during early childhood, can significantly limit movement, and can be progressive, although the skin induration is relatively stable. Hypertrichosis may be associated (primarily of the lumbar area), but viscera are not affected. Biopsies show a characteristic lattice-like array of thick collagen, although the site is variable (e.g., may involve dermis and subcutaneous tissue or fascia or both); inflammation and mucin deposition are absent.<sup>288,289</sup> The condition needs to be distinguished from scleredema neonatorum, subcutaneous fat necrosis, scleroderma, and other scleroderma-like conditions, including progeria.<sup>290</sup> Systemic administration of corticosteroids and other immunosuppressive agents has resulted in no improvement. Management is through physical therapy, which should be initiated as early as possible.<sup>291</sup>



**Figure 6-18** Progeria. Alopecia, subcutaneous atrophy, prominent scalp veins, and bird-like facies. (Courtesy of Schachner LA, Hansen RC, editors. Pediatric dermatology, 3rd ed. New York: Elsevier; 2003.)

## Winchester Syndrome

This autosomal recessive disorder has been described in fewer than a dozen patients<sup>292</sup>; in the reported cases, parents have been consanguineous. It is characterized by short stature, coarse facies, corneal opacities, thickened leathery and hypertrichotic skin, hypertrophic lips and gingivae, generalized osteolysis and progressive painful arthropathy with joint stiffness and contractures of distal phalanges.<sup>293</sup> Osteolysis may first be detectable after 1 year of age and can be progressive. Symmetrical restrictive banding has been reported to develop in early adulthood.<sup>294</sup> The disorder has been attributed to mutations in both alleles of matrix metalloproteinase 2 (*MMP2*).<sup>295,296</sup> Nodulosis, arthropathy, and osteolysis (NAO) and Torg syndromes are allelic.<sup>296,297</sup>

## Buschke–Ollendorff Syndrome

Buschke–Ollendorff syndrome is an autosomal dominant disorder that when fully expressed manifests as connective tissue nevi (with increased elastic fibers, collagen, or both) and osteopoikilosis.<sup>298–302</sup> The estimated incidence is estimated at 1:20,000.<sup>303</sup> It results from loss-of-function mutations in the *LEMD3* gene, which lead to enhanced TGF-β signaling.<sup>304,305</sup> Defects in *LEMD3* have also been detected in cases of isolated osteopoikilosis. In some affected individuals, dermal lesions are absent<sup>306</sup>; in others the radiographic changes are not seen.<sup>307</sup>

The connective tissue nevi appear as collections of subtle, 3-mm, skin-colored to yellow papules or plaques (dermatofibrosis lenticularis disseminata) on the buttocks, proximal trunk, and limbs. Most patients first develop lesions in early childhood.<sup>308–310</sup> The bony lesions most commonly appear after 15 years of age. They are discrete spherical areas of increased radiodensity, most often noted in the epiphyses and metaphyses of long bone, pelvis, scapulae, and carpal and tarsal bones (Fig. 6-19). The osteopoikilosis causes no clinical problems, but in the absence of cutaneous changes may be misdiagnosed as bony metastases. Other skeletal abnormalities including short stature, otosclerosis, spinal stenosis,<sup>299</sup> supernumerary vertebrae and ribs, syndactyly,<sup>311</sup> and ossifying fibromas<sup>312</sup> have been described. Limited anterior-posterior X-rays of the hands, wrists, ankles, knees, and pelvis rather than a full skeletal survey have been recommended.<sup>313</sup> Connective



**Figure 6-19** Buschke–Ollendorff syndrome. An oncology consultation was recommended, because the small round radiodensities on X-rays of this boy with Buschke–Ollendorff syndrome were not recognized to be osteopoikilosis.

tissue nevi (isolated or in association with tuberous sclerosis or Proteus syndrome,<sup>313,314</sup> papular elastorrhexis,<sup>315</sup> morphea, and PXE are the most common disorders considered in the differential diagnosis. The lesions of papular elastorrhexis resemble dermatofibrosis lenticularis disseminata but show decreased, fragmented elastic fibers rather than elastomas. Although usually sporadic, papular elastorrhexis has been described as familial with an AD mode of inheritance.<sup>316</sup> No therapy is available or necessary.

## Lipoid Proteinosis

Lipoid proteinosis (hyalinosis cutis et mucosae) is an autosomal recessive disorder characterized by hoarseness beginning in infancy and the later appearance of yellowish, beaded papules and nodules in the skin.<sup>317–319</sup> Both the hoarseness and the cutaneous lesions result from the abnormal deposition of hyaline material at the dermal–epidermal and microvascular basement membranes and papillary dermis.<sup>320</sup> The underlying molecular basis of lipoid proteinosis is mutations in extracellular matrix protein 1 (*ECM1*), a secreted protein that may play roles in skin adhesion and protein interactions near the basement membrane.<sup>321,322</sup> Interestingly, *ECM1* is an autoantigen in lichen sclerosus (see Chapter 22).<sup>323</sup>

Hoarseness secondary to vocal cord involvement is a clinical feature in virtually every case, and adolescents and adults with this disorder can be recognized instantly because of their husky voice and thickened eyelids. The voice may be hoarse from birth or become so within the first few years of life and becomes progressively worse during early childhood. Young children most commonly show vesicles or bullae that rapidly erode and become crusted.<sup>324,325</sup> Ultrastructural analysis of these lesions and cultured keratinocytes shows “free-floating” intact desmosomes, consistent with the role of *ECM1* in cell–cell adhesion.<sup>326</sup> Peculiar linear or discrete varioliform scars subsequently develop, particularly on the face, trunk, and upper extremities (Fig. 6-20). Herpes simplex infection, impetigo, or epidermolysis bullosa may be considered as alternative diagnoses.

Patients first develop the typical discrete or confluent 2- to 3-mm yellowish-white to yellowish-brown papules in later childhood. These papules are found most commonly on the face, eyelids, neck, and hands. In about 50% of individuals, a string of bead-like papules, often followed by a loss of cilia, appears on the free eyelid margins. The flexural areas often show a yellow waxy appearance with diffuse thickening of the skin. Many adults with lipoid proteinosis have hyperkeratotic plaques on elbows, knees, and palms, with infiltrative plaques at sites of trauma.

Also characteristic in patients with extensive manifestations are eversion of the lips (with their surfaces studded with tiny yellow nodules), hypertrophic or vegetative lesions at the corners of the mouth, round papules just below the lip on the midline of the chin, and radiating fissures at the corners of the mouth. Partial alopecia of the scalp, eyebrows, eyelashes, or bearded area is common by later childhood. Other features that have been described are hypohidrosis, hypertrichosis, hypoplasia or aplasia of permanent teeth, parotid pain and recurrent parotid swelling as a result of obstruction of the Stensen duct, and impaired nail growth.

Because of hyaline deposition, the tongue becomes thick, firm, and woody; is bound to the floor of the mouth; and is difficult to extrude. The soft palate, tonsils, uvula, and undersurface of the tongue show extensive irregular yellow-white infiltrations. Dysphagia caused by pharyngeal infiltration and respiratory obstruction as a result of severe laryngeal involvement can complicate the disorder. Central nervous system involvement has been associated with attacks of rage and psychomotor or grand mal seizures. Usually, however, the central nervous system involvement is restricted to asymptomatic calcification (seen in 70% of patients older than 10 years of age), which can be seen on radiographic examination as bilateral bean-shaped opacities above the sella turcica.

Diagnosis is aided by a history of hoarseness from early childhood; thickening, stiffening, and difficulty in extrusion of the tongue; an impaired ability to swallow; characteristic involvement of the skin and mucous membranes; and histopathologic examination of involved tissue. Histologic features consist of thick homogeneous bands of



**Figure 6-20** Lipoid proteinosis. **(A)** Linear or varioliform scars develop after clearance of the vesicular, crusted lesions of childhood. **(B)** Confluent bead-like papules line the upper eyelid in about 50% of individuals with lipoid proteinosis but tend to first appear later in childhood.

eosinophilic, periodic acid-Schiff-positive, hyaline-like amorphous material in the upper dermis, with an associated patchy distribution surrounding blood vessels, sweat glands, and arrector pili muscles.

Lipoid proteinosis has a chronic but relatively benign course. Treatment is chiefly symptomatic and consists of surgical or laser removal of laryngeal nodules or tracheostomy for laryngeal obstruction and cosmetic measures such as laser resurfacing or dermabrasion for unappealing cutaneous lesions on the face or other exposed surfaces. Acitretin can improve the hoarseness<sup>327</sup> and skin lesions.<sup>325</sup>

## Infantile Systemic Hyalinosis and Juvenile Hyaline Fibromatosis

Infantile systemic hyalinosis (ISH) and juvenile hyaline fibromatosis (JHF) are similar autosomal recessive conditions that represent allelic variants resulting from mutations in the gene that encodes capillary morphogenesis gene 2 (CMG2; also called *anthrax toxin receptor 2* or *ANTXR2*).<sup>328–330</sup> CMG2 is thought to play a role in basement membrane matrix assembly and endothelial cell morphogenesis (in addition to being the receptor for anthrax).<sup>331</sup> The histologic and ultrastructural features of ISH and JHF are also similar, and a unified classification based on severity has been suggested.<sup>332</sup> The deposition of hyaline material, characterized as an acellular proteinaceous material that appears pink and glassy in routine sections, occurs in multiple organ systems.

ISH represents the most severe end of the spectrum<sup>333</sup> with manifestations present within the first few weeks of life, although intrauterine growth retardation and reduced fetal movements have been described. The predominant cutaneous findings of ISH are diffusely



**Figure 6-21** Juvenile hyaline fibromatosis. Note the nodules on the nose and the gingival hypertrophy. Fine papules can be seen on the nose and perinasal area; the patient had dozens of visible 1- to 2-mm papules on the chin as well.

thickened skin; small nodules of the perianal region, ears, and lips; and a reddish-blue to hyperpigmented discoloration overlying bony prominences.<sup>334–336</sup> The joint contractures and osteopenia lead to the frog-leg position and virtual immobility that are typical of affected infants.<sup>337</sup> Patients with ISH also develop malabsorption and a protein-losing enteropathy, leading to diarrhea and failure to thrive. Oral manifestations include thickening of the oral mucosa, extensive overgrowth of the gingival tissue, marked curvature of the dental roots, and replacement of periodontal ligament by hyaline fibrous material. These oral findings may cause difficulty in feeding and compound the nutritional deficiency resulting from malabsorption. Thyroid dysfunction has also been described.<sup>338</sup> The condition is usually fatal by 2 years of age because of recurrent pulmonary infections and diarrhea.

JHF, also known as *juvenile systemic hyalinosis*, encompasses mild to moderate disease within the spectrum of CMG2 mutations.<sup>339</sup> JHF has a later onset than ISH and patients survive into adulthood. JHF is characterized by joint contractures (especially of the small joints of the hands and feet), gingival hypertrophy, generalized osteopenia, and papular and nodular skin lesions, typically on the scalp, perianal and perinasal areas (Fig. 6-21), palms, and trunk.<sup>340,341</sup> Some children experience rectal bleeding because of the anal lesions.<sup>342</sup>

There is no satisfactory treatment at this time, although administration of interferon  $\alpha$ -2b led to remarkable improvement in skin nodules, gingival hypertrophy, and joint mobility in a girl with JHF.<sup>343</sup> Early dental intervention is important, and gingivectomy may be required<sup>344</sup> with careful anesthetic management.<sup>345,346</sup> Lesions can be partially excised if ulcerated or disfiguring.

The complete list of 346 references for this chapter is available online at <http://expertconsult.inkling.com>.

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## Hair

Hair is a protein by-product of follicles distributed everywhere on the body surface except the palms, soles, vermillion portion of the lips, glans penis, penile shaft, nailbeds, and sides of the fingers and toes. Although hair is of minimal functional benefit to humans, the psychologic effects of disturbances of hair growth are commonly a source of great concern to children, adolescents, and their parents.

In the human fetus, groups of cells appear in the epidermis at about the eighth week of gestation. These differentiate to form the hair follicles, and hair begins to develop between the eighth and twelfth weeks of fetal life. This growth continues throughout fetal development. Although there are indications that some hair is lost during gestation and at the time of birth, the majority of hairs on the newborn are 5 to 6 months old.

Lanugo hairs are fine, soft, unmedullated, and poorly pigmented hairs seen only in fetal and neonatal life, except in the rare hereditary syndrome hypertrichosis lanuginosa. They appear as a fine, dense growth over the entire cutaneous surface of the fetus. Lanugo hair is normally shed *in utero* in the seventh or eighth month of gestation but may cover the entire cutaneous surface of the premature newborn infant. Postnatal hair may be divided into vellus and terminal types. Vellus hairs are the fine, lightly pigmented hairs seen on the arms and faces of children. Terminal hairs are the mature, thick, darker hairs on the scalp, eyebrows, eyelashes, and areas of secondary-sexual hair distribution. The number and distribution of individual hair follicles are genetically determined and constant from birth. As the infant's skin grows, however, the density of hair follicles reduces from 1135 per cm<sup>2</sup> at birth to 615 per cm<sup>2</sup> by adulthood.

The average human scalp contains 100,000 hairs. The average growth rate of terminal hair is approximately 2.5 mm/week (1 cm/month). The hair shaft represents the equivalent of the stratum corneum of skin, with the follicular keratinocytes dictating the characteristics of the shaft. The hair root is characterized by three definable cyclic stages of growth: anagen (Fig. 7-1, A), catagen, and telogen (Fig. 7-1, B; Box 7-1). The human hair follicle has a fairly long phase of regular growth (the anagen phase) that lasts 2 to 6 years, with an average of 3 years. The hairs then undergo a period of partial degeneration (the catagen phase), lasting up to 3 weeks, followed by a resting (telogen or club) phase. The telogen phase of the follicle lasts for about 3 months. At the end of this time, new growth is initiated. As new hairs grow, they push out the old telogen hairs that have remained in the resting follicles. In healthy individuals, 85% to 90% of the scalp is in the actively growing anagen stage, and 1% is in the brief transitional (catagen) stage; 10% to 15% is in the resting or telogen stage, with an average of 50 to 100 hairs shed and simultaneously replaced each day. Although scalp hair has a long anagen phase, eyelash and extremity hair have a lower anagen/telogen ratio and thus tend to be shorter.

### Neonatal Hair

The first crop of terminal scalp hair is in the actively growing anagen phase at birth, but within the first few days of life there is a physiologic conversion to the telogen phase. Consequently a high proportion of neonatal scalp hairs are shed during the first 4 months of life (Fig. 7-2). This telogen shedding (telogen effluvium of the newborn) usually is gradual hair loss, particularly between 2 and 4 months and most noticeable at the occipital area. Rarely the hair loss occurs in the first 4 weeks of life in a frontal-temporal pattern.<sup>1</sup> This physiologic hair

shedding at the occipital area is not related to the baby's sleeping position (i.e., friction).<sup>2</sup> Replacement of the first terminal hairs is generally completed before the first 6 months of life. The neonatal hairline commonly extends along the forehead and temples to the lateral margin of the eyebrows. These terminal hairs gradually convert to vellus hairs during the first year of life. Premature infants are often covered by lanugo hairs, which are more densely distributed on the face, limbs, and trunk. This retention of lanugo hair is probably related to the cyclic activity *in utero* and the normal shedding of telogen vellus hairs in the fetus during the last few weeks of gestation.

### Alopecias

Clinical examination allows hair loss disorders to be divided into non-scarring (non cicatricial) or scarring (cicatricial) types (Box 7-2).<sup>3-5</sup> Causes of non-scarring alopecia include alteration of the hair growth cycle, inflammatory cutaneous disease, and structural abnormalities of the hair.<sup>6,7</sup> Some traumatic disorders such as traction alopecia, pressure alopecia, or trichotillomania can scar if severe but often resolve without clinical evidence of scarring. Evaluation typically involves gentle traction on the hair (hair-pull test) to determine if hair comes out easily (as in loose anagen syndrome, alopecia areata [AA], or telogen effluvium) and microscopic or trichoscopic evaluation of hair shafts to seek hair shaft abnormalities (Box 7-3).

#### NONSCARRING ALOPECIAS WITH HAIR SHAFT ABNORMALITIES

##### Hair Shaft Abnormalities with Increased Fragility

Variations in the structure of the hair shaft are a common occurrence and at times may provide clues to other pathologic abnormalities (Box 7-4). Because each hair shaft anomaly has a distinctive morphology, the diagnosis often can be established in the office by trichoscopy (using a dermatoscope)<sup>8</sup> (see Box 7-3)<sup>5</sup> or by microscopic examination of snipped hairs.<sup>9</sup> Other than reduction of trauma to reduce breakage, there is no effective treatment for this group of disorders.

**Trichorrhexis Nodosa.** Trichorrhexis nodosa, the most common hair shaft anomaly, is a distinctive disorder manifested by increased fragility.<sup>6,9</sup> Grayish-white nodules may be seen on the hair (Fig. 7-3), which under trichoscopy or light microscopy have the appearance of two interlocking brushes or brooms, the result of segmental longitudinal splitting of fibers without complete fracture. The disorder features dry, lusterless, short hair that is easily fractured.

Usually "acquired" in adolescents without other issues, trichorrhexis nodosa most commonly results from trauma to the hair. The injury may result from the use of hot combs, excessively hot hairdryers, hair straighteners, other chemical treatments, or from the cumulative cuticular damage from vigorous combing and brushing, repeated salt-water bathing, prolonged sun exposure, and frequent shampooing. Cream rinses and protein conditioners are helpful. If hair-straightening procedures, vigorous grooming habits, and thermal and chemical trauma to the hair are discontinued, the acquired form of trichorrhexis nodosa generally improves within 2 to 4 years.

Less commonly trichorrhexis nodosa is genetic and manifests during infancy. Infants with the autosomal dominant form show normal hair at birth, but the hair that regrows within a few months is abnormal; the hair defect tends to improve with advancing age. Trichorrhexis nodosa may also be a manifestation of children with the late-onset form of argininosuccinic aciduria, a condition that results



**Figure 7-1** Stages of growth of the hair root. **(A)** Anagen hairs are the growing hairs that comprise 90% of hair at any time and persist for several years. Anagen hairs are pigmented and have a translucent sheath. **(B)** Telogen hairs are in a resting phase that persists for 3 months. Note the small bulb and lack of sheath.

#### Box 7-1 Cyclic Stages of Human Hair Growth

1. Anagen phase (active growth phase) lasts 2 to 6 years (average 3 years)
2. Catagen phase (stage of partial degeneration) lasts 10 to 14 days
3. Telogen phase (resting stage) lasts 3 to 4 months



**Figure 7-2** Telogen shedding of the newborn. This 4-month-old girl shows generalized thinning of scalp hair, reflecting telogen effluvium.

#### Box 7-3 Special Tests of Hair and Scalp

**Hair pull:** Grasp about 50 hairs between first three fingers and pull gently but firmly away from scalp at four scalp regions (i.e., frontal, occipital, temporal bilaterally); positive pull test means more than 10% of hairs pull out easily (are in telogen) and is seen with active alopecia areata.

**Hair tug:** Hold a group of hairs with one hand and use other hand to pull away at distal end, looking for hair breakage (which can then be analyzed microscopically in a hair mount). This can be helpful with fragile hair syndromes such as monilethrix.

**Hair mount:** Hairs are separated, oriented side-by-side on a glass slide, covered with mounting medium (such as Permount), and covered with a coverslip without air bubbles. This technique allows one to distinguish anagen from telogen bulbs based on shape and pigmentation, distorted bulbs and cuticles (as in loose anagen syndrome), and hair shaft abnormalities.

**Trichoscopy:** Can replace hair mounts and microscopy when examining shaft. Disease-specific findings such as for alopecia areata (follicular openings showing yellow dots; "exclamation-point" hairs), tinea capitis (comma or corkscrew hairs), and trichotillomania (coiled or flame hairs); black dots at follicular opening suggest broken hairs and can be seen with alopecia areata, tinea, and trichotillomania.

from lack of argininosuccinase. In this condition, the hair is usually normal at birth and first becomes fragile at 1 to 2 years of age with a dull, matted appearance, especially at the occipital area. The hair defects are associated with psychomotor retardation, cerebellar ataxia, and a marked increase of argininosuccinic acid in the blood, urine, and cerebrospinal fluid.<sup>10,11</sup> Dietary treatment of the metabolic abnormality leads to normalization of the appearance and integrity of the hair. Similar clinical manifestations are found in infants with citrullinemia, caused by a deficiency of argininosuccinic acid synthetase. Trichorrhexis nodosa is the most common hair shaft abnormality, but pili torti has been described and hair bulbs may be atrophic. Some patients show an eruption that resembles acrodermatitis enteropathica. Trichorrhexis nodosa has also been described in oculodentodigital dysplasia (see [Group 2 Ectodermal Dysplasia](#) section),<sup>12,13</sup> trichothiodystrophy (TTD), and trichohepatointestinal syndrome, characterized by facial dysmorphism, liver disease, immune defects, and severe diarrhea requiring intravenous nutrition.<sup>14</sup>

**Monilethrix.** Monilethrix (beaded hair) is an autosomal dominant disorder characterized by partial alopecia from breakage and variation in hair shaft thickness with small node-like deformities that produce a beaded appearance and internodal fragility. The nodal pattern can be seen by trichoscopy but can be subtle.<sup>15</sup> In individuals with this disorder, normal neonatal lanugo hairs are shed during the first few weeks of life. The regrown hair, which generally appears at about the second month of life, is dry, lusterless, and brittle and fails to grow to

#### Box 7-2 Clinical Examination of Alopecia

1. Overall characteristics: pattern of loss, extent, color, texture, length, breakage
2. Scalp features: scarring vs. nonscarring, inflammation, trichoscopy (follicular openings), pigmentary change, scaling, crusts, pustules
3. Hair beyond scalp: eyebrows, lashes, extremity hair, secondary sexual hair if adolescent
4. Special tests: trichoscopy of shaft, hair pull, hair tug, hair mount (see Box 7-3)

#### Box 7-4 Structural Hair Shaft Defects with Fragility (and Associated Disorders)

##### Trichorrhexis Nodosa

- Trauma (most common)
- Argininosuccinic aciduria
- Citrullinemia
- Oculodentodigital dysplasia
- Trichoiodystrophy
- Trichohepatoenteric syndrome

##### Monilethrix

- Hair keratin mutations (*KRT81*, *KRT83*, *KRT86*)
- Desmoglein 4 mutations

##### Trichorrhexis Invaginata

- Netherton syndrome

##### Pili Torti

- Menkes syndrome
- Crandall syndrome
- Björnstad syndrome
- Bazek-Dupré-Christol syndrome
- Rombo syndrome
- Hypotrichosis with juvenile macular degeneration
- Mitochondrial enzyme defects

##### Trichoiodystrophy

- Group I: mutations in *XPD*, *XPB*, *p8*
- Group II: mutations in *TTDN1*
- Group III: Pollitt syndrome, Sabinas syndrome (genes unknown)



**Figure 7-3** Trichorrhexis nodosa. Grayish-white nodules, which resemble two interlocking brushes or brooms microscopically, may be seen on the hair.

any appreciable length because of breakage (Fig. 7-4, A). In severe cases, the infant may remain bald or the scalp hair may be sparse, easily fractured, and stubble-like with follicular prominence from keratosis. Although generally a disorder of scalp hair, body hairs may also be affected. The clinical findings are limited to the occiput and nape in more limited cases (Fig. 7-4, B). Occasionally this disorder is not apparent during infancy but becomes apparent later in childhood or during adult life. Follicular keratosis is associated in some pedigrees and may affect the face, scalp, and extremities. Some patients show koilonychia. Spontaneous improvement or remission may occur at puberty or during pregnancy, suggesting a hormonal influence,<sup>16</sup> but the condition may persist unchanged throughout adulthood. Administration of oral retinoids<sup>17</sup> or 2% minoxidil<sup>18</sup> have been reported to improve the alopecia.

Monilethrix most commonly is autosomal dominant and results from mutations in hair (or trichocyte) keratins. These hair keratins have a high cysteine content, making them "hard" keratins with a high degree of crosslinking. Of the 26 known hair follicle-specific



**Figure 7-4** Monilethrix. (A) The hair is dry, lusterless, brittle, and fails to grow to any appreciable length. The occipital area is most commonly and most severely affected in most cases. (B) The follicles are prominent and often hyperkeratotic. This girl was scratching at her occipital area, which led to further breakage and an erosion.

keratins, three have been associated with monilethrix and all are type II keratins.<sup>19</sup> Mutations in *KRT81* and *KRT86* are most common,<sup>20</sup> but a mutation in *KRT83* has been reported. Because keratins provide structural integrity to hair, abnormalities in these keratins lead to hair fragility with breakage occurring at the internodal sites. Mutations in hair keratins have also been linked to pure hair and nail ectodermal dysplasia (PHNED) (*KRT85*), woolly hair with hypotrichosis (*KRT71* and *KRT74*), and pseudofolliculitis barbae (*KRT75*). The majority of the hair keratins remain unlinked to human phenotypes but may impart variants in hair strength, texture, or curliness.<sup>21</sup>

Autosomal recessive monilethrix has been linked to mutations in *DSG4*, which encodes desmoglein 4, a transmembrane cell-adhesion molecule of the cadherin family that is predominantly expressed in the hair cortex and upper cuticle.<sup>22,23</sup> Desmoglein 4 is thought to integrate keratin filaments into desmosomes.<sup>24</sup> Desmoglein 4 mutations may also manifest as autosomal recessive hypotrichosis, which resembles monilethrix but lacks the characteristic beaded appearance of the hair shaft under light microscopy.<sup>25</sup>

**Pseudomonilethrix.** Pseudomonilethrix was originally described as an autosomal dominant developmental defect of fragile hair with irregularly shaped nodes.<sup>7,26</sup> In fact, the hair changes are artifactual and related to overlapping hairs under the pressure of an overlying glass slide.<sup>27</sup> Pseudomonilethrix is seen more commonly when fine hairs are handled by forceps.

**Trichorrhexis Invaginata.** Trichorrhexis invaginata (bamboo hair) is characterized clinically by dry, lusterless, easily fractured, sparse, and short hair. Under light microscopy, the hairs show a

peculiar intussusception or telescope-like invagination along the hair shaft, which microscopically resembles the ball-and-cup joints of bamboo.<sup>6,28</sup> Variations in trichorrhexis invaginata occur, most commonly “golf-tee hair,” presenting the expanded proximal end of an invaginate node.<sup>29</sup> The hair defect in trichorrhexis invaginata is thought to be abnormal keratinization of the hair shaft, which results in softening of the hair cortex and promotes intussusception of the distal portion of the hair shaft into the softer proximal portion.

Although trichorrhexis invaginata may occur as an isolated finding, this hair shaft abnormality is characteristic of Netherton syndrome (Fig. 7-5), an autosomal recessive genodermatosis that has been linked to mutations in *SPINK5* (see Chapter 5).<sup>30</sup> Neonates with this disorder characteristically show generalized exfoliative erythroderma and failure to thrive, often associated with hypernatremic dehydration, recurrent infections, and sepsis. Severely affected neonates may show extremely sparse and even absent hair, making the diagnosis based on hair shaft examination difficult. However, the eyebrows are almost always short and broken (see Fig. 7-5, A); eyebrow hairs should be examined in cases in which the abnormality cannot be demonstrated from scalp hair, and trichoscopy (dermoscopy) can be helpful.<sup>5,31–34</sup>

Beyond infancy, many affected individuals show the characteristic skin finding of ichthyosis linearis circumflexa, with walls of scale surrounding red patches, in addition to their dry, lusterless hair that breaks easily (see Fig. 7-5, B, and Figs. 5-20 and 5-21). Atopic conditions usually accompany the ichthyosis. Although spontaneous remission of the hair defect has been described (generally between 6 and 15 years of age), the vast majority show persistence.

**Pili Torti.** Pili torti hairs show three or four regularly spaced twists that occur at irregular intervals along the hair shaft.<sup>6,35</sup> The hair shaft appears flattened at the site of the twist, which is almost always

through 180 degrees. The dry, fragile hair is often lighter in color than expected and shimmers in reflected light with a “spangled” appearance because of the hair twisting. The hair tends to be short, especially in areas subject to trauma, and may extend out from the scalp. Pili torti must be distinguished from twisted hair, which has been described in association with anorexia nervosa.<sup>36</sup>

Pili torti may occur as an isolated phenomenon with onset at birth or early infancy. This genetic disorder shows both autosomal dominant and autosomal recessive inheritance patterns. The appearance of the hair in patients with pili torti may become more normal with time, although twisted hairs can still be found in the adult scalp; those who still manifest the disorder at puberty, however, are unlikely to show significant improvement with age. A late-onset autosomal dominant form has also been described, in which brittle hair and patchy alopecia develop after puberty. Mental retardation has been noted in some pedigrees. Pili torti has been associated with several mitochondrial disorders (see *Pili Torti* section).

Menkes syndrome (trichopoliodystrophy) is an X-linked recessive neurodegenerative disorder that affects male infants. Classic Menkes syndrome affects 90% to 95% of patients, with a less common mild form associated with long survival and occipital horn syndrome (previously called X-linked cutis laxa or Ehlers-Danlos syndrome type IX) showing largely connective tissue manifestations. Carrier females may exhibit pili torti. Classical Menkes syndrome is characterized by coarse facies; pili torti; temperature instability; seizures; psychomotor retardation; arterial intimal changes; soft, doughy skin; joint laxity; low or absent plasma copper and ceruloplasmin levels; growth failure; increased susceptibility to infection; and death, generally by age 3 or 4 years.<sup>37,38</sup> Clinical features often include premature birth, hypothermia, and relatively normal development until 2 to 6 months of age, when drowsiness and lethargy are noted, intractable seizures begin, and growth and development cease. Rarely neonates demonstrate erythroderma as an early sign.<sup>39</sup>

Usually the hair is fine, dull, sparse, and poorly pigmented in infancy; it stands on end and looks and feels like steel wool (Fig. 7-6). Additional features include tortuosity of cerebral and other medium-sized arteries; osteoporosis; frequent subdural hematomas; widening of the metaphyses with spurring; and frequent fractures, at times simulating the radiologic findings characteristic of patients with battered child syndrome. Although pili torti is generally a prominent feature of this disorder, other less commonly reported hair abnormalities include monilethrix and trichorrhexis nodosa.



**Figure 7-5** Netherton syndrome. (A) The characteristic microscopic features of Netherton hair (trichorrhexis invaginata) are often found in eyebrow hairs. Note the sparse, broken brows and lashes in this young girl who also shows the periorbital dermatitis. (B) Short, broken hair throughout the scalp. Note the desquamative scaling and excoriations.



**Figure 7-6** Menkes syndrome. The hair is fine, dull, hypopigmented compared with other family members, and stands on end. It looks and feels like steel wool.

Menkes syndrome results from mutations in *ATP7A*,<sup>40</sup> which encodes a copper-transporting adenosine triphosphatase (ATPase) that incorporates copper into copper-dependent enzymes and maintains copper levels by removing excessive copper from the cytosol.<sup>41</sup> The combination of clinical features, bone abnormalities, and low plasma copper and ceruloplasmin levels establishes the correct diagnosis. Parenteral administration of copper histidine occasionally prevents neurologic degeneration and pigmentation if initiated in the neonatal or infantile period<sup>42</sup> but often is ineffective.<sup>43</sup>

Crandall syndrome, an X-linked recessive disorder, consists of pili torti with alopecia, sensorineural deafness, and hypopituitarism.<sup>44</sup> Björnstad syndrome is characterized by sensorineural deafness, pili torti, and occasionally mental retardation. The syndrome is autosomal recessive, but families with an autosomal dominant pattern have been described.<sup>45</sup> The recessive form has more recently been linked to mutations in *BCS1L*, which encodes an ATPase needed to assemble complex III in the mitochondria. More severe defects in *BCS1L* markedly increase reactive oxygen species and are lethal to neonatal infants with multisystemic involvement (complex II deficiency and growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death [GRACILE] syndrome).<sup>46</sup>

Bazex–Dupré–Christol and Rombo syndromes are X-linked dominant traits characterized by congenital hypotrichosis with pili torti, number facial milia, trichoepitheliomas, vellus hair cysts, and an increased risk of the early development of basal cell carcinomas.<sup>28,47–50</sup> Distinguishing features are follicular atrophoderma, hypohidrosis, comedones and facial and neck pigmentation in Bazex–Dupré–Christol syndrome, and atrophoderma vermiculatum and photosensitivity in Rombo syndrome. Females often do not show the hypotrichosis, with normal and pili torti hairs intermingled.<sup>51</sup>

Hypotrichosis with juvenile macular dystrophy (HJMD) is characterized by the development of sparse, short hair from birth or in the first months of life. Fusiform beading and pili torti may be seen by microscopy. Macular degeneration first develops in the first or second decade, leading to blindness by early adulthood. Patients suspected of having HJMD should have annual ophthalmologic evaluations, because early retinal pigmentation and atrophy precede the decrease in visual acuity. The disorder is autosomal recessive and caused by mutations in *CDH3*, which encodes P-cadherin.<sup>52,53</sup> *CDH3* mutations also cause ectodermal dysplasia, ectrodactyly, and macular dystrophy (Table 7-1).

Individuals with mitochondrial enzyme abnormalities have shown a wide variety of abnormalities, predominantly failure to thrive and neuromuscular changes; however, skin or hair abnormalities have been described in 10% of affected children.<sup>54</sup> Hair abnormalities range from alopecia to dry, thick brittle hair to hypertrichosis, especially on the back. Syndromic disorders with hair abnormalities may also affect mitochondrial function (e.g., Björnstad syndrome and cartilage-hair hypoplasia). Light-microscopy examination of affected hair has shown a variety of hair shaft defects associated with increased fragility including pili torti, TTD, trichorrhexis nodosa, and diffuse longitudinal grooving with flattened hair shafts.<sup>54,55</sup> Patchy erythematous lesions have been described, and many of the patients with skin manifestations have shown mottled pigmentation.

**Pili Bifurcati.** Pili bifurcati is an uncommon anomaly of hair growth characterized by intermittent bifurcation of the hair shaft in which affected hairs divide into two separate shafts that subsequently become rejoined along the hair shaft.<sup>56,57</sup> This bifurcation is repeated at intervals, and the anomaly appears to be transitory, with only a small percentage of hairs exhibiting the bifurcation. This disorder should not be confused with pili multigemini, a disorder in which multiple hairs project from a single hair follicle.

**Trichothiodystrophy.** TTD is a heterogeneous group of autosomal recessive disorders in which patients have dry, brittle, cysteine-deficient hair as an isolated finding or in association with often-multisystemic disease.<sup>58</sup> To date, four genes have been linked to TTD: *ERCC2* (*XPD*), *ERCC3* (*XPB*), *p8* or *GTF2H5* (*TTDA*), and *C7orf11* (*TTDN1*). The function of *TTDN1* is not well understood, but it likely regulates cell cycling and transcription efficiency.<sup>59</sup> The other three genes encode subunits of transcription/repair factor IIH (TFIIH), a

multiprotein complex involved in transcription and nucleotide excision repair.<sup>60,61</sup> Unlike xeroderma pigmentosum, TTD is not prone to cancer, although squamous cell carcinoma has been described.<sup>62</sup>

Light microscopy of TTD hairs shows a wavy, irregular outline and a flattened shaft that twists like a folded ribbon. Two types of fracture may be seen: trichoschisis (clean transverse fracture) or an atypical trichorrhexis nodosa with only slight splaying of the cortical cells. Polarizing microscopy is critical to show the characteristic alternating light and dark bands, the “tiger-tail” appearance.<sup>63,64</sup> Although the severity of hair shaft defects is inversely proportional to the hair sulfur content, there is no association between the extent of systemic disease and percentage of abnormal hairs.<sup>64</sup> Sparse hair is often associated with the shaft defect. Some patients have described cyclic hair loss with fever, which may reflect a mutation leading to thermosensitive *XPD*.

A recent review of 112 published cases of TTD described the abnormalities beyond hair defects.<sup>65</sup> Ichthyosis has been noted in 65% and clinical evidence of photosensitivity in 24% of these patients. The ichthyosis may resemble autosomal recessive congenital ichthyosis (ARCI) or ichthyosis vulgaris (see Chapter 5), and some patients show marked depletion of the granular layer in skin-biopsy sections.<sup>66</sup> Of the patients who have TTD with ichthyosis, 37% show a collodion phenotype at birth.<sup>65</sup> Patients may also show xerosis, palmoplantar keratoderma, atopic dermatitis, and/or follicular keratosis.<sup>66</sup> Nail abnormalities have been described in 63% of patients overall, especially dystrophy with thickening or yellow discoloration.

Among the most common noncutaneous features are developmental delay/intellectual impairment (86%), short stature and low weight (73%),<sup>67</sup> and ocular abnormalities (51%, especially cataracts). Facial dysmorphisms are seen in 66% of patients, especially microcephaly, large or protruding ears, and micrognathia. Bone abnormalities are seen radiographically in 38%, particularly osteosclerosis and delayed bone age. Gonadal abnormalities were noted in 14% overall, most commonly hypogonadism and cryptorchidism. Recurrent infections have been noted in 46%, particularly involving the respiratory and gastrointestinal tracts and the inner ear, but were uncommonly associated with immunodeficiency or neutropenia.<sup>68,69</sup> Overall, mortality in the first decade of life is increased 20-fold. Complications during pregnancy are noted in 26% of patients, most commonly intrauterine growth retardation, but also preterm delivery; preeclampsia; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; and prematurity.<sup>70,71</sup>

Subgroups of TTD have been classified based on clinical characteristics (brittle hair, intellectual impairment, decreased fertility, and short stature [BIDS]; ichthyosis, brittle hair, infertility, developmental delay, short stature [IBIDS]/Tay syndrome, photosensitivity, ichthyosis, brittle hair, infertility, developmental delay, short stature [PIBIDS]). However, a new classification has been proposed that divides patients based on their mutations as group I (mutations in genes encoding subunits of TFIIH: *XPD*, *XPB*, *p8*), II (*TTDN1*), and III (no known molecular basis).<sup>66</sup> Group I includes patients with photosensitivity (either clinical or *in vitro*) and is the most common subtype. Most individuals in group II are not photosensitive and show an increased risk of delayed bone age, seizures, and autistic behavior.<sup>72</sup> Currently unclassified but nonphotosensitive patients (such as those with Pollitt and Sabinas syndromes)<sup>73</sup> are in group III. Using this classification, ichthyosis and the collodion-baby phenotype are most highly correlated with group I, whereas hypogonadism has been found more in groups II and III.

**Marie Unna Hypotrichosis.** Marie Unna hypotrichosis is an autosomal dominant disorder manifested by almost complete congenital absence of scalp hair, eyebrows, and eyelashes.<sup>74,75</sup> The hair regrows to normal density but is coarse, flattened, and twisted (Fig. 7-7). Beginning at puberty the hair becomes progressively sparser, particularly on the vertex and scalp margins, resulting in a high frontal and nuchal hairline. By adulthood, only a sparse fringe of hair at the scalp margin may remain, and eyelashes, eyebrows, and body hair, including secondary-sexual hair, tend to be sparse. Scattered follicular horny plugs may be associated. Other ectodermal structures are unaffected, except that 50% of affected individuals show exceptionally widely spaced upper incisor teeth. Mutations that cause Marie

**Table 7-1** Classification for Ectodermal Dysplasias

Disorder	Inheritance	Gene	Protein	Function
<b>GROUP 1</b>				
<b>TNF/TNFR Pathway</b>				
Hypohidrotic ectodermal dysplasia	XLR	<i>EDA1</i>	Ectodysplasin (EDA)	Membrane ligand
Hypohidrotic ectodermal dysplasia	AD	<i>EDAR</i> <i>EDARADD</i>	EDA receptor (EDAR) EDAR-associated death domain	Receptor of EDA Adaptor molecule
Hypohidrotic ectodermal dysplasia	AR	<i>EDAR</i> <i>EDARADD</i> <i>TRAF6</i>	See above TNF receptor associated factor 6	See above Activates IKK
<b>NF-κB Inhibitors</b>				
Hypohidrotic ectodermal dysplasia with immune deficiency (males) + osteopetrosis (males)	XLR	<i>NEMO/IKKγ</i>	NF-κB essential modulator	NF-κB activation
Incontinentia pigmenti (females)	XLD	<i>NEMO/IKKγ</i>	NF-κB essential modulator	NF-κB activation
Hypohidrotic ectodermal dysplasia with immune deficiency	AR	<i>IκBα</i>	IκBα	NF-κB activation
<b>Transcription Factors</b>				
Ectrodactyly-ectodermal dysplasia-clefting syndrome	AD	<i>p63</i>	p63	Transcription factor
Rapp-Hodgkin syndrome	AD	<i>p63</i>	p63	Transcription factor
Ankyloblepharon-ectodermal dysplasia-clefting syndrome (AEC)	AD	<i>p63</i>	p63	Transcription factor
Acrodermatogual-lacrimal-tooth (ADULT)	AD	<i>p63</i>	p63	Transcription factor
Limb-mammary syndrome	AD	<i>p63</i>	p63	Transcription factor
Trichodentosseous syndrome	AD	<i>DLX3</i>	DLX3	Transcription factor
Witkop syndrome	AD	<i>MSX1</i>	MSX1	Transcription factor
Ellis van Creveld syndrome	AR	<i>EVC, EVC2</i>	EVC, EVC2	Unknown
<b>GROUP 2</b>				
Clouston syndrome	AD	<i>GJB6</i>	Connexin 30	Intercellular junctions
Oculodentodigital dysplasia (ODDD)	AD	<i>GJA1</i>	Connexin 43	Intercellular junctions
Clefting-ectodermal dysplasia	AR	<i>PVRL1</i>	Nectin 1	Interacts with cadherins, esp. at adherens junctions
Ectodermal dysplasia-syndactyly syndrome	AR	<i>PVRL1</i>	Nectin 4	Interacts with cadherins, especially at adherens junctions
Ectodermal dysplasia: skin fragility syndrome (see Chapter 13)	AR	<i>PKP1</i>	Plakophilin 1	Desmosomal plaque/stability
Ectodermal dysplasia, ectrodactyly, and macular dystrophy	AR	<i>CDH3</i>	Cadherin 3/ P-cadherin	Adhesion molecule for cell-cell binding
Hypotrichosis with juvenile macular dystrophy	AR	<i>CDH3</i>	Cadherin 3/ P-cadherin	Adhesion molecule for cell-cell binding
Odontoonychodermal dysplasia (OODD)	AR	<i>WNT10A</i>	Wnt10A	β-catenin-mediated signaling
Hypohidrotic ectodermal dysplasia	AR, AD	<i>WNT10A</i>	Wnt10A	β-catenin-mediated signaling
Schöpf-Schulz-Passarge syndrome	AR	<i>WNT10A</i>	Wnt10A	β-catenin-mediated signaling

AD, Autosomal dominant; AR, autosomal recessive; IKK, inhibitor of kappa light polypeptide gene enhancer in B cells kinase; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; XLD, X-linked dominant; XLR, X-linked recessive.

Unna hypotrichosis affect *U2HR*, an open-reading frame upstream of the hairless gene that inhibits hairless expression; as a result, hairless expression and Wnt signaling are increased.<sup>76,77</sup>

#### Hair Shaft Abnormalities Without Increased Fragility

**Pili Annulati.** Pili annulati (ringed hair) is an autosomal dominant condition with onset shortly after birth. The hair looks shiny with attractive highlights, but alternating bright and dark bands are seen on close inspection. The bright areas are the result of light scattering from clusters of air-filled cavities within the cortex that appear as dark areas under light microscopy, especially in more proximal hair

regions.<sup>78</sup> Pili annulati may increase the risk of developing AA<sup>79</sup> and has been reported to markedly improve or clear after the occurrence of alopecia totalis.<sup>80</sup> The gene mutated in pili annulati has been linked to chromosome 12q24.33, but no mutations in candidate genes have been found.<sup>81</sup>

Pseudopili annulati is an unusual variant of normal hair in which bright bands are seen at intervals along the hair shaft. Secondary to periodic twisting or curling of the hair shaft, this banding is conspicuous only in blond hairs and represents an attractive optical effect caused by reflection and refraction of light by flattened and twisted hair surfaces.



**Figure 7-7** Marie Unna hypotrichosis. This adolescent's hair is coarse and lusterless. Her hairline is receding at the frontal and nuchal areas, and she paints her sparse brows with eyeliner. Her progressive alopecia will leave her largely alopecic as an adult.



**Figure 7-8** Woolly hair in association with ulerythema ophryogenes. The woolly, curly hair and ulerythema ophryogenes in this boy prompted consideration of Noonan syndrome, but the 11-gene Noonan syndrome panel revealed no mutations.

### Woolly Hair

Woolly hair describes a tight, curly hair that is usually present from birth and shows abnormalities under light microscopy.<sup>6</sup> The individual scalp hairs are fine and dry, light-colored, and corrugated at intervals, resembling the wool of sheep. Recognition of woolly hair is important because of the many associated abnormalities. The autosomal recessive disorders characterized by generalized woolly hair, keratoderma and dilated cardiomyopathy (Naxos disease and Carvajal syndrome) have been linked to mutations in desmoplakin<sup>82,83</sup> and plakoglobin,<sup>84</sup> two desmosomal proteins; keratoderma and woolly hair without cardiomyopathy may also result from mutations in *KANK2* (see Chapter 5). Diffuse woolly hair has also been associated with ocular abnormalities, keratosis pilaris atrophicans and/or ulerythema ophryogenes (Fig. 7-8), keratosis follicularis spinulosa decalvans (KFSD),<sup>85</sup> giant axonal neuropathy (GAN) syndrome, and primary osteoma cutis.

Woolly hair without associated systemic manifestations can be inherited as either an autosomal dominant or autosomal recessive trait, both of which result from abnormalities of the inner-root sheath of the hair follicles. The entire scalp tends to be affected from birth, but nonscalp hair is normal. The hair grows slowly, is hypopigmented, and shows varying degrees of hypotrichosis. Plucked hair shows a dystrophic bulb and sometimes nonspecific shaft defects. The



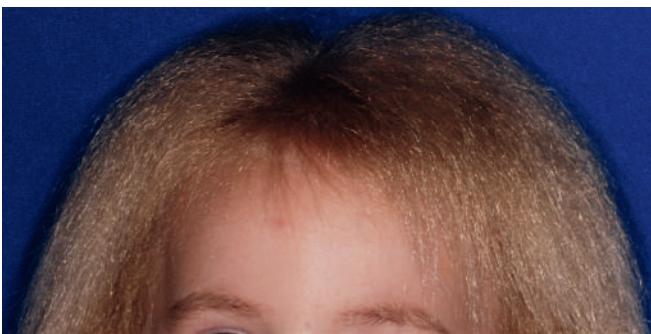
**Figure 7-9** Woolly hair nevus. The affected hair is lighter (**A**), sometimes sparser, and more "woolly" in consistency from the normal surrounding scalp hair (**B**).

dominant form results from mutations in *KRT71* or *KRT74*, encoding hair keratins 71 and 74, respectively.<sup>86,87</sup>

The recessive forms have now been explained by mutations in two interacting genes, *LPAR6* (encoding the lipophosphatidic acid [LPA] receptor 6/P2RY5) and *LIPH* (encoding lipase H).<sup>88,89</sup> Lipase H reduces phosphatidic acid to LPA,<sup>90</sup> which is involved in lipid and energy metabolism. *P2RY5* is thought to be a receptor for lysophosphatidic acid in the hair follicle.<sup>91,92</sup>

The woolly hair nevus is a sporadic condition characterized by the development of one or more patches of hair different in color, shape, and consistency from the normal surrounding scalp hair (Fig. 7-9). The hairs on the affected area are usually smaller in diameter, lighter in color, and sparser than those on the rest of the scalp.<sup>93</sup> When examined under a dissecting microscope, the individual hairs are noted to twist about their long axis. The majority of reported cases of woolly hair nevus have been recognized during the first few months of life, but some have appeared in young adulthood.<sup>94,95</sup> In about 50% of cases, woolly hair nevus coexists with a linear epidermal nevus in the same area or elsewhere.<sup>96,97</sup> Ocular involvement has been described as an associated feature. Epidermal nevi with woolly hair have recently been linked to mutations in *HRAS*.<sup>98</sup>

**Acquired Progressive Kinking of the Hair.** Acquired progressive kinking of the hair is a rare disorder of scalp hair, with onset in adolescence or in young adulthood.<sup>99</sup> The condition is characterized by a rapid onset of extreme curliness of the hair (mainly on the frontoparietal region of the scalp and vertex), often in association with an increased coarse texture, diminished luster, and striking unruliness. The disorder is more common in males than in females. Hair may become darker or remain unaltered in color, and the rate of growth may be decreased or unchanged.<sup>100</sup> Examination of abnormal hairs



**Figure 7-10** Uncombable hair syndrome. Blond hair that is dry and frizzy and does not lie flat on the scalp, thus making combing impossible. (Courtesy of Sarah Chamlin, MD.)



**Figure 7-11** Loose anagen syndrome. (A) The typical patient is a blonde preschool girl whose hair comes out easily and has become lusterless, fine, and sparse. When viewed under light microscope, the hairs that are easily able to be removed without plucking, show a ruffled cuticle (B) and distorted bulb (C).

by light microscopy reveals alterations in hair shaft diameter and partial twisting of the hair on its longitudinal axis.

Although the etiology of this disorder is unknown, it may follow treatment with systemic retinoids including isotretinoin. The localization of hair kinking, family history of androgenetic alopecia (AGA), pathologic features of affected scalp, and tendency to evolve into AGA suggest acquired kinking as a harbinger of AGA.<sup>101</sup> No therapy is effective, and application of topical minoxidil has not affected the progressive thinning of hair in the areas of kinking.<sup>101</sup> Spontaneous reversion to normal hair has been reported.<sup>102</sup> Coarse hair but not woolly hair is also a feature of Hajdu–Cheney syndrome, resulting from mutations in *NOTCH2*. Other features include craniofacial abnormalities, short stature, acroosteolysis with broad nails and digits, synophrys, coarse skin, and premature tooth loss with periodontitis.<sup>103</sup>

**Uncombable Hair Syndrome.** The uncombable hair syndrome (pili trianguli canaliculi, spun-glass hair syndrome) is a unique hair disorder characterized by very pale, silvery, blond, or straw-colored hair. The hair is dry, frizzy, and unruly, and it does not lie flat on the scalp, thus making combing impossible (Fig. 7-10).<sup>104,105</sup> The syndrome is thought to be autosomal dominant with variable penetrance, although no associated gene mutations have been identified. The onset is usually during infancy or early childhood, and eyebrows, lashes, and body hair are normal. Affected children may have minor nail abnormalities<sup>106</sup> and some show both uncombable hair and loose anagen hair (see *Loose Anagen Syndrome* section).<sup>107</sup> The characteristic structural defect, the presence of canalicular depressions along the hair shaft, can be demonstrated by scanning electron microscopy<sup>108</sup> or by routine microscopy of hair in cross-section.<sup>109</sup> Cross-sectional microscopy shows a variety of shapes, including triangular, quadrangular, and reniform. The longitudinal grooving and abnormal shape in cross-section, however, are not specific for uncombable hair syndrome and have been described in several other syndromes, among them Marie Unna hypotrichosis, the ectodermal dysplasias with clefting, hypohidrotic ectodermal dysplasia (HED), oral-facial-digital syndrome type I (OFD1), and progeria. The clinical appearance of the spun-glass hair requires a sizable proportion of abnormal hairs, and at least 50% of hairs are abnormal by scanning electron microscopy. The hair tends to become progressively more manageable by adolescence, and some patients have responded to biotin administration.<sup>106</sup>

Uncombable hair syndrome must be distinguished from extremely unruly hair, which is seen in 2% of individuals. Extremely unruly hair that tends to stand up from the area of the posterior parietal whorl toward the frontal hairline may be associated with microcephaly and is a potential indicator of abnormal brain growth and morphogenesis, similar to upsweep of anterior scalp hair and aberrant parietal whorl position.

#### Loose Anagen Syndrome

Loose anagen syndrome occurs in 10% of all children who have alopecia<sup>110</sup> and is characterized by actively growing anagen hairs that are

loosely anchored and can be easily and painlessly pulled from the scalp.<sup>111</sup> Although considered an autosomal dominant disorder, most cases are sporadic and occur in girls. A mutation in a hair keratin (*KRT75*, formerly called *K6hf*) has been found in some families, but its relevance is unclear because it does not reliably segregate with the loose anagen phenotype.<sup>19</sup> Most patients are blond girls above the age of 2 years (mean, 6 years of age). Affected children generally have sparse, short, scalp hairs that seldom require cutting (Fig. 7-11, A). Examination shows patchy or subtle diffuse thinning with hairs of uneven length. The hair often appears to be limp, and a matted texture has been noted, particularly in occipital hair. Of the actively growing anagen hairs, more than 80% show ruffled cuticles and pigmented misshapen bulbs (Figs. 7-11, B and C). Gentle pulling tends to yield several hairs, allowing the diagnosis to be made by light-microscopic



**Figure 7-12** Congenital triangular alopecia. This usually unilateral triangular patch of alopecia may not appear until 2 to 3 years of age or even later but then persists unchanged.



**Figure 7-13** Congenital atrichia. This boy lost his hair during the first year of life and has never regrown it. A mutation in the hairless gene was demonstrated.

examination of hair; forceful extraction of hairs may lead to misshaping of normal anagen hairs and thus should be avoided. Shedding of the hair is cyclic, and the inability to extract large amounts of hair by gentle pull test does not definitively rule out the diagnosis. Although no treatment is available for this disorder, it is reassuring for patients and their families to know that other abnormalities are not associated with this disorder and individuals with this condition tend to improve with time.

Loose anagen hair is also a feature of an autosomal recessive Noonan-like syndrome (Noonan-like syndrome with loose anagen hair)<sup>112</sup> that has been linked to mutations in *SHOC2*.<sup>113</sup> In addition to the fine, sparse hair, affected children show the Noonan syndrome facies and broad neck; macrocephaly; reduced growth with delayed bone age (often from growth hormone deficiency); variable cognitive defects, hyperactivity; hypernasal voice; darkly pigmented, thickened skin with dermatitis; and cardiac defects.

### NONSCARRING ALOPECIAS WITHOUT HAIR SHAFT ABNORMALITIES<sup>114</sup>

#### Congenital/Genetic Disorders

Congenital triangular alopecia is characterized by an area of alopecia that, although sometimes notable at birth in babies with abundant scalp hair, is usually detected at 2 or 3 years of age (Fig. 7-12).<sup>115,116</sup> Initial appearance during adulthood has been described.<sup>117</sup> The area is triangular and overlies the frontotemporal suture, with the base of the triangle directed forward. The triangular patch may extend to the hairline, but often a fringe of hair may separate it from the forehead. Generally measuring 3 to 5 cm from base to apex, the area may be completely bald or partially covered by vellus hairs and remains unchanged throughout life. Dermoscopy of the affected area shows normal follicular openings with vellus hairs, whereas dermoscopy of AA shows dystrophic and exclamation-point hairs.<sup>118</sup> Although unilateral in 80% of affected individuals, it may be bilaterally symmetric, and on rare occasions similar triangular patches may be noted on the nape of the neck.

The condition is almost always sporadic, although the association with developmental delay and seizures has been described in a mother and daughter.<sup>119</sup> Congenital triangular alopecia has been described in a patient each with phakomatosis pigmentovascularis, Down syndrome, and Dandy–Walker malformation.<sup>116</sup> Hair transplants have been used to repopulate the area of triangular alopecia.<sup>120</sup> Bilateral congenital localized patches of alopecia of the parietal area that resemble the alopecia of congenital triangular alopecia have been seen in patients with Gomez–Lopez–Hernandez syndrome

(cerebellotrigeminal–dermal dysplasia). Although the alopecia classically affects the parietal area, other sites have been reported to show symmetric alopecia.<sup>121</sup> Other features are skull defects (craniostenosis with brachycephaly, midfacial hypoplasia), neurologic abnormalities, short stature, hypertelorism, and corneal opacities.<sup>122</sup>

Individuals who initially have hair but lose it all with the first hair shedding shortly after birth likely have atrichia with papular lesions (APL; resulting from mutations in the hairless gene) or vitamin D-dependent rickets type IIA (caused by mutations in the vitamin D receptor).<sup>123,124</sup> Affected individuals never regrow scalp hair and tend to be nearly totally devoid of eyebrows, lashes, and axillary and pubic hair (Fig. 7-13). Follicular cysts and milia-like lesions may appear on the skin later in life (hence the nomenclature of *with papular lesions*). Scalp biopsies show disintegration of the lower two-thirds of the hair follicle, which is often replaced by cysts. Patients with vitamin D-resistant rickets are clinically and histologically identical to patients with APL<sup>125</sup> but show the additional manifestations of early-onset rickets, hypocalcemia, secondary hyperparathyroidism, and elevated 1,25-dihydroxyvitamin D<sub>3</sub>.<sup>126</sup> The similarity in phenotype reflects the direct regulatory effect of the vitamin D receptor and hairless gene on each other via a transcriptional mechanism.<sup>127,128</sup> This group of patients is often misdiagnosed as having alopecia universalis, and they must be also be distinguished from patients with PHNED, an autosomal recessive disorder resulting from mutations in *KRT85*, *KRT74*, or the *HOXC13* homeobox gene, which usually presents with congenital complete alopecia and uniformly small dystrophic nails.<sup>129–133</sup> Sometimes, very short, sparse, fragile hair may be present in PHNED and is easily visualized by trichoscopy.<sup>134</sup>

#### Hypotrichosis Simplex

Hypotrichosis simplex is a group of rare autosomal dominant and autosomal recessive nonscarring alopecias in which patients are usually born with normal hair. Hair loss can begin in the first months or even as late as the first decade (Fig. 7-14) and can progress to almost complete loss of scalp hair by adulthood. Graying has been reported to coincide with hair loss. Some individuals show sparse, fine, short hairs, especially at the crown, but hair on sites other than the scalp is normal. The disorder has considerable genetic heterogeneity. Autosomal dominant forms result from mutations in genes encoding corneodesmin, a protein of the corneocyte desmosomes and inner hair sheath (see Peeling Skin Syndrome section, Chapter 5)<sup>135,136</sup>; a protein of the pre-messenger-ribonucleic acid (mRNA) processing spliceosome (*SNRPE*)<sup>137</sup>; and *APCDD1*, an inhibitor of Wnt pathway signaling.<sup>138,139</sup> Autosomal recessive forms of hypotrichosis simplex can include hypotrichosis simplex with woolly hair (see Woolly Hair



**Figure 7-14** Hypotrichosis simplex. This girl began to lose hair in the first months of life. She has no other medical issues.

section) or be associated with scalp follicular keratosis, which can be confused with monilethrix.

Hallermann–Streiff, Sensenbrenner, Coffin–Siris, and growth retardation, alopecia, pseudoanodontia, and optic atrophy (GAPO) syndromes all show hypotrichosis in association with facial dysmorphism and other physical signs (see Online only).

In the Hallermann–Streiff syndrome (oculomandibulodyscephaly), hypotrichosis of the scalp, eyebrows, and eyelids is associated with dwarfism, beaked nose, and brachycephaly. The alopecia is most prominent at the frontal and parietal areas and is especially marked along suture lines. Axillary and pubic hair may also be scant, and cutaneous atrophy, largely limited to the scalp and nose, may appear as thin, taut skin and prominent underlying blood vessels. Other features include frontal and parietal bossing, mandibular hypoplasia, microphthalmia, low-set ears, thin and small lips, high-arched palate, atrophy of the skin of the face, congenital cataracts, blue sclerae, motor and occasionally mental retardation, and dental abnormalities.

Sensenbrenner syndrome, or cranoectodermal dysplasia, is a rare autosomal recessive disorder manifested by small stature, dolichcephaly, an unusual facies, and tubulointerstitial nephritis leading to early end-stage renal failure.<sup>140</sup> The typical facies show frontal bossing, hypertelorism, prominent epicantal folds, antimongoloid palpebral fissures, eversion of the lip, and full-rounded cheeks. Patients have small, gray, widely spaced teeth; short, fine, hair; and hypohidrosis.<sup>141</sup> Sensenbrenner syndrome is a ciliopathy that results from mutations in *IFT122*,<sup>142</sup> *WDR35*,<sup>143</sup> or *IFT43*.<sup>144</sup>

Patients with the Coffin–Siris syndrome most commonly show a constellation of severe mental retardation; a characteristic coarse-appearing facies; scalp hypotrichosis with hypertrichosis of the eyebrows, eyelashes, face, and back; hypotonia; hypoplastic to absent fifth fingernails and distal phalanges; and feeding problems with postnatal growth deficiency.<sup>145</sup> Coffin–Siris syndrome is autosomal dominant and results from mutations in one of several components of the SWI/SNF/sucrose nonfermenting (SWI/SNF; also called BAF) adenosine triphosphate (ATP)-dependent chromatin-remodeling complex.<sup>146,147</sup> Of these, mutations in *ARID1B* are most common (76% in one series).<sup>148,149</sup>

GAPO is an acronym for *growth retardation, alopecia, pseudoanodontia, and optic atrophy*.<sup>150</sup> Distinctive craniofacial features include frontal bossing, high forehead, mid-facial hypoplasia, hypertelorism, and thickened eyelids and lips. GAPO syndrome is autosomal recessive and results from mutations in *ANTXR1*, which encodes anthrax toxin receptor 1.<sup>151</sup>

Cartilage-hair hypoplasia syndrome is an autosomal recessive disorder that occurs primarily in inbred Amish or Finnish populations.<sup>152,153</sup> Patients have short limbs and sparse, fine scalp and body hair. Several patients with hyperextensible digits and soft, doughy skin, reflecting degenerated elastic tissue, have been described.<sup>154</sup>

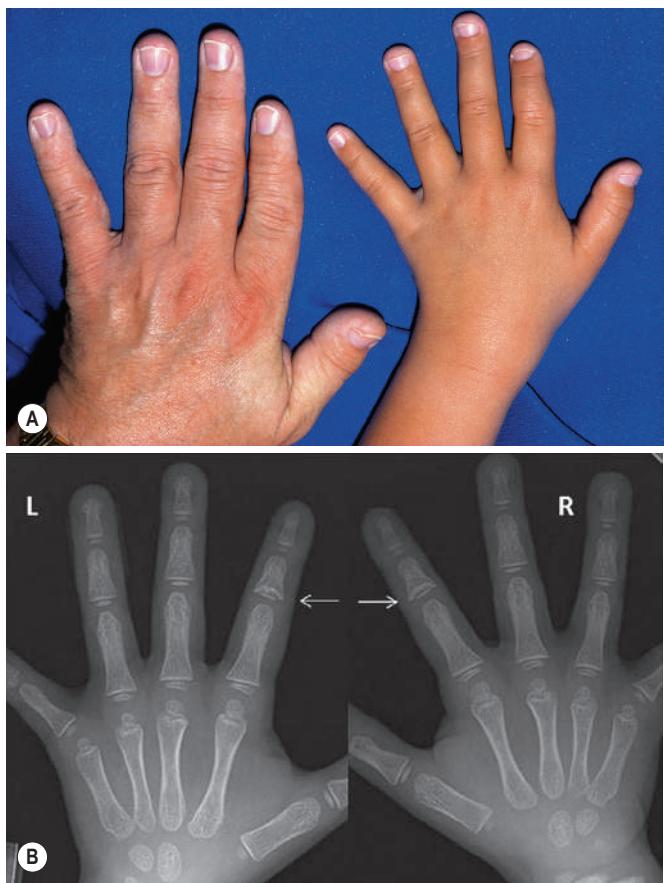


**Figure 7-15** Trichorhinophalangeal syndrome, type I. This 9-month-old boy shows the distinctive facies, including the pear-shaped nose and elongated philtrum, the thin upper lip, and the receding chin, as well as the sparse hair. He had hip dysplasia as well.

Defective cell-mediated immunity is seen in most patients and results in relative anergy, altered T-cell responses, and increased susceptibility to severe viral infections, particularly varicella.<sup>155</sup> Patients may have infantile neutropenia, Diamond–Blackfan anemia, severe combined immunodeficiency, celiac syndrome, and/or toxic megacolon. Mild to severe bronchiectasis has been noted in more than 50% of patients.<sup>156</sup> Approximately 10% develop malignancy, especially lymphoreticular; an increased prevalence of early basal cell carcinomas has also been described.<sup>157</sup> The disorder results from mutations in ribonuclease (RNase) *MRP*, which cleaves RNA in mitochondrial deoxyribonucleic acid (DNA) synthesis and preribosomal RNA in the nucleolus.<sup>158</sup> Alopecia is seen with macrocephaly, cutis laxa, and scoliosis in macrocephaly, alopecia, cutis laxa, and scoliosis (MACS) syndrome (see Chapter 6).

Trichorhinophalangeal syndrome (TRPS) type I is an autosomal dominant disorder characterized by a distinctive facies with pear-shaped nose, elongated philtrum, thin upper lip, supernumerary incisors, and receding chin (Fig. 7-15) and skeletal abnormalities including brachydactyly, deviation of the middle phalanges (Fig. 7-16, A), hip malformation, and short stature.<sup>159,160</sup> Most patients show fine, sparse, slow-growing hair, but almost-normal hair to complete baldness have been described. The underlying molecular basis is mutation in *TRPS1*, which encodes a transcription factor. Individuals with type II TRPS (Langer–Giedion syndrome) have associated multiple cartilaginous exostoses. The diagnosis is made by the demonstration of cone-shaped epiphyses of the fingers seen on plain radiography (Fig. 7-16, B). These findings may not be detectable until 3 years of age or older. The type II form is a contiguous gene syndrome, with deletion of both the *TRPS1* gene and the gene that is mutated in multiple exostosis type I (*EXT1*). Type III TRPS results from mutations in *TRPS1* but manifests with much more severe short stature and generalized shortening of all phalanges and metacarpals than TRPS type I.<sup>161</sup>

OFD1 is an X-linked dominant disorder limited to girls and thought to be lethal in boys.<sup>162</sup> Facial features occur in almost 70% of patients and include hypoplasia of nasal cartilages and hypertelorism with lateral displacement of the inner canthi (dystopia canthorum)<sup>163</sup> (Fig. 7-17). Among the oral anomalies described are tongue hamartomas, lobulated cleft tongue, cleft lip and palate, maldeveloped frenula, asymmetry of the lips and tongue, and maxillary gingival swelling.<sup>164</sup> Associated hand malformations are common and include brachydactyly, syndactyly, clinodactyly, and polydactyly. Almost half of affected individuals show central nervous system (CNS) involvement, most commonly retardation or selective cognitive impairment. Cutaneous abnormalities occur in the minority of patients but include numerous



**Figure 7-16** Trichorhinophalangeal syndrome, type I. **(A)** Brachydactyly in an affected father and daughter with short stature and typical facies. Note the deviation of the middle phalanges. **(B)** Cone-shaped epiphyses of the second finger of this child's left and right hands.



**Figure 7-17** Oral-facial-digital syndrome, type I. This infant girl shows the asymmetric hypoplasia of nasal cartilages and lobulated cleft tongue. Note the many facial milia on the cheek and eyelids. The hair continues to be sparse and dry.

milia at birth<sup>165</sup> and sparse fine or coarse, dry and lusterless hair to frank alopecia. Polycystic kidney disease with renal insufficiency is occasionally seen in children but more often occurs with advancing age (>50% after age 36 years).<sup>166</sup> The disorder results from mutations in *OFD1*, which encodes a centrosomal protein of primary cilia. Other "ciliopathies" share the CNS, skeletal, and cystic renal abnormalities of *OFD1*.

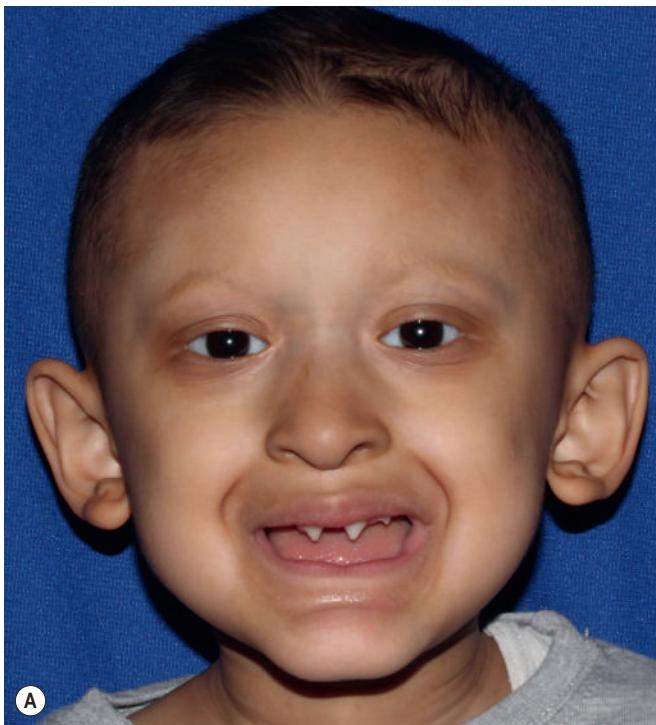
## Ectodermal Dysplasias

Ectodermal dysplasias are a complex group of approximately 200 developmental disorders that were traditionally classified based on their sites of abnormalities (hair, teeth, nails, and/or eccrine glands) and other ectodermal and nonectodermal features.<sup>167</sup> In 2009 Priolo suggested a new classification of ectodermal dysplasias that focuses on the molecular basis of these disorders (now known in approximately 80 of the ectodermal dysplasias),<sup>168</sup> the function of the affected proteins, and the clinical features.<sup>169</sup> As a result, ectodermal dysplasias are divided into two groups (see Table 7-1). The first group includes disorders in which ectodermal derivatives fail to develop or differentiate because of the absence of reciprocal signals from the ectoderm to the mesenchyme. This group can be further divided into: (1) abnormalities of the tumor necrosis factor (TNF)-like/TNF receptor pathway (including HED); (2) the nuclear factor κB (NF-κB), NF-κB essential modulator (NEMO), and inhibitor of κB (IkB) molecules (such as HED with immunodeficiency [HED-ID]); and (3) transcription factors such as p63 and DLX3. Inductive signals for normal differentiation are preserved in the second group, but tissues become dysplastic because abnormal regulation of transcription or expression leads to altered cell–cell interactions or disorganization of the cytoskeleton. Abnormalities in group 2 may affect nectins (e.g., cleft lip/palate–ectodermal dysplasia syndrome), connexins (as in Clouston syndrome and oculodentodigital dysplasia), desmosomal proteins (such as plakophilin in ectodermal dysplasia/skin fragility syndrome, also classified as a form of epidermolysis bullosa simplex, see Chapter 13), and molecules that interact with β-catenins (cadherins and *WNT10A*, as in odontoonychodermal dysplasia [ODDD]).

### Group 1 Ectodermal Dysplasia

**HYPOTHIDROTIC ECTODERMAL DYSPLASIA.** HED is characterized by the triad of reduced sweating, hypotrichosis, and defective dentition.<sup>170</sup> The majority of affected individuals are male, and overall 92% have a mutation in one of four genes (see Table 7-1): ectodysplasin-A1 (*EDA1* at Xq12-q13) in 58%; its ectodysplasin receptor (*EDAR* at 2q13) in 16%; *Wnt10A* (*WNT10A* at 2q35) in 16% (classified with group 2); and EDAR-associated death domain (*EDARADD* at 1q42.2-q43) in 2%.<sup>171</sup> HED may also result from a heterozygous mutation in *TRAF6*, which is upstream of NEMO and promotes NF-κB activity,<sup>172</sup> and in X-chromosome located *XEDAR*, encoding the receptor for *EDA2*, a different *EDA* isoform that binds to *Traf6*.<sup>173</sup> Female carriers with an *EDA1* mutation show random inactivation of the abnormal gene and can show manifestations ranging from none to extensive dental defects, alopecia, and patchy hypohidrosis following the lines of Blaschko, which are lines of embryologic development of skin. Mutations in the receptor (*EDAR*), the death domain (*EDARADD*), or *WNT10A* (*WNT10A*) may be inherited in a recessive or dominant pattern.<sup>169</sup> The phenotype with recessive mutations closely resembles those in X-linked recessive HED, whereas dominant mutations tend to be less severe with respect to sweating and hair loss.<sup>174</sup> Mutations in *WNT10A* can lead to a spectrum of ectodermal defects that can include isolated oligodontia, mild manifestations of HED,<sup>175,176</sup> ODDD, or Schöpf–Schulz–Passarge syndrome. The nail changes of ODDD (fragility, longitudinal ridging, splitting, koilonychias, onycholysis, and pterygium) begin in early childhood and are associated with palmoplantar keratoderma, agenesis of the permanent teeth, and sometimes facial erythema and atrophic tongue papillae. Schöpf–Schulz–Passarge syndrome may manifest solely with bilateral eyelid cysts and palmoplantar keratoderma but often includes nail, hair, and/or dental abnormalities.<sup>177</sup>

HED-ID affects 1:250,000 births<sup>178</sup> and is usually caused by hypomorphic mutations in *NEMO*,<sup>179</sup> an X-linked gene. Autosomal dominant HED-ID has been reported in six patients and results from hypermorphic (gain-of-function) mutations in *IKBA*.<sup>180</sup> *NEMO* mutations cause incontinentia pigmenti in girls (see Chapter 11) and amorphic (i.e., there is effectively no gene product) tend to be lethal in males. Features of HED have been described in 77% of boys with immunodeficiency and *NEMO* mutations; osteopetrosis and lymphedema have been noted in 8% with HED-ID.<sup>181</sup> Boys with HED-ID occasionally show the clinical vesiculopapules and histologic features of incontinentia pigmenti, but the distribution is not blaschkoid given the lack of mosaicism.<sup>182</sup> Most mutations in *NEMO* that lead to HED-ID occur in exon 10 and affect the C-terminal zinc finger domain,

**A****B**

**Figure 7-18** Hypohidrotic ectodermal dysplasia (HED). **(A)** This boy shows the short, sparse hair; large conspicuous nostrils; wide cheekbones with flat malar ridges; periorbital wrinkling; a thick everted lower lip; prominent chin; and low-lying, anteriorly placed, pointed ears. **(B)** Conical incisors in a toddler with HED.

which is critical for normal dendritic cell immune stimulation,<sup>183</sup> but mutations leading to HED-ID are scattered throughout the *NEMO* gene.<sup>184</sup>

**FEATURES OF ECTODERMAL DYSPLASIA.** Affected persons often appear more like each other than like their own unaffected siblings<sup>185</sup>; classic features are usually obvious by infancy. Most have a distinctive pathognomonic facies: a square forehead with frontal bossing, large conspicuous nostrils, wide cheekbones with flat malar ridges, a thick everted lower lip, and a prominent chin. Ears may be small, satyr-like (pointed), low-lying, and anteriorly placed (Figs. 7-18, A, and 7-19). Alopecia is often the first feature to attract attention but is seldom complete; overall 80% of males with the X-linked type have sparse hair.<sup>186</sup> The hair also tends to be lightly pigmented and short. The skin is soft, thin, and light-colored but shows fine wrinkling and sometimes darkening of the periorbital areas. Many affected neonates are born with red, peeling skin, but collodion-like thickening has occasionally been described.<sup>187,188</sup> Atopic dermatitis and other atopic conditions occur with increased incidence, and periorbital dermatitis is particularly common. The paucity of nail changes helps to distinguish HED



**Figure 7-19** Hypohidrotic ectodermal dysplasia (HED). This girl is a carrier for a mutation in ectodysplasin but shows all of the characteristic facies features. Girls with HED may also have a mutation in a gene encoding the receptor for ectodysplasin, inherited as an autosomal disorder.

from other ectodermal dysplasias, although nail changes were described in up to 50% of males and female carriers in a recent self-reported survey.<sup>186</sup>

The decreased capacity for perspiration occurs in virtually all affected males and has a profound effect on life quality.<sup>189</sup> Hypohidrosis often results in hyperthermia, and patients manifest with intermittent fevers, especially during hot weather or after exercise or meals. These recurrent fevers of unknown origin may be the presenting manifestation in affected infants. Hypoplastic lacrimal and mucous glands can lead to decreased tearing or epiphora, chronic nasal discharge, and an increased risk of otitis media and respiratory tract infections.<sup>190</sup> Females and female carriers may have breast hypoplasia. Dentition is generally delayed, and dental anomalies vary from complete to partial absence of teeth with peg-shaped or conical incisors (see Fig. 7-18, B).

**FEATURES OF IMMUNODEFICIENCY.** Boys with HED-ID usually have recurrent infections. Serious pyogenic infections occur in 86% of affected individuals, and mycobacterial infections (especially atypical *Mycobacterium avium*) in 44%.<sup>185,191,192</sup> Pneumocystis and viral and candidal infections occur less often. Bacteremia or sepsis is common,<sup>185,193</sup> and the most common sites of infection are the lungs, sometimes leading to bronchiectasis, and the skin, sometimes with abscesses. Inflammatory colitis affects 21% of boys and presents as intractable diarrhea and/or failure to thrive. Some patients develop autoimmune hemolytic anemia. Natural killer-cell dysfunction has been described in all patients, but otherwise a range of immune defects have been described, largely reflecting the functional impairment in CD40, interleukin (IL)-1, TNF- $\alpha$ , and toll receptor signaling.<sup>185,194</sup> Almost 60% of affected boys show hypogammaglobulinemia, with high levels of immunoglobulin (Ig) M in 15%. Hyper-IgM syndrome much more commonly results from mutations in *CD40L* ligand (*CD40L*)<sup>195</sup> and may manifest with *CD40L* deficiency as oral aphthae and warts.<sup>196</sup> Individuals with HED-ID are at high risk for early death from infections without transplantation.<sup>197-200</sup>

Therapy for patients with all forms of HED is directed toward temperature regulation; cool baths and drenching with water, air conditioning, light clothing, cooling suits, and the reduction of the causes of normal perspiration are beneficial.<sup>201</sup> Lubricating eye drops and nasal irrigation can compensate for the decreased glandular secretion. Minoxidil may promote some hair growth with long-term use.<sup>202</sup> Dental intervention should begin by 2 years of age and can include dental prostheses and dental implants in older adolescents and adults to improve mastication, encourage normal speech development, and



**Figure 7-20** Ankyloblepharon-ectodermal dysplasia-clefting syndrome. Scalp dermatitis with secondary staphylococcal infection is a chronic problem and leads to cicatricial alopecia.

reduce cosmetic disfigurement. In mouse and dog models of X-linked HED, the prenatal or perinatal administration of recombinant Fc-EDA protein or ligand replacement using an *EDAR*-agonist antibody can improve dentition, lacrimation, sweating, and bronchopulmonary gland function,<sup>203–205</sup> whereas postnatal administration in affected adult mice only improves sebaceous gland activity.<sup>206</sup> Most recently, a single injection of *EDA1* replacement protein into the amniotic fluid of pregnant *eda1*-mutant mice provided a depot for recurrent oral ingestion of affected offspring without maternal absorption; treatment led to darker, denser coat; normal eye opening, tail shape, and teeth; and functional sweat glands.<sup>207</sup> Prenatal diagnosis has been made noninvasively by tooth-germ ultrasound.<sup>208</sup> The National Foundation for Ectodermal Dysplasias (NFED) provides excellent education materials on management of the hypohidrosis and dental abnormalities.

**P63-RELATED FORMS OF ECTODERMAL DYSPLASIA.** Mutations in *p63*, a gene that plays a critical role in maturation of ectodermal, orofacial, and limb development, lead to an autosomal dominant disorder with ectodermal dysplasia, orofacial clefting, and limb malformations as key characteristics. These clinical manifestations have traditionally been used to classify subtypes, but significant clinical and genotypic overlap is now recognized.<sup>209–211</sup> Included are Rapp–Hodgkin syndrome (clefts of the lip, palate, and/or uvula; small narrow dysplastic nails; hypodontia with small conical teeth; and maxillary hypoplasia)<sup>212</sup>; ankyloblepharon-ectodermal dysplasia-clefting (AEC or Hay–Wells syndrome; ankyloblepharon or congenital fusion of the eyelids in association with facial clefting and midfacial hypoplasia)<sup>213,214</sup>; ectrodactyly, ectodermal dysplasia, and cleft lip/palate (EEC) syndrome; limb-mammary syndrome (ectrodactyly, cleft palate, and mammary gland abnormalities); acrodermatoganglular-lacrimo-tooth (ADULT) syndrome syndrome; and nonsyndromic split hand/foot malformation.

The skin, hair, teeth, nails, and glands (eccrine, sebaceous, lacrimal, mammary) are abnormally developed.<sup>215</sup> The skin tends to be dry, itchy and hypopigmented. Extensive erosions have been described in 80% of neonates with the AEC phenotype. The hair is often sparse and wiry, and nails tend to be dystrophic. Scalp dermatitis and erosions with secondary chronic staphylococcal infection may be recurrent in the first few years of life and lead to cicatricial alopecia, especially of the vertex and frontal scalp (Fig. 7-20). Teeth are often decreased in number with malformations and enamel hypoplasia.<sup>216</sup> Hypohidrosis may be present, tearing is often decreased, and nipple hypoplasia has been described. Patients may show split hand/foot malformations (lobster claw deformity; ectrodactyly) and/or syndactyly.<sup>217</sup> Short stature, poor weight gain, and hypospadias are other commonly described characteristics.<sup>218</sup> Ectodermal dysplasia with clefting and/or ectrodactyly/syndactyly can be caused by mutations in a variety of other genes, i.e., other disorders (see Table 7-1). Disorders with *p63* mutations also should be distinguished from CHAND syndrome or



**Figure 7-21** Trichodental syndrome (Witkop syndrome). Slow-growing, small, spoon-shaped nails are a characteristic feature, in addition to the slow-growing lusterless hair, sparse outer eyebrows, and small, sometimes absent, teeth.

CHANDS, characterized by curly hair from birth, ankyloblepharon, nail dysplasia and, variably, ataxia<sup>219,220</sup>; the underlying genetic basis is unclear.

The trichodentosseous syndrome is an autosomal dominant disorder characterized by kinky, curly hair at birth that tends to become straighter during childhood; small, widely spaced, pitted, eroded, and discolored teeth with early caries as a result of defective enamel; thickness and splitting of the nails; dolichocephaly, frontal bossing, and a square jaw, giving affected persons a distinctive facies; normal physical development; and increased bone density, especially of the cranial bones. The condition results from mutations in *DLX3*, a crucial regulator of hair follicle differentiation and cycling.<sup>221</sup>

The trichodental syndrome, also known as *Witkop syndrome* or the tooth-and-nail syndrome, is an autosomal dominant disorder characterized by fine, dry, slow-growing lusterless hair; sparseness or absence of the lateral halves of the eyebrows; congenitally missing and small teeth; and slow-growing, small, spoon-shaped nails (especially toenails) (Fig. 7-21).<sup>222,223</sup> Mutations have been described in *MSX1*, which directs the formation of teeth and nails.<sup>224</sup> The other ectodermal dysplasia with mucocutaneous features included in group 1 is Ellis van Creveld syndrome. This autosomal recessive disorder features nail dysplasia in association with chondrodyplasia, polydactyly, orofacial abnormalities, and sometimes cardiovascular malformations.<sup>225</sup> The mutated genes, *EVC* and *EVC2*, localize to cilia and are thought to be involved in hedgehog signaling.<sup>226</sup>

### Group 2 Ectodermal Dysplasia

**CLOUSTON SYNDROME (HIDROTIC ECTODERMAL DYSPLASIA).** The most common hidrotic type of ectodermal dysplasia is Clouston syndrome, an autosomal dominant disorder characterized by nail dystrophy, hyperkeratosis of the palms and soles, and hair defects.<sup>227</sup> Most cases have been reported in French-Canadian families. Unlike HED, individuals with the hidrotic form have a normal facies and show no abnormality of sweating, although eccrine syringofibroadenomas have been described.<sup>228</sup> The teeth develop normally but are prone to caries. The predominant feature is congenital nail dystrophy, which may be the only manifestation in about one-third of affected individuals. The nails are thickened or thinned, striated, and often discolored (Fig. 7-22). They may resemble the nails of pachyonychia congenita (PC) and are difficult to distinguish without genotyping until other features develop such as the painful character of the plantar keratoderma of PC, which is often present by 5 years of age, and the alopecia of hidrotic ectodermal dysplasia. The nails grow slowly and commonly show chronic paronychial infections that may result in partial to complete destruction of the nail matrix. Typically the skin and soft tissue surrounding the nail and at the finger pad appear thickened and swollen, leading to the term *drumstick fingers*. The palmoplantar keratoderma can extend to the dorsal aspects of the hands and feet. Hair may be normal during infancy and childhood but thereafter often becomes sparse, fine, and brittle and may eventuate in total alopecia (Fig. 7-23). Body hair may



**Figure 7-22** Hidrotic ectodermal dysplasia (Clouston syndrome). Nail dystrophy, accentuation of ridging on the digital tips, and bulbous swelling of the soft tissue surrounding the nail and at the finger pad are the most typical manifestations of this syndrome. The nails can be confused with pachyonychia congenita, but the hair changes of hidrotic ectodermal dysplasia and the characteristic discomfort of the plantar keratoderma of pachyonychia congenita help to distinguish the disorders.



**Figure 7-23** Hidrotic ectodermal dysplasia. This child shows the fine, sparse, brittle hair of Clouston hidrotic ectodermal dysplasia. Not uncommonly the hair abnormality does not develop until after puberty.

be sparse; eyebrows and eyelashes may be thinned or absent. The skin may show a mottled hyperpigmentation with thickening and hyperpigmentation over the knees, elbows, and knuckles. Ocular abnormalities may include strabismus, conjunctivitis, and premature cataracts. Clouston syndrome has been attributed to mutations in *GJB6*,<sup>229</sup> encoding connexin 30, a structural component of the intercellular gap junction. One patient with Clouston syndrome and bigenic mutations (one of each allele) of *GJB6* and *GJA1* (encoding connexin 43) have also been described.<sup>230</sup> Mutations in *GJB6* have also been noted in patients with keratitis, congenital ichthyosis, and neurosensory deafness (KID) syndrome (see Chapter 5), who share the palmoplantar keratoderma and sometimes early alopecia with thickening of the scalp. Clouston syndrome should also be distinguished from an autosomal recessive disorder that results from mutations in encoding grainyhead-like 2 (*GRHL2*); in addition to nail dystrophy or loss and marginal palmoplantar keratoderma, patients show hypodontia and enamel hypoplasia, oral hyperpigmentation, dysphagia, and sometimes deafness or asthma.<sup>231</sup> The combination of tretinoin and minoxidil has reportedly caused hair growth in Clouston syndrome.<sup>232</sup>

**OCULODENTODIGITAL DYSPLASIA.** Oculodentodigital dysplasia (ODDD), an autosomal dominant disorder, results from mutations in *GJA1*, which encodes connexin 43<sup>12,13</sup>; mutations in *GJA1* have also been linked to erythrokeratoderma variabilis (see Chapter 5). In addition to abnormalities of the eyes, teeth, and digits, patients show curly hair (sometimes with trichorrhexis nodosa), focal keratoderma, a



**Figure 7-24** Keratosis pilaris. Keratotic, follicular-based plugs with variable associated erythema are common on the lateral cheeks of young children.



**Figure 7-25** Keratosis pilaris. The lateral thighs are a common site. The follicular lesions can be inflamed papules or even pustules, resembling bacterial folliculitis.

characteristic facies with hypoplastic ala nasi, and neurologic, cardiac, and hearing defects. Cleft lip/palate-ectodermal dysplasia features spoon-shaped, slow-growing fingernails and toenails, pili torti, mental retardation, malformed ears, and partial syndactyly. It results from mutations in neitin 1, encoded by *PVRL1*.<sup>233,234</sup> Mutations in neitin 4, encoded by *PVRL4*, lead to ectodermal dysplasia-syndactyly syndrome (EDSS), characterized by alopecia, tooth abnormalities, and syndactyly.<sup>235,236</sup>

## DISORDERS OF FOLLICULAR PLUGGING

### Keratosis Pilaris

Keratosis pilaris is a common skin condition characterized by keratinous plugs in the follicular orifices surrounded by a variable degree of erythema (see Chapter 3).<sup>237</sup> These small follicular-based papules are most commonly distributed on the cheeks (Fig. 7-24), extensor areas of the upper arms, and anterior and lateral thighs (Fig. 7-25) but may be widespread. Children with keratosis pilaris tend to have xerosis and sometimes atopic dermatitis and/or ichthyosis vulgaris. Occasionally, facial keratosis pilaris overlies intense erythema (keratosis pilaris rubra)<sup>238</sup> and may also be pigmented (erythromelanosis follicularis faciei et colli).<sup>239</sup> Keratosis pilaris does not tend to be symptomatic but may be cosmetically distressing, especially if quite inflammatory or extensive. Treatment is difficult but usually requires application of keratolytic agents such as creams or lotions containing lactic acid, glycolic acid, salicylic acid, or urea, and gentle exfoliation by a pumice stone, washcloth, loofah sponge, or Buf-Puf. Responsive

**Table 7-2** Classification of Keratosis Pilaris Atrophicans

	<b>Atrophoderma Vermiculata</b>	<b>Ulerythema Ophryogenes</b>	<b>Keratosis Follicularis Spinulosa Decalvans</b>
Skin lesions	Erythematous papules, follicular plugs, horn cysts, atrophic	Follicular papules, plugging, scarring	Milia, thorn-like follicular projections, atrophic scars
Sites	Cheeks, neck, limbs	Lateral eyebrows, extending medially	Scalp, eyebrows, eyelashes, cheeks, nose, neck, dorsal hands, fingers
Alopecia	Absent	Minimal eyebrows	Scarring alopecia of the scalp
Photophobia	Absent	Absent	Marked, corneal opacities
Inheritance	Sporadic or autosomal dominant	Sporadic or autosomal dominant	X-linked recessive or autosomal dominant

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**Figure 7-26** Ulerythema ophryogenes. Extensive keratosis pilaris with alopecia and scarring of the eyebrow in an adolescent boy.

patients must maintain therapy to achieve continued remission or improvement. The intense erythema of keratosis pilaris rubra may be lessened by pulsed-dye laser therapy<sup>240</sup> or photopneumatic (vacuum-assisted pulsed-light) therapy.<sup>241</sup> The erythema is sometimes decreased by treatment with low-strength topical steroids or calcineurin inhibitors.<sup>242</sup>

### Keratosis Pilaris Atrophicans

Numerous terms have been used to describe a group of interrelated syndromes characterized by inflammatory keratotic follicular papules and later by atrophy. Commonly described as atrophic variants of keratosis pilaris, these include ulerythema ophryogenes, atrophoderma vermiculata, and KFSD (keratosis pilaris decalvans)<sup>243,244</sup> (Table 7-2).<sup>245</sup> This group of disorders has been attributed to abnormal keratinization of the follicular infundibulum, resulting in obstruction of the growing hair shaft, chronic inflammation, and scarring. No therapy is terribly effective,<sup>246</sup> although topical keratolytic and anti-inflammatory agents (topical corticosteroids and calcineurin inhibitors) may reduce the keratotic and inflammatory components, respectively. In general, systemic retinoids have not been helpful. Durable eyebrow reconstruction using individual hair follicle micrografts in an adult with quiescent disease has been reported.<sup>247</sup>

Ulerythema ophryogenes (keratosis pilaris atrophicans faciei) is characterized by persistent reticular erythema, small horny papules, atrophy, and scarring of the outer half of the eyebrows (see Fig. 7-8; Fig. 7-26).<sup>248</sup> The disorder is more common in boys and usually starts in the first months of life. Occasionally the disorder extends to include the adjacent skin, adjacent scalp, and cheeks.

Ulerythema ophryogenes and keratosis pilaris have been described in patients with two similar but distinct "RASopathies" of the RAS-MAPK signaling pathway, the cardiofaciocutaneous (CFC) syndrome<sup>249</sup> and Noonan syndrome. Patients with CFC syndrome often show widespread keratosis pilaris-like lesions of the face, ears,

scalp, and extensor surfaces of the extremities that may be more lichenoid and prominent than keratosis pilaris.<sup>250</sup> Sometimes patients with CFC and Noonan syndromes have alopecia of the eyelashes and eyebrows with follicular hyperkeratosis but lack the atrophy and scarring of ulerythema ophryogenes. Both CFC and Noonan syndromes share features of short stature, congenital cardiac abnormalities (particularly pulmonary valve stenosis), retardation, macrocephaly, hypertelorism, a high forehead, pectus carinatum, curly hair, and many pigmented nevi.<sup>251</sup> Lymphedema and a low posterior hairline are more typical features of Noonan syndrome. Patients with CFC syndrome often show hypoplastic supraorbital ridges, bitemporal constriction, and an antimongoloid slant, features not described in Noonan syndrome.<sup>250</sup>

As with clinical features, there is overlap in genes that are mutated in Noonan and CFC syndromes (*BRAF*, *KRAS*, *MEK1*, and *MEK2*).<sup>252–255</sup> However, the genes most commonly altered in Noonan syndrome are *PTPN11* (50%) and *SOS1* (10% to 13%).<sup>253</sup> Individuals with Noonan syndrome associated with loose anagen syndrome exclusively have a unique mutation in *SHOC2*, a scaffold protein required for the RAS-MAPK signaling cascade.<sup>256</sup> A recent study noted genotype–phenotype correlation during the first year of life, with thin hair linked to mutations in *SHOC2* and *BRAF*, whereas keratosis pilaris was associated with mutations in *SOS1*, *BRAF*, and *SHOC2*.<sup>257</sup> Other RASopathies with skin features are lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness (LEOPARD) syndrome; neurofibromatosis; neurofibromatosis–Noonan syndrome; Legius syndrome; the newly described *CBL*-mutation-associated syndrome (café-au-lait spots, see Chapter 11); and Costello syndrome (see Chapter 6). Ulerythema ophryogenes has also been associated with Cornelia de Lange<sup>258</sup> and Rubenstein–Taybi<sup>259</sup> syndromes, as well as with woolly hair (see Fig. 7-8).<sup>260</sup>

Atrophoderma vermiculata (folliculitis ulerythema reticulata, atrophoderma vermicularis) usually has its onset between 5 and 12 years of age.<sup>243</sup> This disorder is characterized by the formation of numerous tiny symmetric atrophic and at times erythematous pits on the cheeks, periauricular areas, and occasionally the forehead and eyebrows. These cribriform lesions generally measure 1 to 2 mm across and 1 mm deep and are separated from each other by narrow ridges of normal-appearing skin. Laser and dermabrasion have been advocated to improve the cosmetic appearance of affected individuals when the condition is stable, usually after puberty. Low-dose isotretinoin (0.5 mg/kg per day) for two 6-month courses has been reported to cause cosmetic improvement.<sup>261</sup>

KFSD is characterized by atrophic keratotic follicular papules of the scalp, eyebrows, and eyelashes that eventuate in scarring alopecia (Fig. 7-27). Associated features are palmoplantar keratoderma, corneal dystrophy, photophobia, and atopy.<sup>262</sup> KFSD is usually an X-linked recessive disorder, and female carriers may show milder manifestations. The initial signs are photophobia with tearing, ophthalmitis, and conjunctival and corneal inflammation, which occur in the first weeks or months of life; congenital glaucoma and cataracts have been noted in association. Extensive keratosis pilaris of the face, extremities, and trunk tends to begin during early childhood, often in association with facial erythema. Cicatricial alopecia of the scalp begins around puberty and slowly progresses in association with follicular inflammation and fibrosis; eyebrows also tend to be affected.



**Figure 7-27** Keratosis follicularis spinulosus decalvans. This patient showed widespread spiny follicular-based keratoses, photophobia, and abnormal hair with cicatricial alopecia.

Some patients show palmoplantar keratoderma and marked xerosis. Acne keloidalis nuchae (see [Acne Keloidalis](#) section) and tufted hair folliculitis has been described in several patients.<sup>263</sup> Ichthyosis follicularis, congenital atrichia, and photophobia (IFAP) is another X-linked condition in which affected neonates show keratotic follicular papules with a sandpaper feel to the skin, atrichia or severe hypotrichosis, and photophobia from birth (Fig. 7-28).<sup>264–266</sup> In contrast to KSFD, the alopecia of patients with IFAP does not scar. Mental retardation and developmental delay have been described in both KSFD and IFAP syndromes. Other features are gingival hyperplasia and angular stomatitis, psoriasiform plaques, palmoplantar erythema with thickening, short stature, and seizures.

IFAP and KSFD are allelic and result from mutations in a zinc metalloprotease (*MBTPS2*) that is important for cholesterol homeostasis, handling endoplasmic reticulum stress, and cell differentiation.<sup>267,268</sup> Mutations in *MBTPS2* also cause X-linked Olmsted syndrome (see Chapter 5) and BRESEK/BRESHECK syndrome. The latter disorder is characterized by brain anomalies, retardation (intellectual, associated with microcephaly), ectodermal dysplasias (atrichia and photophobia, but not ichthyosis follicularis), skeletal deformities (especially vertebral and hand anomalies), Hirschsprung disease, eye or ear anomalies, cleft lip/palate or cryptorchidism, and kidney



**Figure 7-28** Ichthyosis follicularis, congenital atrichia, and photophobia syndrome. **(A)** Note the total alopecia and the erythematous, scaling skin. **(B)** Note the spiny keratotic follicular papules of the eyebrows and lashes and the atrichia. The patient's photophobia prevents him from looking at the camera and has led to tearing. **(C)** Periungual erythema and marked nail yellowing and thickening; note the psoriasiform plaques at the ankle and on the dorsal aspect of the foot.

anomalies.<sup>269</sup> The most common features are included in the BRESEK acronym.

KFSD may also be autosomal dominant in inheritance,<sup>49,270</sup> although the underlying molecular defect is unclear.<sup>271</sup> Marked facial erythema, extensive folliculitis, onychodystrophy, and multiple caries have been described in these patients.

Ichthyosis in association with hair abnormalities may also be seen in ichthyosis hypotrichosis syndrome, ichthyosis-hypotrichosis-sclerosing cholangitis syndrome, Netherton syndrome (see Chapter 5) and TTD. Another disorder with nonscarring partial alopecia that must be distinguished is hereditary mucoepithelial dysplasia.<sup>272</sup> In addition to extensive keratosis pilaris and psoriasisiform plaques, affected individuals show fiery red mucosal inflammation (hard palate, gingival, tongue, perianal, and perineal), and ocular photophobia with keratitis, cataracts, and corneal opacities.

The follicular scarring of these disorders should be distinguished from disorders of follicular atrophoderma without keratotic plugs. These include perifollicular atrophoderma of acne scarring (see Chapter 8), Conradi-Hünermann syndrome (see Chapter 5), Rombo syndrome, and Bazex syndrome. Treatment of these disorders of follicular plugging is challenging, with most patients refractory to systemic and topical steroids, systemic antibiotics, dapsone, methotrexate, and systemic retinoids.<sup>265,270</sup>

## OTHER SCARRING ALOPECIAS

Scarring or cicatricial alopecia is the end result of a wide number of inflammatory processes in and around the pilosebaceous units, resulting in irreversible destruction of tissue and consequent permanent scarring alopecia.<sup>114,273</sup> The scarring may be the result of a developmental defect (aplasia cutis) (see Figs. 2-34 and 2-35); inflammatory changes due to severe bacterial, viral, or fungal infection; physical trauma (halo alopecia from caput succedaneum<sup>274</sup> [see Chapter 2], irradiation, long-term trichotillomania, thermal or caustic burns); neoplastic or infiltrative disorders (including severe alopecia mucinosa); various dermatoses (lichen planus, lupus erythematosus, localized or systemic scleroderma [see Chapter 22]); keratosis pilaris atrophicans, a group of disorders of hair plugging; or various dermatologic syndromes such as folliculitis decalvans, dissecting cellulitis of the scalp, acne keloidalis, and pseudopelade.

### Follicular Mucinosis

Follicular mucinosis (alopecia mucinosa) is an inflammatory disorder characterized by sharply defined follicular papules or infiltrated plaques with scaling, loss of hair, and accumulation of mucin in sebaceous glands and the outer root sheaths of affected hair follicles.<sup>275-277</sup> A relatively uncommon condition affecting children as well as adults, the disorder is characterized by often pruritic, grouped follicular papules that often coalesce into scaling plaques or nodular boggy infiltrated plaques with overlying erythema and scaling (Fig. 7-29). Lesions usually measure 2 to 5 cm in diameter. Distributed primarily on the face, scalp, neck, and shoulders (occasionally the trunk and extremities), lesions are usually devoid of hair. Except in the scalp or eyebrows, the alopecia is generally not conspicuous.

The cause of follicular mucinosis is unknown. In the majority of cases (in those <40 years of age), it is a benign idiopathic condition.<sup>278</sup> In persons older than age 40, however, the presence of boggy infiltrated plaques of alopecia mucinosa may be the first sign of cutaneous T-cell lymphoma. Cutaneous T-cell lymphoma has rarely been described in children with follicular mucinosis,<sup>279</sup> so affected children must be monitored carefully.<sup>280-282</sup>

Follicular mucinosis must be differentiated from lichen spinulosus,<sup>283</sup> pityriasis rubra pilaris, tinea infection, pityriasis alba, granulomatous diseases, and the papulosquamous group of disorders. When the diagnosis remains in doubt, cutaneous biopsy of an affected area is generally confirmatory, showing accumulation of mucin within the hair and sebaceous glands.

Solitary or few lesions usually clear spontaneously within 2 years. More numerous and widely distributed plaques tend to be more chronic. Destruction of follicles may give rise to permanent alopecia, and the disorder may persist with new lesions continuing to appear over years. Although some cases appear to benefit from topical or



**Figure 7-29** Alopecia mucinosa. An erythematous, mildly scaling, infiltrated hairless plaque. Biopsy shows mucin in the follicular area. Alopecia mucinosa tends to be a benign condition in children but has been associated with cutaneous T-cell lymphoma in adults.

intralesional corticosteroids, such claims are difficult to evaluate because spontaneous healing is the rule.

### Folliculitis Decalvans

Folliculitis decalvans is characterized by successive crops of patchy, painful folliculitis leading to progressive hair loss and scarring.<sup>284</sup> The disorder must be distinguished by culture from bacterial folliculitis caused by *Staphylococcus aureus*, although the two forms often coexist, leading to the hypothesis that folliculitis decalvans results from an abnormal host response to staphylococcal toxins.<sup>285</sup> Folliculitis decalvans may begin during adolescence in male patients but is rarely seen in female patients before 30 years of age. Although the scalp is the most commonly affected site, hair-bearing areas of the trunk, axillae, and pubic region may be affected. Typical lesions show round to irregular bald, atrophic patches, each surrounded by crops of follicular pustules. Tufted folliculitis is a variant in which tufts of hair emerge from dilated follicular openings amid areas of scarring.<sup>285</sup>

Treatment of folliculitis decalvans is difficult. Systemic antibiotics that penetrate the follicle well (tetracyclines, clindamycin, erythromycin) with or without rifampicin often prevent disease extension, but continued administration is required to prevent relapse.<sup>286</sup> Many individuals develop severe alopecia and scarring despite long-term and intensive therapy.

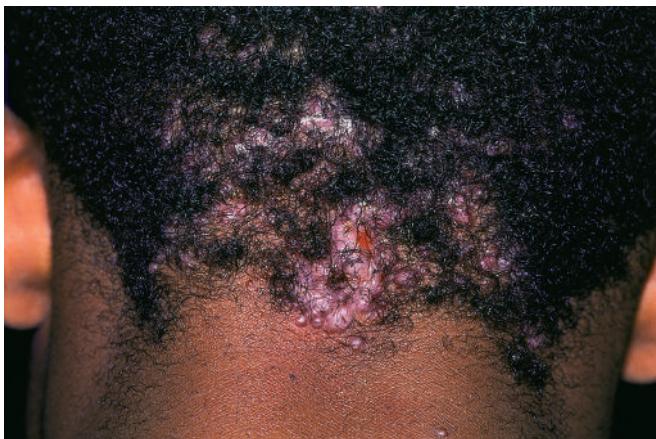
### Dissecting Cellulitis of the Scalp

Dissecting cellulitis of the scalp, also termed *perifolliculitis capitis abscedens et suffodiens*, is characterized by painful fluctuant nodules and abscesses of the scalp connected by tortuous ridges or deep sinus tracts with cicatricial alopecia.<sup>5</sup> The connection can often be demonstrated by applying pressure to one nodule and observing purulent drainage emerging from another. Lesions are usually first noted at the occipital area or vertex but may progress to involve the entire scalp. The disorder occurs most commonly in African-American male teenagers and young adults.<sup>287</sup> An association with acne conglobata and hidradenitis suppurativa has been described ("follicular occlusion triad"), suggesting an inflammatory reaction to *Propionibacterium acnes*. Other pustular disorders of the scalp, including bacterial folliculitis and inflammatory tinea capitis (kerion), must be considered.<sup>288,289</sup>

The disorder has a chronic, relapsing course. Although use of oral tetracyclines or erythromycin with or without surgical drainage of lesions may be effective, many studies suggest systemic administration of isotretinoin to be the treatment of choice.<sup>290</sup> Laser ablation has also been advocated.<sup>291</sup>

### Acne Keloidalis

Acne keloidalis (folliculitis keloidalis) is a chronic scarring folliculitis and perifolliculitis of the nape and occipital scalp.<sup>292-294</sup> Initial lesions tend to be inflammatory papules and occasionally pustules that evolve



**Figure 7-30** Acne keloidalis. Scarring folliculitis with keloidal scarring at the nape and occipital scalp in this 17-year-old African-American adolescent.



**Figure 7-31** Telogen effluvium. Hair shedding is increased and, if a significant amount, a detectable increase in sparsity of hair may be noted. The loss is diffuse across the scalp but tends to stabilize after a few months and usually returns to normal within about 6 months.

into firm keloidal, often coalescent papules and plaques (Fig. 7-30). Severe cases may show abscesses and sinus formation. Patients may complain of pruritus and discomfort. The disorder is seen most commonly in postpubertal males, especially African-Americans between the ages of 14 and 25 years, but is occasionally described in females.<sup>295</sup>

Acute inflammation of the follicle is thought to be the primary pathologic process, followed by a granulomatous foreign body reaction to released hair, and subsequent fibrosis; a variety of triggers have been proposed, among them irritation from shirt collars or helmets, bacterial folliculitis, or ingrown hairs after a short haircut. Treatment of this disorder is difficult and consists of long-term systemic antibiotics and intralesional corticosteroids. Patients should avoid close “clipper” haircuts and scratching of the area. Laser and excision with second-intention healing have been helpful for selected patients, especially with fibrotic nodules.<sup>296,297</sup> Targeted ultraviolet B (UVB) light therapy has shown promise.<sup>298</sup>

#### Pseudofolliculitis Barbae

Pseudofolliculitis barbae, commonly called *razor bumps* or *ingrown hair*, is an inflammatory condition of hair follicles of the beard area that is particularly common in adolescent males of African ancestry with curly, coarse hair (see Chapter 14).<sup>293,294,296,299,300</sup> The condition can affect adolescent girls with tightly curled hair, however, especially if shaving occurs on the face because of hirsutism or because of hair removal elsewhere (waxing plucking or shaving of the axillae or pubic area). Erythematous, 2- to 4-mm, flesh-colored or often hyperpigmented, follicular-based papules are characteristic. The shape of the hair follicle, hair cuticle, and direction of hair growth predispose the patient to the inflammatory response when hair is shaved or plucked.<sup>301</sup> A single-nucleotide polymorphism (SNP) in *KRT75*, encoding hair keratin 75, has been linked with a much greater tendency to develop pseudofolliculitis barbae, especially in individuals with curly hair.<sup>302</sup> It is theorized that the pressure and traction exerted by close and regular shaving destabilizes the hair keratin.<sup>302</sup>

Pseudofolliculitis barbae is thought to represent a foreign-body reaction around an ingrown hair. Therapy largely involves prevention, particularly by temporarily discontinuing shaving or other forms of hair removal and then instituting alternative techniques that decrease the closeness of the shave such as use of an electric razor (avoiding the “closest” shave setting), the Bumpfighter razor (American Safety Razor Company, Staunton, VA),<sup>303</sup> or chemical depilatories. The condition tends to clear 4 to 8 weeks after discontinuation of triggers. Shaving should always be in the direction of hair growth, and pre-treatment with an antibacterial soap or benzoyl peroxide wash may decrease the potential inflammation from bacterial overgrowth. Adjunctive topical agents are retinoids, low-potency topical steroids, topical antibiotics, and depigmenting agents. Nonlaser epilation is not recommended and may exacerbate pseudofolliculitis barbae; however, the neodymium:yttrium-aluminum-garnet (Nd:YAG) 1064 nm and

diode (800 to 810 nm) lasers have been used to epilate the curly hairs and can cause significant improvement.<sup>304–306</sup> Elflornithine cream, which inhibits hair growth, may also be helpful but may be associated with the development of local irritation.

#### Pseudopelade

Pseudopelade is a nonspecific scarring form of slowly progressive alopecia of the scalp generally seen in adults, although it has been described rarely in children. It may represent the end result of discoid lupus erythematosus (see Chapter 22) or lichen planopilaris (see Chapter 4). It is characterized by multiple small round, oval, or irregularly shaped hairless cicatricial patches of varying sizes. Affected areas are shiny, ivory white or slightly pink, and atrophic. Lesions commonly coalesce to form finger-like projections and have been compared to footprints in the snow. Lesions generally appear at the vertex of the scalp. A few hair-containing dilated hair follicles may be interspersed between the patches. The condition tends to resolve spontaneously after several years, leaving the alopecia. Therapy is often unsuccessful, although intralesional injections of triamcinolone have temporarily benefited some patients. Cosmetic improvement has also been achieved by the multiple-punch autograft technique of hair transplantation.

#### Telogen Effluvium

The normal cyclic pattern of anagen and telogen hair phases may be interrupted by a variety of different stimuli, resulting in telogen effluvium. Telogen effluvium represents the most common type of alopecia in children and is characterized by diffuse thinning of scalp hair to varying degrees (Fig. 7-31).<sup>4</sup> The average individual who shampoos at least every other day loses 50 to 100 telogen hairs per day, but 25% of scalp hair (25,000 hairs) must be shed before unmistakable thinning becomes apparent.<sup>307–309</sup>

Several stimuli are capable of producing an interruption in the anagen phase of the hair follicles (Box 7-5). Telogen effluvium may be suggested by a history of a stressful event preceding the onset of alopecia by 6 to 16 weeks that shifts more hairs into telogen phase. Most common are acute illnesses, especially with fever, major trauma, surgery, or childbirth. Initiation of medications (Box 7-6) or discontinuation of medications, particularly oral contraceptives, isotretinoin, anticonvulsants, cimetidine, and terbinafine, has also been implicated.<sup>310,311</sup> More chronic telogen effluvium has been associated with chronic illness, thyroid abnormalities, iron deficiency anemia, malabsorption (e.g., celiac disease), malnutrition (e.g., anorexia nervosa),<sup>36</sup> systemic lupus erythematosus,<sup>312</sup> and zinc deficiency. The proportion of follicles affected and the severity of the subsequent alopecia depend on the duration and severity of the trigger and individual variations in susceptibility.

The diagnosis may be confirmed by both counting the number of hairs shed each day and determining the percentage of telogen hairs

### Box 7-5 Potential Triggers of Telogen Effluvium

- Emotional stress
- Fever (high)
- Medications (see Box 7-6)
- Nutritional disorders
  - Biotin deficiency
  - Dieting, crash; anorexia
  - Essential fatty acid deficiency
  - Iron deficiency
  - Hypervitaminosis A
- Physiologic telogen effluvium of the newborn
- Parturition
- Severe chronic illness
- Severe infection
- Surgery
- Thyroid disease (hyperthyroidism or hypothyroidism)

### Box 7-6 Pediatric Medications That May Be Associated with Telogen Effluvium

- Albendazole
- Amphetamines
- Angiotensin converting enzyme inhibitors (e.g., captopril, enalapril)
- Anticoagulants (e.g., heparin, warfarin)
- Anticonvulsants (e.g., valproic acid, carbamazepine)
- $\beta$ -Blockers (e.g., propranolol)
- Cimetidine
- Danazol
- Interferon- $\alpha$
- Lithium
- Oral contraceptives (during use or with discontinuation)
- Retinoids (e.g., isotretinoin)

in the scalp. Telogen hair represents approximately 15% and anagen 85% of scalp hair. If 25% or more of gently pulled hairs are telogen, telogen effluvium can be diagnosed. Anagen hair roots can be recognized by their intact outer and inner hair sheaths, with or without a portion of the dermal papilla adherent to the tip of the root (see Fig. 7-1, A). Telogen hair roots have uniform shaft diameters, contain no pigment, and are club shaped (see Fig. 7-1, B), much like the tip of a cotton-tipped applicator.

Increased telogen hair loss can also be seen in children with short anagen syndrome, in which the short, fine hair does not require haircuts and is present from birth. The shortening of the anagen phase, despite a normal rate of growth, leads to the decrease in the maximal hair length and an increase in the number of hairs in telogen. The disorder tends to resolve spontaneously during puberty and adulthood.<sup>313</sup> Elongation of the anagen phase has also recently been described as a result of mutations that deplete fibroblast growth factor 5 (FGF5), a regulator of hair length.<sup>314</sup> Because anagen hairs are already the majority of scalp hair but represent the minority of hairs of the eyelashes and extremities, trichomegaly (very long eyelashes) and longer extremity hair are the clinical manifestations in this recessive disorder that is homologous to the "angora" mutation in several species.

There is no effective treatment for telogen effluvium, but complete regrowth almost invariably occurs within months unless the stressful event is repeated or the underlying trigger is sustained. Careful explanation of the cause of this disorder and its favorable prognosis, with careful instructions to the patient to avoid unnecessary manipulation, tends to suffice. Blood tests for underlying disorders should be performed based on personal and family history and on examination, especially if no trigger is obvious. Adolescents predisposed to AGA may show incomplete regrowth after telogen effluvium with a residual pattern of hair loss consistent with AGA. Rarely, prolonged illness with high fevers destroys some follicles completely and only partial recovery ensues. Telogen effluvium occasionally occurs more than once in an individual, suggesting a predisposition to more significant hair loss with stress.



**Figure 7-32** Alopecia areata. Individuals with this common hair disorder suddenly develop one or more round or oval well-circumscribed, clearly defined patches of hair loss.

### Anagen Effluvium

In anagen effluvium, hair shaft production is markedly reduced, leading to tapering of the shaft and shedding.<sup>315</sup> Given that more than 80% of scalp hair is in anagen phase, hair loss is usually profound. Anagen effluvium usually occurs in patients administered radiation or chemotherapy for malignancy. Most commonly implicated are cyclophosphamide, methotrexate, 6-mercaptopurine, and doxorubicin.<sup>310,311</sup> In addition, anagen effluvium may be associated with exposure to colchicine and toxic levels of boric acid, lead, thallium, arsenic, bismuth, and warfarin.<sup>310</sup>

The clinical features of anagen effluvium depend on the degree of toxicity created by the causative agent. With lower doses of the toxic agent, only segmental thinning or narrowing may occur without actual fracture of the hair shaft. Gentle hair pulls yield "pencil point" dystrophic hairs with proximal tips tapered to a point.<sup>308</sup> With extensive anagen effluvium, the remaining hairs are telogen, and the hair plucks late in the course may show as many as 100% telogen hairs. A careful history, documented evidence of hair loss, microscopic examination of spontaneously shed and manually epilated hairs, and appropriate physical and toxicologic examinations help to establish the correct diagnosis. Cessation of the responsible drug or toxin generally results in regrowth of hair.

### Alopecia Areata

Alopecia areata (AA), one of the most common hair loss disorders with a prevalence of 0.1% to 0.2% of the population, is characterized by the sudden appearance of sharply defined round or oval patches of hair loss.<sup>316–318</sup> Alopecia totalis (loss of all scalp hair) or alopecia universalis (loss of all body hair) develops in approximately 5% of cases. The cumulative lifetime risk of developing AA is 2.1%, with the peak incidence occurring during young adulthood.<sup>319</sup> Prepubertal onset occurs less often than onset during adolescence but is not uncommon and is associated with a family history of AA and a poorer prognosis. Occurrence in young infants is unusual, and the disorder is very rare in neonates.<sup>320</sup>

There is a strong association between AA and atopic dermatitis, which is greatest among prepubertal children and in individuals with alopecia totalis and alopecia universalis.<sup>321–324</sup> Loss-of-function mutations in *FLG* (encoding filaggrin) have been associated with a more severe course and associated atopy but not a higher risk.<sup>325</sup> There is no sexual predilection for the disorder. Familial occurrence is reported in 8% to 52% of children, with an estimated lifetime risk of 7.1% in siblings, 7.8% in parents, and 5.7% in offspring.<sup>326</sup> Occurrence in both identical twins is 55%, emphasizing the importance of genetic as well as environmental factors.

The typical clinical picture of AA generally consists of a sudden (overnight or several days) appearance of one or more round or oval, well-circumscribed, clearly defined patches of hair loss (Fig. 7-32). Overall 83% of children have this patchy loss involving less than 50%



**Figure 7-33** Alopecia areata. Regrowing hair may be vellus hair or appear hypopigmented but is eventually replaced by normally pigmented terminal hair.



**Figure 7-35** Alopecia areata. The ophiasis pattern involves hair loss in a band extending from the occiput bilaterally along the hair margin toward the region above the ear and sometimes circling to the anterior scalp.



**Figure 7-34** Alopecia areata. "Exclamation-point hairs" in a girl with an ophiasis pattern of hair loss. Under the microscope, these hairs demonstrate a tapered shaft to an attenuated bulb (the "dot" of the exclamation point).



**Figure 7-36** Alopecia universalis. All hair is lost on the scalp and elsewhere. This is associated with a much poorer prognosis for hair regrowth.

of the scalp. Occasionally the initial patches may lack a regular outline and at times may demonstrate scattered long hairs within the bald areas. In other instances the initial loss may be diffuse, with discrete patches of alopecia being apparent only after 1 or 2 weeks, if at all. The primary patch may appear on any hairy cutaneous surface but usually occurs on the scalp. The skin is smooth, soft, and almost totally devoid of hair. Rarely, slight erythema or edema may be found at an early stage. Depigmented or hypopigmented hair shafts, simulating poliosis, may be seen (Fig. 7-33). Discrete islands of hair loss sometimes are separated by completely uninvolved or partially involved scalp. Around the margins of patches of alopecia, pathognomonic "exclamation-mark" hairs may be detected (Fig. 7-34). These loose hairs, with attenuated bulbs and short stumps, are easily plucked out of the scalp. Examination of such hairs under a low-power microscope reveals an irregularity in diameter and a poorly pigmented hair shaft that tapers to an attenuated bulb. The hair bulb represents the dot of the exclamation point. Dermoscopic evaluation of affected scalp can be very helpful, showing the tapered hairs and sometimes yellow perifollicular dots, demarcating the hyperkeratotic follicular plugs.<sup>327,328</sup>

The ophiasis pattern of hair loss begins as a bald spot on the posterior occiput and extends anteriorly and bilaterally in a 1- to 2-inch wide band encircling the posterior scalp, usually extending above the ear but occasionally to the anterior aspect of the scalp (Fig. 7-35). The ophiasis pattern is generally associated with a poor prognosis.<sup>329</sup> Progression to the totalis or universalis forms (Fig. 7-36) occurs more slowly but more often in children than in adults. Alopecia may involve



**Figure 7-37** Alopecia areata. The alopecia may involve the eyebrows and eyelashes, even without hair loss on the scalp; in this situation, trichotillomania must also be considered.

any hair; eyebrows and eyelashes may be lost with or without patches of hair loss on the scalp (Fig. 7-37).

Nail defects are seen in 10% to 20% of cases. Although more extensive disease is associated with more nail involvement, some patients may have extensive nail dystrophy with little hair change. The most



**Figure 7-38** Alopecia areata with nail changes. **(A)** The nails in this boy with alopecia areata are covered with shallow pits resulting from alteration in the proximal matrix. **(B)** Punctate opacification, proximal shedding (onychomadesis), Beau lines (horizontal dells), and serration of the free edges are all seen in the nails of this young girl with alopecia universalis.

characteristic nail abnormality is a fine, grid-like stippling, regularly arranged in horizontal and/or vertical rows with smaller and shallower pits than those seen in patients with psoriasis (Fig. 7-38, A). Proximal shedding (onychomadesis), opacification, and serration of the free edges may also be seen (Fig. 7-38, B). Longitudinal ridging (trachonychia) is another associated finding. Nail dystrophy tends to occur more often and be more severe in patients with alopecia totalis and universalis.

The diagnosis of AA is based on its clinical picture. The sudden appearance and circumscribed nonscarring, patterned nature of hair loss distinguish it from other disorders of alopecia. Trichotillomania is typically associated with bizarre, irregular patches of hair loss with areas of broken hairs of different lengths. The absence of signs of inflammation and scaling will generally help distinguish this disorder from that of tinea capitis. When the diagnosis is in doubt, microscopic examination of hairs, potassium hydroxide mounts, fungal cultures, and cutaneous punch biopsy will generally establish the proper diagnosis. Alopecia universalis beginning in infants must be distinguished from congenital alopecias such as atrichia with papules.<sup>330</sup> The AA spectrum can be a feature in 33% of children with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED; see Chapter 23) syndrome because of mutations in AIRE.<sup>331</sup> Although associated autoimmune disorders in affected children are quite rare, a family history of other autoimmune disorders, especially thyroiditis, is common, and autoantibodies may be detected in patient sera.<sup>332</sup> An increased incidence has also been noted in patients with trisomy 21.

The course of AA is variable and difficult to predict.<sup>333</sup> New patches of hair loss may appear for 4 to 6 weeks and occasionally for several months. Spontaneous regrowth may occur. In general, when the process is limited to a few patches, the prognosis is good, with complete

regrowth occurring within 1 year in 60% to 80% of patients; progression to total loss of scalp hair is unusual (<10%) and portends a considerably worse prognosis. About 30% of patients with patchy AA will have future episodes once regrown. In general, the earlier the onset, the poorer the prognosis. Other prognostic indicators of a worse outcome are family history of autoimmune disease, personal history of atopy, and nail abnormalities. Therapy for AA at best controls the condition but does not cure it or prevent development of new areas.<sup>334-336</sup> Because of the chronic nature of the condition and the slow growth of hair, any trial of a treatment modality requires at least 4 months. The sudden hair loss, cosmetic ramifications, and unpredictable course make AA a frightening disorder for affected patients and families<sup>337</sup>; psychological support and counseling are required for all patients and parents. Adequate camouflage of alopecic areas may be achieved by hats, headbands, or hairstyle changes. In children with severe involvement, wigs can be helpful. Locks of Love is an organization that provides hair prostheses to financially disadvantaged children under the age of 18 years ([www.lockslove.org](http://www.lockslove.org)).<sup>338</sup> The National Alopecia Areata Foundation ([www.alopeciaareata.com](http://www.alopeciaareata.com)) is a national support group for affected children and their families. Given the high percentage of children with patchy AA who show spontaneous remission within a year, some physicians prescribe no therapy for this condition. In general, patients with more extensive AA or with limited involvement unresponsive to topical corticosteroids should be referred to a dermatologist.

The most commonly used therapy for more limited AA in children is topical corticosteroids, with or without occlusion (such as may be achieved under a wig, bathing cap, or Saran Wrap); class II (potent) steroids are usually administered. Because the regrowth rate without medications is high, it has been hard to demonstrate clear evidence of the efficacy of steroids. If a class I (ultrapotent) steroid is employed, its use should be limited to intermittent pulse therapy; longer use may result in significant local atrophy and systemic absorption. In one study, clobetasol cream was more effective than 1% hydrocortisone in decreasing extent of hair loss by 12 weeks of twice daily use when used for 6 weeks on and 6 weeks off for a total of 24 weeks.<sup>339</sup> Intra-dermal corticosteroid injections commonly result in regrowth in tufts at injection sites within 4 to 6 weeks but are too uncomfortable for most children, even with the use of topical anesthetic creams. When an intralesional corticosteroid is used, a syringe with a 30-gauge needle or jet injection is best. Triamcinolone acetonide is injected in concentrations of 2.5 mg/mL (eyebrow area) to 10 mg/mL (scalp). Dosage should be limited to 0.1 mL per site, spaced at least 1 cm apart, with injections at intervals of at least 4 to 6 weeks.<sup>317</sup> Transient local atrophy may occur. Efficacy appears to be greatest in those who have less than 75% hair loss and with a relatively short duration of hair loss.

Minoxidil has been shown to stimulate follicular DNA synthesis. Although largely used for AGA, 2% to 5% topical minoxidil solution has been shown to cause cosmetically acceptable hair regrowth in approximately 20% to 45% of patients when used twice daily for 2 months.<sup>340</sup> Best results occur in patients with limited hair loss and when used concurrently with topical corticosteroids or anthralin. Cutaneous side effects may include local irritation, allergic contact dermatitis, and hypertrichosis, especially on the forehead (Fig. 7-39). Although quite rare, three children treated with topical minoxidil developed tachycardia, palpitations, and dizziness.<sup>341</sup> Prostaglandin F2a analogues (e.g., latanoprost, bimatoprost, travoprost) have not been helpful for alopecia of the eyelashes or brows<sup>342</sup> and have been linked to periorbital hyperpigmentation.<sup>343</sup>

Anthralin cream is an alternative therapy that seems to elicit hair growth by nonspecific immunostimulation. The 1% cream is usually applied as short-contact therapy, initially for 30 minutes with a gradual increase in exposure as tolerated to a maximum of 2 hours before shampooing of the scalp. A mild dermatitis is often required for regrowth, so concurrent use of topical corticosteroids is not recommended. New hair growth is usually seen in 3 months, but 6 months or more may be required for an acceptable response. Scalp irritation, folliculitis, and staining of the skin or clothes are potential adverse effects.

Two studies have demonstrated significantly low levels of vitamin D in individuals with AA,<sup>344,345</sup> and a boy with AA responded to topical



**Figure 7-39** Hypertrichosis induced from topical medications. Children who apply both topical corticosteroids and minoxidil are at particularly high risk for developing localized hypertrichosis, especially on the forehead (**A**) and nape (**B**).

calcipotriol,<sup>346</sup> but no causal relationship with vitamin D deficiency has been confirmed. Excimer laser therapy twice weekly is painless and caused hair regrowth in 60% of recalcitrant patches of AA in children in less than 3 months; only 22% of responders relapsed after 6 months.<sup>347</sup>

Treatment of more extensive AA (>50%), alopecia totalis, and alopecia universalis is very difficult. Topical application of corticosteroids is generally not helpful, but anthralin has shown greater responses. Topical immunotherapy is considered the treatment of choice for chronic, severe AA<sup>318</sup> and has been shown to decrease the T-cell infiltration.<sup>348</sup> Patients are initially sensitized to the contact allergen (2%); then increasing concentrations of the allergen beginning at 0.001% (occasionally stronger) are applied to the scalp until mild erythema and scaling develop. Squaric acid dibutyl ester and diphenylcyclopropane are used most commonly, because they are effective but not mutagenic or carcinogenic. Contact dermatitis at the sensitization site (about 20% of treated children)<sup>349</sup> or treatment site and regional lymphadenopathy are the risks of this therapy but only occasionally lead to discontinuation.<sup>350,351</sup> Immunotherapy may be performed weekly by the physician or administered with careful monitoring by responsible parents at home on a daily basis, gradually increasing the frequency of application and dosing. Up to 40% respond to immunotherapy with complete regrowth, although 70% to 80% show some response.<sup>352,353</sup> Unfortunately, relapse occurs in 81% of responders.<sup>354,355</sup> In patients who are atopic with extensive AA, the addition of oral fexofenadine to the contact allergen treatment may increase the response.<sup>356</sup> Although photochemotherapy with systemic psoralen followed by ultraviolet A (PUVA) light and cyclosporine therapy have been successful in some adults with this disorder, their efficacy and potential toxicity probably do not justify their use in children.

Although not recommended for general use, systemic corticosteroids may be considered for carefully selected patients with severe involvement and rapidly progressive hair loss who are psychologically

handicapped by their disorder. In such instances, prednisone may be administered in dosages of 0.5 to 1 mg/kg per day for 4 weeks until hair loss ceases and then tapered to alternate-day therapy for a few months. It must be emphasized that close follow-up evaluation is indicated in such cases and that the potential side effects associated with systemic corticosteroid therapy must be explained to the patient and parents. Pulse therapy with intravenous methylprednisolone has also been administered at a dosage of 250 mg twice daily for three sequential days with cessation of hair loss,<sup>357</sup> but the long-term outcome after corticosteroid therapy is poor.<sup>358</sup> In one retrospective study of 24 children with multifocal disease to alopecia universalis, 5 to 6 monthly treatments on 3 consecutive days of 8 mg/kg intravenous methylprednisolone led to a complete response in 38% and no response in 33%, but 81% relapsed within a mean of 9.5 months after therapy.<sup>359</sup> Not surprisingly, patients with duration of less than 6 months and an onset at younger than 10 years of age and multifocal vs. diffuse disease responded better. Continuing application of topical minoxidil after a steroid taper has been shown to decrease hair loss. Methotrexate (0.3 to 0.6 mg/kg per week) led to greater than 50% hair regrowth in 5 of 12 children (>40%) with recalcitrant AA in whom it was used for more than 2 months. The mean time to regrowth was 4.4 months, and all responders experienced improvement within 6 months.<sup>360</sup> Sulfasalazine has shown cosmetically acceptable improvement in about 25% of treated adults<sup>361</sup> when used at a dosage of 1.5 g twice daily (starting instead with 0.5 g/dose and then 1 g/dose for the first and second month, respectively). Trials with TNF inhibitors have been disappointing,<sup>362,363</sup> and AA has developed during TNF inhibitor therapy.<sup>364</sup>

Recent studies, including a genome-wide association study (GWAS) of more than 1000 affected individuals,<sup>365</sup> have shed light on the underlying pathomechanism of AA.<sup>365-373</sup> Whereas most of the linked genes involve the immune system, a receptor for stress-induced proteins (NKG2D) is also strongly linked, which is of interest because a stressful event precedes the onset of AA in 9.5% to 58% of patients.<sup>374,375</sup> These mechanistic studies have led to the discovery that systemic administration of Janus kinase (JAK) inhibitors (ruxolitinib, tofacitinib) prevent the development of AA in the C3H/HeJ-grafted mouse model and in pilot studies lead to almost complete hair regrowth after up to 5 months of 20 mg ruxolitinib twice a day orally in adults with severe AA.<sup>376</sup> Topical administration of ruxolitinib and tofacitinib to established mouse AA also led to full hair regrowth within 12 weeks, suggesting the applicability of topical therapy for pediatric AA.<sup>376</sup>

### Androgenetic Alopecia

Androgenetic alopecia (AGA) occurs in both males (common baldness or male-pattern baldness) and females (hereditary thinning or female-pattern hair loss) and is the most common cause of hair loss in adolescents<sup>377</sup> and adults. In many cases, it begins in teenage years with onset as young as 7 years<sup>378,379</sup>; in general, the earlier the onset, the more profound the subsequent alopecia. The disorder is characterized by patterned, progressive hair loss from the scalp and results from the effects of circulating androgens in genetically susceptible individuals. Dihydrotestosterone is the primary androgen implicated, converted from testosterone by the enzyme 5- $\alpha$ -reductase. These androgens gradually decrease the size of scalp hair follicles, resulting in miniaturized hairs. In addition, the anagen growth phase is shortened, leading to more hairs in telogen phase. The condition is inherited as a polygenic trait influenced by both maternal and paternal genes<sup>380</sup>; in one study, 83% of adolescents with AGA had an affected first-degree relative.<sup>377</sup>

Most patients with AGA note thinning of scalp hair rather than shedding, although shedding may occur early in the course and be confused with telogen effluvium or diffuse AA. AGA during adolescence occurs twice as often in males as in females and is generally more severe. The mildest and often earliest form of androgenetic male-pattern alopecia in males is thinning at the vertex, often in conjunction with symmetrical bitemporal triangular recession of the hairline (Fig. 7-40). In girls, the frontal hairline is relatively unaffected and there is either just vertex thinning or more commonly, diffuse thinning, particularly from the frontal scalp to the vertex (see Fig. 7-38). Widening of the central hair part is often seen, leading to scalp



**Figure 7-40** Androgenetic alopecia. The scalp hair is thinned progressively but most notably between the frontal region of the scalp and the vertex.



**Figure 7-41** Androgenetic alopecia. Widening of the central hair part is often seen, leading to scalp visibility.

visibility (Fig. 7-41). This female pattern of more diffuse hair loss is observed in 20% to 33% of adolescent males.<sup>377,379</sup>

The diagnosis of AGA can be suspected by the patterning of the scalp hair loss. Dermoscopy is a useful adjunctive measure to visualize the miniaturized hairs in affected areas.<sup>3</sup> If confirmation is required, scalp biopsy can be performed, particularly with horizontal sectioning to determine the ratio of terminal to vellus hairs (>7:1 is normal; <4:1 is diagnostic). Other supporting histologic features are the perifollicular inflammation and fibrosis. Hormonal evaluation and endocrinologic consultation for female patients should be considered, especially in the presence of menstrual irregularities, moderate to severe acne, seborrhea, and evidence of virilization such as hirsutism. Laboratory evaluation should include testing for thyroid disease, iron deficiency, free and total testosterone, dehydroepiandrosterone sulfate (DHEA-S), 17-OH-progesterone (to consider late-onset congenital adrenal hyperplasia) and if appropriate, prolactin levels. In one study 37.5% of 19 affected adolescent girls had increased levels of androgens, and 47% showed at least one additional clinical feature of hyperandrogenism. Laboratory testing should also be considered in boys

who have diffuse thinning (more of a female pattern) or abnormal pubertal development.

The occurrence of AGA during teenage years can be quite disturbing to both young men and women. Careful examination and repeated reassurance are required to discourage expensive and ineffective therapeutic regimens. Without treatment, AGA is progressive; the aim of treatment is to retard the further thinning of the hair and to promote hair growth.

Topical minoxidil and oral finasteride are US Food and Drug Administration (FDA)-approved treatments (minoxidil is over-the-counter) but are only approved for use in patients over the age of 18 years. Minoxidil promotes hair growth and decreases hair loss in approximately 60% of male and female patients when applied twice daily.<sup>381–383</sup> Evidence of hair growth requires at least 3 to 6 months. The mechanism of action of topical minoxidil most likely involves its stimulation of follicular proliferation and vascularization of the follicle. Although 2% has been approved for women and 5% for men, the 5% strength can be initiated off-label in either girls or boys, with 2% as an alternative should any issue arise. Application of minoxidil must be continued to maintain hair growth, and hair loss resumes 4 to 6 months after discontinuation. The most common side effect of topical minoxidil is irritation, usually from the propylene glycol in the solution, although orthostatic hypotension has rarely been described. Hypertrichosis has been described on nonscalp sites, possibly from transfer of the solution.<sup>384</sup> The addition of weekly microneedling, which stimulates hair follicle stem cells but may also improve minoxidil penetration, markedly increased the hair count and improved the patient evaluation during a 12-week period in comparison with minoxidil alone.<sup>385</sup> Oral finasteride (1 mg daily) is often combined with the minoxidil for treatment in males, given their different mechanisms of action. Finasteride specifically inhibits type II 5- $\alpha$ -reductase, leading to reduction in both serum and scalp levels of dihydrotestosterone. The only statistically significant side effect of finasteride is sexual dysfunction, and decreased libido or erectile or ejaculatory dysfunction have each been described in 1% to 2% of patients. Postmarketing reports suggest that these adverse sexual effects sometimes persist more than 3 months after discontinuation, but a causal relationship has not been demonstrated. Although sometimes used in boys with AGA, finasteride is known to cause feminization of the male fetus and thus should be used with caution, if at all, for adolescent girls.<sup>386</sup> Oral dutasteride 0.5%, which inhibits both type I and type II 5- $\alpha$ -reductase and is available outside of the United States, has been shown to be more effective than finasteride with the same side effect profile.<sup>387</sup>

Spirostanolactone has shown some benefit in girls with AGA at doses of 50 to 200 mg/day<sup>388</sup>; similarly, cyproterone acetate in doses of 50 to 100 mg/day in combination with ethynodiol has been successful in inducing hair regrowth and preventing progression but is not currently available in the United States. Food supplements with plant extracts including of *Serenoa repens*, a treatment of benign prostatic hyperplasia, have been proposed as a "natural" alternative for treating male AGA.<sup>389</sup> A report of hot flashes in an 11-year-old girl linked to oral ingestion of *Serenoa repens* for telogen effluvium warns of their danger in pediatric patients.<sup>390</sup>

Randomized, double-blind, controlled office- or home-based studies have suggested efficacy of office-based low-level laser therapy, either as monotherapy or with other interventions.<sup>391–393</sup> Surgical procedures, such as scalp reduction with or without tissue expansion, scalp flaps, and multiple-punch autografting hair transplantation, may also be considered in patients with advanced AGA but is inappropriate for use in adolescents, given that the course of the AGA is unpredictable.<sup>394</sup>

### Traumatic Alopecia

Traumatic alopecia results from the forceful extraction of hair or the breaking of hair shafts by friction, pressure, traction, or other physical trauma. The usual causes are cosmetic practices and trichotillomania. Other causes of traumatic alopecia include pressure, such as occurs in neonates who develop caput succedaneum with a scalp ring from birth trauma or use of suction at delivery<sup>474</sup> (see Chapter 2) and as is seen in association with the habit of head banging; prolonged bed rest in one position such as may be seen in chronically ill patients; postoperative alopecia (as a result of pressure-induced ischemia during long



**Figure 7-42** Traction alopecia. Hair loss can be seen at the margins where hair is pulled most tightly through use of barrettes.

surgical procedures); thermal or electric burns; repeated vigorous massage; a severe blow to the scalp; occipitoparietal alopecia such as may be induced by spinning on the crown of the head during break dancing; pressure from orthodontic headgear<sup>395</sup>; or prolonged use of wide-strapped heavy headphones such as those commonly used by individuals while jogging. Prolonged or forceful trauma may cause scarring alopecia.

Alopecia from cosmetic practices most often results from traction but has been described as resulting from pulling, frequent brushing with nylon bristles, the use of hot combs and oils, and hair-straightening practices such as teasing. Traction alopecia is characterized by oval or linear areas of hair loss at the margins of the hair line, along the part, or scattered through the scalp, depending on the type of traction or trauma.<sup>396,397</sup> Peripheral scalp hair loss may occur in individuals who wear their hair in pony-tails or braids or use hair extensions<sup>398</sup> or barrettes (Fig. 7-42). Overall, 17.1% of school-aged African girls showed traction alopecia, with the percentage increasing toward the end of high school and with a history of braids on relaxed hair.<sup>399</sup> In one study, traction alopecia occurred 3 times more often in girls with cornrows versus ponytails or braids.<sup>400</sup> Hair loss from hair rollers is usually most conspicuous in the frontocentral area or around the margins of the scalp. Hot-comb alopecia, seen primarily in African-American individuals who straighten their hair for cosmetic purposes, generally occurs on the vertex or marginal areas of the scalp. In severe chronic forms, however, the entire scalp may be involved. Traction folliculitis may present as perifollicular erythema and pustules at sites of traction.<sup>401</sup>

Trichotillomania is a self-limiting, self-induced form of traction alopecia produced either consciously or by habitually plucking, pulling, or cutting the hair in a bizarre manner.<sup>402–404</sup> Trichotillomania-by-proxy has also been described, in which a parent with trichotillomania pulls the hair of a child as part of the overwhelming urge to depilate.<sup>405</sup> Seen in both sexes, it more commonly occurs in adolescents, although the condition may occur in preschool children. The scalp is the most common site of involvement, but the eyebrows, eyelashes, and even pubic hair may also be affected as the patient plucks, twirls, or rubs hair-bearing areas, resulting in the epilation or breakage of hair shafts (Fig. 7-43).

The habit is usually practiced in bed before the child falls asleep (when the parent does not notice the habit) or when the child is reading, writing, or watching television. In young individuals the condition is commonly associated with a habit of finger or thumb sucking (Fig. 7-44). In older children, other compulsive behaviors such as nail biting (onychophagia), skin picking, picking at acne (acne excoriée), nose picking, lip biting, and cheek chewing may be seen as well. In 2013 the American Psychiatric Association changed trichotillomania in its *Diagnostic and Statistical Manual of Mental Disorders (DSM) 5* classification tool from an impulse-control disorder not elsewhere classified to an obsessive-compulsive disorder.

Trichotillomania usually begins insidiously as an irregular linear or rectangular area of partial hair loss. Affected areas are generally single; often frontal, frontotemporal, or frontoparietal; and commonly



**Figure 7-43** Trichotillomania. The eyebrows and eyelashes may be pulled out or broken by repetitive plucking, twirling, or rubbing.



**Figure 7-44** Trichotillomania. In younger children trichotillomania is often a habit of twirling or plucking associated with finger or thumb sucking and does not reflect significant psychologic disturbance.

appear on the contralateral side of right- or left-handed individuals. The affected patches have irregularly shaped angular outlines and are never completely bald (Fig. 7-45). Within the involved regions, the hair is short or stubby and broken off at varying lengths (Fig. 7-46).

If one maintains a high index of suspicion, trichotillomania can generally be distinguished from other forms of hair loss by its characteristic configuration and distribution. Trichoscopy can be helpful, showing the irregularly broken hairs as well as a variety of other specific signs (such as the V sign, flame hairs, and coiled hairs).<sup>406</sup> Occasionally the diagnosis can be confirmed by the finding of wads of hair under the pillow or bed or by observation of the habit by a parent, teacher, or physician. When the diagnosis is suspected, regrowth of hair in a carefully shaved or occluded patch of scalp in the involved area (to prevent manipulation) may confirm the correct diagnosis. The possibility of associated trichophagia and trichobezoar should be also be entertained.<sup>407</sup>

Trichotillomania should be distinguished from AA, although both have been described in the same individuals, often with the AA as the trigger to the trichotillomania.<sup>408</sup> Clinical differentiation from AA is usually based on the bizarre configuration, irregular outline, and presence of short, stub-like, broken hairs. Differentiation from tinea capitis may require microscopic examination of plucked hairs with potassium hydroxide and fungal culture (see Chapter 17). Of particular significance is the fact that the broken hairs of trichotillomania, unlike those of certain forms of tinea capitis, remain firmly rooted in the



**Figure 7-45** Trichotillomania. The affected areas have irregularly-shaped, angular outlines and are never completely bald. They tend to be sites that are easy to reach.



**Figure 7-46** Trichotillomania. This boy tried to cover a patch of trichotillomania with eyebrow pencil but continued to pluck hairs.

scalp, and the cutaneous surface is normal and stubbled rather than erythematous or scaly. If the diagnosis remains in doubt, biopsy of the involved area may be helpful.

The management of trichotillomania is often difficult and requires a strong relationship among the doctor, patient, and parents. Although patients occasionally will admit to touching the affected areas, they commonly will deny plucking, rubbing, or excessive manipulation. Blunt accusation is often detrimental, but gentle suggestion of the cause may lead to dialog that is important for reversal. Psychopathologic changes are reported to be present in some 50% to 75% of affected individuals. These changes are usually mild, but severe psychologic disturbance occurs in approximately 5% of patients with trichotillomania, most commonly in older children and teenagers. In general, the disorder is limited in preschool-age children and may be more episodic in children than in affected teenagers.

If patients are reassured, given an opportunity to express their emotional needs, and offered a reasonable therapeutic regimen such as a mild shampoo, mild topical steroid (e.g., hydrocortisone 1%) lotion, and behavioral modification techniques, the habit will sometimes disappear, especially in young children. For those individuals with persistent or severe obsessive-compulsive or emotional problems, however,



**Figure 7-47** Vellus hair cysts. Size 1- to 3-mm, skin-colored to hyperpigmented follicular papules on the anterior chest.

psychiatric intervention should be considered. Cognitive behavioral therapy with relapse prevention can reduce trichotillomania severity by 64% at 6-month follow-up evaluation.<sup>409,410</sup> For habitual trichotillomania in young children, substitution therapy (such as with a soft tag to stroke or a long-haired doll) and provision of rewards can be helpful.<sup>411</sup> Olanzapine, clomipramine, or a highly selective serotoninergic reuptake inhibitor (SSRI) (e.g., fluvoxamine, fluoxetine, paroxetine, sertraline, or citalopram) may be of benefit. Despite the value of oral N-acetylcysteine in a large trial of adults with trichotillomania, a recent trial of 39 children ages 8 to 17 years did not show benefit during 12 weeks of treatment.<sup>412</sup> A trichotillomania support group, the Trichotillomania Learning Center, is available at [www.trich.org](http://www.trich.org).

## Eruptive Vellus Hair Cysts

Eruptive vellus hair cysts are characterized by 1- to 3-mm, skin-colored to hyperpigmented follicular papules, most commonly on the anterior chest (Fig. 7-47).<sup>413</sup> Lesions usually are not grouped and tend to be smooth-surfaced with a round or domed shape. Vellus hair cysts have less commonly been described on the upper and lower extremities, face, neck, abdomen, axillae, posterior trunk, and/or buttocks. If darker blue in color and on the face, they have been confused with nevus of Ota.<sup>414</sup> Although usually seen in children between 4 and 18 years of age, these cysts can occur at any age.

The histologic picture of eruptive vellus hair cysts shows small, mid to upper dermal keratinizing cysts filled with lamellar keratin and small-diameter nonpigmented or lightly pigmented hair shafts. Vellus hair cysts can be distinguished from steatocystoma multiplex by the inclusion of sebaceous glands in the cyst wall of steatocystoma multiplex.<sup>415</sup> However, lesions with features of both types of cysts have been described; both types of lesions have been seen in the same individuals, and kindreds with the autosomal dominant inheritance of both vellus hair cysts and steatocystoma multiplex have been reported with keratin 17 mutations, suggesting a common causation for the two types of cystic lesions.<sup>416,417</sup> An alternative diagnostic technique to biopsy is to perform a tiny incision at the top and examine the expressed contents microscopically for vellus hairs.<sup>418</sup>

Vellus hair cysts are most commonly confused with comedonal acne, milia, molluscum contagiosum, syringomas, folliculitis, keratosis pilaris, steatocystoma multiplex, and other adnexal tumors; dermoscopic evaluation can be helpful in making the diagnosis.<sup>419</sup> The cysts may resolve spontaneously during a few months to years by transepidermal elimination. Patients desiring therapy can be treated by incision of individual cysts and expression of their contents followed by gentle curettage, light electrodesiccation with expression of contents,<sup>420</sup> therapy with topical vitamin A acid (tretinoin), lactic acid (12% lotion), or laser.<sup>421</sup>

## Hypertrichosis and Hirsutism

Excessive hairiness may be localized or diffuse, congenital or acquired, and normal or pathologic.<sup>312</sup> Hair in the pubic area of infants may be benign and often resolves spontaneously by 1 year of age, especially if on the scrotum in boys and labia majora or mons in girls without other evidence of virilization or sexual development.<sup>422</sup> The terms *hypertrichosis* and *hirsutism* are commonly and inappropriately used synonymously to describe excessive hair on the body.<sup>423,424</sup> *Hirsutism* implies an excessive growth of body hair in women or children (mostly girls) in an androgen-induced hair pattern (upper lip, chin, sideburn areas, neck, anterior chest, breasts, linea alba, abdomen, upper inner thighs, and legs).<sup>425</sup> *Hirsutism* most commonly represents a physiologic variant of hair growth, often seen in several family members, which comes to medical attention only because of societal pressure to remove excessive hair (Fig. 7-48). *Hypertrichosis*, conversely, refers to a generalized or localized pattern of non-androgen-dependent excessive hair growth in a male or female without evidence of masculinism or menstrual abnormality.

### ACQUIRED GENERALIZED HYPERTRICHOSIS

Generalized hypertrichosis may be associated with neurologic disorders (postencephalitic hypertrichosis, multiple sclerosis), anorexia nervosa, acrodynia, hypothyroidism, porphyria, dermatomyositis, gross malnutrition, and various forms of drug-induced hypertrichosis. Drug-induced hypertrichosis (Fig. 7-49) is most commonly seen in children who are administered phenytoin or cyclosporine, usually after 2 or 3 months of treatment, but other medications have been implicated as well (Box 7-7; see Fig. 22-21). Reversible generalized hypertrichosis has also been described in an infant exposed to topical minoxidil from her caregiver grandfather who held her extensively on his shoulders.<sup>426</sup> Localized hypertrichosis can be acquired from topical application as well, including with minoxidil (see Fig. 7-39) and topical corticosteroids (Fig. 7-50). In adults but not in children, acquired forms of hypertrichosis lanuginosa are strongly associated with internal malignancy, especially adenocarcinoma.

### CONGENITAL HYPERTRICHOSIS

The original fine, soft, unmedullated, and usually unpigmented lanugo hairs are shed *in utero* during the seventh or eighth month of gestation. Premature infants, however, commonly display this fine coat of lanugo hair, particularly on the face, limbs, and trunk. In these



**Figure 7-48** Familial hirsutism. This 6-year-old girl has excessive terminal hair on the upper lip, which led to embarrassment. Her mother and maternal grandmother experienced the same increase in mustache hair.



**Figure 7-49** Drug-induced hypertrichosis. This infant girl developed hypertrichosis from administration of diazoxide for hyperinsulinemia.



**Figure 7-50** Drug-induced hypertrichosis. Overgrowth of terminal hair was noted strictly at the site at which this boy's parents continued to apply a medium-strength topical corticosteroid for many months after clearance of his nummular dermatitis.

### Box 7-7 Medications That May Cause Hypertrichosis

- Adrenocorticotropic hormone (ACTH)
- Corticosteroids
- Cyclosporine
- Danazol
- Diazoxide
- Glucocorticosteroids
- Hexachlorobenzene (drug-induced porphyria cutanea tarda)
- Minoxidil
- Penicillamine
- Phenytoin
- Psoralens and ultraviolet light exposure
- Streptomycin
- Testosterone
- Valproic acid

infants the fine lanugo hairs are shed during the first 3 months of life and replaced by normal terminal hair growth, generally before the first 6 months.

Hypertrichosis lanuginosa is a rare inherited disorder in which lanugo hairs persist or are overproduced throughout life.<sup>427</sup> Affected infants may be unusually hairy at birth or may develop hypertrichosis during early childhood. In some children, the hair will be spontaneously lost during childhood; in others, it will remain into adulthood. Generalized hypertrichosis can be very disfiguring. Affected children have been called *monkey-men*, *dog-face*, and *human Skye terriers*. Sporadic, autosomal recessive, and autosomal dominant cases have been described. Congenital glaucoma, skeletal abnormalities, and missing teeth have been described in association.

Ambras syndrome is a generalized condition of hypertrichosis in which the hair appears to be vellus rather than lanugo hair.<sup>428–430</sup> The hypertrichosis is most evident on the face, ears, and shoulders, and persists throughout life. Dysmorphic facial features have been associated. Ambras syndrome has been linked to a rearrangement in chromosome 8q that downregulates the expression of *TRPS1* (mutated in trichorhinophalangeal syndrome).<sup>431</sup>

Hypertrichosis with gingival hyperplasia is a distinct autosomal dominant disorder in which affected individuals have excessive body and facial hair in an identical distribution to that of hypertrichosis lanuginosa, but patients tend to have terminal hair and have associated gingival hyperplasia (Fig. 7-51). Although the hypertrichosis is most commonly present at birth or in infancy, in up to half of reported cases the hypertrichosis begins at puberty. The gingival hyperplasia is usually noted with delayed tooth eruption and has been described as pink, firm, and pebbly. The disorder is complicated by interference with chewing, respiration, and speech, and periodontal abscesses have been described because of difficulty in dental eruption. Gingival debulking may be required. A large deletion on 17q24.2-q24.3 has been found to be responsible for congenital generalized hypertrichosis, with or without gingival hyperplasia.<sup>432</sup> Whole exome sequencing in a girl with congenital generalized hypertrichosis and gingival hyperplasia showed a homozygous intronic mutation in the ABC lipid transporter gene *ABCA5*, which is within the deleted region on chromosome 17; the mutation caused aberrant splicing of the transcript and decreased follicular protein levels.<sup>433</sup> Generalized hypertrichosis can also be a manifestation of a “potassium channelopathy,” resulting from heterozygous activating mutations in *ABCC9*, which encodes the sulfonyl-

urea receptor *SUR2*. In addition to the hypertrichosis, affected individuals have a spectrum of features ranging from acromegalic facies (with or without gingival hypertrophy)<sup>434</sup> to Cantú syndrome with its neonatal macrosomia, coarse facial features, osteochondrodysplasia, and cardiomegaly.<sup>435</sup> *SUR2* is expressed in the dermal papilla and is stimulated by minoxidil in inducing hair growth.<sup>436</sup>

X-linked dominant hypertrichosis has been described in a Mexican pedigree. Affected males show excessive generalized terminal hair growth, especially on the face and upper torso; female individuals are less severely affected and can show asymmetric hairiness thought to represent random inactivation (lyonization) of the affected chromosome. This condition sometimes improves after puberty.<sup>437</sup> In another Mexican kindred, congenital universal hypertrichosis was associated with deafness and dental anomalies as an X-linked recessive disorder.<sup>438</sup>

Generalized hypertrichosis is also a feature of several syndromes (Box 7-8), among them congenital erythropoietic porphyria (see Chapter 19) and most commonly, the Cornelia de Lange syndrome.<sup>439</sup> This congenital, genetically heterogeneous disorder features marked hypertrichosis; cutis marmorata; hypoplastic genitalia, nipples, and umbilicus; prenatal and postnatal growth retardation; malformation of the limbs, gastrointestinal tract, diaphragm, heart, and genitourinary systems; mental retardation; and a characteristic low-pitched and growling cry. The face of afflicted individuals is characterized by overgrowth of the eyebrows, long eyelashes, high upper lip, saddle-nose, and a cyanotic hue about the eyes, nose, and mouth. Children with this disorder often have recurrent respiratory-tract infections and gastrointestinal reflux; seizures have been observed in about 20% of reported cases, and most patients die before the age of 6 years. To date, heterozygous mutations in five genes have been described, most commonly *NIPBL* (60%).<sup>439</sup> These genes all encode structural or regulatory proteins involved in cohesin, a protein complex that regulates the separation of sister chromatids during cell division.<sup>440</sup>

## LOCALIZED FORMS OF HYPERTRICHOSIS

### Nevoid Hypertrichosis

Growth of hair abnormal in length, shaft diameter, or color may occur in association with other nevoid abnormalities or as isolated circumscribed developmental defects.<sup>441</sup> Abnormal tufts of hair in the lumbarosacral and, at times, the posterior cervical or thoracic areas (the



**Figure 7-51** Hypertrichosis. Generalized terminal hair growth in this girl with gingival hyperplasia.

### Box 7-8 Congenital Syndromes Associated with Generalized Hypertrichosis

- Barber-Say syndrome
- Cantu syndrome (hypertrichosis with osteochondrodysplasia)
- Coffin-Siris syndrome
- Cornelia de Lange (Brachmann-de Lange) syndrome
- Craniofacial dysostosis
- Hemimaxillofacial dysplasia
- Lipodystrophies
  - Berardinelli-Seip syndrome
  - Donohue syndrome (leprechaunism)
- Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome
- Mucopolysaccharidoses
  - Hunter syndrome
  - Hurler syndrome
  - Sanfilippo syndrome
- Rubinstein-Taybi syndrome
- Schinzel-Giedion syndrome
- Porphyrrias (see Chapter 19)
  - Erythropoietic porphyria (Gunther disease)
  - Familial porphyria cutanea tarda
  - Hepatoerythropoietic porphyria
- Stiff skin syndrome
- Toxin exposure
  - Fetal alcohol syndrome
  - Fetal hydantoin syndrome
- Winchester syndrome (see Chapter 6)



**Figure 7-52** Faun-tail deformity. Abnormal tufts of hair in the lumbosacral area suggest an underlying tethered cord or diastematomyelia.



**Figure 7-54** Nevoid circumscribed hypertrichosis. This hair follicle hamartoma shows congenital growth of thicker, darker, and longer hairs without associated hyperpigmentation or associated follicular prominence.



**Figure 7-53** Anterior cervical hypertrichosis. A form of nevoid hypertrichosis, this patch of hair at the anterior aspect of the neck is usually not associated with other pathology.

faun-tail nevus, Fig. 7-52) may be associated with an underlying kyphoscoliosis, duplication of a portion of the spinal cord (diastematomyelia), or tethered cord. Although neurologic signs of this disorder generally appear during early childhood, they may be delayed until the affected person's teenage or adult years. Early detection by imaging allows neurosurgical intervention and prevents the potential neurologic sequelae. Symmetric localized hypertrichosis has also been described at the elbows (hypertrichosis cubiti)<sup>442,443</sup> and anterior cervical area (anterior cervical hypertrichosis) (Fig. 7-53). Hypertrichosis cubiti and anterior cervical hypertrichosis are usually isolated disorders. However, anterior cervical hypertrichosis has been described as an autosomal recessive disorder in association with developmental delay, peripheral neuropathy with or without retinal abnormalities,<sup>444</sup> and hypertrichosis cubiti with short stature, facial asymmetry, intrauterine growth retardation, developmental and speech delay, and infantile spasms.<sup>445</sup>

Hypertrichosis is often a characteristic of melanocytic nevi, smooth muscle hamartomas and Becker nevus, plexiform neurofibromas, and linear epidermal nevus. Nevoid circumscribed hypertrichosis (Fig. 7-54), a hair follicle nevus, presents as an isolated patch of hypertrichosis. Increased local hair growth may be seen after wearing a cast or at sites of thrombophlebitis, stasis dermatitis, X-ray or ultraviolet light irradiation, chemical irritation, or local hormonal stimulation. Extensive congenital smooth muscle hamartomas may show hypertrichotic and skin-colored to lightly hyperpigmented patches in association with excessive skin folds and follicular dimpling (sometimes called *Michelin baby syndrome*).<sup>446</sup> Multiple patches of congenital hypertrichosis in association with blaschkoid streaks of hypopigmentation have spontaneously cleared shortly after birth.<sup>447</sup>

Symmetric, large, hypertrichotic, indurated hyperpigmented patches on the middle and lower body first appear during the first or second decade in autosomal recessive H syndrome.<sup>448</sup> In addition to hyperpigmentation and hypertrichosis, patients show hepatosplenomegaly, heart anomalies, hearing loss, hypogonadism, hallux valgus, low height, camptodactyly and occasionally hyperglycemia. Mutations have been found in the nucleoside transporter hENT3, encoded by SLC29A3.<sup>449</sup>

### Idiopathic Hirsutism

Idiopathic hirsutism describes the presence in girls of excessive body hair in a male sexual pattern (the face, particularly the upper lip, chest, abdomen, arms, and legs) in the absence of clinical evidence of disturbed endocrine or metabolic function (see Fig. 23-13).<sup>450,451</sup> Idiopathic hirsutism is assumed to relate to increased stimulation of the hair follicles of genetically predisposed girls by normal levels of androgenic hormones. Hirsutism is quantified by the Ferriman-Gallwey scale, with scores of 6 to 8 considered mildly hirsute, 8 to 15 serious, and greater than 15 overt hirsutism. Other signs of hyperandrogenism are acne, oligomenorrhea or amenorrhea, and AGA.

The incidence of hirsutism in any population is difficult to assess, because the range of normal is quite wide and subject to individual acceptance and includes that which is not always socially acceptable in a particular culture. Hispanic, Jewish, and Welsh women in general have more hair than their counterparts of Northern European, Japanese, and Indian heritage. The physician should be cognizant of what is normal and acceptable to some individuals, yet unacceptable and a source of anguish to others. Performing a history and physical

examination (including body mass index [BMI] and waist circumference) will determine the need for full endocrinologic investigation. When hirsutism is observed in a postpubertal girl without other signs of masculinity (receding hairline, deepening of the voice, or evidence of menstrual disturbance), endocrine disease is unlikely. When the disorder does not appear to be physiologic and particularly if associated with other signs of androgen excess or premature puberty (sexual hair before 8 years of age in girls), abnormalities of the pituitary, adrenals, and ovaries must be ruled out. These include “exaggerated adrenarche,” late-onset congenital adrenal hyperplasia, virilizing tumors,<sup>452,453</sup> Cushing syndrome, hyperprolactinemia, acromegaly, Achard-Thiers (diabetes, hypertension, and hirsutism) syndrome, and polycystic ovary syndrome (PCOS) (see Chapter 8).<sup>454,455</sup> Of these, PCOS is by far the most common and is increasing in prevalence in parallel to the increasing trend toward obesity in teenagers (3% of unselected adolescents in one study).<sup>456</sup>

In addition to signs of hyperandrogenism,<sup>457</sup> the presence of oligomenorrhea or amenorrhea and acanthosis nigricans are a clue to PCOS.<sup>458</sup> Oligomenorrhea is defined as menstrual cycles of more than 35 days, with fewer than eight menstrual cycles defined as chronic anovulation. It is harder to diagnose oligomenorrhea in adolescents, but persistent irregularity more than 2 years after the onset of menses should be considered abnormal. Obesity is a significant risk factor for PCOS, and 40% to 60% of women with PCOS are overweight or obese, especially with abdominal adiposity.

If an endocrine abnormality is suspected, minimal laboratory testing for excessive androgen production should include levels of 17-ketosteroids (for mild adrenal hyperplasia), free plasma testosterone, dehydroepiandrosterone sulfate levels, and morning and evening cortisol; luteinizing hormone (LH) and follicle-stimulating hormone (FSH) ratios and transabdominal ultrasound (to rule out small ovarian cysts) may be useful. Hormonal evaluations are best carried out in the morning during the third to fifth day of menstruation. If PCOS is suspected, fasting levels of glucose and insulin should be obtained.<sup>459</sup> A proposed definition of PCOS in adolescents includes four of the following criteria: (1) clinical hyperandrogenemia; (2) biochemical hyperandrogenemia (serum testosterone >50 ng/dL and LH/FSH ratio of greater than 2); (3) insulin resistance and hyperinsulinemia (acanthosis nigricans, visceral adiposity, and impaired glucose tolerance); (4) oligomenorrhea persisting 2 years after menarche; and (5) polycystic ovarian morphology on ultrasound.<sup>460</sup>

### Treatment of Hypertrichosis and Hirsutism

The appearance of excessive hair may be modified in several ways.<sup>450</sup> Cutting with scissors or shaving with a razor or electric shaver, although occasionally not psychologically acceptable to the patient, are the simplest methods and least likely to irritate the skin. These techniques do not stimulate faster or thicker growth.<sup>423</sup> Bleaching with hydrogen peroxide may make excessive hair less conspicuous for up to 4 weeks and works best for light-skinned children, because yellow bleached hair may be emphasized when viewed against darkly pigmented skin. Plucking and wax epilation (essentially a form of widespread plucking) by application of a warm wax preparation to the affected areas are too painful for children but may be an option for older adolescents. Chemical depilatories that contain sulfides, thioglycolates, or enzymatic depilatory agents destroy the projecting hair shafts, causing minimal damage to underlying skin. Of these, the sulfide-containing preparations are more effective but more irritating and produce a disagreeable hydrogen sulfide odor. The thioglycolate-containing agents are less irritating but slower in action and less effective on coarse hairs. Enzymatic agents are less offensive but not as effective as other types. Children with extensive hypertrichosis must limit treatment with chemical depilatories to localized sites because of the risk of systemic absorption and toxic reactions.

Electrolysis and laser are more permanent hair removal techniques that are uncomfortable and thus their use may be limited for prepubertal children. In electrolysis, an electric current is delivered to the hair follicle, destroying it. In contrast, laser and intense pulsed light remove unwanted hair through the selective photothermolysis of the melanin-rich hair follicles with minimal absorption by surrounding tissues.<sup>461,462</sup> Laser systems used for the treatment of hirsutism include the ruby laser (694 nm), the long-pulsed diode laser (800 or 810 nm),

the alexandrite laser (755 nm) and the Nd:YAG laser (1084 nm); broad-spectrum intense pulsed light (570 to 1200 nm) has also been used.<sup>463</sup> The diode, alexandrite, and Nd:YAG laser are safest for treatment of hirsutism in dark-skinned patients.<sup>464,465</sup> Application of topical anesthesia may be required. By 4 years of age, 20 sessions of diode laser depilation beginning at 9 months of age reduced facial and body hair by 80% in a girl with hypertrichosis lanuginosa congenita.<sup>466</sup> Eflornithine cream 15% is prescription medication for twice-daily application that inhibits ornithine decarboxylase, a hair follicle enzyme that participates in hair growth. As a result, eflornithine may decrease further growth, although it does not minimize existing hair. Local irritation may occur.

If an adolescent has hirsutism and hyperandrogenemia, therapy should be specific to the underlying trigger under the guidance of a gynecologist or endocrinologist. For example, dexamethasone 0.25 to 0.5 mg at night generally reverses the hyperandrogenic signs of adrenal hyperplasia.<sup>467</sup> For PCOS in adolescents, the most important intervention is lifestyle modification with increasing exercise and controlling dietary intake. In PCOS, loss of at least 10% of initial body weight improves menstrual function and metabolic abnormalities.<sup>468</sup> The administration of metformin or other insulin sensitizers is adjunctive to lifestyle changes but can improve insulin resistance, adiposity, oligomenorrhea, and serum androgen levels as well as hirsutism.<sup>469,470</sup>

Antiandrogens and oral contraceptives are the traditional treatment for management of hirsutism. The combination of ethynodiol and drospirenone, for example, reduces the Ferriman-Gallwey score in adolescents by approximately 50% over a 12-month period.<sup>471</sup> Spironolactone in doses of 50 to 200 mg/day; cyproterone acetate, 50 to 100 mg/day (available in Europe); and cimetidine have antiandrogenic activity. Intermittent low-dose finasteride (2.5 mg every 3 days) for 6 months has recently been shown to be effective in reducing the hirsutism score in teenaged girls with idiopathic or PCOS-related hirsutism.<sup>472</sup>

## Pigmentary Changes of Hair

### PREMATURE GRAYING

Graying of human hair is caused by a reduction in the activity of melanocytes within hair follicles. Premature graying of hair, termed *canities*, refers to a loss of color, especially of scalp hair, at an age earlier than that generally accepted as physiologic (before the age of 20 in Caucasians and 30 in African-Americans). It most commonly occurs in children with vitiligo or AA. Canities have also been described in children with pernicious anemia, hyperthyroidism and other thyroid disorders, progeria, Werner syndrome, ataxia-telangiectasia, Rothmund-Thomson syndrome, tuberous sclerosis, neurofibromatosis, and the Waardenburg and Vogt-Koyanagi syndromes. Premature graying may be readily masked, if desired, by chemical rinses and dyes. Chloroquine interferes with pheomelanin synthesis and may lead to lightening of hair with a silvery discoloration in blonde and red-haired persons.<sup>473</sup>

### GREEN DISCOLORATION

The spontaneous appearance of green discoloration in the hair of light-haired individuals may occur as a result of exposure to copper used as an algae-retardant in swimming pools or household tap water containing excessive amounts of copper.<sup>474,475</sup> The introduction of fluoride into a town water supply may acidify water and cause copper to be leached from the plumbing system. Sometimes a ground wire connects a faulty electric apparatus to the copper water pipes, thus diverting sufficient flow of electric current through the water system to dissolve copper.

If resulting from swimming, the use of a copper-based algicide should be discontinued. In cases related to household tap water, electric grounding of household plumbing and adjustment of the pH of the tap water will help to prevent recurrences. Copper-induced discoloration of the hair can be treated in several ways: bleaching with 3% hydrogen peroxide for 2 to 3 hours; washing with the chelating agent edetic acid (EDTA-Metalex) for 30 minutes; use

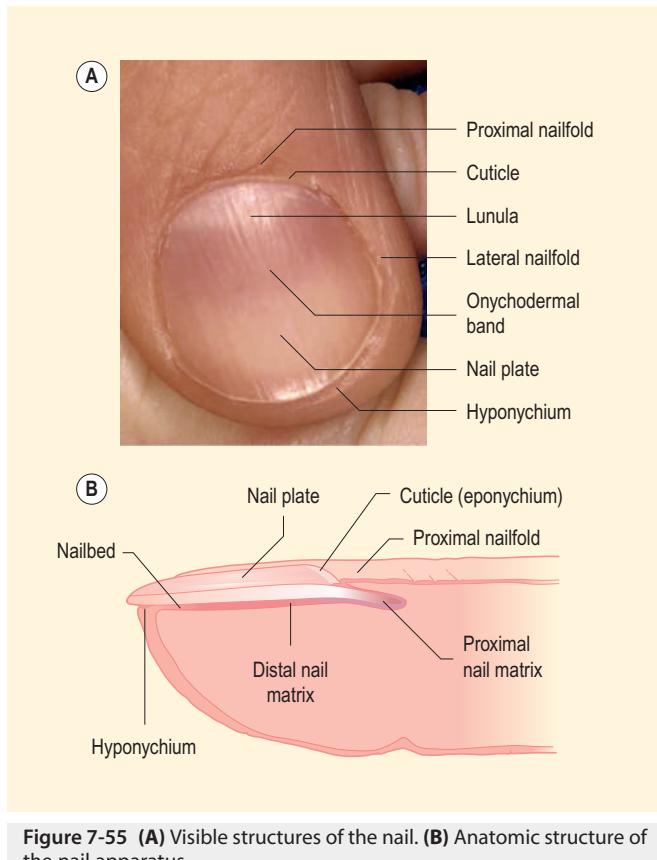
of a penicillamine-containing shampoo; or application of 1.5% 1-hydroxethyl diphosphonic acid.

## Nails

The nails are convex horny structures originating from a matrix that develops from a groove formed by epidermal invagination on the dorsum of the distal phalanges at 9 weeks' gestation. At 10 weeks' gestation, a smooth, shiny quadrangular area can be recognized on the distal dorsal surface of each digit, and formation is completed by 20 weeks' gestation. The nail apparatus consists of a nail matrix of proliferating epidermal cells (Fig. 7-55), largely located under the proximal nailfold. In the thumbs and in a variable number of digits, a white crescent-shaped lunula is usually seen projecting from under the proximal nailfolds, and represents the distal portion of the matrix. The cells of the lunula form the lower surface of the nail plate, whereas the more proximal matrix forms the exposed surface of the nail plate. Although the nail plate is translucent and essentially colorless, most of the exposed nail appears pink as the result of transmission of color from the adherent richly vascular underlying nailbed. The lateral borders of the nail plate lie under the edge of the lateral nailfolds. The hyponychium is the area of skin where the distal border of the nail plate becomes detached from the nailbed.

Unlike hair, nails grow continuously throughout life and normally are not shed. Although the nails of individual fingers grow at different rates, the normal rate of growth of fingernails varies between 0.5 and 1.2 mm per week; the rate of toenail growth is slower than that of the fingernails. Nails grow more quickly in children than in adults.

Many dermatoses that characteristically involve the skin and hair may also affect the nails. Among these are atopic dermatitis, psoriasis, lichen planus, Darier disease, AA, onychomycosis, dyskeratosis congenita (DC) and other ectodermal dysplasias, and certain forms of epidermolysis bullosa.<sup>476</sup> Some nail deformities require surgical correction for cosmetic or functional improvement.<sup>477</sup>



**Figure 7-55** (A) Visible structures of the nail. (B) Anatomic structure of the nail apparatus.

## MEDIAN NAIL DYSTROPHY AND HABIT-TIC DYSTROPHY

Median nail dystrophy (also termed *solenonychia* or *dystrophia unguium mediana canaliformis*) and habit-tic dystrophy (also termed *onychotilomania* or *habit-tic deformity*) are uncommon disorders that usually affect the thumbs. Both disorders have a central canal-like depression or split of varying severity with cracks or lines extending from the central longitudinal lesion toward the lateral nail edges (Fig. 7-56). In median nail dystrophy the lines are typically described as feathery cracks resembling a Christmas tree, and in habit-tic dystrophy they are described as more horizontally arrayed and irregularly spaced; however, the two disorders can look identical, leading to their grouping by some experts as one disorder. A temporary defect in the matrix that interferes with nail formation is thought to be the cause, leading to the depression or split initially appearing at the cuticle and proceeding outward as the nail grows. Median nail dystrophy has been described during administration of isotretinoin<sup>478,479</sup> and with habitual use of smartphones and tablets,<sup>480</sup> whereas habit-tic dystrophy is commonly linked to continuous picking of the nail cuticle of the affected digit and has been described in association with guitar playing.<sup>481</sup> The disorder may at times improve spontaneously after years, especially after the causative trauma ceases. Other than avoidance of trauma, there is no effective treatment, although 4 months of tacrolimus 0.1% ointment led to significant improvement in a 19-year-old man with median nail dystrophy.<sup>482</sup>



**Figure 7-56** Median nail dystrophy/habit-tic dystrophy. (A) and (B) Central depression to varying degrees and fine tree-like or irregularly spaced horizontal splits extending toward the lateral margins. Neither boy admitted to any trauma to the nail, although scaling and swelling of the periungual area can be seen in (B).

## ONYCHOSCHIZIA

Lamellar splitting of the nail plate at its distal free edge, or onychoschizia, is a common complaint of girls and women. The condition usually results from repeated trauma, frequent exposure to nail polish, or excessive immersion in water with detergents. The defect is aggravated by excessive manicuring and the frequent use of solvents to remove nail polish, which further dehydrates the nail. The regular use of an emollient hand cream to the nail and its cuticles, the avoidance of excessive manipulation, the use of several layers of nail polish in an effort to splint the nail, and avoidance of all but oily polish removers are beneficial.

## NAIL PITTING

Pitting of the nails is a common problem of children and most commonly is associated with the nail involvement of psoriasis,<sup>483</sup> atopic dermatitis, or AA. Less common associations are lichen planus, vitiligo, reactive arthritis, and chronic renal failure. The punctate depressions result from alterations in the proximal matrix and may vary from small to large and deep. One nail or several may be affected. Clustered pits may be seen in children who have experienced localized trauma, whereas shallow, randomly distributed pits are usually seen in children with psoriasis or atopic dermatitis. Transverse rows of regularly spaced pits have been described in children with AA (see Fig. 7-38, A). The pathomechanism for nail pits likely involves pinpoint areas of aberrant epidermis and inflammation of the nail matrix.

## NAIL MATRIX ARREST (BEAU LINES AND ONYCHOMADESIS)

Nail matrix arrest develops as a nonspecific reaction to any stress that temporarily interrupts nail formation and become visible on the surface of the nail plate several weeks or more after onset of the disease that caused the condition. Beau lines are transverse grooves or furrows that originate under the proximal nailfold (Table 7-3). They first appear at the cuticle and move forward with the growth of the nail. Because normal nails grow at a rate of approximately 1 mm per week, the duration and time of the illness often can be estimated by the width of the furrow and its distance from the cuticle. Onychomadesis (proximal complete separation of the nail) results from full but temporary arrest of growth of the nail matrix (Fig. 7-57).<sup>484,485</sup> Triggers are similar for Beau lines and onychomadesis and involve stressful events (see Table 7-3) such as birth trauma,<sup>486,487</sup> chemotherapy and other drugs,<sup>488,489</sup> infections and febrile illnesses,<sup>484,490,491</sup> and prolonged intensive-care hospitalization.<sup>492</sup> Of these, nail matrix arrest after Coxsackie infection is most common in children<sup>484,493,494</sup>; in one study of 28 pediatric patients with Coxsackie A16 infection, nail matrix arrest was noted on average 52 days after onset of signs, and the nail changes correlated with the presence of mouth ulcers.<sup>493</sup>

## SPOON NAIL

Spoon nail (koilonychia) is a common deformity in which the normal contour of the nail is lost. The nail is thin, depressed, and concave from

side-to-side, with turned-up distal and lateral edges. Koilonychia of the hallux nails is common in newborns and young infants and resolves spontaneously during childhood. The condition may be a secondary feature of several dermatologic disorders. It occurs in association with nail thickening in psoriasis, onychomycosis, and PC, in which subungual thickening from the hyponychium changes the direction of nail growth. Koilonychia can also be seen in disorders with nail thinning or ridging such as in lichen planus, trachonychia, and focal dermal hypoplasia. Spoon nails have been described in individuals with severe iron-deficiency anemia, although the pathomechanism is unclear. Koilonychia may also be inherited as an isolated autosomal dominant trait. Koilonychia can be confused with platonychia, or flattened nails, which have been described primarily in patients with cirrhosis, and with pincer nails, characterized by excessive curvature at the lateral aspects of the nail plate, leading to an appearance of ingrown nails. Pincer nails are usually a congenital deformity but can be acquired in individuals with epidermolysis bullosa, digital epidermoid cysts, and distal phalangeal exostosis. Because they can be quite painful, pincer nails are often corrected surgically.

## RACKET NAIL

Racket nails, or brachyonychia, are short, wide nails that show loss of curvature. Most commonly found on the thumb and halluces, racket nails are associated with short, stubby phalanges, presumably reflecting an arrest in distal phalangeal formation. This disorder may be inherited in an autosomal dominant mode as an isolated entity but has been described in association with several pediatric syndromes such as acrodyostosis, acroosteolysis, cartilage-hair hypoplasia syndrome, Larsen syndrome, pyknodysostosis, and Rubinstein-Taybi syndrome. Racket nails may be confused with nail clubbing or acropachy (Table 7-4), which results from overgrowth of the fibrovascular support stroma of the distal phalanx. Increased flexibility of the distal



**Figure 7-57** Onychomadesis. Nails showed this deep transverse groove and nail separation.

**Table 7-3** Associations with Nail Matrix Arrest

Conditions	Infection	Medications	Trauma
Acrodermatitis enteropathica	Coxsackie virus*	Antibiotics	Perinatal, often superimposed candida
Alopecia areata	Streptococcus	Antiseizure	Periungual
Amelogenesis imperfect	Syphilis	Chemotherapy	
Epidermolysis bullosa	<i>Trichophyton tonsurans</i>	Retinoids	
Febrile illness	Varicella	Nutritional deficiency	
Hypoparathyroidism	Kawasaki disease	Pemphigus vulgaris	
		Pemphigus vulgaris	
		Radiation therapy	
		Stevens-Johnson syndrome	
		Systemic lupus erythematosus	

\*Most common cause.

**Table 7-4** Clubbing in Children

History	System	Disease
Acquired Generalized	Pulmonary	Cystic fibrosis Bronchiectasis Tuberculosis, aspergillosis Asthma complicated by lung infections Sarcoidosis Pulmonary fibrosis Tumors
	Cardiovascular	Cyanotic congenital heart disease Subacute bacterial endocarditis Myxomas
	Gastrointestinal	Inflammatory bowel disease Gardner syndrome Parasitosis Cirrhosis
	Endocrine	Chronic active hepatitis Diamond syndrome (myxedema, exophthalmos, and clubbing) Hypervitaminosis A Malnutrition
Limited to one or more digits		Aortic/subclavian artery aneurism Brachial plexus injury Trauma Maffucci syndrome Gout Sarcoidosis Severe herpetic whitlow Pachydermoperiostosis
Hereditary		Familial, isolated Apert syndrome Pfeiffer syndrome Rubinstein-Taybi syndrome
Pseudoclubbing*		

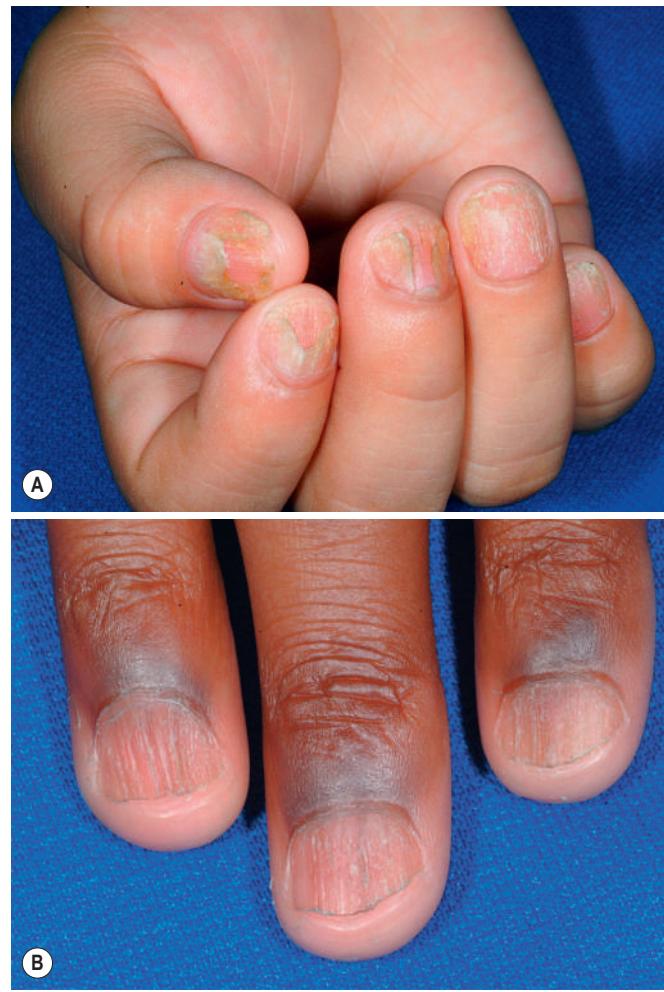
Modified from Baran R, Dawber PR. *Diseases of the nails and their management*. London: Blackwell Scientific; 2001. Reprinted with permission from Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 4th ed. Edinburgh: Mosby; 2011.

\*Broad distal phalanges with normally shaped nails.

nail plate because of edematous tissue is an early sign of clubbing. Also typical is the angle greater than 180 degrees (Lovibond angle) formed by the proximal nailfold and nail plate when viewed from a lateral position. Clubbing in children is usually a sign of internal disease.

### TRACHYONYCHIA

Trachyonychia is characterized by excessive ridging, longitudinal grooves and striations, opalescent discoloration, a rough sandpaper-like quality of the nails, a tendency toward breakage and fragmentation (onychorrhexis), and splitting at the free margins<sup>495</sup> (Fig. 7-58). When all nails are involved, the condition has been called *twenty-nail dystrophy*. Trachyonychia is usually an isolated entity but has been described primarily in association with psoriasis, atopic dermatitis, and AA, but the trachyonychia may occur months to years before other signs of cutaneous disease. The course of trachyonychia is variable, but spontaneous improvement may occur in months to years; in one study 50% showed total resolution or marked improvement in the first 6 years.<sup>496</sup> Application of potent topical corticosteroids to the base of the nail, particularly in the form of flurandrenolide tape, may reverse the changes of trachyonychia after several months of nightly usage. Filing the nails and application of clear nail polish may reduce the tendency toward snagging and tearing of the nail plates.



**Figure 7-58** Twenty-nail dystrophy (trachyonychia). Opalescent discoloration, excessive ridging, longitudinal striations, and a rough texture of all 20 nails in a school-age child (A) and in an adolescent (B). Note the rough edges associated with the longitudinal striations in (B).

### ONYCHOGRYPHOSIS

Onychogryphosis is a hypertrophic nail deformity most commonly seen in the toenails. Some cases of nail hypertrophy are developmental. The nails become thick and circular in cross-section instead of flat (thus resembling a claw). The disorder is most commonly seen in elderly individuals but may occur in children with poor hygiene. Management requires regular paring or trimming and when severe, treatment by a podiatrist using files, nail clippers, or mechanical burrs. Onychogryphosis is commonly associated with secondary onychomycosis but may be seen in a variety of forms of ichthyosis, such as Haim-Munk syndrome (see Chapter 5) and in severe epidermolysis bullosa simplex (see Chapter 13).

### CONGENITAL MALALIGNMENT OF THE GREAT TOENAILS

Congenital malalignment of the great toenails is a disorder in which lateral rotation of the nail matrix leads to lateral deviation of the great toenail from the longitudinal axis of the distal phalanx and, at times, thickening, discoloration, and shortening of the nail plate (Fig. 7-59).<sup>497,498</sup> Resultant onychodystrophy may lead to onychogryphosis and chronic ingrown toenails. The disorder may be inherited as an autosomal dominant disorder<sup>499</sup> and often improves spontaneously.<sup>500</sup> If improvement is not seen during the first year and the deviation is



**Figure 7-59** Congenital malalignment of the great toenails. Lateral rotation of the nail matrix leads to lateral deviation of the great toenail from the longitudinal axis of the distal phalanx and at times, thickening, discoloration, and shortening of the nail plate. Note the secondary severely ingrown toenails and overgrowth of the medial nailfold.

severe, surgical realignment of the nail with local anesthesia can be performed, preferably before age 2 years.<sup>477</sup>

### INGROWN NAILS

Ingrown toenails (onychocryptosis) are a common disorder in which the lateral edge of the nail is curved inward and penetrates the underlying tissue with resulting erythema, edema, pain, and in chronic forms, the formation of granulation tissue. Generally seen on the great toes of affected individuals, the main cause of the deformity is compression of the toe from side-to-side by ill-fitting footwear and improper cutting of the nail (in a half-circle rather than straight across). Pseudo-ingrown toenails, also seen as a transient deformity in newborns, are a common phenomenon (2.4% of infants)<sup>501</sup> and are generally self-corrected by the time the child reaches the age of 12 months. Treatment, if required, consists of the wearing of properly fitting footwear, allowing the nail to grow out beyond the free edge, control of acute infection by compresses, topical and at times systemic antibiotics, and in many instances (once the infection has subsided), surgical treatment. The traditional therapy for recurring cases has been excision of the lateral aspect of the nail (wedge resection) with the use of local anesthesia followed by curettage or chemical destruction (e.g., with phenol) of the nail matrix to prevent regrowth of the offending portion of the nail.<sup>502–504</sup> An alternative technique uses a flexible tube secured with a suture (FTSS) was associated with a lower recurrence rate than matricectomy and faster recovery.<sup>505</sup> Alternatively, one can excise the nailfold itself rather than the matrix. In one study in children, excellent cosmesis was achieved with no recurrences.<sup>506</sup>

*Retronychia* refers to inflammation of the proximal nailfold and occurs when the new nail growing from the matrix pushes the old nail upwards, interrupting longitudinal nail. It usually results from trauma and can be treated initially in children with clobetasol ointment nightly for a few months. Alternative therapy for recalcitrant or recurrent retronychia is complete nail-plate avulsion, although permanent nail dystrophy results in approximately one-third of treated patients.<sup>507</sup>

### NAIL ATROPHY

Atrophic nails range from complete absence of the nail (anonychia) to nails that are poorly or partially developed (micronychia). Congenital anonychia is an autosomal recessive disorder characterized by isolated congenital anonychia or hypoplasia, usually of all the fingernails and toenails. The disorder results from mutations in the R-spondin 4 (*RSPO4*) gene, which is only expressed in the mesenchymal tissue underlying the digit tip epithelium and activates Wnt/β-catenin signaling.<sup>508,509</sup> Anonychia can be associated with junctional epidermolysis bullosa, trauma, infectious paronychia, and inflammation (e.g., Stevens–Johnson syndrome, chronic graft-versus-host disease, and

lichen planus). Micronychia has been described in patients with ectodermal dysplasias, teratogen exposure (e.g., fetal hydantoin syndrome), and chromosomal abnormalities (e.g., Turner syndrome, Noonan syndrome, and trisomies of chromosomes 3, 8, 13, and 18). Micronychia is a prominent feature of the nail-patella syndrome and congenital onychodysplasia of the index fingers (COIF).

### NAIL-PATELLA SYNDROME

The nail-patella syndrome, also termed *osteonychodysplasia*, is an autosomal dominant disorder that results from mutations in *LMX1B*. *LMX1B* encodes a transcription factor (LIM homeobox) that regulates dorsoventral polarity in the developing limb (including nail development), as well as bone, eye, and glomerular basement-membrane development.<sup>510,511</sup> Nail changes are seen in 98% of affected individuals.<sup>512,513</sup> They vary from a triangular lunula (most consistent feature), especially of the thumbs and index fingers, to severe dysplasia and micronychia to absence of the medial and distal aspects of the index and thumb nails. Nail involvement is symmetric and often shows progression from index to fifth fingernails. Occasionally the toes are affected. Softening, spooning, discoloration, central grooving, splitting and cracking, narrowing, and less commonly, thickening of nails have been described.

The knees have a flattened profile with a small or absent patella and the elbows show radial head dysplasia. Both are subject to recurrent dislocation, flexion contractures, and arthritis. The pathognomonic iliac horns extend from the center of the iliac bones. Renal involvement occurs in 30% to 60% of patients and presents with (often asymptomatic) proteinuria and/or microscopic hematuria, edema, and hypertension. Progression to nephrotic syndrome occurs in fewer than 20% of patients, and renal failure requiring dialysis or transplantation occurs in 10%.<sup>514</sup> Affected patients also risk the development of glaucoma and dystrophic dental enamel. An increased risk of attention-deficit/hyperactivity disorder and depression has been described, perhaps related to the role of *LMX1B* in the development of mesencephalic dopaminergic neurons and the serotonergic system.<sup>515</sup> Support groups are available at: [www.nailpatella.org](http://www.nailpatella.org), [www.npsw.org](http://www.npsw.org), and [www.npsuk.org](http://www.npsuk.org).

### CONGENITAL ONYCHODYSPLASIA OF THE INDEX FINGERS

Congenital onychodysplasia of the index fingers (COIF), also known as *Iso* and *Kikuchi* syndrome, is characterized by asymmetric, ulnar-deviated micronychia of the index fingers. Involvement may be unilateral or bilateral, and polyonychia may be associated. X-rays of the underlying phalangeal bone show a characteristic Y-shaped bifurcation or a sharp distal phalangeal tip. Deformities of other fingers are rarely present.<sup>516</sup> Usually a sporadic condition, autosomal dominant inheritance and occurrence in twins have been described.<sup>517</sup> Use of a new device to correct that deviation (and treat ingrown nails as well) has been described.<sup>518,519</sup>

### PACHYONYCHIA CONGENITA

*Pachyonychia congenita* (PC) describes a group of autosomal dominant conditions characterized by a characteristic nail dystrophy (see Chapter 5); in association with painful plantar keratoderma.<sup>520</sup> Mutations occur in one of five keratins: *KRT6a*, *KRT6b*, *KRT6c*, *KRT16*, and *KRT17*,<sup>521–525</sup> and a new classification is now based on the underlying affected gene (i.e., PC-6a, PC-6b, PC-6c, PC-16, and PC-17). Of these, PC-6a (41%) and PC-16 (31%) are most common. The historical terms PC-1 (Jadassohn–Lewandowsky syndrome) and PC-2 (Jackson–Lawlor syndrome) are no longer used, given their overlapping features and lack of concordance with underlying gene changes. At this time, genotyping is being performed free of charge through the Pachyonychia Congenita Project ([http://www.pachyonychia.org/pc\\_data.php](http://www.pachyonychia.org/pc_data.php) and [www.pachyonychia.org](http://www.pachyonychia.org)).

At birth, fingernail and toenail changes are present in almost 70% and 60% of patients, respectively (Fig. 7-60), but the plantar keratoderma is in only 7%. By 5 years of age, however, more than 75% of patients have toenail and fingernail dystrophy, as well as plantar



**Figure 7-60** Pachyonychia congenita. The nails may be thickened or discolored at birth but often show changes first on the toenails and during infancy.



**Figure 7-61** Pachyonychia congenita. Nails show progressive discoloration, tenting, and thickening, particularly owing to accumulation of a horny, yellowish-brown material of the undersurface that causes the nail to project upward from the nailbed at the free margin.

keratoderma. Ultimately, 98% of affected individuals show toenail dystrophy, and fingernail dystrophy occurs in 76%. Typical nails have marked subungual hyperkeratosis with a pinched V-shape (Fig. 7-61), but premature nail termination is common. Most individuals have dystrophic changes of all 10 toenails. Periungual infection (especially staphylococcal and candidal) is reported by most affected individuals, and nails may be shed. The keratoderma tends to be predominantly at pressure points but can be exquisitely painful with a profound impact on quality of life and functioning (see Chapter 5). The pain in part results from underlying bullae.<sup>526</sup> Hyperhidrosis of the palms and soles may be associated.

Additional clinical manifestations include cysts, follicular keratoses, hoarseness, and oral leukoplakia. The steatocysts and pilosebaceous cysts, formerly thought to be specific to PC-6b and PC-17, are now known to be common in PC-6a as well. These cysts usually first manifest at early puberty, particularly on the head, neck, upper chest, and upper arms. Pinhead-sized follicular papules may appear in areas of trauma on the extensor surfaces of the extremities, popliteal fossae, lumbar region, buttocks, and less commonly, on the face and scalp. Early oral lesions are often present in the form of opaque white plaques

(leukokeratosis) on the dorsum of the tongue or the buccal mucosa at the interdental line and are often confused with thrush (candidal infection) in the infant. Less common associated findings include cheilitis, scrotal tongue, corneal dystrophy, and hoarseness, the latter specific for PC-6a.

Differences that distinguish PC subtypes include: (1) later onset and less frequent occurrence of nail dystrophy and keratoderma in PC-K6b, PC-K6c, and PC-K16; (2) concurrent fingernail and toenail thickening in PC-K6a and PC-K17; (3) more palmar (vs. plantar) keratoderma in PC-K16; (4) cysts primarily in PC-K17 and follicular hyperkeratoses primarily in PC-K6a; (5) hoarseness and/or oral leukokeratoses in the first year of life, most often in PC-K6a; and (6) natal teeth exclusively in PC-K17. Among pediatric patients, PC affects the social interactions and function of adolescents more profoundly than younger children, related to the highly visible nail changes and painful plantar thickening.

In the young child, PC must be distinguished from hidrotic ectodermal dysplasia (Clouston syndrome, see *Group 2 Ectodermal Dysplasia* section), which can show similar nail alterations at birth and painful keratoderma.<sup>527</sup> The presence of alopecia and if present, hearing loss can distinguish hidrotic ectodermal dysplasia. Indeed, alopecia is not a feature of PC except in the rare situation in which biallelic mutations in *KRT17* are inherited.<sup>528</sup> Hypertrophic nail dystrophy at birth is also a feature of biallelic mutations in *FZD6*, encoding frizzled 6, a Wnt-signaling pathway receptor in the nail matrix.<sup>529,530</sup>

The subungual hyperkeratosis persists for life, and treatment is directed toward relief of the painful hyperkeratosis of the soles and the nail dystrophy.<sup>531</sup> Mechanical nail treatment (filing, grinding, and trimming) is particularly effective after soaking the nails.<sup>532</sup> As for the nails, mechanical intervention can improve the keratoderma, but topical agents (retinoids, steroids, keratolytics, emollients) are not very helpful, and pain control management is key. Administration of systemic retinoids has been successful for some but not all patients but is rarely appropriate in pediatric patients.<sup>533</sup> As a last resort, surgical avulsion and matrix destruction followed by scarification of the nailbed to prevent regrowth can be performed. Plantar sweating has been shown to increase the painful blistering of at hyperkeratotic sites and can be controlled by oral administration of glycopyrrolate or injections of botulinum toxin.<sup>534</sup> Oral rapamycin decreased painful plantar thromboses and keratoses in patients with *K6a* mutations (based on suppression of *K6a* expression) but led to unacceptable gastrointestinal and mucocutaneous adverse events.<sup>535</sup> Interestingly, chemotherapy in an adult with lifelong painful plantar keratoderma led to complete resolution.<sup>536</sup> *K16* small interfering ribonucleic acid (siRNA) injections into the palmoplantar keratoderma have resulted in clearance but are too painful to sustain.<sup>537</sup> A support group is available for affected families ([www.pachyonychia.org](http://www.pachyonychia.org)).

## DYSKERATOSIS CONGENITA

Dyskeratosis congenita (DKC) is characterized in 80% to 90% of patients by the triad of nail dystrophy, reticular pigmentation, and oral leukoplakia, but many additional features have been described (Table 7-5).<sup>538–540</sup> Most cases have been in males, consistent with an X-linked disorder, but carrier females may show mild to complete clinical features. The median age of diagnosis is 15 years, because many patients first seek treatment as teens or young adults.

The disorder may also be inherited as autosomal dominant or recessive, and nine mutated genes have been described to date, accounting for 60% of studied individuals with DKC (Table 7-6).<sup>541,542</sup> The protein products of these genes affect the maintenance of telomeres, which are repetitive base pairs at the ends of chromosomes to prevent the loss of genetically encoded information. Telomerase catalyzes DNA synthesis to maintain telomere length; when too short, cells become senescent or apoptotic. This is particularly important in rapidly dividing cells. DKC is considered a “telomeropathy,” because most patients show severe shortening of telomeres. The most common cause of DKC is mutations in *DKC1* (a gene on the X chromosome that encodes dyskerin, a nucleolar protein that stabilizes telomerase), but features of DKC have been described from mutations affecting other components of the telomerase complex (*TINF2*, *TERT*, *TERC*, *C16orf57*, *NOLA3*, *NOLA2*, *WRAP53/TCAB1*, and *RTEL1*). Although DKC is

**Table 7-5** Complications of Dyskeratosis Congenita and Suggested Monitoring

System	Findings	Potential Complications	Monitoring/Treatment
Skin	Nail dystrophy* Reticulated pigmentation* Hyperhidrosis Early graying or sparse hair Telangiectasia Acrocyanosis Cutaneous atrophy Palmoplantar keratoderma Absent dermatoglyphics	Cutaneus SCCs	Annual skin examination Sun protection
Oral	Leukoplakia* Erythematous patches Dyspigmentation Taurodontism Tooth decay and loss	Oral cancer	Biannual dental examinations
Growth and development	Short stature Developmental delay		
Head and neck		SCC	Annual otolaryngology examinations
Eyes	Epiphora Ectropion, entropion Trichiasis, sparse lashes	Corneal abrasion Infections	Annual eye examinations
Gastrointestinal	Esophageal stenosis Hepatic fibrosis	Dysphagia	Esophageal dilatation Annual liver function tests Liver ultrasounds
Genitourinary	Urethral stenosis Epithelial malignancy		
Lungs	Pulmonary fibrosis	High risk with transplant	Annual PFTs
Bones	Osteoporosis Avascular necrosis hips, shoulder	Fractures	Ca <sup>++</sup> , Vitamin D <sub>3</sub>
Hematologic	Low blood counts*	Bone marrow failure* Myelodysplastic syndrome Leukemia	Biannual blood counts Baseline bone marrow Chemotherapy as appropriate

Ca<sup>++</sup>, Calcium; PFT, pulmonary function test; SCC, squamous cell carcinoma.

\*Present in more than 75% of patients.

**Table 7-6** The Nine Genes Mutated in Dyskeratosis Congenita

Gene	Protein	Inheritance	Frequency (%)
<i>DKC1</i>	Dyskerin	XLR	17–36
<i>TINF2</i>	TIN2: TRF1-interacting nuclear factor 2	AD	11–24
<i>TERC</i>	TERC: telomerase RNA component	AD	6–10
<i>TERT</i>	TERT: telomerase	AD, AR	1–7
<i>C16orf57</i>	Mpn1 RNA exonuclease	AR	2
<i>NOLA2</i>	NHP2: nuclear protein family A, member 2	AR	<1
<i>NOLA3</i>	NOP10: nuclear protein family member A, 3	AR	<1
<i>WRAP53/TCAB1</i>	WD repeat-containing protein encoding RNA antisense to p53	AR	<1
<i>RTEL1</i>	Replication of telomere	AR	<1

AD, Autosomal dominant; AR, autosomal recessive; RNA, ribonucleic acid; XLR, X-linked recessive.



**Figure 7-62** Dyskeratosis congenita. Shortened nails with pterygium formation.

sometimes classified among disorders of aging, patients do not appear old and have no increased risk of atherosclerosis.

The thin, dystrophic nails usually appear first between the ages of 5 and 13 years. Mildly affected nails show ridging and longitudinal grooving; severely affected nails are shortened and show pterygium formation, resembling the nails of lichen planus or graft-versus-host disease (Fig. 7-62). Cutaneous changes usually develop after the onset of nail changes, most commonly during late childhood to teenage years. A fine reticulated grayish-brown hyperpigmentation, sometimes surrounding hypopigmented, atrophic, telangiectatic



**Figure 7-63** Dyskeratosis congenita. Reticulated hyperpigmentation surrounding hypopigmented, atrophic, telangiectatic patches.



**Figure 7-64** Dyskeratosis congenita. Leukoplakia of the oral mucosa.

patches, on the face, neck, shoulders, upper back, and thighs is characteristic (Fig. 7-63). The poikilodermatosus change is sometimes confused with Rothmund-Thomson syndrome (*RECQL4* mutations), epidermolysis bullosa simplex with mottled pigmentation (usually *KRT5* mutation), Naegeli–Franceschetti–Jadassohn syndrome/dermatopathia pigmentosa reticularis (*KRT14* mutation) or Clericuzio-type poikiloderma with neutropenia (another *C16orf57* mutation).<sup>543</sup> Other cutaneous changes may include telangiectasia of the trunk; redness and atrophy of the face with irregular macular hyperpigmentation; acrocytosis; palmoplantar hyperkeratosis; hyperhidrosis and bullae of the palms and soles; wrinkled atrophic skin over the elbows, knees, and penis; and a diffuse atrophic, transparent, and shiny appearance on the dorsal aspects of the hands and feet. The hair of the scalp, eyebrows, and eyelashes is often sparse and lusterless, and patients with this disorder commonly have atrophic changes of the muscles and bones of the feet and hands, giving a “cupped” appearance to the palms.

Mucous membrane changes consist of leukoplakia and rarely, blisters and erosions of the oral (Fig. 7-64) and anal mucosae, esophagus, and urethra. Similar changes of the tarsal conjunctiva may result in atresia of the lacrimal ducts, excessive lacrimation, chronic blepharitis, conjunctivitis, and ectropion. The teeth tend to be defective and subject to early decay. Periodontitis may develop, and affected persons have an increased incidence of cutaneous malignancy, predominantly squamous cell carcinoma in the areas of leukoplakia.

Overall, approximately 90% of patients develop life-threatening bone marrow failure characterized by severe aplastic anemia with neutropenia, splenomegaly, and a hemorrhagic diathesis. Acute myeloid leukemia and myelodysplastic syndrome have also been described. Pulmonary fibrosis and hepatic cirrhosis are other life-threatening complications. Epithelial tumors often first develop by the mid-teens, commonly in areas of mucosa with leukoplakia. Squamous cell carcinoma of the tongue is most common, but cutaneous squamous cell carcinoma, acute myeloid leukemia, and myelodysplastic syndrome are not uncommon. Variants of DCK include Hoyeraal-Hreidarsson syndrome, which is DCK with cerebellar hypoplasia, developmental delay, and intrauterine growth retardation<sup>544</sup> and Revesz syndrome with bilateral exudative retinopathy, cerebellar hypoplasia and growth retardation.<sup>545</sup> The average life expectancy is 44 years. Patients usually die of bone marrow failure (≈60% to 70%), pulmonary disease (≈10% to 15%) or malignancy (≈10%).

Screening for DCK is best performed by flow cytometry and fluorescence *in situ* hybridization (flow-FISH) of leukocyte subsets<sup>540</sup> to detect telomere shortening. Recommended disease surveillance includes biannual blood counts, bone marrow evaluations annually, hepatic ultrasounds, annual pulmonary functional tests, and skin cancer screening. Treatment of bone marrow failure is recommended with a hemoglobin persistently below 8 g/dL, platelets less than 30,000/mm<sup>3</sup>, and neutrophils less than 1000/mm<sup>3</sup>. If a matched donor without genetic and clinical evidence of DCK is available, stem cell transplantation should be considered but carries substantial risk. The 10-year survival rate probability is 30% with mortality generally attributed to pulmonary fibrotic or vascular complications related to disease progression or toxicity related to myeloablative regimens.<sup>546</sup> Long-term survival after transplantation has been poor. A trial of androgens such as oxymetholone may be considered before transplantation from an unrelated donor and has improved blood counts in 60% of treated patients<sup>547</sup>; however, androgens may cause hepatic tumors, and the combination of androgen and granulocyte colony stimulating factor (G-CSF) has led to splenic rupture. Management of patients otherwise consists of bougienage for esophageal stenosis; fulguration, curettage, and surgical excision of leukokeratosis of the buccal and anal mucosae; and lifelong, regular supervision for early detection of mucosal or cutaneous carcinomas. A support group called *Dyskeratosis Congenita Outreach* is available at <http://www.dcoutreach.org/>.

## DISORDERS OF THE NAILBED

**Onycholysis** refers to separation of the nail plate from the underlying hyponychium and can occur for a wide variety of reasons (Box 7-9).<sup>548,549</sup> Vigorous cleaning of the subungual debris that tends to accumulate exacerbates this condition. Onycholysis may result from exposure to sunlight (photoonycholysis)<sup>550</sup> in individuals administered tetracyclines, especially doxycycline (see Fig. 8-16),<sup>551</sup> griseofulvin,<sup>552</sup> or thiazides.

Abnormalities of the nailbed may be seen through the transparent nail plate. Onycholysis that occurs proximal to the hyponychium may resemble a yellow-brown oil spot, a nail change that is considered pathognomonic of psoriasis but is rarely seen in children. Notching of the distal nail plate may be seen in Darier disease in association with longitudinal red and white streaks (Fig. 7-65) (see Disorders of Nail Coloration section and Chapter 5). Nailbed hemorrhages are usually the result of trauma. As the hemorrhage ages, it changes color from red to purple to brown and moves more distally. Larger hematomas may resemble melanocytic nevi, although more commonly melanocytic nevi of the nailbed manifest as longitudinal pigmented streaks of the nail.

Injuries to fingers or toes may result in nail avulsion, painful subungual hematoma, or nailbed laceration, which are often managed in the emergency room. Nailbed removal results in scarring and deformity and is generally not necessary when the nail plate is intact and well adherent, especially with just a minimally displaced underlying distal phalanx fracture.<sup>553</sup> Hematomas should be decompressed through trephining, in which a hole is created in the nail plate by electrocautery or rotating a hot paperclip to drain the blood, thereby reducing pain and pressure.<sup>554</sup> Nailbed lacerations are repaired with 6-0 sutures or octyl-2-cyanoacrylate.<sup>555,556</sup>

### Box 7-9 Underlying Causes of Onycholysis

#### Chemical Irritants

Cosmetics, especially with formaldehyde  
Depilatories  
Detergents  
Nail polish removers  
Organic solvents

#### Inflammatory Disorders

Alopecia areata  
Atopic dermatitis  
Contact dermatitis  
Lichen planus  
Psoriasis

#### Infectious Disorders

Bacterial paronychia  
Candidiasis  
Herpes simplex (whitlow)  
Onychomycosis  
Verrucae

#### Medications

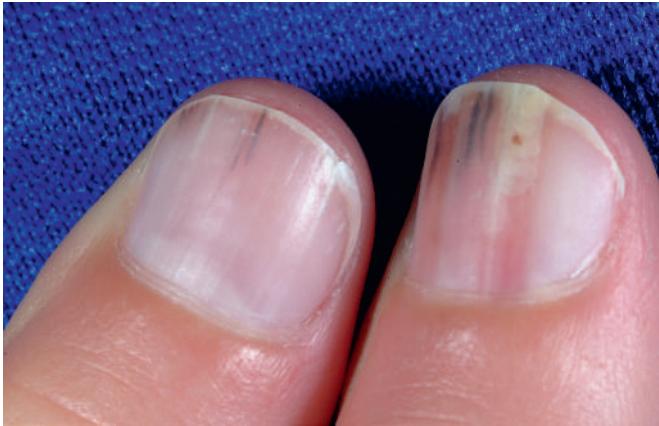
Anticonvulsants (valproic acid)  
Chemotherapeutic agents (especially taxanes)  
Griseofulvin  
Retinoids (isotretinoin)  
Tetracyclines (photoonycholysis)  
Thiazides (photoonycholysis)

#### Systemic Disorders

Iron-deficiency anemia  
Rheumatic disease  
Thyroid disease (hyperthyroidism or hypothyroidism)

#### Trauma

Compulsive subungual cleaning  
Sportsman toe



**Figure 7-65** Darier disease. Longitudinal reddish-purple and white streaks of the nail.

## PARONYCHIA

*Paronychia* refers to inflammation surrounding the nail, generally after breakdown in the barrier between the nail plate and the adjacent nailfold.<sup>557,558</sup> At times, the cuticle is obscured, and the nailfold is replaced by granulation tissue. Acute paronychia, characterized by painful, erythematous, indurated swelling of the proximal or lateral nailfolds, often with purulent draining, is usually caused by *S. aureus* infection; bacterial cultures can be performed to consider a bacterial etiology (see Chapter 14). Abscesses associated with acute staphylococcal infections may spontaneously decompress or may require drainage and local wound care along with a course of appropriate antibiotics. Chronic paronychia with nail dystrophy presenting with

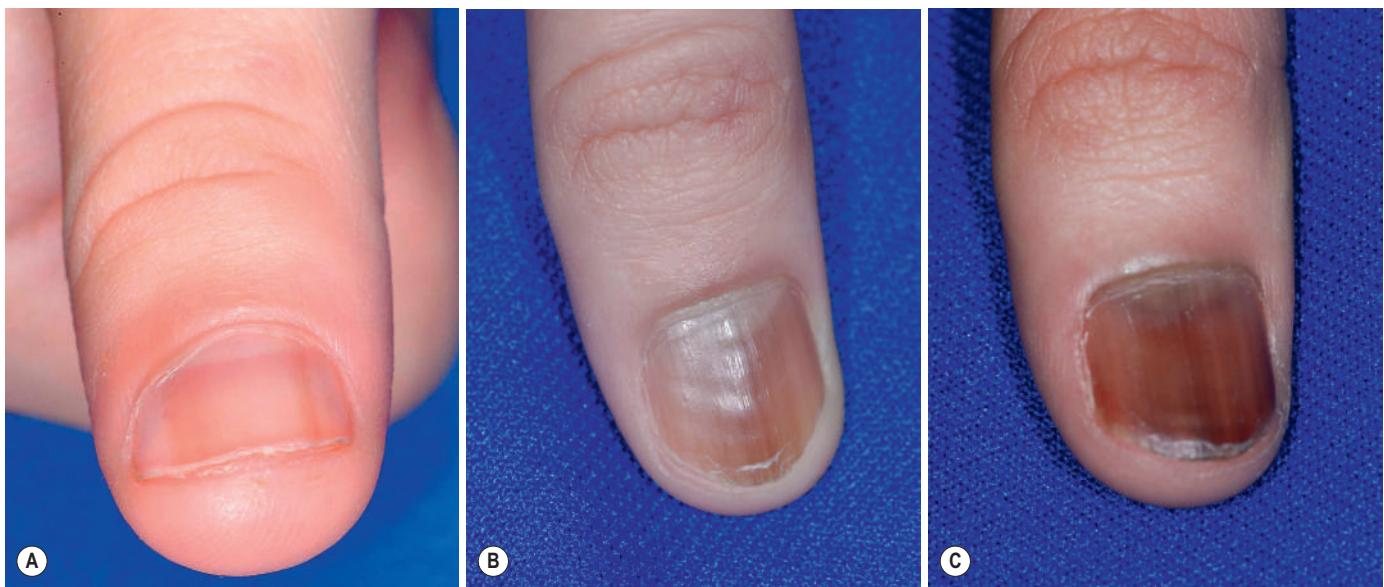
nonpurulent erythema of the periungual areas, nail ridging, and cuticle loss, is more commonly owing to candidal infection. Candidal paronychia is often associated with repeated exposure of the fingers to wetness (see Figs. 17-41 and 17-45). Toddlers who suck their fingers or thumb usually have candidal paronychia, but a more acute process with purulence and crusting overlying the erythema and swelling may also reflect a herpetic whitlow of the finger or toe. Infants with sucking blisters show blisters filled with clear fluid. Potassium hydroxide scrapings to detect the pseudohyphae of *Candida albicans* (see Chapter 17) and direct fluorescence assays and cultures to consider herpes simplex infection (see Chapter 15) should be performed to distinguish these disorders. Treatment of paronychia should be directed toward clearance of the infecting organism. In individuals beyond the age of infancy, efforts to keep the fingers dry, including avoidance of sucking and wet work, are critical for clearance. Paronychia is rarely seen with tinea unguium (see Chapter 17).

Periungual inflammation may also result from noninfectious causes. These include psoriasis and acropustulosis (see Chapter 4), medications (particularly isotretinoin<sup>549</sup> and indinavir<sup>550</sup>), and chemical irritants including nail cosmetics.<sup>560</sup>

## DISORDERS OF NAIL COLORATION

A longitudinal streak of brown pigmentation of the nail (melanonychia striata), which may even extend to involve the entire nail (Fig. 7-66), almost always represents a benign melanocytic nevus in children (see Chapter 9), as opposed to melanoma, the concern with new onset of melanonychia striata in an adult. Melanonychia can also be horizontally arrayed (transverse melanonychia) or involve the entire nail. Abnormal nail pigmentation may be seen in systemic diseases<sup>561</sup> or in association with the ingestion of various chemicals or medications. Brown pigmentation of multiple nails may be associated with the ingestion of phenolphthalein, as a reaction to antimalarials, minocycline, gold therapy, cancer chemotherapy, or zidovudine in pediatric human immunodeficiency virus (HIV) infection.<sup>562</sup> Brown-black pigmentation of the nailfold and nail matrix can be seen as a sign of melanoma of the nailbed (Hutchinson sign), Peutz–Jeghers syndrome, and Laugier–Hunziker syndrome (see Chapter 11). Brown nail pigmentation has also been described as a manifestation of Addison disease or Graves disease.<sup>563</sup> Orange-brown chromonychia has been observed in Kawasaki disease, including in 72% of 40 pediatric patients from India in a recent series.<sup>564</sup> The transverse discoloration of the acral nail begins 5 to 8 days after the onset of fever and clears entirely 2 to 3 weeks later. In argyria the lunulae show a distinctive slate blue disoloration, and in hepatolenticular degeneration (Wilson disease) the lunulae may present an azure blue disoloration. Blue disoloration of the nails has also been described from administration of azidothymidine (AZT).<sup>549</sup> Lithium carbonate can cause brownish-black transverse bands at the margins of the lunulae, and pigmentation in the form of transverse bands has been reported in patients receiving zidovudine, bleomycin, and doxorubicin. Gray or blue-gray nails can occur in individuals with ochronosis or argyria or as a reaction to quinacrine or phenolphthalein. When a green disoloration is seen in association with onycholysis, *Pseudomonas aeruginosa* infection must be considered.

Longitudinal erythronychia is characterized by one or more linear pink-red, usually asymptomatic bands on the nail plate that originate at the proximal nailfold, cross the lunula, and extend to the free edge of the nail plate.<sup>565</sup> With time, the lesion may become brown, especially if hemorrhage is associated. One or more digits may be involved. Localized cases in children can be associated with a wart, vascular or glomus tumor, epidermal nevus, or a postsurgical scar, whereas polydactylous cases are seen in Darier disease (see Chapter 5) and lichen planus.<sup>566</sup> Nail fragility with splitting or V-shaped nicks, onycholysis, splinter hemorrhage, and/or subungual keratosis may be associated. Red lunulae can be seen in patients with AA, lupus erythematosus, dermatomyositis, congestive heart failure, reticulosarcoma, psoriasis, carbon monoxide poisoning, and lymphogranuloma venereum. When the distal 1- to 2-mm portion of the nail has a normal pink color and the rest of the nail has a white appearance, the disorder has been termed *Terry nails* (Fig. 7-67). Seen in patients with cirrhosis, chronic congestive heart failure, adult-onset diabetes, and



**Figure 7-66** Melanonychia. Nail pigmentation can progress, as occurred in this girl over 12 years. This benign nail pigmentation began as discrete longitudinal streaks (**A**) and progressively covered half (**B**) and then all (**C**) of the nail. Although no biopsy was performed, this most likely represents a benign pigmented nevus of the nail matrix.



**Figure 7-67** Terry nails. The distal 1 to 2 mm of the nail have a normal pink color, and the rest of the nail has a white appearance. This girl had hepatic cirrhosis.



**Figure 7-68** Nail discoloration from onychomycosis. Horizontal striations were colored yellow on the hallux nail but white on other nails. Note the annular scaling erythematous lesion on the top of the foot and the erythema and scaling interdigitally, both signs of tinea pedis.

polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes (POEMS) syndrome, Terry nails may also be seen in normal children younger than 4 years of age, in the very elderly, and at times in normal individuals without evidence of cirrhosis or other systemic disease.

The term *leukonychia* (white nails) is used to describe a disorder in which at least a portion of the nail becomes white. The white color may be seen as punctuate, striate, or encompassing much or all the nail. Several forms of leukonychia striata have been described. Most common are variably sized white areas, sometimes multiple, that result from local manipulation. They tend to be horizontal in orientation (rather than following the shape of the nailfold or lunula), do not extend across the entire nail, are not depressed (vs. Beau lines from nail matrix arrest), and grow out with the nail. Mees bands are transverse 1- to 2-mm white bands that follow the lunula, tend to extend to the margins, and move distally as the nail grows out; they have been described in arsenic or heavy metal poisoning, septicemia, dissecting aortic aneurysm, and renal failure. The white transverse bands in Muehrcke nails affect the vascular bed under the nail plate and do not move as the nail grows out; they have been associated with hypoalbuminemia such as from nephrotic syndrome, cirrhosis, or cytostatic chemotherapy agents. The half-and-half nail results from renal disease and azotemia and shows whitening of the proximal nailbed

with red, pink, or brown coloration of the distal half. The toenail may also be white because of superficial onychomycosis or proximal subungual onychomycosis (see Chapter 17); however, these forms of onychomycosis are uncommon in children in comparison with the more typical distal lateral subungual onychomycosis, in which the nail plate is yellow with subungual debris, thickening, and onycholytic (Fig. 7-68). Leukonychia is associated with palmoplantar keratoderma, knuckle pads, and hearing loss in Bart–Pumphrey syndrome, caused by mutations in *GJB2*, encoding connexin 26, and with erythrokeratodermia variabilis from mutations in *connexin 43* (see Chapter 5). Congenital porcelain-like whitening of all (leukonychia totalis) or part (leukonychia partialis) of the 20 nails can be inherited as an autosomal recessive or autosomal dominant disorder without other manifestations as a result of mutations in *PLCD1*, encoding a phospholipase of the nail matrix that controls nail growth.<sup>567</sup>

The yellow nail syndrome is a disorder associated with severe long-term lymphedema and most commonly, respiratory disease, especially chronic bronchitis, bronchiectasis, interstitial pneumonitis, and pleural effusion. Other associations include persistent hypoalbuminemia, thyroid disease, immunologic deficiencies (IgA), lymphoreticular malignancy, rheumatoid arthritis, lupus erythematosus, Hodgkin disease, and the nephrotic syndrome. Most often a phenomenon of middle-aged individuals but also described in neonates



**Figure 7-69** Yellow nail syndrome. Yellowish discoloration of the nails is associated with slow growth, thickening, excessive curvature, and an absence of lunulae in some of the nails of this 8-year-old boy who had congenital chylothorax. The toenails were also affected.

and young children, the nails show a pale yellow or greenish-yellow to brown discoloration of the nails (Fig. 7-69) associated with slow growth; thickening; excessive curvature from side to side (on its long axis); increased hardness, onycholysis, or spontaneous shedding of the nails; absence of lunulae; and swelling of the periungual tissues,

as might be seen in patients with chronic paronychia. The nail changes are often permanent, but administration of oral and topical vitamin E has been reported to be effective in some individuals.<sup>568–570</sup>

The complete list of 570 references for this chapter is available online at <http://expertconsult.inkling.com>.

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## Disorders of the Sebaceous Glands

### ACNE VULGARIS

Acne vulgaris is the most common skin problem in the United States, affecting nearly 80% to 85% of individuals at some point between 11 and 30 years of age.<sup>1,2</sup> Although not a serious disease, acne may be the source of permanent scarring and even more importantly, psychosocial morbidity and decreased emotional well-being. Withdrawal from society, depression, and decreased self-esteem may occur in individuals with more significant disease. Girls and boys with acne have more feelings of uselessness and lower body satisfaction compared with those without acne, and these features are compounded by the fact that acne typically presents in adolescents, who tend to be psychologically vulnerable and sensitive to modification in their physical appearance.<sup>3</sup> In one study, acne severity was directly correlated with extent of embarrassment and lack of enjoyment of or participation in social activities.<sup>4</sup> Patients with even mild to moderate acne have demonstrated high scores on the Carroll Rating Scale for Depression and an increased prevalence of suicidal ideation (SI).<sup>5</sup> In addition, patients with severe acne may have poorer academic performance<sup>6</sup> and higher unemployment rates.<sup>7</sup> Issues such as these highlight that the potential benefits of acne therapy extend far beyond the simple cosmetics of the disease.

Pediatric acne is the terminology applied to acne occurring from birth through 11 years of age; adolescent acne describes patients from age 12 to adulthood.<sup>8</sup> The contemporary classification of pediatric acne based on age of onset of the disease is shown in Figure 8-1.

Acne vulgaris is seen routinely by primary care physicians, and so familiarity with the treatment of this condition is vital. The majority of acne patients with mild to moderate disease respond well to traditional therapies; patients with severe or recalcitrant disease may merit treatment with agents most appropriately prescribed by dermatologists. Although the underlying cause of acne vulgaris remains unknown, considerable data concerning its pathogenesis have accumulated in recent decades to allow a rational and therapeutically successful approach to its management. There is no single “gold standard” therapy for acne, and treatment regimens must be individualized and occasionally fine tuned in order to achieve the optimal response.

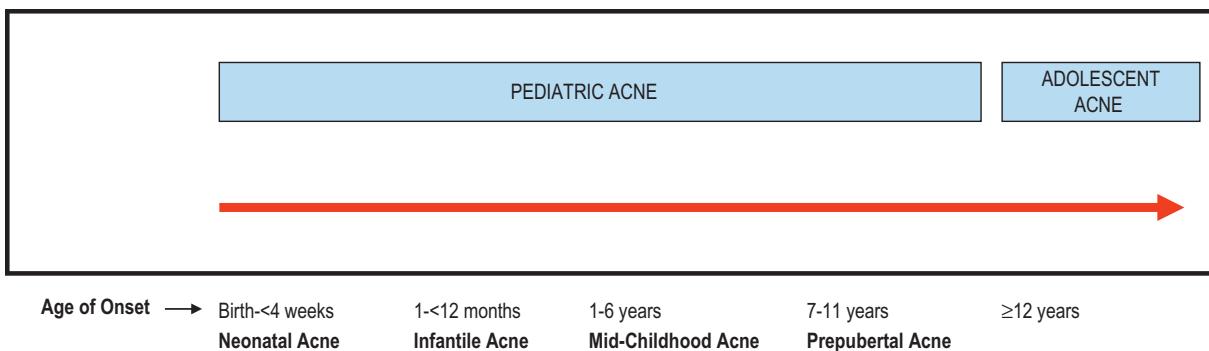
The tendency to develop acne is often familial and is felt by some to be inherited as an autosomal dominant trait. However, because of the high prevalence, the genetics of the disease remain unclear. Adolescent acne usually begins around the time of onset of puberty, occurring earlier in girls than boys. However, the onset of acne may occur significantly earlier, and it may be the first sign of pubertal maturation in girls, correlating with increasing levels of dehydroepiandrosterone (DHEA), an adrenal androgen.<sup>9</sup> Natural history studies show that in 80% of patients the incidence and severity of acne decline by the early 20s, although as many as 50% of adults older than 25 years are affected and a minority may have persistence into middle age.<sup>10,11</sup> An important consideration is the timing of onset of puberty, which has followed a downward trend for many years. Studies from the mid-twentieth century onward suggest that breast and pubic hair development in American girls is occurring at younger ages, with African-American girls disproportionately represented.<sup>12</sup> As a result the regional definitions of precocious puberty have been revised such that puberty is currently considered precocious if it occurs before 8 years of age in European girls, before 7 years of age in American white girls, and before 6 years of age in African-American girls. A similar trend has not been identified in boys, in whom the cut-off age for precocious puberty continues to be 9 years.<sup>13,14</sup>

An understanding of acne pathogenesis helps the practitioner conceptualize and formulate the therapeutic plan. Four interrelated processes, including hyperkeratinization, androgen stimulation, bacterial infection, and inflammation, are traditionally believed to be involved in this multifactorial disease. A pictorial representation of acne pathogenesis is shown in Figure 8-2.<sup>15</sup> Individual acne lesions usually begin with obstruction of the pilosebaceous unit (composed of the hair follicle and the sebaceous gland). These units are localized primarily to the face and trunk, and these “follicular plugs” (or microcomedones) are caused by excessive numbers of desquamated epithelial cells from the wall of the follicle in combination with excessive amounts of sebum, the oily, lipid-rich substance produced by the sebaceous glands. Sebum production is stimulated by adrenal and gonadal androgens and rises to maximum levels during late adolescence. These microcomedones enlarge into comedones, which may be open (blackheads) or closed (whiteheads). The reason for the black appearance of open comedones is unclear; one hypothesis suggests compaction and oxidation of the keratinous material at the follicular opening results in this finding. Melanin pigment may also play a role.<sup>16,17</sup>

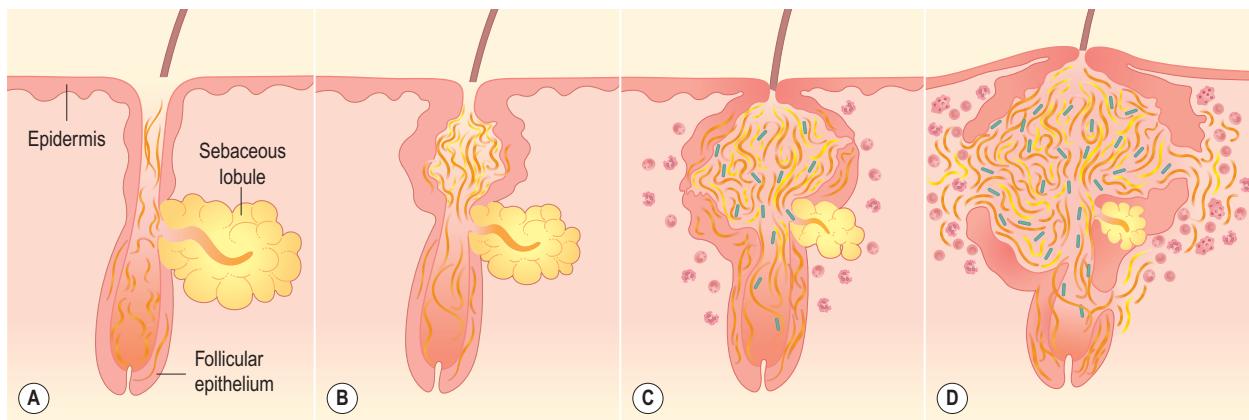
Propagation of acne lesions occurs when *Propionibacterium acnes*, a resident anaerobic organism, proliferates in this environment of sebum and follicular cells with the production of chemotactic factors and proinflammatory mediators, which contribute to inflammation.<sup>18</sup> Hypersensitivity to this organism may also play a part in the more severe forms of acne.<sup>19</sup> The clinical counterpart to these infectious and inflammatory events are papules and pustules. With continued inflammation and macrophage recruitment, larger lesions (cysts and nodules) may result. Finally, sequelae of active acne lesions include dyspigmentation (usually hyperpigmentation or, occasionally, hypopigmentation) and scarring. Box 8-1 summarizes the various types of acne lesions.

Although the pathway in Figure 8-2 has traditionally been used to explain acne pathogenesis, ongoing research continues to shed more light on these processes. Subclinical inflammation, even before the formation of the microcomedone, may be present in acne as demonstrated by upregulated levels of inflammatory cytokines and cells in uninvolved skin from acne patients.<sup>20</sup> Another study supporting this hypothesis utilized digital photographic images to follow the evolution of acne lesions and showed that nearly 30% of inflammatory lesions arose from normal-appearing skin (as opposed to comedones).<sup>21</sup> Further elucidation of the mechanisms that give rise to acne lesions will enable better targeting of acne therapies.

In addition to the established pathogenic factors discussed previously, there may be other triggers or exacerbating conditions that contribute to acne vulgaris. These other factors are less well understood and in some cases controversial. Stress appears to be a common trigger for acne, possibly via increased activation of the hypothalamic-pituitary-adrenal axis and the resultant increase in androgen production. Acute worsening of acne has been documented in college students during examination periods and correlated with an increased perceived stress score.<sup>22</sup> Mechanical factors such as skin occlusion from sports gear (i.e., helmets, chin straps, shoulder pads) may exacerbate the condition. Topically applied preparations, especially pomades and greasy ointments, to hair or skin may contribute to physical obstruction of the pilosebaceous unit and worsen the disease. Several medications may worsen acne, including anabolic steroids, progestins, lithium, isoniazid, hydantoin, and gold.<sup>23</sup> Pathologic androgen excess is often associated with acne (see below), and although endocrinologic evaluation is not indicated for the majority of patients, it should be considered in patients who have additional signs as listed in Box 8-2.<sup>24</sup>



**Figure 8-1** Contemporary classification of acne vulgaris in childhood and adolescence. (Modified from references 40, 56, and 194.)



**Figure 8-2** Traditional view of acne pathogenesis. (A) Early comedone, with mild follicular plugging. (B) Later comedone. (C) Inflammatory papule/pustule. (D) Nodule/cyst. It should be noted that emerging studies suggest that subclinical inflammation may occur earlier in the pathogenesis, even before follicular plugging (A). (Reprinted with permission from Bolognia et al. 2003, reference 15.)

### Box 8-1 Types of Acne Lesions

#### Active lesions (increasing severity)

- Microcomedone (may not be clinically apparent)
- Open comedone (blackhead)
- Closed comedone (whitehead)
- Papule
- Pustule
- Nodule
- Cyst-like nodule

#### Sequelae

- Dyspigmentation (usually hyperpigmentation)
- Scarring (sometimes keloidal)

### Box 8-2 Potential Signs of Androgen Excess in Acne Patients

- Young children
  - Body odor
  - Axillary hair
  - Pubic hair
  - Clitoromegaly
- Adult women
  - Recalcitrant/late-onset acne
  - Menstrual irregularity
  - Hirsutism
  - Male- or female-pattern alopecia
  - Infertility
  - Acanthosis nigricans
  - Truncal obesity

Modified from Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. *J Am Acad Dermatol* 2007;56:651–63.

The role of diet in the pathogenesis of acne vulgaris remains controversial, and controlled studies have refuted the value of dietary restrictions. For many years the elimination of various foods such as chocolate, soft drinks, milk, ice cream, fatty foods, shellfish, and iodides was recommended. The misconception that iodine is injurious to patients with acne vulgaris originated with the concept that iodides administered orally as a medication occasionally initiate a papulopustular acneiform eruption. The concept that chocolate exerts an adverse effect on acne has been challenged, and in one controlled double-blind study, it was found that it failed to affect either the course of the disease or the production and composition of sebum.<sup>25</sup> However, the possibility that diet plays a role in the pathogenesis or exacerbation of acne remains unclear. A review of two non-Westernized populations (one in Papua New Guinea and the other in Paraguay) revealed an astonishing difference in acne prevalence in comparison to individuals in Westernized societies.<sup>26</sup> One potential explanation asserted for these differences is the diets of these populations, which are composed mainly of minimally processed plant and animal foods and are nearly devoid of the carbohydrates typical in Western diets, which may result in high insulin levels. Hyperinsulinemia, in turn, may promote the development of acne by its ability to increase androgen production.<sup>26</sup> It remains unclear whether adhering to a diet with a low glycemic load (LGL) can effect a change in acne, although several studies seem to suggest an association.<sup>27–30</sup> Studies have suggested increased sex hormone-binding globulin, reduced androgen levels, and reduced acne lesion development in young males who ate an LGL diet, although the associated weight loss in this cohort, as well as the lower saturated fat content and higher fiber level in the LGL diet, are considered by some as potential confounders.<sup>31,32</sup> The association between milk consumption and development of acne has been explored, with some studies (some of which were limited by their retrospective design) suggesting a positive association, possibly related to a combination of



**Figure 8-3** Acne vulgaris: comedonal. Open comedones present as blackheads.



**Figure 8-5** Acne vulgaris: inflammatory. Note the erythematous papules and pustules, as well as open and closed comedones.



**Figure 8-4** Acne vulgaris: comedonal. Closed comedones present as whiteheads.



**Figure 8-6** Acne vulgaris: inflammatory. This adolescent female has inflammatory papules and papulopustules, as well as hirsutism.

exogenous hormones and growth factors, and stimulation of endogenous hormones.<sup>33–35</sup> Interestingly, skim milk was consistently associated with acne in these studies, suggesting that fat content may not explain the acne-causing ability of milk in the studied cohorts.<sup>31</sup> Other dietary factors being studied with regard to acne pathogenesis include omega-3 fatty acids, antioxidants, zinc, vitamin A, and dietary fiber.<sup>32,36</sup>

Acne presents with a combination of the various lesion types previously discussed: comedones, papules, pustules, cysts, nodules, scarring, and dyspigmentation. The earliest lesion type is usually the comedone, and mild acne may be limited to these lesions (Figs. 8-3 and 8-4). With increasing severity, patients develop inflammatory lesions, including papules and pustules (Figs. 8-5 and 8-6). Nodules and cyst-like nodules may be present in patients with moderate to severe disease (Figs. 8-7 and 8-8) and may result in permanent acne scarring (Figs. 8-9 and 8-10). Dyspigmentation is a common sequela, especially in patients with darker complexions (Figs. 8-11 and 8-12). The primary sites for acne lesions correlate with the areas most concentrated with sebaceous glands: the face, chest, back, and shoulders. In patients with regressing acne lesions, macular erythema (Fig. 8-13) and hyperpigmentation are commonly seen. Although patients commonly regard these as active lesions and “scars,” they usually imply effectiveness of the therapy, and their temporary nature should be explained to the patient. The scarring that occurs in patients with the more severe papulopustular and nodulocystic forms of acne develops because of fibrous contraction after the inflammatory phase. In addition to sharply punched-out pits and craters, hypertrophic or keloidal scars may also develop. The severity of the scarring depends on the depth and degree of the inflammation and on the patient’s individual susceptibility.

Acne fulminans is a rare and severe form of acne vulgaris, occurring almost exclusively in young males. Patients present with an acute



**Figure 8-7** Acne vulgaris: nodulocystic.

onset of painful, nodular, and occasionally ulcerative acne lesions concentrated on the chest (Fig. 8-14), shoulders, back, and face. Fever, leukocytosis, and musculoskeletal pain may also be present, and the skin lesions usually result in permanent scarring. Osteolytic bone lesions may be present, especially in the clavicle, sternum, and long bones.<sup>37</sup> Systemic corticosteroids are the mainstay of therapy, with the addition of isotretinoin after the acute inflammatory stage has subsided.

### Acne Therapy

Before any attempt is made to treat acne, patient education is vital. Important considerations include explaining the nature and natural history of acne vulgaris; dispelling acne myths regarding causes and treatments; highlighting the need for adherence with therapy and



Figure 8-8 Acne vulgaris: nodulocystic.



Figure 8-9 Acne scarring. This patient has severe nodular acne vulgaris with scarring involving the trunk.



Figure 8-10 Acne scarring.



Figure 8-11 Acne-induced dyspigmentation.



Figure 8-12 Acne-induced dyspigmentation. Note the "T-zone" distribution corresponding to prior acne lesions.



Figure 8-13 Residual postacne erythema. Note erythematous macules at sites of prior lesions.

appropriate follow-up care with the physician; reviewing the correct usage of medications and the potential side-effects; and emphasizing the expected gradual improvement in symptoms with therapy. Patient-education materials are very useful to this end and will help increase adherence with treatment. Such materials can be created and personalized by the physician or purchased from national organizations such as the American Academy of Dermatology ([www.aad.org](http://www.aad.org)) or the American Academy of Pediatrics ([www.aap.org](http://www.aap.org)). Box 8-3 lists some clinical pearls for increased adherence in acne therapy.

Acne treatment in the past was hindered by mythical concepts regarding its causes, a more limited armamentarium of treatment options, and a lack of appreciation for the dire psychosocial consequences that can result for the acne patient. With the current level of understanding of acne pathogenesis, the ever-expanding array of



**Figure 8-14** Acne fulminans. This patient developed acute worsening of his acne lesions upon starting isotretinoin therapy and required systemic corticosteroids.

therapeutic approaches, and recognition of both the physical and emotional benefits of successful therapy, every patient with acne who desires treatment should be able to benefit from physician intervention. The primary care provider is optimally situated to offer therapy to patients with mild and moderate disease. For those with recalcitrant or severe involvement, referral to a dermatologist is often necessary. Although acne therapy is a combination of art and science, a solid understanding of the various classes of medication and their proper use in both monotherapy and combination therapy provides the foundation for designing treatment plans. A conceptual framework is shown in Table 8-1 for an acne treatment algorithm. Contemporary treatment algorithms are also available in the published literature.<sup>38-40</sup>

Topical therapies are first-line treatment for patients with mild acne and are very useful as part of a combination therapy regimen for patients with moderate or severe acne. Prescription-strength topical agents are summarized in Table 8-2. Benzoyl peroxide (BP) and topical retinoids (vitamin A acids), although potential irritants, appear to be

### Box 8-3 Pearls for Increasing Adherence in Acne Therapy

- Use written action plans for topical and systemic medication use.
- Keep the treatment regimen as simplified as possible; use of fixed-dose combination agents (when possible) may facilitate this goal.
- Consider the vehicles of prescribed agents and tolerability by the individual patient.
- Take time to educate the patient regarding expectations (length of time to see improvement, likelihood of mild irritation early in the course of therapy, potential side effects).
- Review appropriate application of topical medications.
- Reinforce the importance of ongoing use (maintenance therapy), once improved.
- Consider psychologic comorbidities and encourage open discussion regarding acne-associated stressors.

Modified from references 40, 101, 195.

**Table 8-1** Acne Treatment Algorithm

Therapy	SEVERITY (LESION TYPE)				
	Mild (Comedonal)	Mild (Inflammatory/Mixed)	Moderate (Inflammatory/Mixed)	Severe (Inflammatory/Mixed)	Severe (Nodular/Scarring)
<i>Initial therapy options*</i> <sup>,†</sup>	Topical retinoid BP Salicylic acid cleanser	BP/retinoid combo BP/antibiotic combo Antibiotic/retinoid combo + BP	BP/retinoid combo BP/antibiotic combo ± topical retinoid Antibiotic/retinoid combo + BP ± oral antibiotic	BP/retinoid combo + oral antibiotic BP/antibiotic combo + topical retinoid + oral antibiotic Antibiotic/retinoid combo + BP + oral antibiotic	Isotretinoin
<i>Alternative therapy options*</i> <sup>,†,‡</sup>	Add BP or retinoid if not already prescribed BP/antibiotic combo BP/retinoid combo Antibiotic/retinoid combo	Substitute another combo product Add missing component (i.e., topical retinoid, BP, topical antibiotic, oral antibiotic) Change type, strength or formulation of topical retinoid	Substitute another combo product Add missing component (i.e., topical retinoid, BP, topical antibiotic, oral antibiotic) Change type, strength or formulation of topical retinoid Consider hormonal therapy for females Consider oral isotretinoin	Consider changing oral antibiotic Consider isotretinoin Consider hormonal therapy for females	Consider hormonal therapy for females
<i>Maintenance therapy</i>	Topical retinoid or BP/retinoid combo	Topical retinoid or BP/retinoid combo	Topical retinoid or BP/retinoid combo	Topical retinoid or BP/retinoid combo	Topical retinoid or BP/retinoid combo

Modified from references 38-40, 192 and 193.

BP, benzoyl peroxide.

\*If combination products not available to patient, consider substitution of individual components as separate prescriptions.

†Topical dapsone may be considered in place of topical antibiotic.

‡If needed as determined by physician assessment and patient satisfaction.

**Table 8-2** Prescription Topical Therapies for Acne Vulgaris

Drug	Brand*	Formulation
<b>ANTIBIOTICS</b>		
Clindamycin	Cleocin T	1% solution, gel, pledgets, lotion
	ClindaMax	1% lotion
	Clindets	1% pledgets
	Clindagel	1% gel
	Evoclin	1% foam
Clindamycin/BP <sup>†</sup>	BenzaClin	1% (5% BP) gel
	Duac	1% (5% BP) gel
	Acanya	1.2% (2.5% BP) gel
	Onexton	1.2% (3.75% BP) gel
Dapsone	Aczone	5% gel
Erythromycin	Emgel, Erygel	2% gel
	Eryderm, Erymax, T-Stat	2% solution
	Staticin	1.5% solution
	Akne-Mycin	2% ointment
	Theramycin Z	2% solution + ZA
Erythromycin/BP <sup>†</sup>	Benzamycin	3% (5% BP) gel, pak
Sulfacetamide	Klaron	10% lotion
	Plexion	10% (5% sulfur) cloths, wash
	Clenia	10% (5% sulfur) cream, wash
	Rosula	10% (4% sulfur) wash
Azelaic acid	Azelex	20% cream
<b>RETINOIDS</b>		
Adapalene	Differin	0.1% cream, gel, lotion 0.3% gel
Adapalene/BP <sup>†</sup>	Epiduo	0.1% (2.5% BP) gel
Tazarotene	Tazorac	0.05, 0.1% cream 0.05, 0.1% gel
	Fabior	0.1% foam
Tretinoin	Retin-A	0.025, 0.05, 0.1% cream 0.01, 0.025% gel
	Retin-A Micro	0.04, 0.1% gel
	Avita	0.025% cream, gel
	Atralin	0.05% gel
Tretinoin/ Clindamycin <sup>†</sup>	Ziana	0.025% (1.2% clindamycin) gel
	Veltin	0.025% (1.2% clindamycin) gel

BP, Benzoyl peroxide; ZA, zinc acetate.

\*Listed are examples; this list is not exhaustive. Many of these preparations have generic alternatives.

†Combination therapy product.

the most effective topical agents. Based on current understanding of acne pathogenesis, these two products offer a highly effective therapeutic approach that can be tailored to each patient. Although success in the management of acne vulgaris can be achieved by the use of these agents alone, the therapeutic effect can be increased substantially by their use in combination, although they are applied at separate times.

Daily facial cleansing, preferably in the morning and at bedtime, is a useful step in acne management. The goals of cleansing are to remove excess oil, dirt, and makeup. Use of a gentle, soap-free, pH-balanced cleanser or acne wash is recommended.<sup>40</sup> It is important that the acne patient be appropriately educated that harsh scrubbing and use of abrasive devices or sponges may increase inflammation and actually worsen acne or increase the risk of scarring.

BP and salicylic acid are the active ingredients in most over-the-counter (OTC) acne products. In fact most BP acne products are now limited to OTC status, excepting some prescription combination

products. Salicylic acid helps reduce sebum and decrease comedones and is found in various concentrations as a gel, lotion, wash, or cream. It may be an alternative comedonal therapy for those who cannot tolerate topical retinoids (now considered the mainstay of comedonal acne therapy). Glycolic acid, one of the  $\alpha$ -hydroxy acids, is found naturally in fruits and yogurt and may be useful in decreasing hyperkeratosis associated with acne.

BP is traditionally the most commonly used topical preparation for acne vulgaris and as noted above is available as an OTC product and in some select prescription (primarily fixed-dose combination) products. It is a powerful antimicrobial, useful for reducing colonization of *P. acnes*, and also has some comedolytic and anti-inflammatory effects. BP is available in a variety of strengths and comes as a gel, wash, cream, lotion, and even shaving cream. It is usually used once to twice daily. BP products may bleach colored clothing or linens, and patients should be warned of this possibility. Combination products of BP with topical antibiotics (erythromycin or clindamycin) are readily available, and these agents appear to be more effective than either ingredient used alone.<sup>41-43</sup> A combination BP/topical retinoid product is also available. These agents are discussed in more detail in the paragraphs that follow.

Potential side effects of BP include an irritant contact dermatitis and rarely an allergic contact dermatitis.<sup>23,44</sup> Irritant dermatitis is particularly problematic when the product is used excessively or in association with abrasive soaps or astringents or both. Therapy must be individualized and initiated gradually, particularly in fair-skinned or atopic individuals. BP should be applied as a thin film and rubbed in gently, gradually increasing the frequency and strength of the preparation as tolerance is developed (generally over several weeks). As with most topical agents, a small portion of the product is generally sufficient for application to the entire face. If irritation or excessive dryness develops, the preparation may be discontinued for several days and then restarted more sparingly, and/or noncomedogenic facial emollients may be used (in small amounts).

Topical retinoids (see Table 8-2) are a very effective class of medication used in the treatment of acne. These drugs normalize the keratinization process within the follicles, which reduces obstruction and therefore the formation of microcomedones and comedones. Some topical retinoids may also have anti-inflammatory activity. These agents are thus both comedolytic and anticomедogenic, and as such, function to help prevent new acne as well as treat existing lesions. The prototype drug in this class is tretinoin, an acid of vitamin A. Newer-generation agents include adapalene and tazarotene. Tazarotene was used initially in the treatment of psoriasis and subsequently received approval for the treatment of acne vulgaris. Although success in the management of acne can often be achieved by the use of topical retinoids alone, the therapeutic effect can be substantially increased by their use in combination with BP or a topical antibiotic. A tretinoin/clindamycin combination (see Table 8-2) has been found to improve both comedonal and inflammatory acne. More recently, an adapalene/BP combination product has become available and was found to be more effective than either agent alone and placebo.<sup>45</sup>

Topical retinoids are generally applied once nightly and should be applied sparingly. A useful analogy for the patient is to use a “pea-sized” or “chocolate chip-sized” amount of product for a full-face application. The traditional recommendation was for retinoids to be applied to a dry face, with 30 to 45 minutes of “air drying” allowed after washing and before applying the product. However, this appears to be unnecessary with the newer formulations of tretinoin, adapalene, and tazarotene. The primary side effect of topical retinoids is irritation, which can be minimized by appropriate application and use. In general, the cream forms are less drying than the gels, solutions, or pledgets, although again, newer formulations have minimized this effect, even with the gel vehicle. In patients with sensitive skin, good initial choices for retinoid therapy would be tretinoin cream (in a lower strength), adapalene cream, or one of the micro preparations. If the product is tolerated well and more effect is desired, the patient can then be advanced to higher strengths, a gel or paged formulation, or tazarotene. Another useful strategy to decrease the incidence of irritation is to have the patient begin therapy 3 nights weekly, increasing as tolerated over a few weeks to nightly application.<sup>46</sup> Since retinoids may degrade significantly when mixed with BP, such combination

therapy should be used only in the form of preformulated combination products (see Table 8-2).<sup>47</sup>

Increased sun sensitivity is another potential side effect of topical retinoids, and patients should be counseled regarding the appropriate use of a sunscreen with a sun protection factor of 30 or higher, especially if they are also using a photosensitizing oral agent. The risk of teratogenicity with use of the topical retinoids is controversial but remains a concern given the well-established teratogenic potential of the oral retinoid, isotretinoin. There are sporadic reports of congenital malformations in infants born to women who used topical tretinoin during pregnancy, but controlled human studies are lacking for this drug, which is classified as a pregnancy category C (studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women or studies in women and animals are not available). The limited transdermal uptake, lack of alteration of plasma retinoid levels, epidemiologic data, and margin of safety when compared with known teratogens all suggest the unlikelihood of tretinoin being a human developmental toxicant.<sup>48-51</sup> However, until a formal consensus exists, the potential risks of topical retinoids should be discussed in detail with women of childbearing potential, and their use should probably be avoided during pregnancy.

Topical antibiotics (see Table 8-2) exert their effect primarily by decreasing the population of *P. acnes*, and they may also have anti-inflammatory effects. The most commonly utilized topical antibiotics for acne are clindamycin, erythromycin, and sulfacetamide. These agents are most useful for inflammatory acne, and in patients with mixed inflammatory and comedonal disease they should be used in combination with another agent that has comedolytic properties (i.e., BP or retinoid). These agents are usually well tolerated and are applied once to twice daily. As with other topical agents, lotions and creams are less drying than solutions, pledgets, and gels. Monotherapy with topical antibiotics should be discouraged, given the greater development of bacterial resistance, which can be lessened by the concomitant use of a preparation containing BP (see below).

Topical erythromycin has been used for decades in the treatment of acne and is usually well tolerated. The addition of zinc to erythromycin may increase its therapeutic efficacy.<sup>52</sup> For patients with extremely dry skin, an ointment-based topical erythromycin product (Akne-Mycin) is available. Topical clindamycin is another well tolerated antibiotic preparation for acne. Although pseudomembranous colitis is usually associated with oral clindamycin, there are only rare reports of this complication with topical application of this agent.<sup>53,54</sup> Therefore if a patient using topical clindamycin develops persistent diarrhea, this rare complication should be considered. Topical sulfonamide preparations (mainly sulfacetamide) are also available by prescription and may be particularly useful in patients who also show evidence of rosacea. These medications are often well accepted, although some patients may find their odor offensive. Patients with allergies to oral sulfa drugs should not use topical sulfonamides. Topical dapsone, a newer arrival in the acne antibiotic market, appears to be most effective against inflammatory lesions, although its mechanism may not be related to *P. acnes* reduction. Topical dapsone may result in clinically insignificant mild hemolysis in patients with glucose 6-phosphate dehydrogenase deficiency.<sup>55</sup>

The landscape of topical acne therapy has evolved significantly in recent decades, with the increasing availability of fixed-dose combination therapies. These agents are approved for mild to moderate acne vulgaris, and they offer the advantages of improved adherence and complementary mechanisms of action of the individual active ingredients.<sup>56</sup> Available fixed-dose combination products include those combining BP and clindamycin, BP and adapalene, clindamycin and tretinoin, and BP and erythromycin. Each of these products, in order to receive US Food and Drug Administration (FDA) approval, was demonstrated to have superior efficacy over placebo as well as the individual active ingredients ("monads") in large, multicenter clinical trials.

With increasing use of topical antibiotics for the treatment of acne vulgaris, the development of resistant strains of *P. acnes* is being observed. Cross-resistance of *P. acnes* to erythromycin and clindamycin is now widespread.<sup>57</sup> In one study, erythromycin-resistant organisms were isolated from 51% of patients treated with oral erythromycin but also from 42% of patients treated with topical clindamycin.<sup>58</sup>

Antibiotic-resistant propionibacteria may be transmissible between acne-prone individuals as well as between patients and their physicians.<sup>59</sup> Data suggest that the concomitant use of BP with topical (as well as oral) erythromycin or clindamycin diminishes the emergence of resistant bacterial strains.<sup>24,38,60</sup>

Azelaic acid is a naturally occurring dicarboxylic acid produced by the fungal organism *Pityrosporum ovale*. It has antibacterial and antimicrobial properties and is felt by some to be equal in efficacy to BP or tretinoin. The effectiveness of azelaic acid may be increased by using it in combination with other topical medications such as retinoids, antibiotics, or BP.<sup>61</sup> Another benefit of this agent is its ability to decrease hyperpigmentation caused by acne. Azelaic acid is marketed as a 20% cream and is applied twice daily. Side effects are rare but include burning, tingling, mild erythema, and pruritus.

Physicians are commonly consulted regarding the safety of acne treatment in women who are pregnant, may become pregnant, or are breastfeeding an infant. Although there are no long-term studies on the use of topical antibiotics during pregnancy, erythromycin seems to be safe. Since it is estimated that approximately 8% of topically applied clindamycin can be absorbed,<sup>48</sup> this drug is probably best avoided for women who are breastfeeding, are pregnant, or are contemplating pregnancy. Although approximately 5% of topically applied BP is absorbed through the skin, it is rapidly metabolized to benzoic acid, enters the dermal blood vessels as benzoate, and is then transported to the kidneys and excreted in the urine. Thus BP appears to be safe during pregnancy, although controlled studies are lacking. The use of tretinoin is discussed earlier in this section.

Oral antibiotics (Table 8-3) are the most common form of systemic therapy utilized in the treatment of acne vulgaris, despite the fact that the only agent with FDA-approval for this indication is extended-release minocycline. These agents are quite effective and are best reserved for patients with moderate or severe inflammatory acne. They are useful in decreasing *P. acnes*, free fatty acids found in sebum, and inflammation (via their inhibitory effect on neutrophil chemotaxis). Oral antibiotics generally require 4 to 8 weeks to achieve their maximum effect, and it is usually necessary to continue therapy for several months, with gradual tapering as tolerated once the disease activity has diminished. The most commonly utilized antibiotics for treating acne are the tetracycline-class drugs (tetracycline, minocycline, doxycycline) and erythromycin. Less commonly, clindamycin, trimethoprim-sulfamethoxazole, azithromycin, and cephalexin are used. These medications are usually given on a twice-daily basis.

The safety of long-term antibiotic therapy for acne has been a concern of patients, parents, and physicians. Although the risk-to-benefit ratio of the most commonly used medications is favorable, each agent carries its own inherent potential toxicities, some of greater concern than others. The development of *P. acnes* resistance has been demonstrated for most of the agents utilized in this setting, especially erythromycin and clindamycin, in which case cross-resistance patterns may emerge.<sup>62,63</sup> General guidelines for oral antibiotic use in acne include avoiding the oral agent if topical agents will suffice, continuing treatment for no longer than is necessary, reusing the same drug when possible (if restarting oral therapy is required), and avoidance of concomitant oral and topical treatment with dissimilar antibiotics.<sup>63</sup> In patients who do not respond to oral antibiotics, the possibility of resistant strains should be considered. Overall, the commonly used oral antibiotics for acne are well tolerated, side-effects are uncommon, and routine laboratory testing is unnecessary. Concomitant use of antibiotics and oral contraceptive agents may result in decreased efficacy of the latter, and this possibility should be discussed with female patients.

Tetracyclines are the gold standard of oral antibiotic therapy for acne. These agents have a long track record of safety and efficacy, although side effects are possible. The possibility of dental staining (Fig. 8-15) in children under 9 years of age precludes their use in this population, who only occasionally have moderate to severe acne. Tetracycline-class antibiotics should also not be used in pregnant females, given the deposition of the drug in developing teeth as a result of its chelating properties and the formation of a tetracycline–calcium orthophosphate complex.

The most common side effects of the tetracyclines are photosensitivity and gastrointestinal upset. The risk of phototoxicity is greatest with

**Table 8-3** Oral Antibiotics for Acne Vulgaris

Drug	Usual Dosage*	Comments/Side-Effects
<b>COMMONLY USED</b>		
Tetracycline	250–500 mg	Dental staining <9 years Dairy products decrease absorption GI upset, photosensitivity, teratogenic, PTC, VVC, IBD
Minocycline	50–100 mg 55, 65, 80, 105, 115 mg ER (1 mg/kg once daily)	Dental staining <9 years Dairy products decrease absorption  Vertigo (lower incidence with ER preparation), GI upset, blue-gray skin pigmentation, severe drug reactions with hepatitis/pneumonitis, lupus-like reactions, SJS, teratogenic, hepatitis, PTC, VVC, IBD
Doxycycline	50–100 mg 75, 100, 150 mg ER, once daily 20 mg ("subantimicrobial dose")	Dental staining <9 years Dairy products decrease absorption  Photosensitivity, photoonycholysis, GI upset (rare), teratogenic, PTC, VVC, IBD
Erythromycin	250–500 mg	GI upset (common), VVC, drug-drug interactions, prolongation of the QT interval; no longer recommended by most experts given increased resistance
<b>LESS COMMONLY USED</b>		
Trimethoprim-sulfamethoxazole	80/400 mg, 160/800 mg	Severe drug reactions, SJS, bone marrow suppression, hepatitis, GI upset, VVC, fixed drug eruption; routine use for acne strongly discouraged
Clindamycin	75–150 mg	Pseudomembranous colitis, GI upset, drug reactions, VVC
Cephalexin	250–500 mg	GI upset, drug reactions, VVC

ER, Extended release formulation; GI, gastrointestinal; IBD, inflammatory bowel disease; PTC, pseudotumor cerebri; SJS, Stevens-Johnson syndrome; VVC, vulvovaginal candidiasis.

\*Usually given twice daily for acne unless otherwise noted in table.



**Figure 8-15** Dental staining from tetracycline. (Courtesy of Maria Simon, DDS.)

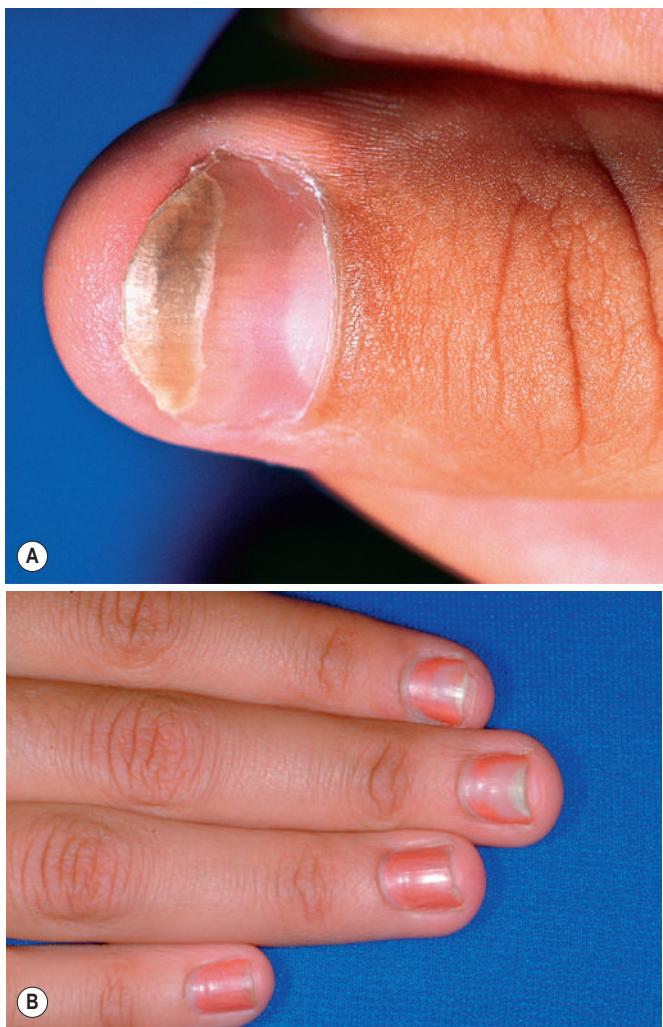
tetracycline and doxycycline and extremely rare with minocycline. Pseudotumor cerebri is a rare side effect, the risk being greatest when isotretinoin and a tetracycline are taken concomitantly. Tetracyclines cannot be taken with dairy products or antacids, which impair absorption. In addition, tetracycline (but not doxycycline or minocycline) absorption is impaired in the presence of food, and thus the medication must be taken 1 hour before or 2 hours after a meal. This feature may result in decreased compliance among active teenagers. Tetracyclines should be used with caution in patients with renal disease.

Doxycycline has the benefit of sustained absorption in the presence of food but may result in severe photosensitivity reactions. One such type of reaction is "photoonycholysis," which presents with erythema and separation of the nail plate from the nailbed (Fig. 8-16). These patients usually also have an associated photosensitivity rash on exposed areas of skin. Pill esophagitis is another potential side effect of oral doxycycline and can usually be prevented by taking the medication with a full glass of water and avoiding recumbency for at least

1 hour after dosing. In a retrospective cohort study of patients with acne who were treated with oral tetracycline-class antibiotics, the hazard ratio (HR) for developing inflammatory bowel disease (IBD) was increased for all agents in this class but most notably for doxycycline (HR of 1.63).<sup>64</sup> However, a definitive causal link between tetracycline-class antibiotics and development of IBD remains to be proven. Off-label use of subantimicrobial-dose doxycycline hydiate (20-mg tablets taken twice daily) has been reported in acne vulgaris and has been shown to significantly reduce the number of lesions without any detectable antimicrobial effect on skin flora or alteration of resistance patterns.<sup>65</sup> An extended-release formulation of doxycycline is available and can be administered once daily.

Minocycline is the most widely prescribed systemic antibiotic for the management of acne in the United States, Canada, and the United Kingdom, and it is estimated that 65% of prescriptions for this drug are for acne.<sup>66</sup> It is particularly effective against *P. acnes* and also has anti-inflammatory properties. Similar to doxycycline, an extended-release formulation of minocycline is available and may improve adherence as well as decrease the incidence of vestibular side effects. Although the side-effect profile is somewhat similar to that of other tetracyclines, minocycline rarely causes photosensitivity. Other side effects more specific to minocycline are headache, dizziness, vertigo, and a blue-gray pigmentation of mucosae (see Fig. 11-57) or at sites of previous inflammation such as acne scars.

Occasional yet potentially serious toxicities may be associated with minocycline, including autoimmune hepatitis, drug-induced lupus (DIL), serum sickness-like reaction (SSLR), and a drug hypersensitivity reaction (HSR).<sup>66,67</sup> This HSR is characterized by a diffuse erythematous rash, facial (especially periorbital) edema, lymphadenopathy, fever, and internal organ involvement (most commonly the liver). It tends to occur within 6 to 8 weeks of starting the drug and is similar to the hypersensitivity reaction occasionally seen with the aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital, lamotrigine). SSLR presents with fever, urticarial rash, periarticular swelling with arthralgia, and occasional nephritis and lymphadenopathy. A comparative study reviewing adverse events of tetracycline, minocycline, and doxycycline revealed that these reaction patterns (DIL, SSLR, and HSR) are all more commonly seen with minocycline than with the other two medications.<sup>68</sup> Also of note is the fact that



**Figure 8-16** Doxycycline-induced photoonycholysis in two patients. Note distal nail plate separation with new nail growing in proximally (A) and separation of nail plate from underlying nailbed in the index and middle fingers (B).

SSLR and HSR usually occur within 2 months of beginning treatment, whereas DIL may be delayed for up to 2 years.<sup>68</sup> Like doxycycline, minocycline use has been linked to a possible increased risk of IBD, but this link remains definitively unproven.

Autoimmune hepatitis, DIL, arthritis, vasculitis, and development of autoantibodies have been unified under the moniker of minocycline-induced autoimmunity (MIA). A study of 27 children with MIA revealed a mean duration of treatment of 13 months before the diagnosis. The majority of patients had polyarthralgia or polyarthritis, mostly of the hands and feet. Other features included constitutional symptoms, livedo reticularis, Raynaud phenomenon, elevation of liver enzymes, and elevated antinuclear antibody titers. Importantly, 26% of patients had chronic autoimmunity, manifested mostly as persistent arthritis.<sup>69</sup> Many patients with minocycline-associated DIL have no skin eruption. Polyarteritis nodosa has been reported in some patients, and positivity for perinuclear antineutrophil cytoplasmic antibody (p-ANCA) is believed to strongly support the diagnosis.<sup>40</sup> Antihistone antibodies, traditionally considered pathognomonic for DIL, are often negative in patients with minocycline-associated disease.

Although these major types of tetracycline class drug reactions are rare overall, their possibility should be discussed with the patient, especially when minocycline is being considered. Many experts consider doxycycline to be a safe alternative, even in patients who have a history of MIA.

Erythromycin is a useful antibiotic for acne vulgaris, but its use is often limited by the fairly high incidence of gastrointestinal disturbance, even with the enteric-coated preparations. Otherwise it has few side effects and carries the distinct benefit of no phototoxicity. However, the high prevalence of erythromycin-resistant *P. acnes* organisms may further limit its clinical utility. Other antibiotics occasionally used for acne include clindamycin, trimethoprim-sulfamethoxazole, and cephalaxin. Prolonged use of oral clindamycin is not desirable because of the risk of pseudomembranous colitis caused by the toxin liberated by *Clostridium difficile*, which is able to grow in large numbers in the intestinal tract of some patients who receive this drug. Trimethoprim-sulfamethoxazole can be very effective for acne, but it is not recommended as a first-line agent given the severe and potentially life-threatening reactions (i.e., HSR, Stevens-Johnson syndrome, and toxic epidermal necrolysis) as well as bone marrow suppression that may occur.

The most common complication of antibiotic therapy in adult female patients is vaginal candidiasis, but it rarely occurs in teenagers. This complication is proportionately more common in women who take combined oral contraceptives (COCs) concomitantly with their systemic antibiotics. Another concern in patients who are also taking COCs is the possibility of the oral antibiotic diminishing the effectiveness of the contraceptive. Although this possibility remains controversial, it should be discussed with patients and alternative forms of birth control considered during the period of treatment. Patients on long-term antibiotic therapy may rarely develop a condition termed *Gram-negative folliculitis*, caused by superinfection of the pilosebaceous units with Gram-negative organisms. This complication is manifested by a pustular folliculitis or deep nodulocystic lesions recalcitrant to the acne regimen. It may respond to a change in antibiotics to reduce Gram-negative organisms, but it responds more consistently to isotretinoin.<sup>70</sup>

Hormonal therapies are another option for the treatment of acne in female patients. The primary goal of these therapies is to oppose the effects of androgens on the sebaceous glands.<sup>71</sup> Hormonally driven acne may have some distinguishing clinical features, including larger and deep-seated inflammatory nodules in the mandibular and antero-lateral neck regions, menses-associated flares, and associated signs of hyperandrogenism such as hirsutism and menstrual irregularities. If polycystic ovary syndrome (PCOS) is suspected, initial laboratory testing should include serum total and free testosterone, DHEA, and luteinizing hormone (LH)/follicle stimulating hormone (FSH) levels, as well as the 17-hydroxyprogesterone level if late-onset congenital adrenal hyperplasia is suspected. Abnormal findings should prompt referral to an endocrinologist.

Hormonal acne therapies include androgen receptor blockers, adrenal androgen production blockers, ovarian androgen blockers, and enzyme inhibitors, and they may be prescribed in consultation with a gynecologist or endocrinologist. This group of medications may have other beneficial effects on the hirsutism, androgenetic alopecia, and menstrual irregularities in some females.<sup>23</sup> COCs contain both an estrogen and a progestin, and those with a lower intrinsic androgenic activity type of progestin (desogestrel, norgestimate, and drospirenone) are most desirable for acne therapy. Drospirenone, a novel progestin, has both antiandrogenic and antimineralcorticoid activity and is reportedly better tolerated in terms of weight gain and mood changes.<sup>72</sup> Norgestimate and ethynodiol (Ortho Tri-Cyclen); norethindrone and ethynodiol (Estrostep); and drospirenone and ethynodiol (Yaz) are FDA-approved for use in the treatment of acne vulgaris. COCs may be the first-line treatment in females with skin manifestations of hyperandrogenemia.<sup>73</sup> Risks of COCs include venous thromboembolism, myocardial infarction, and ischemic or hemorrhagic stroke, although these risks seem to be more clinically significant in patients with other risk factors such as tobacco use, diabetes mellitus, and hypertension.<sup>74</sup>

Antiandrogenic agents include spironolactone, flutamide, cyproterone, gonadotropin-releasing hormone antagonists, and 5- $\alpha$ -reductase inhibitors. Spironolactone, which is used primarily as a diuretic in the treatment of hypertension, competes for androgen receptors on target cells. It is usually started at 25 to 50 mg/day, and maintenance doses, which vary by the individual, are in the range of 25 to 200 mg/day.<sup>75</sup> Potential side effects of spironolactone therapy include menstrual

irregularities, breast tenderness, hyperkalemia, and fatigue. In a study of 27 women with severe acne who were treated with spironolactone and a combined contraceptive (drospirenone and ethinylestradiol), this combination was demonstrated effective and safe, without hyperkalemia or other serious side effects.<sup>75</sup>

Isotretinoin (13-cis retinoic acid, Amnesteem, Claravis, Sotret, Absorica, Zenatane) is a derivative of vitamin A that is highly effective for recalcitrant nodulocystic acne, and the availability of this agent revolutionized the treatment of severe disease. Although the precise mechanism of action is unknown, its effects appear to be related to marked inhibition of sebum synthesis; lowering of *P. acnes* concentration; inhibition of neutrophil chemotaxis; and comedolytic and anti-inflammatory effects. Isotretinoin therapy often results in complete and often, but not always, permanent remission of acne vulgaris.<sup>76</sup> Preteens and young teenagers seem to have the highest rate of relapse. In patients who experience a recurrence of disease, however, the flares may be milder and more responsive to therapies utilized before isotretinoin therapy. Repeat courses may occasionally be necessary.

Patients usually start by taking 0.5 mg/kg per day of isotretinoin and increase the dosage to 1 mg/kg per day, usually for 16 to 24 weeks. Cumulative dosing goals, ranging from 100 to 150 mg/kg for the entire course of treatment, have been advocated, because they may decrease the rate of relapse.<sup>77,78</sup> Early in the course of isotretinoin therapy, there may be a temporary flare of lesions, and patient education regarding this possibility is vital. Although isotretinoin is truly a "miracle" drug for severe forms of acne, it has many potential side effects and prescribing should be done only by physicians experienced in its use.

Potential adverse effects of isotretinoin are numerous and are summarized in Table 8-4. A newer risk management program, iPLEDGE ([www.ipledgeprogram.com](http://www.ipledgeprogram.com)), was approved by the FDA and drug manufacturers and implemented in March of 2006. This program requires prescribers, patients, pharmacies, drug wholesalers, and manufacturers in the United States to register and comply. This mandatory distribution program was created in an effort to prevent the use of isotretinoin during pregnancy because its teratogenic effects (see

below). Under this system, prescribers must record two negative pregnancy tests before a female patient can commence therapy with isotretinoin. The iPLEDGE program represents the most rigorous risk-management program in history for such a widely prescribed drug.<sup>79</sup> Overall the risk of major side effects from isotretinoin (assuming pregnancy is avoided) is quite low. Unfortunately, a recent retrospective cohort study found no significant decrease in fetal exposure in females of childbearing age when compared to the prior risk management program (System to Manage Accutane-Related Teratogenicity [SMART]).<sup>80</sup>

Isotretinoin is a known human teratogen and is a pregnancy category X drug. Major fetal malformations have been observed in exposed infants, including abnormalities of the skull, ear, eye, central nervous system, and heart. As little as one pill can have devastating consequences on the developing fetus.<sup>23</sup> To qualify for therapy, females of childbearing potential must have two negative serum or urine pregnancy tests, and commitment to two forms of contraception, one of which must be a primary form (COC, intrauterine device, injectable or implantable hormonal birth control product, partner's vasectomy, or tubal ligation), for at least 1 month before initiation of therapy and for 1 month after discontinuing therapy. Abstinence is most desirable for females on isotretinoin therapy. A signed patient consent form is required. Unfortunately, even with dedicated pregnancy prevention programs and education regarding isotretinoin-associated teratogenicity, inadequate birth control efforts continue to be practiced by some females being treated with isotretinoin. Ongoing fetal exposure to isotretinoin has been demonstrated to be an international problem, highlighting the need for more effective strategies that incorporate considerations for cultural differences.<sup>81</sup>

The risks of isotretinoin-related depression and SI have come to the forefront in recent years. The exact association, if any, remains controversial, and arguments both supporting and refuting the potential for mood disturbance have been made. Epidemiologic data have demonstrated a lower suicide rate of 12- to 18-year-old isotretinoin users when compared with the annual rate of suicide for that population in the United States. Critical literature reviews have failed to confirm an association, and although retinoid receptors are widely distributed in the brain, there is no known pharmacological mechanism to account for isotretinoin-induced psychiatric symptoms.<sup>82-84</sup> In one systematic literature review, it was noted that studies comparing depression before and after treatment did not show a significant increase and that, surprisingly, some revealed a trend toward fewer or less severe depressive symptoms after isotretinoin therapy.<sup>84</sup> In a cross-sectional questionnaire-based study exploring the relationship of SI, mental health problems, and social functioning to acne severity among adolescents, SI was reported two to three times more often in those with increasingly severe acne when compared to those with little to no acne. Mental health problems and poorer school functioning were also associated with substantial acne, and the authors concluded that adverse events such as depression and SI that have been ascribed to acne therapies may actually reflect the burden of the disease rather than a medication effect.<sup>85</sup> Nonetheless, until more conclusive data are available, patients and parents must be thoroughly informed of the potential risks of depression and SI, and patients on isotretinoin therapy should be monitored closely and referred for psychiatric evaluation if indicated.

The potential association between isotretinoin use and IBD, which was first suggested in the mid-1980s, continues to be debated, with conflicting findings. A case-control study of over 8000 cases of IBD compared with nearly 22,000 controls revealed a strong association between previous isotretinoin exposure and ulcerative colitis, but not Crohn disease, with the risk increasing in a dose-dependent manner.<sup>86</sup> In another case-control study and meta-analysis, there was no increased risk ratio for IBD in patients who had been treated with isotretinoin.<sup>87</sup> In a retrospective population-based cohort study in Canada, no significant association between isotretinoin use and IBD was found, although in a secondary analysis of individuals limited to the ages of 12 through 19 years, a weak IBD association was noted for both isotretinoin and topical acne medications.<sup>88</sup> The significance of confounding variables (such as preceding antibiotic therapy for acne; see earlier in this chapter) and the possibility that another factor (i.e., inherently increased risk of IBD in patients with inflammatory

**Table 8-4** Potential Isotretinoin-Associated Adverse Effects

Side Effect	Comment
Dry skin and nasal membranes	Occasional epistaxis
Dry eyes	Most problematic for contact-lens wearers; may develop conjunctivitis, chalazion, hordeolum
Cheilitis	May be quite severe
Photosensitivity	
Decreased night vision	
Corneal opacities	
Alopecia	Diffuse thinning; generally reversible but can be the start of androgenetic alopecia
Headache	
Pseudotumor cerebri	Most common with concomitant use of tetracycline-class antibiotic
Musculoskeletal pain	
Hyperostosis	Mainly seen with prolonged use
Elevated triglycerides, cholesterol	Rare pancreatitis
Hepatitis	
Inflammatory bowel disease	Controversial
Rhabdomyolysis	
Teratogenicity	See text for discussion
Depression, suicidal ideation	See text for discussion

**Table 8-5** Alternative Treatments for Acne Vulgaris

Treatment	Comment
Comedone extraction	Performed with comedone extractor
Injections	Intralesional triamcinolone injected into large cysts or nodules
Light therapy	Blue light (may photoinactivate <i>P. acnes</i> ) Red light (may have anti-inflammatory effect) Combination blue-red light Intensed pulse light (IPL) Photodynamic therapy (PDT)
Laser therapy	KTP, pulsed dye laser (rarely used) Resurfacing laser (including both nonablative and ablative resurfacing lasers); useful for acne scarring
Dermabrasion/dermasanding	Useful for acne scarring
Collagen injection	Useful for acne scarring
Chemical peels	Useful for acne scarring and hyperpigmentation
Punch grafts/tissue augmentation	Useful for acne scarring
Trichloroacetic acid	Useful for atrophic acne scars
Radiation therapy	Outdated modality

Adapted from references 23, 89, 90, 91.

KTP, Potassium titanyl phosphate.

#### Box 8-4 Acne Treatment Vignettes\*

##### Mild comedonal acne

Topical retinoid once daily, or  
Topical retinoid/BP combination product once daily, or  
BP wash once daily

##### Mild-moderate combined acne (inflammatory and comedonal lesions)

BP cleanser daily and topical retinoid once daily, or  
BP/topical antibiotic combination product in AM and topical retinoid in PM, or  
BP cleanser daily and topical retinoid/topical antibiotic combination product once daily

##### Moderate-severe combined acne (inflammatory and comedonal lesions)

Oral antibiotic and topical retinoid once daily, or  
Oral antibiotic and topical retinoid/BP combination product once daily, or  
Oral antibiotic and spironolactone (female patient), or  
COC and oral antibiotic and topical retinoid once daily

##### Severe or scarring acne

Isotretinoin

BP, Benzoyl peroxide; COC, combined oral contraceptive.

\*The above vignettes are therapeutic examples only and not intended to be specific recommendations; acne therapy should always be tailored to the specific patient and severity of involvement.

acne vulgaris) may explain these observations precludes confirmation of causality. Until more is known, however, it is prudent to mention this possible association to patients and parents and to monitor patients appropriately during therapy.

There are a variety of miscellaneous treatments for acne vulgaris, and these are listed in Table 8-5.<sup>23,89-91</sup> Box 8-4 lists examples of therapeutic approaches based on acne type and severity.

#### NEONATAL ACNE

Although acne is usually a disorder of adolescents and young adults, neonates and infants are occasionally affected. Neonatal acne has its onset within the first weeks of life and may be congenital in up to 20% of newborns.<sup>92</sup> Infantile acne (see *Infantile Acne* section), on the other hand, usually presents between 1 and 12 months of life and tends to



**Figure 8-17** Neonatal acne. This newborn had typical papules and pustules with rapid resolution over 1 month.

be more severe and more persistent.<sup>93</sup> Both types occur more often in boys than in girls.

Neonatal acne typically presents with mildly erythematous papules involving the face and scalp and less commonly the chest and back (Fig. 8-17). Comedones may occasionally be present, although these tend to be more characteristic of infantile acne. Neonates presenting with more pustular lesions may have a variant referred to as *neonatal cephalic pustulosis* (see below). Neonatal acne should be distinguished from other potentially papulopustular disorders of the neonate, including infection (bacterial, candidal, or viral), erythema toxicum neonatorum, miliaria (prickly heat), eosinophilic folliculitis and milia (typically noninflamed white papules rather than pustules).

The etiology of neonatal acne is believed to relate to increased production of DHEA by the fetal adrenal glands. Another factor may be androgens, both transplacentally delivered as well as those manufactured by the neonatal testicles. Testicular androgen production serves as a stimulus to primed adrenal glands, which may partially explain the increased incidence of neonatal acne in males.<sup>76</sup> In babies with neonatal acne, a family history of acne may or may not be present.<sup>94</sup>

In recent years, a neonatal pustular eruption that presents in a similar fashion to neonatal acne has been described and has been termed *neonatal cephalic pustulosis*. This disorder presents with multiple facial papules and pustules (see Fig. 2-12), and direct examination of pustule smears may reveal yeasts of *Malassezia furfur* or *Malassezia sympodialis*.<sup>95,96</sup> In a 1996 series of 13 neonates with such a pustular eruption, smears were notable for *M. furfur* in 8 of the patients, all of whose conditions cleared rapidly after application of ketoconazole cream.<sup>95</sup> Colonization of neonates with *Malassezia* begins at birth and increases over the first few weeks of life.<sup>97</sup> However, the exact role of *Malassezia* in this setting is poorly understood with inconsistent findings in subsequent reports.<sup>98</sup> The association between neonatal cephalic pustulosis and neonatal acne remains unclear.<sup>99</sup>

Neonatal acne usually regresses spontaneously over 3 to 6 months, only occasionally persisting longer. In mild cases, therapy is generally unnecessary; daily cleansing with a gentle soap and water may be all that is required. Exogenous oil such as baby oils, creams, ointments, and lotions may aggravate the condition and should be avoided. For infants with more inflammatory or persistent disease, a low-strength (2.5% to 5%) BP gel or a topical antibiotic (i.e., erythromycin gel) are reasonable treatment options. In the otherwise-well neonate with a significantly pustular facial eruption (i.e., more suggestive of neonatal cephalic pustulosis), topical antifungal therapy can be considered. If there is a significant comedonal component or nodules are present, the infant more likely has infantile acne (see *Infantile Acne* section),

and other therapeutic options may be necessary, including oral antibiotics.

### INFANTILE ACNE

Infantile acne presents between 1 and 12 months of life. Clinically, the infant most often has open and closed comedones, but inflammatory papules and pustules occasionally occur. They may also develop larger papules and nodules (Fig. 8-18) with the potential for scarring, even without comedonal lesions. Lesions occur most commonly on the face, but the neck, back, and chest may also be involved. Most experts consider treatment of infantile acne vital in order to prevent scarring and permanent facial disfigurement.

The patient with infantile acne should have a concomitant growth assessment (with charting of height and weight) and examination for any features of precocious puberty or androgen excess, including axillary odor, clitoromegaly, presence of axillary or genital hair, breast development, and increased muscle mass. If any concerns are noted, an evaluation for hyperandrogenism should be performed (Box 8-5).

Treatment for infantile acne depends on the severity of the clinical lesions. Mild to moderate disease is usually treated with a combination of BP, topical antibiotics, and/or topical retinoids. The latter should always be included in patients with more comedonal disease. For disease that does not respond to topical measures, oral erythromycin is an excellent first-line antibiotic therapy, and the ethylsuccinate form is generally well tolerated. Refractory involvement or the presence of nodules or scarring suggest the need to consider oral isotretinoin therapy.<sup>100</sup> Intralesional steroids have also been used to treat larger nodules.

### MID-CHILDHOOD ACNE

*Mid-childhood acne* is defined as acne that has its onset between 1 and 7 years of age. This is an important diagnosis to render, because acne that begins during this age range is generally considered abnormal. This is related to the fact that children of these ages do not produce



**Figure 8-18** Infantile acne. This infant had more persistent involvement with larger lesions such as the deep papulopustule on the left cheek.

#### Box 8-5 Recommended Laboratory Evaluation for the Child with Acne and Suspected Hyperandrogenism

- Serum testosterone (free and total)
- Luteinizing hormone
- Follicle-stimulating hormone
- Dehydroepiandrosterone
- 17-Hydroxyprogesterone
- Prolactin
- Radiographic bone age

significant levels of either adrenal or gonadal androgens. Mid-childhood acne is the most likely type to be associated with an underlying endocrinologic disorder. Diagnoses such as late-onset congenital adrenal hyperplasia, androgen-secreting tumors of the adrenal glands or gonads (benign or malignant), and true precocious puberty can all present with early acne.<sup>56,101</sup> A hyperandrogenism evaluation (see Box 8-5) or referral to a pediatric endocrinologist is strongly recommended in this setting. Treatment for mid-childhood acne is similar to that outlined in the previous section for infantile acne.

An important consideration for any infant or young child with acne is the possibility of virilization related to exogenous androgen exposure. Topical androgens (primarily in the form of testosterone gel or cream) are being increasingly utilized by males with hypogonadism as well as for an off-label therapy for increased libido and enhanced manhood.<sup>102,103</sup> Inadvertent exposure of young children through contact with the treated individual has been increasingly reported and may result in clitoromegaly, appearance of secondary sexual hair, penile/testicular enlargement, frequent erections, growth acceleration, increased muscle mass, greasy hair, and acne.<sup>103,104</sup> This resultant pseudo-precocious puberty (PPP) highlights the need to obtain a thorough family history and inventory of medications being used by close contacts.

### ANDROGEN EXCESS AND ACNE

It is well recognized that androgens precipitate acne in both men and women, in addition to the potential effects of hyperandrogenemia in younger children as discussed in the previous sections. Acne may be produced or aggravated by increased adrenal gland production in response to stress, adrenal tumors, gonadal dysgenesis, Cushing syndrome, and ovarian androgen excess, such as that occurring in patients with PCOS (see Chapter 23). This condition seems to be quite common. In one study of women with acne (but lacking menstrual disorders, obesity, or hirsutism), polycystic ovaries were found in 45%, compared with 17% of age-matched controls.<sup>105</sup> Adolescent females with severe, persistent, or recalcitrant forms of acne, especially in the setting of other signs of androgen excess (i.e., menstrual irregularity and hirsutism) should be screened for this disorder with laboratory examinations (as discussed earlier) and transabdominal ovarian ultrasound. In patients with acne who show rapid development of virilizing signs such as voice deepening, increased muscle mass, or androgenetic alopecia, the evaluation should focus more on a search for a tumor rather than polycystic ovaries.<sup>106</sup> *Metabolic syndrome* (previously referred to as *syndrome X*) describes the clinical presentation of severe insulin resistance, obesity, hypertension, dyslipidemias, and microvascular angina. Occasionally, ovarian hyperandrogenism and polycystic ovaries may occur in this setting.<sup>107</sup> Treatment for PCOS typically consists of hormonal agents and antiandrogens such as spironolactone.

### ACNE ROSACEA

Acne rosacea (also known simply as *rosacea*) is a chronic vascular inflammatory disorder usually limited to the face and characterized by erythema, telangiectasia, papules and pustules, and occasionally, hyperplasia of the sebaceous glands and the soft tissues of the nose (rhinophyma). Rosacea is primarily a disease of adults between the ages of 30 and 50 but may also appear as early as the second decade of life, at times coexisting with acne vulgaris. Rosacea most often manifests as erythema and telangiectasia of the cheeks. A variety of ocular lesions may occur in the setting of rosacea. This association is termed *ocular rosacea* and is characterized by blepharitis, conjunctivitis, episcleritis, iritis, keratitis, and occasionally corneal ulceration and subsequent opacity. Several aberrant responses have been identified in rosacea, including altered toll-like receptor 2 (*TLR2*) expression, enhanced vasodilation triggered by cathelicidin, and greater lesional skin activity of reactive oxygen species.<sup>108</sup>

There are several potential exacerbating factors in rosacea, including sun exposure, stress, cold weather, hot beverages, alcohol consumption, and certain foods.<sup>109</sup> Avoidance of these factors may help prevent flares in certain individuals. Although the etiologies of rosacea and ocular rosacea are not well understood, a primary genetic predisposition is suggested, because single genes may control mediators

involved in rosacea pathways, namely enzymes, neuroendocrine transmitters, and cytokines.<sup>110</sup> Complete clearing of rosacea is rarely achieved, but satisfactory control can usually be accomplished by the use of topical or oral agents. Systemic therapy options include metronidazole, doxycycline, minocycline, tetracycline, or clarithromycin, and the most useful topical therapy appears to be metronidazole.<sup>111</sup> Topical sulfonamide preparations, azelaic acid, and sulfa-based washes may also be useful. Patients with rosacea tend to tolerate topical retinoids and BP poorly. Oral isotretinoin has been effective in patients with severe rosacea, predominantly of the granulomatous type. The telangiectasias may improve after pulsed-dye laser therapy or photodynamic therapy with red light, and recently a topical vasoconstrictor (brimonidine gel) was approved for the facial erythema of rosacea. Rhinophyma, if it develops, is a difficult finding to treat and usually requires aggressive dermatologic surgical procedures with or without laser surgery.

Although clinically classic acne rosacea does not typically occur in young children, two entities that do classically occur in childhood may be related: periorificial dermatitis and idiopathic facial aseptic granuloma (IFAG). These are discussed in more detail below.

### POMADE ACNE

A variety of external agents can induce acne-like eruptions upon repeated exposure to the skin of susceptible persons. These include greasy or oily sunscreen preparations, heavy make-up bases, and grooming agents. An acneiform eruption induced by various grooming substances used on the scalp has been termed *pomade acne*. It is usually seen on the forehead and temples and consists of numerous, closely set, closed comedones. The cheek and chin may also be involved if the agent has been applied over the entire face. Pomade acne may in fact represent true acne vulgaris potentiated by the use of occlusive products. It usually responds to standard acne therapy along with discontinuation of the offending comedogenic preparation.

### ACNE COSMETICA

Acne cosmetica is a variant of acne described in women, usually women who are older than 20 years of age, that is attributed to the frequent or heavy use of cosmetics,<sup>112</sup> particularly those containing lanolin, petrolatum, certain vegetable oils, butyl stearate, isopropyl myristate, sodium lauryl sulfate, lauryl alcohol, or oleic acid. The lesions are predominantly small, scattered, closed comedones on the face. Although common in women without a history of acne, those with a history of adolescent acne seem to be the most susceptible. A prominent feature is a coarse facial appearance associated with prominent dark follicles that is often more distressing to the patient than the actual acne lesions themselves. The most extensive eruptions are seen in women who attempt to mask the lesions under a heavy coating of cosmetics. Fortunately, most cosmetic companies today are aware of the problem of comedogenicity and many cosmetics are now marketed as "noncomedogenic." A variant of acne cosmetica, consisting of deep-seated nodules and closed comedones that heal very slowly with hyperpigmentation, may occur after facial beauty treatments.<sup>113</sup>

### ACNE EXCORIÉE

Acne excoriée is a form of acne most commonly seen in adolescent girls. It is a self-inflicted skin condition in which the patient feels compelled to pick real or imagined acneiform lesions, which then propagates the disorder.<sup>114</sup> Associated comorbidities may include obsessive-compulsive disorder, anxiety, body dysmorphic disorder, substance use disorders, eating disorders, trichotillomania, kleptomania, compulsive buying, and borderline personality disorder.<sup>115</sup> Patients usually spontaneously admit the self-inflicted nature of the condition, unlike most artifactual dermatoses<sup>114,116</sup> (see Chapter 26). Acne excoriée is often precipitated by emotional stress. Excoriation or squeezing of acne lesions may vary from mild to moderate irritation (Fig. 8-19) to severe scarring and occasional gross mutilation. Therapeutic options include behavioral modification or pharmacologic therapies, including selective serotonin reuptake inhibitors, doxepin, clomipramine, pimozide, and olanzapine.<sup>115,117</sup>



**Figure 8-19** Acne excoriée. Note the numerous excoriated and crusted papules of the forehead.

### PYODERMA FACIALE

Pyoderma faciale is a relatively rare condition that presents with the sudden onset of coalescent fluctuant cysts, nodules, and papulonodules with draining sinuses. It is usually confined to the face and occurs exclusively in postadolescent females. Pyoderma faciale seems to represent a severe form of rosacea, and isotretinoin is the most effective therapy, especially when used in combination with corticosteroids.<sup>118,119</sup> Most patients develop scarring as a sequela.<sup>120</sup> Although it is usually sporadic, a patient with concomitant erythema nodosum has been reported.<sup>121</sup>

### ACNE CONGLOBATA

Acne conglobata is a severe suppurative form of acne vulgaris that is usually chronic and seen in men (especially African-Americans) between 18 and 30 years of age. It is characterized by cysts, abscesses, and sinus tracts and often heals with cosmetically disfiguring keloidal scars. Axial and/or peripheral arthritis may be associated, and the latter tends to involve large joints in an oligoarticular pattern.<sup>122</sup> Treatment is challenging, and may include nonsteroidal anti-inflammatory drugs (NSAIDs), prednisone, methotrexate, penicillamine, and isotretinoin.

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is an association of musculoskeletal disorders (synovitis, arthritis, hyperostosis, osteitis) with skin conditions, including palmoplantar pustulosis and acne conglobata.<sup>123,124</sup> Sacroiliitis may also occur, with or without hidradenitis suppurativa (HS) (see below) or a peripheral arthropathy.<sup>125,126</sup> Skin involvement is very common in SAPHO syndrome and may occur before or after the onset of bone and joint symptoms. Palmoplantar pustulosis appears to be the most common associated skin finding,<sup>127</sup> but the diagnosis is based on the typical oligoarticular findings (including erosions and joint space narrowing) in the absence of infectious or other etiologies, and skin findings are not required.<sup>127</sup> Acne occurs in around 25% of patients. The most common skeletal site of involvement in adults is the anterior chest wall. Treatment options for SAPHO syndrome may include NSAIDs, steroids, joint injections, antibiotics, methotrexate, colchicine, bisphosphonates, infliximab, and surgical interventions.<sup>122,128</sup>

### ACNE WITH FACIAL EDEMA

Acne may at times be associated with an inflammatory edema of the middle face (cheeks, forehead, periorbital areas, base of the nose, and glabella). Although its pathogenesis is unknown, it is believed to be a manifestation of chronic cutaneous inflammation and edema, analogous to that occurring in the legs of patients with recurrent cellulitis and venous insufficiency. This complication, which tends to be unresponsive to oral antibiotics or topical therapy, may respond to oral corticosteroids and isotretinoin.<sup>129</sup>



**Figure 8-20** Periorificial dermatitis. Numerous erythematous papules in a perioral distribution.



**Figure 8-21** Periorificial dermatitis. Erythematous papules and papulopustules and hyperpigmented macules of the inferior eyelid and periorbital region.

## PERIORIFICAL DERMATITIS

Periorificial dermatitis (known traditionally as *perioral dermatitis*) is a fairly common acneiform condition in children as well as young women, in whom it was originally described. Patients exhibit erythematous discrete papules and papulopustules distributed in the perioral (Fig. 8-20), nasolabial, and periocular (Fig. 8-21) locations. Occasionally, flesh-colored papules or nodules may be present.<sup>130</sup> As the papules resolve, they may be replaced by a diffuse redness or erythematous scale.

Some consider periorificial dermatitis to be a juvenile form of acne rosacea and in particular the subtype of ocular rosacea, in part related to the overlapping histologic features in these conditions. The etiology of periorificial dermatitis is unknown, but in many patients, use of mid- to high-potency topical corticosteroids seems to be related to the pathogenesis.<sup>131,132</sup> In one retrospective study of 79 children with the disorder, 72% had a history of previous topical, inhaled, or systemic steroid exposure.<sup>133</sup> However, periorificial dermatitis also occurs in children who have no preceding history of corticosteroid therapy. Blepharitis, conjunctivitis, chalazion and hordeolum (stye) (Fig. 8-22) may occur in children with periorificial dermatitis and account for the significant clinical overlap with ocular rosacea.<sup>134</sup>

Granulomatous periorificial dermatitis is a less common variant of periorificial dermatitis and is characterized by discrete yellow-brown papules (Fig. 8-23), less prominent erythema, and a granulomatous



**Figure 8-22** Hordeolum (stye) in a patient with periorificial dermatitis. This toddler male had a history of recurrent perioral and periorbital papules and pustules, as well as recurrent styes.



**Figure 8-23** Granulomatous periorificial dermatitis. Note the translucent quality of the erythematous papules and the nasolabial fold involvement.

infiltrate on histologic examination. In addition to facial involvement, patients with this disorder may have extrafacial lesions clinically and histologically identical to the facial ones.<sup>135</sup> Ocular features such as those as previously listed may also be present. Most reported cases of granulomatous periorificial dermatitis have been in prepubertal children, especially in those with a preceding history of topical corticosteroid application to the affected areas. Some patients have been initially misdiagnosed as having sarcoidosis, based primarily on histopathological findings. Nonetheless, sarcoidosis and Blau syndrome (see Chapter 25), an entity that may be difficult to distinguish from sarcoidosis, may be in the differential diagnosis in patients with more extensive periorificial dermatitis (and with more generalized involvement).

Periorificial dermatitis is generally self-limited, although resolution may take months to years, and the lesions may occasionally heal with scarring. Treatment options include topical antibiotics (the most effective being metronidazole, erythromycin, or sulfur-based products) and in more severe cases, oral erythromycin or tetracyclines (in patients >8 years of age). In patients treated with oral antibiotics, treatment should be continued for a minimum of 6 to 8 weeks, with gradual tapering, in an effort to avoid the rapid rebounding that is commonly seen with shorter courses of therapy. If erythromycin is used (i.e., in younger children), enteric-coated preparations are recommended and generally well tolerated.

### IDIOPATHIC FACIAL ASEPTIC GRANULOMA

Idiopathic facial aseptic granuloma (IFAG) was initially described in the French literature as *pyodermitre froide du visage* and believed to be a pyoderma.<sup>136</sup> More recently it has been viewed as a possible manifestation of granulomatous rosacea in childhood.<sup>136–138</sup> The possible link of IFAG to rosacea is based on its association with relapsing chalazions, facial telangiectasias, erythema and flushing, conjunctivitis and conjunctival hyperemia, as well as its response to therapies traditionally used in rosacea.<sup>138–140</sup> IFAG presents as a large inflammatory nodule, often solitary, on the face (usually the cheek) of a child. Histologic evaluation reveals follicular and perifollicular inflammation with granulomas, a similar picture to that of granulomatous rosacea. Lesions of IFAG resolve spontaneously in some patients, but others may require treatment. Reported therapies for the condition have included oral antibiotics (erythromycin or tetracycline-class antibiotics), oral metronidazole, and topical azelaic acid or metronidazole. Fortunately, most lesions resolve without scarring.

### FORDYCE SPOTS

Fordyce spots are a relatively common benign condition characterized by minute yellow to yellow-white macules and globoid papules distributed on the vermillion region of the lips and the buccal mucosa. Other less common locations include the glans penis or labia minora. Fordyce spots are composed of “free” (i.e., not associated with hair follicles) sebaceous glands, and they probably represent a normal anatomic variant. They may present or become more prominent during puberty. Fordyce spots are asymptomatic, and treatment is unnecessary.

## Disorders of the Apocrine Glands

Apocrine sweat glands are found in only a few areas: the axillae, anogenital region, and areolae of the breasts. They are poorly developed in childhood but begin to enlarge with the approach of puberty, triggered by androgen production. Apocrine secretion is sterile and odorless when it initially appears on the cutaneous surface. Associated odor develops as a result of bacterial decomposition of the secreted substances.

### FOX–FORDYCE DISEASE

Fox–Fordyce disease (also known as *apocrine miliaria*) is a chronic papular eruption of apocrine gland-bearing areas, principally the axillae, the breast areolae, and the pubic and perineal regions. It is seen primarily in young women and is a disorder of unknown etiology. It appears to be related to apocrine sweat retention associated with obstruction and rupture of the intraepidermal portions of the affected apocrine glands. Fox–Fordyce disease is usually seen in postpubescent females and is quite rare in prepubertal children owing to quiescence of the apocrine glands.

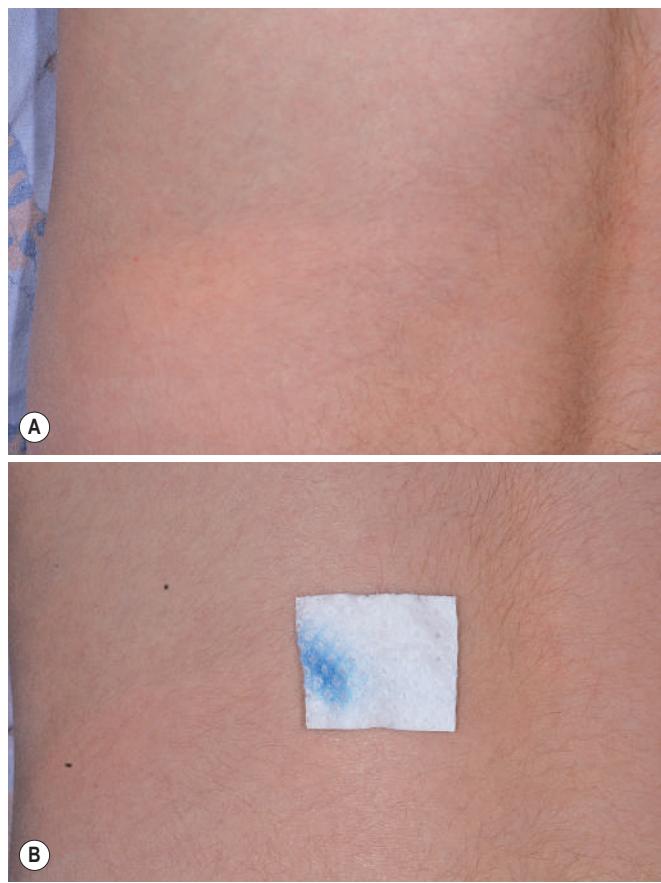
This disorder presents with dome-shaped, flesh-colored to erythematous follicular papules (Fig. 8-24) in the affected areas. Pruritus may be severe, is often paroxysmal, and is aggravated by emotional stress. Treatment is notoriously difficult and may include topical or intralesional corticosteroids, topical antibiotics, or topical retinoids. Topical pimecrolimus was helpful in one reported patient.<sup>141</sup> Surgical excision of the affected areas is occasionally necessary in severely afflicted patients.

### CHROMHIDROSIS

Chromhidrosis is a rare disorder in which the sweat appears colored. It typically involves the apocrine glands (apocrine chromhidrosis), although eccrine chromhidrosis may also occur, albeit less often. The etiology of chromhidrosis is unclear, although it may be associated with drug ingestion in some patients. The reported colors include yellow, blue (Fig. 8-25), green, red, and black. *Pseudochromhidrosis* refers to chromhidrosis occurring as the result of an extrinsic factor, such as skin surface chemicals found in dyes (e.g., from clothing) and other colored chemicals or from chromogenic organisms, including



**Figure 8-24** Fox–Fordyce disease (apocrine miliaria). Small, round, follicular papules in the axilla of an adolescent girl.



**Figure 8-25** Chromhidrosis. This 9-year-old boy had diffuse cutaneous pigmentation that improved after showering but rapidly reaccumulated. Note the blue hue to the skin, highlighted by the normal-colored stripe seen after rubbing (**A**) and the accumulation of blue pigment on the alcohol pad used to rub (**B**). Surface cultures for bacteria and fungi were negative, but some improvement was noted after antifungal therapy.



**Figure 8-26** Hidradenitis suppurativa. Erythematous papules, cysts, nodules, and sinus tracts are seen in the axilla of this adolescent male.

*Corynebacteriae* (which may result in red pseudochromhidrosis), *Bacillus* spp., and *M. furfur* (the latter two associated with blue pseudochromhidrosis).<sup>142,143</sup> Treatment for chromhidrosis is difficult and may include topical antiperspirants, capsaicin, and botulinum toxin type A.<sup>144–148</sup>

### HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa (HS) is a chronic suppurative and scarring disease that primarily involves apocrine gland-bearing skin in the axillary, inguinal, and anogenital regions. The breasts and scalp are less commonly involved. HS affects African-Americans and females more often than Caucasians or males, usually develops after puberty, and has traditionally been ascribed to plugging of the apocrine duct and associated bacterial infection. Prepubertal individuals may occasionally be affected.<sup>149</sup> Studies have more recently suggested that the primary event may be a folliculitis with secondary involvement of the apocrine glands.<sup>150,151</sup> Some authors have thus suggested the alternative name, *acne inversa*. The etiology of HS is poorly understood. Genetic factors, hormonal influences, obesity, smoking, and tight-fitting clothing have each been hypothesized to play a role.<sup>151,152</sup> Dysregulation of the immune response may be implicated and is supported by the beneficial effect of biologic agents in some patients, studies demonstrating upregulation of some immune components such as *TLR2*, and the observed potential association with other inflammatory conditions such as Crohn disease.<sup>153</sup> Familial HS has been shown to segregate in an autosomal dominant manner and may be associated with mutations in the  $\gamma$ -secretase genes, which include *NCSTN*, *PSENEN*, and *PSEN1*.<sup>154–157</sup> These observations offer insight that may facilitate the development of new therapies.

The earliest clinical finding in HS is a painful, inflammatory abscess-like swelling, usually 0.5 to 1.5 cm in diameter, in the affected apocrine area(s). Within hours to days, the abscess enlarges and may open onto the overlying skin, resulting in purulent drainage. With further development and enlargement of abscesses, sinus tracts form (Fig. 8-26) and eventual scarring ensues with the development of deep fibrosis. Hypertrophic scarring may be seen, as may open comedones (Fig. 8-27). HS may be extremely debilitating in severely afflicted patients, with chronic pain, drainage, and secondary infection. Bacteriologic study of early lesions often reveals coagulase-positive staphylococci or streptococci, probably representing secondary infection. Occasionally *Escherichia coli*, *Pseudomonas aeruginosa*, or other Gram-negative organisms contaminate lesions. HS has a significant impact on quality of life and has been shown to result in more impairment than found with several other dermatologic conditions including chronic urticaria, psoriasis, and atopic dermatitis.<sup>158</sup>

Therapy for HS may be challenging. Management must be individualized based on the severity of disease and symptomatology. Initial



**Figure 8-27** Hidradenitis suppurativa. Sinus tracts with chronic scarring and cyst-like papules in the inguinal region of a young boy with chronic disease. Note the associated open comedones.

measures include antibiotics (especially tetracyclines) and local wound care. Topical clindamycin, intralesional steroid injections, oral cyclosporine, and combination oral clindamycin-rifampin therapy have been reported as useful.<sup>153,159,160</sup> Incision and drainage may be useful in certain instances, but for more severe cases surgical modalities are generally necessary. These include local excision, unroofing of lesions with marsupialization, and wide excision with primary or secondary closure, skin grafting, or flaps.<sup>161,162</sup> Carbon dioxide or neodymium:yttrium-aluminum-garnet (Nd:YAG) laser therapy are other options that seem to be quite effective.<sup>160,163</sup> Low efficacy or a high risk-to-benefit ratio have been suggested as possible limitations for isotretinoin and the tumor necrosis factor (TNF)- $\alpha$  inhibitors etanercept and infliximab in this setting,<sup>164–166</sup> although these agents, as well as adalimumab, have been demonstrated helpful in some studies.<sup>160,167–169</sup>

Several disorders have been described in which HS is present in conjunction with other inflammatory processes. These presentations seem to fall under the umbrella of auto-inflammatory disorders (see Chapter 25). The association of pyoderma gangrenosum, acne and HS (PASH) was described as a syndrome sharing some clinical overlap with pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome (see Chapter 25) but lacking the joint inflammation and with the added feature of suppurative hidradenitis in skin folds.<sup>170</sup> Whereas PAPA syndrome is related to mutations in the *PSTPIP1* gene, no mutations (aside from some microsatellite repeats of unclear significance in the promoter region) were found in this original cohort with PASH syndrome, nor were there mutations found in other genes linked to several other auto-inflammatory disorders. The association of pyogenic arthritis with pyoderma gangrenosum, acne, and hidradenitis suppurativa (PAPASH) has significant clinical overlap with PASH, and in the originally reported patient a missense mutation in the *PSTPIP1* gene was noted and felt to be related to the clinical presentation.<sup>171</sup> A patient has also been reported with the findings of pyoderma gangrenosum, acne, suppurative hidradenitis, and axial spondylarthritis, for which the author proposed the term PASS.<sup>172</sup> The clinical overlap in these described associations highlights the need for continued study of the clinical presentations and molecular bases.

## Disorders of the Eccrine Glands

The eccrine sweat glands are distributed over the entire skin surface and are found in greatest abundance on the palms and soles and in the axillae. They represent the principal means of maintaining homeostatic balance by evaporation of water. Their secretion depends on their sympathetic nerve supply, which is controlled by various stimuli, including thermal and emotional types. By these mechanisms the quantity and quality of sweat may be varied. Disorders associated with decreased eccrine sweating (i.e., ectodermal dysplasia) are discussed in Chapter 7.

### HYPERHIDROSIS

Hyperhidrosis (idiopathic hyperhidrosis or primary pediatric hyperhidrosis) is a disorder characterized by the excessive production of sweat in response to heat or emotional stimuli and not related to an underlying disease or drug toxicity. It is a poorly understood disorder, and the clinical spectrum ranges from a mild increase over the normal level of physiologic sweating to an extreme, debilitating expression of the disease. Such extreme sweating may be socially embarrassing and occupationally disabling and may negatively affect the patient's psychological well-being.<sup>173,174</sup> Hyperhidrosis may be palmoplantar and/or axillary and in rare instances, generalized. In patients with these forms of idiopathic hyperhidrosis, neurovascular or metabolic abnormalities are absent. Idiopathic localized unilateral hyperhidrosis is a rare form of hyperhidrosis localized to a sharply demarcated area on the face or upper extremities of an otherwise healthy individual.<sup>175,176</sup> Auriculotemporal nerve (Frey) syndrome is the constellation of facial flushing and hyperhidrosis in response to gustatory stimuli and is discussed in Chapter 12.

There are a variety of treatment options for idiopathic hyperhidrosis (Table 8-6). The first-line therapies are topical, and consist of both OTC and prescription-strength antiperspirant preparations. The active

ingredient in many of these is either aluminum chloride or formaldehyde. These products are best applied to dry skin at bedtime, and their effect may be potentiated when they are used along with plastic wrap occlusion overnight (when practical). However, for some patients occlusion results in more irritation. Systemic anticholinergic agents such as glycopyrrolate or propantheline bromide are often useful but may occasionally be limited by their side-effect profiles, which include dry eyes, dry mouth, and bowel and bladder dysfunction. Oral glycopyrrolate appears to be very effective and well tolerated in children with hyperhidrosis. It is usually started at a dose of 1 mg taken once to twice daily and may be titrated to a maximal dose of 6 mg daily (usually divided into twice or three times daily dosing). In a series of 31 pediatric patients (between 9 and 18 years of age) treated with oral glycopyrrolate, 90% reported improvement, and nearly three-quarters reported no side effects, with dry mouth and dry eyes reported by 26% and 10% of patients.<sup>177</sup> The  $\alpha$ -adrenergic receptor agonist clonidine has also been used for hyperhidrosis, and in one series of 13 patients receiving this therapy, the response rate was 46%.<sup>178</sup> Sedative agents such as diazepam may be useful before an anxiety-provoking event, but their continual use is not recommended.

Iontophoresis is a successful therapy for some patients. This therapy utilizes a small device that delivers a direct current utilizing tap water (with or without anticholinergic agents) as the conductive medium. Its proposed mechanism of action is the development of keratotic plugs in the eccrine sweat ducts, and its effect may last up to 6 weeks between treatments. This treatment appears to be quite safe, with side effects limited to dryness and fissuring of treated sites. Iontophoresis units (Drionic, General Medical Co., Los Angeles, CA) are available without a prescription via mail or internet ([www.drionic.com](http://www.drionic.com)).

Botulinum toxin type A, injected either intradermally or "intracutaneously" (more superficial injections), has been demonstrated to be quite effective in the treatment of axillary or palmoplantar hyperhidrosis.<sup>176,179,180</sup> Studies have revealed improved quality of life and an excellent safety profile of this modality.<sup>180-182</sup> Botulinum toxin type B has also been efficacious for this condition but may be more limited by injection site pain and autonomic side effects. In patients with severe and recalcitrant idiopathic hyperhidrosis, surgical therapy may be indicated. Thoracoscopic sympathectomy (or endoscopic thoracic sympathectomy) is the traditionally utilized procedure, although postoperative compensatory and gustatory sweating may be a problem.<sup>183-186</sup> Up to 20% of patients may have such severe disabling compensatory sweating that they regret having had the procedure.<sup>187</sup>

### DYSHIDROSIS

*Dyshidrosis* (dyshidrotic eczema or pompholyx) is the term applied to a condition of recurring vesiculation of the palms, soles, and lateral aspects of the fingers in which hyperhidrosis is often associated. It is not a primary disorder of eccrine glands but rather a type of eczematous eruption. It is discussed in more detail in Chapter 3.

### ANHYDROSIS

Anhidrosis is the abnormal absence of (or in the case of hypohidrosis, decrease in) perspiration from the surface of the skin in the presence of appropriate stimuli, which may result in hyperthermia. This condition may be caused by a deficiency or abnormality of the sweat glands (as in hypohidrotic ectodermal dysplasia; see Chapter 7) or of the nervous pathways from the peripheral or central nervous system leading to the sweat glands (as in syringomyelia, leprosy, anticholinergic drug therapy, or sympathectomy). Cool baths, air conditioning, light clothing, and reduction of the causes of normal perspiration help to relieve symptoms.

In congenital insensitivity to pain with anhidrosis (CIPA), also known as *hereditary sensory and autonomic neuropathy type IV*, patients have recurrent episodes of fever, anhidrosis, absence of reaction to noxious stimuli, self-mutilating behavior, and mental retardation. These patients commonly show evidence of oral self-mutilation, including biting injuries and scarring of soft tissues of the mouth and oral mucosa.<sup>188</sup> They are prone to infections of the skin and skeleton, most often caused by *S. aureus*.<sup>189</sup> This autosomal recessive condition

**Table 8-6 Therapeutic Options for Primary Hyperhidrosis**

Treatment	Comment
Topical antiperspirants	Aluminum chloride, formaldehyde, others Both OTC and prescription strengths Usually applied at bedtime
Oral anticholinergic agents	Glycopyrrolate, propantheline bromide, oxybutynin May be limited by side effects (dry eyes, dry mouth, bowel/bladder dysfunction) Clinical experience greatest with glycopyrrolate
Other systemic agents	Clonidine, calcium channel blockers, benzodiazepines
Iontophoresis	Safe and well tolerated Tap water utilized, with or without anticholinergic agents Efficacy variable
Botulinum toxin types A or B	Injected intradermally or intracutaneously Effective, but painful Often requires repeat injections at 3–6 month intervals
Thoracic sympathectomy	Reserved for patients with severe or recalcitrant disease Postoperative compensatory sweating may occur Video-assisted surgery: quicker and fewer complications

Modified from Stolman LP. Treatment of hyperhidrosis. Dermatol Clin 1998;16(4):863-9; and Gelbard CM, Epstein H, Hebert A. Primary pediatric hyperhidrosis: a review of current treatment options. Pediatr Dermatol 2008;25(6):591-8. © 2008 by John Wiley & Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.  
OTC, Over the counter.

has been ascribed to mutations in the *NTRK1* (*TRKA*) gene as well as the *SCN9A* gene. Defects in the *NTRK1* gene, which encodes the receptor tyrosine kinase for nerve growth factor, impair intracellular signal transduction in response to nerve growth factor.<sup>190</sup> The *SCN9A* gene is one of the nine genes encoding voltage-gated sodium channels, which play a crucial role in converting mechanical or chemical stimuli into electrical signals within excited cells. Nav1.7 is the sodium channel encoded by the *SCN9A* gene, and mutations have also been linked to primary erythromelalgia (PE) (see Chapter 12) and paroxysmal extreme pain disorder (PEPD).<sup>191</sup>

## BROMHIDROSIS

Bromhidrosis is an embarrassing malodorous condition in which an excessive and usually offensive odor emanates from the skin. It may be of two types: (1) apocrine, resulting from bacterial degradation of apocrine sweat; or (2) eccrine, from the microbiologic degradation of stratum corneum softened by excessive eccrine sweat.

The term *apocrine bromhidrosis* refers to an exaggeration of the axillary odor normally noted by all postpubertal individuals. *Eccrine bromhidrosis* refers to the excessive odor produced by bacterial action on the stratum corneum when it becomes macerated by eccrine sweat. This disorder occurs primarily on the plantar surfaces of the feet and intertriginous areas, particularly the inguinal region. Eccrine bromhidrosis may also occur in association with metabolic disorders including phenylketonuria, maple syrup urine disease, and isovaleric academia.

Bromhidrosis is best managed by regular thorough cleansing (preferably with an antibacterial soap), the use of commercial deodorants and antiperspirants, the application of topical antibiotics as necessary, and frequent changes of clothing. Plantar bromhidrosis may be associated with pitted keratolysis (see Chapter 14).

## MILIARIA

Miliaria (see Chapter 2) is a common dermatosis caused by sweat retention and is characterized by a papulovesicular eruption secondary to prolonged sweating with obstruction of the eccrine ducts. The pathophysiologic events that lead to this disorder are keratinous plugging of eccrine ducts followed by disruption of the normal escape of eccrine sweat into the skin. The clinical findings vary depending on the depth of obstruction of the eccrine duct within the skin. The three forms of miliaria are miliaria crystallina (sudamina), miliaria rubra (prickly heat), and miliaria profunda. The incidence of miliaria is greatest in the first few weeks of life, owing to a relative immaturity of the eccrine ducts that favors poral closure and sweat retention. In addition, older infants and children may develop miliaria in any situation predisposing them to increased sweating and/or skin obstruction (i.e., warm summer climates, swaddling with several layers of clothing during winter months, febrile illnesses).

Miliaria crystallina is characterized by clear, thin-walled, noninflammatory vesicles, 1 to 2 mm in diameter, occurring in crops on otherwise normal-appearing skin. The vesicles are asymptomatic and occur most often in intertriginous areas, particularly on the neck and axillae, or on parts of the trunk covered by clothing. Lesions of miliaria crystallina are highly characteristic and easily differentiated from other vesicular diseases. When the diagnosis is in doubt, rupture of vesicles with a fine needle results in release of the clear, entrapped

sweat. The obstruction in miliaria crystallina is quite superficial, either within or just beneath the stratum corneum.

Miliaria rubra (prickly heat) is the most common form of miliaria. These lesions have a predilection for occluded areas of skin, especially the upper trunk, back, volar aspects of the arms, and body folds. The face may also be involved. Clinically there are discrete but closely aggregated, small erythematous papules or papulovesicles (see Chapter 2, Fig. 2-8). The lesions of miliaria rubra are always nonfollicular, which helps to differentiate this disorder from folliculitis. Viral exanthems and drug reactions may sometimes be in the clinical differential diagnosis, but the distribution of lesions combined with the history and physical examination usually allow for distinction. Miliaria pustulosa is a variant of miliaria rubra consisting of distinct superficial pustules that are also not associated with hair follicles. Lesions tend to occur in areas of skin that have had previous inflammation and often appear coexistent with lesions of miliaria rubra.

Miliaria profunda is a more pronounced form of miliaria quite uncommon outside of the tropics. This disorder usually follows repeated episodes of miliaria rubra and is characterized by firm, white, 1- to 3-mm papules. This papular presentation is related to the deep level of obstruction. Lesions are most prominent on the trunk and proximal extremities, and this form of miliaria is extremely rare in infants and children.

The key to the management of miliaria is prevention by avoidance of excessive heat and humidity. In infants, all that is generally required is parental reassurance and advice on proper clothing and temperature regulation. The lesions of miliaria are self-limited, but simple strategies such as cool baths, light clothing, and use of air conditioning can make the patient more comfortable while awaiting resolution. Topical preparations are of little value and in fact may further propagate the condition by compounding eccrine duct obstruction.

The complete list of 195 references for this chapter is available online at <http://expertconsult.inkling.com>.



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Because of the increasing public awareness and incidence of skin cancer, physicians are often consulted regarding tumors of the skin. In children, the vast majority of cutaneous tumors are benign, and their importance lies predominantly in the cosmetic defect they may create or in their occasional association with systemic disease. Malignant skin lesions, however, despite their relative rarity in children, cannot be completely disregarded or ignored. Each lesion in children, as in adults, must be assessed individually with a consideration of its cosmetic effect, its possible association with systemic manifestations, and its capacity for malignant degeneration.

Cutaneous tumors can be differentiated into those arising from epidermal (or mucosal) cells, from melanocytes, from the epidermal appendages, or from dermal or subcutaneous cells or tissues. The latter category includes tumors of fibrous, neural, vascular, fatty, muscular, and osseous tissues. Skin tumors can also be divided into benign (the vast majority of lesions in children) and malignant. The term *nevus* (plural *nevi*) has a broad meaning in dermatology. Strictly defined, this term refers to a circumscribed congenital abnormality of the skin. When this term is used, therefore, it is appropriate to include a qualifying adjective (i.e., epidermal nevus, melanocytic nevus, or vascular nevus), thus specifying the cell of origin. In commonplace practice, however, the term *nevus* is usually used to imply a benign tumor of pigment cells (melanocytes). Hence to many practitioners, a nevus is the same as a "mole."

In this chapter, we will discuss several cutaneous tumors (and corresponding tumor syndromes where applicable). Pigmented lesions are discussed as a separate entity apart from the above classification, given their high incidence.

## Pigmented Lesions

Pigmented lesions, especially melanocytic nevi (moles), are the most common neoplasms found in humans. In this section, we will discuss melanocytic nevi (both congenital and acquired) and several variants, including dysplastic, Spitz, and halo types. Nevus spilus and Becker nevus, two distinct pigmented lesions, will also be discussed, as will malignant melanoma (MM), which although rare in childhood, does occasionally occur.

### MELANOCYTIC NEVI

Melanocytic nevi are extremely common skin neoplasms composed of "nevocytes" or nevus cells that are believed to be slightly altered melanocytes. The melanocyte is a dendritic cell that produces melanin and transfers it to keratinocytes (epidermal cells) and hair cells, thus supplying the normal brown pigment to skin and hair. Both melanocytes and nevus cells are of neural origin. Melanocytes originate in the neural crest and early in fetal life migrate from there to the skin. After birth some melanocytes occasionally remain in the dermis of certain races (Asians, Native Americans, African-Americans, and individuals from the Mediterranean region), where they may appear as Mongolian spots (see Chapter 11). Blue nevi and the nevi of Ota and Ito (see Chapter 11) also represent examples of arrested melanocytic migration in which the melanoblasts remain in the dermis.

Melanocytic nevi can be either congenital (described in more detail below) or acquired. Acquired nevi usually appear after infancy, increase in size and number during early childhood, and peak during the third or fourth decade, with slow involution as aging progresses. The predisposition of an individual to the development of acquired

melanocytic nevi seems to be related to several factors, including skin type, race, genetic predisposition, and ultraviolet light exposure. These lesions tend to be few in childhood, increasing in number with age to a peak in the third decade. Sun exposure, sunburns, and fair skin pigmentation seem to be associated with their development in childhood.<sup>1</sup> In one large cross-sectional study, nevus counts were found to steadily increase with age from a median of three at age 2 years to 19 at age 7 years.<sup>1</sup> High numbers of nevi were associated with moderate sun exposure and outdoor activities. In another study, 5- and 6-year-old children with a history of sunburns or an increased number of holidays in foreign countries with a sunny climate had significantly higher nevus counts than controls without these characteristics.<sup>2</sup> Higher numbers of childhood nevi have been demonstrated in areas of skin chronically exposed to the sun and in children with lighter skin, blond hair, and blue eyes.<sup>3</sup> Higher nevus counts are noted in children who reside in sunny climates (i.e., Australia) when compared with age- and race-matched control children. Melanocytic nevi may also occur in higher numbers in children with a history of leukemia and/or a history of chemotherapy, and in these settings the lesions may occur with greater incidence on acral areas such as the palms and soles.<sup>4-6</sup>

The primary importance of melanocytic nevi lies in their possible transformation into MM. These lesions are felt to be both markers of an increased risk of cutaneous melanoma and in some cases, direct precursor lesions.<sup>7</sup> The annual transformation rate of a single mole into melanoma seems extremely low, with an estimate of 0.0005% or lower for individuals younger than 40 years.<sup>7</sup> Nonetheless, melanocytic nevus cells were seen histologically in proximity to MM in 51% of cases in one study.<sup>8</sup> Genetic analyses of nevi and melanoma reveal nonrandom patterns of genetic alteration (loss of heterozygosity), confirming the notion that the former are precursor lesions for the latter.<sup>9</sup> These findings highlight the relevance of close monitoring of melanocytic nevi for atypical features as well as the importance of sun protection education.

Melanocytic nevi are subdivided into types and clinically described based on the microscopic location of the nevus cells. Accordingly they are classified as junctional, intradermal, or compound lesions. Junctional nevi have proliferation of nevocytes at the dermal–epidermal junction, compound nevi reveal cells at the junction and in the dermis, and intradermal nevi reveal loss of the epidermal component with nests of cells limited to the dermis. Interestingly, these histologic subtypes progress in parallel to the natural history of nevus maturation (junctional nevi early in life, then compound nevi, and finally intradermal nevi with eventual atrophy of the dermal component during later adulthood).<sup>10</sup> Melanocytic nevi have a wide range of clinical appearances. They may occur anywhere on the cutaneous or mucocutaneous surface and may be flat, slightly elevated, dome-shaped, nodular, verrucous, polypoid, cerebriform, or papillomatous.

#### Junctional Nevi

Junctional nevi usually occur as hairless, light to dark brown or black macules (Fig. 9-1). They range from 1 mm to 1 cm in diameter, with a smooth and flat (nonpalpable) surface and preservation of skin furrows. Although most junctional nevi are round, elliptical, or oval and show a relatively uniform pigmentation, some may be slightly irregular in configuration and color. Most junctional nevi represent a transient phase in the development of compound nevi and are found only in children. An exception to this rule, however, is seen on the palms, soles, and genitalia where the lesions often retain their junctional appearance.



**Figure 9-1** Junctional melanocytic nevus. A well-demarcated, tan macule.



**Figure 9-3** Compound melanocytic nevus. Note the coarse, terminal hairs within the nevus.



**Figure 9-2** Compound melanocytic nevus. A well-demarcated, tan papule with some darker speckling centrally.



**Figure 9-4** Intradermal melanocytic nevus. A tan, fleshy papule with adjacent intradermal nevus.

### Compound Nevi

Compound nevi are more common in older children and adults but may also be present in younger children. They may appear similar to junctional nevi but tend to be more elevated and accordingly vary from a slightly raised papule to a larger, papillomatous papule or plaque. They are flesh-colored to brown (Fig. 9-2), may have a smooth or verrucous surface, and may have dark coarse hairs within them (Fig. 9-3), especially when occurring on the face. During later childhood and adolescence, compound nevi tend to increase in thickness and depth of pigmentation. It is at this stage that many children are brought to the physician for evaluation.

### Intradermal Nevi

Intradermal nevi are seen most commonly in adults. They are usually dome-shaped, soft, "fleshy" papules (Fig. 9-4). They may be sessile (attached by a broad base) or more pedunculated (attached by a more narrow base) and range from a few millimeters to 1 cm or more in diameter. Intradermal nevi may be clinically indistinguishable from compound nevi, and their color varies from nonpigmented (flesh-colored) lesions to those of varying shades of brown. They may occur anywhere on the skin surface and are often found on the head and neck; coarse hairs often are present. After the third decade of life, as nevus maturation continues, there is destruction and replacement of nevus cells by fibrous or fatty tissue, and by 70 years of age most individuals have few remaining nevi. In fact, nevi that persist into old age appear to have an increased risk of malignant degeneration.<sup>7</sup>

Treatment decisions regarding melanocytic nevi are usually related to their cosmetic appearance, repeated irritation of the lesion, or fear

of potential malignant transformation. The majority of melanocytic lesions require no treatment; by careful clinical evaluation the patient can often be reassured as to their benign nature. Removal of nevi, when indicated, is best achieved by punch biopsy or complete surgical excision. Any nevus being removed because of concern for malignant degeneration should be removed with a full-depth excision, because microscopic tumor depth is the primary prognostic indicator in MM. Every excised nevus should be subjected to histopathologic examination.

Many authors advocate for the routine excision of pigmented lesions in certain anatomic locations (i.e., palms, soles, scalp, and genitalia), owing to the belief that the likelihood of malignant transformation is greater in these areas. It seems that prophylactic excision of all nevi in these locations is unwarranted. However, lesions in acral sites may reveal atypical clinical and histologic features,<sup>11,12</sup> possibly in relation to repetitive trauma. Recognition of these histologic variations is vital in order to avoid the misdiagnosis of the "acral lentiginous" subtype of MM, which occurs primarily after the seventh decade of life. Additionally, scalp nevi in children (and particularly adolescents) may commonly reveal mild clinical atypia, both clinically and histologically, although the vast majority behave in a biologically benign fashion (see more below).<sup>13</sup> Scalp nevi that reveal significant atypia and/or that may be difficult to monitor clinically, however, may merit excision.

Occasionally, pigmented nevi show recurrence after excision, which may be a significant source of anxiety for the patient, parent, and at times the physician. Recurrent lesions (which have been called *pseudomelanoma* by some) present as circumscribed pigmentation within



**Figure 9-5** Recurrent melanocytic nevus (within a surgical scar). The initial nevus had been incompletely excised.

the surgical scar (Fig. 9-5). This finding is usually not an indication of malignancy but instead represents proliferation of nevus cells from the peripheral epidermis, sweat ducts, or hair follicles. Options for management include close clinical follow-up care (assuming the original pathologic examination revealed no atypical findings) or repeat excision.

#### Meyerson Nevus

The term *Meyerson nevus* (also known as *Meyerson phenomenon* or *halo dermatitis*) refers to a localized eczematous eruption that occurs in the region of a melanocytic nevus and was originally described by Meyerson in 1971.<sup>14</sup> The inflammatory reaction does not appear to be a marker for atypia within the nevus, although there are reports of the phenomenon in association with dysplastic lesions.<sup>15</sup> The Meyerson phenomenon may be associated with acquired or congenital melanocytic nevi (CMN).<sup>16</sup> It has also been described in association with non-melanocytic lesions including nevus sebaceous, dermatofibroma, and smooth muscle hamartoma.<sup>17–19</sup> The Meyerson nevus presents clinically as a scaly erythematous plaque overlying a pigmented nevus. The overlying dermatitis may be treated with a topical corticosteroid, which often leads to complete resolution, enabling closer inspection of the underlying nevus (Fig. 9-6). If left untreated, the dermatitis often resolves spontaneously over time.<sup>20</sup>

#### MELANONYCHIA STRIATA

Melanonychia striata (also known as *longitudinal melanonychia*) is most commonly seen in individuals with darker skin complexions, especially African-Americans, of whom up to 90% may have at least one such streak. It is significantly less common in children with white skin. Melanonychia striata presents as a brown to brown/black linear band of pigmentation on a fingernail (Fig. 9-7) or toenail. The pigmentation extends from the proximal nailfold to the distal margin of the digit, and the width may vary from less than 1 mm to several millimeters. Drugs, pregnancy, trauma, and human immunodeficiency virus (HIV) infection may all be associated with melanonychia striata, although the majority of patients have no underlying association.

Melanonychia striata may represent benign melanocytic hyperplasia (i.e., melanocytic nevus or lentigo) or a nail matrix melanoma. In children, the majority of cases seem to be related to benign lesions,<sup>21,22</sup>



**Figure 9-6** Meyerson nevus. (A) This 9-month-old boy sought treatment for this scaly plaque on the proximal forearm (note the faint outline of the underlying pigmented nevus). (B) At the follow-up examination, the congenital melanocytic nevus can be clearly appreciated after 2 weeks of treatment with a topical corticosteroid.



**Figure 9-7** Melanonychia striata. A 2-mm, evenly pigmented band. Note the absence of pigmentation of the proximal nailfold (negative Hutchinson sign).



**Figure 9-8** Hutchinson sign. Note pigmentation involving both the proximal nailfold and the distal nailfold regions. This patient underwent nail matrix biopsy; the lesion was a compound nevus without atypia.



**Figure 9-9** Early congenital melanocytic nevus. Note the various shades of brown and red in this 2-week-old infant boy.

although the possibility of melanoma must always be entertained. The presence of multiple bands, as occasionally seen in darker races, is reassuring and mitigates against malignancy. Worrisome features may include very dark, broad bands and extension of the pigmentation onto the proximal or lateral nailfolds (Hutchinson sign; Fig. 9-8).<sup>23</sup> Dermatoscopic evaluation may be useful for monitoring in the hands of clinicians experienced in its use, but the patterns and accuracy remain to be confirmed in this setting.<sup>24,25</sup> In patients with melanonychia striata and any such atypical or concerning features, nail matrix biopsy for histologic evaluation should be highly considered. Although this procedure may result in permanent nail plate dystrophy, this risk is justified when concerns for possible melanoma exist.

### CONGENITAL MELANOCYTIC NEVI

CMN represent a special group of melanocytic lesions with an increased risk of transformation to MM. By strict definition, these lesions are present at birth. However, in some patients with small and medium-sized lesions, they may be initially noted sometime during the first year of life rather than immediately at birth. Congenital nevi have been classified traditionally according to their greatest diameter in adulthood. According to this nomenclature, they have been traditionally defined as *small* (<1.5 cm in greatest diameter), *medium-sized* (1.5 to 19.9 cm), or *large* ( $\geq 20$  cm) congenital nevi. An interdisciplinary group of experts in the field developed a consensus-based categorization scheme for CMN that includes modified size categories (again, based on projected adult size) as follows: *small* (<1.5 cm), *medium* (M1: 1.5 to 10 cm; M2: >10 to 20 cm), *large* (L1: >20 to 30 cm; L2: >30 to 40 cm), and *giant* (G1: >40 to 60 cm; G2: >60 cm).<sup>26</sup> This classification includes other descriptors of CMN, including number of satellite nevi, anatomic localization, color heterogeneity, surface rugosity, hypertrichosis, and presence of dermal or subcutaneous nodules. Such a standardized classification scheme will hopefully facilitate collaborative international studies and database development for the study of large and giant CMN.<sup>26</sup>

It is estimated that approximately 1% of newborns have a small congenital nevus, and large lesions occur in around 1 in 20,000 newborns.<sup>27-30</sup> Giant melanocytic nevi occur in 1 in 500,000 newborns.<sup>31</sup> Nevus spilus, or speckled lentiginous nevus (see below), may represent a distinct subtype of congenital melanocytic nevus that presents early in life as a café-au-lait macule, with the development of the more characteristic nevi a bit later in life.<sup>32</sup> Whereas malignant potential may be a primary concern with CMN, the potential psychosocial consequences, especially with large or giant lesions, are significant and may include social difficulties, psychologic morbidities, behavioral and emotional impairment, and predisposition to taunting or bullying.<sup>33</sup>



**Figure 9-10** Congenital melanocytic nevus. A well-demarcated, brown plaque with some pigment variation and hypertrichosis.

Congenital nevi have some characteristic histopathologic features, including extension of nevus cells into the deeper dermis and subcutis, between the collagen bundles (as single cells), and in association with appendages, nerves, and vessels.<sup>34,35</sup> These features may be useful when histologic confirmation of a congenital lesion is desired, but such findings may not be noted in every congenital nevus. This pattern of deep extension is important to keep in mind when surgical intervention of such a lesion is being considered. Activating mutations in the NRAS gene have been noted within congenital nevi, distinct from nevi developing after birth (acquired nevi), which are more likely to reveal mutations in BRAF (see also below).<sup>36,37</sup> In a series of large and giant CMN, NRAS mutations were noted in nearly 95% of cases, whereas in small- and medium-sized CMN, 70% bore NRAS mutations and 30% revealed BRAF mutations.<sup>38</sup> In a series of patients with multiple CMN and neurocutaneous melanosis (see below), both the cutaneous and neural lesions contained missense mutations in codon 61 of NRAS, whereas unaffected tissues and blood were negative for this mutation, suggesting postzygotic mutation in a progenitor cell within the neuroectoderm.<sup>39</sup>

Small and medium-sized CMN usually present as flat, light- to dark-brown or pink macules (Fig. 9-9) or papules or as brown to dark brown, well-circumscribed patches or plaques. They may reveal some pigment variation and the surface may have hair (Fig. 9-10). With time they tend to become more elevated, and coarse dark brown hairs may become more prominent. When an extremity is circumferentially involved with a medium- or large-sized congenital nevus, limb underdevelopment may occur (Fig. 9-11).<sup>10</sup>



**Figure 9-11** Congenital nevus of the lower extremity. Note the limb hypoplasia in the ankle region associated with this circumferential lesion.



**Figure 9-13** Giant congenital melanocytic nevus. Note the marked hypertrichosis and adjacent satellite lesions.



**Figure 9-12** Large congenital melanocytic nevus.

Large CMN are uniformly present at birth and present as dark brown to black plaques, often with a verrucous or cobblestoned surface and hypertrichosis (Fig. 9-12). Color variation is common in these lesions and may make clinical examination for concerning features more challenging. Giant CMN often occur on the posterior trunk and may occupy a significant portion of the skin surface. They may have a dermatomal distribution and may involve an entire upper or lower extremity or the scalp. These lesions have been variably named *coat-sleeve*, *stocking*, *bathing trunk*, or *giant hairy nevi*, depending on their site(s) of involvement. As with large CMN, giant nevi present as large, brown to black plaques with varying degrees of nodularity, color variation, and hypertrichosis (Fig. 9-13). Erosions or ulcerations in these giant lesions may occur (Fig. 9-14), and although once believed to be consistently ominous findings, are often benign and usually not indicative of MM.<sup>40</sup> Large and giant congenital nevi may be associated with cosmetic disfigurement, an increased risk of MM, and underlying neurocutaneous melanosis (see below). These lesions often have associated "satellite" nevi that may be disseminated over the entire skin surface. Satellite nevi are usually tan to brown macules or papules, with varying degrees of hypertrichosis (Fig. 9-15). They may be present at birth or continue to develop during infancy.<sup>30</sup>



**Figure 9-14** Giant congenital melanocytic nevus with erosions. Surface erosion and crusting was present at birth and healed rapidly over a few weeks with topical care.

The congenital nature of nevi is one of several known risk factors for MM, but the exact magnitude of risk remains controversial, especially for small and medium-sized lesions. All congenital nevi should be considered as potential precursors to melanoma. The risk in small and medium-sized lesions seems low, and if melanoma occurs it tends to occur during adulthood.<sup>10,41,42</sup> Factors that might increase the level of concern include atypical clinical features (e.g., deeply or irregularly pigmented or rapidly growing), an abnormal nevus phenotype, or a strong family history of MM. The risk of malignant transformation of congenital nevi in African-American patients is extremely small.<sup>43</sup>



**Figure 9-15** Satellite melanocytic nevi. This patient had a giant nevus of the scalp.

The risk of MM in large and giant CMN appears to be significantly greater than that for small and medium-sized lesions, with melanoma often (but not always) occurring before the age of 5 years.<sup>44,45</sup> It is unclear whether axial lesions pose a greater risk than those occurring on the extremities, as traditionally suggested.<sup>46</sup> When melanoma occurs in patients with large or giant CMN, it may occur within the skin or in extracutaneous sites such as the central nervous system.<sup>47,48</sup> Development of melanoma in satellite lesions is exceedingly unlikely.<sup>47</sup> The overall lifetime risk of development of MM in patients with large CMN has been reported to range from 0% to 31% but is best estimated at between 2% and 10%.<sup>44,45,49–51</sup> In two large systematic reviews of the published data on melanoma risk in CMN, the rate of melanoma was 2% to 2.5% in large CMN and 3.1% in giant CMN.<sup>50,51</sup> In addition to melanoma, other malignancies may occur with increased rates in these patients, including rhabdomyosarcoma, liposarcoma, malignant peripheral nerve sheath tumor, and other sarcomas.<sup>28,47</sup>

Large and giant CMN, particularly those on the head, neck and back, may be associated with a condition termed *neurocutaneous melanosis* (NCM). NCM, as well as melanoma risk, appears to be more common in patients with greater numbers of satellite nevi.<sup>52,53</sup> Patients with NCM have a proliferation of nevus cells in the central nervous system (leptomeningeal melanocytosis), and are predisposed to seizures, MM of the central nervous system (CNS), and neurologic symptoms related to increased intracranial pressure or spinal cord compression. They often seek treatment for symptoms during the first 3 years of life, including lethargy, irritability, headache, recurrent vomiting, seizures, increased head circumference, bulging anterior fontanel, photophobia, papilledema, neck stiffness, and occasionally nerve palsies, particularly of cranial nerves VI and VII. Magnetic resonance imaging (MRI) of NCM reveals focal areas of high signal on T1-weighted images in one or multiple areas of the brain, including the temporal lobes, cerebellum, pons, and medulla.<sup>54,55</sup> T2 shortening may also occur.<sup>55</sup> In one study, 45% of neurologically asymptomatic children with giant congenital nevi had these radiologic findings.<sup>54</sup> However, a questionnaire-based study of 186 patients with large congenital nevi who were imaged revealed that only 4.8% of those with positive MRI findings for NCM were asymptomatic.<sup>56</sup> Hence the exact prevalence of asymptomatic NCM remains unclear. Other findings in children with NCM may include dorsal spinal arachnoid cysts and amygdalar neuromelanosis (that may be associated with intractable seizures).<sup>57–61</sup> Overall, the prognosis for *symptomatic* NCM is poor, with more than 90% of patients dying of the disease and around 70% of those dying before 10 years of age.<sup>48,62</sup>

The management of CMN must be individualized for each patient. There are many factors that must be considered in the decision-

making process regarding surgical excision of such lesions. These include location of the nevus, size, cosmetic issues (and potential psychosocial ramifications), and the risks of anesthesia, MM, and neurocutaneous melanosis.<sup>63</sup> There appears to be less consensus regarding the role of surgical excision of small and medium-sized CMN than that of large lesions. Small congenital nevi with uniform pigmentation, smooth texture, and lack of nodules can be clinically monitored, whereas lesions with atypical or deep pigmentation or uneven textures may warrant surgical excision given the heightened difficulty of melanoma detection in this setting.<sup>28</sup> Other risk factors, such as a strong family history of MM or the presence of numerous atypical-appearing nevi, may influence the decision regarding surgical removal of small and medium-sized CMN. Lesions located in areas that may be difficult to follow clinically, such as the scalp or groin, may be better served by excision, although in the case of benign-appearing lesions, this decision may be delayed until the child is older and the procedure can be performed under local anesthesia.

Large CMN are often treated with full-thickness surgical excision. The primary reason for this recommendation is the potentially decreased risk of malignant transformation, although controlled studies supporting this hypothesis are lacking.<sup>63,64</sup> Unfortunately, excision of large lesions does not usually result in complete removal of all nevus cells, and melanoma may still develop from this residual tissue. In addition, melanoma may develop with increased incidence at extracutaneous sites in these patients, and the significance of neurocutaneous melanosis (if present) must also be factored into this decision. Nonetheless, most still advocate for surgical excision in an effort to reduce the risk of malignancy.<sup>65,66</sup> Removal of these lesions has been refined with the use of tissue expanders and skin grafting, but multiple procedures are usually required. Partial thickness removal techniques (i.e., dermabrasion, dermatome excision, curettage, chemical peels and laser therapy) have been advocated by some, but the impact of these procedures on malignant transformation or clinical surveillance of the lesion must be further defined. They may, however, be reasonable considerations when more aggressive procedures are impractical. There is no consensus on the timing of surgical procedures for large and giant CMN. Although many experts advocate for early referral and initiation of excisional therapy, other considerations may come into play, including anesthesia concerns surrounding neurocognitive effects on the developing brain. Ongoing prospective studies in this arena will hopefully clarify the optimal use and timing of sedation and anesthesia in young children.<sup>64,67,68</sup>

Close periodic clinical surveillance is important for all patients with CMN. Parent education in the importance of sun protection, sunscreen use, and danger signs of atypical nevi or melanoma (see below) is vital. Risks of malignant transformation should be discussed, and parents and patients should be allowed to reach an informed decision regarding therapy. Educational materials regarding moles, melanoma, and sun protection are useful and may be obtained from the American Academy of Dermatology ([www.aad.org](http://www.aad.org)). A multidisciplinary approach must be employed for families of children with large congenital nevi. This includes the primary care physician, dermatologist, plastic surgeon, and diagnostic radiologist. Emotional support should be provided, and the family should be given information on support groups. One such organization is Nevus Outreach ([www.nevus.org](http://www.nevus.org)), which was founded by parents of children with large CMN and offers an annual family conference, newsletters, and a social support network.

### ATYPICAL NEVI/FAMILIAL ATYPICAL MULTIPLE MOLE–MELANOMA SYNDROME

Atypical nevi, also known as *dysplastic nevi*, are defined based on their clinical and/or histologic appearance. These acquired nevi, which often do not present until at or after puberty, are regarded as markers and potential precursors for MM. The incidence of histologically confirmed atypical nevi in patients under 18 years of age is very low,<sup>69</sup> although in children who come from melanoma-prone families, their incidence seems much higher.<sup>70</sup> Clinically these lesions share some or all of the features of MM (Box 9-1). These include larger size and irregularities of color, texture, or borders (Fig. 9-16). Atypical nevi are often larger than common acquired nevi, usually measuring 6 to

**Box 9-1 Risk Factors for Malignant Melanoma in Children**

Familial atypical multiple mole-melanoma (FAMMM) syndrome  
Xeroderma pigmentosum  
Congenital melanocytic nevi  
Atypical (dysplastic) nevi  
Personal history of melanoma  
Family history of melanoma  
High numbers of melanocytic nevi  
Fair complexion  
Excessive sun exposures  
History of blistering sunburns  
History of immunosuppression



(A)



(B)



(C)

**Figure 9-16 (A–C)** Atypical melanocytic nevi. These lesions revealed clinically atypical features, including asymmetry and border and color irregularity. All of them were benign histologically.



**Figure 9-17** “Fried egg” melanocytic nevus. Note the elevated, dark brown papule centrally and surrounding tan macular area.



**Figure 9-18** Cockade nevus. This pattern refers to a central darkly pigmented portion surrounded by an intervening rim of minimal to no pigmentation and an outer rim of darker pigment, giving a target-like appearance. These nevi are usually benign.

15 mm in diameter, and display marked lesion-to-lesion variability, often with a cobblestone appearance or a dark, central papular component surrounded by a lighter tan flatter periphery (the “fried egg” appearance, Fig. 9-17). Other patterns of clinically atypical nevi include the eclipse nevus (tan to hypopigmented center with a darker brown peripheral rim and irregular outer border) and the cockade nevus (target-like morphology with a central pigmented region, an intervening hypopigmented area, and an outer rim of pigmentation; Fig. 9-18).<sup>71</sup> These patterns may occur more with greater incidence on the scalp of children (see below).

Atypical nevi may occur anywhere, especially on sun-exposed sites, but also commonly occur on covered areas such as the back and in unusual locations such as the buttocks, breasts, and scalp.<sup>72</sup> In fact, a fairly high proportion of nevi removed from the scalp may demonstrate histologic features of atypical nevi.<sup>21,73</sup> Individuals with atypical nevi have been demonstrated to have an increased risk of melanoma despite the presence or absence of a family history of melanoma.<sup>74,75</sup> A distinct clinical phenotype characterized by numerous (>100) small, darkly pigmented atypical nevi has been described and termed the *cheetah* phenotype.<sup>76</sup> Longitudinal follow-up study of such patients is very challenging given the similar clinical appearance of several histologic patterns ranging from benign to cytologically atypical.<sup>76</sup>

Scalp nevi in children deserve special mention, as they may be a source of anxiety for parents and clinicians alike. These lesions, which are more common in boys, tend to be somewhat larger in size and may often reveal irregular borders and some color variations (Fig. 9-19).



**Figure 9-19** Scalp nevus. These nevi may be larger and often reveal irregular borders and color variation, although the majority of them are histologically benign.

The observed patterns may include the fried-egg, cockade, and eclipse phenotypes discussed previously, as well as clinically benign nevi patterns. Although scalp melanoma does occur in children, it seems that the majority of these lesions are benign; however, they may reveal mild to moderate atypia microscopically. Dermatoscopic (magnified light) examination may be helpful in demonstrating benign patterns (i.e., globular or reticular–globular pigmentation and perifollicular hypopigmentation).<sup>77</sup> It should be remembered that although the majority of scalp nevi in children are benign, their presence may suggest an increased risk for the development of numerous melanocytic nevi, which itself is a risk factor for MM.<sup>78</sup>

The familial atypical multiple mole–melanoma (FAMMM) syndrome is a disorder of autosomal dominant inheritance in which atypical nevi develop during the late second to third decade of life.<sup>79</sup> It was originally described in 1978 by Clark and colleagues when they noted individuals with increased numbers of melanocytic nevi that displayed atypical clinical and histologic features.<sup>80</sup> Since the original description, FAMMM syndrome has been better characterized as a hereditary cancer predisposition syndrome, entailing not only an increased risk of MM but also other cancers in some kindreds, especially pancreatic cancer.<sup>81–83</sup> FAMMM syndrome is characterized by the familial occurrence of melanoma in combination with multiple dysplastic nevi (>50) in first-degree relatives, although around 10% of the melanoma patients may have very few to no dysplastic nevi.<sup>84,85</sup> It has been estimated that individuals with a family history of FAMMM syndrome and atypical nevi have nearly a 100% lifetime risk of acquiring MM. In addition to melanoma of the skin, these individuals may develop intraocular melanoma. Recent observations of families displaying the association of pancreatic cancer and melanoma have led to the alternative terminology of *FAMMM–pancreatic cancer (FAMMM–PC) syndrome*. The phenotype of these families is variable, however, with several reported members lacking the dysplastic nevus phenotype. Some have therefore suggested the possibility of two distinct hereditary cancer syndromes, FAMMM–PC and the pancreatic cancer/melanoma syndrome (PCMS).<sup>86</sup>

The classic features of FAMMM syndrome are high numbers of melanocytic nevi, often more than 50, some of which are atypical and often have large variability in size (Fig. 9-20), that occur in the setting of a family history of MM in one or more first- or second-degree relatives.<sup>72</sup> Identification of at-risk children is vital, because melanoma may occur before 20 years of age in up to 10% of individuals.<sup>10</sup> Although most of the atypical nevi develop during or after adolescence, prepubertal children may occasionally show the atypical nevus phenotype, particularly in scalp nevi. In fact, the development of scalp nevi during childhood, as well as large nevus counts early in life, may represent early indicators of increased risk for the atypical mole phenotype later in life.<sup>70,87</sup>

There are several known melanoma susceptibility loci, most notably the p16 CDKN2A gene on chromosome 9, which is a tumor-



**Figure 9-20** Multiple atypical melanocytic nevi (familial atypical multiple mole–melanoma [FAMMM] type). This adolescent male had a family history of atypical nevi and malignant melanoma.

suppressor gene responsible for melanoma susceptibility in some kindreds with FAMMM syndrome.<sup>79</sup> Deletion of p16 may play a role in the development of atypical nevi as an early event, as well as in the development of MM (see below).

Management of the patient with atypical nevi should include a thorough family history, total body inspection, and a regular clinical follow-up examination every 6 to 12 months, depending on the individual patient. Patients (and parents) should be educated regarding sun protection, regular skin self-examination, and atypical features of nevi, and surgical excision should be performed for lesions with concerning features. A helpful guideline in monitoring children with many nevi is the “ugly duckling” principle, which dictates that a lesion that stands out from the rest (i.e., markedly darker pigmentation, more irregularity of texture or borders) should be more closely scrutinized and considered for removal. Epiluminescence microscopy (dermatoscopy) is a useful noninvasive instrument that provides magnification of nevi and may be useful in differentiating benign from atypical lesions. It is most often used by dermatologists, and its use requires training and experience in order to provide acceptable sensitivity and reliability. Serial photography of nevi may also be a useful adjunct in the longitudinal follow-up study of patients with multiple or atypical nevi.

## MALIGNANT MELANOMA

The incidence of MM, the most deadly form of skin cancer, continues to rise, and although childhood MM continues to be rare, the incidence in this population may also be rising.<sup>88,89</sup> The lifetime incidence of melanoma is estimated at around 1 in 58 individuals,<sup>90</sup> which is an alarming increase from the incidence of 1 in 1500 estimated in

1935.<sup>91</sup> The challenges of diagnosing MM in children are multiple and include lack of recognition, hesitancy to perform skin biopsies in children, and poor reliability in making the histopathologic diagnosis in this population.<sup>92</sup> Melanoma in individuals under 20 years of age accounts for only 1% to 3% of all MM, and prepubertal cases are even rarer, accounting for 0.3% to 0.4% of all cases.<sup>93-95</sup> Despite this rarity, the course of melanoma, when it does occur in a child, bears the same prognosis as it does in adults.<sup>94,96,97</sup> Importantly, the incidence of pediatric melanoma is increasing at an estimated 1% to 4% per year.<sup>98</sup> Interestingly, many lesions previously thought to be melanomas of childhood are now recognized to be benign Spitz nevi (see below). Congenital MM represents a small subset of all pediatric MM and is extremely rare, with only 23 cases reported in the English literature between 1925 and 2002.<sup>94</sup> It most commonly arises in a congenital melanocytic nevus and less commonly is *de novo* or related to transplacental transmission of MM from the mother.

MM most commonly affects individuals with fair skin, blue eyes, and red or blond hair, particularly those of Celtic origin whose pigment cells have a limited capacity to synthesize melanin. Approximately one-half to 65% of MM arises in a preexisting nevus. Although melanomas may occur in African-American individuals, the incidence is extremely low when compared with that of Caucasians. In African-Americans, tumors usually arise in areas that are lightly pigmented, especially the mucous membranes, nailbeds, or the sides of the palms and soles. Exposure to high levels of sunlight in childhood seems to be a strong determinant of risk for MM, although adult sun exposure also plays a role.<sup>99</sup> Some studies have not supported this “critical risk period” hypothesis of ultraviolet radiation exposure, suggesting that sun protection education should be directed at the entire population with equal effort rather than concentrating solely on younger age groups.<sup>100</sup> However, maintaining a stringent focus on childhood sun protection still seems reasonable, because a large proportion of overall lifetime sun exposure is likely to occur during these years.<sup>101</sup>

The genetics of MM continue to be elucidated, and it is now established that molecular defects in both tumor-suppressor genes and oncogenes may be pathogenetically linked to melanoma.<sup>102</sup> Mutations in the *CDKN2A* (p16) gene predispose a patient to the FAMMM syndrome and have also been noted in families in which only one or two individuals are affected by MM.<sup>103</sup> A subset of melanoma-prone families with *CDKN2A* mutations also manifests an increased risk of pancreatic cancers (as discussed earlier).<sup>83,102</sup> Activating mutations in one of two Ras/mitogen-activated protein kinase pathway genes, *BRAF* or *NRAS*, are present in up to 80% to 90% of melanomas.<sup>104,105</sup> Some of the other genes potentially mutated in melanoma include *PTEN*, *CDK4*, *CCND1*, *KIT*, *p53*, *EphA2*, *ERBB4*, *GRIN2A*, *GRM3*, *MEK1*, *MEK2*, *MITF*, *β-catenin*, and various apoptosis genes.<sup>104-106</sup>

Melanoma is classically categorized according to its clinical and histologic features. The most common forms are superficial spreading, nodular, lentigo maligna (usually confined to adults), and acral lentiginous melanoma. However, pediatric cases of MM often cannot be neatly classified into one of these categories. Pediatric melanoma seems to follow the same distribution patterns as adult melanoma, with head and trunk lesions predominating in boys, and arm and leg lesions predominating in girls. Risk factors for pediatric MM are listed in Box 9-1.

The classic signs of MM are summarized in Table 9-1. Melanoma typically presents with a rapidly enlarging papule or nodule, most often brown to brown-black in color (Fig. 9-21), although blue, red, or white discoloration may also be noted. Importantly, a significant proportion of pediatric melanomas may present in an amelanotic (i.e., pink, white, red, or a combination of these colors) fashion.<sup>107</sup> A halo of hypopigmentation or depigmentation may be present around a primary lesion of MM, although most often these halos occur in the setting of benign nevi (see Halo Nevus section). Melanomas often reveal asymmetry and irregularity of the borders, especially scalloping or notching, and tend to be larger than benign nevi, often (but not always) larger than 10 mm in diameter. Bleeding, itching, ulceration, crusting, and pain may be present. In a recent single-center retrospective review of 70 children (<20 years of age) with melanoma or other atypical melanocytic tumors, several clinical features were highlighted that may contradict the traditional “ABCD” portion of the ABCDE criteria (as shown in Table 9-1). These include the amelanotic

**Table 9-1** Clinical Features (ABCDE Signs) of Malignant Melanoma

Clinical Feature*	Comment
A Asymmetry	The two halves of the lesion are not alike
B Border irregularity	Borders notched, scalloped, irregular
C Color changes	Especially blue, red, black, white
D Diameter >6 mm	Size of a pencil eraser; not applicable to congenital nevi, which are often >6 mm early in their evolution
E Enlargement	Evolutionary change in the lesion

\*See text for important discussion of features that may be more specific to pediatric melanoma.



**Figure 9-21** Malignant melanoma (MM). This small, black papule was noted on this 10-year-old male with fair skin and red hair; excision confirmed a nodular malignant melanoma.

(flesh-colored, pink, or red) nature of the lesions, bleeding, uniformity of color, small diameter (often <6 mm) and *de novo* development (as opposed to arising in an existing nevus).<sup>108</sup> These characteristics should be kept in mind when evaluating children with atypical “bumps” and may facilitate earlier recognition of (and hence therapy for) pediatric MM.

Lymph nodes may be palpable and if present, are an ominous prognostic sign, suggesting metastatic spread. When MM goes undetected and undiagnosed, the lesion proliferates locally and may spread by satellite lesions or extend through the lymphatics or bloodstream, from which it may eventually invade any organ of the body. Once metastatic disease occurs, the prognosis of MM significantly declines.

Early detection of melanoma is germane to long-term survival. The survival rate for children and adults seems to be similar, and the primary determinants of prognosis have traditionally been tumor thickness and depth of invasion.<sup>91,96</sup> The presence or absence of ulceration has been added to the American Joint Committee on Cancer (AJCC) staging system for MM as another important prognostic criterion (the presence of ulceration correlating with poorer prognosis).<sup>109</sup> The pediatrician (or other primary care provider of children) is in good position to observe pigmented skin lesions over time in their patients. Early referral should be considered for any melanocytic lesion that displays substantial growth changes, especially if asymmetry, ulceration, or other atypical features are present. Melanoma is diagnosed by histopathologic examination of skin tissue from biopsy. When MM is suspected, full-thickness excision of the lesion should be performed, as depth of the lesion must be fully visualized in order to assess this prognostic indicator. Shave biopsies or excisions should be avoided in the removal of concerning pigmented lesions.

Surgical excision is the initial step in melanoma management, along with adequately staging the disease. Once the diagnosis of MM is confirmed, the site is reexcised with appropriate margins (0.5 to 3 cm), depending on tumor depth in the initial specimen. Clinically suspected lymph nodes are surgically removed and histologically evaluated. Developments in tracer techniques have enabled sampling of the first lymph node draining the affected skin site (the “sentinel” lymph node), which assists in determining whether to proceed with regional lymph

node dissection for further staging and therapy. This technique, which is usually performed concurrently with reexcision of the primary lesion, allows for accurate staging of the regional lymph nodes with minimal morbidity.<sup>96</sup> In a series of 126 patients younger than 21 years of age who were diagnosed with MM, sentinel lymph node metastases were present in 29%, yet the survival was equal to or better than that reported for adults, suggesting that the biology of pediatric melanoma may be different than that in adult melanoma.<sup>98</sup> It appears that lymph node metastases and thicker tumors may be more common in younger children (<10 years of age) with MM.<sup>110</sup> In addition to histopathologic analysis and lymph node examination, staging for pediatric MM may also include computed tomography (CT), positron emission tomography (PET) and PET-CT scanning in patients with thicker lesions to evaluate for distant metastases.<sup>111</sup>

Treatment of more advanced stages of MM includes chemotherapy, radiotherapy, and immunotherapy, although the results have been somewhat discouraging.<sup>112</sup> Adjuvant interferon  $\alpha$ -2b therapy has received much attention in the treatment of high-risk melanoma in adults, with reports of improved disease-free survival and overall survival rates with use of the Kirkwood regimen (high-dose therapy for 4 weeks followed by a lowered dose for 48 weeks). Recommendations for use of this agent in children have primarily been extrapolated from the adult data, and although its use is potentially effective, it may be associated with some toxicities at higher doses, which may be limiting when treating the pediatric melanoma patient.<sup>113,114</sup> Immunotherapeutic approaches to MM include melanoma vaccines, cytokine therapy, and passive immunotherapy with monoclonal antibodies, and these and other approaches continue to be the topics of active investigation.<sup>115</sup> Traditional chemotherapy regimens have shown minimal activity against melanoma.<sup>89</sup> Biologic agents such as high-dose interleukin (IL)-2 have resulted in durable responses in some adult patients, but experience in children is limited.<sup>116</sup> More recently, treatments that target growth-factor pathways or molecular targets have received increasing attention, including *BRAF* inhibitors such as dabrafenib and vemurafenib, and MEK inhibitors such as trametinib.<sup>116</sup> The combination of *BRAF* and MEK inhibition appears to provide greater benefit than *BRAF* inhibitor monotherapy in adults.<sup>117</sup> These treatments have not yet been well studied in pediatric melanoma.

The prognosis for pediatric melanoma is strongly correlated with initial stage. In a review of data from the National Cancer Database of 3158 patients aged 1 to 19 years with melanoma, average 5-year survival rates were 98.7% (*in situ* disease), 93.6% (localized invasive disease), 68% (regionally metastatic disease), and 11.8% (distant disease).<sup>118</sup> Some studies have found decreased survival in prepubescent patients with MM, whereas others have found no difference or a better prognosis in this group.<sup>111</sup> Hence there still exists no consensus on the overall prognosis for pediatric MM.

## SPITZ NEVUS

Spitz nevus is a distinct subtype of melanocytic nevus that occurs primarily in children. The importance of the Spitz nevus, which was formerly known as *benign juvenile melanoma*, lies in its histologic differentiation from MM. This lesion was originally recognized in 1948 when Dr. Sophie Spitz realized that a subset of juvenile melanomas did not behave in the same fashion as adult melanomas.<sup>119</sup> Spitz nevi have subsequently been identified as a distinct nevus variant, occurring most commonly on the face of children and adolescents.

Spitz nevi present usually as a smooth-surfaced, hairless, dome-shaped papule or nodule with a distinctive red-brown color (Fig. 9-22). They are most often solitary, although multiple clustered (agminated, Fig. 9-23) or disseminated lesions have been described.<sup>120,121</sup> They may vary in size from a few millimeters to several centimeters, although most range from 0.6 to 1 cm in diameter. The lesion may be so red that the differential diagnosis for some includes pyogenic granuloma or early juvenile xanthogranuloma. The presence of brown pigmentation (Fig. 9-24), either with regular clinical examination or when examined through a glass slide compressing the surface (diascopy), may be useful in confirming the melanocytic nature of the lesion. Surface telangiectasia may also be a prominent feature. In some lesions, particularly those on the extremities, the red color is replaced by a mottled brown to tan or black appearance, often with verrucous



**Figure 9-22** Spitz nevus. This patient had the erythematous type of Spitz nevus on her nose.



**Figure 9-23** Agminated Spitz nevi. This child had multiple lesions of the lateral cheek, ear, and neck, several of which were excised, revealing characteristic histologic features of Spitz nevus.

surface changes and irregular borders. Clinically it is this type of lesion that is most easily confused with MM (Fig. 9-25).

Although most Spitz nevi behave in a benign fashion, local recurrence after excision may occur in as many as 5%.<sup>122</sup> It has been suggested by some that occasional Spitz nevi are malignant in origin and have the potential for more aggressive biologic behavior. Whether these represent a subtype of Spitz nevus or a "spitzoid" MM is unclear. It is obvious that some Spitz nevus-like lesions may pose substantial diagnostic difficulties especially when atypical features are present, even among dermatopathology experts.<sup>123</sup> These lesions have been variably called *spitzoid tumor of uncertain malignant potential* or *atypical spitzoid tumor*. A grading system has been proposed for Spitz nevi with atypical features, and application of such a system may be useful in guiding management for patients with atypical Spitz tumors.<sup>124</sup> *BRAF* mutations have occasionally been observed in a subset of Spitz nevi, suggesting that this finding should not be relied upon for distinguishing Spitz nevus from melanoma.<sup>125</sup> The expression of cell cycle and



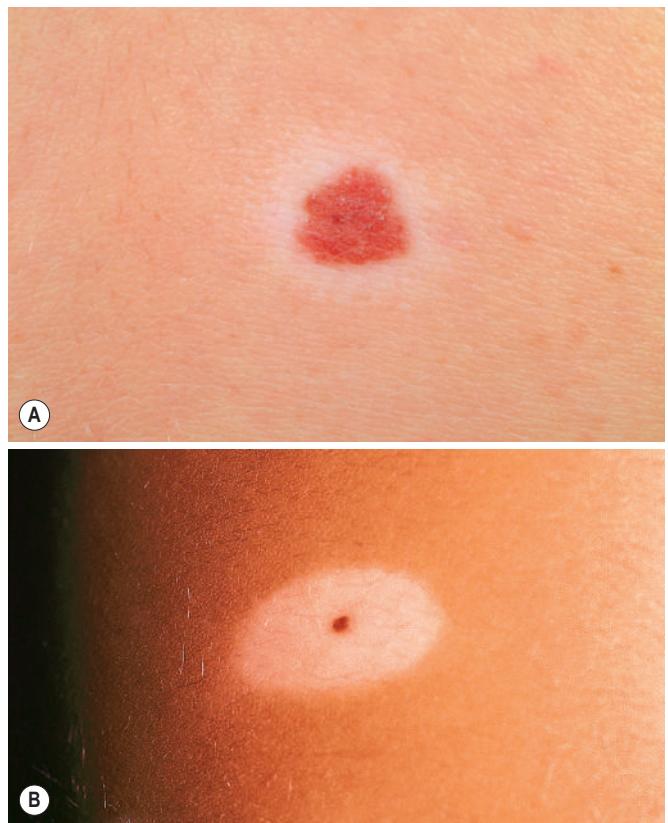
**Figure 9-24** Spitz nevus. This pink papule reveals brown speckling, which was easier to see when pressure was applied with a glass slide (diascopy).



**Figure 9-25** Spitz nevus. The dark brown or black type is most often confused clinically with MM.

apoptosis regulators in Spitz nevi appears to more closely parallel the findings in benign nevi rather than melanoma.<sup>126</sup> More recently, fluorescent *in situ* hybridization (FISH) using probes for chromosomal loci has been used in an attempt to predict biologic behavior in atypical spitzoid tumors; gains in 6p25 or 11q13 and deletions in 9q21 have been shown to correlate with more aggressive clinical behavior.<sup>127</sup> Deletions in 9q21 appear to correlate most with lymph node spread and distant metastasis.<sup>128</sup>

The management of Spitz nevi is controversial. Many experts recommend excision of these lesions on the basis of uncertainty in their biologic behavior, occasional reports of aggressive potential, and the increasing observation of the amelanotic nature of many melanomas in children. Others advocate for watchful waiting, reserving excision for lesions that demonstrate atypical features or those of psychosocial significance. When these lesions are excised, however, complete removal is advisable. More importantly, surgical specimens should be



**Figure 9-26** Halo nevi. **(A)** Small halo surrounding a small congenital nevus. **(B)** Larger halo surrounding an acquired compound nevus.

examined by a dermatopathologist or pathologist experienced in the diagnosis of melanocytic lesions and familiar with Spitz nevi. If an excised lesion is diagnosed unequivocally as a Spitz nevus without atypical features, no further therapy is necessary. However, because incompletely removed lesions may recur and result in a histopathologic appearance that may be more likely to be misinterpreted as MM, conservative reexcision is recommended for lesions with positive margins noted on the initial biopsy.

### HALO NEVUS

A halo nevus is a unique skin lesion in which a centrally placed, usually pigmented nevus becomes surrounded by a 1- to 5-mm halo of hypopigmentation or depigmentation (Fig. 9-26). These lesions are common in children and young adults. The cause of the spontaneous loss of pigmentation is unknown but appears to be related to an immunologic destruction of melanocytes and nevus cells.<sup>129,130</sup> Adding support to this hypothesis is the fact that several patients with halo nevi have a tendency toward the development of vitiligo (see Chapter 11; Fig. 9-27). Histologic examination of halo nevi reveals reduction or absence of melanin and a dense inflammatory infiltrate around the central nevus. Although compound or intradermal nevi are the tumors most commonly associated with the halo phenomenon, it may also occur around blue nevi, Spitz nevi, neurofibromas, melanomas, and metastatic lesions of melanoma. Giant CMN may also reveal the halo phenomenon with pigment regression and at times, self-destruction.<sup>131,132</sup>

Typical halo nevi are notable for loss of pigmentation in the nevus, with a pink appearance and commonly, eventual disappearance of the original melanocytic lesion. Occasionally, darkening of the central nevus may occur.<sup>133</sup> Halo nevi may appear on almost any cutaneous surface, but the site of predilection for most lesions is the trunk, particularly the back. In most patients, eventual repigmentation of the halo occurs over a period of months to years.

**A****B**

**Figure 9-27** Halo nevus with vitiligo. **(A)** Small halo nevus in the inferior ear crease. **(B)** The same patient had generalized depigmented macules and patches consistent with vitiligo, as seen here on the flank.

Halo nevi tend to be benign, although the halo phenomenon may occur around lesions revealing varying degrees of histologic atypia.<sup>134</sup> Potential concern has been raised over reports of MM exhibiting the halo phenomenon and the increased incidence of halo nevi in adults with melanoma.<sup>135</sup> In a survey of pediatric dermatologists, no diagnoses of MM in pediatric patients with halo nevi were noted.<sup>135</sup> Clinical features that may suggest an increased probability of an atypical melanocytic lesion within a halo include the ABCDE diagnostic criteria of melanoma (see Table 9-1) and asymmetry or irregularity of the surrounding depigmentation. Any patient with a halo nevus, especially if multiple halo lesions are present, should receive a complete skin and mucous membrane examination to assess for melanocytic lesions revealing atypical features. Patients with the halo nevus phenomenon, concomitant vitiligo, and ocular melanoma have been described,<sup>136</sup> but in general ophthalmologic evaluation is not routinely indicated. If the melanocytic lesion in the central portion of a halo reveals concerning or atypical features, complete excision should be performed. If, on the other hand, the central lesion has benign characteristics, excision is unnecessary and the lesion may be observed at intervals until it has resolved.



**Figure 9-28** Nevus spilus. A tan patch is studded with numerous darker brown macules and papules.



**Figure 9-29** Nevus spilus. This larger patch on the chest of a young boy reveals numerous superimposed nevi along with mild hypertrichosis.

## NEVUS SPILUS

Nevus spilus is a solitary, nonhairy, flat, brown patch of melanization dotted by smaller dark brown to black macules (Fig. 9-28). This relatively common lesion, although usually present at birth, may first become noticed during infancy, childhood, or even later. However, clinical and histologic data suggest that these lesions are most likely a subtype of CMN.<sup>32</sup> The earliest findings are usually similar to a café-au-lait patch, with eventual development of the secondary superimposed darker melanocytic lesions. Nevi spili may vary in size from 1 to 20 cm in diameter and may appear on any area of the face, trunk, or extremities without relation to sun exposure. Subtle hypertrichosis may occasionally be present (Fig. 9-29). Although the darker melanocytic components of these lesions have the potential to develop MM, the incidence of this transformation appears to be low.<sup>137,138</sup> Histologic evaluation of a nevus spilus usually reveals components of junctional and congenital nevi.<sup>32,137</sup> Patients with nevus spilus should be monitored longitudinally with serial clinical examinations and if possible, photographic surveillance. Any areas revealing atypical clinical features should be selectively excised and subjected to histologic evaluation, but widespread prophylactic excision seems unwarranted.<sup>30</sup> These lesions (especially when larger) have also been called *speckled lentiginous nevi* (SLN). Although they usually occur in isolation, they may sometimes be associated with other organ abnormalities as part of a syndrome such as phakomatosis pigmentovascularis (see Chapter 12), phakomatosis pigmentokeratotica (PPK), or SLN syndrome (see below).



**Figure 9-30** Becker melanosis. This adolescent boy has hyperpigmentation of the upper back and shoulder with extension onto the right upper chest in association with surface hypertrichosis.

### BECKER MELANOSIS

Becker melanosis, also known as *Becker nevus*, is an acquired, unilateral hyperpigmentation usually involving the upper trunk of adolescent males. Occasionally it may present very early in life (as early as birth) and may be distributed in other locations, including the extremities.<sup>139</sup> This pigmentation, which is caused by increased melanization of the epidermis and not by nevocellular proliferation, may be associated with hypertrichosis (Fig. 9-30) and occasionally proliferation of smooth muscle derived from erector pili muscles. Becker melanosis is discussed in more detail in Chapter 11.

## Tumors of the Epidermis

Tumors of the epidermis range in spectrum from benign lesions to those that are malignant. Benign tumors appear much more often than malignant lesions in children, and the latter, when they do occur, may be overlooked and/or the diagnosis delayed.

### EPIDERMAL NEVI

Epidermal nevi (EN) are benign congenital lesions characterized by hyperplasia of epidermal structures. They are usually apparent at birth or become noticeable during early childhood, affect both sexes equally, and are known by several descriptive names, including *nevus verrucosus*, *nevus unius lateris*, and *ichthyosis hystrix*. In addition, EN can be divided into nonorganoid (keratinocytic) nevi and organoid EN, such as *nevus sebaceous* or *follicular nevi*. Although the exact etiology of EN is unknown, activating fibroblast growth factor receptor 3 (*FGFR3*) mutations have been demonstrated in some,<sup>140,141</sup> as have mutations in the p110  $\alpha$ -subunit of *PI3K* (*PIK3CA*), *HRAS*, *KRAS*, and *NRAS*.<sup>142–144</sup>

Keratinocytic EN (often referred to simply as *EN*) may be slightly or darkly pigmented and unilateral or bilateral in distribution. They often favor the extremities, although they may occur anywhere on the cutaneous surface. EN are usually distributed in a mosaic pattern of alternating stripes of involved and uninvolved skin. This pattern is termed *Blaschko lines* and occurs as a result of migration of skin cells during embryogenesis. Disorders that occur along the Blaschko lines usually reveal a linear pattern on the extremities and a wavy or arcuate pattern on the trunk. Although a single EN is most common, multiple



**Figure 9-31** Epidermal nevus. This multifocal, verrucous plaque was present since birth.

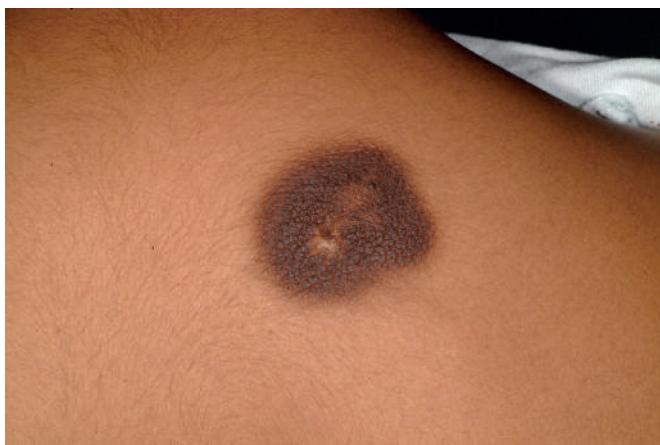


**Figure 9-32** Epidermal nevus. Note the warty nature and linear configuration.

lesions may be present, sometimes in association with the epidermal nevus syndrome (ENS; see below). The localized form is often present at birth and presents as a tan to brown, velvety or verrucous (warty) papule or plaque. There may be a single lesion (Fig. 9-31) or multiple lesions, and a linear configuration is common (Fig. 9-32). One subtype of epidermal nevus has been termed the *acanthosis nigricans form* of EN and is characterized by a clinical (Fig. 9-33) and histologic resemblance to acanthosis nigricans.<sup>145</sup>

The term *nevus unius lateris* has been used traditionally to describe extensive unilateral lesions. Nevus unius lateris may present as a single or spiral linear, verrucous lesion or at times as an elaborate, continuous, or interrupted pattern affecting multiple sites (Fig. 9-34) and occasionally involves more than half of the body. *Systematized epidermal nevus* has been used to describe extensive lesions that are bilateral and in which truncal involvement predominates.

EN may reveal a variety of histologic features. Importantly, those that reveal epidermolytic hyperkeratosis, a distinct pattern of clumping of keratin filaments in the suprabasal cells of the epidermis, imply a mosaic disorder of keratin genes. Patients with this condition, especially when skin involvement is extensive, may transmit these mutations to offspring, resulting in a more widespread ichthyosiform condition termed *epidermolytic ichthyosis* and *epidermolytic hyperkeratosis* (also known as *bullous congenital ichthyosiform erythroderma*; see Chapter 5).<sup>146</sup> These EN may be clinically indistinguishable from other EN (Fig. 9-35).



**Figure 9-33** Acanthosis nigricans form of epidermal nevus. This form of epidermal nevus reveals a well-demarcated area of velvety thickening, as classically seen with more widespread acanthosis nigricans.



**Figure 9-35** Epidermal nevus. This lesion demonstrated epidermolytic hyperkeratosis on histologic evaluation (see text).



**Figure 9-34** Nevus unius lateris. Numerous linear and "whorled" lesions were present on the right side of this 10-year-old female.

EN are challenging to treat, given the observation that most superficial destructive therapies are followed by recurrence of the lesions. These superficial therapies have included cryotherapy with liquid nitrogen, dermabrasion, electrodesiccation, and laser ablation. In a series of 71 treated lesions, cryotherapy of small EN resulted in an excellent response in 90%.<sup>147</sup> Carbon dioxide (CO<sub>2</sub>) laser therapy may offer excellent results, but response to therapy is unpredictable.<sup>148</sup> Staged CO<sub>2</sub> laser ablation has been used successfully, both with and without preceding surgical debulking.<sup>149</sup> Topical therapies used with variable success include retinoids, 5-fluorouracil, steroids, and podophyllin, among others. Photodynamic therapy with methylaminolevulinate was reportedly successful in a young girl, although hypertrophic scarring occurred.<sup>150</sup> Full-thickness surgical excision or deeper destructive procedures (such as deep dermabrasion) appear effective at removing these hamartomas but are generally limited to smaller, more localized lesions. Since these lesions may continue to extend during childhood, surgical intervention should be delayed until the full extent of the process is determined.

## EPIDERMAL NEVUS SYNDROME

ENS is a sporadic association of EN with abnormalities in other organ systems. Some believe that this syndrome is actually a group of several syndromes, each with distinguishing cutaneous and extracutaneous features. Happle suggests that the five well-defined ENSs are Schimmelpenning syndrome, nevus comedonicus syndrome, pigmented hairy ENs, Proteus syndrome (see Chapter 12), and congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD) syndrome (see Chapter 5).<sup>151</sup> Keratinocytic ENS also merits inclusion on this list.<sup>152</sup> Regardless, patients who fall into the spectrum of having an ENS generally have organoid or nonorganoid EN in conjunction with defects in the CNS, eyes, musculoskeletal system, connective tissue and occasionally other organ systems. The manifestations of ENS are believed to represent genomic mosaicism with the effects of the genetic defect(s) and timing of the mutation during development determining the spectrum of clinical involvement.<sup>152</sup>

*Phakomatosis pigmentokeratotica (PPK)* has been used to describe the association of speckled lentiginous nevus with an epidermal nevus that has sebaceous differentiation and is accompanied by skeletal and neurologic abnormalities.<sup>153</sup> It has been suggested that patients with PPK may have systemic features suggestive of either Schimmelpenning syndrome (extensive sebaceous nevi, mental retardation, seizures, coloboma, lipodermoids of the conjunctiva, skeletal defects, and vascular abnormalities) or what has been termed *SLN syndrome* (presenting with SLN, hyperhidrosis, sensory and motor neuropathy, nerve palsy, and spinal muscular atrophy).<sup>154,155</sup>

Examples of extracutaneous abnormalities seen in patients with ENS include seizures, mental retardation, hemiparesis, hypotonia, cranial nerve palsies, developmental delay, deafness, kyphosis, scoliosis, limb hypertrophy, hemihypertrophy, facial bone deformity, macrocephaly, ocular lipodermoids, coloboma, corneal changes, cortical blindness, cataracts, and retinal changes.<sup>151,152,156,157</sup> CNS imaging may reveal hemimegalencephaly, agenesis of the corpus callosum, cerebral heterotopia, cortical agyria or microgyria, or Dandy–Walker malformation; brainstem and cerebellar malformations and neonatal medulloblastoma have also been reported.<sup>158,159</sup> In addition, hypophosphatemic vitamin D-resistant rickets has been observed in patients with ENS, and in some reports the hypophosphatemia improved after surgical revision of the EN.<sup>160–162</sup> It has been suggested that some EN may produce a phosphaturic substance that contributes to this association.<sup>160,161</sup> Hyponatremia has also been observed as an early manifestation in a patient with ENS.<sup>163</sup> Cardiac and genitourinary defects may also be associated.

The features of the cutaneous lesions in ENS range from large unilateral nevus unius lateris-like lesions to diffusely distributed, whorled lesions (Figs. 9-36 and 9-37) involving variable degrees of the skin surface or linear, orange-yellow plaques as seen in nevus sebaceous of Jadassohn (see *Nevus Sebaceous* section). Plaques of dilated follicular pits filled with keratin may be seen in the nevus comedonicus type of



**Figure 9-36** Epidermal nevus syndrome. This infant had numerous widespread epidermal nevi in conjunction with multiple congenital anomalies.



**Figure 9-37** Epidermal nevus syndrome. Multiple, whorled verrucous plaques are present in this child with multiple musculoskeletal, CNS, and ophthalmologic defects as well as profound developmental delay.

ENS, and extensive Becker nevus is seen in the pigmented hairy type of ENS. In the CHILD syndrome, a unilateral inflammatory epidermal nevus with a sharp midline demarcation and an affinity for body folds is seen in conjunction with the characteristic ipsilateral hypoplasia of limbs and other organ defects. Patients with Proteus syndrome have verrucous EN in association with partial gigantism, macrocephaly, and vascular malformations.

Patients with large or extensive EN require careful medical, family, and developmental histories and thorough physical evaluation, with particular emphasis on the musculoskeletal, neurologic, ocular, and cardiovascular examinations. Management of ENS should be multidisciplinary including a dermatologist, pediatrician, neurologist, ophthalmologist, and plastic surgeon, with utilization of other subspecialists as necessary. EN can be treated as noted earlier, although treatment is even more challenging given their extensiveness in this setting. Malignant transformation of EN is rare but may occur, both in syndromic and nonsyndromic lesions, and includes basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), depending on the type of epidermal nevus.

### INFLAMMATORY LINEAR VERRUCOUS EPIDERMAL NEVI

Inflammatory linear verrucous epidermal nevi (ILVEN) appear to be a unique variant of epidermal nevi that presents as a chronic pruritic



**Figure 9-38** Inflammatory linear verrucous epidermal nevus (ILVEN). Multiple red, scaly papules coalescing into a linear plaque on the medial leg, malleolus, and foot of a 7-year-old girl.

process with erythematous, scaly, and verrucous papules that coalesce into linear plaques (Fig. 9-38). These lesions are often present at birth or may appear during early childhood and most often occur on an extremity. They are notable for their chronic and intermittent course and resistance to therapy.<sup>164</sup> Occasionally lesions may spontaneously improve or resolve only to eventually reappear. The differential diagnosis of ILVEN includes linear psoriasis, lichen striatus, linear lichen planus, and verrucous epidermal nevus. ILVEN can usually be confirmed by the clinical course, morphologic appearance of lesions, intense pruritus, and resistance to therapy.

Treatment of ILVEN is difficult, as discussed previously for EN. Topical or intralesional corticosteroids may reduce inflammation and pruritus and produce a temporary remission, but the lesions generally recur. Topical retinoids, 5-fluorouracil, calcineurin inhibitors (i.e., tacrolimus or pimecrolimus), CO<sub>2</sub> laser therapy, and vitamin-D derivatives (i.e., calcitriol) have been used with varying results.<sup>165–167</sup> Photodynamic therapy with methyl-aminolevulinate was reportedly successful in an adult with ILVEN.<sup>168</sup> Patients with extensive and symptomatic ILVEN have been treated surgically, with tissue expansion, serial full-thickness excisions, and split-thickness skin grafting with excellent outcomes.<sup>169</sup>

### BASAL CELL CARCINOMA

Basal cell carcinoma (BCC) is a slow-growing, usually nonmetastasizing but invasive malignant skin tumor with varying clinical patterns that may be triggered by ultraviolet radiation exposure. This disorder arises from the basal cells of the epidermis or its appendages and is most commonly seen in persons of middle age. BCC is the most common form of skin cancer, and although rarely seen in children, it can occur in childhood and must be considered even in the very young.<sup>170,171</sup> However, misdiagnosis must also be considered in a child, as several benign hamartomas of follicular differentiation (trichoepithelioma, trichoblastoma, trichofolliculoma) may histologically appear similar to BCC to the inexperienced pathologist.

When the diagnosis of BCC is confirmed in a child, one must consider an associated predisposing condition such as basal cell nevus syndrome (BCNS, or Gorlin syndrome, see below), xeroderma pigmentosum (see Chapter 19), Bazex syndrome, and Rombo syndromes

(see Chapter 7), albinism (see Chapter 11), or an underlying nevus sebaceous of Jadassohn (see [Nevus Sebaceous](#) section). Other genetic skin disorders that may entail an increased risk for BCC include Bloom syndrome, Werner syndrome, Rothmund–Thomson syndrome, Muir–Torre syndrome, Brooke–Spiegler syndrome (BSS), Cowden syndrome (CS), and some immunodeficiency disorders.<sup>172</sup> Children treated with irradiation for malignancy or with solid organ transplantation may develop BCC years to decades after the treatment.<sup>170,173</sup> In a review of childhood cancer survivors who were subsequently diagnosed with BCC, the majority of tumors developed between 20 and 39 years of age, and the risk was noted to be increased when patients received radiation doses to the skin of more than 1 Gy.<sup>174</sup> BCC lesions have occasionally been reported as sporadic cases in children without any underlying predisposition and appear to be most often located on the head, back, and chest.<sup>170,175,176</sup> The diagnosis of BCC in childhood is often delayed because of a low index of suspicion.

The majority of BCCs have a predilection for the upper central part of the face. Although they may arise without apparent cause, prolonged exposure to the sun is a predisposing factor, particularly in individuals with a fair skin phenotype. BCC may occur in several clinical forms. Nodoulcerative BCC, the most common type, begins as a small, elevated, translucent papule or nodule with telangiectatic vessels on its surface. It may enlarge, develop central necrosis, and result in an ulceration surrounded by a pearly rolled border. Although this form usually occurs as a single lesion, patients who develop this form of basal cell tumor often are likely to develop other such lesions. Superficial BCC presents as an erythematous, scaly, minimally elevated papule or plaque that may have superficial crusting. Often multiple, these lesions tend to occur on the trunk or extremities, expand slowly, and are easily mistaken for lesions of psoriasis, dermatitis, or tinea. Pigmented BCCs are similar to nodoulcerative lesions but also contain irregular brown pigmentation that may simulate the appearance of a nevus or MM. Sclerosing or morphaform BCC presents as a firm, yellow-white waxy papule or plaque with an ill-defined border and absence of the translucent rolled edge. Tumors of this type have been known to arise in early childhood and may grow for years before attracting medical attention.

In the pediatric patient who is diagnosed with a BCC, a thorough history and physical examination should be performed with attention to the regional lymph node examination. An evaluation for an associated predisposing condition should be performed when indicated. No single method of therapy is applicable to all BCC lesions. The goal, as with any skin tumor, is for permanent cure with the best functional and cosmetic result. Curettage and electrodesiccation is a simple office therapy most commonly used by dermatologists for low-risk, small BCC in areas without a dense hair pattern. Excision (with or without Mohs micrographic surgery [MMS]) is the treatment of choice for childhood-onset BCC.<sup>170</sup> Radiation therapy can be an effective treatment but is not desirable in children (and contraindicated in the setting of BCNS, discussed later in this chapter, because it may increase the risk for invasive BCC).<sup>171</sup> Other treatment modalities include cryotherapy, CO<sub>2</sub> laser therapy, photodynamic therapy, systemic retinoids, topical chemotherapy (i.e., topical 5-fluorouracil), and biologic-response modifiers. The latter include imiquimod, a topical immune-response modifier demonstrated to be effective against superficial BCCs and small nodular BCCs.<sup>177</sup> This agent promotes innate immune responses and exhibits antitumor as well as antiviral effects, having been initially approved for the treatment of anogenital condylomata. Experience with these therapeutic methods in childhood BCC is primarily anecdotal. Sun protection and skin self-examination education is vital.

## BASAL CELL NEVUS SYNDROME

BCNS (also known as *Gorlin syndrome* or *nevroid BCC syndrome*) is an autosomal dominant disorder with complete penetrance and variable expressivity characterized by childhood onset of multiple BCCs and associated with other abnormalities, including odontogenic jaw cysts, bifid ribs, and intracranial calcification.<sup>178–181</sup> The most obvious cutaneous feature in patients with BCNS is the appearance of multiple BCCs early in life. These basal cell epitheliomas are indistinguishable on histopathologic examination from ordinary BCCs. The diagnostic

## Box 9-2 Diagnostic Criteria for Basal Cell Nevus Syndrome\*

### Major criteria

- Multiple basal cell carcinomas (>5 in a lifetime or a BCC before 30 years)
- Lamellar calcification of the falx (or clear evidence of calcification in an individual younger than 20 years)
- Jaw keratocyst (odontogenic keratocyst, confirmed histologically)
- Palmar or plantar pits (>2; may be most easily seen after soaking of the hands and feet in warm water)
- First-degree relative with BCNS

### Minor criteria

- Macrocephaly
- Childhood medulloblastoma
- Cleft lip/palate
- Rib/vertebral anomalies: bifid, splayed, missing or extra ribs; bifid, wedged, or fused vertebrae
- Preaxial or postaxial polydactyly
- Cardiac or ovarian fibroma
- Lymphomesenteric or pleural cysts
- Ocular anomalies (cataract, coloboma, microphthalmia)

Modified from High A, Zedan W. Basal cell nevus syndrome. *Curr Opin Oncol* 2005; 17:160–6, and Evans DG, Farndon PA. Nevoid basal cell carcinoma syndrome. *Gene Reviews* (Internet), Seattle (WA): University of Washington, Seattle; 1993–2015. 2002 (updated 2013). Accessed April 2015.

BCC, Basal cell carcinoma; BCNS, basal cell nevus syndrome.

\*Diagnosed when an individual has two major criteria and one minor criterion, OR one major criterion and three minor criteria.

<sup>†</sup>See text for further discussion.

criteria for BCNS are shown in [Box 9-2](#). In a consensus statement from an international colloquium on BCNS, a modification of the diagnostic criteria was suggested such that medulloblastoma, typically desmoplastic, be included as a major (rather than a minor) criterion.<sup>182</sup>

The skin lesions of BCNS may appear as early as the first year of life but have a mean age of onset of around 20 to 23 years.<sup>180,181</sup> They involve, in decreasing order of incidence, the face, neck, back, trunk, and upper extremities. The distribution of BCCs may differ by gender, with male patients having more in the facial M-zone (forehead, temples, periorbital areas, and nose), upper back, neck, and upper extremities, and female patients having more lesions located in the scalp, upper and lower back, and lower extremities.<sup>183</sup> The BCCs in BCNS may range in number from one to well over a thousand. In addition, patients with BCNS may develop skin lesions that appear similar to nevi or seborrheic keratoses and tend to follow a more benign course, although after puberty the cutaneous lesions of BCNS tend to be more aggressive. The BCC lesions appear as flesh-colored to pink or tan dome-shaped papules that measure 1 to 10 mm ([Fig. 9-39, A](#)). Secondary changes such as ulceration, crusting, and bleeding rarely occur before puberty, but if left untreated these lesions can become extremely destructive. Unlike ordinary BCCs, BCNS-associated lesions do not appear to be induced by prolonged exposure to sunlight.

In addition to nevoid BCCs, affected individuals have a characteristic facies with coarse features, broad nasal root, hypertelorism, and other cutaneous stigmata. These include multiple small facial milia, comedones, large epidermal cysts, lipomas, fibromas, and café-au-lait macules. Shallow 2- to 3-mm palmar and plantar pits ([Fig. 9-39, B](#)), a characteristic feature of the syndrome, are seen in 70% to 90% of affected individuals. They may become more prominent after immersion of the hands or feet in water. These defective areas of keratinization usually first appear during the second decade of life or later. Palmar and plantar pits tend to have associated erythema, which on casual observation appears as multiple small red spots on the palms and soles.

Odontogenic jaw cysts occur in around 75% of patients and may present with painless swelling, jaw pain, abnormal taste, or a discharge in the mouth. The first jaw cyst often occurs before the age of 20 years, and symptoms referable to these lesions are often the presenting complaint. Jaw cysts occurring in patients with BCNS present earlier in life than those occurring in patients without BCNS.<sup>184</sup> The cysts may be multiple and may result in loosening and loss of teeth. Patients with BCNS may become edentulous at an early age.



**Figure 9-39** Basal cell nevus syndrome (BCNS). **(A)** Pigmented basal cell carcinoma on the scalp of a 12-year-old girl. **(B)** Shallow erythematous depressions (pits) on the plantar surface of an adult female with BCNS.

Musculoskeletal anomalies present in 60% to 80% of patients and include macrocephaly, frontoparietal bossing, high-arched palate, and broad nasal bridge.<sup>180</sup> Other abnormalities include splayed or bifid ribs, mandibular and maxillary bone cysts, prognathism, kyphoscoliosis, Sprengel deformity, cervical or thoracic vertebral anomalies, spina bifida, pectus excavatum and carinatum, and shortened fourth metacarpals.

The most common neurologic abnormality is calcification of the falx cerebri, which is seen in up to 90% of patients with BCNS. In addition, mental retardation, electroencephalographic abnormalities, agenesis of the corpus callosum, seizures, hydrocephalus, and deafness may occur. Other associations include anosmia, renal malformations, endocrinopathy, and blindness. Patients with BCNS appear to have a predisposition to malignancy, especially medulloblastoma, which may present early in life.<sup>185</sup> The desmoplastic subtype of medulloblastoma in children younger than 2 years of age is considered by some a major diagnostic criterion for the diagnosis of BCNS.<sup>185,186</sup> This desmoplastic variant has a favorable prognosis.<sup>187</sup> Ovarian and cardiac fibromas and meningiomas also occur at an increased rate in these patients.

The molecular cause of BCNS has been elucidated. Mutations in the human patched gene (*PTC*) have been identified in patients with BCNS as well as in those with sporadic BCCs.<sup>188–190</sup> *PTC* is located on chromosome 9q and encodes a transmembrane receptor that represses growth-factor gene transcription. The gene product of *PTC* functions as a tumor suppressor, and *PTC* mutations results in dysregulation of several genes known to play a role in both organogenesis and car-

cinogenesis.<sup>191</sup> Sequence analysis to detect mutations as well as deletion testing are both clinically available to assist in diagnosis of BCNS.

The management of patients with BCNS must be multidisciplinary and individualized. Genetic counseling is important given the autosomal dominant mode of inheritance. Family members judged to be at risk may be screened with skeletal surveys, dental radiographs, and neurologic evaluation (both clinical and radiographic). Molecular diagnosis is also possible (GeneDx, Gaithersburg, MD), with a sensitivity around 60% to 75%. Removal of cutaneous BCC may be accomplished with the same techniques as discussed earlier, and general anesthesia may be required for treatment of multiple lesions. Systemic retinoids (i.e., isotretinoin) may be useful in preventing BCCs, but its use must be balanced by potential side effects and in females the known teratogenicity. In addition, if the retinoid is discontinued, the patient may show rapid disease progression. Vismodegib, an inhibitor of the hedgehog signaling pathway approved for treatment of locally advanced or metastatic BCC, has been shown to reduce the BCC tumor burden and block growth of new lesions in patients with BCNS, though its potential benefit has been limited by adverse events that led to discontinuation by more than 50% of patients in recent study.<sup>192</sup>

It is recommended that all pediatric patients with BCNS be monitored by a medical geneticist who ensures all appropriate referrals and follow-up evaluations. Patients require regular follow-up examinations with a dermatologist, pediatric dentist/oral surgeon, and ophthalmologist, as well as referral to a neurologist and psychologist as indicated. Annual vision, hearing, and speech screenings; routine developmental screening at well-child visits; and baseline brain MRI, digital Panorex of the jaw, and spinal films are also recommended.<sup>182</sup>

## SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC) is a malignant tumor of the epidermis rarely seen in children. Occasionally it may arise in normal skin, but generally it is seen in skin that has been injured by sunlight, trauma, thermal burn, or chronic inflammation. Children who develop SCC often have an underlying predisposing condition, including xeroderma pigmentosum (see Chapter 19), human papillomavirus infection (especially in the immunocompromised host), or a history of organ transplantation, chemotherapy with immunosuppression, or radiation therapy. In addition, scars related to dystrophic epidermolysis bullosa (see Chapter 13) may be predisposed to the development of SCC. Although these tumors generally do not present until the third or fourth decade, they may occasionally occur during childhood.<sup>193</sup> SCC has also been reported to occur within the lesions of pansclerotic morphea of childhood.<sup>194</sup>

The most common sites for SCC are the face (in particular the lower lip and pinna of the ear) and the dorsal aspect of the hands and forearms. Lesions usually present as red, scaly papules or plaques, often with induration. Telangiectasias may be present, as may ulceration or necrosis. Lesions that arise *de novo* usually appear as solitary, slowly enlarging, firm nodules with central crusting, underlying ulceration, and an indurated base. The histologic evaluation of SCC offers prognostic information based on the depth of the lesion and the cytologic features and degree of differentiation of the cells.

The prognosis for SCC of the skin is quite variable. Easily cured small lesions arising in sun-damaged skin have a low propensity to metastasize. Lesions arising in burn scars, prior radiation fields, and chronic wounds (i.e., ulcers or epidermolysis bullosa scars; see Chapter 13) tend to be more aggressive with higher rates of metastases. Complete excision is the treatment of choice for SCC. Other treatment options that may be considered include electrodesiccation and curettage, cryotherapy, photodynamic therapy, and MMS. Sun protection and skin self-examination education is again vital.

## KERATOACANTHOMA

Keratoacanthoma (KA) is an epithelial tumor that may be clinically and histologically indistinguishable from SCC. These lesions are considered by many to be benign, and they often involute spontaneously without therapy. However, given rare reports of extensive local destruction and metastases, some consider KAs to be a variant of SCC.

KAs are usually seen in older adults with rare reports of neonatal or childhood involvement.<sup>195,196</sup> Multiple KAs characteristically have their onset in adolescence or early adult life and may occur in several clinical settings such as Ferguson Smith, Muir–Torre, or Witten–Zak syndromes. Generalized eruptive KA with the sudden onset of multiple lesions may also occur (termed the *Grzybowski type*).<sup>197</sup>

KA presents as a firm, dome-shaped nodule that generally measures 1 to 3 cm or more. The center contains a horny plug or is covered by a crust that conceals a central keratin-filled crater. The nodule generally grows rapidly and reaches its full size within 2 to 8 weeks. After a period of quiescence that may last for 2 to 8 weeks, most lesions heal spontaneously over several months with only a slightly depressed, somewhat cribriform scar in the previously affected area.

The main problem in the diagnosis of KA is its differentiation from SCC. In most cases, the rapid evolution and typical clinical appearance help to establish the correct diagnosis. Because the architecture of the lesion is as important as the cellular characteristics, full excisional biopsy is recommended to enable appropriate histopathologic evaluation. The treatment of KA is usually approached with a view toward its spontaneous resolution. Its close resemblance to SCC, however, often results in excisional biopsy. Other reported treatment options include intralesional corticosteroids, topical imiquimod, intralesional methotrexate, topical 5-fluorouracil, electrodesiccation and curettage, and radiation therapy.<sup>198–201</sup>

## Tumors of the Oral Mucosa

### WHITE SPONGE NEVUS

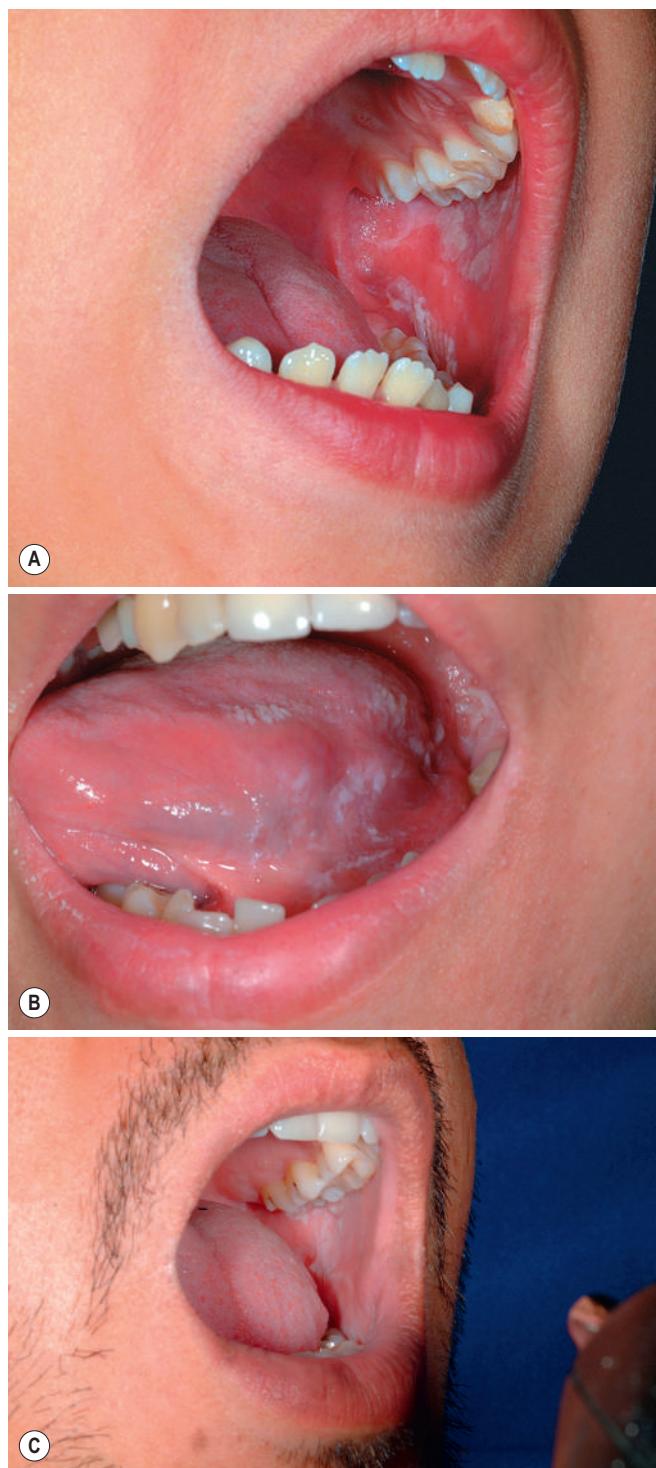
White sponge nevus is a rare, autosomal dominant condition that most often affects the oral mucosa and less commonly the mucosae of other regions. It presents as exuberant, asymptomatic white plaques on the buccal mucosae (Fig. 9-40), palate, gingivae, or sides of the tongue. Other regions that may be involved include the nasal, vaginal, labial, and anal mucosae. In some instances, the plaques may be quite thickened with fissures and folds, and occasionally a raw, denuded surface may be evident. White sponge nevus may be present at birth or may have its onset any time from infancy through adolescence. The lesions are most commonly misdiagnosed as candidiasis in young children.<sup>202</sup> It reaches its maximum severity during adolescence or early adulthood, and the lesions are entirely asymptomatic and often noted incidentally during examination. Both genders are equally affected. The differential diagnosis of white sponge nevus may include oral leukoplakia, pachyonychia congenita, dyskeratosis congenita, cheek biting, chemical burn, syphilis, betel nut or tobacco use, and lichen planus.

Defects in the genes for keratins 4 and 13 have been demonstrated to be responsible for white sponge nevus.<sup>203,204</sup> This disorder is generally benign and asymptomatic and requires no specific therapy. White sponge nevus should not be confused with focal epithelial hyperplasia (Heck disease), a rare disorder of the oral mucosa of children believed to be caused by infection with human papillomavirus, especially types 13 and 32. In patients with Heck disease, the mucosa of the lower lip is most commonly involved and reveals soft papules and plaques that tend to regress spontaneously over several months.

### LEUKOPLAKIA

*Leukoplakia* is a term generally used to describe a white plaque involving the oral mucosa that cannot be easily removed by scraping or rubbing with a cotton swab or tongue blade. It is a nonspecific term inconsistently applied to a variety of different etiologic lesions, including white sponge nevus, pachyonychia congenita, dyskeratosis congenita, hereditary benign intraepithelial dyskeratosis, hereditary mucoepithelial dysplasia, and many others. It is also used to describe white changes on the vulva of females, where its use is equally nonspecific.

*Oral leukoplakia* is the terminology usually used to describe a condition seen most often in adults and is related to a variety of factors including trauma, poor oral hygiene, chronic irritation, and use of tobacco products. It may occasionally be seen in children and has been



**Figure 9-40** Oral white sponge nevus. This 4-year-old boy (A), his two brothers, one of whom is pictured in (B), father (C), and uncle all had similar white plaques of the oral mucosa.

reported in pediatric patients with HIV infection.<sup>205,206</sup> The clinical presentation is notable for either focal or more diffuse involvement with white plaques of the buccal mucosae, hard or soft palate, lateral surfaces of the tongue, and the floor of the mouth. Mucosal biopsy with histopathologic evaluation is usually necessary to confirm the exact diagnosis, and treatment depends on the etiology. Meticulous attention to oral hygiene is useful regardless of the cause. Since oral leukoplakia may have malignant potential (eventuating into SCC),



**Figure 9-41** Nevus sebaceous. Yellow-orange, hairless plaque on the scalp.



**Figure 9-43** Nevus sebaceous. The lesion in this adolescent male demonstrates verrucous (warty) changes that are common with older age.



**Figure 9-42** Nevus sebaceous. Linear yellow verrucous plaque on the inferior chin of an infant.



**Figure 9-44** Nevus sebaceous with syringocystadenoma papilliferum. This verrucous, exophytic papule developed on the surface of a previously flat nevus sebaceous.

long-term follow-up observation is indicated, with repeat tissue biopsy when necessary.

## Tumors of the Epidermal Appendages

### NEVUS SEBACEOUS

Nevus sebaceous of Jadassohn is a common congenital lesion that occurs mainly on the face and scalp. These lesions are usually solitary and present as a well-circumscribed, hairless plaque. They are generally present at birth but may first be noted during early childhood and rarely in adult life. Although rare familial forms have been reported, these hamartomas tend to be sporadic. Multiple nevi sebaceos may occur in association with cerebral, ocular, and skeletal abnormalities as part of an ENS. This association has been termed *Schimmelpenning syndrome*.<sup>151</sup> Recently, somatic mutations in *HRAS* and *KRAS* were demonstrated in lesions of nevus sebaceous.<sup>144,207</sup>

Classic nevus sebaceous presents as a hairless, yellow to tan plaque on the scalp or face (Figs. 9-41 and 9-42). The surface may be verrucous or velvety, and the lesions are often oval or linear. In some patients hyperpigmentation may be a prominent feature, making the distinction from a verrucous epidermal nevus difficult. Nevus sebaceous may vary in size from a few millimeters to several centimeters in length. Their yellow color is related to sebaceous gland secretion, and often this color becomes less prominent after infancy. The lesions tend to enlarge proportionate with growth of the child, until puberty when they may become significantly thicker, more verrucous, and

more greasy in appearance (Fig. 9-43) as a result of hormonal stimulation of the sebaceous glands within them. Papillomatous projections may occur, sometimes simulating the appearance of verruca vulgaris.

Surgical excision, the treatment of choice for nevus sebaceous, has traditionally been recommended out of concern for the development of secondary malignant neoplasms within these lesions. Multiple secondary appendageal neoplasms may occur within nevus sebaceous, including syringocystadenoma papilliferum (the most common secondary benign neoplasm, Fig. 9-44), apocrine cystadenoma, spiradenoma, and trichoblastoma.<sup>208–210</sup> The secondary tumor that raises the most concern, however, is BCC, which in the past was estimated to occur in anywhere from 6.5% to 50% of lesions depending on the source.<sup>211</sup> More recent investigations have documented that the incidence of BCC is actually quite low, and in fact trichoblastoma (a benign proliferation that appears to be quite common) may be easily mistaken for BCC.<sup>209,212–214</sup> Other tumors that have been reported within lesions of nevus sebaceous include KA, leiomyoma, piloleiomyoma, SCC, apocrine carcinoma, and malignant eccrine poroma. Malignant degeneration is usually heralded by the appearance of a discrete nodule with or without ulceration.

The timing of surgery in those patients for whom it is chosen is controversial. Many factors need to be considered, including size and location of the nevus, its cosmetic significance, and the risk-to-benefit ratio of general anesthesia (needed early in life) versus local anesthesia (a possibility when surgery for smaller lesions is delayed until later childhood or adolescence). These decisions must be made by the



**Figure 9-45** Nevus comedonicus. Multiple open (blackheads) and closed (whiteheads) comedones in a linear distribution.

parents (and patient, where appropriate) with input from the involved physician(s). The practitioner should provide parents with the objective data and allow them to make this personal decision, offering support and guidance as necessary.

### NEVUS COMEDONICUS

Nevus comedonicus is a rare type of organoid nevus with a hair follicle origin. These lesions are often present at birth, or they may become evident over the first decade of life. There is no racial or sexual predisposition. Nevus comedonicus presents as a plaque composed primarily of hyperkeratotic papules and horny plugs (resembling the comedones of acne vulgaris) with varying degrees of erythema (Fig. 9-45). Lesions are most common on the face, neck, trunk, and upper extremities and are often linear or band-like in distribution. They tend to grow as the child matures, and large lesions extending above the surrounding cutaneous surface may give a grater-like feeling to the skin. There is a spectrum of involvement with nevus comedonicus, from simple comedonal lesions to those with significant inflammation, cysts, and even scarring.<sup>215</sup> Secondary infection and abscess formation rarely occur.

The differential diagnosis of nevus comedonicus includes nevus sebaceous, acne neonatorum, and in older patients, comedonal acne. Although the lesions usually occur as a sporadic finding, multiple or extensive lesions may be associated with abnormalities in other organ systems as part of the nevus comedonicus type of ENS.<sup>151,216</sup>

Management of nevus comedonicus is challenging. Topical retinoids, ammonium lactate lotion, or topical antibiotics may each be useful for some patients. Pore strips have been reported useful for removal of the keratin plugs.<sup>217</sup> However, most medical therapies are ineffective, and the definitive therapy for cosmetically significant lesions is surgical excision.

### TRICHOEPITHELIOMA

Trichoepitheliomas may occur as a benign, autosomal dominantly inherited disorder characterized by the presence of multiple small lesions occurring primarily on the face or as a solitary nonhereditary tumor seen in early adult life or occasionally during childhood. BSS has traditionally been used to describe an autosomal dominant disorder characterized by numerous trichoepitheliomas, cylindromas (see also *Cylindroma* section) and spiradenomas, all benign skin appendageal tumors. *Multiple familial trichoepithelioma* (MFT) refers to an autosomal dominant disorder characterized by numerous trichoepitheliomas involving the central face and often starting during childhood. The term *trichoblastoma* has been used to denote benign



**Figure 9-46** Multiple trichoepitheliomas. Multiple flesh-colored papules of the medial cheek and nose. (Courtesy of Keren Horn, MD.)

neoplasms of follicular differentiation. Some now consider these two conditions to be interchangeable, with others considering trichoepithelioma to be one type of trichoblastoma.

Multiple trichoepitheliomas generally begin during early childhood or around puberty as small, firm, flesh-colored papules and nodules on the face (Fig. 9-46), particularly in the nasolabial folds and over the nose, forehead, upper lip, and eyelids and occasionally the scalp, neck, trunk, scrotum, and perianal area. The lesions measure 2 to 5 mm in diameter, are firm, and have a translucent sheen. Occasionally, telangiectatic vessels are present over the rounded translucent surface of larger lesions. Trichoepitheliomas may enlarge slowly, reaching up to 5 mm on the face and ears and up to 2 to 3 cm in other sites; they often coalesce to form nodular aggregates. Mutations in the CYLD gene, a tumor-suppressor gene, appear to be the genetic basis for MFT, BSS, and familial cylindromatosus (FC; also known as *turban tumor syndrome*), a disorder characterized by multiple cylindromas as the only tumor type (see also *Cylindroma* section).<sup>218–220</sup>

Solitary, nonhereditary trichoepitheliomas usually develop during the second or third decade of life and generally appear on the face. They may also be distributed on the scalp, neck, trunk, upper arms, or thighs. Solitary lesions appear as firm, flesh-colored papules and papulonodules and generally reach 5 mm or slightly larger in diameter.

Desmoplastic trichoepithelioma is a variant that presents as an indurated, flesh-colored to red papule or plaque with an elevated annular border and central depression. It occurs most commonly on the face, especially the cheek. Although most commonly seen in early adulthood, desmoplastic trichoepitheliomas may appear during the second decade, are much more common in females, and may occur in a familial fashion.<sup>221</sup> In one report, desmoplastic trichoepithelioma was initially mistakenly diagnosed as SCC.<sup>222</sup>

Although trichoepitheliomas are benign lesions, treatment may be cosmetically desirable, and at times biopsy is indicated to differentiate the lesion from other cutaneous neoplasms. Surgical excision is the treatment of choice, although electrodesiccation, cryotherapy, radiotherapy, dermabrasion, and laser therapy have also been utilized.<sup>220</sup>

### TRICHILEMMOMA

Trichilemmoma is another benign appendageal neoplasm derived from the hair follicle. These lesions may be solitary or multiple and present as flesh-colored papules or nodules, occasionally with a verrucous (wart-like) surface. The most common location for trichilemmomas is the face, although genitals are another common site and they can occur anywhere on the cutaneous surface. A desmoplastic form (desmoplastic trichilemmoma) may occur, and at times the

deeper component of these lesions may histologically simulate invasive carcinoma.<sup>223</sup> Treatment of these benign lesions may be accomplished with surgical excision or ablative procedures when desired.

Multiple trichilemmomas may be seen in the setting of the multiple hamartoma syndrome, CS. This autosomal dominant disorder is characterized by hamartomas in multiple organ systems including skin, breast, thyroid, gastrointestinal (GI) tract, endometrium, and brain.<sup>224</sup> Mucocutaneous lesions, which are present in nearly all patients, include multiple trichilemmomas, palmoplantar keratoses, oral papillomatosis, and sclerotic fibromas.<sup>224,225</sup> Pigmented macules of the genitalia, café-au-lait macules, acanthosis nigricans, skin tags, lipomas, and vascular malformations may also occur in CS.<sup>226</sup> Other benign extracutaneous manifestations include fibrocystic breast disease, breast fibroadenomas, thyroid adenomas, goiter, neuromas, meningiomas, and intestinal polyposis. Lhermitte–Duclos disease, considered to be a component of CS, results in hamartomatous growths arising in the cerebellum and presents with headache, ataxia, and visual disturbance. Patients with CS also have an increased risk of certain malignancies, including those of the breast (up to 30% to 50% of female patients) and thyroid gland (nonmedullary thyroid carcinoma, 3% to 10%).<sup>224,227</sup> The potentially increased risk of other cancers, including renal cell carcinoma, MM, and colon cancer is less clear.<sup>227</sup> Skeletal abnormalities may include macrocephaly, scoliosis, and pectus excavatum. Patients may also have mental retardation.

Management of patients with CS consists of early recognition, specialist referral, treatment for cutaneous lesions (as needed/available), genetic counseling, and appropriate cancer surveillance, which should include breast self-examination, regular physician examinations, mammography, breast MRI, and thyroid ultrasound.<sup>228</sup>

Mutations in the tumor-suppressor gene *PTEN*, which encodes a tumor-suppressor phosphatase involved in cellular regulation, have been detected in patients with CS as well as in patients with Bannayan–Riley–Ruvalcaba syndrome (BRRS; see below and Chapters 11 and 12), Proteus or Proteus-like syndrome (see Chapter 12), adult Lhermitte–Duclos disease, and autism-like disorders associated with macrocephaly.<sup>227</sup> CS and BRRS share many similarities, including the mucocutaneous findings of facial trichilemmomas, acanthosis nigricans, lipomas, palmoplantar keratoses, pigmented macules of the genitalia, and oral papillomatosis.<sup>226</sup> Mucocutaneous neuromas have been highlighted as another overlap finding that may be seen in both CS and BRRS.<sup>229</sup> Macrocephaly and developmental delay are also seen in BRRS. The identification of kindreds with both diseases in the family, as well as identical *PTEN* mutations and overlapping clinical features, suggested that CS and BRRS may represent different phenotypic expressions of the same disease.<sup>224,226,230</sup> Recently the disorders thus far attributable to *PTEN* mutations have been collectively referred to as *PTEN* hamartoma tumor syndrome.<sup>231</sup> In a prospective study of 368 individuals meeting criteria for CS and with confirmed germline *PTEN* mutation, incidence ratios were elevated not only for breast and thyroid cancer, but also for colorectal cancer, kidney cancer, and melanoma, suggesting the need for surveillance for these malignancies in this patient cohort as well.<sup>232</sup>

## TRICHOFOLLICULOMA

Trichofolliculoma is an uncommon benign appendageal neoplasm, again of hair follicle derivation, that usually occurs as a solitary lesion. Trichofolliculomas most often involve the head and neck regions of adults but may occur during childhood. Trichofolliculomas present as a 2- to 10-mm, slow-growing, flesh-colored or pearly papule or nodule with a smooth surface. There is often a central pore with a protruding woolly or cotton-like tuft of hair (a highly diagnostic clinical feature). On occasion, the protruding hairs may be so fine that a magnifying lens may be required to detect their presence. Treatment of trichofolliculoma by local surgical excision generally produces a good cosmetic outcome.

## PILOMATRICOMA

Pilomatrixoma (also known as *calcifying epithelioma of Malherbe* or *pilomatixoma*) is a benign tumor derived from the hair matrix that usually develops within the first two decades of life. Pilomatrixomas

usually present as solitary lesions of the face, neck, upper trunk, or upper extremities. The two most common locations in studies appear to be the head and neck and the upper extremities.<sup>233,234</sup> Clinically, pilomatrixomas appear as flesh-colored to white, firm papules or papulonodules that may have an overlying pink to blue hue (Fig. 9-47). They are generally very hard, owing to calcification, and may demonstrate a positive “teeter-totter sign,” whereby downward pressure directed at one end of the lesion causes the other end to spring upward in the skin. Another useful sign is the “tent sign,” whereby multiple facets and angles (resembling a tent) are visualized when the skin overlying the lesion is stretched (Fig. 9-48).

Pilomatrixomas range in size from 5 mm to over 5 cm in diameter. Although pilomatrixomas are usually not hereditary, familial cases have been recognized, and some familial forms have been associated with myotonic dystrophy, an uncommon autosomal dominant disorder characterized by hypotonia, muscle wasting, cataracts, hypogonadism, progressive mental retardation, and frontal baldness.<sup>235–237</sup> Multiple pilomatrixomas have also been noted in patients with Gardner syndrome, Rubinstein–Taybi syndrome, and trisomy 9.<sup>238–241</sup> Other



**Figure 9-47** Pilomatrixoma. This preauricular blue papulonodule was very firm to palpation.



**Figure 9-48** Pilomatrixoma. This lesion exhibits the “tent sign” as the adjacent skin is stretched.

variants include cystic-appearing pilomatrixomas, in which hemorrhage may result in blue-red translucent nodules with rapid enlargement; perforating pilomatrixomas; pilomatrix carcinoma (extremely rare); and extruding pilomatrixomas (draining lesions that spontaneously discharge a chalky material containing calcium). Activating mutations in  $\beta$ -catenin, a participant in the Wnt signaling pathway, have been identified in pilomatrixomas.<sup>242</sup> In patients with multiple pilomatrixomas, mutations in the adenomatous polyposis coli (*APC*) gene have been identified.<sup>243</sup>

Pilomatrixomas may occasionally develop inflammation or swelling and may be painful when subjected to pressure on the affected region of skin. Definitive therapy is accomplished by surgical excision. Patients with multiple lesions or familial disease should be examined and monitored closely for potentially associated disorders, especially myotonic dystrophy and Gardner syndrome. Importantly, the onset of myotonic dystrophy may not occur until adulthood, and molecular diagnosis is possible.<sup>236</sup>

### SYRINGOMA

Syringomas represent benign tumors of eccrine (sweat gland) structures and are predominantly seen in females. The lesions may occur at any age but commonly present initially during puberty or adolescence as small, firm, flesh-colored to yellow, translucent 1- to 3-mm papules (Fig. 9-49). They are usually multiple but may occasionally be solitary. In more than half of the patients the lesions are located on the lower eyelids. Other common locations include the lateral neck, chest, abdomen, back, upper arms, thighs, and genitalia. Syringomas occur with increased incidence in patients with Down syndrome. They may occasionally occur in an eruptive fashion and tend to be influenced by hormones, as evidenced by increased size during pregnancy or the premenstrual period and enlargement in women receiving hormone therapy.

Syringomas gradually enlarge until they attain their full size and then persist, with little tendency for spontaneous resolution. Although they are benign, they may be of significant cosmetic concern. Treatment, however, is difficult. Therapeutic options include electrode desiccation, cryosurgery with liquid nitrogen, or local surgical excision. CO<sub>2</sub> laser ablation and trichloroacetic acid have also been found useful.<sup>244</sup>

### ECCRINE POROMA

Eccrine poromas are benign cutaneous tumors that generally arise from the intraepidermal eccrine sweat duct unit. They occur most often during middle age or later but have been noted to develop as early as 15 years of age. Eccrine poromas present as firm papules, plaques, or nodules, and may be flesh-colored to red. They are usually solitary, and range in size between 2 and 12 mm in diameter. They



**Figure 9-49** Syringomas. These multiple, flesh-colored small papules were present bilaterally in the inferior periorbital regions of this young girl with Down syndrome.

most commonly occur on the plantar surface of the foot and occasionally on the palms, fingers, neck, or trunk. In some lesions, the appearance is quite vascular and may simulate pyogenic granuloma. A striking clinical feature is the presence of a cup-shaped shallow depression from which the tumor grows and protrudes. Malignant eccrine poroma, also known as eccrine porocarcinoma, is a very rare tumor usually occurring in adults, although pediatric cases have been reported.<sup>245</sup> The treatment of choice for eccrine poroma is surgical excision.

### CYLINDROMA

Cylindromas (also known as *turban tumors*) are benign neoplasms of either eccrine or apocrine origin and characterized by firm, rubbery, pink to bluish plaques and nodules. They may range in size from a few millimeters to several centimeters and are located primarily on the scalp and occasionally the face, trunk, or extremities. Cylindromas may occur singly or in multiples, and occasionally they coalesce to result in large mosaic tumors. Multiple lesions may occur as part of the autosomal dominant BSS (with multiple trichoepitheliomas and occasionally other appendageal tumors; see also *Trichoepithelioma* section). This disease has been mapped to 16q12-13, and mutations in the *CYLD* gene have been identified in families with this disorder.<sup>246,247</sup> Treatment consists of surgical excision, although CO<sub>2</sub> laser surgery has also been demonstrated useful.<sup>248</sup> Cylindromas are almost invariably benign, although malignant transformation has been rarely reported.

## Dermal Tumors

### ANGIOFIBROMA

Angiofibromas are benign dermal neoplasms that may occur as isolated or multiple lesions. The term *angiofibroma* actually describes the histologic appearance of these lesions (which reveals dermal fibroplasia and dilated blood vessels), but they may present in a variety of clinical fashions. Clinical subtypes include fibrous papules, pearly penile papules, and periungual fibromas. Another presentation pattern is that of multiple facial angiofibromas, which are commonly seen in patients with tuberous sclerosis (see Chapter 11), in which setting they have been erroneously referred to as *adenoma sebaceum*, multiple endocrine neoplasia type 1 (see Chapter 23), and Birt-Hogg-Dube syndrome (characterized classically by fibrofolliculomas, trichodiscomas, and acrochordons).<sup>249</sup>

A fibrous papule presents as a solitary, flesh-colored shiny papule, most often on the nose of adults. The differential diagnosis may include intradermal nevus, BCC, or another appendageal tumor. These lesions are treated with shave excision or electrocautery. Pearly penile papules present as tiny, flesh-colored to white papules on the glans penis of postpubertal men. They are most commonly distributed along the corona, and their importance lies in distinguishing them from genital condylomata (often a source of anxiety for the affected individual). This distinction is usually quite simple given their appearance, multiplicity, and localization. Treatment of pearly penile papules is unnecessary. Periungual fibromas present as flesh-colored filiform growths arising from the proximal nailfold region. Although they occasionally occur sporadically, multiple lesions are pathognomonic for tuberous sclerosis.

### CONNECTIVE TISSUE NEVUS

Connective tissue nevus (also known as *connective tissue hamartoma*) is a localized hamartoma of either dermal collagen or elastic fibers or both. These benign skin lesions may be sporadic or hereditary and can be seen as a component of several syndromes. For instance, the shagreen patch and fibrous forehead plaque seen in tuberous sclerosis (see Chapter 11) are both forms of connective tissue nevi. In addition, the palmoplantar cerebriform hyperplasia that occurs in patients with Proteus syndrome (see Chapter 12) represents excess collagen and thus could also be classified under this umbrella term. This section discusses primarily the sporadic, nonsyndromic form of connective tissue nevus.



**Figure 9-50** Connective tissue nevus. This flesh-colored, dermal plaque on the back of a school-aged boy had been present for several years.



**Figure 9-52** Darier sign in mastocytosis. Edema and surrounding erythema developed within minutes after firmly stroking this lesion.



**Figure 9-51** Connective tissue nevus. A cerebriform, fleshy plaque on the cheek of a newborn male.

These lesions usually present as asymptomatic, flesh-colored dermal plaques composed of multiple papules. They may be quite subtle (Fig. 9-50), or they may be associated with significant thickening, cobblestoning, or cerebriform changes (Fig. 9-51). Solitary plaques may occur anywhere on the cutaneous surface, and multiple lesions are often distributed symmetrically on the back, buttocks, and extremities. The differential diagnosis may include smooth muscle hamartoma (see [Congenital Smooth Muscle Hamartoma](#) section).

Another form of connective tissue nevus, dermatofibrosis lenticularis disseminata, has been reported in association with a specific bone dysplasia termed *osteopoikilosis*. This association is also known as Buschke-Ollendorf syndrome (see Chapter 6). The cutaneous lesions in this setting usually appear in adult life, but their onset has also been reported during the first year or early childhood. They appear as flesh-colored to yellow papules, usually a few millimeters in size, distributed on the trunk, buttocks, and extremities. They often represent hamartomas of elastic tissue (elastomas) histologically. The bony lesions are usually asymptomatic and are often noted incidentally as focal sclerotic areas on bone radiographs. They may occasionally be mistaken for foci of metastatic malignancy, highlighting the importance of familiarity with this disorder and its associated skin lesions.

Connective tissue nevi are generally asymptomatic and not usually of cosmetic significance. If the diagnosis is unclear, incisional biopsy is useful. Surgical excision is otherwise unnecessary.

## MASTOCYTOSIS

The term *mastocytosis* refers to a group of clinical disorders characterized by the accumulation of mast cells in the skin and at times other organs of the body. It may appear at any time from birth to middle age. In approximately 55% of patients, the onset occurs before the age of 2 years, and for 10%, the onset is between 2 and 15 years of age.<sup>250</sup> Mastocytosis may be congenital in up to 25% of pediatric-onset cases. The growth and regulation of mast cells is dependent on stem cell factor, which is the ligand for the protein product of the *c-KIT* gene. Studies have documented *c-KIT* mutations in adult patients with mastocytosis, and activating *c-KIT* mutations have also been demonstrated in pediatric mastocytosis in codon 816 (exon 17) as well as exons 8 and 9.<sup>251</sup> Although mastocytosis is generally a sporadic disorder, familial cases have been reported.<sup>252–254</sup>

The clinical spectrum of cutaneous mastocytosis includes mastocytomas (single or multiple), urticaria pigmentosa, bullous mastocytosis, diffuse cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans (TMEP). The traditional classification of adult disease includes indolent mastocytosis, mastocytosis with an associated hematologic disorder, mast cell leukemia, and lymphadenopathic mastocytosis with eosinophilia.<sup>250</sup> Alternatively, for either pediatric or adults patients, mastocytosis may be divided into cutaneous and systemic forms with the potential for overlap between these two. Although the disease may be classified by several different schemas, there appear to be some fairly consistent differences between adult and pediatric mastocytosis. These include the following for pediatric disease: early onset, usually within the first year of life; rare occurrence of TMEP; tendency toward spontaneous resolution, often before puberty; rare association with hematologic disorders; and rare infiltration of other organs aside from the skin.<sup>255</sup>

Although the classification of mastocytosis is often confusing, it can be somewhat simplified when considering the typical childhood presentations. Children most commonly present with mastocytomas (either solitary or multiple), urticaria pigmentosa, or occasionally diffuse cutaneous mastocytosis. All three of these childhood forms may display vesicular or bullous variants. Vesiculation is presumably related to histamine- or other chemical mediator-induced transudating leakage in a group susceptible to blister formation by less secure attachments of the epidermis to the underlying dermis.<sup>256</sup>

The diagnosis of all forms of cutaneous mastocytosis is aided by the phenomenon known as the Darier sign. This finding, a hallmark of the disorder, is seen in 90% of patients with skin disease and consists of localized erythema and urticarial wheals (Fig. 9-52) that develop after gentle mechanical irritation, such as might be induced by rubbing with a tongue blade or the blunt end of a pen or pencil. This urtication develops within a few minutes after the stimulus and may persist as long as 30 minutes to several hours. Occasionally, blister formation may result. It should be noted, though, that the Darier sign

### Box 9-3 Potential Triggers of Mast Cell Degranulation

#### Physical

Exercise, heat, hot baths, hot beverages, cold exposure, sunlight, stress

#### Medications (systemic)

Aspirin, alcohol, morphine, codeine, dextromethorphan, NSAIDs, opiates, amphotericin B, thiamine

#### Medications (topical)

Polymyxin B

#### Medications sometimes used with general anesthesia

D-tubocurarine, scopolamine, decamethonium, gallamine, pancuronium

#### Local anesthetics

Tetracaine, procaine, methylparaben

#### X-ray contrast

Iodine-containing contrast media

#### Venoms

Snakebites, bee stings, jellyfish stings

#### Foods

Egg white, crawfish, lobster, chocolate, strawberries, tomatoes, citrus, ethanol

NSAIDs, Nonsteroidal anti-inflammatory drugs.



**Figure 9-53** Solitary mastocytoma. An edematous plaque with mild surrounding pigmentation.

may be negative in mastocytosis, especially in patients with entirely flat lesions at baseline.

Mast cell mediators include histamine, prostaglandin D<sub>2</sub>, heparin, tryptase, chymase, leukotrienes, and others. Cutaneous symptoms related to release of these mediators in the setting of mastocytosis may include flushing, blistering, and itching. Systemic symptoms may include nausea, abdominal pain, diarrhea, bone pain, hypotension, and less often, pulmonary signs. Whereas the extent and density of cutaneous lesions may correlate with systemic symptoms in adults, such a correlation is lacking in children with mastocytosis.<sup>257</sup> There are many potential triggers of mast cell degranulation, including physical stimuli, drugs, and foods, and these are listed in **Box 9-3**. Most of these triggers are clinically insignificant in children with more mild forms of the disease, but exposures should be minimized in those at the more severe end of the spectrum or with a history of related systemic symptoms. A disease severity index, referred to as the *Scoring Mastocytosis (SCORMA) index*, has been developed and was demonstrated to correlate with the serum tryptase level in pediatric and adult cutaneous mastocytosis.<sup>258</sup> This index incorporates extent of surface area involvement, lesion intensity, and subjective symptoms (i.e., flushing, diarrhea, pruritus).

Mastocytomas are a common type of childhood mastocytosis. They may be either solitary or multiple and present as flesh-colored to yellow-orange-tan papules (**Fig. 9-53**) or plaques. Some lesions may have a bruise-like appearance, and others may present in similar fashion to café-au-lait macules.<sup>255</sup> They may range in size from a few



**Figure 9-54** *Peau d'orange* appearance of a mastocytoma. This plaque-like mastocytoma shows the characteristic surface changes.

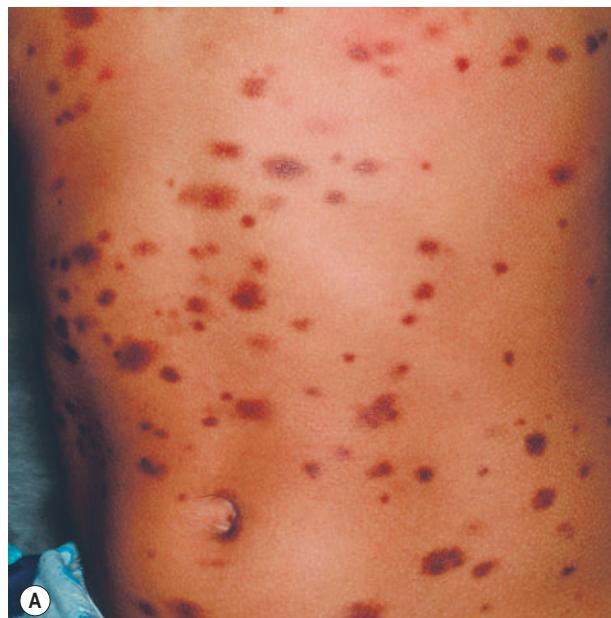
millimeters to several centimeters and are present at birth in around 40% of patients.<sup>259</sup> In the remainder, they generally appear by one year of age. The surface of the lesion often reveals a *peau d'orange* (orange peel-like) appearance (**Fig. 9-54**), and the Darier sign is notoriously positive. Occasionally stroking or rubbing of even a solitary lesion may provoke symptoms of flushing or colic. Mastocytomas may occur on any part of the body but are noted most often on the arms, neck, and trunk. A history of intermittent blistering of the affected area may be obtained, and in this setting misdiagnosis of bullous impetigo or herpes simplex infection is common. The tendency toward vesiculation tends to disappear within 1 to 3 years. Although the course of mastocytomas is generally benign and the lesions usually involute over several years, there have been reports of solitary mastocytosis eventuating in generalized urticaria pigmentosa.<sup>260</sup>

Urticaria pigmentosa is the most common presentation of mastocytosis. It presents with multiple, well-demarcated, tan to red-brown macules and papules (**Fig. 9-55**) that may occur anywhere on the cutaneous surface. Mucous membranes may be involved, and palms and soles are usually spared. Some lesions may have a purpuric quality, and occasionally a yellow coloration is noted. There may be tens to hundreds of lesions ranging in size from a few millimeters to several centimeters. The Darier sign is positive, and dermatographism may be present in 30% to 50% of patients. The lesions of urticaria pigmentosa may become vesicular or bullous (**Fig. 9-56**), a presentation termed *bullous mastocytosis*. These blisters may result in pain and secondary infection but generally heal without scarring. Beyond the age of 2 years, bullous changes are unusual.<sup>250</sup>

Diffuse cutaneous mastocytosis is a less common variant of mastocytosis, especially in children. This presentation is characterized by diffuse infiltration of the skin by mast cells with skin that may appear grossly normal, thickened, doughy, reddish-brown, or *peau d'orange* in texture (**Fig. 9-57**). There may be a yellow, carotenemia-like color present, and occasionally these patients present with extensive bullous eruptions. Patients with the diffuse cutaneous form appear to have the highest rate of systemic disease and may experience intense generalized pruritus, flushing, temperature elevation, vomiting, diarrhea, abdominal pain, GI ulceration, or respiratory distress. Overt shock may occur in this form of mastocytosis.

TMEP is a variant of mastocytosis seen usually in adults and only rarely reported in children. Patients with TMEP have an eruption of small, red-brown, telangiectatic macules on the trunk and extremities with little or no tendency toward urtication.

Systemic mastocytosis is markedly more common in adults than in children with mastocytosis. The most commonly involved systems are GI and skeletal, although the lungs, kidneys, lymph nodes, myocardium, pericardium, liver, spleen, and bone marrow may also be affected. Skeletal lesions may consist of radiopacities, radiolucencies, or a mixture of both. These changes are quite rare in children with the disorder.<sup>261</sup> Hepatomegaly, splenomegaly, and lymph node



A



B

**Figure 9-55** Urticaria pigmentosa. **(A)** Multiple hyperpigmented macules and papules in this 2-year-old girl. **(B)** Light tan macules and papules in a school-age boy. Note the Darier sign, which occurred after rubbing the lesion.



**Figure 9-57** Diffuse cutaneous mastocytosis. This child had diffuse erythematous yellow plaques and *peau d'orange* surface changes.

enlargement may also occur. GI symptoms include abdominal pain, diarrhea, nausea, and vomiting. GI hemorrhage may occasionally occur and is often secondary to gastritis or peptic ulcer disease. Children with the diffuse cutaneous form of mastocytosis may be at particular risk for this complication.<sup>250</sup> The "mastocytosis syndrome" results from massive histamine release with symptoms including bronchospasm, headache, flushing, diarrhea, pruritus, and hypotension. It occurs most often in infants or young children with the diffuse cutaneous form of the disease, and death may occasionally result.

The increased risk of development of a hematologic malignancy is a major concern in adults with mastocytosis, but significant hematologic consequences in children are extremely rare.<sup>262</sup> In a series of 15 patients with pediatric mastocytosis who were observed for approximately 20 years, some bone marrow specimens revealed increased mast cells, but this finding was not predictive for disease severity or persistence of symptoms. Furthermore none of the patients in this series developed hematologic malignancy. The authors recommended bone marrow studies only in children with evidence of systemic disease including organomegaly, elevated tryptase, or unexplained peripheral blood abnormalities.<sup>263</sup>

Anesthetic management of pediatric patients with mastocytosis has traditionally been viewed as complex and risky given the nature of the disease, the degranulation effects of some anesthetic agents, and the reported adult literature. Recent reports, however, suggest that pediatric patients with cutaneous (vs. systemic) mastocytosis are at fairly low risk for major anesthesia-related complications.<sup>264,265</sup> Anesthesia considerations for patients with pediatric mastocytosis are listed in Box 9-4.

The diagnosis of pediatric mastocytosis is often based on the characteristic cutaneous findings and a positive Darier sign. Although it is usually a straightforward diagnosis, atypical or unusual presentations or those lacking skin involvement may pose a diagnostic challenge. When skin lesions are present, the diagnosis can be confirmed with skin biopsy, which reveals an accumulation of mast cells in the dermis. Special immunohistochemical stains such as Giemsa, toluidine blue, or tryptase antibodies may be useful in confirming the mast cell nature of the infiltrate. Biopsy of the bone marrow or GI tract may be necessary if such organ involvement is suspected and the patient lacks cutaneous lesions.

Indirect methods for diagnosing mastocytosis are also available. Measurement of serum tryptase, a protease produced by mast cells, is helpful in supporting the diagnosis.<sup>266</sup> Two forms ( $\alpha$  and  $\beta$ ) have been identified, and measuring both of these mediators can be useful for correlation with the extent of mast cell disease. Urinary histamine and its metabolites may also be helpful. High levels of urinary N-methylhistamine may be suggestive of more extensive involvement.<sup>267</sup> Urinary N-methylimidazoleacetic acid is another histamine metabolite that is useful as a chemical marker for the disease.<sup>268</sup>

Extensive laboratory or radiographic studies or invasive diagnostic procedures in pediatric patients with mastocytosis are generally not



**Figure 9-56** Bullous mastocytosis. This 8-month-old female had widespread mastocytosis with blister formation. Note the diffuse distribution of infiltrative plaques, *peau d'orange* changes, superficial erosions, and intact bullae of the shoulders, upper back, and flank.

#### Box 9-4 Anesthesia Considerations in Pediatric Mastocytosis Patients

- Ensure adequate familiarity of anesthesiologist with pediatric mastocytosis and preparedness to treat possible adverse events during anesthesia
- Review detailed history of past clinical drug reactions before anesthesia
- Consider baseline serum tryptase, which may be useful to:
  - Suggest systemic mastocytosis (and concomitant higher risk of anesthetic reaction), if extreme elevation
  - Diagnose possible anesthesia-related adverse events, if significantly elevated from baseline
- Avoid preoperative drug skin testing
- Continue scheduled maintenance mastocytosis medications
- Consider administration of incremental (vs. single boluses) of necessary agents known to be mast cell degranulators
- Administer NSAIDs with caution and only in the absence of a history of sensitivity
- Consider patient positioning to minimize mechanical pressure on skin during anesthesia

Modified from Carter MC, Uzzaman A, Scott LM, et al. Pediatric mastocytosis: routine anesthetic management for a complex disease. *Anesth Analg* 2008;107:422–7, and Ahmad N, Evans P, Lloyd-Thomas AR. Anesthesia in children with mastocytosis: a case based review. *Paediatr Anaesth* 2009;19(2):97–107. NSAIDs, Nonsteroidal anti-inflammatory drugs.

indicated. However, in patients with extensive disease (i.e., extensive urticaria pigmentosa or diffuse cutaneous mastocytosis), complete blood cell count with peripheral smear and blood chemistry studies should be performed with occasional follow-up tests. Other diagnostic studies such as abdominal ultrasound, endoscopy, bone scan, or bone marrow biopsy should be reserved for patients in whom specific symptoms suggest systemic disease.<sup>250,262,263</sup>

The course and prognosis of mastocytosis depends on the clinical subtype, severity of disease, and age of onset. In general, the prognosis for childhood mastocytosis is favorable in most patients. Symptoms are estimated to improve by adolescence in up to 50% of patients,<sup>269</sup> but complete resolution may occur less often than previously believed. In one study, 5 of 33 children had complete resolution, and 21 of the 33 had improvement by adolescence.<sup>270</sup> In the previously mentioned series of 15 pediatric patients with mastocytosis studied longitudinally over 20 years, complete regression of disease occurred in 67%, and another 20% experienced major regression of symptoms.<sup>263</sup>

The treatment of mastocytosis is primarily symptomatic, because no specific therapy or cure currently exists for this disorder. Patients (and/or their parents) should be counseled about the disease, its natural history, differences between pediatric and adult mastocytosis, and possible triggers of mast cell degranulation (see Box 9-3). Nonselecting histamine type 1 (H1) receptor antagonists are a good initial treatment of choice and include cetirizine, levocetirizine, loratadine, and fexofenadine. The long half-life and nonsedating nature of these medications offer advantages over traditional antihistamines. In patients with severe involvement or symptoms, a classic H1 antagonist (i.e., hydroxyzine, diphenhydramine, and cyproheptadine) may be useful. The addition of an H2 antagonist (i.e., cimetidine, ranitidine, famotidine) may be considered, especially in patients with flushing or marked GI symptoms.

Oral cromolyn sodium has been found useful in treating GI symptoms of mastocytosis, although controlled studies in children are lacking. Ketotifen, a mast cell stabilizer unavailable in the oral form in the United States, has shown promise in alleviating symptoms. Psoralen plus ultraviolet A light (PUVA) therapy has been demonstrated useful in urticaria pigmentosa, diffuse cutaneous mastocytosis, and systemic mastocytosis.<sup>271,272</sup> This therapy is more challenging though, and has a higher risk-to-benefit ratio in children. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), although they may induce mast cell degranulation, may paradoxically be used to reduce prostaglandin-dependent flushing in some patients. Although topical agents are not typically effective, some mastocytomas have been noted to improve or disappear after therapy with a potent topical corticosteroid under occlusion. Additionally, two patients were reported whose mastocytomas responded to topical pimecrolimus cream in



**Figure 9-58** Granuloma annulare. Annular, flesh-colored, non-scaly plaques.

conjunction with a daily oral antihistamine.<sup>273</sup> A brief course of oral corticosteroids (i.e., 1 mg/kg per day of prednisone or prednisolone for 4 to 6 weeks) may be quite effective for symptomatic patients but obviously is not an appropriate long-term therapy. Cyclosporine and interferon  $\alpha$ -2b have been used in some adults with more aggressive forms of mastocytosis, and imatinib (a tyrosine-kinase inhibitor used in the treatment of some malignancies) was reportedly effective in a young adult with pediatric-onset, indolent systemic mastocytosis.<sup>274</sup> Lastly, patients (parents of children) at risk for recurrent hypotensive episodes or mastocytosis syndrome should have a premeasured epinephrine pen kit (EpiPen or EpiPen Jr) with them at all times for emergency use. Information regarding patient support groups and education for pediatric mastocytosis ([www.mastokids.org](http://www.mastokids.org)) should be given.

#### GRANULOMA ANNULARE

Granuloma annulare (GA) is a fairly common skin disorder characterized by papules or nodules grouped in a ring-like or circinate configuration. Although GA may occur on any part of the body, it often involves the lateral or dorsal surfaces of the hands, feet, wrists, and ankles. Patients may have solitary lesions or multiple sites of involvement. GA may occur at any age and is especially common in school-age children.

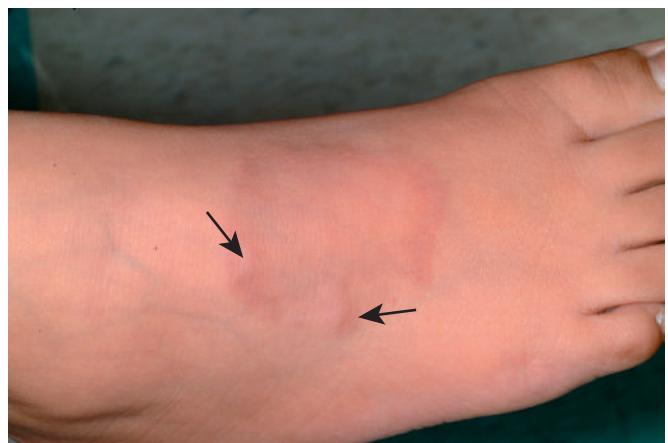
The cause of GA is unknown. Various studies have suggested a possible association between GA and diabetes mellitus, but this hypothesis remains controversial and some studies refute it.<sup>275–277</sup> There appears to be a greater risk of dyslipidemia in adult patients with GA, notably the generalized form; in one case-control study, adults with GA had four times the odds of developing dyslipidemia (including significant differences in total cholesterol, triglycerides and low-density lipoprotein-C levels) compared to age- and sex-matched controls.<sup>278</sup> This association has not been confirmed in children. Other purported associations have included tetanus or bacille Calmette-Guérin (BCG) vaccination, hepatitis B infection, *Borrelia* infection, Hodgkin disease, leukemia, or a hypersensitivity reaction to an unidentified antigen.<sup>279–282</sup> In some individuals GA has been noted following trauma, sun exposure, and insect bites.

GA most classically presents with an annular, smooth, non-scaly plaque with a border composed of numerous small papules (Figs. 9-58 and 9-59). Patients are often misdiagnosed with tinea corporis and have previously failed topical antifungal therapy. Early lesions begin as smooth, flesh-colored to pink papules that slowly enlarge peripherally and undergo central involution to form the classic rings with clear centers and elevated borders. Lesions may range in size from 5 mm to several centimeters.

There are several clinical variants of GA. A generalized form may occur, in which patients have multiple, disseminated, small papular lesions. Perforating GA presents as grouped papules, some of which have a central umbilication or crusting and scaling. This form is seen mainly on the extremities. Subcutaneous GA (Figs. 9-60 and 9-61) is



**Figure 9-59** Granuloma annulare. This patient has a semiannular, flesh-colored to pink plaque on the dorsal foot.



**Figure 9-61** Granuloma annulare. This patient's plaque reveals both cutaneous and subcutaneous (arrows) involvement.



**Figure 9-60** Subcutaneous granuloma annulare. Subcutaneous nodules on the forearm.

an important subtype in children, in whom it is most common. This form presents as subcutaneous nodules, distributed mainly on the feet, anterior tibial surfaces, fingers, hands, and scalp.<sup>283,284</sup> Penis lesions have also been rarely reported.<sup>285</sup> These lesions are usually painless and only occasionally slightly tender. The differential diagnosis of these lesions includes rheumatoid nodules, trauma, infection, malignancy, and tumor. Incisional biopsy is often necessary to confirm the diagnosis, unless there are classic cutaneous GA lesions present elsewhere on the skin surface.

Lesions of GA usually disappear spontaneously without sequelae and within several months to years. There is no satisfactory therapy for GA, but since the lesions are nearly always asymptomatic, watchful waiting is often acceptable. Topical corticosteroids, either ointments, creams, or impregnated into tape may be effective but are limited by their potential in causing skin atrophy. Intralesional corticosteroid

injection has also been utilized in some patients. Cryotherapy has been used, as have a variety of systemic agents (including isotretinoin, prednisone, dapsone, doxycycline and cyclosporine), but the risk-to-benefit ratio is generally not justified for these drugs. Occasionally the lesions spontaneously regress after skin biopsy. Until the association with diabetes mellitus is clearly established or refuted, patients with GA should be monitored by their primary physician for signs or symptoms, and if there is any concern or a strong family history, testing should be considered. Serum lipid testing should be considered in patients with more generalized involvement.

## NEUROFIBROMA

Neurofibromas may appear as isolated, usually single lesions in a healthy individual or as a cutaneous marker of dominantly inherited type 1 neurofibromatosis (NF1, von Recklinghausen disease; see Chapter 11). Lesions not associated with NF1 are discussed here.

Neurofibromas are benign tumors composed of neuromesenchymal tissue, including Schwann cells, endoneurial and perineurial cells, and other cellular components. They often present during young adulthood and occasionally early in life. Clinically, a neurofibroma presents as a soft, flesh-colored, solitary papule or papulonodule. They may occasionally be red, blue, or brown. They range in size from 2 mm to 2 cm, and with further growth they become globular, pear-shaped, pedunculated, or pendulous. Neurofibromas exhibit a positive “buttonhole” sign that is felt to be pathognomonic, whereby direct pressure on top of the lesion results in easy invagination into the dermis. This sign may be useful in differentiating neurofibromas from intradermal nevi or dermatofibromas.

When multiple neurofibromas are present, the diagnosis of NF1 must be considered. The presence of café-au-lait macules, axillary or inguinal freckling, or a plexiform neurofibroma lends further support to this diagnosis. Plexiform neurofibroma presents as a large, lobulated nodular plaque that may have a “bag of worms” consistency on palpation. These lesions are considered pathognomonic for NF1 (see Chapter 11). Sporadic neurofibromas are best treated with surgical excision.

## DERMATOFIBROMA

Dermatofibroma (fibrous histiocytoma) is a benign neoplasm of connective tissue generally seen in adults; occasionally it is seen in children. It presents as a small, well-defined dermal nodule that is firmly fixed to the skin but freely movable over the subcutaneous fat. There is often a tan to brown color of the surface (Fig. 9-62). Dermatofibromas may be found on any part of the body and are common on the extremities, particularly the anterior surface of the leg. They range in size from 1 mm to 2 cm. A useful diagnostic feature is the “dimple sign,” whereby pinching the lesion results in downward displacement.



**Figure 9-62** Dermatofibroma. This gray-brown papule on the right superior buttock was very firm to palpation and showed a “dimple sign” with lateral pinching (see text for discussion).

The differential diagnosis may include melanocytic nevus or cyst. Although treatment of dermatofibromas is unnecessary, surgical excision may be performed for cosmetic purposes or diagnostic confirmation.

### DERMATOFIBROSARCOMA PROTUBERANS

Dermatofibrosarcoma protuberans (DFSP) is a slowly growing fibrohistiocytic tumor with intermediate malignant potential seen primarily in adults between the second and fifth decades of life. These lesions tend to be locally invasive, have a high recurrence rate after excision, and occasionally result in metastatic disease. Pediatric and even congenital cases are occasionally observed, although most lesions present during the second to fifth decades of life.

DFSP usually begins as erythematous to blue papules and nodules that increase in size and may ultimately become multinodular and protuberant. Some lesions present as atrophic plaques. Ulceration may be present. The majority of lesions occur on the trunk or proximal extremities (Fig. 9-63), and the scalp, neck, and face are occasionally involved. During infancy or early childhood, DFSP may be misdiagnosed as a vascular malformation or tumor given the vascular appearance of many lesions.<sup>286,287</sup> Other initial impressions may include keloid, dermatofibroma, morphea, scar, or epidermal cyst.<sup>288</sup> Significant variability in presentation appears to be common with congenital lesions, which are rare but well documented.<sup>287</sup>

DFSP has been linked to a chromosomal translocation, t(17;22), which fuses the collagen type 1, alpha 1 (COL1A1) and PDGF $\beta$  genes.<sup>289</sup> The treatment of choice for DFSP is complete surgical excision with adequate margins. In recent years, MMS has evolved as the therapeutic standard of care, and it has been demonstrated to offer superior cure rates, smaller surgical margins, and fewer surgical sessions when compared with wide local excision in treating congenital DFSP.<sup>290</sup> MMS in conjunction with a vacuum-assisted closure system has been reported as useful for treatment of pediatric DFSP, with associated decreased rates of infection and complications.<sup>291</sup> Radiation therapy and imatinib have been recommended when clear surgical margins are unobtainable, the tumor recurs, or there is concern about metastases.<sup>292</sup> In patients with DFSP, lifelong clinical follow-up care is recommended given the risk of recurrence; however, metastatic spread is fortunately quite rare.<sup>293</sup>

### Fibromatoses

The fibromatoses are a group of disorders marked by fibrous and fibrohistiocytic proliferations in the skin. These disorders may represent neoplastic or reactive processes and tend to be benign in nature, although several have the potential for recurrence after excision. In this section, three pediatric fibromatoses are discussed.



**Figure 9-63** Dermatofibrosarcoma protuberans (DFSP). This red nodule was present at birth on the proximal thigh of this young boy. Punch biopsy revealed changes of DFSP, and it was ultimately treated with complete surgical excision.



**Figure 9-64** Recurring digital fibroma of childhood. A firm, erythematous tumor on the lateral surface of the fourth toe.

### RECURRING DIGITAL FIBROMA OF CHILDHOOD

Recurring digital fibroma of childhood (RDFC; also known as *recurring infantile digital fibomatosis*) is a rare, benign childhood fibromatosis. It usually occurs on the dorsal and lateral aspects of the fingers and toes and presents at birth or less commonly during infancy or later childhood. The majority of lesions are present by 12 months of age.<sup>294</sup> Interestingly, the thumbs and great toes are usually spared.

RDFC presents as flesh-colored to slightly erythematous papules and nodules (Fig. 9-64). Lesions are usually multiple and tend to affect multiple digits. They may become as large as 2 cm in size. Joint deformities and lateral deviation or flexion deformities may occasionally be associated.<sup>294,295</sup>

The etiology of RDFC is unknown, and although a viral etiology was once postulated based on eosinophilic inclusion bodies seen on histologic examination, there appears to be little evidence in support of this



**Figure 9-65** Solitary myofibroma. This lesion was congenital and spontaneously resolved by 1 year of age.



**Figure 9-66** Multiple myofibromas. Firm, rubbery nodules and plaques on the thigh of an infant.

hypothesis.<sup>296</sup> Management of RDFC is controversial. Arguments in favor of a conservative watchful waiting approach include the observation that many lesions spontaneously regress over a few years, that excision of the lesions does not alter the natural history of the joint disease (when present), and that excision is often followed by recurrence.<sup>297</sup> However, some assert that surgical excision is indicated to prevent continuous growth and involvement of deeper tissues and because some lesions do not spontaneously resolve. Medical approaches including topical imiquimod, intralesional fluorouracil, and topical or intralesional corticosteroids have yielded inconsistent results.<sup>298</sup> For smaller lesions without functional impairment, it seems that conservative management of RDFC is most appropriate.

### INFANTILE MYOFIBROMATOSIS

*Infantile myofibromatosis* is a term used to describe two fibrous disorders (infantile myofibromatosis and congenital generalized myofibromatosis) that represent two variants of the same process. Patients with these conditions have neoplasms composed of myofibroblasts, a distinct cell type that appears to also be involved in RDFC (see the previous section). Some cases of infantile myofibromatosis may mimic congenital infantile fibrosarcoma, and in these patients, molecular analysis for the *ETV6–NTRK3* gene fusion transcript (present in some infantile fibrosarcomas) may be useful.<sup>299</sup> Both autosomal recessive and autosomal dominant forms of infantile myofibromatosis have been reported. Missense mutations in *PDGFRB*, which encodes the platelet-derived growth factor receptor-β, have been identified in several families with autosomal dominant infantile myofibromatosis.<sup>300</sup>

In infantile myofibromatosis, fibrous nodules may occur in skin, subcutaneous tissue, skeletal muscle, and bone. Most patients have solitary lesions, and the most common sites of involvement are the head and neck regions.<sup>301</sup> The myofibromas, which are often congenital,<sup>302</sup> appear as flesh-colored to purple, firm or rubbery papules (Fig. 9-65), nodules, or plaques. The differential diagnosis of a solitary myofibroma may include infantile hemangioma, histiocytoma, mastocytoma, and infantile digital fibroma. Visceral involvement is rare when the cutaneous lesion is solitary.

Multiple myofibromas, a condition that has also been termed *congenital generalized myofibromatosis*, presents with scattered cutaneous and subcutaneous tumors (Fig. 9-66) in addition to lytic bony lesions. Radiography reveals multiple radiolucent areas in the metaphyseal regions.<sup>303</sup> These patients may also have muscle and visceral involvement, with lesions in the GI tract, lungs, kidneys, spleen, lymph nodes, meninges, nerves, thyroid, adrenal gland, and heart. Spinal canal involvement has also been reported.<sup>304</sup> Although the lesions do not tend to be locally aggressive or metastasize, their space-occupying nature in some anatomic regions may interfere with vital functions. The differential diagnosis of multiple myofibromas includes heman-



**Figure 9-67** Fibrous hamartoma of infancy.

giomatosis, juvenile xanthogranulomas, cutaneous metastases (i.e., from neuroblastoma or leukemia), mastocytosis, and sarcomas.

Since the cutaneous and subcutaneous nodules of infantile myofibromatosis tend to regress spontaneously, surgical excision is indicated only for diagnostic confirmation, to alleviate obstruction or potential trauma, or to treat lesions in which the clinical course is prolonged and progressive. Patients with lesions limited to skin and/or bone have a good prognosis. Those with disseminated multiorgan involvement have a higher incidence of morbidity and mortality. Chemotherapy has been utilized for patients with severe involvement, and a regimen of low-dose vinblastine and methotrexate has been reported as useful while minimizing chemotherapy-related toxicity.<sup>305</sup>

### FIBROUS HAMARTOMA OF INFANCY

Fibrous hamartoma of infancy is a rare, benign, soft-tissue tumor that usually presents during the first 2 years of life. One in four cases is congenital, and around 90% occur within the first year of life.<sup>306</sup> It appears to be more common in boys and has a predilection for the upper trunk, axillae, upper extremities, groin, or genitalia.<sup>307</sup>

Fibrous hamartoma presents as a painless, flesh-colored subcutaneous nodule or nodular plaque (Fig. 9-67). Most cases are solitary, although multiple lesions may occur. They may be mobile or appear to be fixed to underlying tissues. The size of fibrous hamartoma is usually under 4 to 5 cm, although significantly larger lesions have been reported.<sup>308</sup> The clinical differential diagnosis may include infantile myofibromatosis (see previous section), calcifying aponeurotic fibroma, fibrolipoma, juvenile hyaline fibromatosis, and malignant



**Figure 9-68** Nevus lipomatosus superficialis. This soft, multilobulated plaque was present at birth in the superior gluteal cleft region.

soft-tissue sarcomas such as fibrosarcoma or rhabdomyosarcoma.<sup>309</sup> The natural history of fibrous hamartoma is characterized by slow growth, although rapid growth of lesions has been reported.<sup>306</sup> Histologic examination of biopsy tissue reveals the characteristic triad of tissues: adipose, fibrous, and myxoid mesenchymal tissue.

The treatment of choice for fibrous hamartoma of infancy is full surgical excision, although for excessively large lesions this may not be a feasible option. Local recurrence may occur in up to 15% of cases and is often noted within a few months after the primary surgery.<sup>310</sup> In lesions left untreated, growth continues until around 5 years of age, at which time it plateaus.<sup>311</sup>

## Tumors of Fat, Muscles, and Bone

### LIPOMAS

Lipoma, one of the most common benign tumors, is composed of mature fat (adipose) cells. It can be seen at any age but usually occurs at or after puberty. Lesions may be present on any part of the body but predominantly involve the subcutaneous tissues of the neck, shoulders, back, and abdomen. They may be single or multiple, and their size is variable with a characteristic soft, rubbery or putty-like consistency. Microscopic examination reveals encapsulated tumors of adipose tissue with essentially the same appearance as that of normal subcutaneous fat.

A rare nevoid variety, nevus lipomatous superficialis (Fig. 9-68), is characterized by clusters of soft, flesh-colored to yellowish papules, nodules, or plaques often located on the buttocks, lumbosacral region, or thighs. These lesions are often present at birth or develop over the first decade of life. Another lipoma variant, angiolioma, is clinically indistinguishable except that the lesions are often tender or painful and have a greater tendency to be multiple. Angiolipomas occur primarily in teenagers and young adults and commonly present on the upper extremities or trunk.

Lipomas and the discussed variants are benign lesions. Surgical excision is generally curative and is indicated for lesions that are painful or of cosmetic significance or for those lesions for which the diagnosis is uncertain (although incisional biopsy is another option in this setting). Three syndromes that have lipomas as a component will be briefly discussed: BRRS, encephalocriocutaneous lipomatosis (ECCL), and the Michelin tire baby syndrome.

### Bannayan–Riley–Ruvalcaba Syndrome

BRRS, or Bannayan–Zonana syndrome is an autosomal dominant, multiple hamartoma syndrome shown to be caused by mutations in the *PTEN* gene. The hallmark of BRRS is macrocephaly. Patients also have multiple subcutaneous or visceral lipomas and vascular malformations. Pigmented macules of the penis are common. Facial trichilemmomas as described in CS may also be seen, and the same *PTEN* mutations have similarly been described in this syndrome (see earlier this chapter). *PTEN hamartoma tumor syndrome* is the terminology currently used to describe a collection of rare syndromes (including BRRS, CS, and possibly Proteus syndrome) characterized by germline mutations in this tumor-suppressor gene.<sup>312,313</sup> Other clinical findings in BRRS include oral papillomas, acral (palmarplantar) keratoses,

acanthosis nigricans, joint hyperextensibility, scoliosis, pectus excavatum, and downslanting palpebral fissures. Hypotonia, developmental delay, and hamartomatous intestinal polyps may also occur.<sup>324</sup> The latter may result in chronic anemia, diarrhea, failure to thrive or small bowel intussusception.<sup>314</sup> Careful phenotyping has suggested that BRRS and CS represent one condition with variable expression and age-related penetrance.<sup>315</sup>

### Encephalocriocutaneous Lipomatosis

ECCL is a rare neurocutaneous syndrome characterized by mental retardation and unilateral skin and ocular lesions with ipsilateral cerebral malformations. The cutaneous lipomas in ECCL are most often limited to the scalp and may be accompanied by alopecia. A smooth, hairless fatty tissue nevus of the scalp is considered a hallmark finding and has been termed *nevus psiloliparus*.<sup>316</sup> Other cutaneous lesions may include skin tags, especially on the eyelids or along a line from the outer canthus to the tragus. Various ocular abnormalities including eyelid defects, epibulbar or limbal dermoids (also called *choristomas*), scleral desmoid tumors, and corneal clouding may occur.<sup>317,318</sup> CNS malformations are variable and include intracranial/spinal lipomas (most common), hemisphere asymmetry, cortical dysplasia, cysts, ventricular dilation, calcifications, and corpus callosum abnormalities.<sup>319</sup> Seizures are common and tend to start during infancy, and the developmental status of affected patients is varied, ranging from normal to profoundly delayed.<sup>316</sup> MRI of the brain and spine in patients with ECCL may reveal intracranial lipomas (often at the cerebellopontine angle), spinal lipomas, enlarged ventricles, widening of arachnoid spaces, arachnoid cysts, cortical dysplasia, and asymmetric cerebral atrophy.<sup>320</sup> The differential diagnosis includes Proteus syndrome, epidermal nevus (nevus sebaceous) syndrome, and oculocerebrocutaneous syndrome.

### Michelin Tire Baby Syndrome

*Michelin tire baby syndrome* (*Michelin tire syndrome*) is a term used to describe a very rare disorder of newborns characterized by numerous, conspicuous cutaneous folds (Fig. 9-69), presumably caused by excessive fat. Elastic fiber abnormalities have also been noted on ultrastructural examination of lesional skin (see Chapter 6).<sup>321</sup> The terminology is derived from the resemblance of affected patients to the mascot for the tire manufacturer Michelin. Recently, this disorder has also been referred to as *congenital symmetrical circumferential skin creases*, and it has been reported in both autosomal dominant and recessive forms.<sup>322</sup> Other histologic abnormalities that have been noted in these patients include nevus lipomatosis and smooth muscle hamartoma. A variety of extracutaneous defects including developmental delay/mental retardation, facial dysmorphism, microcephaly, musculoskeletal anomalies (including rocker-bottom feet, metatarsus abductus, and lax joints), hirsutism, hemiplegia, hemihypertrophy, chromosomal abnormalities, abnormal ears, and neurologic abnormalities may be associated, although there is significant phenotypic variability. Michelin tire baby syndrome may represent a nonspecific clinical presentation related to a variety of different causes.<sup>323</sup> Spontaneous improvement in the numerous folds often occurs with increasing age.<sup>324</sup>

### CONGENITAL SMOOTH MUSCLE HAMARTOMA

Congenital smooth muscle hamartoma is a benign skin disorder characterized by a proliferation of smooth muscle within the reticular dermis. It may be seen within or without an associated Becker nevus (see *Pigmented Lesions* section). Smooth muscle hamartoma, when presenting independent of Becker nevus, appears as a localized, slightly elevated, flesh-colored to faintly hyperpigmented plaque. The lesions may be extremely subtle on examination, but a useful feature is mild overlying hypertrichosis (Fig. 9-70) that may best be visualized with side lighting using a penlight or otoscope head. Rubbing of the plaque may cause a “pseudo-Darier” sign, with transient piloerection and the appearance of gooseflesh-like surface changes.

Although most lesions are congenital, they may not be noted until childhood or even early adulthood. Smooth muscle hamartoma is nearly always asymptomatic and rarely of cosmetic significance. Surgical excision is curative but rarely necessary.



**Figure 9-69** Michelin tire syndrome. This young girl had excess skin folds since early infancy (**A**), with gradual normalization as she aged (**B–D**). Her history was otherwise notable only for mild linear growth delay, which also improved.

## LEIOMYOMAS

Leiomyomas represent benign tumors principally derived from cutaneous smooth muscle. The majority of these lesions arise from arrector pili muscles, the media of blood vessels, or smooth muscle of the scrotum, labia majora, or nipples. Although found among all age groups, leiomyomas generally occur during the third decade of life and are relatively uncommon in childhood.

Cutaneous leiomyomas may be solitary or multiple and generally present as pink, red, or dusky brown, firm dermal nodules of varying size. They are subject to episodes of paroxysmal spontaneous pain. When multiple, leiomyomas are usually red-brown to blue, firm

intradermal nodules (Fig. 9-71) with a translucent or waxy appearance. They tend to occur on the back, face, or extensor surfaces of the extremities and are usually arranged in groups. Enlarging lesions may coalesce to form plaques with an arcuate or linear configuration. Multiple leiomyomas may be associated with common uterine fibroids, an autosomal dominant association termed *multiple cutaneous and uterine leiomyomatosis syndrome* (formerly known as *Reed syndrome*). This disorder, as well as another hereditary leiomyoma syndrome, hereditary leiomyomatosis and renal cell cancer, are both caused by heterozygous mutations in the fumarate hydratase (*FH*) gene.<sup>325,326</sup>



**Figure 9-70** Smooth muscle hamartoma. Note the mild hypertrichosis overlying this flesh-colored, dermal plaque.



**Figure 9-71** Leiomyomas. This 5-month-old male had clusters of flesh-colored to pink dermal papules in the popliteal region and the inguinal crease, confirmed on histology to represent piloleiomyomas.

Leiomyomas may be classified as hereditary or nonhereditary types and are characterized by unencapsulated tumors of smooth muscle bundles and masses with an irregular arrangement. Cutaneous leiomyomas have been divided into three types:

1. Piloleiomyomas, the most common type
2. Solitary genital or mammary leiomyomas, derived from the smooth muscle of the nipple and genital regions (referred to as the *dartoic type*)
3. Angioleiomyomas, arising from the tunica media of the blood vessels and embryonic muscle rests and most often found on the lower leg.

Leiomyosarcoma, a rare soft-tissue sarcoma, occurs primarily in older individuals and may have histologic overlap with leiomyoma. Clinically, these sarcomas are larger than leiomyomas and present as nondescript subcutaneous masses that may enlarge rapidly and ulcerate. Metastases, when they occur, generally spread through the bloodstream and lymphatics, and lung involvement is common. The histologic features most useful in distinguishing these tumors from benign leiomyomas are high cellularity, cytologic atypia, and obvious mitotic figures.

Leiomyomas are benign but have a high incidence of recurrence after removal. Surgical excision is the treatment of choice and is curative for smaller, localized tumors. When multiple leiomyomas are present, therapy is challenging and has included CO<sub>2</sub> laser ablation.



**Figure 9-72** Calcinosis cutis in juvenile dermatomyositis. This patient had painful, firm nodules of both knees and both elbows.

## MYOBLASTOMA

Myoblastoma (granular cell tumor) is an uncommon tumor that occurs most often as a solitary nodule in the head and neck regions and especially on the tongue. It is rare overall in children. Laryngeal involvement may occur in the posterior or anterior larynx, vocal folds, and arytenoids.<sup>327</sup> Patients with multiple tumors have been reported, occasionally in association with NF1.<sup>328</sup> Congenital epulis represents a granular cell tumor of the gingivae in a newborn that is usually marked by spontaneous involution. The origin of granular cell tumors is believed to be neural, with a Schwann cell derivation hypothesized but not proven. Surgical excision is the treatment of choice.

## CALCINOSIS CUTIS

*Calcinosis cutis* is a general term for calcium deposition in the skin. It may be related to abnormal calcium or phosphorus metabolism or damage to the dermal collagen, or it may be idiopathic in origin.<sup>329</sup> It may be focal or widespread. Calcinosis cutis has traditionally been divided into the following subtypes: dystrophic, idiopathic, metastatic, and iatrogenic. Tumoral calcinosis is another distinct subtype. Calcinosis occurring in association with some inherited disorders (such as pseudoxanthoma elasticum, Ehlers–Danlos syndrome, and Werner syndrome) is discussed elsewhere.

Dystrophic calcinosis cutis occurs after trauma or inflammation in the skin. This form may also be noted in the setting of diseases that predispose to deposition of calcium in the skin, such as juvenile dermatomyositis (Fig. 9-72; see Chapter 22, Figs. 22-30 and 22-31) scleroderma, and systemic lupus erythematosus. Calcium deposition in the skin may occur years before other stigmata of dermatomyositis become noticeable,<sup>330</sup> although more typically the calcifications occur years after the disease onset. In dystrophic calcinosis cutis, calcium and phosphorus metabolism are normal. Clinically, patients exhibit firm to rock-hard papules or larger subcutaneous plaques. Elbows, knees, and shoulders are common locations. Secondary ulceration and transepidermal elimination of calcium may occur (presenting as white, chalky material protruding from the affected area). In calcinosus universalis, as may be seen in juvenile dermatomyositis, extensive



**Figure 9-73** Calcinosis cutis in CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome. Painful, firm deposits with overlying skin breakdown on the distal digits of this teenaged girl with CREST syndrome.



**Figure 9-74** Heel-stick calcinosis cutis. Firm, white papulonodule at the site of prior heel-stick procedures.

subcutaneous deposits of calcium occur, and patients may appear to have an exoskeleton. This form has a particularly poor prognosis. Patients with the calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia (CREST) variant of scleroderma present with painful, calcified papules and nodules over bony prominences and distal digits (Fig. 9-73). Dystrophic calcinosis cutis can also be seen in the setting of some porphyrias, notably porphyria cutanea tarda, which is rarely encountered in children.<sup>331</sup>

A common setting for dystrophic calcinosis cutis is in infants after heel-stick procedures. These calcifications appear as firm, white to yellow papules on the heels (Fig. 9-74) and are most often seen in high-risk neonates after multiple needle sticks to these locations.<sup>332</sup> They can also occur in healthy neonates after only a single heel stick.<sup>333</sup>

Idiopathic calcinosis cutis occurs in individuals who have normal calcium and phosphorus metabolism and have no history of trauma or underlying inflammatory diseases. It may occur in various areas of the body, most commonly the scrotum (scrotal calcinosis), face, and female genitalia. Labial calcinosis cutis presents as white papules or nodules on the labia majora and is important to recognize, because it may be misdiagnosed as a condition associated with potential sexual abuse (i.e., condylomata or mollusca).<sup>329</sup> A subepidermal calcified nodule is a solitary, white to flesh-colored, firm papule or papulonodule (Fig. 9-75), most commonly occurring in children. These lesions are often seen on the face. Milia-like idiopathic calcinosis



**Figure 9-75** Subepidermal calcified nodule. Solitary, firm, white to flesh-colored papulonodule on the cheek.



**Figure 9-76** Milia-like idiopathic calcinosis cutis in Down syndrome. These firm, white papules were asymptomatic.

cutis presents with small, white papules that may discharge a chalk-like substance. These lesions occur most commonly on the hands (Fig. 9-76) and feet, and are usually seen in patients with Down syndrome.<sup>334,335</sup>

Metastatic calcinosis cutis occurs when calcium deposits form in the skin and soft tissue of patients who have altered metabolism of calcium and/or phosphorus. One association is chronic renal failure, which results in hypocalcemia with resultant secondary hyperparathyroidism with increased mobilization of both calcium and phosphate. Hypervitaminosis D and milk-alkali syndrome are other potential causes of metastatic calcinosis cutis. Calciphylaxis, or calcifying panniculitis, is a severe disorder characterized by vascular calcification with resultant ischemic necrosis of skin and soft tissue. It may result in gangrene and sepsis, and the mortality rate is high.

Tumoral calcinosis presents with calcifications in juxtaarticular sites, predominantly on extensor surfaces. These grow over months to years and often recur after surgical removal.<sup>336</sup> These lesions may attain a fairly large size (up to 20 cm) and may result in disfigurement or impaired function. This disorder may occur sporadically or in an autosomal dominant fashion and usually affects otherwise healthy adolescents.

Iatrogenic calcinosis cutis occurs when there is a precipitation of calcium salts in the skin. It most commonly occurs after extravasation of calcium gluconate or calcium chloride. It presents as yellow-white plaques (Fig. 9-77) that often reveal secondary inflammation. Lesions are most commonly (but not always) located around sites of prior intravenous line insertions.<sup>337</sup> Central ulceration may occur. These lesions tend to resolve over 4 to 6 months. Calcinosis cutis has also been reported after application of calcium chloride-containing electrode paste for electroencephalography, electromyography, and auditory-brainstem evoked potential recordings.<sup>338</sup>

Treatment of calcinosis cutis is challenging and may include surgical excision, curettage, low calcium and phosphate diet, and administration of aluminum hydroxide, diltiazem, colchicine, or etidronate (a



**Figure 9-77** Calcinosis cutis after extravasation injury.

bisphosphonate). Systemic warfarin therapy has been shown to be helpful for small calcified deposits but not with larger or long-standing lesions. Other reported treatments in various settings have included minocycline, ceftriaxone, intravenous immunoglobulin, probenecid, intralesional steroid injection, and CO<sub>2</sub> laser.<sup>339</sup> The underlying disorder, if present, should obviously be treated.

### OSTEOMA CUTIS

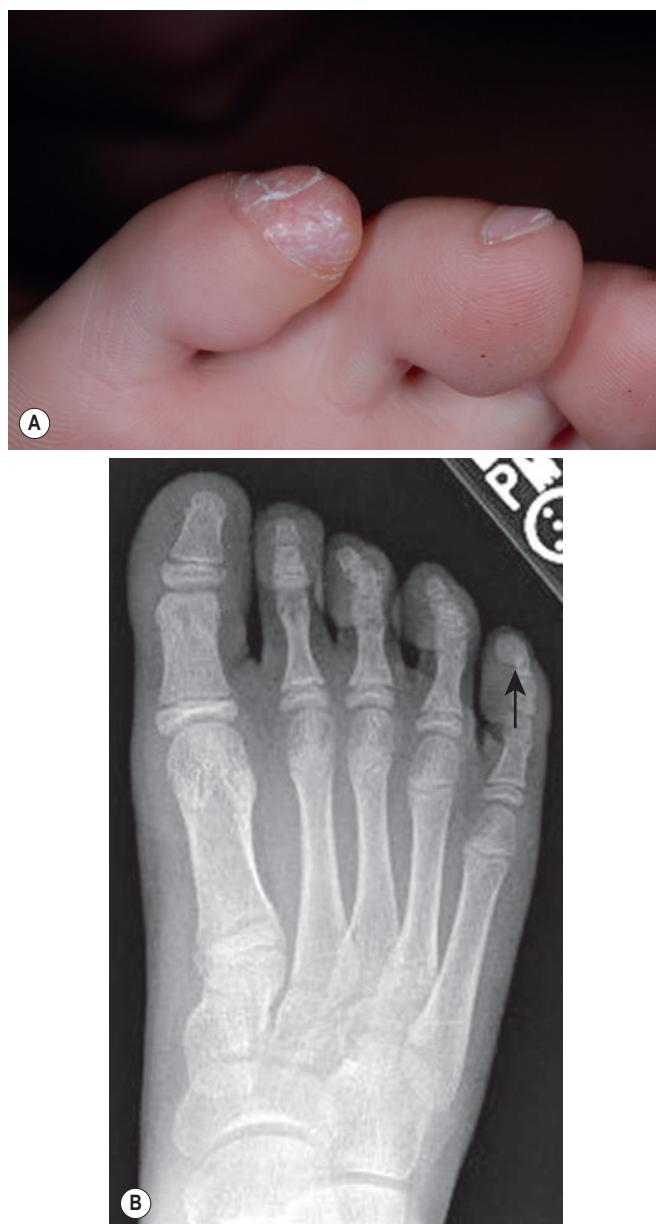
Cutaneous ossification (bone formation) is a rare phenomenon, especially in children, that may occur in a variety of settings. It may be primary or secondary. The term *osteoma cutis* is nonspecific but has traditionally been used to refer to a primary form of spontaneous bone formation in the skin associated with Albright hereditary osteodystrophy (AHO) or as an isolated idiopathic occurrence. Secondary cutaneous ossification occurs in areas of inflammation or neoplastic tissue and may also be seen in any disorder where calcification is present and in benign skin tumors or cysts.

AHO (see Chapter 23) is a genetic condition that may present with diffuse cutaneous ossification in conjunction with pseudohypoparathyroidism or pseudo-pseudohypoparathyroidism. These patients tend to be short and obese with a variety of dysmorphic features, including a classic foreshortening of the fourth and fifth metacarpals and metatarsals.

Progressive osseous heteroplasia (POH) is a rare disorder characterized by progressive ossification of skin, muscle, and connective tissue that may result in significant functional and cosmetic deformity. It usually begins in infancy and tends to be progressive.<sup>340</sup> It can be distinguished from another ossification disorder, fibrodysplasia ossificans progressiva (FOP), by the presence of cutaneous ossification, the absence of congenital malformations of the skeleton, the absence of tumor-like swellings, the asymmetric distribution of lesions, and the predominance of intramembranous rather than endochondral ossification.<sup>341</sup> In both of these disorders, calcium and phosphorus metabolism are normal, in distinction to patients with AHO. The prognosis of FOP is poor, whereas the prognosis of POH is variable. Plate-like osteoma cutis (POC) presents in infancy with one or a few areas of cutaneous ossification. These lesions tend to remain fairly localized, and these patients do not have abnormalities in calcium or phosphorus metabolism or other associated defects. The prognosis in POC tends to be good.

As can be seen, disorders of ossification may have a variety of presentations. Some of these disorders may be linked in some patients to mutations in the *GNAS* gene (also known as *GNAS1*), including isolated osteoma cutis, AHO, pseudohypoparathyroidism type 1a, pseudo-pseudohypoparathyroidism, and POH.<sup>342–344</sup>

Miliary osteomas of the face present as small, firm, flesh-colored to white or blue papules on the face. They have been observed in patients both with and without a history of acne vulgaris.



**Figure 9-78** Subungual exostosis. **(A)** This rock-hard nodule of the distal fifth digit was painful. **(B)** Radiographic evaluation revealed a well-demarcated bony projection projecting off the tip of the affected phalanx (arrow). Surgical excision was curative, with histology revealing trabecular bone with a cartilage cap, consistent with osteochondroma.

### SUBUNGUAL EXOSTOSIS

Subungual exostosis is a solitary hard nodule that occurs on the terminal border of the distal phalanx of a finger or toe. Although the great toe tends to be the most commonly afflicted, this disorder may involve other toes or occasionally a finger. However, fifth-toe involvement is unusual.<sup>345</sup> Subungual exostosis is a benign osteochondroma that occurs primarily in the second or third decade of life. Patients may report a history of preceding trauma, although for many this history is lacking.

Subungual exostosis presents as a pink or flesh-colored, 5- to 15-mm exophytic papulonodule that projects from the distal portion of the affected digit (Fig. 9-78, A). The surface of the lesion may become hyperkeratotic. Pain is common, and the portion of the nail overlying the lesion may be lifted and in some instances become detached. The

differential diagnosis includes wart, pyogenic granuloma, glomus tumor, epidermoid carcinoma, and amelanotic melanoma. The bony consistency upon palpation will usually suggest the correct diagnosis, and plain radiography (Fig. 9-78, B) can usually confirm it, revealing an exostotic tumor arising from the dorsal aspect of the tip of the distal phalanx.<sup>345</sup>

Surgical excision, with curettage of the base, is the treatment of choice for subungual exostosis. Recurrences happen occasionally.

## Miscellaneous

### EPIDERMAL CYST

Epidermal cyst (epidermoid cyst, epidermal inclusion cyst) is a discrete, slow-growing nodule that may appear any time after puberty and most commonly occurs on the face, scalp, neck, trunk, or scrotum. This is a true cyst with an epithelial lining. The term *sebaceous cyst* is an antiquated misnomer for this common tumor.

Epidermal cysts present as well-demarcated, firm to slightly compressible nodules, measuring from a few millimeters to several centimeters. An overlying central punctum, through which keratinous, foul-smelling debris may be extruded, is characteristic. Occasionally the lesions become inflamed, but true secondary infection is quite rare. Such inflammation occurs when rupture of the cyst wall occurs, and this is a common scenario prompting a visit to the physician.

Tiny epidermal cysts are termed *milia* (see Chapter 2). These lesions tend to be multiple, 1 to 2 mm in size, and white in color. In addition to occurring sporadically in healthy newborns, they may occur after abrasion trauma to the skin or in the course of bullous disorders such as epidermolysis bullosa and porphyria. Multiple cysts on the scrotum may occur and occasionally result in calcinosis cutis (see *Calcinosis Cutis* section). Pilar cysts (trichilemmal cysts, wens) are epidermal cysts that occur on the scalp, and chalazions represent analogous cystic tumors of the eyelids that develop from meibomian glands.

An important association with multiple epidermal cysts is Gardner syndrome. This autosomal dominant condition is characterized by cutaneous cysts and intestinal polyposis. Gardner syndrome is a form of familial adenomatous polyposis (FAP), an inherited colorectal cancer syndrome characterized by hundreds of adenomas involving the large bowel with progression (if untreated) to colorectal cancer by the fourth decade.<sup>346,347</sup> The term *Gardner syndrome* is used to describe the extracolonic manifestations that occur commonly in patients with FAP.<sup>348</sup> The epidermal cysts in Gardner syndrome, which are the most common cutaneous manifestation, are usually multiple, often present during early childhood, and can occur in any location, although they tend to occur most often on the face, scalp, and extremities. Multiple pilomatrixomas may also be seen in patients with Gardner syndrome.<sup>349</sup> Other findings include desmoid tumors, osteomas, fibromas, lipomas, abnormal dentition, thyroid tumors, and congenital hypertrophy of the retinal pigment epithelium (CHRPE).<sup>349</sup> The latter finding is often present at birth and as such usually precedes the development of intestinal polyposis.<sup>346</sup> Both FAP and Gardner syndrome have been mapped to the adenomatous polyposis coli (APC) gene, a tumor-suppressor gene.<sup>346,347,350</sup> Genotype–phenotype correlation studies have led some to suggest that the term *Gardner syndrome* is obsolete.<sup>347</sup>

Malignant degeneration (squamous cell or BCC) of epidermal and pilar cysts is rarely reported. Treatment consists of surgical excision with an attempt to remove the entire epithelial lining of the cyst in order to minimize the chance of recurrence.

### MUCOCELE (MUCOUS CYST)

Mucoceles (mucous cysts of the oral mucosa) present as soft, white to blue, solitary asymptomatic lesions, usually on the mucous surface of the lower lip and occasionally on the gingivae, tongue, or buccal mucosa. They are usually less than 1 cm in diameter and translucent (Fig. 9-79), containing a clear viscous fluid. Mucoceles are the result of minor trauma, causing rupture of a mucous duct and extravasation of sialomucin into the tissues. Treatment options include surgical excision, incision, and drainage followed by coagulation of the sac, CO<sub>2</sub> laser ablation, or cryosurgery. Occasionally lesions may rupture



**Figure 9-79** Oral mucocele. This lesion was ultimately excised because of continued enlargement.



**Figure 9-80** Congenital lingual melanotic macule. These dark brown macules on the dorsal tongue were congenital in onset for this 7-week-old healthy male.

spontaneously, although this is usually followed by eventual recurrence.

### CONGENITAL LINGUAL MELANOTIC MACULE

Melanotic macules of the oral mucosae include oral and labial melanotic macules, which are most often seen in young and middle-aged adults. The congenital lingual melanotic macule presents as a well-circumscribed, hyperpigmented macule (or macules) on the dorsal tongue (Fig. 9-80). Histopathologic evaluation reveals increased basal-layer melanin with some pigment-laden macrophages but normal melanocyte number and no nests of melanocytes, as would be expected in a congenital melanocytic nevus.<sup>351</sup> These lesions tend to grow proportionately with the child, and in some cases lightening may be noted with aging.<sup>352</sup>

### DIGITAL MUCOUS CYST

Digital mucous cyst (myxoid cyst) is a focal accumulation of mucin that presents as a soft, translucent, pink to blue, dome-shaped nodule on the dorsal aspect of the distal interphalangeal joint or proximal nailfold. Occasionally, the overlying nail plate reveals a longitudinal depression distal to the cyst. There is controversy over whether these lesions arise from degenerative changes or as a direct extension from the underlying joint space. Regardless, there appears to be a metabolic derangement of fibroblasts with increased production of hyaluronic acid in sites exposed to friction or minor trauma. In some patients,



**Figure 9-81** Steatocystoma multiplex. Yellow-tan, small papules of the forearm in this patient who also had lesions on the chest.

there may be a communication between the cyst and the underlying joint space.

Surgical excision is usually effective, but recurrences are common. Other therapeutic options include corticosteroid injection, cryosurgery, repeated incision and drainage, and CO<sub>2</sub> laser ablation.<sup>353–355</sup>

### STEATOCYSTOMA MULTIPLEX

Steatocystoma multiplex (SM) is a disorder characterized by numerous, 2- to 4-mm moderately firm, yellow to flesh-colored cutaneous cysts located primarily on the chest and occasionally the face, genitals, arms (Fig. 9-81), and thighs. The disorder has a high familial tendency and is often inherited in an autosomal dominant fashion. Lesions often appear or become larger around the time of puberty. In some patients, there may be overlap with eruptive vellus hair cysts (see Chapter 7), and both conditions seem to originate from the pilosebaceous duct.<sup>356</sup> SM may also occur in association with pachyonychia congenita (see Chapter 7), and both conditions may be caused by mutations in keratin 17.<sup>357</sup> In addition, persistent infantile milia may at times be associated with both SM and eruptive vellus hair cysts and may represent a disorder with predisposition to multiple pilosebaceous cystic lesions.<sup>358</sup>

The lesions of SM are rarely symptomatic but may occasionally be of cosmetic concern to the patient. Treatment can be accomplished with surgical excision or cyst puncture with evacuation of the contents. Other reported approaches include CO<sub>2</sub> laser therapy, oral isotretinoin, and cryotherapy.<sup>359</sup>

### KELOID

Keloids, which are benign dermal tumors characterized by invasive growth of fibroblasts and increased synthesis of collagen, represent an exaggerated connective tissue response to skin injury. They are rare in infancy, and their incidence increases throughout childhood, reaching a maximum between puberty and 30 years of age. African-American individuals and other darkly pigmented persons are more susceptible to keloids than individuals with fair skin, and the tendency toward keloid formation often runs in families.

Early lesions are pink, smooth, and rubbery (Fig. 9-82) and may be tender. With increasing age, keloids become less erythematous, more pigmented (Fig. 9-83), and firmer to palpation. Although they may occur anywhere on the skin surface, keloids are most common on the earlobes, upper chest, and back and in wounds located in areas under tension. As opposed to hypertrophic scars, keloids often persist at the site of injury, often recur after excision, and always overgrow the original boundaries of the wound.<sup>360</sup>

Treatment of keloids is notoriously difficult and often ineffective. In fact, lesions not uncommonly become larger after attempts at therapy. Regardless, these lesions are a source of much psychosocial anxiety



**Figure 9-82** Keloid. This early lesion is erythematous and only slightly firm to palpation.



**Figure 9-83** Keloid. This older keloid is very firm and hyperpigmented; it had recurred after an initial attempt at surgical removal.

and suffering for patients, and hence therapy is often attempted. Intralesional injection of corticosteroid (usually triamcinolone acetonide) is the most commonly utilized treatment and often requires multiple injections. This therapy is most effective for smaller lesions. Surgery is generally not recommended, given the propensity for lesions to recur or even worsen, but it is often used given the lack of other consistently effective therapies. It is often combined with adjunctive therapies such as steroid injections, silicone sheeting, and compression. Keloid core extirpation, a surgical approach involving excision of the inner core followed by a keloid rind flap, may be a more effective approach.<sup>360</sup> Other therapeutic options, each used with varying levels of success, include radiotherapy; pulsed dye, argon, or CO<sub>2</sub> laser therapy; and intralesional injections of bleomycin, interferon, mitomycin C (usually topically applied), or fluorouracil. Silicone gel and silicone sheeting have been used with variable success to treat both keloids and hypertrophic scars, but their mechanism of action remains unclear. It appears that the increased wound hydration that occurs with occlusive therapies may prompt keratinocytes to alter growth-factor secretion and thereby may affect fibroblast regulation.<sup>361</sup> Intralesional verapamil injections and topical imiquimod cream have also been used in combination with surgical excision.<sup>361,362</sup> Compression therapy via the use of compression garments may be helpful but can be difficult in terms of patient adherence and tolerability.<sup>363</sup>



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# 10 *Histiocytoses and Malignant Skin Diseases*

The histiocytoses are a broad group of disorders characterized by an abnormal proliferation of the histiocyte, a type of progenitor cell in the bone marrow (Box 10-1). Some clinically relevant types of histiocytes include the Langerhans cell, the dermal dendrocyte, and cells of mononuclear cell/macrophage lineage. Malignant disorders to be discussed include hematologic malignancies (including leukemia, lymphoma, and Hodgkin disease), neuroblastoma, and some sarcomas.

## Langerhans Cell Histiocytosis

*Langerhans cell histiocytosis (LCH)* is the term now used to describe a disorder characterized by infiltration of Langerhans cells into various organs of the body. Older synonymous terms, which are now largely obsolete or unnecessary, include histiocytosis X, eosinophilic granuloma, Letterer–Siwe disease, Hand–Schüller–Christian disease, and Hashimoto–Pritzker disease.<sup>1</sup> The term *histiocytosis X* was coined by Lichtenstein in 1953 to identify three related clinical entities of unknown etiology and characterized by histiocyte proliferation.<sup>2</sup> This classification included the triad of Letterer–Siwe disease, Hand–Schüller–Christian disease, and eosinophilic granuloma. The X in this original nomenclature was used to denote the unknown derivation of the histiocyte involved in this disorder. Ultrastructural studies eventually confirmed the relationship of these three different presentations by showing the Langerhans cell to be the proliferative cell in each of them. LCH may occur at any age, from newborn to elderly, although the peak incidence appears to be between the ages of 1 and 4 years.<sup>3</sup>

Langerhans cells are derived from the bone marrow and are a type of dendritic cell found primarily in the epidermis (as well as mucosal epithelia, thymus, esophagus, and lung). They are involved in antigen presentation for the skin- and mucosa-associated immune systems and are identified by strong staining with S100 (a neuronal protein) and cluster designation (CD) 1a (a cell surface marker). Langerhans cells also have a characteristic organelle, the Birbeck granule, which is visible on electron microscopy. The function of this organelle remains unknown. Immunohistochemical demonstration of langerin (CD207), a mannose-specific lectin found in association with Birbeck granules, has also been demonstrated useful for diagnostic confirmation of LCH.<sup>4</sup>

Although numerous etiologies have been proposed for LCH, the pathogenesis remains obscure. Hypothetic causes include somatic mutations, infection (especially viral), immune or cytokine dysregulation, and programmed cell death (apoptosis).<sup>3–6</sup> Whether LCH is a neoplastic versus a reactive disorder also remains debated. The cells in LCH have been demonstrated to be clonal, and such monoclonality has been demonstrated both in multisystem disease and with solitary organ involvement. Although this clonality suggests that LCH may be a neoplastic process with variable biologic behavior, the exact significance and implications remain controversial.<sup>3,4</sup> There are arguments both in favor of and against LCH being a neoplastic process.<sup>7</sup>

LCH may involve multiple organ systems, the most common being the skin and the bones. Table 10-1 lists the spectrum of organ involvement. The older classification system was based on the involved organ systems such that *eosinophilic granuloma* referred to localized bone disease; *Hand–Schüller–Christian disease* the multifocal triad of bone (usually skull) lesions, exophthalmos, and diabetes insipidus (DI); and *Letterer–Siwe disease*, the acute or subacute disseminated form of the disease. Under the more modern classification, LCH is the umbrella term for the disease with notation made of the various organ systems involved. Patients may have unifocal, multifocal, or disseminated

disease. In general, patients with widespread, multiorgan involvement have the poorest prognosis, and those with isolated bone LCH have the best prognosis.<sup>8</sup>

Cutaneous involvement is very common in LCH and is often the presenting complaint. The spectrum of skin findings is listed in Table 10-2. The most classic presentation is that of a seborrheic dermatitis-like eruption with prominent involvement of the scalp, posterior auricular regions (Fig. 10-1), perineum, and axillae. The rash tends to be resistant to standard therapy, which is an important clue that should prompt consideration of the diagnosis. Erythematous, red-brown papules are often seen, especially on the scalp and in flexural areas, and may have secondary erosion, hemorrhage, or crusting (Fig. 10-2). Crusted papules on the palms and/or soles (Fig. 10-3) are another important feature, especially in infants in whom the diagnosis of scabies has been excluded. Although this finding has traditionally been felt to portend a poor prognosis, this observation has not been validated.

In neonates with LCH, vesiculopustular lesions (Figs. 10-4 and 10-5) tend to predominate and may be misdiagnosed as congenital varicella or herpes.<sup>9</sup> These lesions may become hemorrhagic or crusted. Petechiae and hemorrhage may also be present in association with the dermatitis or the papular lesions of LCH, and they may be seen both with and without associated thrombocytopenia. Other less commonly seen cutaneous presentations include nodules and granulomatous, ulcerative lesions.<sup>10</sup> Box 10-2 lists some cutaneous clues to the diagnosis of LCH.

Mucosal involvement may occur in patients with LCH, especially those with more disseminated involvement. Gingival erythema, erosions, and hemorrhage may be seen. In some infants, gingival and oral mucosal erosions with premature eruption of teeth may be the initial manifestations of LCH.<sup>11</sup> Loosening of the teeth may occur as a result of severe gingivitis, especially when there is concomitant bony involvement of the alveolar ridge and jaw. Involvement of the external auditory canals may result in chronic otitis externa.

Bone lesions are very common in patients with LCH. When they occur, pain (with or without swelling) is the most common presenting complaint, and patients may complain of discomfort both during activity and when at rest.<sup>8</sup> Bony involvement occurs most commonly in the skull, followed by the long bones of the extremities and the flat bones (pelvis, vertebrae, ribs). Radiographic studies usually reveal single or multiple lytic lesions of bone (Fig. 10-6) that often have a “punched-out” appearance.<sup>11</sup> Proptosis may result from orbital wall involvement, and the radiographic appearance may simulate mastoiditis when there is involvement of the mastoid process.<sup>3</sup> Middle-ear extension may cause destructive changes with resultant deafness, and chronic otitis media may also occur as a result of mastoid and temporal bone disease. Vertebral body involvement may result in compression with the radiographic finding of vertebra plana (Fig. 10-7). Plain radiographs are usually sufficient for diagnosing bony LCH, but computed tomography (CT), magnetic resonance imaging (MRI), and technetium (Tc)-99 bone scans may also be useful, especially in the setting of multifocal osseous disease.<sup>12</sup>

The classic triad (historically Hand–Schüller–Christian disease) of skull lesions, DI, and exophthalmos is the prototype for multifocal LCH, but many other organs may be involved in this setting. Disseminated LCH (historically Letterer–Siwe disease) is the most serious form of the disorder, differing only in extent and severity from multifocal involvement.<sup>11</sup> Lymph node involvement may be seen with localized or widespread LCH, and most often the cervical nodes are involved. Hepatosplenomegaly, biliary cirrhosis, and liver dysfunction may

**Box 10-1 Histiocytoses**

Langerhans cell histiocytosis  
 Juvenile xanthogranuloma  
 Xanthoma disseminatum  
 Benign cephalic histiocytosis  
 Necrobiotic xanthogranuloma  
 Generalized eruptive histiocytoma  
 Progressive nodular histiocytoma  
 Indeterminate cell histiocytosis  
 Multicentric reticulohistiocytosis  
 Sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease)  
 Hemophagocytic syndromes  
 Malignant histiocytic syndromes

**Box 10-2 Cutaneous Clues to Langerhans Cell Histiocytosis**

Recalcitrant seborrheic dermatitis-like eruption  
 Localization of rash to scalp, posterior auricular regions, perineum, axillae  
 Eroded papules in flexural areas  
 Petechial or purpuric papules  
 Crusted papules on palms and/or soles (scabies preparation negative)  
 Any of the above lesions in combination with lymphadenopathy

**Table 10-1** Organ Involvement in Langerhans Cell Histiocytosis

Organ	Comment
Skin	Often the initial presenting sign
Bone	Painful swelling common; incidence: skull > long bones > flat bones (ribs, pelvis, vertebrae)
Lymph nodes	Cervical most common
Liver	
Spleen	
Lungs	Diffuse micronodular pattern on radiography
Gastrointestinal tract	
Thymus	
Bone marrow	Pancytopenia portends a poor prognosis
Gingivae, buccal mucosa	Swelling, erythema, erosions, petechiae
Kidney	
Endocrine glands	Diabetes insipidus most common
Central nervous system	

**Table 10-2** Cutaneous Manifestations of Langerhans Cell Histiocytosis

Presentation	Comment
Scaly red-brown papules	Especially in scalp, flexural areas; may have associated crusting; may be umbilicated or lichenoid; palm and sole involvement common
Erythematous, scaly dermatitis	May simulate seborrheic dermatitis
Erosion or ulceration	Common secondary finding, especially in fold areas
Petechiae, hemorrhage	With or without associated thrombocytopenia
Vesiculopustular lesions	Most common in neonates; may simulate congenital varicella or herpes; often have hemorrhagic crusts
Red nodules or plaques	Less common
Granulomatous plaques	Rare

occur. Pulmonary LCH may present with cough, hemoptysis, dyspnea, or pain and is most common in the third decade of life.<sup>3</sup> Pulmonary involvement may also be asymptomatic, especially in younger children. Chest radiography reveals a diffuse micronodular or reticular pattern, and pneumothoraces may result. Gastrointestinal tract involvement may present as anorexia, malabsorption, vomiting,

**Figure 10-1** Langerhans cell histiocytosis. Erythematous, crusted papules and plaques, with accentuation in the posterior auricular scalp.

diarrhea, and failure to thrive. However, gastrointestinal involvement may be asymptomatic and thus is at times overlooked. Thymus abnormalities have been reported and may present with enlargement of the gland on chest radiography. Bone marrow involvement may result in pancytopenia and with concomitant hypersplenism may contribute to life-threatening sepsis and hemorrhage.<sup>3,11</sup> Nonspecific constitutional symptoms, including fever, weight loss, and malaise, are common in patients with multiorgan involvement.

Central nervous system (CNS) involvement in LCH may include infiltration of the hypothalamic–pituitary regions, which can result in DI even years after the initial diagnosis. DI seems to develop more often in patients with bony involvement of the skull and multisystem disease.<sup>3</sup> Posterior pituitary infiltration may be evident on MRI as absence of a normally bright signal in the posterior pituitary gland or thickening of the pituitary stalk.<sup>13</sup> Growth retardation may result from anterior pituitary involvement, and growth hormone deficiency, which is relatively uncommon, may occur and was noted in 6% of patients in one large series.<sup>14,15</sup> Other manifestations of CNS involvement include hyperreflexia, dysarthria, cranial nerve defects, and rarely seizures. Progressive or rarely, acute ataxia has been observed as a complication.<sup>16</sup> Basilar invagination, which is associated with hydrocephalus and usually occurs as part of the Arnold–Chiari malformation or in patients with diseases that result in bone softening (i.e., osteogenesis imperfecta), has been reported in long-term survivors with LCH.<sup>17</sup> MRI is useful in diagnosing CNS disease. Positron emission tomography (PET) scan has been demonstrated useful in identifying areas with altered metabolism related to CNS LCH and may provide a tool for longitudinal involvement in some patients.<sup>18</sup> Neuropsychologic deficits that may occur in children with LCH include cognitive deficiencies and deficits in memory, attention and concentration, and perceptual–organizational capabilities.<sup>19</sup> Cognitive defects are noted especially in patients with multisystem LCH with CNS involvement.<sup>20</sup> Psychiatric deterioration and cognitive defects may both be more common in patients who develop cerebellar involvement.<sup>21</sup>

Congenital self-healing reticulohistiocytosis deserves special mention. This entity, also known as *Hashimoto–Pritzker disease* (and also as *congenital self-healing LCH [CSHLCH]*), is marked by the congenital presence of LCH lesions, usually papules and nodules,<sup>22</sup> which may break down in the center and form crater-shaped ulcers. Systemic



**Figure 10-2** Langerhans cell histiocytosis (LCH). **(A–C)** Erythematous and eroded papules in the neck fold, inguinal creases, and over the trunk. Note the associated crusting, purpura, and umbilicated nature of some of the papules. **(D)** Eroded, erythematous, and hemorrhagic papules in the groin of this infant with disseminated LCH. Note the associated jaundiced appearance, a result of massive liver involvement.

signs are often absent, and the lesions involute over a few months and are usually gone by 12 months.<sup>22</sup> There may be some distinct histologic features but not always. It is generally accepted that CSHLCH is a variant of LCH and that most patients have a favorable prognosis. However, patients do not always have disease limited to the skin and thus require an evaluation for systemic involvement. In addition, reports of cutaneous and systemic relapse (including DI) months to years after resolution of the skin lesions highlight the importance of vigilant long-term follow-up observation as one would do for patients with classic LCH.<sup>4,23,24</sup>

Erdheim–Chester disease is a rare, non-Langerhans systemic histiocytosis characterized by xanthomatous or xanthogranulomatous infiltration of tissues and a cellular phenotype that is CD68 positive but CD1a and S100 negative.<sup>25</sup> It may present in a fashion similar to LCH, including bony involvement, although it most commonly causes osteosclerosis affecting the metaphyseal regions of long bones (and presenting with bilateral knee and ankle pain). The cutaneous lesions are best characterized as a variant of juvenile xanthogranulomas (JXGs) (see below), and the clinical findings in the skin usually consist of xanthelasma-like lesions on the eyelids.<sup>26</sup> Erdheim–Chester disease occurs predominantly in adults.

LCH is diagnosed by examination of tissue specimens from affected organs. Skin is a readily accessible organ for biopsy in patients who have cutaneous involvement. Routine histologic sections reveal an infiltrate of typical Langerhans cells, which can be confirmed by positive S100, CD1a, or langerin immunostaining. Electron microscopy, although rarely performed now because of the availability of special stains, reveals the characteristic Birbeck granules within the cytoplasm of the cells. The prognosis for patients with LCH is quite variable and dependent on many factors, including the extent of organ involvement. In general, the younger the age at diagnosis, the shorter the event-free survival and overall survival rates, although this association does not appear to be as strong as once believed.<sup>27</sup> Interestingly, neonates with isolated cutaneous lesions tend to do very well.<sup>28</sup> Other prognostic factors include the type and number of disease sites, organ dysfunction, and response to therapy.<sup>29</sup> Morbidity and mortality may be related to progressive disease or late sequelae, which include skeletal defects, dental problems, DI, growth failure or other endocrinopathies, hearing loss, and CNS dysfunction.<sup>24</sup> DI, which presents with polyuria and polydipsia, occurs in around 15% to 25% of patients and may even occur as a late complication in patients who present with “skin-limited” disease or CSHLCH.<sup>27–30</sup>



**Figure 10-3** Langerhans cell histiocytosis (LCH). Erythematous, crusted papules on the palm in this newborn with congenital multisystem LCH.



**Figure 10-5** Neonatal Langerhans cell histiocytosis (LCH). These crusted, vesicular lesions were initially felt to be suggestive of neonatal varicella in this 10-day-old female. Biopsy confirmed LCH.



**Figure 10-4** Neonatal Langerhans cell histiocytosis (LCH). Hemorrhagic papules and papulovesicles in a neonate with congenital cutaneous LCH.

The recommended evaluation for the patient suspected of having LCH is shown in **Box 10-3**. Clinical stratification based extent of disease has been recommended as follows: single-organ-system disease (unifocal or multifocal), multiorgan disease (without organ dysfunction), and multiorgan disease (with organ dysfunction). The latter category, multiorgan disease with organ dysfunction, is further stratified as low risk (skin, bone, lymph node, pituitary) or high risk (lung, liver, spleen, hematopoietic cells).<sup>28</sup> Patients with single-organ-system disease seem to have the best outcome and a low reactivation rate.<sup>15</sup>

Therapy for LCH depends on the extent of disease. In patients with disease limited to the skin, observation alone is often appropriate, because the lesions may resolve spontaneously. Topical corticosteroids are only occasionally effective. Topical treatment with nitrogen mustard may be used, and in patients with severe skin disease, systemic therapy as is given for multiorgan LCH may be considered. Treatment for disease limited to bone is dictated by the extent of bone

### Box 10-3 Recommended Evaluation of the Patient with Suspected Langerhans Cell Histiocytosis

Physical examination, including growth parameters

Laboratory evaluation:

- Complete blood cell count
- Coagulation studies
- Hepatic function testing
- Urine osmolality

Complete skeletal radiographic survey

Chest radiography

More specific studies as guided by initial results (i.e., bone marrow examination, pulmonary function testing, lung biopsy, liver biopsy, panoramic dental films, CT or MRI of the CNS, endocrine evaluation)

Modified from Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. *Pediatr Dermatol* 2008;25(3):291–5.

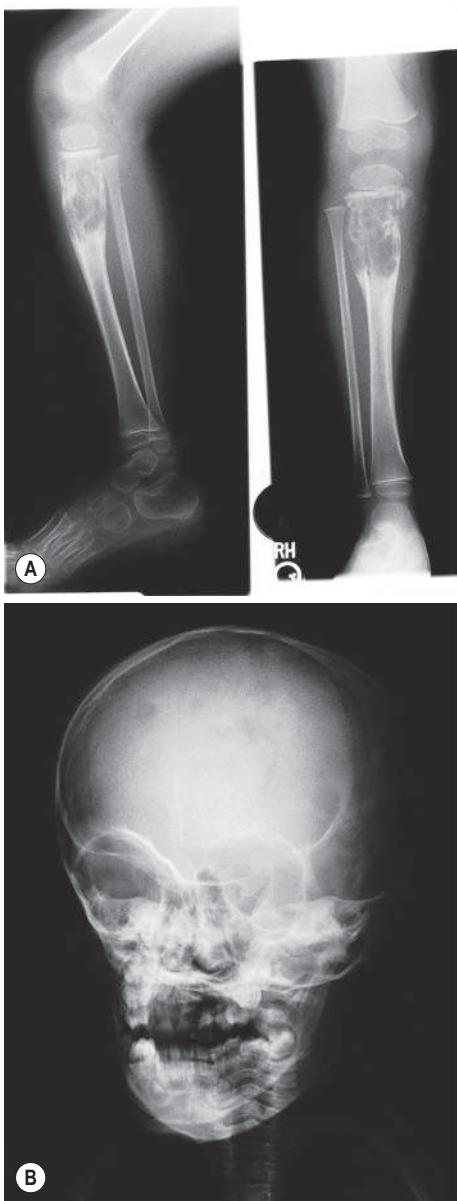
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CNS, Central nervous system; CT, computed tomography; MRI, magnetic resonance imaging.

involvement and symptomatology. Single-bone lesions may resolve spontaneously, and simple observation is appropriate in this setting in patients who are not experiencing pain.<sup>3,11</sup> Painful lesions may be treated with curettage, surgical excision, or intralesional steroid injection. Localized radiation therapy is another treatment option.

In patients with more extensive LCH, there are a variety of therapeutic options. Most patients are treated with systemic chemotherapy, most commonly vinblastine or etoposide. These two agents have been found equally effective in the treatment of multisystem LCH.<sup>31</sup> Prednisone or methylprednisolone is commonly used during the induction phase of therapy for patients with multisystem LCH. Other reported therapies include cyclosporine A, 2-chlorodeoxyadenosine, interferon- $\alpha$ , cladribine, cytarabine, and allogeneic bone marrow or cord-blood transplantation.<sup>32–36</sup>

LCH is a potentially fatal disorder that can be recognized and diagnosed early based on the characteristic cutaneous manifestations. The skin signs may appear alone or in combination with systemic disease,



**Figure 10-6** Langerhans cell histiocytosis. Plain radiography reveals multiple lytic lesions in the tibia (**A**) and the skull (**B**) of a 4-year-old child with disseminated disease.

and all patients require a thorough evaluation for extracutaneous involvement before they can be diagnosed as having skin-limited disease. Although there is often a delay in the diagnosis of patients with LCH, becoming familiar with the cutaneous clues (see Box 10-2) will optimally position the pediatrician or other pediatric healthcare providers to recognize the disorder. Patients with LCH are usually treated by a pediatric oncologist, and all patients require long-term surveillance for late sequelae or relapse.

## Juvenile Xanthogranuloma

JXG is a common form of non-LCH. It is generally a benign, self-limited disease of infants, children, and occasionally adults. Lesions occur most often in skin, although extracutaneous disease may occasionally be present. Most JXGs occur early in life, and the true incidence may be underestimated because many of them may go undiagnosed or misdiagnosed as other common skin tumors such as nevi. JXG seems



**Figure 10-7** Langerhans cell histiocytosis. Plain radiography demonstrates vertebral body compression (vertebra plana, arrow) in the same patient as that shown in **Figure 10-6**.

to be derived from dermal dendrocytes, and although the term *xantho*- appears in the name, there is no association of this condition with hyperlipidemia or other metabolic abnormalities.<sup>37</sup>

JXG presents as a firm, round papule or nodule, varying in size from 5 mm to 2 cm, with giant lesions (i.e., up to 5 or 10 cm) occasionally seen. Some authors have divided JXG into a “micronodular” form (lesions <10 mm) and a “macronodular” form (lesions >10 mm). Early JXGs are erythematous (Fig. 10-8) to orange or tan (Fig. 10-9), but with time they become more yellow in color (Figs. 10-10 and 10-11). Lesions may be solitary (up to 90% of all patients with JXG<sup>38</sup>) or less commonly multiple (Fig. 10-12), and they are usually asymptomatic. Ulceration and crusting may occasionally occur. The head, neck, and trunk are the most common areas to be involved. Lesions may also occur on mucous membranes or at mucocutaneous junctions (mouth, vaginal orifice, and perineal area). Oral lesions occur on the lateral aspects of the tongue, gingival, buccal mucosa, and midline hard palate and may ulcerate and bleed. Oral lesions may appear verrucous, pedunculated, umbilicated, or fibroma-like.<sup>39</sup> Typically, the lesions of JXG present at birth (20%) or during the first 6 months of life, and they may persist or continue to erupt for years.<sup>40</sup>

Histologic evaluation of JXG tissue reveals a dense dermal infiltrate of foamy histiocytes, foreign body cells, and the characteristic Touton giant cells, which are virtually pathognomonic for the condition. The Touton giant cell is a giant cell with a central wreath of nuclei and a peripheral rim of eosinophilic cytoplasm.<sup>41</sup> Lymphocytes and eosinophils are often seen, and the histiocytes in JXG are S100 and CDla negative on special staining.

Extracutaneous involvement occasionally occurs with JXG. The eye is the most common organ of involvement second to the skin. The iris is the site most often involved, and potential complications of ocular JXG include hyphema, glaucoma, or blindness.<sup>42</sup> Patients may complain of eye redness, irritation, or photophobia. Children at greatest risk for ocular JXG include those 2 years of age or younger and those with multiple skin lesions.<sup>42</sup> Intramuscular JXG presents as a deep, soft-tissue lesion that may have imaging features similar to those of malignant tumors of infancy.<sup>43</sup> This form tends to affect exclusively infants and toddlers and occurs as a solitary lesion in skeletal muscles of the trunk.<sup>44</sup> Other sites of extracutaneous involvement include lung, liver, testis, pericardium, spleen, CNS, bone, kidney, adrenal



**Figure 10-8** Juvenile xanthogranuloma. An early lesion demonstrates erythema and mild surface scaling.



**Figure 10-9** Juvenile xanthogranuloma. This early lesion reveals a red to orange color.



**Figure 10-10** Juvenile xanthogranuloma. An established lesion revealing the characteristic yellow to orange-brown appearance.



**Figure 10-11** Juvenile xanthogranuloma. Solitary yellow, dome-shaped nodular papule (**A**) and plaque (**B**) both distributed on the scalp.



**Figure 10-12** Juvenile xanthogranuloma. Multiple lesions, with spontaneous involution evident, were present in this 11-year-old boy. Note the fibrofatty tissue residua.

glands, and larynx.<sup>37,41</sup> Solitary as well as multiple intracranial and intracerebral lesions have rarely been reported, including one patient who experienced leptomeningeal spread and several who required therapy with chemotherapy and steroids.<sup>45–49</sup> Intraspinal JXG with spinal-cord compression has been reported.<sup>50</sup> Systemic JXG generally exhibits a benign clinical course but may occasionally be fatal, especially when the liver is involved.<sup>38</sup> There are rare reports of JXG in association with LCH, suggesting a possible common progenitor cell and overlap within the histiocytic spectrum of disorders.<sup>51–53</sup>

An important association is that of JXG and childhood leukemia. The most common association has been with juvenile chronic myelogenous leukemia (JCML), which may be seen with increased incidence in patients with multiple JXG lesions. It has been noted that several such reported patients also had café-au-lait macules and a family history of type 1 neurofibromatosis (NF).<sup>54</sup> A systematic review of the literature revealed that the frequency of the triple association of JXG, JCML, and NF is 30- to 40-fold higher than expected, and it is estimated that children with NF and JXG have a 20- to 32-fold higher risk for JCML than do patients with NF who do not have JXG.<sup>55</sup> However, it should be noted that the vast majority of patients with multiple JXG, even those with associated NF, do not develop JCML. The role of surveillance complete blood cell counts is controversial, and most practitioners monitor these patients primarily with regular, thorough physical examinations.

JXG usually runs a fairly benign course, with spontaneous regression occurring over 3 to 6 years. Pigmentary alteration, atrophy, or “anetoderma-like” changes may persist in areas of prior skin involvement. Although rare cases lasting until adulthood have been reported, generally those that have their onset early in life manifest complete spontaneous healing. The risk of complications is fairly high when ocular involvement is present. For this reason, once disease has been confirmed in the eye, therapy should be initiated. Intraocular JXG is treated with intralesional or systemic steroids, radiation therapy, or excision.<sup>56,57</sup> Lesions limited to skin require no therapy, although surgical excision is occasionally performed for diagnostic or cosmetic purposes. Systemic involvement is treated if it interferes with vital functions and has shown response to chemotherapy regimens similar to those used in LCH.<sup>37,38</sup> Patients with JXG and NF should be monitored for the development of leukemia given the increased risk.

## Xanthoma Disseminatum

Xanthoma disseminatum (XD), a rare disorder of mucocutaneous xanthomatous lesions, is another non-LCH. This disorder usually occurs in adults, although it may have its onset during childhood.<sup>58,59</sup> Patients have numerous (sometimes hundreds) round to oval, yellow-orange or brown papules, nodules, and plaques. They occur primarily on the face and the flexural and intertriginous surfaces, including the neck, antecubital fossae, periumbilical area, perineum, and genitalia. The lips, eyelids, and conjunctivae may be involved, and xanthomatous deposits have also been observed in the mouth and upper respiratory tract (epiglottis, larynx, and trachea), occasionally leading to respiratory difficulty.<sup>60,61</sup> Facial lesions may become exuberant and may cause disfigurement.<sup>62</sup> Osseous lesions, presenting radiographically as well-demarcated areas of osteolysis, may be present.<sup>62</sup> Ocular mucosal lesions may result in blindness. Liver involvement is occasionally present.<sup>63</sup> When XD involves the CNS, it is characterized by infiltration of the pituitary gland and termed *xanthomatous hypophysitis*, and may result in DI, hyperprolactinemia, or hypopituitarism.<sup>64</sup>

As with JXG, there is no perturbation in lipid metabolism in patients with XD, although it has been rarely reported in affected children.<sup>63</sup> DI occurs in many patients with the disorder, and severe laryngeal involvement may necessitate tracheostomy. The lesions of XD often persist indefinitely but have been known to involute spontaneously.<sup>65</sup> Treatment of the cutaneous lesions has been performed with cryotherapy, excision, and carbon dioxide laser ablation.<sup>66</sup> Despite the normolipemic nature of XD, lipid-lowering agents have been utilized in some patients with reported improvement.<sup>67,68</sup> Respiratory tract involvement, when severe, may justify a more aggressive approach with localized radiation therapy or chemotherapy.

## Benign Cephalic Histiocytosis

Benign cephalic histiocytosis (BCH) is a self-healing, cutaneous, non-LCH that classically involves the face and head. The average age of onset is 15 months, and 45% of cases occur in infants under 6 months of age.<sup>69</sup> Clinically BCH is characterized by small, 2- to 6-mm, yellow-brown macules and minimally elevated papules (Fig. 10-13). The lesions may occasionally coalesce to give a reticulate pattern.<sup>70</sup>



**Figure 10-13** Benign cephalic histiocytosis. Faintly tan to erythematous macules and papules on the cheek.

BCH most commonly occurs on the face and head (more than 80% of 45 patients in one review) and less commonly on the neck and trunk.<sup>71</sup> The extremities, buttocks, and pubic area may be involved later in the course.<sup>69</sup> The differential diagnosis may include flat warts, micronodular JXG, LCH, multiple melanocytic nevi, and urticaria pigmentosa.

The diagnosis of BCH can be confirmed by skin biopsy, which reveals a histiocytic infiltrate with negative stains for S100 and CDla. Electron microscopy is useful in confirming the diagnosis, because the cells classically reveal intracytoplasmic comma-shaped or worm-like bodies and the absence of Birbeck granules,<sup>70,72</sup> clearly differentiating it from LCH.

There is significant clinical overlap between some of the non-LCHs. Some authors have considered BCH to be a variant of generalized eruptive histiocytoma (GEH) (see below). In addition, there are reports of BCH progressing into JXG,<sup>73,74</sup> and although BCH tends to be limited to the skin, there are some reports of associated internal involvement. One patient with BCH developed DI 1 year later with infiltration of the pituitary stalk on imaging.<sup>75</sup> In another patient with classic lesions of BCH on the face, lytic lesions in the skull, spine, and tibia were demonstrated to be LCH on tissue examination.<sup>76</sup> These clinical observations again highlight the potential overlap among the histiocytic syndromes.

BCH generally runs a benign course with spontaneous healing, often leaving behind flat or atrophic pigmented scars. Treatment is unnecessary, but given the clinical variation in presentation and overlap with other histiocytic syndromes, clinical follow-up observation for progression or internal involvement is advisable.

## Necrobiotic Xanthogranuloma

Necrobiotic xanthogranuloma, a rare disorder usually reported in adults, is characterized by sharply demarcated, indurated plaques and nodules that are usually yellow to red-brown or violaceous and have a predilection for periorbital areas, the trunk, and proximal extremities.<sup>77</sup> Lesions vary in size, may at times be as large as 10 cm or more in diameter, and often ulcerate and heal with areas of atrophy and telangiectasia. Ocular involvement is fairly common and includes ectropion, ptosis, keratitis, uveitis, proptosis, and orbital masses. Visceral lesions of necrobiotic xanthogranuloma may involve the heart, skeletal muscles, larynx, spleen, and ovary. A hallmark of this disease is an associated paraproteinemia, immunoglobulin (Ig) G monoclonal gammopathy. The course of necrobiotic xanthogranuloma is chronic and progressive and may be associated with proliferation of plasma cells in the bone marrow or multiple myeloma. Treatment options include systemic or intralesional corticosteroids, cytotoxic drugs, radiation therapy, and plasmapheresis. Intravenous immunoglobulin

has been reportedly useful in some patients.<sup>78</sup> Surgical removal of lesions is associated with a high recurrence rate.<sup>79</sup>

## Generalized Eruptive Histiocytoma

Generalized eruptive histiocytoma (GEH) is a rare, self-healing histiocytosis characterized by recurrent crops of small, yellow to red-brown papules on the face, trunk, extensor extremities, and rarely, mucous membranes. The lesions number in the hundreds and tend to occur in a symmetric distribution. They resolve over months with hyperpigmented macules left in their place. As a result of the continuous development of new lesions, however, the disorder may persist indefinitely. Although generally regarded as a disorder of adults, GEH has been seen in childhood and even in infants as young as 1 month of age.<sup>80</sup>

The differential diagnosis includes JXG (which may be very difficult to differentiate histologically from early lesions of GEH), LCH, BCH, and urticaria pigmentosa. XD has developed in a child with the prior diagnosis of GEH.<sup>58</sup> No treatment is generally necessary for this disorder. However, since there is considerable overlap within non-LCH, patients should be monitored carefully for the development of signs or symptoms of other organ involvement. Isotretinoin treatment has been reported in a patient with GEH, with transient improvement but eventual recurrence.<sup>81</sup>

## Progressive Nodular Histiocytoma

Progressive nodular histiocytoma is characterized by a widespread eruption of hundreds of yellow-brown, 2- to 10-mm papules and deeper, larger subcutaneous nodules. Conjunctival, oral, and laryngeal lesions may occur. The face typically is heavily involved with numerous coalescent lesions, which may result in a leonine appearance. New lesions progressively occur, and ulceration is common. Occasionally, bleeding may occur within the subcutaneous nodules, resulting in marked pain.<sup>82</sup> Lesions of progressive nodular histiocytoma histologically show features typical of xanthogranuloma, and some authors suggest that this entity and JXG may represent a variation of the same process.<sup>83</sup> Treatment for this condition is difficult and includes excision of large or symptomatic lesions, chemotherapy with vinblastine, and electron beam therapy.

## Multicentric Reticulohistiocytosis

Multicentric reticulohistiocytosis is a rare systemic disorder of unknown cause. It is characterized by cutaneous lesions and a destructive arthritis and is seen almost exclusively in adults (mean age at diagnosis of 40 to 50 years) with rare reports of pediatric disease.<sup>84–86</sup> The skin lesions present as firm red-brown papules and nodules, most often distributed on the hands, fingers, lips, ears, and nose. Facial disfigurement may occur, with cartilaginous destruction and the appearance of a leonine facies. The coral bead sign refers to the presence of a chain of papules along the cuticle.<sup>82</sup> Nodular lesions on the arms, elbows, and knees may occur and at times resemble rheumatoid nodules.<sup>87</sup> Mucous membrane involvement may occur in up to one-half of patients. They most often present on the lips, buccal mucosa, nasal septum, tongue, palate, and gingivae.

Joint involvement is the presenting sign in more than half of the patients and is highly destructive. It may involve any joint, especially the interphalangeal joints, and coexisting synovitis is common. Shortening of the digits may occur with a “telescopic” or “opera-glass” deformity. Rheumatoid arthritis may be mistakenly diagnosed in some patients. Microscopic examination of skin, bone, or synovial tissue reveals a characteristic histiocytic process with multinucleated giant cells and a “ground-glass” appearance. Visceral involvement may include pleural effusion, pulmonary fibrosis, pericardial effusion, congestive heart failure, salivary gland enlargement, muscle weakness, lymphadenopathy, and gastric ulcer.<sup>88</sup> Multicentric reticulohistiocytosis may regress spontaneously over 6 to 8 years, but for many patients the articular destruction results in permanent joint deformities. The response of this disorder to therapy is often disappointing,

with treatments including nonsteroidal anti-inflammatory agents, corticosteroids, cyclophosphamide, chlorambucil, methotrexate, hydroxychloroquine, infliximab, tocilizumab, and interferon.<sup>82,88–92</sup>

## Hemophagocytic Lymphohistiocytosis

*Hemophagocytic lymphohistiocytosis* (HLH; also known as *hemophagocytic syndrome*) refers to a condition characterized by fever, wasting, jaundice, and hepatosplenomegaly resulting from diffuse infiltration of phagocytizing histiocytes in various tissues.<sup>93</sup> This disorder is heterogeneous in its etiologies, which include a familial form (familial HLH) and a secondary/reactive form that may be associated with a variety of infectious agents (most notably viral, bacterial, or parasitic), malignancy, and collagen vascular disorders.<sup>94,95</sup> These have also been referred to as *genetic* and *acquired* forms of HLH. The infection-associated form is seen primarily in immunocompromised patients with evidence of preceding viral (usually Epstein-Barr virus [EBV]) infection, in which case it is also known as *virus-associated hemophagocytic syndrome*. The other viral agents reported in association with HLH include cytomegalovirus, enterovirus, and parainfluenza virus.<sup>94,95</sup> The term *malignant histiocytosis* has also been used to describe this condition, in response to the cytologic atypia and malignant nature of the infiltrating histiocytes.

HLH has been observed as a complication of allogeneic hematopoietic stem-cell transplantation and in association with hematologic malignancies.<sup>93,96</sup> There also seems to be a relationship between EBV-associated HLH and EBV-associated T-cell lymphoma, with HLH representing the major cause of death in these patients.<sup>93</sup> Lymphoma-associated hemophagocytic syndrome (LAHS) is a rarely reported variant of HLH that has been described in the setting of systemic and cutaneous lymphomas, including subcutaneous panniculitic T-cell lymphoma (SPTCL) and epidermotropic cutaneous T-cell lymphoma, in which case it often occurs several years after the lymphoma diagnosis.<sup>97</sup> The pathway most commonly implicated in familial HLH is that of perforin-dependent cytotoxicity, an essential function of natural killer and cytotoxic T lymphocytes. The genetic forms of HLH have been shown to be related to mutations in any of several genes involved in this pathway, including *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, and *BIRC4*.<sup>98,99</sup> HLH may also be related to a primary immunodeficiency syndrome.<sup>100</sup> Macrophage activation syndrome (see Chapter 22) is a severe condition with features very similar to HLH that is seen in association with the systemic form of juvenile idiopathic arthritis and, less often, other autoimmune inflammatory diseases.<sup>101</sup> Box 10-4 summarizes the various subtypes of HLH.<sup>100,102</sup>

The cutaneous manifestations seen in patients with HLH are variable. Most common is a transient, generalized maculopapular eruption. Petechial and purpuric macules, generalized erythroderma, and morbilliform erythema may also occur.<sup>103</sup> Although the skin findings are not specific, their presence in the patient with a supportive history and/or the concomitant findings of fever, lymphadenopathy, hepatosplenomegaly, and cytopenias should prompt consideration for this diagnosis. The most common hematologic findings are leukopenia and thrombocytopenia, and coagulopathy is fairly common.<sup>94</sup> Other findings may include liver dysfunction and elevated triglyceride, lactate dehydrogenase (LDH), and ferritin levels. The clinical differential diagnosis may include extramedullary hematopoiesis (as may be seen with a variety of infectious or malignant disorders) and metastatic lesions from an underlying malignancy. LCH and myofibromatosis may also be in the differential.<sup>103</sup> Skin biopsy may be useful in eliminating some diagnoses, but the histologic findings are often nonspecific and the changes of erythrophagocytosis are often absent in skin specimens. Examination of bone marrow or other solid organ (lymph node, spleen, liver) biopsy tissue may be necessary to confirm the diagnosis. HLH has a high mortality rate, although chemotherapy, steroids, intravenous immunoglobulin, and hematopoietic stem-cell transplantation may offer hope for some patients. Etoposide and dexamethasone often induce clinical remission of the inflammatory symptoms, and improved survival has been noted with newer reduced-intensity transplant conditioning protocols. Cyclosporine A has been utilized to inhibit T-cell activation.<sup>99,100</sup>

#### Box 10-4 Subtypes of Hemophagocytic Lymphohistiocytosis

##### Genetic Forms

Familial hemophagocytic lymphohistiocytosis (FHL)  
FHL1–FHL5  
Immunodeficiency disorders  
Griscelli syndrome type 2  
Chediak-Higashi syndrome  
Hermansky-Pudlak syndrome type 2  
X-linked proliferative syndrome (XLP), types 1 and 2  
IL-2 inducible T-cell kinase (ITK) deficiency

##### Acquired Forms

Viral (especially EBV and other herpes viruses)  
Other infections (bacterial, fungal, parasitic)  
Malignancy (peripheral lymphomas, cutaneous lymphomas, leukemia, myeloma, some solid tumors)  
Immunosuppression (post-organ transplantation or post-HSCT)  
Autoimmune disease (systemic-onset JIA, SLE, spondyloarthropathies, Kawasaki disease; termed *macrophage activation syndrome*)

Modified from Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Pathol* 2013;139:713–27, and Bode SFN, Lehberg K, Maul-Pavlic A, et al. Recent advances in the diagnosis and treatment of hemophagocytic lymphohistiocytosis. *Arthritis Res Ther* 2012;14:213.

*EBV*, Epstein-Barr virus; *HSCT*, hematopoietic stem cell transplantation; *JIA*, juvenile idiopathic arthritis; *SLE*, systemic lupus erythematosus.

#### Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease)

Sinus histiocytosis with massive lymphadenopathy (SHML; or Rosai-Dorfman disease) is a rare disorder of reactive proliferation of histiocytes in the sinuses of lymph nodes. It occurs primarily in children, who show massive painless bilateral lymphadenopathy, especially cervical. Extrnodal involvement may occur, and when it does the head and neck region is the most common site, with a predilection for the nasal cavity and paranasal sinuses.<sup>104</sup> Papules and nodules are the most common skin lesions, and purely cutaneous SHML may occasionally occur.<sup>105,106</sup> The lesions of SHML often involute spontaneously, although surgical or medical therapy (that may include radiation, corticosteroids, or chemotherapy) may be indicated for lesions that are symptomatic, extensive, compromising vital organ function, or cosmetically deforming.<sup>104</sup> There are isolated reports of patients with both SHML and lymphoma.<sup>107,108</sup>

#### Cutaneous Pseudolymphoma

Cutaneous pseudolymphoma (CPL; *lymphocytoma cutis*, *lymphadenosis benigna cutis*, *Spiegler-Fendt pseudolymphoma*, *cutaneous lymphoid hyperplasia*) refers to a benign process that may clinically and/or histologically mimic lymphoma. CPL may occur at any age but most characteristically develops during early adult life. The diagnosis of CPL is nonspecific and does not imply the etiology. Some of the various causes of this process are listed in Box 10-5.

One of the most common etiologic categories of CPL is drugs. Many classes have been implicated, including anticonvulsants, antipsychotics, antihypertensives, angiotensin-converting enzyme inhibitors,  $\beta$ -blockers, calcium channel blockers, antibiotics, cytotoxic agents, and even antihistamines.<sup>109</sup> The anticonvulsant hypersensitivity syndrome, or drug rash with eosinophilia and systemic symptoms (DRESS) (see Chapter 20), is a prototype for such a reaction, presenting with fever, lymphadenopathy, edema, hepatosplenomegaly with hepatitis, and a diffuse cutaneous eruption that may reveal histologic changes of pseudolymphoma.

Typically, CPL presents as a more localized process with papules, nodules, and tumors in the skin. The lesions are flesh-colored to red or violaceous (Fig. 10-14) and may be single or multiple. They are

#### Box 10-5 Some Causes of Cutaneous Pseudolymphoma

Idiopathic  
Arthropod bite reaction  
Drug reaction  
Contact dermatitis  
Infestation (i.e., scabies nodules)  
Lymphomatoid papulosis  
*Borrelia burgdorferi*  
Tattoo pigment  
Vaccinations  
Actinic reticuloid  
VZV infection  
HIV infection  
*Molluscum contagiosum*

HIV, Human immunodeficiency virus; VZV, varicella-zoster virus.



Figure 10-14 Cutaneous pseudolymphoma. Infiltrative, erythematous papules and nodular plaques on the chest of a 7-year-old boy.

usually not associated with a drug ingestion, and they may reach up to 4 or 5 cm in size with continued enlargement. The most common locations are the face, ears, and scalp, with occasional involvement of other body regions. Borrelial lymphocytoma, which follows infection with the Lyme disease agent *Borrelia burgdorferi*, occurs primarily in Europe and usually presents with red nodules involving the ear lobe and areola.<sup>110</sup> CPL resulting from past scabies infestation (scabies nodules) presents as erythematous to red-brown papules and nodules, usually in an infant previously treated for scabies (Fig. 10-15). These lesions may persist for several months after adequate therapy for the infestation. CPL may occasionally be noted in association with *molluscum contagiosum* (see Chapter 15, Fig. 15-42), a common childhood viral infection.<sup>111</sup>

A more disseminated form of CPL may occur; it usually appears in adults and presents with firm, red to violaceous papules and nodules with a more diffuse distribution. These lesions may grow rapidly, are prone to recurrence, and tend to persist throughout life. Actinic reticuloid is a severe, chronic photosensitive dermatosis that occurs primarily in older men and presents with erythematous to violaceous, lichenified papules and plaques on sun-exposed skin. It is categorized as a form of CPL by several authors.

The diagnosis of CPL is based upon the combination of clinical features, histologic evaluation, and often immunohistochemical and/or gene rearrangement studies.<sup>109</sup> At times, the microscopic findings of CPL may be very difficult to differentiate from cutaneous lymphoma and consist of a mixture of B, T, or mixed lymphocytes with macrophages and dendritic cells.<sup>112</sup> Treatment of CPL depends on the underlying etiology. Removal of any offending drug or physical stimulus that is identified may be sufficient. In idiopathic cases, lesions may involute spontaneously over months to years. For persistent lesions, treatment options include topical or intralesional corticosteroids, cryosurgery, surgical excision, local radiation therapy,



**Figure 10-15** Nodular scabies. Erythematous papulonodules with mild scaling in a 10-month-old infant who was treated for scabies 3 months before.



**Figure 10-16** Leukemia cutis. Erythematous nodule in a 3-year-old with diagnosed acute lymphocytic leukemia.

photochemotherapy, and antimarial and cytotoxic agents.<sup>109</sup> Antibiotics appropriate for Lyme disease are indicated for treatment of borrelial lymphocytoma.

## Leukemia Cutis

Leukemia is the most common malignancy of childhood. Cutaneous findings in leukemia may be primary (i.e., leukemic infiltrates in the skin) and secondary (i.e., Sweet syndrome, see Chapter 20; pyoderma gangrenosum, see Chapter 25; opportunistic infections). Cutaneous leukemic infiltrates may be known by a variety of names, including leukemia cutis, granulocytic sarcoma, and chloroma. Myelosarcoma is the more contemporary term for any extramedullary infiltrate with myeloid blasts.<sup>113</sup> Hence leukemia cutis is a form of myelosarcoma that results from infiltration of the epidermis, dermis, or subcutaneous tissues by neoplastic leukocytes or their precursors. Although biopsies of lesions of leukemia cutis may suggest the diagnosis, the findings may mimic a variety of inflammatory or neoplastic diseases. Therefore immunophenotyping and examination of peripheral blood smears and bone marrow aspirates are often required in an effort to confirm the diagnosis.

Cutaneous involvement may be associated with various types of childhood leukemias, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML, also called acute nonlymphocytic leukemia [ANLL]), and chronic leukemias (i.e., chronic myeloid leukemia [CML] and chronic lymphoblastic leukemia [CLL]). In general, leukemia cutis is associated with a grave prognosis, the exception being in patients with congenital leukemia (see below). Cutaneous leukemic infiltrates are most common with the myeloid leukemias (between 3% and 30% of patients, depending on the subtype), especially acute myelomonocytic and monocytic leukemia.<sup>113-115</sup> Gingival hypertrophy is a notable feature seen with these subtypes of leukemia, less so with other acute leukemias, and rarely with chronic leukemias.<sup>114</sup> Leukemia cutis is less common in patients with ALL (around 1% to 3%); in these cases it seems to be most common on the head and may be an early manifestation in children in both standard-risk and high-risk categories.<sup>114,116</sup> Leukemia cutis may also occur in patients with myelodysplastic syndrome, usually before or simultaneously with identifiable leukemic transformation in the peripheral blood or bone marrow.<sup>117,118</sup> Rarely leukemia cutis may present as a manifestation of secondary leukemia after prior chemotherapy.<sup>119</sup>

The clinical appearance of leukemia cutis is variable. Lesion types include macules, papules, plaques, nodules, ecchymoses, erythroderma, palpable purpura, ulcers, bullous lesions, and urticaria-like lesions.<sup>114</sup> A “seborrheic-dermatitis-like” presentation with scaling and papules of the scalp was observed in a 7-month-old with AML in remission.<sup>120</sup> Brown macules and nodules exhibiting a positive Darier sign and mimicking mastocytosis have been noted.<sup>117</sup> The most characteristic lesions of leukemia cutis are flesh-colored to red-brown to violaceous papules (Fig. 10-16), nodules, and plaques that may become purpuric (especially with coexisting thrombocytopenia). Leukemia cutis lesions may localize to sites of skin trauma, burns, surgical sites, or sites of cutaneous infections.

The clinical features of the skin lesions are not distinct for the different types of leukemias. However, certain subtypes may be more likely to result in cutaneous infiltrates with certain characteristics. For example, granulocytic sarcoma (or chloroma) presents as a rapidly growing, firm nodule that at times has a green hue. This tumor is usually associated with AML, and the greenish color is related to myeloperoxidase in the granulocytes. Granulocytic sarcoma may occur in patients with known AML, in those with a myeloproliferative disorder with an impending blast crisis, or in patients without any known hematologic disease.<sup>115</sup> At times leukemia cutis may precede the development of the systemic leukemia. This phenomenon is termed *aleukemic leukemia cutis*, and the cutaneous lesions can sometimes precede the systemic malignancy (most commonly AML) by years.<sup>121</sup>

## CONGENITAL LEUKEMIA CUTIS

Congenital leukemia is defined as leukemia presenting at birth or within the first month to 6 weeks of life. Congenital leukemia cutis, as compared with later-onset leukemia cutis, is believed to be quite common in the setting of this malignancy, with incidence estimates in the literature ranging between 25% and 30% of patients with congenital AML.<sup>122</sup> The cutaneous lesions range in size from a few millimeters to several centimeters and are usually red to brown to violaceous papules and nodules (Fig. 10-17). This latter clinical presentation in the neonate (with multiple violaceous papules and nodules) has been termed *blueberry-muffin baby*, and such skin findings may represent malignant cutaneous infiltrates or any of several possible causes of extramedullary hematopoiesis. Box 10-6 lists the various causes of blueberry-muffin skin lesions. As with noncongenital leukemia cutis, cutaneous infiltrates are more common with the myelogenous type of congenital leukemia.<sup>122</sup> Congenital leukemia cutis is felt to portend a poor prognosis, although some reports describe spontaneous remission.<sup>123,124</sup> However, because late relapses have been noted in some of these patients, they deserve close long-term follow-up observation. Occasionally infants with congenital leukemia cutis may have a solitary nodule.<sup>125,126</sup>



**Figure 10-17** Congenital leukemia cutis. Congenital acute lymphocytic leukemia with cutaneous facial lesions. (Courtesy of Anne Lucky, MD.)

#### Box 10-6 Causes of Blueberry-Muffin Cutaneous Lesions in a Newborn

Neoplastic infiltrates
Leukemia
Neuroblastoma
Histiocytosis
Extramedullary hematopoiesis
Congenital infection
Rubella
Toxoplasmosis
Cytomegalovirus
Parvovirus B19
Anemia
Hemolytic disease of the newborn
Hereditary spherocytosis
ABO incompatibility
Twin-twin transfusion syndrome
Transient myeloproliferative disorders:
with Down syndrome
without Down syndrome

Patients with Down syndrome have an increased risk of hematologic aberrations, including leukemia, leukemoid reaction, and transient myeloproliferative disorder. A leukemoid reaction is a temporary overproduction of leukocytes in response to infection, hemolysis, or other stress. Transient myeloproliferative disorder, which is also self-limited, is similar except that there is no identifiable trigger.<sup>127</sup> Patients with Down syndrome who have a leukemoid reaction or transient myeloproliferative disorder have been described with pustular or vesiculopustular skin eruptions, and smears or biopsies of these lesions have revealed immature myeloid forms.<sup>127,128</sup> This vesiculopustular presentation (Fig. 10-18) is quite distinct from the typical papules and nodules that occur with leukemia cutis. The significance of this eruption is unclear, and the findings resolve without therapy as the hematologic disorder subsides. However, true leukemia may develop months to years later, and therefore long-term follow-up monitoring is again indicated.

## Lymphoma Cutis

Lymphoma involving the skin is quite rare in children. The most common form of cutaneous lymphoma is cutaneous T-cell lymphoma (CTCL; mycosis fungoides; see below). Other forms of lymphoma cutis include subcutaneous panniculitic T-cell lymphoma (SPTCL), anaplastic large cell lymphoma (ALCL), cutaneous B-cell lymphoma, natural killer-cell lymphoma, angiocentric CTCL, and Hodgkin lymphoma. Some types of lymphoma that can also have skin involve-



**Figure 10-18** Vesiculopustular eruption in a patient with Down syndrome and a transient myeloproliferative disorder. (Courtesy of Beth Drolet, MD.)

ment but are not be discussed here include lymphoblastic lymphoma, marginal zone lymphoma, Burkitt lymphoma, and human T-lymphotropic virus (HTLV)-1-associated lymphoma. Lymphoma cutis may be a primary cutaneous process, or skin involvement may be associated with a systemic lymphoma. In patients with non-Hodgkin lymphoma overall, cutaneous involvement occurs in 1% to 5% of cases, and skin as the primary site (primary cutaneous lymphoma) is quite rare.<sup>129–131</sup>

Head and neck involvement is the most common pattern of cutaneous lymphoma in children.<sup>129–131</sup> The second most common site of involvement appears to be the abdomen.<sup>129</sup> Most patients present with solitary nodules in the skin, and less often multiple nodules are present. Papules or plaques are occasionally seen. The lesions are usually 5 to 10 cm in diameter, erythematous, and firm. SPTCL is a T-cell lymphoma that presents with subcutaneous nodules or nodular plaques and is most commonly seen in young adults (rarely in children). This tumor involves the subcutaneous fat in a manner similar to panniculitis and presents with multiple subcutaneous, inflammatory, poorly demarcated plaques and tender nodules, ranging in size from 0.5 to 10 cm. The lesions are most commonly localized to the lower extremities and occur less often on the trunk and upper extremities.<sup>132,133</sup> Ulceration may occasionally occur. The clinical presentation of SPTCL may mimic several processes, including lupus panniculitis and erythema nodosum, and hence this disorder may elude diagnosis.<sup>134</sup> SPTCL has been associated in some patients with hemophagocytic syndrome, and concomitant histiocytic cytophagic panniculitis has been observed.<sup>135,136</sup> Hence in any child with panniculitis and laboratory values suggestive of possible hemophagocytic syndrome, investigations for T-cell lymphoma should be performed.

Ki-1/CD30-positive ALCL is a form of lymphoma that may simulate a metastatic carcinoma or malignant histiocytosis.<sup>137,138</sup> A significant proportion of patients with ALCL are children or young adults. Patients show signs of fever, wasting, lymphadenopathy, and often cutaneous lesions. Skin involvement may consist of fleeting eruptions or more specific lesions, usually painful nodules, that occasionally undergo spontaneous involution.<sup>137,139</sup> In 36% of children in one series with peripheral lymph node involvement, lymphomatous infiltration of contiguous skin occurred and presented as erythematous, thickened, desquamating, and ulcerative plaques.<sup>140</sup> Primary cutaneous ALCL (C-ALCL) presents as a rapidly evolving cutaneous tumor, often with ulceration. It is most often solitary but may occur in regional or generalized forms.<sup>141</sup> ALCL is a high-grade non-Hodgkin

lymphoma that has a relatively good prognosis with early multiagent chemotherapy.<sup>138,140</sup> The primary cutaneous form is often treated with excision or radiation without chemotherapy, because some studies have shown that chemotherapy does not affect the rates of recurrence or survival.<sup>142,143</sup> Biopsies of affected skin reveal large, atypical lymphoid infiltrates that stain positive with the activation antigen Ki-1, also known as CD30.

The systemic form of ALCL (S-ALCL) has been further divided into anaplastic lymphoma kinase (ALK)-positive and ALK-negative types, based on staining for this fusion protein. ALK-positive S-ALCL tends to have a better prognosis than the ALK-negative subtype and is the primary type of this systemic lymphoma to occur in children. C-ALCL is typically ALK-negative, but primary cutaneous ALK-positive ALCL has been reported in children and may follow a relatively benign course.<sup>144</sup>

Cutaneous B-cell lymphoma is fairly rare, even though B-cell lymphomas represent the majority of non-Hodgkin lymphomas occurring in lymph nodes. As with T-cell lymphomas, B-cell lymphomas may involve the skin in a primary fashion or be secondary in relation to dissemination of nodal disease. Hence complete staging and evaluation is indicated for any patient diagnosed with a cutaneous B-cell lymphoma. This form of lymphoma cutis is notoriously rare in the pediatric population. The clinical presentation of B-cell lymphoma cutis includes papules, plaques, and tumors, occasionally with associated ulceration. The head, neck, upper trunk, and extremities seem to be sites of predilection in most patients, although some subtypes favor the lower extremities.

Natural killer-cell (CD56+ NK/T-cell) lymphoma is classically an aggressive nasal lymphoma, although patients can also have cutaneous plaques and subcutaneous nodules. This neoplasm may occur in a primary cutaneous or secondary form, and these two variants show considerable clinicopathologic differences with a more favorable prognosis associated with primary skin disease.<sup>145</sup> This neoplasm occurs primarily in older adults, seems to have an association with EBV infection, and usually is associated with a high mortality rate. Angiocentric CTCL is an unusual T-cell lymphoma of childhood that presents with a vesiculopapular eruption that may mimic hydroa vacciniforme (see Chapter 19).<sup>146</sup> It occurs mainly in children from Asia and Latin America and may be related to EBV infection.

Hodgkin lymphoma is a fairly common childhood lymphoma that often occurs before adolescence. It rarely occurs before the age of 5 years, and there is another peak of involvement later in adulthood. In the majority of cases, Hodgkin lymphoma, which is now classified as a B-cell lymphoma, is initially limited to the lymph nodes, with superficial lymph nodes more commonly initially involved than visceral lymph nodes. It presents as painless lymph node enlargement, usually in the neck. Hodgkin lymphoma is histologically characterized as one of several subtypes, and staging depends on the extent of lymph node involvement and the presence or absence of constitutional symptoms. Skin involvement resulting from infiltration of the malignant cells is quite rare (<1%), but nonspecific secondary findings may occur and include pruritus, purpura, ichthyosis, and pigmentary changes. When specific cutaneous lesions are present, they are usually pink to red-brown or violaceous papules or nodules that may coalesce to form larger plaques or tumors.

The treatment of cutaneous lymphomas can be planned only after thorough evaluation and staging for the extent of extracutaneous disease. Occasionally patients with low-grade neoplasms with limited involvement may be appropriately managed by watchful waiting. Therapeutic options otherwise include radiotherapy, chemotherapy, surgical excision (i.e., for localized primary cutaneous tumors), and newer cytokine and biologic therapies.

## Cutaneous T-cell Lymphoma

CTCL (mycosis fungoides) is a primary cutaneous lymphoma that occurs primarily in adults. Although approximately 75% of patients are diagnosed after the age of 50,<sup>147</sup> onset of the disease during childhood may occur in 0.5% to 5% of cases.<sup>147,148</sup> It has been diagnosed in patients as young as 22 months of age<sup>147</sup> and is suspected to have started in patients as young as 10 months of age.<sup>149</sup> Many factors may

contribute to the seemingly lower incidence of CTCL in children, including lack of recognition of its occurrence and hesitancy to perform skin biopsies in younger patients. Delay in diagnosis is most common in the youngest age group (0 to 3 years old).<sup>149</sup> The possibility of CTCL should be considered in the setting of chronic dermatoses recalcitrant to therapy, and serial skin biopsies may be necessary.<sup>150</sup> In general, patients who have CTCL during childhood are more likely to have limited disease and as a result seem to have a better disease-specific survival rate than older patients with CTCL.<sup>147,151</sup> Some studies, however, have found no statistically significant differences in the course between early childhood- and adult-onset disease.<sup>152</sup> Table 10-3 lists the staging and classification for CTCL.

The clinical presentation of CTCL is quite variable. Most pediatric patients have erythematous, scaly patches, papules, and plaques (Fig. 10-19) with variable degrees of pruritus. Thin, erythematous, atrophic patches on the trunk and buttocks are a classic presentation. At times, central clearing develops and the lesions assume serpiginous, arciform, horseshoe, or other bizarre shapes. The lesions of CTCL may simulate many other skin disorders, including atopic dermatitis, psoriasis, parapsoriasis, hypopigmenting or depigmenting disorders (i.e., vitiligo or pityriasis alba; see below), and pityriasis lichenoides.<sup>153,154</sup> Some patients show changes of poikiloderma characterized by the

**Table 10-3 TNMB Staging/Classification of Cutaneous T-Cell Lymphoma**

Stage	Skin (T)*	Nodes (N)†	Viscera (M)‡	Blood (B)§
Ia	1	0	0	0
Ib	2	0	0	0
IIa	1–2	1	0	0
IIb	3	0, 1	0	0
III	4	0, 1	0	0
IVa	1–4	2, 3	0	1
IVb	1–4	0–3	1	1

BSA, Body surface area; TNMB, tumor, nodes, metastasis, blood.

\*Skin: T0, clinically suspicious lesions; T1, limited papules or plaques (<10% BSA); T2, generalized papules or plaques (>10% BSA); T3, tumors; T4, generalized erythroderma.

†Nodes: N0, none; N1, clinically abnormal nodes, negative pathology; N2, no clinically abnormal nodes, positive pathology; N3, clinically abnormal nodes and positive pathology.

‡Viscera: M0, no visceral involvement; M1, visceral involvement confirmed by pathology.

§Blood: B0, atypical circulating cells not present (<5%); B1, atypical circulating cells present (>5%).



**Figure 10-19** Cutaneous T-cell lymphoma. Erythematous macules, papules, plaques, and nodules in this 6-year-old male. Skin biopsy revealed an atypical T-cell infiltrate with similar circulating cells noted in the blood.



**Figure 10-20** Lymphomatoid papulosis in a patient with cutaneous T-cell lymphoma (CTCL). This 10-year-old male with a long history of patch- and plaque-stage CTCL developed intermittent self-healing ulcerative nodules that were noted to be CD30+ on histologic evaluation.

combination of hyperpigmentation and hypopigmentation, atrophy, and telangiectasia. Although the lesions themselves may not be pathognomonic for CTCL, their chronic nature and history of recalcitrance to therapy often prompt further diagnostic investigations. Skin nodules and tumors, which may grow aggressively and occasionally ulcerate, are an uncommon presentation of pediatric CTCL and are more often seen in adult and elderly patients. Occasionally, focal skin nodules may intermittently occur superimposed on a background of patch- or plaque-type CTCL, with CD30+ cells and a self-limited clinical course consistent with lymphomatoid papulosis<sup>155</sup> (Fig. 10-20) (see Chapter 4). Occasionally, patients exhibit skin findings suggestive of pigmented purpuric dermatosis.<sup>156,157</sup> In some patients, the entire cutaneous surface may become infiltrated, producing thickened red skin with or without scaling and with islands of normal skin often remaining for a time before the universal erythroderma becomes complete.

Hypopigmented CTCL is a variant of the disease that occurs most commonly in children. It tends to present most often in patients with black or darkly pigmented skin, although more fair-skinned individuals may also manifest these findings.<sup>158–160</sup> Patients with this form of CTCL show hypopigmented macules and patches (Fig. 10-21) that are usually asymptomatic. The clinical appearance most often simulates disseminated pityriasis alba, tinea versicolor, or postinflammatory hypopigmentation. Lesions may be round, arcuate, or gyrate, and often there is some subtle overlying scale.<sup>148</sup> Histologically, biopsies of hypopigmented lesions show the same features as the inflammatory lesions of CTCL, although on immunophenotyping, the infiltrate may be shown to be composed predominantly of CD8+ T cells rather than CD4+ T cells.<sup>161</sup>

Granulomatous slack skin is an extremely rare form of CTCL characterized by the insidious onset of papules and violet-colored plaques with progression to pendulous skin masses.<sup>162</sup> The lesions appear erythematous and wrinkled and are most commonly distributed in the axillary and inguinal regions. There is a male predominance in the literature.<sup>148</sup> Histologically, a granulomatous T-cell infiltrate is seen along with fragmentation of elastic fibers.<sup>163</sup>

Follicular mucinosis (alopecia mucinosa) (see Chapter 7) has also been seen as a feature of CTCL, primarily in adults. Although it occasionally occurs as a manifestation of the disorder in children, in the majority of patients (children and adults <40 years), it is generally regarded as a benign condition not associated with CTCL. In a series of 31 children with follicular mucinosis, 12 fulfilled criteria for CTCL, and the vast majority responded to treatment with mild- to moderate-potency topical corticosteroids.<sup>164</sup> In another series of 11 patients with the condition, three were found to have CTCL based on immunophenotyping and/or T-cell-receptor gene cell rearrangement.<sup>165</sup> Follicular mucinosis presents as well-demarcated flesh-colored to hypopigmented patches with prominent superimposed follicular



**Figure 10-21** Hypopigmented cutaneous T-cell lymphoma. Hypopigmented patch with mild scaling on the posterior axillary region in a boy with histologically confirmed cutaneous lymphoma.



**Figure 10-22** Follicular mucinosis. This hypopigmented patch with superimposed follicular erythematous papules was present on the leg of a young boy with a known history of cutaneous T-cell lymphoma.

papules (Fig. 10-22), often with associated hair loss. It occurs most commonly on the lower extremities, although it may also involve the trunk or face, and there are usually multiple lesions. Although most cases in childhood represent a benign self-limiting process, when lesions are persistent or other suggestive features are present, evaluation for possible CTCL should be considered. Pityriasis lichenoides-like CTCL presents with erythematous papules with scaling and crusting that simulate pityriasis lichenoides chronica or pityriasis lichenoides et varioliformis acuta (see Chapter 4).<sup>166,167</sup>

Sézary syndrome, which is characterized by erythroderma, lymphadenopathy, and circulating atypical lymphocytes (Sézary cells), is felt to be a systemic variant of CTCL. It is rare in children. The cutaneous eruption is scaly, pruritic, and resistant to multiple therapies. As with many forms of CTCL, repeat skin biopsies may be necessary to confirm the diagnosis.

The diagnosis of CTCL is established based on the histologic findings of skin biopsy tissue in conjunction with immunohistochemical

studies. Although there are characteristic histologic features in well-developed disease, biopsy findings in patients with early involvement may be difficult to distinguish from other, more benign processes such as inflammatory dermatoses.<sup>148</sup> Immunohistochemical studies usually reveal an infiltrate of CD4+ T cells with loss of CD7+ (leu-9) cells. Southern blot analysis and polymerase chain reaction (PCR) may be used to evaluate for T-cell receptor  $\gamma$  gene rearrangement, which is seen in many but not all CTCL specimens.<sup>168</sup> A more specific technique, combining PCR and denaturing gradient gel electrophoresis (DGGE), demonstrates more sensitivity for detecting clonality but poorer specificity, because it may detect rearrangements in a subset of patients with chronic dermatitis.<sup>169</sup>

There are a variety of treatment options for children with CTCL, but no standard protocols exist and the ideal therapy remains unclear. Potent topical corticosteroids are often sufficient for limited patch- or plaque-stage CTCL, but patients must be monitored for adrenal suppression and cutaneous atrophy.<sup>170</sup> Topical nitrogen mustard has demonstrated efficacy in adults with patch- or plaque-stage disease, and long-term follow-up studies have confirmed its safety.<sup>171</sup> Psoralen plus ultraviolet A (PUVA) photochemotherapy is effective but may be difficult and have limiting side-effects in children. Topical PUVA has been demonstrated useful in children with patch- and plaque-stage disease.<sup>172</sup> Other therapies used for CTCL include ultraviolet B (UVB) therapy, carmustine, imiquimod, tazarotene, electron-beam therapy, systemic chemotherapy, denileukin diftitox (a fusion toxin), interferon, photopheresis, and bexarotene (a systemic retinoid, a cousin of the retinoids). Narrow-band UVB therapy may offer similar results as those seen in adults and has the potential advantages of being well tolerated in children, having fewer unpredictable phototoxic reactions, and requiring shorter treatment sessions.<sup>173</sup> However, pediatric experience with many of these treatments is quite limited. Young patients with CTCL may have an increased risk of Hodgkin lymphoma and hence should be monitored on a long-term basis.

## Neuroblastoma

Neuroblastoma, a tumor derived from primitive cells of the sympathetic nervous system, is the most common malignant tumor affecting infants in the first month of life and accounts for 30% to 50% of all tumors occurring in the newborn period.<sup>174</sup> It is a tumor with large variability in its clinical presentation and natural history. Neuroblastoma may regress spontaneously (particularly in infants), mature into a benign ganglioneuroma, or result in extensive metastatic disease with a poor prognosis.<sup>175</sup> These tumors typically present as an abdominal mass because of liver infiltration with malignant cells and may originate in the adrenal medulla, visceral ganglia, or paravertebral sympathetic ganglia.

Cutaneous metastases of neuroblastoma are seen in around 2% of all patients and 32% of those with a neonatal presentation. These skin lesions, which may be the presenting sign of the disease, appear as firm, blue-purple papules and nodules (Fig. 10-23). When occurring in a neonate, they fall into the spectrum of blueberry-muffin lesions (see Box 10-6). The catecholamines produced by the tumor cells may result in the classic blanching and peripheral halo of erythema noted after firm stroking. Subcutaneous nodules mimicking deep infantile hemangiomas have also been observed.<sup>176</sup> When cutaneous metastases of neuroblastoma are encountered in the infantile period, it confers a more favorable prognosis than other patients with metastatic neuroblastoma, although tumor biology is the most critical prognostic consideration.<sup>174,177</sup> Very hard subcutaneous nodules arising from the skull and orbital ridges are caused by skeletal metastases. Orbital metastases may result in the classic presentation of periorbital ecchymoses, so-called "raccoon eyes." Another ocular finding is that of heterochromia irides, which is related to involvement of the ophthalmic sympathetic nerve.

Staging of neuroblastoma is based on clinical and radiographic extent of disease and surgical resectability. Tumor tissue is usually necessary to confirm the diagnosis, and when cutaneous lesions are present, skin biopsy with histologic evaluation, immunophenotyping, and genetic analysis may be indicated. Measurement of urine and serum catecholamines or metabolites, CT and/or MRI, bone marrow



**Figure 10-23** Neuroblastoma with cutaneous metastases. This male infant had numerous firm, blue subcutaneous nodules that revealed neuroblastoma on histologic examination. He was found to have a large retroperitoneal primary tumor with disseminated metastatic disease.



**Figure 10-24** Fibrosarcoma. This congenital, vascular, friable mass was initially thought to be an infantile hemangioma; it grew rapidly and ultimately required full excision with amputation.

aspirate and biopsies, and iodine-123 metaiodobenzylguanidine (MIBG) scintigraphy are recommended as part of the staging evaluation.<sup>178</sup>

## Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft-tissue sarcoma in children and adolescents, accounting for 50% of all soft-tissue sarcomas in those under 15 years of age.<sup>179,180</sup> It is a malignant soft-tissue neoplasm of skeletal muscle origin and is seen primarily in the first and second decades of life. Although rhabdomyosarcoma is not typically a primary skin tumor, it is included in this section, because it may simulate other cutaneous tumors, may extend or metastasize to the cutaneous surface, and may initially present to the pediatrician or other pediatric healthcare provider.

Rhabdomyosarcoma usually presents as an asymptomatic mass that is occasionally painful.<sup>181</sup> The head and neck, especially the nasal cavity and paranasal sinuses, are the most common sites of involvement in children. The genitourinary tract and extremities are other common sites of predilection. Patients may present with small to large nodules or rapidly expanding swellings. The surface may be flesh-colored to erythematous and at times may appear vascular with prominent vessel markings. The differential diagnosis may include infantile hemangioma, vascular malformation, fibrosarcoma (Fig. 10-24),

cyst, infection, or other inflammatory or neoplastic process. Perianal rhabdomyosarcoma may mimic perirectal abscess.<sup>182</sup> Primary cutaneous rhabdomyosarcoma refers to a tumor that arises in the dermis or subcutis with no other identifiable primary tumor elsewhere and that tends to display aggressive behavior in both adults and children.<sup>183</sup> Congenital alveolar rhabdomyosarcoma is a rare subtype, with more than 50% of patients presenting with multiple cutaneous metastases.<sup>184</sup> Tumor-specific translocations are detected in the majority of cases, and the disorder is invariably fatal.

Treatment of rhabdomyosarcoma consists primarily of surgery, radiotherapy, and chemotherapy. Although challenging, the overall 5-year survival rate of children and adolescents with both nonmetastatic and metastatic tumors approaches 80%.<sup>185</sup>



The complete list of 185 references for this chapter is available online at <http://expertconsult.inkling.com>.

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Although chiefly of cosmetic significance, disorders of pigmentation are among the most conspicuous and thus can have profound psychosocial implications for pediatric patients. The most important pigments in skin are melanin, reduced and oxygenated hemoglobin, and carotene. Melanin is a pigment produced by melanocytes, specialized dendritic cells derived from the neural crest that migrate to the basal layer of the epidermis during embryogenesis. Melanocytes synthesize and package melanin within discrete membrane-bound organelles called *melanosomes*, which are then transferred via melanocytic dendrites to surrounding keratinocytes of epidermis and hair follicles; on average, there is one melanocyte to every 36 surrounding keratinocytes.<sup>1-4</sup> Variations in skin color among different individuals reflect the number and size of mature melanosomes, not the number of melanocytes.

Four stages of melanosome maturation have been described and can be distinguished by ultrastructural examination:

1. Membrane vesicles that contain no visible pigment (stage I or premelanosomes)
2. More elongated vesicles with an ordered internal membrane but no pigment (stage II melanosome)
3. The presence of melanin on ordered internal fibers (stage III melanosome)
4. Structures so full of melanin that the luminal structures cannot be seen (mature or stage IV melanosomes).

Darkly pigmented individuals have more numerous, larger, singly dispersed melanosomes, whereas individuals with light pigmentation have fewer, smaller melanosomes that are aggregated into complexes and are more rapidly degraded.<sup>5</sup> The presence of melanin in the epidermis helps protect against ultraviolet (UV) radiation and associated cutaneous damage, including pigmented nevi,<sup>6</sup> actinic damage, and cutaneous neoplasia. Red hair color, usually associated with an inability to tan, increases the risk of developing melanoma fourfold and has been associated with polymorphisms in the melanocortin receptor 1 (MCR1).<sup>7</sup>

Melanin exists in two forms in human skin: brown-black eumelanin and yellow-red pheomelanin. Melanin biosynthesis is primarily regulated by tyrosinase, a copper-dependent enzyme that allows the initial conversion of tyrosine to dihydroxyphenylalanine (DOPA). Eumelanin synthesis involves increased levels of tyrosinase activity and additional melanogenic enzymes such as tyrosinase-related protein (TRYP)-1 and TRYP-2/dopachrome tautomerase, both regulators of distal steps in the pathway to melanin and/or stabilizers of tyrosinase. Pheomelanin synthesis, however, involves the addition of a cysteinyl group that accounts for the yellow-red color and is associated with reduced tyrosinase activity and absence of TRYP-1, TRYP-2, and a protein called pink-eyed dilution (P) protein.

The ratio of eumelanin to pheomelanin, as well as the total content of melanin, is higher in skin types V–VI (the darkest skin colors) than in skin types I and II (the lightest skin colors, most prone to burning with UV light exposure). Pheomelanin levels tend to be greatest in individuals with bright red hair, whereas eumelanin is the predominant pigment in individuals with brown or black hair.<sup>8</sup>

In all races the dorsal and extensor surfaces are relatively hyperpigmented, and the ventral surfaces are less pigmented. This is most evident in races with darker skin (African-Americans, Hispanics, and Asians). The separation of the dorsal and ventral pigmentation is most conspicuous on the extremities (Voigt–Futcher lines) (Fig. 11-1).<sup>9</sup> This differentiation of dorsal and ventral pigmentation is present from infancy and persists throughout adulthood. Approximately 75% of

African-Americans and 10% of whites have at least one line of pigmentary demarcation.

## Disorders of Abnormal Pigmentation

Disorders of decreased pigmentation may be classified as:

1. Genetic or developmentally controlled disorders, in which pigmentation tends to be abnormal from birth or early infancy
2. Disorders associated with depigmentation or loss of previously existing melanin.

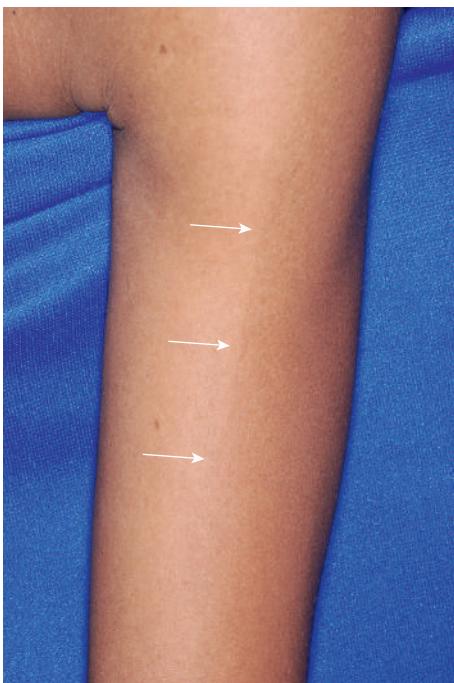
Genetic disorders of decreased pigmentation include tuberous sclerosis, piebaldism, Waardenburg syndrome (WS), and albinism. Acquired disorders of decreased pigmentation include vitiligo, postinflammatory hypopigmentation, pityriasis alba, and tinea versicolor. Hypopigmentary disorders may be further divided into patterned and unpatterned groups. Patterned forms of decreased pigmentation include pityriasis alba, cutaneous T-cell lymphoma, tinea versicolor, postinflammatory hypopigmentation, leprosy, pinta, tuberous sclerosis, pigmentary mosaicism, vitiligo, piebaldism, and the Waardenburg and Vogt–Koyanagi syndromes. Unpatterned decreases in pigmentation may be seen in albinism, phenylketonuria, and the silvery hair syndromes.

### VITILIGO

Vitiligo, an acquired form of patterned loss of pigmentation, is a polygenic, multifactorial disorder that involves at least 16 susceptibility genes,<sup>10,11</sup> encoding a variety of proteins involved in regulation of the immune system and tyrosinase, the principal vitiligo autoimmune antigen. Melanocytes are destroyed by antigen-specific cytotoxic T cells, resulting in patchy depigmentation. Both lesional and nonlesional skin show up regulation of markers of heightened innate immunity, although only lesional skin shows suppression or absence of melanocyte-specific genes.<sup>12</sup> Autoantibodies that can destroy melanocytes have been detected in serum samples of patients with vitiligo, further emphasizing that alterations are not limited to lesional skin.

Vitiligo affects approximately 1% of the population.<sup>13</sup> Although rarely congenital, its onset in about half of affected patients is before the age of 20 years and in one-quarter before 8 years of age.<sup>14–16</sup> The disorder has a prevalence of 7% to 12% among first-degree relatives, 6% among siblings, and 23% among monozygotic twins,<sup>17</sup> but a recent study suggested a family history of vitiligo in approximately 30% of patients.<sup>18</sup> Relative to postpubertal onset (after 12 years of age), prepubertal onset is associated with a greater likelihood of a family history of vitiligo and a personal history of atopic dermatitis.<sup>18</sup> Autoimmune disorders are seen with significantly increased incidence in immediate family members of affected individuals, most commonly vitiligo itself,<sup>14</sup> but other autoimmune disorders (particularly hypothyroidism and alopecia areata) occasionally occur in pediatric patients with vitiligo.<sup>19–21</sup> Thyroid autoimmune antibodies have been described in 11% of patients.<sup>19,22</sup>

The location, size, and shape of individual lesions vary considerably, yet the overall picture is characteristic. Lesions usually appear as partially or completely depigmented ivory-white macules or patches, usually with well-defined, sometimes hyperpigmented, convex borders<sup>23</sup> (Figs. 11-2 through 11-7). They tend to have an oval or linear contour and range in size from several millimeters to large patches. Rarely, extensive or near-total depigmentation of the body (universal



**Figure 11-1** Voigt–Futcher line. This persistent line of demarcation separates dorsal and ventral pigmentation.



**Figure 11-2** Vitiligo. Depigmented, usually well-defined, white macules or patches that tend to have an oval or linear contour.

or total vitiligo) occurs (see Fig. 11-4). Although usually considered to be a bilateral disorder, vitiligo may be asymmetric; segmental vitiligo, in which the depigmentation is confined to a localized, usually unilateral area, occurs more often in children than in adults (see Fig. 11-5). In 75% of affected individuals the first lesions occur as depigmented spots on exposed areas such as the dorsal surfaces of the hands, face, and neck. Other sites of predilection include the body folds (the axillae and groin), body orifices (the eyes, nostrils, mouth, navel, areolae, genitalia, and perianal regions (see Figs. 11-6 and 11-7), and areas over bony prominences such as the elbows, knees, knuckles, and



**Figure 11-3** Vitiligo. Symmetrical depigmentation of the knees and lower extremities. The dorsal aspect of the feet and hands are particularly hard to repigment.



**Figure 11-4** Vitiligo. Extensive depigmentation in this 13-year-old girl. Virtually all of her skin was depigmented, except for the pigmented areas on the back. After years of unsuccessfully trying to stimulate repigmentation, at 16 years of age this girl and her parents elected to initiate 20% monobenzyl ether of hydroquinone.

shins (see Fig. 11-3). Approximately 12% of patients show white hairs (leukotrichia or poliosis) (Fig. 11-8). Vitiligo has been divided into several subtypes based on the distribution of lesions. In descending order of incidence in pediatric patients, these include generalized, focal, segmental, acrofacial, mucosal, and universal. Patients with vitiligo, especially those with prepubertal onset,<sup>18</sup> commonly show halo nevi,<sup>24</sup> pigmented nevi surrounded by a zone of depigmentation (Fig. 11-9) (see Chapter 9, Fig. 9-26). The discovery of a halo nevus



**Figure 11-5** Segmental vitiligo. Segmental distribution of depigmentation on the right side of the philtrum and upper lip. Note the sharp midline demarcation.



**Figure 11-8** Vitiligo with poliosis. When the hair in the affected area is white, there is a decreased likelihood of repigmentation.



**Figure 11-6** Vitiligo. Periorbital depigmentation. Although eyebrows and eyelashes are occasionally affected as well (poliosis), in this boy the hair has retained its pigmentation. The perioral and perinasal areas are also commonly affected on the face.



**Figure 11-9** Vitiligo. Halo nevi are commonly seen in children with vitiligo and can partially or fully clear the nevus. Any patient with a halo nevus should be completely examined for the possibility of vitiligo elsewhere. The mechanism of clearance of pigmentation in vitiligo and halo nevi is thought to be the same.



**Figure 11-7** Vitiligo. The vitiligo was limited to the genital and perianal areas in this African-American boy.

and particularly multiple halo nevi<sup>25</sup> should prompt the search for vitiligo elsewhere.

The Koebner phenomenon (development of a lesion after trauma) has been described in approximately 15% of affected children with vitiligo, particularly related to sunburn. A recent study showed that skin friction induces melanocyte detachment in persons with vitiligo but not in individuals with normal skin, further emphasizing the role of trauma in triggering new lesions.<sup>26</sup> Other individuals associate the onset of vitiligo with periods of severe physical or emotional trauma.

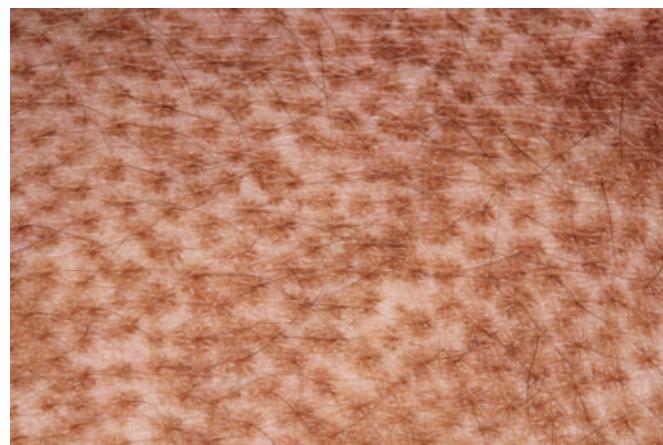
Ordinarily the diagnosis of vitiligo is not difficult, especially when there is symmetric depigmentation about the eyes, nostrils, mouth, nipples, umbilicus, or genitalia. In fair-skinned individuals it may be difficult to differentiate areas of vitiligo from the adjacent normal skin. In such cases examination under Wood light in a darkened room may help delineate a contrast between normal and depigmented skin. When the diagnosis is in doubt, the distribution of lesions, the age at onset, the presence of a convex hyperpigmented border, and the characteristic sites of predilection may help establish the correct diagnosis.

Lesions of postinflammatory hypopigmentation are hypopigmented, not depigmented, and patients usually provide a history of previous localized inflammation. However, it is not uncommon to see residual depigmentation in severe atopic dermatitis, especially in darker skinned patients and involving the wrists, hands, ankles, and feet. Nevus depigmentosus tends to be a well-defined, usually

hypopigmented patch that may be present at birth or appear during infancy as normal pigmentation increases but is subsequently stable (see Fig. 11-22). Pityriasis alba is a hypopigmentary disorder and may be further differentiated by its common distribution on the face, upper arms, neck, and shoulders and its occasional fine adherent scale (see Chapter 3, Fig. 3-33). Lesions of tinea versicolor may be differentiated by their discrete or confluent small, round hypopigmented macules; their fine scales; and their typical distribution on the trunk, neck, upper arms, or particularly in pediatric patients, the face (see Chapter 17, Figs. 17-33 and 17-34). The demonstration of hyphae on microscopic examination of epidermal scrapings is confirmatory (see Fig. 17-36). The diagnosis of cutaneous T-cell lymphoma of the hypopigmented type should be considered in adolescents with more extensive hypopigmented macules resembling pityriasis alba (see Chapter 10, Fig. 10-21).<sup>27</sup>

The presence of a white forelock and the pattern of depigmentation suggest a diagnosis of piebaldism or WS (see Figs. 11-17 and 11-19). Most individuals with WS show characteristic facial features. The diagnosis of albinism (see Oculocutaneous Albinism section) may be established by its presence at birth and by the facts that normal eye color is retained in vitiligo (but not in albinism); in addition, hair on glabrous skin in the patient with vitiligo, in contrast to that in the patient with albinism, often retains most of its pigment (see Fig. 11-11). Adolescents with GM3 synthase deficiency progressively develop depigmented patches as well as acral lentiginous.<sup>28</sup> The hypopigmented macules of tuberous sclerosis (see Fig. 11-21, A) usually lack the characteristic milk-white appearance of lesions of vitiligo, are present at birth or during the first years of life, do not change with age, and have a normal number of melanocytes (with reduction in size of melanosomes and melanin granules within them) in contrast to the absence or decrease in number of melanocytes in patients with vitiligo.

The course of vitiligo is variable. Long periods of quiescence may be interrupted by periods of extension or partial improvement. Complete spontaneous repigmentation is very rare, and in one study, more than 50% repigmentation occurred in only 2.4% of patients over 6 months.<sup>29</sup> At least partial repigmentation is more likely in children with lesions of recent onset and during the summer months because of increased exposure to UV light. Loss of pigmentation in lesions that have at least partially repigmented is common in temperate climates during the winter months. The repigmentation process proceeds slowly, although children tend to respond with more permanent and complete repigmentation than adults. Repigmentation most commonly appears as small, freckle-like spots of repigmentation, reflecting the migration of melanocytes from the hair follicle (Fig. 11-10). As such, the chance of repigmentation in a site is greater if pigmentation of regional hairs is retained. Diffuse repigmentation of lesions or repigmentation from the margins has also been described. The preferential tendency to repigment the face and neck versus other body sites has been attributed to the high density of hair follicles at these sites, as well as exposure to UV light. In contrast, sites lacking or poor in



**Figure 11-10** Vitiligo. Note the perifollicular pattern of repigmentation.

hair follicles, such as the dorsal surfaces of the fingers, hands, feet, and the volar aspect of the wrists, do not respond as well as other areas.

Quality-of-life studies have shown that children with vitiligo have impaired social development as young adults, stressing the importance of intervention.<sup>30</sup> Risk factors associated with the highest risk for quality-of-life impairment are age (15 to 17 years), location (face and legs), and greater extent of involvement.<sup>31</sup> In one study, anxiety was observed in 42% of caregivers of children with vitiligo, even higher than that in caregivers of children with atopic dermatitis or psoriasis, and was correlated with poor quality-of-life scores in the children.<sup>32</sup> Patients with vitiligo and their families can find support through the National Vitiligo Foundation ([www.vitiligofoundation.org](http://www.vitiligofoundation.org) or [www.nvfi.org](http://www.nvfi.org)).

Full repigmentation is challenging, especially in children with more extensive involvement and when vitiligo involves more recalcitrant areas. At least partial repigmentation can often be accomplished by the twice-daily application of mid-strength to potent topical corticosteroids or topical calcineurin inhibitors (tacrolimus ointment, pimecrolimus cream).<sup>33,34</sup> The skin of the head and neck responds best to both of these treatment modalities. Overall, 40% to 90% of pediatric patients show a response to these treatments, although moderate to high potency steroids can theoretically be associated with systemic absorption, especially if applied over large body-surface areas or on the head and neck continuously.<sup>21,35,36</sup> Application of a topical calcineurin inhibitor, especially for facial vitiligo, eliminates the risk of cutaneous atrophy and ocular toxicity carried by application of topical corticosteroids. However, hyperpigmentation in sun-exposed areas has been described after use of tacrolimus ointment.<sup>37</sup> Although topical anti-inflammatory therapy has been standard, one study described good to excellent repigmentation in 65% of 400 children treated with minipulses of oral methylprednisolone on 2 consecutive days weekly and fluticasone ointment twice daily.<sup>38</sup> Topical application of vitamin D<sub>3</sub> analogues (calcipotriene, calcipotriol) has also been used but has the potential to be more irritating.

The repigmentation of lesional skin can be stimulated most effectively by exposure to UV light, generally in combination with topically applied anti-inflammatory medications or vitamin D<sub>3</sub> analogues. Avoidance of burning with phototherapy is important, because cutaneous burning can lead to further depigmentation via the Koebner phenomenon. Most commonly narrow-band (nb) UVB is utilized, because it has been shown to be as effective as psoralen and UVA (PUVA) therapy,<sup>39-41</sup> which is now rarely used in children because of its toxicity. nbUVB phototherapy is largely reserved for older pediatric patients who are highly motivated and completely informed about their chances for improvement with these therapies. Treatment is traditionally 2 to 3 times weekly, beginning at a relatively low dose and increasing by about 20% each treatment until slight erythema is reached. Should there not be a good response within 6 months, nbUVB can be stopped.<sup>42</sup> The 308-nm monochromatic excimer laser (in the UVB range) is a painless therapy for more localized lesions.<sup>43</sup> The best responses to excimer laser are at sites that also respond best to nbUVB, with the dorsal aspect of the hands and feet, genital area, and suprapubic area the most difficult sites to repigment.<sup>44</sup> In one study of chronic stable vitiligo, more than 50% of patients showed more than 75% repigmentation.<sup>45</sup> Responses to the excimer laser may be improved by concurrently using anti-inflammatory therapy.<sup>46</sup> Treatment with the combination of topical tacalcitol (vitamin D derivative) and excimer laser for 12 sessions (over 12 weeks) was significantly more effective than the excimer laser treatments alone.<sup>47</sup> The use of antioxidants, particularly pseudocatalase, has been based on the demonstration of decreased enzymatic and nonenzymatic oxidants in the skin of patients with vitiligo.<sup>48</sup> Although in one retrospective uncontrolled study, twice-daily full-body application of pseudocatalase cream coupled with daily low-dose nbUVB stopped vitiligo progression and led to more than 75% repigmentation in 93% of treated children,<sup>49</sup> most experience with pseudocatalase cream has been disappointing. Oral antioxidants for vitiligo are under investigation.

Surgical modalities are based on the autologous grafting of nonlesional epidermis or cultured melanocytes from healthy skin sites to depigmented areas that have been deepithelialized by ablative procedures.<sup>50,51</sup> Chinese cupping has recently been shown to be a technique to induce blisters for capturing donor melanocytes.<sup>52</sup> Grafting has

been demonstrated to lead to at least 75% repigmentation in 30% to 90% of patients and is most successful for more localized lesions.<sup>53,54</sup> Although minigrafting with or without UV light exposure has shown success, especially in patients with facial grafts and with segmental and limited subtypes,<sup>55,56</sup> these approaches are time-consuming, costly, and can result in recurrence of vitiligo (including at the donor site), scarring, infection, and keloids in at-risk patients; grafting should only be considered for stable vitiligo in selected adolescents at sites that are resistant to medical treatment.

When treatment is unsatisfactory, lesions can be hidden by the use of camouflage therapy,<sup>57</sup> which has been shown to improve the quality of life in children with vitiligo.<sup>58</sup> Camouflage can be achieved most effectively with cosmetics (e.g., Cover FX, Dermablend, or Covermark), but aniline dye stains, such as Vitadye (Elder) and quick-tan preparations<sup>59</sup> have also been used.

In those few recalcitrant cases in which vitiligo has progressed to such an extent that more than 50% of the body is involved (particularly in those persons in whom only a few islands of normal skin remain), an attempt at depigmentation with 20% monobenzyl ether of hydroquinone (Benoquin) may be considered. Such patients should be reminded that the depigmentation is permanent, requiring lifelong vigilant use of sun protection. Owing to the permanence of depigmentation therapy, this treatment is not generally offered to preadolescent patients.

### VOGT-KOYANAGI-HARADA SYNDROME

Vogt–Koyanagi–Harada syndrome is a rare autoimmune disorder characterized by bilateral granulomatous uveitis, alopecia, vitiligo, poliosis, dysacusia (in which certain sounds produce discomfort), deafness, and sometimes meningeal irritation or encephalitic symptoms.<sup>60</sup> Usually seen in adults in the third and fourth decades of life,<sup>61</sup> the disorder also occurs in children and adolescents.<sup>62,63</sup>

The bilateral uveitis occurs in all patients and generally takes a year or more to clear. The uveitis is often accompanied by choroiditis and optic neuritis. As the uveitis begins to subside, poliosis (in 80% to 90%), usually bilateral vitiligo (in 50% to 60%), alopecia (in 50%), and temporary auditory impairment develop. A prodromal febrile episode with lymphocytosis, encephalitic or meningeal symptoms, and increased pressure of the cerebrospinal fluid may precede the bilateral uveitis. The poliosis may be limited to the eyebrows and eyelashes or may also involve the scalp and body hair. The pigmentary changes, which generally appear 3 weeks to 3 months after the onset of the uveitis, tend to be permanent. Although most patients show some recovery of visual acuity, the majority of children and adolescents have a residual visual defect related to the development of cataracts, glaucoma, choroidal neovascularization, and subretinal fibrosis.<sup>64</sup>

Early and aggressive systemic corticosteroids are the primary intervention, but refractory cases may respond to cyclosporine, methotrexate, or tumor necrosis factor (TNF) inhibitors.<sup>65,66</sup>

### ALEZZANDRINI SYNDROME

Alezzandrini syndrome is a rare disorder of unknown origin primarily seen in adolescents and young adults. Possibly related to Vogt–Koyanagi–Harada syndrome, it is characterized by unilateral degenerative retinitis with visual impairment followed after an interval of months or years by bilateral deafness and unilateral vitiligo and poliosis, which appear on the side of the retinitis.<sup>67,68</sup>

### OCULOCUTANEOUS ALBINISM

Albinism is a group of inherited disorders of melanin synthesis manifested by a congenital decrease of pigmentation of the skin, hair, and eyes.<sup>69,70</sup> Although some classifications include nonsyndromic and syndromic (e.g., silvery hair and Hermansky–Pudlak syndromes) forms, the pigmentary changes are very different among these disorders. Most albinism is oculocutaneous, but affected individuals may have ocular albinism, usually an X-linked recessive form caused by mutation in OA1/GPR143, with the abnormal pigmentation limited to the eye. An oculocerebral syndrome with hypopigmentation (Cross–

McKusick–Breen syndrome) is characterized by oculocutaneous albinism (OCA), microphthalmos, spasticity, and mental retardation.<sup>71</sup> Although albinism associated with immunodeficiency is primarily seen in the silvery hair syndromes (especially Chédiak–Higashi and Griscelli type 2), immunodeficiency is a feature of OCA associated with short stature (owing to mutations in LAMTOR2)<sup>72</sup> and in Hermansky–Pudlak syndrome (HPS) types 2 and 9, all related to the requirement for secretion of lysosomes and cytosolic granules for cytotoxic T- and natural killer cell function, antigen presentation to T cells, and neutrophil antimicrobial activity.<sup>73</sup>

### Nonsyndromic Oculocutaneous Albinism

Nonsyndromic oculocutaneous albinism (OCA) encompasses seven subtypes (Table 11-1) with decreased or absent melanin biosynthesis in the melanocytes of the skin, hair follicles, and eyes.<sup>74,75</sup>

OCA affects 1 in 17,000 persons in the United States. The highest prevalence (as high as 1% of the population) occurs in the indigenous Cuna tribe on the San Blas Islands off the coast of Panama. Affected Cuna children have been called *moon children* because they have marked photosensitivity and photophobia and prefer to go outdoors only at night. In some African tribes, the frequency is 1:1500. OCA is characterized by varying degrees of unpatterned reduction of pigment in the skin and hair, translucent irides, hypopigmented ocular fundi, and an associated nystagmus. Melanocytes and melanosomes are present in the affected skin and hair in normal numbers but fail to produce normal amounts of melanin. Regardless of subtype, affected individuals require vigorous sun protection of the skin and eyes and are at risk of adverse psychosocial effects because of the cosmetic aspects of albinism, especially in children from darker-skinned backgrounds. In addition to the stigma and potential social isolation, affected individuals in Africa have been maimed or killed because of the myths associated with albinism (contagion, body parts with magical and medicinal powers, intercourse with an affected woman will cure human immunodeficiency virus [HIV] infection).<sup>76</sup>

In the past, albinism was divided into tyrosinase-negative and tyrosinase-positive forms based on the ability (tyrosinase-positive) or inability (tyrosinase-negative) of plucked hair to become pigmented in the presence of tyrosine or DOPA. Tyrosinase-negative albinism, now called *type I albinism* (OCA1), results from absence (OCA1A) or partial reduction of the activity (OCA1B) of tyrosinase, the critical enzyme in melanin formation (see Table 11-1).<sup>77</sup> The underlying genetic bases for most forms of tyrosinase-positive albinism are also known. Type II albinism (OCA2) results from the absence of P protein,<sup>78</sup> OCA3 from absence of TRYP1,<sup>79,80</sup> and OCA4 from mutations in membrane-associated transporter protein (MATP).<sup>81</sup> Types OCA5–7 have been only been described in one to a few families (see Table 11-1).<sup>82–85</sup>

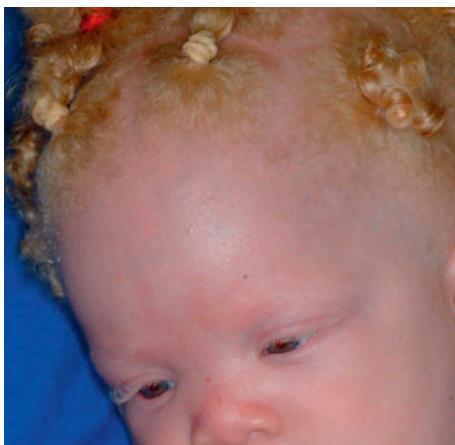
Individuals with OCA1A are unable to produce melanin at all and show white skin, white hair, and blue irides regardless of familial skin coloration.<sup>86</sup> Hair may show a slight yellow tint with advancing age because of denaturation of hair keratins. Similarly, ocular abnormalities are most severe with OCA1A. Eye findings include photophobia (with squinting), nystagmus (which typically develops at 6 to 8 weeks of age), strabismus, and decreased visual acuity; patients with OCA1A are often legally blind. The optic fibers are misrouted, resulting in monocular vision, which is usually not altered by surgical correction of the nystagmus or strabismus.<sup>87,88</sup> Although neurologic development is otherwise generally normal, an increased risk of attention-deficit/hyperactivity disorder (ADHD) has also been described.<sup>89</sup> Actinic damage (cutaneous atrophy, telangiectasia and wrinkling, actinic cheilitis, actinic keratoses) and malignant skin tumors (especially squamous cell carcinoma and nodular basal cell carcinoma but also melanoma) are almost always seen in affected young adults<sup>90</sup> but may present during childhood if the skin and eyes are not protected.

Patients with OCA1B have been divided into different phenotypic subgroups (see Table 11-1) that occur because of differences in degree of tyrosinase activity and the localization within the TYR gene of the mutation. In the yellow mutant form, the hair turns yellow in the first few years and a golden blond to light brown by the end of the second decade. Patients with platinum OCA develop small amounts of pigment with a metallic tinge in late childhood. Those with minimal-pigment OCA show darkening of the eyes with time, but the skin

**Table 11-1** Forms of Oculocutaneous Albinism

Type	Percentage of Patients Worldwide	Mutation	Function of Affected Gene	Comments
OCA1A	50%	TYR (absence) = tyrosinase negative	Critical enzyme in melanin formation	1:40,000; most severe cutaneous and ocular defects; highest risk of skin cancer; most common type in Caucasians
OCA1B		TYR (decreased)	Critical enzyme in melanin formation	Subtypes: yellow mutant (yellow hair); platinum (metallic tinge); minimal pigment (only eyes darken)
OCA1-TS		TYR (mutation site functions at higher temperatures)	Temperature-sensitive	Melanin at cooler sites (arms, legs)
OCA2	30%	P protein	Melanosome biogenesis and normal processing and transport of TYR and <i>TRYP1</i>	1:36,000 (whites); TYR-positive; includes Brown albinism (1:3900–1:10,000; most common form in patients of African origin; more pigment with advancing age)
OCA3 (Rufous)	3%	<i>TRYP1</i>	Catalyzes oxidation of 5, 6-dihydroxyindole-2-carboxylic acid monomers into melanin and stabilizes TYR so it can leave endoplasmic reticulum for incorporation into melanosomes	1:8500 Africans; reddish-bronze color to skin and hair
OCA4	17%	<i>MATP/SLC45A2</i>	Membrane transporter in melanosomes; mutations misroute TYR	Rare (whites); 1, 000 Japanese (27% of OCA in Japan); resembles OCA2
OCA5		Unknown (4q24)	–	One Pakistani family
OCA6		<i>SLC24A5</i>	Solute carrier protein involved in melanosome maturation and melanin biosynthesis	Heterogeneous extent of pigmentation
OCA7		<i>c10orf11</i>	Melanocyte differentiation	Rare

*MATP*, Membrane-associated transporter protein; OCA, oculocutaneous albinism; *P protein*, pink-eyed dilution protein; *TS*, temperature-sensitive; *TYR*, tyrosinase; *TRYP1*, tyrosinase-related protein 1.



**Figure 11-11** Albinism. This African-American girl has type II albinism (mutations in *P* gene) with light skin and yellow hair.



**Figure 11-12** In type II albinism, pigmentation can develop with time, including in pigmented nevi.

remains without pigmentation. Individuals with temperature-sensitive OCA1B are born with white skin and hair and blue eyes. Usually during the second decade of life, however, areas with lower temperature (especially hair at acral sites on the upper and lower extremities) are able to produce melanin, because the tyrosinase activity is only inactivated above 35 °C. This interesting phenotype is shared with that of the Siamese cat, a breed that also results from temperature-sensitive tyrosinase activity.

The OCA2 type of albinism, which includes tyrosinase-positive albinism and Brown OCA, is the most common form and is usually the type that occurs in African-American individuals (Fig. 11-11). The phenotype may vary from a slight to moderate decrease in pigmentation of the skin, hair, and eyes. With time, however, dark lentigines

and pigmented nevi usually develop at sun-exposed sites (Fig. 11-12). These individuals can also have problems with their eyes and an increased risk of cutaneous malignancy, but significantly less than that seen in individuals with tyrosinase-negative albinism. Although the degree of pigment dilution in affected individuals is variable, the diagnosis is usually easily established in those who have striking pigment loss or relative pigment dilution when compared with unaffected siblings or parents. Some patients with OCA2 have red hair, which has been shown to result from concomitant mutations in the melanocortin 1 receptor.<sup>91</sup> OCA2 has also been described in approximately 1% of patients with Angelman syndrome or Prader-Willi syndrome, disorders that result from deletion of the long arm of chromosome 15, the site of the *P* gene. Prader-Willi syndrome results

**Table 11-2** Clinical Features of Hermansky–Pudlak Syndrome

Type	Mutation	Underlying Cause	Findings Associated with the Cutaneous Pigment Dilution
HPS-1	<i>HPS1</i>	HPS1 and HPS4 associate in a complex (BLOC-3) that regulates biogenesis of melanosomes, platelet dense bodies, and the lung lamellar body	Nystagmus, decreased visual acuity; prolonged bleeding; pulmonary fibrosis; granulomatous colitis (up to $\frac{1}{3}$ of patients)
HPS-4	<i>HPS4</i>		
HPS-2	<i>AP3B1</i>	<i>AP3B1</i> encodes a subunit of AP-3, which mediates protein trafficking into transport vesicles of the lysosome (and is thus also involved in immune function)	Nystagmus, decreased visual acuity; prolonged bleeding; neutropenia; recurrent bacterial and viral infections; conductive hearing loss
HPS-3	<i>HPS3</i>	HPS3, HPS5, and HPS6 are associated in a complex (BLOC-2) that localizes tyrosinase and <i>TRYP1</i> , allowing them to function normally	Nystagmus, decreased visual acuity; mild extraocular manifestations: high cholesterol and slightly elevated triglycerides in HPS-5
HPS-5	<i>HPS5</i>		
HPS-6	<i>HPS6</i>		
HPS-7	<i>DTNBP1</i>	Dysbindin and BLOC1S3 are subunits of BLOC-1 and also involved in skin melanosome biogenesis and platelet function	Nystagmus, decreased visual acuity; prolonged bleeding
HPS-8	<i>BLOC1S</i>		
HPS-9	<i>HPS9/PLDN</i>	Subunits of BLOC-1	Nystagmus, immunodeficiency; may not have bleeding manifestations
Others		Subunits of BLOC-1 ( <i>MUTED</i> ; <i>CNO</i> ; <i>KXD1</i> ) and component of other subunits ( <i>AP3D</i> of AP-3; <i>VPS33A</i> , <i>RABGGTA</i> )	

BLOC, Biogenesis of lysosome-related organelles complex; *DTNBP1*, dystrobrevin binding protein 1.

from deletion of the paternal chromosome at 15q and is characterized by hyperphagia with obesity, hypogonadism, and mental retardation. In contrast, Angelman syndrome results from deletion of the maternal chromosome at 15q and is characterized by microcephaly, severe mental retardation, ataxia, and inappropriate laughter. Pigment dilution occurs when both copies of the *P* gene are mutated or deleted. Interestingly, duplication of the 15q chromosomal region has been associated with generalized skin hyperpigmentation.<sup>92</sup>

Rufous OCA or OCA3 presents as “ginger” red hair, a reddish-bronze color of skin, and blue or sometimes brown irides. This form may be underreported, because the decrease in pigmentation is slight and may be undetectable in lighter skinned patients. OCA4 is now considered one of the most common forms in Japan,<sup>93</sup> and affected individuals resemble patients with OCA2.<sup>81</sup>

Patients with albinism should be monitored by an ophthalmologist in addition to the dermatologist. Glasses may help the poor vision, and contact lenses and tinted glasses may ameliorate the photophobia. Nystagmus may be helped by surgery of the eye muscles or contact lenses; eye patching may be needed for the strabismus. High-contrast written material, large-type textbooks and computers that can enlarge text are all helpful for patients with poor visual acuity. Early actinic changes, keratoses, basal cell tumors, and particularly squamous cell carcinomas are common; the risk of melanoma (often amelanotic)<sup>94</sup> is also increased, even in children and adolescents. Thus individuals with cutaneous albinism must learn to avoid sunlight exposure, to wear sunglasses, and to use protective clothing and sunscreen preparations on exposed surfaces. The National Organization for Albinism and Hypopigmentation (NOAH) is a national support group for patients and their families ([www.albinism.org](http://www.albinism.org)).

### HERMANSKY–PUDLAK SYNDROME

Hermansky–Pudlak syndrome (HPS) is a group of at least 9 autosomal recessive disorders (HPS1–9) characterized by pigment dilution, a hemorrhagic diathesis secondary to a platelet storage pool defect, and ceroid-lipofuscin deposits within the reticuloendothelial system, oral and intestinal mucosae, lung, and urine.<sup>95–97</sup> HPS is a disorder of biogenesis of melanosomes and other lysosome-related organelles<sup>98–100</sup> including platelet dense granules (Table 11-2), and all of the mutations found are in genes encoding components of protein complexes (e.g., *BLOC-1*, *BLOC-2*, *BLOC-3*, and *AP-3*) that regulate vesicle trafficking in these organelle systems.<sup>101</sup> HPS is most commonly seen in Hispanics from Puerto Rico (1:1800 to 1:400 persons; HPS-1 and sometimes HPS-3), in persons of Dutch origin, and in East Indians from Madras. The platelet defect in patients with HPS does not produce a severe problem in children. Its expression, however, can be aggravated by ingestion of aspirin and other prostaglandin blockers.



**Figure 11-13** Hermansky–Pudlak syndrome. The legs of this baby show both the pigmentary abnormality and extensive ecchymoses as a sign of the bleeding diathesis.

Special precautions and sometimes platelet transfusions must be given to avoid excessive bleeding after minor trauma or dental surgery.

The diffuse pigmentary features of the skin and eyes of individuals with HPS include pigmentary dilution of the skin and often the irides with hair that has a peculiar sheen, although not as silvery as in Chédiak–Higashi syndrome (CHS), another syndrome of lysosome-related organelles. The degree of generalized pigment loss is quite variable in intensity, ranging from white skin to brown and light to brown eyes. Ocular pigmentation generally correlates with cutaneous pigmentation. Ocular findings include nystagmus, photophobia, and decreased visual acuity. Extensive ecchymoses are a common clinical manifestation (Fig. 11-13). The bleeding diathesis also commonly manifests as epistaxis and menometrorrhagia. Patients with both HPS and systemic lupus erythematosus have been described.<sup>102</sup> The life-threatening complications of HPS, other than the bleeding diathesis, have been described in certain subtypes and are unusual in most affected children. These include granulomatous colitis (including two patients with cutaneous granulomatous disease that resembled metastatic Crohn disease),<sup>103,104</sup> progressive pulmonary fibrosis,<sup>105</sup> and less

commonly, cardiomyopathy and renal failure. Immunodeficiency is a feature of HPS-2 and the newest described form, HPS-9, which to date has not been associated with a bleeding diathesis.<sup>106,107</sup> The life expectancy is 30 to 50 years of age. Glasses or contact lenses can help to correct the refractive errors. The bleeding from skin wounds may be stopped with thrombin-soaked Gelfoam, and desmopressin (DDAVP) has been administered for tooth extraction and other invasive procedures. Transfusions of platelets or erythrocytes are occasionally required. The pulmonary fibrosis and enterocolitis are most commonly seen in HPS-1 and are often recalcitrant to therapy; infliximab is sometimes helpful.<sup>108</sup> Gene testing is available for mutations of *HPS1* and *HSP3*.

### Phenylketonuria

Phenylketonuria results from deficiency in phenylalanine hydroxylase, the enzyme that converts phenylalanine to tyrosine. Although rarely an issue because of widespread perinatal Guthrie testing, untreated patients with phenylketonuria may develop generalized hypopigmentation of the hair, skin, and/or eyes in comparison with family members, related to the deficiency of tyrosine, the substrate for melanin. Neurologic features predominate (mental retardation, seizures, hyperreflexia), but patients may also show dermatitis and rarely, focal morphea-like skin lesions (see Chapter 22). Treatment is by avoidance of dietary phenylalanine.

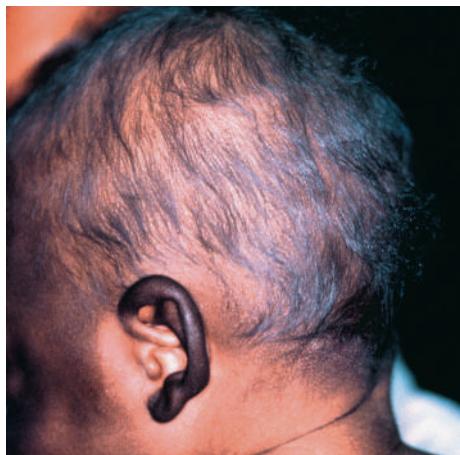
### SILVERY HAIR SYNDROMES

Three syndromes, CHS, Griscelli syndrome (GS), and Elejalde syndrome (probably a subset of GS), are autosomal recessive disorders characterized by an early silvery sheen to the hair, relative pigmentary dilution of skin with a grayish coloration, and in some patients ocular hypopigmentation.<sup>97</sup>

#### Chédiak–Higashi Syndrome

Patients with Chédiak–Higashi syndrome (CHS) usually have a characteristic silvery sheen to the hair and skin, with a skin color that may appear lighter than that of other family members.<sup>109,110</sup> In affected individuals of family backgrounds of darker skin, however, the skin of acral, sun-exposed areas (ears, nose) may become intensely hyperpigmented (Fig. 11-14) or show only speckled hypopigmentation.<sup>111,112</sup> Decreased iris pigmentation results in an increased red reflex and photophobia. Strabismus and nystagmus are common, but visual acuity is usually normal. Inflammation and ulceration of the oral mucosa, especially of the gingivae, have been described.

The immunodeficiency of patients with CHS leads to infectious episodes. These episodes are associated with fever and predominantly involve the skin, lungs, and upper respiratory tract. The most common organisms found are *Staphylococcus aureus*, *Streptococcus pyogenes* and



**Figure 11-14** Chédiak–Higashi syndrome. Note the silvery sheen to the hair and the intense pigmentation of the ear in this affected 8-month-old boy.

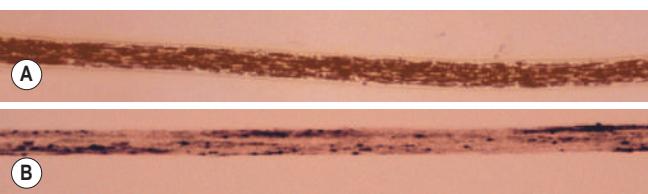
*pneumococcus*. The skin infections are primarily pyoderma, but infections with these organisms that result in deeper ulcerations resembling pyoderma gangrenosum have been reported.

Approximately 50% to 85% of patients with CHS undergo an “accelerated” lymphohistiocytic phase during the first decade of life, characterized by widespread visceral tissue infiltration with lymphoid and histiocytic cells that are sometimes atypical in appearance.<sup>113,114</sup> Hepatosplenomegaly, lymphadenopathy, pancytopenia, jaundice, a leukemia-like gingivitis, and pseudomembranous sloughing of the buccal mucosa are associated features. The thrombocytopenia, platelet dysfunction, and depletion of coagulation factors may lead to petechiae, bruising, and gingival bleeding. Granulocytopenia and anemia are found in 90% of patients during the accelerated phase. Neurologic manifestations may range from seizures to cranial nerve palsy to loss of consciousness. Viral infection, particularly from Epstein–Barr virus (EBV) infection, has been implicated in causing the accelerated lymphohistiocytic phase. The pigmentary changes that help to distinguish the CHS-related accelerated phase must be distinguished from autoimmune hemophagocytic syndromes and familial hemophagocytic lymphohistiocytosis (genetic defects in the cytolytic granule-dependent exocytosis pathway such as perforin). Neutropenia is common, and neutrophils are deficient in chemotactic and bactericidal capability. Selective deficiency of natural killer (NK) cells is characteristic. These immune abnormalities have been thought to cause the increased susceptibility to infections and the lymphohistiocytic phase.

Patients who survive into early adulthood may develop progressive neurologic deterioration, particularly with clumsiness, abnormal gait, paresthesias, and dysesthesias. Peripheral and cranial neuropathies and occasionally a form of spinocerebellar degeneration may occur.

CHS results from biallelic mutations in *LYST*, a lysosomal transport protein that regulates the fusion of primary lysosome-like structures. The skin pigmentary disorder has been attributed to the inability of melanosomal fusion and transfer to keratinocytes, leading to giant melanosomes within melanocytes. Giant granules are found in circulating leukocytes, melanocytes of skin and hair, renal tubular epithelial cells, central nervous system (CNS) neurons, and other tissues. In the hair shaft, these giant melanosomes are smaller than those of GS and regularly spaced (Fig. 11-15, A). The giant granules within phagocytic cells of affected children cannot discharge their lysosomal and peroxidative enzymes into phagocytic vacuoles. Of note, patients with leukemia may show granules that resemble those of CHS in leukocytes.

The mean age of death for patients with CHS without immune reconstitution is 6 years of age. Fatality usually results from overwhelming infection or hemorrhage during the accelerated phase. Approximately 10% to 15% of affected patients have a milder clinical phenotype and survive into adulthood but tend to develop the progressive neurologic dysfunction.<sup>115</sup> For all of the silvery hair syndromes, early bone marrow or stem-cell transplantation is the treatment of choice for patients with a human leukocyte antigen (HLA) match. Bone marrow transplantation reverses the immunodeficiency and prevents the often-fatal accelerated phase but has no effect on pigmentation or on neurologic deterioration. Otherwise, management of the disorder is largely supportive. Antibiotics help to control the recurrent infections, and immunoglobulin or immunosuppressive agents have been administered in an attempt to control the lymphohistiocytic or hemophagocytic phases. Splenectomy has been advocated in patients with the accelerated phase unresponsive to other forms of therapy.



**Figure 11-15** Silvery hair syndromes. The giant melanosomes are easily seen in the hair shaft of individuals with Chédiak–Higashi syndrome (CHS) (A) and Griscelli syndrome (B). Note the more regular spacing of the melanosomes in the hair from a patient with CHS.

### Griscelli Syndrome

Three subsets of patients with Griscelli syndrome (GS) have been described based on clinical manifestations and underlying gene defects. Two of these subsets are caused by mutations in genes close to each other on chromosome 15q21, *myosin Va* (type 1) and *RAB27A* (type 2). *Myosin Va* encodes a protein that binds organelles such as melanosomes to actin. *RAB27A* is a guanosine triphosphate (GTP)-binding protein involved in the movement of melanosomes. Melanocytes are unable to transfer melanosomes to epidermal cells, and ultrastructural examination of skin biopsies reveals accumulation of melanosomes in melanocytes but few in surrounding keratinocytes.

Patients who have uncontrolled activation of T lymphocytes and macrophages (hemophagocytic syndrome) and immune deficits (especially reduction in T-cell cytotoxicity and cytolytic granule exocytosis) have mutations in *RAB27A*,<sup>116</sup> whereas those patients with neurologic problems and without immune abnormalities or hemophagocytosis tend to have *myosin Va* mutations.<sup>117</sup> Elejalde syndrome (neuroectodermal melanolysosomal disease), characterized by similar abnormal pigmentation in the skin and hair and severe neurologic dysfunction (seizures, severe hypotonia, ocular abnormalities, and mental retardation) but no immunodeficiency or hemophagocytosis<sup>118,119</sup> is now considered a subset of GS type 1.<sup>120</sup> Rare patients with neurologic abnormalities with or without hemophagocytosis have shown a *RAB27A* mutation.<sup>118,121</sup> Type 3 GS shows a phenotype restricted to the pigmentary defects and results either from mutation in the gene that encodes melanophilin (*MLPH*) or from a deletion in the F-exon of *myosin Va*.<sup>122–124</sup>

Patients with GS, especially GS type 2, may be difficult to distinguish clinically from patients with CHS, because the silver-gray hair and skin color (Fig. 11-16), recurrent episodes of fever with or without infection, increasing hepatosplenomegaly owing to lymphohistiocytic infiltration, and progressive neurologic deterioration may be part of the clinical spectrum of both disorders.<sup>125</sup> In contrast to CHS, the lymphohistiocytic infiltration tends to occur in the first year of life. Blood smears show pancytopenia, but in contrast to the patients with CHS, no leukocyte inclusions. Microscopic examination of hair shows clumping of pigment in the hair shaft similar to that of CHS but with larger, more irregularly spaced macromelanosomes (see Fig. 11-15, B).

Intervention is similar to that of CHS, primarily through hematopoietic stem-cell transplantation. Given the lack of success of transplantation in patients with mutations in *myosin Va*,<sup>126</sup> restriction of transplantation to patients with *RAB27A* mutations has been



**Figure 11-16** Griscelli syndrome. The silvery hair suggests the reason for this child's hepatosplenomegaly and pancytopenia. The child died before bone marrow transplantation could be performed.

suggested. Early transplantation can prevent complications including the neurologic sequelae.<sup>127</sup>

### PIEBALDISM

Piebaldism is an autosomal dominant disorder characterized by congenital patterned areas of depigmentation, including a white lock of hair above the forehead (the white forelock) in most affected individuals.<sup>128,129</sup> The disorder usually results from mutations in the *KIT* protooncogene, which encodes a cell-surface receptor for the stem-cell/mast cell growth factor<sup>130</sup>; deletions in *SNAI2/SLUG* (encoding snail homolog of 2), a transcription factor, have also been described.<sup>131</sup> The clinical manifestations of piebaldism may be explained by the resultant defective migration of melanoblasts from the neural crest to the ventral midline and a defect in the differentiation of melanoblasts to melanocytes. The distinctive patterns of hypopigmentation or depigmentation usually persist unchanged throughout life, but affected individuals with progressive depigmentation,<sup>132</sup> response to UV light and partial repigmentation,<sup>133,134</sup> or forelock regression during infancy<sup>135</sup> have occasionally been described. The white forelock, with a depigmented triangular patch of the scalp and forehead (widest at the forehead with the apex pointing backward) occurs in 80% to 90% of individuals with piebaldism (Fig. 11-17). Depigmented areas on the forehead often include the whole or inner portions of the eyebrows and eyelashes and extend to the root of the nose. Hypopigmented or depigmented areas have also been noted commonly on the chin, anterior neck, anterior portion of the trunk and abdomen, and on the anterior and posterior aspects of the mid-arm to the wrist and the mid-thigh to mid-calf. Typical of the lesions of piebaldism are islands of normal and increased pigmentation within the hypomelanotic areas and sometimes hyperpigmented borders (Fig. 11-18). Intertriginous freckling and multiple café-au-lait (CAL) macules may occasionally be noted in patients and do not reflect the concurrence of piebaldism and neurofibromatosis (NF) 1 or Legius syndrome.<sup>136,137</sup>

The depigmentation of piebaldism can be differentiated from that of vitiligo by the usual presence at birth, lack of convex borders, and



**Figure 11-17** Piebaldism. This young girl shows the white forelock with depigmentation on the forehead as two triangular patches. The left cheek is also depigmented.



**Figure 11-18** Piebaldism. Note the sharply demarcated areas of depigmentation with the islands of normal pigmentation within the depigmented areas.

predisposition for ventral surfaces in contrast to the predilection on exposed areas, body orifices, areas of trauma, and intertriginous regions in vitiligo. The typical facial characteristics of type I WS are not seen in patients with piebaldism, although sensorineural deafness has rarely been described in piebaldism.<sup>138</sup> Biallelic homozygous mutations in *c-KIT* have been described from affected consanguineous parents; affected neonates show generalized depigmentation of the skin and hair, blue irides, and profound sensorineural deafness.<sup>139</sup> Incomplete penetrance has been described (e.g., a parent without evidence of piebaldism who has children with piebaldism and shares the *c-KIT* mutations).<sup>140</sup>

Treatment consists of cosmetic masking of areas of leukoderma<sup>59</sup> and vigorous sun protection. In the rare patients who show increased pigmentation after UV exposure, phototherapy may be considered. Reepithelialization by grafting from suction blisters and autologous cultured or noncultured epidermis, with or without laser, has provided permanent repigmentation.<sup>141,142</sup>

## WAARDENBURG SYNDROME

Waardenburg syndrome (WS) is a heterogeneous group of autosomal dominant disorders characterized by heterochromia irides, a white forelock, cutaneous depigmentation, and in many patients, congenital sensorineural deafness.<sup>143,144</sup> WS reportedly accounts for 2% to 5% of cases of congenital deafness.<sup>145</sup> Four major subtypes of WS have been described (Tables 11-3 and 11-4). Individuals with type I WS, the most common form, have characteristic facial features including a broad nasal root and lateral displacement of the medial canthi and lacrimal puncta of the lower eyelids (dystopia canthorum) (Fig. 11-19). For clinical diagnosis, an individual must have two major criteria or one major plus two minor criteria to be considered affected (see Table 11-3). Dystopia canthorum can be confirmed by a W index of greater than 1.95 (see Table 11-3).<sup>144</sup> Congenital, usually nonprogressive, sensorineural hearing loss occurs in 47% to 58% of affected individuals, whereas the white forelock and cutaneous depigmentation occur in approximately 45% and 30%, respectively. The white forelock may be present at birth, may appear later (typically during teenage years), or may become pigmented with time. The heterochromic irides and/or hypoplastic (often brilliant) blue eyes (Fig. 11-20) are less common than the hair or skin depigmentation. Type I WS results from loss-of-function mutations in *PAX3*, a gene critical for both melanocyte migration and facial embryogenesis.<sup>146,147</sup> Spina bifida has been described in several affected families, leading to the firm recommendation for folate supplementation during pregnancy.

Type II WS is a heterogeneous group of disorders that commonly shows the iris pigmentary changes (almost all patients, particularly the blue irides) and deafness (80%) of WS type I but not the facial

**Table 11-3** Diagnostic Criteria for Type I Waardenburg Syndrome

**Two Major Criteria or One Major Plus Two Minor Criteria Allows for the Diagnosis of WS Type I**

Major Criteria	Minor Criteria
White forelock, hair depigmentation	Skin depigmentation
Pigmentary abnormality of the iris	Synophrys/medial eyebrow flare
Dystopia canthorum, W index* >1.95	High/broad nasal root
Congenital sensorineural hearing loss	Hypoplastic alae nasi
Affected first-degree relative	Gray hair before 30 years old

WS, Waardenburg syndrome.

\*W index: The measurements necessary to calculate the W index (in mm) are as follows: the inner canthal distance (a), the interpupillary distance (b), and the outer canthal distance (c).

Calculate X = (2a - 0.2119c + 3.909)/c.

Calculate Y = (2a - 0.2479b + 3.909)/b.

Calculate W = X + Y + a/b.

**Table 11-4** Subtypes of Waardenburg Syndrome

Disorder	Inheritance	Gene	Other Comments
WS1	AD	<i>PAX3</i>	Most common form; dystopia canthorum
WS2A	AD	<i>MITF</i>	No facial dysmorphism; high risk of hearing loss; iris heterochromia
WS2B	AD	?	No facial dysmorphism; high risk of hearing loss; iris heterochromia
WS2C	AD	?	No facial dysmorphism; high risk of hearing loss; iris heterochromia
WS2D	AD	<i>SLUG</i>	No facial dysmorphism; high risk of hearing loss; iris heterochromia
WS2E	AD	<i>SOX10</i>	No facial dysmorphism; high risk of hearing loss; iris heterochromia
WS3	AD	<i>PAX3</i>	Associated limb abnormalities
WS4A	AD/AR	<i>EDNRB</i>	Aganglionic megacolon
WS4B	AD/AR	<i>EDN3</i>	Aganglionic megacolon
WS4C	AD	<i>SOX10</i>	Aganglionic megacolon
PCWH	AD	<i>SOX10</i>	Severe hypotonia with central nervous system and peripheral nerve abnormalities

AD, Autosomal dominant; AR, autosomal recessive; EDN, endothelin; EDNRB, endothelin receptor beta; PCWH, peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease.

characteristics.<sup>148</sup> Mutations in the microphthalmia-associated transcription factor (*MITF*) gene have been described in 15% to 21% of patients with type II WS.<sup>149</sup> Tietze syndrome, also linked to *MITF* mutations on one allele, was originally characterized by generalized, albino-like pigmentary deficiency and hearing loss but no iris heterochromia; subsequent studies have shown clinical variability within families with heterozygous *MITF* mutations, ranging from a generalized decrease in pigmentation to patchy loss to no cutaneous manifestations in association with profound hearing loss and blue irides.<sup>148</sup> Patients with WS2 may have strabismus. Freckling in sun-exposed areas without depigmentation is common, especially among patients of Asian descent.<sup>148,149</sup> Other patients with type II WS have mutations in *SOX10* (~15%, encoding sex-determining region Y [SRY]-box10) or *SNAI2/SLUG* (as in piebaldism), transcription factors critical for the



**Figure 11-19** Waardenburg syndrome, type I. Note the white forelock, dappled skin, broad nasal root, and dystopia canthorum. This young woman also had an affected son.



**Figure 11-20** Waardenburg syndrome, type II. This affected individual shows iris heterochromia with the brilliant blue iris. She had sensorineural deafness but none of the facial features seen in type I Waardenburg syndrome.

migration and development of neural-crest cells. Type III WS is an extreme presentation of type I WS with musculoskeletal abnormalities and rarely associated neural-tube defects.<sup>150</sup> Some but not all patients with type III WS have homozygous mutations in *PAX3*. Type IV WS includes the pigmentary defects and sensorineuronal deafness in association with absence of enteric ganglia in the distal part of the intestine (Hirschsprung disease); presentation with chronic constipation beginning in the neonatal period is not unusual.<sup>151,152</sup> Facies are normal. Mutations have been described in three genes: *EDN3*, *EDNRB*, and *SOX10*, encoding endothelin 3,<sup>153</sup> endothelin B receptor,<sup>154</sup> and Sox 10, respectively.<sup>155</sup> Patients with Sox 10 mutations may also have severe hypotonicity with CNS and peripheral-nerve abnormalities because of the important role of Sox 10 in glial cell development.<sup>156</sup> All of the forms of WS show marked variability of clinical characteristics, even within families and in monozygotic twins,<sup>157</sup> and subtle features may be seen, especially in WS1. The white forelock may be a feature of several other genetic and acquired disorders, but most commonly piebaldism.<sup>158</sup> Iris heterochromia has also been described in HPS.<sup>159</sup>

## TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with variable expressivity that occurs in as many as 1 in 6000 to 1 in 10,000 persons.<sup>160-163</sup> Up to 70% of patients are thought to have new mutations. The disorder results from mutation in one of two different genes, *TSC1* (encoding hamartin; approximately 20% of patients) and

### Box 11-1 Features of Tuberous Sclerosis

Pathogenic mutation in *TSC1* or *TSC2* or two major features or 1 major feature + 2 minor features = definite tuberous sclerosis  
One major feature + 1 minor feature = probable tuberous sclerosis  
One major feature or two or more minor features = possible tuberous sclerosis

#### Major Features

- Hypopigmented macules  $\geq 5\text{ mm}$  across ( $\geq 3$ )
- Angiofibromas ( $>3$ ) or fibrous cephalic plaque
- Shagreen patch (connective tissue nevus)
- Ungual fibromas ( $\geq 2$ )
- Cortical dysplasias
- Subependymal nodules
- Subependymal giant-cell astrocytoma
- Cardiac rhabdomyoma
- Multiple retinal hamartomas
- Angiomyolipomas ( $\geq 2$ )
- Lymphangioleiomyomatosis
- Minor features
- "Confetti" skin lesions
- Intraoral fibromas ( $>2$ )
- Dental enamel pits ( $>3$ )
- Multiple renal cysts
- Nonrenal hamartomas
- Retinal achromic patch

*TSC2* (encoding tuberin; approximately 60% of patients); gene mutations have not been discovered in 10% to 25% of affected individuals. Tuberin and hamartin form a complex that suppresses cell growth through regulation of several signaling pathways, most importantly the mammalian target-of-rapamycin (mTOR) pathway signaling through switching Rheb from an active (GTP-bound) to inactive (guanosine diphosphate [GDP]-bound) state.<sup>162</sup> In general, patients with mutations in *TSC1* have milder disease.<sup>164</sup> The disorder is characterized by the development of hamartomas of the skin, brain, eye, heart, kidneys, lungs, and bone (Box 11-1).<sup>162</sup> A variety of cutaneous features, including hypopigmented macules, angiofibromas, fibrous tumors, and periungual and gingival fibromas, may be seen.

Three or more hypopigmented macules (white spots) of TSC are seen in 97% of patients at birth or shortly thereafter, although the appearance of additional lesions as late as 6 years of age has been described.<sup>165</sup> Once present, the hypopigmented macules tend to be persistent and stable in shape and relative size but may become less apparent during adulthood. Wood lamp examination in a completely darkened room may be useful in accentuating the macules in fair-skinned children. The white spots most commonly occur on the trunk, but hypopigmented tufts of scalp or eyelash hair meet the criterion for a hypopigmented macule. They range in size from a millimeter to several centimeters and number from a few to more than 75; 18% to 20% of individuals with TSC have 1 or 2 hypopigmented macules. The hypopigmented macules (Fig. 11-21) are often round ("thumbprint"), confetti-like hypopigmented macules (particularly over the pretibial areas), and oval or linear, but a lance-ovate shape ("ash leaf spots") is commonly described and is unusual in other disorders of localized decreased skin pigmentation such as nevus depigmentosus and vitiligo. Lesions of vitiligo tend to be depigmented and show a bright white coloration with Wood lamp examination. The hypopigmented white spots of TSC are most difficult to distinguish from nevus depigmentosus (also called *nevus achromicus*; Fig. 11-22), which occurs in 1.6% to 4.7% of children,<sup>166,167</sup> suggesting that the majority of young children with a white spot do not have TSC. *Nevus depigmentosus* may be present at birth or appear during early infancy as normal pigmentation increases and then persist. Despite its name, most *nevus depigmentosus* lesions are hypopigmented, not depigmented. Most individuals will have a solitary lesion of *nevus depigmentosus*, but multiple lesions and segmental forms of *nevus depigmentosus* have been described. *Nevus depigmentosus* and the hypomelanotic macules of TSC must also be distinguished from *nevus anemicus*, a developmental anomaly characterized by a circumscribed round or oval patch of pale or mottled skin<sup>168</sup> (see Chapter 12, Fig. 12-60).



**Figure 11-21** Tuberous sclerosis. **(A)** Several lance-ovate ("ash-leaf") and "thumbprint" white macules are noted on this infant's back. **(B)** Confetti-like macules on the lower extremities in a 13-year-old boy.



**Figure 11-22** Nevus depigmentosus. Well-demarcated patch of hypopigmentation that tends to be round or oval in configuration. Nevus depigmentosus, also known as *nevus achromicus*, may be noted at birth or may become apparent during infancy.

Cutaneous angiofibromas (adenoma sebaceum), which are hamartomas composed of fibrous and vascular tissue, appear in 75% of cases. They typically develop between 2 and 6 years of age and continue to increase in number thereafter but have been described at birth or as late as the mid-20s. These lesions characteristically are 1- to 4-mm, pink to red, dome-shaped papules with a smooth surface. They occur on the nasolabial folds, cheeks, and chin and sometimes more



**Figure 11-23** Tuberous sclerosis. Facial angiofibromas (adenoma sebaceum) are typically 1- to 4-mm, skin-colored to red, dome-shaped papules with a smooth surface. The facial angiofibromas largely involve the cheeks and nose with relative sparing of the upper lip.



**Figure 11-24** Tuberous sclerosis. The fibrous cephalic plaque may be present at birth and, together with the hypopigmented macules, may allow a definitive diagnosis of tuberous sclerosis.

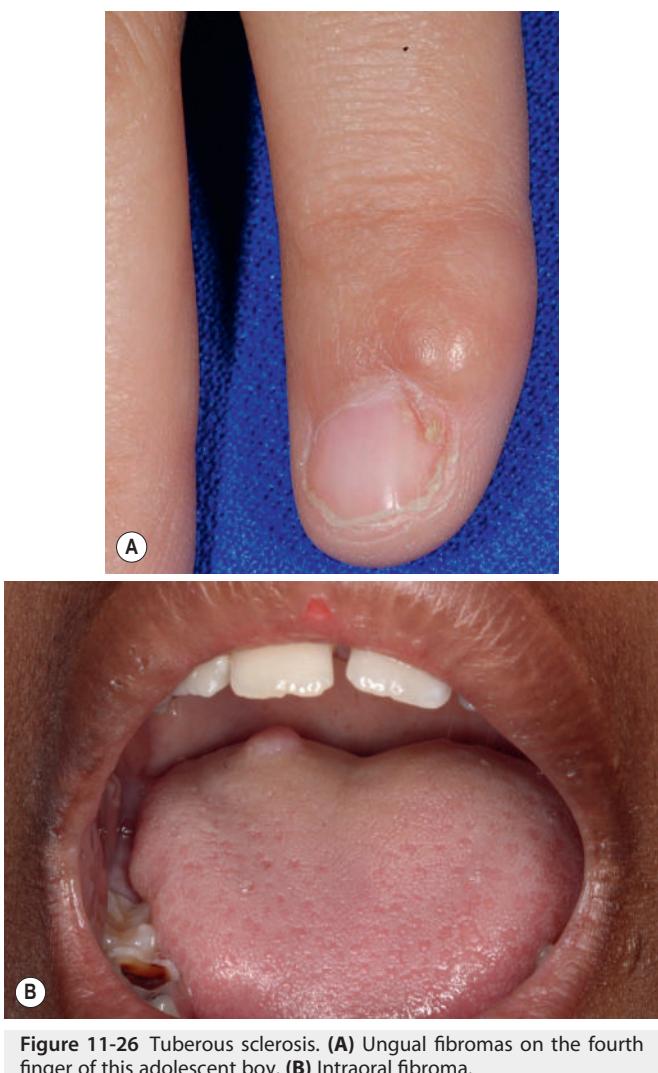
extensively on the face (Fig. 11-23). The upper lip is relatively spared, except immediately below the nose. The angiofibromas in affected adolescents may be masked by or misdiagnosed as acne. Their distribution is usually symmetrical but may be asymmetrical, especially in patients with a mosaic form of TSC.<sup>169</sup>

Large fibrotic plaques or nodules may occur on the forehead (fibrous cephalic plaque; Fig. 11-24), cheeks, or scalp in 25% of patients and are often present at birth. In 14% to 20% of patients, collagenomas also develop on the trunk, especially in the lumbosacral area, and most commonly during later childhood (shagreen patches or *peau de chagrin* lesions) (Fig. 11-25). They may be solitary or multiple and vary from smaller than 1 cm to palm-sized. Collagenomas are usually slightly raised with focal depression at follicular openings, leading to comparison with pigskin, elephant skin, orange peel, or gooseflesh. Fibromas under or around the nails of the fingers and especially the toes (ungual fibromas, sometimes called Koenen tumor; Fig. 11-26, A) and on the gums and other intraoral sites (intraoral fibromas) are also considered pathognomonic (Fig. 11-26, B). Seen in up to 80% of patients,<sup>170</sup> these fibromas do not tend to appear until after puberty but may be the only sign of TSC.<sup>171</sup>

Confetti-like hypopigmented macules have been noted in 6% of patients with multiple endocrine neoplasia (MEN) type 1<sup>172</sup> and multiple angiofibromas in 43% to 88% of adolescents and adults with MEN1.<sup>172,173</sup> Facial angiofibromas in patients with MEN1 tend to be fewer in number than in patients with TSC, may involve the upper lip or vermillion border, and fail to cluster in the nasolabial folds. Collagenomas have been observed in 72% of patients with MEN1.<sup>172</sup>



**Figure 11-25** Tuberous sclerosis. The shagreen patch is characteristically found at the lumbosacral area and has a *peau d'orange* texture.



**Figure 11-26** Tuberous sclerosis. (A) Ungual fibromas on the fourth finger of this adolescent boy. (B) Intraoral fibroma.

Patients with MEN1 are at high risk for the development of parathyroid, pituitary, pancreatic, and duodenal tumors.<sup>174</sup> Multiple facial angiofibromas with onset during adulthood have also been noted in patients with Birt–Hogg–Dube syndrome,<sup>175</sup> but facial fibrofolliculomas or trichodiscomas are more typical. Multiple biopsy-proven angiofibromas without other signs and with negative molecular testing have been described.<sup>176</sup> Having one to a few facial fibrous

papules is common in normal adults and may begin during adolescence; they resemble angiofibromas and have recently been shown to have activated mTOR signaling as well.<sup>177</sup>

The systemic lesions of TSC may produce severe symptoms and possibly death. Seizures, seen in 80% to 90% of patients with TSC, may begin as infantile spasms in which sudden repetitive myoclonic contractions of most of the body musculature are combined with flexion, extension, opisthotonus, and tremors. By 2 or 3 years of age, focal or generalized seizures and mental retardation may become evident. Extensive CNS involvement leads to hypsarrhythmia (salaam seizures) with electroencephalographic findings of multifocal high-voltage spikes and slow chaotic waves. Later in life the seizure pattern may change to a *petit mal* variety, and in less severe cases generalized or focal motor seizures may develop.

Retardation may be mild or severe and appears in 62% of affected individuals. The severity of mental retardation correlates well with the age of seizure onset. In approximately 90% of patients with TSC, the brain shows areas of cortical dysplasia (including cortical “tubers” and white-matter migrational abnormalities). These areas of cortical dysplasia can calcify and be visible on skull radiographs as curvilinear opacities. Periventricular or subependymal nodules may be seen by computed tomography (CT) or magnetic resonance imaging (MRI) scanning before calcification occurs.<sup>178,179</sup> Subependymal nodules are not malignant but may enlarge to cause obstructive hydrocephalus.

By the end of the first decade of life, 80% of patients show renal involvement. Renal hamartomas (angiomyolipomas) occur in about 70% of patients, and larger ones may lead to hemorrhage; of note, angiomyolipomas may be found in other organs as well, and having at least two angiomyolipoma without organ specificity is a major diagnostic feature. With advancing age, 20% to 30% of patients develop multiple bilateral renal cysts resembling those of polycystic kidney disease. These cysts can occur in individuals with *TSC1* or *TSC2* mutations, but a subset of individuals with aggressive renal cysts have deletions involving both *TSC2* and the contiguous polycystic kidney disease (*PKD1*) genes.<sup>180</sup> Abdominal ultrasound or scans are able to detect renal hamartomas or cysts in asymptomatic patients. Cardiac rhabdomyomas are most commonly present in the ventricles prenatally or in infancy and tend to regress spontaneously.<sup>181</sup> Although usually asymptomatic, rhabdomyomas may be associated with congestive heart failure, murmurs, cyanosis, arrhythmias, and sudden death, particularly during the first year of life. Two-dimensional echocardiography is a noninvasive technique that allows detection of asymptomatic cardiac rhabdomyomas.

The eyes may have characteristic retinal lesions (gliomas) referred to as *phakomas*. These retinal hamartomas have been described in 30% to 50% of patients. Funduscopy may show one of two types of lesions: multiple, raised, mulberry-like lesions on or adjacent to the optic nerve head; or flat, disk-like lesions in the periphery of the retina. Pulmonary lymphangioleiomyomatosis occurs overall in 2.3% of individuals with TSC, particularly in women between the ages of 20 and 40 years.<sup>182</sup> Affected individuals experience shortness of breath, hemoptysis, or pneumothorax and show diffuse interstitial infiltrates with cystic changes by CT examination. About 85% of patients with TSC have osseous manifestations with the bones, particularly those of the hands and feet, demonstrating cysts and periosteal thickenings. At least three dental pits (seen as punctate, round or oval, 1- to 2-mm randomly arranged enamel defects), particularly in the permanent teeth, are another marker of TSC and may be visualized better with use of dental disclosing solution.

The diagnosis of TSC may be difficult, because many affected individuals have subtle manifestations. However, the appearance of characteristic skin lesions in children with seizures, retardation, or both should establish a diagnosis of TSC (see Box 11-1).<sup>163,183</sup> Diagnosis depends on the cutaneous manifestations, family history (with careful clinical and sometimes imaging examination of family members), MRI of the brain, renal ultrasound, cardiac echocardiography in infants and young children, and in some cases ophthalmologic examination and chest radiography for honeycombing of the lungs.

The prognosis of TSC depends on the severity of the disorder and the presence of neurologic involvement.<sup>184</sup> The leading causes of premature death, status epilepticus and bronchopneumonia, are related to the associated neurologic issues. Seizures can be controlled by

anticonvulsant therapy in many patients, and prevention of seizures early in life has been shown to lower the risk of developmental delay and retardation. With routine MRI evaluations and the availability of microscopic surgery for neoplastic brain lesions, patients are surviving longer and have a better quality of life. Neurosurgical intervention may be required in patients with signs of increased intracranial pressure such as visual disturbances, papilledema, vomiting, or headaches. Sun protection is important for patients, not just at the sites of the hypopigmented macules, but also to prevent facial angiofibromas, which show second-hit mutations in TSC genes with a UV-signature mutation that is not seen in TSC germline mutations, in 50% of patients.<sup>185</sup>

The facial angiofibromas may be a cosmetic problem that responds to cryosurgical, surgical, or laser therapy.<sup>186</sup> However, a meta-analysis of 16 reports noted improvement in 94% of 84 patients with use of a variety of formulations of compounded topical rapamycin (ointment, gel, solution, cream; there is no commercially available formulation) with concentrations from 0.003% to 1%).<sup>187–190</sup> Recent-onset fibrous angiofibromas respond best, and topical rapamycin has also been used for maintenance after laser or surgical therapy. Local irritation is unusual but has been described with the use of rapamycin solution. Topical rapamycin has also led to improvement in early ungual fibromas.<sup>191</sup> Mammalian TOR inhibitors such as rapamycin and everolimus cause regression of astrocytomas, renal angiomyolipomas, and pulmonary lymphangioleiomyomas, as well as facial angiofibromas.<sup>192,193</sup> The Tuberous Sclerosis Alliance (at [www.tsalliance.org](http://www.tsalliance.org)) and the Tuberous Sclerosis Association (of the United Kingdom, at [www.tuberous-sclerosis.org](http://www.tuberous-sclerosis.org)) are among the groups that offer support for patients with TSC.

## CHEMICALLY INDUCED DEPIGMENTATION

A number of chemical agents are known to cause depigmentation after topical exposure. Among these compounds are the rubber antioxidant monobenzyl ether of hydroquinone, hydroquinone photographic developer, sulfhydryl compounds, azo dyes, diphenylcyclopropenone, phenolic germicidal agents (paratertiary butylphenol and amyłphenol), hydroxyanisole, and 4-tertiary butyl catechol (an additive to polyethylene film). The biochemical mechanism by which phenolic chemicals induce such hypopigmentation appears to be the competitive inhibition of tyrosinase or the release of toxic metabolites that produce injury to the melanocytes. Depigmentation has also occurred after topical exposure to paraphenylenediamine,<sup>194</sup> injections of triamcinolone, and in the periorbital area after injection of botulinum A toxin.<sup>195</sup> Oral ingestion of chloroquine,<sup>196</sup> arsenic, ST1571 (imatinib),<sup>197</sup> and dasatinib<sup>198</sup> have also led to depigmentation. A progressive generalized decrease in pigmentation has been reported after drug reaction to sulfonamide.<sup>199</sup>

## IDIOPATHIC GUTTATE HYPMELANOSIS

Idiopathic guttate hypomelanosis is a common disorder of adults, and its incidence increases with increasing age. It occasionally occurs in children and is more common in female individuals, although the latter may represent reporting bias. More striking in individuals with darker pigmentation, the lesions of idiopathic guttate hypomelanosis are characteristically 0.5- to 6-mm sharply defined, porcelain white macules. They are asymptomatic and once present do not tend to change. The macules most commonly occur on the extensor forearms and on the shins. The diagnosis is usually made clinically, and no treatment is effective. The underlying cause is unknown, although sun exposure is thought to be a trigger.

## POSTINFLAMMATORY HYPOPIGMENTATION

Postinflammatory hypopigmentation (or leukoderma) may be associated with a wide variety of inflammatory dermatoses or infections. This relative pigmentary deficiency may be noted after involution of certain inflammatory skin disorders, particularly burns, bullous disorders, infections, eczematous or psoriatic lesions, and pityriasis rosea (see Fig. 3-17). In the inflammatory dermatoses the intensity of the inflammatory reaction may bear little relationship to the development

of postinflammatory leukoderma. Postinflammatory hypopigmentation is generally self-limiting, clearing after months to years. It often becomes cosmetically obvious in individuals with darker skin, particularly during summer months, because the preferential darkening with UV light exposure of surrounding skin accentuates the hypopigmentation.

Although the pathophysiology of postinflammatory hypopigmentation is unclear, it is postulated that the hypopigmentation is caused when keratinocytes injured by the inflammatory process are temporarily unable to accept melanosomes from the melanocyte dendrites. No therapy is effective, but the condition tends to improve with time.

Pityriasis alba (see Chapter 3) is a common cutaneous disorder characterized by asymptomatic, sometimes scaly hypopigmented patches on the face, neck, upper trunk, arms, shoulders, and at times the lower aspect of the trunk and extremities of children and young adults (see Fig. 3-33). Seen predominantly in children 3 to 16 years of age, individual lesions vary from 1 to several centimeters in diameter and have sharply delineated margins and a fine, branny scale. Although the cause is unknown, this disorder appears to represent a nonspecific dermatitis. Postinflammatory hypopigmentation is commonly seen in children with atopic dermatitis, psoriasis (see Fig. 4-15, A), pityriasis lichenoides, and contact dermatitis; in the latter the pattern of the hypopigmentation may provide the clue to the contactant.<sup>200</sup>

Tinea versicolor ( pityriasis versicolor; see Chapter 17) is a common condition often found on the upper part of the trunk and neck of young adults. Caused by overgrowth of a yeast that normally inhabits skin, *Pityrosporum orbiculare* (*Malassezia furfur*), the condition is characterized by small, either hypopigmented or occasionally hyperpigmented macules, particularly on the trunk and upper arms. The round, individual lesions often coalesce. Facial involvement is more common in affected children than in older individuals. The hypopigmentation results from the production of azelaic acid, which inhibits tyrosinase; the hyperpigmentation is postinflammatory (see Figs. 17-33 through 17-34).

Sarcoidosis (see Chapter 25) is a granulomatous disorder of unknown origin with widespread manifestations involving the skin and many of the internal organs. In addition to the characteristic yellowish brown, flesh-colored, pink, red, and reddish brown to black or blue lesions, subcutaneous nodules, and infiltrated plaques, the spectrum of sarcoidal skin lesions includes hypomelanotic macules and papules. Measuring up to 1.5 cm in diameter, these hypopigmented lesions reveal sarcoid-type granulomas on cutaneous biopsy.

Leprosy (Hansen disease; see Chapter 14), a chronic infection in which the acid-fast bacillus *Mycobacterium leprae* has a special predilection for the skin and nervous system, can be divided into several types depending on the patient's cellular immune response to *M. leprae*. Tuberculoid leprosy shows characteristic well-defined anesthetic hypopigmented lesions and thickened and palpable peripheral nerves. Lepromatous leprosy, in contrast, more commonly shows nodules or diffuse infiltrates, especially on the eyebrows and ears, resulting in a leonine facies. A granulomatous infiltrate on microscopic examination of cutaneous lesions and particularly in the lepromatous lesions, demonstration of *M. leprae* on cutaneous smear or biopsy specimen generally confirm the diagnosis.

Pinta (see Chapter 14) is a treponemal infection caused by *Treponema carateum*. Seen almost exclusively among the dark-skinned population of Cuba and Central and South America, the disorder is commonly found in children of parents afflicted with this disorder. The cutaneous manifestations may be divided into primary, secondary, and tertiary stages. The late dyschromic stage takes several more years to develop. These lesions have an insidious onset and usually appear during adolescence or young adulthood. They consist of slate-blue hyperpigmented lesions that after a period of years become widespread and are replaced by depigmented macules resembling those seen in patients with vitiligo. Located chiefly on the face, waist, and areas close to bony prominences (elbows, knees, ankles, wrists, and the dorsal aspect of the hands), these depigmented lesions of pinta can be differentiated from those of other depigmented disorders by the presence of pigmented lesions, histologic examination of lesional specimens, identification of antibodies directed against *T. carateum* by serologic testing, and darkfield examination.

## Disorders of Both Hypopigmentation and Hyperpigmentation

### DYSCHROMATOSES

Two major forms of dyschromatoses have been described: dyschromatosis symmetrica hereditaria (DSH; reticulate acropigmentation of Dohi) and dyschromatosis universalis hereditaria (DUH), both of which are seen most commonly in Japanese and Chinese individuals (in about 2 per 100,000 individuals). These disorders show only pigmentary manifestations and affected individuals are almost always otherwise healthy. The reticulate hyperpigmentation of these disorders tends to appear more spotty than the more net-like reticulated

hyperpigmentation of disorders like dyskeratosis congenita (see Chapter 7), Rothmund–Thomson (see Chapter 19) and Kindler (see Chapter 13) syndromes. The differential diagnosis of these dyschromatoses includes other disorders with more or a macular pigmentation (such as xeroderma pigmentosum (see Chapter 19), Kitamura reticulate acropigmentation, and dyschromic amyloidosis (Table 11-5). Keratin disorders with hyperpigmentation also tend to have a more net-like reticulated pigmentation (e.g., EB simplex with mottled pigmentation [see Chapter 13], Dowling–Degos disease, Naegeli–Franceschetti–Jadassohn syndrome and dermatopathia pigmentosa reticularis).

DSH is an autosomal dominant disorder characterized by pinpoint to pea-sized hyperpigmented and hypopigmented macules on the dorsal aspects of the distal extremities and face.<sup>201</sup> Lesions first appear

**Table 11-5** Disorders with Reticulate Hyperpigmentation (and Sometimes Hypopigmentation)

Disorder	Inheritance	Gene	Onset	Features	Other Comments
Familial forms of amyloidosis		Unknown	Early childhood	Generalized hyperpigmentation with tiny generalized hypopigmented macules	AD form: focal subepidermal amyloid deposition in biopsies
Amyloidosis cutis dyschromica	AD			Carriers of X-linked form: along lines of Blaschko, resembling incontinentia pigmenti	
X-linked reticulate hyperpigmentation	XL			XL form: failure to thrive, developmental delay, seizures, hemiplegia, colitis, gastroesophageal reflux, inguinal hernia, urethral stricture, dental anomalies, hypohidrosis, photophobia, corneal clouding, skeletal changes	XL form: often no amyloid in biopsies of children
Dowling–Degos disease	AD	Keratin 5; <i>POFUT1</i> ; <i>POGLUT1</i>	Early adolescence	Reticulate pigmentation of flexures, neck, and sometimes generalized; sometimes pitted perioral scars and comedo-like follicular plugs	No acantholysis More generalized reticulated pigmentation in EBS with mottled pigmentation ( <i>KRT5</i> mutations; see Ch. 13)
Familial progressive hyperpigmentation and hypopigmentation	AD	<i>KITLG</i>	Birth or early infancy; increase in number with time	Face, neck, trunk, limbs with reticulate hyperpigmentation as well as diffuse background hyperpigmentation; café-au-lait macules and freckling; sometimes larger hypopigmented macules	Called familial progressive hyperpigmentation if no hypopigmentation; distinguish from NF1 and Legius syndrome
Dyschromatosis symmetrica hereditaria	AD	<i>ADAR1</i>	Infancy to early childhood	Hyperpigmented and hypopigmented small macules on dorsum of hands and feet	
Dyschromatosis universalis hereditaria	AD	<i>ABCB6</i>	First months of life (starts on trunk)	Generalized pigmented macules; may involve palms and soles, oral mucosa, and nails (dystrophy with pterygium)	
Galli–Galli disease	AD	Keratin 5	Early adolescence	Reticulate pigmentation of flexures	Moderate to severe suprabasal acantholysis in biopsies
Kitamura disease	AD	<i>ADAM10</i>	First to second decade	Acral reticular pigmentation with subtle atrophy, palmar pits, and rete ridge breaks	
Dyskeratosis congenita (see Ch. 7)	Esp. XL	Esp. <i>DCK1</i>	Late childhood	Net-like pigmentation, esp. in sun-exposed areas, often poikilodermatosus; associated with mucosal leukokeratosis, nail dystrophy, risk of bone marrow failure, mucosal squamous cell carcinomas	Nine known genes can be mutated; can be AD or AR
Naegeli–Franceschetti–Jadassohn syndrome	AD	<i>KRT14</i>	First 2 years	Reticulate hyperpigmentation, primarily of abdomen, perioral, and periocular areas; palmoplantar keratoderma, absence of dermatoglyphics, onychodystrophy, hypohidrosis, dental anomalies Pigmentation fades during adolescence	
Dermatopathia pigmentosa reticularis	AD	<i>KRT14</i>		Pigmentation primarily truncal distribution; nonscarring alopecia; palmoplantar keratoderma, absence of dermatoglyphics, onychodystrophy, hypohidrosis	

AD, Autosomal dominant; *ADAM10*, a disintegrin and metalloproteinase domain-containing protein 10; *ADAR1*, adenosine deaminase acting on RNA 1; AR, autosomal recessive; *DCK1*, dyskerin; *EBS*, epidermolysis bullosa simplex; *Esp.*, especially; *KITLG*, KIT ligand; *KRT*, keratin; *NF*, neurofibromatosis; *POFUT1*, protein O-fucosyltransferase 1; *POGLUT1*, protein O-glucosyltransferase 1; *XL*, X-linked.



**Figure 11-27** Dyschromatoses universalis hereditaria. Reticulated hyperpigmented and hypopigmented macules of various shapes and sizes on the trunk. (Courtesy of Drs. S. Worobec and S. Reddy.)

during infancy or early childhood, commonly spread until adolescence, and persist lifelong. Neurologic disease has been described in the minority of patients.<sup>202,203</sup> Molecular studies have uncovered mutations in ribonucleic acid (RNA)-specific adenosine deaminase (*ADAR1*, also called *DSRAD*).<sup>204–207</sup> Reticulate acropigmentation of Kitamura is another autosomal dominant disorder characterized by reticulated or lentiginous hyperpigmentation localized primarily to the dorsal areas of the hands and feet. It is caused by mutations in *ADAM10*.<sup>208</sup> The lesions have their onset during childhood and tend to be more atrophic than those of DSH. Pits on the palms, soles, and dorsal surface of the fingers and toes are associated.<sup>209</sup> DSH has recently been treated with miniature punch grafting and excimer light therapy.<sup>210</sup>

DUH is an autosomal dominant disorder (rarely recessive) in which patients show hyperpigmented and hypopigmented macules of various shapes and sizes with a mottled appearance (Fig. 11-27). In DUH skin lesions appear within the first months of life, predominantly on the trunk, and subsequently generalize, including the palms and soles in some cases. The oral mucosa may be involved, and nails may show dystrophy with pterygium formation. The numbers of melanosomes is normal, and the disorder presumably reflects increased melanocyte activity. DUH is caused by mutations in *ABCB6*.<sup>211</sup> Dyschromatoses resembling DUH may also be caused by heterozygous mutations in *KITLG*, encoding KIT ligand (familial progressive hyperpigmentation and hypopigmentation)<sup>212</sup> or *SASH1* (SAM and SH3 domain-containing protein 1), a tumor suppressor gene.<sup>213,214</sup> *SASH1* mutations on both alleles lead to the reticulate hypopigmentation and hyperpigmentation in association with alopecia, palmoplantar keratoderma, nail dystrophy, dental anomalies, skin ulcers, and recurrent squamous cell carcinoma.<sup>215</sup> The hyperpigmented lesions of DUH have been treated with Q-switched alexandrite laser.<sup>216</sup>

Reticulated hyperpigmentation is also seen in X-linked reticulate pigmentary disorder (also called Partington syndrome or familial cutaneous amyloidosis).<sup>217</sup> Affected boys show generalized reticulate hyperpigmentation in association with xerosis, failure to thrive, developmental delay, seizures, hemiplegia, colitis, gastroesophageal reflux, inguinal hernia, and urethral stricture. Dental anomalies, hypohidrosis, photophobia, and corneal clouding are also seen. Skeletal changes may include delayed bone age and shortened metacarpals. The amyloid found in skin biopsies of some affected adults has not been demonstrated in the skin of affected children. Pigmentation distributed along the lines of Blaschko in female carriers resembles the pigmented streaks and whorls of *incontinentia pigmenti*. Familial dyschromic amyloidosis with only the pigmentary abnormalities may be inherited in an autosomal dominant manner with incomplete penetrance.<sup>218,219</sup> The underlying genetic cause of these familial cutaneous amyloidoses is unknown.

Dowling–Degos disease and its acantholytic variant Galli–Galli disease are both autosomal dominant disorders usually caused by mutations in keratin 5.<sup>220</sup> Reticulated hyperpigmentation is localized to the intertriginous areas, primarily the axillae and the inguinal folds. Comedonal lesions and pitted acneiform facial scars are associated.<sup>221</sup> A more generalized form of Dowling–Degos disease has also been associated with mutations that affect glycoprotein synthesis, protein O-fucosyltransferase 1 and protein O-glucosyltransferase 1.<sup>222,223</sup> Naegeli–Franceschetti–Jadassohn syndrome and dermatopathia pigmentosa reticularis are autosomal dominant disorders with reticulate hyperpigmentation, palmoplantar keratoderma, absence of dermatoglyphics, onychodystrophy, and decreased sweating with lifelong heat intolerance. Both disorders result from heterozygous nonsense or frameshift mutations in keratin 14 that increase the susceptibility of keratinocytes to apoptosis.<sup>224,225</sup> In Naegeli–Franceschetti–Jadassohn syndrome, the reticulated hyperpigmentation is present during the first 2 years of life and primarily involves the abdomen, perioral, and periocular areas.<sup>226</sup> The pigmentation commonly fades during adolescence and may disappear altogether. Dental abnormalities are associated. The pigmentation in dermatopathia pigmentosa reticularis is primarily in a truncal distribution and is associated with nonscarring alopecia.<sup>227</sup>

The hyperpigmentation in all of these disorders is nonpalpable in contrast to the hyperpigmented papules and plaques of confluent and reticulated papillomatosis of Gougerot and Carteaud, an asymptomatic disorder of hyperkeratotic hyperpigmented papules in a reticulated pattern.<sup>228</sup> Seen primarily in adolescents and young adults, this disorder usually occurs on the upper anterior trunk, often in individuals with acanthosis nigricans (see Chapter 23, Figs. 23-26 through 23-28).

## POIKILODERMA

The term *poikiloderma* (*poikiloderma atrophicans vasculare*) is used to describe a triad of telangiectasia, atrophy, and reticulated dyschromia (hyperpigmentation and hypopigmentation). The disorder may be seen in patients with poikiloderma congenitale (Rothmund–Thomson syndrome), xeroderma pigmentosum, Bloom syndrome (see Chapter 19), dyskeratosis congenita (see Chapter 7), juvenile dermatomyositis (see Chapter 22), and cutaneous T-cell lymphoma (see Chapter 10). Actinic, thermal (see Erythema Ab Igne section, Chapter 20), and radiation damage can also leave poikilodermatous changes. Histopathologic examination of areas of poikiloderma reveals varying degrees of epidermal hyperkeratosis and atrophy, hydropic degeneration of the basal layer, varying numbers of pigment-laden melanophages, and a lymphocytic band-like or perivascular infiltration in the dermis. Management consists of early recognition, avoidance of sun exposure, and the use of protective clothing and topical sunscreen preparations in an attempt to arrest progression of the dermatosis.

## INCONTINENTIA PIGMENTI

*Incontinentia pigmenti* (Bloch–Sulzberger syndrome) is an X-linked disorder that predominantly affects the skin, teeth, CNS, and eyes.<sup>229–231</sup> The disorder results from mutations in nuclear factor-kappa B (NF-κB) essential modulator (*NEMO*; *IKBKG*), a gene localized to the X chromosome. In approximately 80% of patients, the mutation is a rearrangement in the *NEMO* gene that eliminates its activity.<sup>232,233</sup> Less commonly, affected girls (often with milder disease) have a missense mutation in the *NEMO* gene, particularly involving exon 10; these girls are at risk of having a son with hypohidrotic ectodermal dysplasia with immunodeficiency (see Chapter 7). *De novo* mutations occur in 65% of patients.<sup>234</sup> The mutation in *NEMO* prevents the activation of NF-κB, which is a regulator of cell proliferation, inflammation, and TNF-α-induced apoptosis. Approximately 97% of patients are female, suggesting that the disorder is lethal to affected hemizygous male individuals.<sup>235</sup> Male patients with Klinefelter syndrome (XXY genotype) or with *incontinentia pigmenti* as a mosaic condition have been described.<sup>236–240</sup> Affected girls show functional mosaicism because of the random inactivation early in embryologic development of one of the X chromosomes (lyonization). As such, the cutaneous lesions of *incontinentia pigmenti* tend to follow lines of

### Box 11-2 Manifestations of Incontinentia Pigmenti

X-linked dominant disorder; random X-chromosome inactivation dictates extent of disease  
 Mutations in NF- $\kappa$ B essential modulator (*NEMO*)  
 97% of patients are females; probably lethal in males; living males usually represent somatic mosaicism  
 Four cutaneous phases that may overlap  
 Inflammatory vesicles or bullae  
 Verrucous lesions  
 Streaks of hyperpigmentation  
 Streaks of atrophy/hypopigmentation  
 May have cicatricial alopecia and nail dystrophy  
 Eosinophilia in >70% of patients (often lasts for 4 to 5 months)  
 Systemic manifestations  
 Dental  
 Ocular  
 Central nervous system

*NF- $\kappa$ B*, Nuclear factor kappa B.

Blaschko, representing the clonal outgrowth of cells that express the affected allele. The variable severity and expression of clinical involvement in the eyes and brain reflect the random activation of the affected X allele in these tissues.

The disorder generally appears at birth or shortly thereafter (90% of patients have cutaneous lesions within the first 2 weeks of life; 96% have their onset before the age of 6 weeks). Although the cutaneous lesions have four distinct phases, their sequence is irregular and overlapping of stages is common (Box 11-2).

The first phase of incontinentia pigmenti begins with inflammatory vesicles or pustules that develop in crops over the trunk and extremities, often persisting for months. These may range from largely papular with scattered vesicles to pustules (Fig. 11-28). Biopsy of a blister during this vesicular stage reveals epidermal vesicles filled with eosinophils, and 74% of affected neonates show eosinophilia (from 18% to 89%). The vesicles clear spontaneously through cellular apoptosis and repopulation by continuous normal keratinocytes. However, the vesicular phase may be reactivated focally, especially in infants after infection, immunization, or physical trauma; less commonly erythematous whorls without vesication may occur in older individuals.<sup>241,242</sup>

In 70% of patients, the vesicular stage is followed by a verrucous phase characterized by irregular, linearly arrayed warty papules on one or more extremities and often on the hands and feet (Fig. 11-29). This stage resolves spontaneously, usually within a period of up to 2 years.

During or shortly after this verrucous stage, the highly characteristic pigmentary phase occurs in approximately 80% of patients. Lesions typically are thin bands of slate-brown to blue-gray coloration arranged in lines and swirls on the extremities and trunk (Fig. 11-29). These pigmentary bands may coalesce in areas and more closely resemble Chinese writing figures than linear streaks or whorls. When more linear, they must be distinguished from X-linked macular amyloidosis in carrier females.<sup>243,244</sup> Occasionally, these bands appear purpuric at onset (Fig. 11-30), and this appearance has raised the question of child abuse.<sup>245</sup> These pigmentary lesions progress until the patient's second year of life, then stabilize and persist for years. By adolescence they gradually fade and disappear in two-thirds of affected individuals. Biopsy sections from lesional skin show incontinence of pigment during this phase, leading to the name *incontinentia pigmenti*. Although the pigmentary changes were originally considered to be a postinflammatory phenomenon secondary to the vesiculobullous or verrucous stages, the pigment fails to follow the pattern, shape, or location of the vesicular or verrucous lesions.

A fourth phase is characterized by persistent atrophic streaks that are often hypopigmented (Fig. 11-31). Most commonly noted on the arms, thighs, trunk, and particularly the calves of affected individuals, these affected areas show diminished hair, eccrine glands, and sweat pores. These streaks are often subtle and may be accentuated by viewing with side lighting or by Wood lamp examination. Skin biopsy shows characteristic changes with scattered apoptotic cells, thickened



**Figure 11-28** Incontinentia pigmenti. (A) The lesions of incontinentia pigmenti tend to follow a curvilinear pattern along lines of Blaschko, lines of the embryological development of ectoderm, as a manifestation of functional mosaicism (i.e., the X chromosome with the mutation in the *NEMO* gene is the activated X chromosome in the skin at these sites). The lesions of the vesicular phase may range from largely papular with a minor vesicular component to vesiculopustular as shown here and occasionally to bullous. (B) Sometimes the lesions of incontinentia pigmenti do not show a linear pattern. Note the residual inflammation and scaling as the vesicular lesions clear.

dermis, and absence of hair follicles and sweat glands, allowing diagnosis in older individuals.<sup>246</sup>

Cicatricial alopecia is seen in 38% to 66% of patients (Fig. 11-32). It occurs most often near the vertex and does not necessarily relate to the previous presence of lesions at the site. Nail dystrophy is present in 7% to 51% of affected individuals. In addition, painful grayish-white verrucous or keratotic subungual tumors are seen in up to 10%, usually during the second or third decades of life<sup>247</sup> and rarely lead to squamous cell carcinomas.<sup>248</sup> Lytic defects on roentgenographic examination of the distal phalanges may be seen as well.

Noncutaneous manifestations occur in a high percentage of patients with incontinentia pigmenti. Some 70% to 95% of patients show



**Figure 11-29** Incontinentia pigmenti. Characteristic slate-brown lines on the legs may coalesce in areas and more closely resemble Chinese writing figures or a reticulated pattern than linear streaks. The hyperpigmentation usually fades by late in childhood. Note the warty papules of the verrucous phase, which are most commonly found on the hands and feet.



**Figure 11-30** Incontinentia pigmenti. The bands of brownish-gray pigmentation may initially appear purpuric, raising the question of child abuse.

dental anomalies (delayed dentition, partial anodontia, pegged or conical teeth)<sup>249,250</sup> (Fig. 11-33) reminiscent of those in boys with hypohidrotic ectodermal dysplasia (see Chapter 7). Ectodysplasin (which is usually mutated in boys with hypohidrotic ectodermal dysplasia), the ectodysplasin receptor, and *NEMO* all participate in NF- $\kappa$ B signaling, providing an explanation for these shared phenotypic features. In fact, boys with a form of ectodermal dysplasia with



**Figure 11-31** Incontinentia pigmenti. Atrophic streaks that are often hypopigmented can be found in the minority of affected individuals. Most commonly noted on the arms and legs, these affected areas show diminished hair, eccrine glands, and sweat pores. The atrophic, hypopigmented streaks are often subtle and may be accentuated by viewing with side lighting or by Wood lamp examination.



**Figure 11-32** Incontinentia pigmenti. Cicatricial alopecia most commonly appears near the vertex and does not necessarily relate to the previous presence of lesions at the site.

immunodeficiency (see Chapter 7) have mutations in *NEMO* that decrease its function but do not eliminate it.

Up to 30% of patients with incontinentia pigmenti demonstrate involvement of the CNS, most commonly seizures.<sup>251,252</sup> These seizures have been attributed to acute microvascular hemorrhagic infarcts,<sup>253</sup> although recurrent stroke has also been described.<sup>254</sup> Many such neonates are mistakenly thought to have neonatal herpes simplex infection because of the presence of vesiculopustular lesions and seizures. Overall, 7.5% have severe neurologic abnormalities including continuing seizures, retardation, and/or spastic abnormalities.<sup>251</sup> Seizures during the first week of life have been associated with the worst prognosis for normal development. Learning disabilities are common.<sup>255</sup>

Ophthalmic changes are present in 37% of patients; 18% have strabismus, and an equal number demonstrate more serious eye involvement (cataracts, optic atrophy, or retinal neovascularization or detachment). Bilateral blindness has been described in 4% to 8% of individuals with incontinentia pigmenti. Occasionally, cardiac anomalies and skeletal malformations (such as microcephaly, syndactyly, supernumerary ribs, hemiatrophy, or shortening of the arms or legs) may occur.



**Figure 11-33** Incontinentia pigmenti. Dental anomalies (delayed dentition, partial anodontia, pegged or conical teeth) occur in the majority of affected individuals. Interestingly, these dental changes mirror those of boys with hypohidrotic ectodermal dysplasia, a disorder that shares the NF- $\kappa$ B signaling pathway.



**Figure 11-34** Pigmentary mosaicism. Narrow to broad linear streaks of hypopigmentation following lines of Blaschko on the trunk of a patient with developmental delay (**A**) and on the face and neck of an otherwise normal baby (**B**). The term *pigmentary mosaicism* encompasses previous terms such as *incontinentia pigmenti achromians* and *hypomelanosis of Ito*. Most patients with pigmentary mosaicism are otherwise normal, but evidence of neurologic, ocular, and bony defects should be sought, especially with more extensive pigmentary changes.

The characteristic cutaneous lesions of incontinentia pigmenti allow early diagnosis and investigation for associated ocular and neurologic abnormalities. No special therapy is required for the skin lesions of incontinentia pigmenti, because they tend to clear spontaneously, but regular ophthalmologic evaluations are important.<sup>256</sup> If retinal involvement is discovered, early intervention with laser, cryotherapy, or intravitreal bevacizumab should be initiated.<sup>257</sup> If seizures or evidence of developmental delay appear, neurologic consultation is appropriate. High-dose glucocorticoids in the neonatal period have helped to control seizures recalcitrant to antiepileptics.<sup>258</sup> Dental evaluation by 2 years of age will allow investigation of missing or misshapen secondary teeth; prostheses can be made in patients with significant dental abnormalities.

Obtaining a history of cutaneous disorders during the neonatal and infantile periods and careful physical examination of mothers who may be carriers is important for genetic counseling. A mother of an affected individual who shows subtle manifestations is at increased risk for having another affected daughter (50% probability in daughters) and aborting a male fetus (50% probability in sons). Affected mothers may show subtle signs, most commonly hypopigmented, atrophic, hairless streaks along Blaschko lines (sometimes seen best by side lighting)<sup>259</sup> and sometimes a patch of cicatricial alopecia,<sup>260</sup> conical incisor, or nail dystrophy.<sup>261</sup> Sometimes carrier mothers show no signs, despite a history of a previous blistering disorder in the neonatal period. Prenatal diagnosis is possible, and preimplantation genetic diagnosis has been performed.<sup>262</sup> Treatment with topical corticosteroids<sup>263</sup> or tacrolimus<sup>264</sup> may halt the progression of the vesicular phase, although lesions ultimately clear spontaneously. The retinal neovascularization may regress with laser photocoagulation,<sup>265</sup> and preliminary studies of vascular endothelial growth factor (VEGF) inhibitors appear promising.<sup>266</sup> The Incontinentia Pigmenti International Foundation provides education and support (<http://www.ipif.org/>).

## PIGMENTARY MOSAICISM

The term *pigmentary mosaicism* is preferred for this heterogeneous group of disorders that includes hypomelanosis of Ito (incontinentia pigmenti achromians), linear and whorled nevoid hypermelanosis,<sup>267</sup> and the segmental form of nevus depigmentosus,<sup>268</sup> which is characterized by patterned streaks of hypopigmentation and/or hyperpigmentation (Figs. 11-34 and 11-35). The linear streaks and whorls tend to follow lines of mosaicism,<sup>269</sup> particularly the lines of Blaschko (lines of ectodermal embryologic development), or a phyllid pattern of mosaic distribution.<sup>270,271</sup> Both hypopigmented and hyperpigmented streaks may be seen in the same individual.



**Figure 11-35** Pigmentary mosaicism. Patterned hyperpigmented patches on the neck and trunk in a phyllid pattern. This child was otherwise normal.

The pigmentary mosaicism reflects gene mosaicism of affected areas. These mosaic conditions do not tend to be hereditary, although familial cases have rarely been reported.<sup>272</sup> Gross chromosomal abnormalities have been described in 60% of affected pediatric patients with more extensive pigmentary mosaicism and/or associated noncutaneous abnormalities when peripheral blood leukocytes and cultured fibroblasts or keratinocytes are evaluated.<sup>273–275</sup> In another study, an unselected patient population with pigment mosaicism showed an incidence of associated abnormalities (particularly of the bones, eyes, and/or CNS) in 30% of patients.<sup>276</sup> The majority of patients, however, do not have widespread involvement with pigmentary mosaicism and show no other problems by history and examination; these children require no further investigation.

The streaks of hypopigmentation or hyperpigmentation along Blaschko lines of embryologic development must be distinguished from the hypopigmented or hyperpigmented streaks of *incontinentia pigmenti*. The term *incontinentia pigmenti achromians* for the streaks of hypopigmentation has been abandoned to avoid confusion, because *incontinentia pigmenti* is unrelated. The lack of preceding vesicular or verrucous lesions of *incontinentia pigmenti* and the finding of increased melanin deposition at the basal cell layer in hyperpigmented streaks of pigment mosaicism (linear and whorled hypermelanosis) rather than the pigment incontinence of *incontinentia pigmenti* help to distinguish these disorders.<sup>277</sup> Epidermal nevi may present as flat brown streaks but more commonly are hyperkeratotic (see Chapter 9).

## Disorders of Hyperpigmentation

Pigmented nevi are among the most common hyperpigmented lesions and are reviewed in Chapter 9, as are streaks of pigmentation involving the nails (longitudinal melanonychia; see Chapter 7). Treatment of hyperpigmented lesions with topical agents has generally been unsuccessful. Sun protection is a critical aspect of management in preventing darkening. Lasers have been used to treat a variety of hyperpigmented disorders in children,<sup>278</sup> in particular CAL macules, nevus of Ota, and other forms of dermal melanocytosis, Becker nevi, and tattoos. Several therapeutic sessions are required, and results are rarely permanent.

### EPIDERMAL MELANOCYTE LESIONS

#### Freckles

Freckles (ephelides) are light brown, well-circumscribed macules, usually smaller than 3 mm in diameter, that appear in childhood, especially between 2 and 4 years of age and tend to fade during the winter and adult life. Their presence correlates with fair skin, red hair, and an increased risk of developing melanoma.<sup>279</sup> Freckles are most common on the sun-exposed areas of the face (especially the nose and cheeks), shoulders, and upper back.

Freckles become darker and more confluent after UV light exposure in the sunburn spectrum (290 to 320 nm) as well as in the long-wave UV (UVA) range (320 to 400 nm). UVA light is not blocked by window glass and sunscreen agents that filter out only the sunburn spectrum. They often become smaller, lighter, and fewer during the winter months. Histopathologic features of ephelides include increased melanin pigmentation of the basal layer without an increase in the number of melanocytes or elongation of the epidermal rete ridges.

Freckles bear cosmetic but no systemic significance. Treatment includes avoidance of sun exposure and appropriate covering makeup. Use of "full-spectrum" sunscreens that provide protection against both UVA and UVB light (e.g., with avobenzene or titanium dioxide) are more protective than sunscreens that only provide UVB protection. When desired, although seldom necessary, gentle chemical peels or laser may remove the superficial pigmentation and make many of the freckles less conspicuous.

#### Becker Nevus

Becker nevus (Becker melanosis), an irregular macular hyperpigmentation with hypertrichosis, is sometimes congenital, but more commonly starts during early adolescence. It occurs much more commonly



**Figure 11-36** Becker nevus. This light brown, irregularly bordered patch without hypertrichosis was recently noticed on the axillary area and shoulder of this 12-year-old boy.



**Figure 11-37** Becker nevus. Large patch of grayish-brown pigmentation on the back with associated coarse terminal hairs. These lesions usually appear during late childhood or early adolescence on the upper trunk.

in males than females, and affected individuals tend to be otherwise healthy. The first change generally appears as a brown pigmentation, most commonly on the chest, back, or upper arm, that expands to 10 to 15 cm in diameter (about the size of a hand or larger) (Fig. 11-36). The outline is irregular and sometimes surrounded by islands of blotchy pigmentation. Although characteristically seen unilaterally on the upper half of the trunk, especially around the shoulder, it has also been reported in other areas on the trunk, forehead, cheeks, supraclavicular region, abdomen, forearm, wrist, buttocks, and shins and may be bilateral.<sup>280,281</sup> After a period of time (often 1 or 2 years), coarse terminal hairs appear in the region of, but not necessarily coinciding with, the pigmented area (Fig. 11-37). The intensity of pigmentation may fade somewhat as the patient becomes older, but the hyperpigmentation and hypertrichosis tend to persist for life.

The etiology of Becker nevus is unknown, but a localized increase in androgen receptor sensitivity may explain the time of onset and clinical features seen in most individuals with this disorder.<sup>282</sup> Reports of familial cases<sup>283</sup> raise the question of a genetic influence in some patients, and the occasional association of significantly increased smooth muscle suggests that Becker nevus and smooth muscle hamartoma may perhaps represent two poles of the same hamartomatous change. Although most Becker nevi occur without other pathologic findings, association with a variety of other abnormalities (such as unilateral breast and areolar hypoplasia, focal acne, pectus



**Figure 11-38** Lentigines. This girl showed hundreds of lentigines, particularly on the face and extensor surfaces of the extremities. These sharply demarcated macules tend to be larger than a freckle but smaller than a café-au-lait spot and range in color from tan to black. Although one might consider LEOPARD syndrome or Carney complex in this girl, genetic testing showed no mutations in *PTPN11*, *RAF1*, *BRAF*, *MAP2K1*, or *PRKAR1A*.



**Figure 11-39** Speckled lentiginous nevus. This large patch of lentigines of different sizes overlying an increase in cutaneous pigmentation may represent a mosaic form of multiple lentiginosis syndrome.

carinatum, limb asymmetry, and spina bifida<sup>284,285</sup> has been called *Becker nevus syndrome*.<sup>283,286</sup>

Histopathologic features reveal epidermal thickening, elongation of the rete ridges, and hyperpigmentation of the basal layer with increased melanocytes.<sup>282</sup> Malignant transformation does not occur. Treatment of this disorder is purely cosmetic and is generally discouraged. Laser therapy or excision usually does not improve the appearance. The hypertrichosis may be treated with laser depilation<sup>287</sup> (see Chapter 7).

### Lentigines

Lentigines are small, tan, dark brown, or black flat, oval, or circular, sharply circumscribed lesions that usually appear in childhood and may increase in number until adult life. These may occur on sun-exposed areas (especially the face and dorsal aspect of the hands) as “lentigo simplex.” Lentigines usually measure 3 to 15 mm in diameter and may occur on any mucocutaneous surface (Fig. 11-38) including the lips or conjunctivae. The pigmentation is uniform and darker than that seen in ephelides (freckles) and CAL macules, and the color is unaffected by exposure to sunlight. Lentigines are typically larger than freckles and smaller than a typical CAL macule and can be distinguished from freckles and CAL macules histologically.<sup>288</sup> Multiple facial lentigines can be an early sign of xeroderma pigmentosum, especially in association with a history of sun burning after limited sun exposure. Lentigines have rarely been described after use of topical tacrolimus.<sup>289,290</sup>

Lentigines that appear early in life may fade or disappear; those appearing later in life tend to be permanent. Treatment other than for cosmetic purposes is ordinarily not indicated. When desired, however, excision by a small punch biopsy, cryosurgery, or laser may be beneficial. Interestingly, a patient with multiple lentigines shows marked lightening when treated with ST1571 (imatinib) for familial gastrointestinal stromal tumor syndrome.<sup>291</sup>

Patients with speckled lentiginous nevus or segmental lentiginosis show patches of lentigines, usually overlying a slight increase in cutaneous pigmentation (Fig. 11-39). Eruptive, agminated Spitz nevi may be seen within a segmental lentiginosis.<sup>292</sup> Eruptive lentiginosis is a disorder characterized by a widespread eruption of several hundred lentigines that may develop over a few months or years, usually in adolescents or young adults, without systemic manifestations. Inherited patterned lentiginosis is an autosomal dominant disorder of dark-skinned individuals with the onset of lentiginosis during early



**Figure 11-40** Bannayan–Zonana–Ruvalcaba syndrome. Lentigines of the penis are characteristic of Bannayan–Zonana–Ruvalcaba syndrome, an autosomal dominant disorder that also commonly features macrocephaly and lipomas.

childhood. Lentigines occur on the centrofacial area, lips, oral mucosae, buttocks, elbows, palms, and soles, and affected individuals are otherwise healthy.

Localized or extensive lentiginosis may also be a component of a multisystem disorder. Although they may occur in children without medical problems, lentigines of the penis are characteristic of Bannayan–Zonana (Bannayan–Zonana–Ruvalcaba) syndrome, an autosomal dominant disorder that results from mutations in the *PTEN* gene and is allelic with Cowden syndrome (Fig. 11-40) (see Chapter 9). Other major features are macrocephaly and lipomas. Lentigines of the hands, feet, and buccal mucosa may also be a feature of Cronkhite–Canada syndrome, in which nail dystrophy, hair loss, and intestinal polyposis are other characteristics. Centrofacial lentiginosis (also called *centrofacial neurodysraphic lentiginosis* or *Touraine syndrome*) is an autosomal dominant process in which lentigines are first noted in the

first year of life, particularly on the nose and cheeks. Patients with centrofacial lentiginosis may have associated mental retardation, congenital mitral valve stenosis, seizures, sacral hypertrichosis, coalescence of the eyebrows, high-arched palate, absent upper middle incisors, bony abnormalities, defective fusion of the neural tube (dysraphia), psychiatric disorders, dwarfism, and endocrine dysfunction.

The major lentiginous syndromes are Peutz–Jeghers syndrome, multiple lentiginosis/lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness (LEOPARD) syndrome, and Carney complex.

### Peutz–Jeghers Syndrome

The prevalence of this autosomal dominant disorder of mucocutaneous lentiginous macules and multiple hamartomatous intestinal polyps is approximately 1 in 100,000 individuals.<sup>293</sup> Mutations in the serine-threonine kinase *STK11/LKB1* gene have been found in 70% of familial cases and up to 67% of sporadic cases.<sup>293,294</sup>

Characteristic bluish-brown to black spots, often apparent at birth or in early infancy, represent the cutaneous marker of this syndrome. These discrete, flat pigmented lesions are irregularly oval and usually measure less than 5 mm in diameter. They are most commonly seen on the lips (Fig. 11-41), buccal mucosa, nasal and periorbital regions, elbows, dorsal aspects of the fingers and toes, palms, soles, and periumbilical, perianal, and labial regions; occasionally the gums and hard palate and on rare occasions, even the tongue may be involved. An umbilical lentigo has recently been described at birth in an affected neonate.<sup>295</sup> The pigmented lesions on the skin and lips often fade after puberty; those on the buccal mucosa, palate, and tongue, however, persist.

The hamartomatous gastrointestinal polyps seen in this disorder may be found from the stomach to the anal canal, although the small bowel represents the most commonly involved portion of the intestinal tract. Polyps vary from minute pinhead lesions to those measuring several centimeters in diameter. They may occur in early childhood, with one study showing a median age of presentation of 5 years; 50% of patients have symptoms in the first 2 decades of life, including abdominal pain, melena, or intussusception.<sup>296</sup> The most common symptom, recurrent attacks of colicky abdominal pain, is thought to result from recurring transient episodes of incomplete intussusception. A recent prospective multicenter study found a 15% risk of cumulative intussusception by age 10 years and 50% by age 20.<sup>297</sup> Hematemesis, although less common, may occur owing to involvement of the stomach, duodenum, or upper jejunum. Polyps of the nasal mucosae and gallbladder have occasionally been described, and rarely polyps involve the respiratory and urogenital tracts.<sup>298</sup>

Although the polyps of Peutz–Jeghers syndrome are generally benign, adenocarcinomas of the gastrointestinal tract (stomach, small intestine, colorectum, pancreas, and biliary tract), breast and uterine cervical carcinomas, and gonadal sex tumors (Sertoli cell tumors of the testis and sex-cord tumors of the ovary) have been



**Figure 11-41** Peutz–Jeghers syndrome. Characteristic bluish-brown to black spots were first noted in early childhood on the lips of this boy who later developed hamartomatous gastrointestinal polyps.

described.<sup>294,299</sup> Sertoli cell tumors can occur prepubertally and may present with gynecomastia.<sup>300</sup> However, most cancers occur during adulthood<sup>301</sup> with an 81% to 94% lifetime cumulative risk for all cancers (18-fold that of the general population) and an almost 70% risk for gastrointestinal cancer.

In the past, therapeutic management focused on relief of symptoms and recurrent resections with the risk of malabsorption. The recommendation now is to remove polyps if technically feasible (especially if larger than 5 mm).<sup>302,303</sup> Guidelines for initiating screening for polyps vary. Some suggest initially screening at 8 to 10 years with esophagogastroduodenoscopy (EGD) or capsule endoscopy and if these are negative, colonoscopy at age 18 unless a concern arises. In a case series of 14 children, however, the median age of polyp detection was 5 years,<sup>300</sup> leading to the suggestion that initial screening occur at 4 to 5 years of age. Sertoli cell tumors should be sought prepubertally, but yearly evaluation of other organs at risk of malignancy (breast, thyroid gland, pancreas, uterus, and ovaries) should begin by the end of adolescence. The lentigines of Peutz–Jeghers syndrome have responded to laser<sup>304</sup> and intense pulsed light<sup>305</sup> therapies, although the lentigines not uncommonly recur.<sup>306</sup>

Laugier–Hunziker syndrome is a benign pigmentary disorder that manifests as macular hyperpigmentation of the lips and buccal mucosa. Many patients also show long pigmented bands of the nails (melanonychia striata), but the visceral manifestations of Peutz–Jeghers syndrome are absent.<sup>306,307</sup>

### Carney Complex

Carney complex comprises an autosomal dominant disorder that features the pigmentary abnormalities of lentigines, epithelioid blue nevi, and pigmented schwannomas.<sup>308</sup> Nevi, atrial myxoma, and neurofibroma ephelides (NAME)<sup>309</sup> and lentigines, atrial myxoma, and blue nevi (LAMB)<sup>310</sup> syndromes are included in Carney complex.<sup>311–314</sup> Most cases are sporadic. The group of disorders is considered a form of MEN, in that endocrine abnormalities and tumors are common features, especially pituitary adenomas, ovarian tumors,<sup>315</sup> testicular (Sertoli cell) tumors, and pigmented nodular adrenocortical disease.<sup>316</sup>

Skin manifestations are seen in 80% of patients, most commonly lentigines that typically fade during adulthood in 70% to 75% of patients. The lentigines tend to appear peripubertally and most commonly involve the center of the face, especially the vermillion border of the lips, (leading to the misdiagnosis of Peutz–Jeghers syndrome,<sup>317</sup> as well as the conjunctivae and occasionally the intraoral area. Peutz–Jeghers and Carney syndromes share several other features including the occurrence of gynecomastia and growth acceleration, as well as Sertoli cell tumors and tumors of the breast and thyroid. The blue nevi, including epithelioid blue nevi, occur in 40% of Carney complex patients. They tend to be multiple, most commonly on the face, trunk and extremities, and characteristically are dome-shaped dark blue papules. The majority of epithelioid blue nevi in children are associated with Carney complex, but this form of blue nevus has also been described in children without other features of the syndrome.<sup>318</sup> The lentigines and blue nevi are often accompanied by CAL spots. Multiple cutaneous myxomas occur in 30% to 55% of studied patients and are most commonly seen on the eyelids, ears, nipples, and external genitalia. They are usually diagnosed during the late teen years but can occur as early as infancy.<sup>319,320</sup> Patients often show myxomas of the oropharynx, heart, and breast and may develop other neoplasia of mesenchymal and neural-crest origin. The typical psammomatous melanotic schwannomas occur in 10% of affected individuals and may involve the skin, posterior spinal nerve roots, gastrointestinal tract, and bone. Biopsies of the blue nevi and schwannomas show characteristic histologic features.<sup>321</sup> Patients have been described both with predominantly cutaneous features<sup>322</sup> and without cutaneous lentigines. The most common endocrine tumors or overactivity include primary pigmented nodular adrenocortical disease (25% of patients), growth hormone-producing pituitary adenoma (10% of patients), large cell calcifying Sertoli cell tumor, and thyroid adenoma (up to 75% of patients). Development of carcinoma is rare.

Mutations in the protein kinase A type I- $\alpha$  regulatory subunit (*PRKAR1A*)<sup>323</sup> occur in approximately 57% of patients. An additional 20% of families with Carney complex show linkage to 2p16 (gene not yet identified) and have a milder phenotype with later onset.

## Multiple Lentiginos/LEOPARD Syndrome

Multiple lentiginoses/LEOPARD syndrome (also called *Noonan syndrome with multiple lentigines [NSML]*) comprises a spectrum of patients who show manifestations ranging from generalized lentigines alone to the complete syndrome that characteristically shows lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness.<sup>324–327</sup>

Affected individuals typically are thin; show an elongated, marfanoid facies; and have CAL macules admixed within the myriad of lentigines (Fig. 11-42). The disorder is within the spectrum of “RASopathies,” and mutations in *PTPN11* have been found in 90% patients; genotyping may be required to confirm the diagnosis. Rarely, affected individuals have mutations in *RAF1* (3%), *BRAF*, or *MAP2K1*.<sup>328–331</sup> Variable expressivity is seen within families, so that some affected individuals show only the multiple lentigines, whereas others show a variety of the visceral manifestations. Nevertheless, the underlying mutation of a family with multiple lentigines without other features maps to chromosome 6q, a site that is distinct from *PTPN11* and *RAF1*.<sup>332</sup>

The dark, 1- to 5-mm lentigines that define the syndrome often first appear at 4 to 5 years of age but then increase dramatically (to thousands of lentigines) by puberty. The cutaneous lesions tend to be concentrated on the neck and upper trunk, but they may also appear on the skin of the face and scalp, arms, palms, soles, and genitalia. The lentigines characteristically spare the mucosa. Occasionally forms frustes of this disorder occur, in which the characteristic lentigines are absent. In most patients, the CAL macules are present before the onset of the lentigines, leading to consideration of the alternative diagnosis of NF type 1 or its allelic variant with CAL spots and pulmonary valve stenosis, Watson syndrome.

Cardiac abnormalities occur in about 85% of affected individuals—mostly hypertrophic cardiomyopathy (up to 75%), which usually appears during infancy and subsequently progresses. Pulmonary valve stenosis and conduction defects have been described in 10% and 7% of patients, respectively.<sup>330</sup> Skeletal aberrations may include retardation of growth (below the 25th percentile), hypertelorism, an elongated facies, pectus deformities (carinatum or excavatum), dorsal kyphosis, winged scapulae, and prognathism. Endocrine disorders include gonadal hypoplasia, hypospadias, undescended testes, hypo-

plastic ovaries, and delayed puberty. The hearing loss of LEOPARD syndrome is congenital and neurosensory and can be detected by early auditory evoked potentials.

## Café-au-Lait Spots

Café-au-lait (CAL) spots are large, round or oval, flat lesions of light brown pigmentation found in up to 33% of normal children; having a greater number of CAL spots is more common in children with darker skin color, but having more than five is rare other than in NF or Legius syndrome.<sup>333–336</sup> Commonly present at birth or developing soon thereafter, they vary from 1.5 cm or less in their smallest diameter to much larger lesions that may measure up to 15 to 20 cm or more in diameter (Fig. 11-43). CAL spots may rarely occur anywhere on the body. A recent study suggested that neonatal blue-light phototherapy increases CAL spots in preschool children.<sup>337</sup>

The CAL spots of McCune–Albright syndrome are seen in approximately 50% of patients. They tend to be present during infancy or early childhood, with a predilection for areas with particularly bony prominences (the forehead, nuchal area, thorax, sacral areas, and buttocks). However, CAL spots may be seen elsewhere, including on the oral mucosae.<sup>338</sup> They are commonly unilateral, stopping abruptly at the midline and following a dermatomal distribution. They tend to have irregularly jagged or serrated borders (described as resembling the coast of Maine, in contrast to the smooth-bordered CAL spots of NF, which have been compared to the coast of California). The McCune–Albright syndrome in its complete form is a triad characterized by CAL spots, polyostotic fibrous dysplasia, and endocrine dysfunction, often manifesting as precocious puberty (see Chapter 23, Fig. 23-23). McCune–Albright syndrome is a mosaic disorder resulting from activating mutations in *GNAS*, but next-generation sequencing techniques enable detection of the low-abundance mutations in blood samples.<sup>339</sup>

CAL spots are increased in number in Russell–Silver syndrome,<sup>340</sup> a disorder that also features short stature, musculoskeletal abnormalities, craniofacial dysmorphism, and genitourinary malformations, as well as in multiple lentiginoses/LEOPARD syndrome (see Multiple Lentiginos/LEOPARD Syndrome section and Fig. 11-42). Johnson–McMillin syndrome is an autosomal dominant disorder in which families show truncal CAL spots in association with facial nerve palsy and mild developmental delay.<sup>341</sup> Other disorders with increased numbers of CAL spots are ring chromosomes (chromosomes 7, 11, 12, 15, 17, 22), Cowden and Fanconi syndromes, TSC, and piebaldism.



**Figure 11-42** Multiple lentiginosis/LEOPARD syndrome. Myriad of lentigines with scattered café-au-lait macules overlying generalized hyperpigmentation in this adolescent with only cutaneous changes. In some individuals, the pigmentary changes are associated with a spectrum of visceral abnormalities, including lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness, leading to the term *LEOPARD syndrome*.



**Figure 11-43** Café-au-lait (CAL) spot. Round or oval patches of light brown pigmentation are common in children but usually are up to a few centimeters in diameter, in contrast to this larger CAL spot of the face. Although a rare disorder, the segmental distribution of the CAL spot should alert one to consider the possibility of McCune–Albright syndrome.

### Box 11-3 Diagnostic Criteria for Neurofibromatosis Type 2

Bilateral vestibular schwannomas seen by MRI scan  
or  
A first-degree relative with NF2  
AND  
Unilateral vestibular schwannoma  
or  
Two of the following criteria:  
Meningioma  
Glioma  
Schwannoma  
Juvenile posterior subcapsular cataract

Modified from Mulvihill JJ, Parry DM, Sherman JL, et al. NIH conference. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis): an update. Ann Intern Med 1990;113(1):39–52; and Nunes F, MacCollin M. Neurofibromatosis 2 in the pediatric population. J Child Neurol 2003;18(10):718–24.

*MRI*, Magnetic resonance imaging; *NF*, neurofibromatosis

Not uncommonly, infants may show what appears to be a CAL, but sometimes years later the CAL develops tiny more darkly hyperpigmented macules or papules. This lesion is called *nevus spilus* (see Chapter 9), and biopsy of the more darkly pigmented lesions will show typical features of pigmented nevi (see Fig. 9-28). Individuals with red hair or with parents of markedly different skin pigmentation may show hyperpigmented macules that resemble CAL spots. They can be differentiated by their often irregular shape, tendency to be less well defined than the CAL spots of NF, and the paler coloration of the hyperpigmentation. Observation of these CAL-like macules during the first 5 to 6 years of life should be performed, and annual ophthalmologic evaluations should be considered to be convinced that the macules merely represent a pigment variation. Lichen aureus, a form of pigmented purpuric eruption, can also be confused with a CAL but tends to show pinpoint petechiae and purpura on a hyperpigmented base<sup>342</sup> (see Chapter 12).

### Neurofibromatosis

Neurofibromatosis (NF) is an autosomal dominant disorder characterized by an increased propensity toward the development of tumors, particularly of the nerve sheath.<sup>343–345</sup> NF encompasses three distinct disorders: NF type 1 (NF1; von Recklinghausen disease), NF type 2 (NF2; bilateral acoustic or central NF),<sup>346</sup> and schwannomatosis. The latter is characterized by painful peripheral (nonvestibular, non-dermal) schwannomas and is largely diagnosed in adults.<sup>347</sup> More than 90% of cases of NF are NF1, which occurs in approximately 1 in 3000 births.<sup>348–351</sup> NF2 occurs in 1 in 25,000 to 40,000 individuals, and its diagnosis during childhood is unusual. Both disorders show variable expressivity; NF1 shows an approximately 50% rate of new mutations, whereas two-thirds of children with NF2 have an affected parent. Patients with NF1 have mutations in neurofibromin, a large gene that encodes a large GTPase-activating cytoplasmic protein that negatively regulates Ras activation.<sup>345</sup> The gene mutated in NF2, merlin or schwannomin, encodes a cytoskeletal protein that inhibits a serine/threonine kinase PAK1, which is essential for Ras transformation.<sup>352</sup>

The cutaneous manifestations of NF1 are of major importance, and thus most discussion of NF in this chapter will focus on NF1. However, skin tumors are an important diagnostic clue for patients with NF2 and are often present months to years before other features. These tumors, predominantly schwannomas or neurofibromas, are the presenting sign in 27% of individuals with NF2 and eventually occur in 59% of patients.<sup>353,354</sup> A higher number of skin tumors has been correlated with a worse prognosis. CAL spots are found in 33% of individuals with NF2, but only 2% have six or more CAL spots. Although NF2 is commonly considered a disorder of adults, approximately 15% of patients with NF2 are diagnosed before 18 years of age,<sup>355</sup> and onset during childhood predicts a worse prognosis. The major criteria for NF2 are shown in Box 11-3. NF2 in children most commonly presents with hearing impairment (one-third of children) or cranial-nerve dysfunction (one-third of children). Tumor load is often

### Box 11-4 Diagnostic Criteria for Neurofibromatosis Type 1

Must have two or more of the following:  
Six café-au-lait macules that measure  $\geq 0.5$  cm before puberty and  $\geq 1.5$  cm in diameter in adults\*  
Freckling of the axillary and/or inguinal areas\*  
A plexiform neurofibroma or two or more dermal neurofibromas  
Two or more Lisch nodules  
Optic nerve glioma  
Pathognomonic skeletal dysplasia; i.e., tibial or sphenoid wing dysplasia  
An affected first-degree relative

\*Given the recognition that Legius syndrome is distinct from neurofibromatosis type 1 (NF1) clinically and genetically but shares two of the major features, experts on NF1 have recently suggested that having the cutaneous pigmentary lesions alone (café-au-lait spots and freckling) is insufficient for a definitive diagnosis of NF1.



**Figure 11-44** Neurofibromatosis type 1 (NF1). The presence of six or more café-au-lait (CAL) spots larger than 0.5 cm in diameter in children and 1.5 cm in adolescents suggests the possibility of NF1, although having CAL spots alone does not allow for definitive diagnosis.

extensive in pediatric patients (especially vestibular and cranial schwannomas, cranial meningiomas, and spinal cord tumors). Overall, 75% of affected children develop hearing loss. Removal of vestibular schwannomas does not preserve hearing, although early detection and smaller tumors are associated with a better prognosis. Visual impairment owing to cataracts and amblyopia occurs in 83% of affected children. Treatment is primarily surgical. Auditory brainstem implants may partially restore hearing.<sup>356</sup>

Although NF1 is best known because of Joseph Merrick, the famed “Elephant Man” of the 1800s, he is now thought to have had Proteus syndrome, a disorder characterized by segmental overgrowth with asymmetry, macrocephaly, lipomas, linear verrucous epidermal nevi, and vascular malformations (see Chapter 12). The diagnostic criteria for NF1 (Box 11-4) have not been modified since 1988 and thus do not yet include having a pathogenic mutation in neurofibromin. These criteria are of limited value for young children who typically show only multiple CAL spots and in 50% of cases have no affected first-degree family member. As such, the diagnostic criterion of six or more CAL spots of greater than 5 mm in diameter prepubertally and more than 15 mm postpubertally probably indicates the presence of NF1 (Fig. 11-44)<sup>357</sup> but is not definitively diagnostic. About 95% of patients with NF1 meet these criteria by 8 years of age, and all meet it by age 20 years. There is marked variability in the overall severity and progression of NF. It can cause serious problems and even death in the newborn, or it may produce only mild or insignificant problems during the lifetime of the affected individual.

**Cutaneous Manifestations of Neurofibromatosis Type 1.** CAL spots and dermal and plexiform neurofibromas are the characteristic cutaneous findings of pediatric NF1. The severity of cutaneous involvement is not indicative of the extent of disease in other organs. In fact,



**Figure 11-45** Neurofibromatosis type 1 (NF1). Axillary freckling (Crowe sign) is present in 20% to 50% of individuals with NF1 and commonly appears between 3 and 5 years of age. Although the presence of both axillary freckling and multiple *café-au-lait* spots currently allows a definitive diagnosis of NF1, these features are also seen in Legius syndrome.

the number of CAL spots has recently been shown to be a function of germline sequence variants of other genes involved in pigment biology.<sup>358</sup>

CAL spots may occur anywhere on the body. They may be present at birth but often first appear during the first few months. They continue to increase in size and number during the first decade, especially the first 2 years of life. CAL spots in NF1 tend to have a greater melanocyte density and increased fibroblast secretion of stem-cell factor than CAL spots without associated NF1.<sup>359</sup> Large CAL spots may be a sign of an underlying plexiform neurofibroma.

Another form of pigmentation, termed *axillary freckling* (Crowe sign), also serves as a valuable diagnostic aid in the early recognition of NF (Fig. 11-45).<sup>360</sup> Axillary freckling appears as multiple 1- to 4-mm CAL spots in the axillary vault. These most commonly appear between 3 and 5 years of age. Lack of sun exposure in this area prevents confusion with true freckles. These freckles are also commonly seen in the inguinal region and may be more generalized. Overall almost 90% of affected children have intertriginous freckling by 7 years of age.

Multiple CAL spots and axillary and/or inguinal freckling are features of Legius syndrome (sometimes called NF type 1-like syndrome), which results from mutations in *SPRED1*. *SPRED1* interacts directly with Ras and is involved in its function. Although the clinical features during childhood generally do not allow Legius syndrome to be distinguished from NF1, distinction is important prognostically, because Legius syndrome has been associated with macrocephaly and learning disabilities but not with the cutaneous or plexiform neurofibromas, NF1 osseous lesions, or symptomatic optic-pathway gliomas.<sup>361</sup> Almost 2% of individuals with a previous diagnosis of NF1 are now thought to have Legius syndrome. Although CAL spots and freckling have been distinct criteria that, if both present, allow the definitive diagnosis of NF1, the discovery that Legius syndrome presents with these two criteria has led to the suggestion that multiple CAL spots and freckling be combined into a single criterion for diagnosis.<sup>362</sup>

NF1 is also characterized by dermal or subcutaneous neurofibromas that represent tumors primarily comprised of Schwann cells, mast cells, and fibroblasts. The Schwann cell has been shown to be the cell of origin, in which loss of the normal neurofibromin allele leads to uncontrolled growth in the setting of NF1 (loss of heterozygosity).<sup>363,364</sup> The dermal and subcutaneous neurofibromas usually occur in late childhood or adolescence; thus they are generally not found in affected children. Their appearance is commonly associated with puberty and pregnancy, and they have been noted in 84% of affected



**Figure 11-46** Neurofibromatosis type 1. Dermal and subcutaneous neurofibromas are rarely found before adolescence. These tumors, which originate from Schwann cells, increase in number progressively thereafter.

adults.<sup>365</sup> They are soft in consistency, may range in size from a millimeter to several centimeters in diameter, and often have an overlying violaceous, pink, or blue hue (Fig. 11-46). They may be sessile or pedunculated. With pressure from a finger, dermal neurofibromas may be invaginated, a sign called *buttonholing*. “Pseudoatrophic macules” and “red-blue macules” are unusual variants of dermal neurofibromas that show replacement of dermal collagen with neural tissue and thick-walled blood vessels in the superficial dermis overlying the neurofibroma, respectively. By adulthood, dermal neurofibromas may number from a few to hundreds, with a progressive increase in size and number as the patient becomes older. Neurofibromas may occur anywhere on the body with no specific site of predilection. Not uncommonly, patients complain of itchiness at the site of a dermal neurofibroma, perhaps related to the presence of mast cells.

Plexiform neurofibromas may be superficial or deep and occur in approximately 25% of children.<sup>366,367</sup> They often are oriented along the length of a nerve and involve several fascicles. They may be barely palpable, may be quite firm, or may become huge with a “bag of worms” consistency. Plexiform neurofibromas not uncommonly are present at birth and have a predilection to involve the extremities. Commonly, a large CAL spot, often with irregular borders, overlies the plexiform neurofibroma (Fig. 11-47); hypertrichosis maybe associated as well (Fig. 11-48). Underlying soft-tissue and bone hypertrophy (Fig. 11-49) or bone erosion may be seen. Plexiform neurofibromas may at times cause pain, muscle weakness, atrophy, or slight sensory loss. Given the hyperpigmentation and associated hypertrichosis, a plexiform neurofibroma may be confused with a congenital nevus, Becker nevus, or smooth muscle hamartoma. Orbital plexiform neurofibromas present with eyelid swelling and ptosis,<sup>368</sup> leading to amblyopia in 62% of affected children.<sup>369</sup> Isolated plexiform neurofibromas have been described in patients without NF1, although the possibility of mosaicism should be considered (Fig. 11-50).

Although a benign course for neurofibromas is usual, malignant peripheral nerve sheath tumors (MPNSTs) occur in 8% to 13% of affected individuals, peak in their occurrence during the second and third decades of life, and are the primary cause of early mortality. MPNSTs have been attributed to the occurrence of a second mutation within tumor cells, commonly a p53 mutation.<sup>370</sup> Malignant degeneration may be heralded by rapid enlargement, pain, change in texture, and neurologic deficit. Positron emission tomography (PET)-CT imaging of MPNSTs can distinguish benign neurofibromas from MPNSTs.

Two other skin changes in NF1 are juvenile xanthogranulomas (JXGs) and nevus anemicus. JXGs are discussed in Chapter 10, and these yellow dome-shaped papules (Fig. 11-51) are found overall in up to 37% of affected children with a mean age of onset of 24 months of age.<sup>366,371,372</sup> Most children have more than one JXG (mean  $\approx$ 3), and 90% clear by a mean age of 47 months. Nevus anemicus tends to be

**A****B**

**Figure 11-47** Neurofibromatosis type 1. **(A)** Plexiform neurofibromas are commonly present at birth and can resemble giant café-au-lait spots, although borders are often more irregular. **(B)** With advancing age, plexiform neurofibromas may enlarge and become more elevated with a firm or “bag of worms” consistency. **(A)** shows a plexiform neurofibroma in a 3-year-old boy, and **(B)** shows the same plexiform neurofibroma when the child is 11 years of age. This boy passed away as a teenager from a malignant peripheral nerve sheath tumor at a different site.

present at birth or infancy and has been described in 9% of children with NF<sup>373</sup> and 35% of those under 2 years of age.<sup>372</sup> These skin signs may add to the suspicion of NF1 in an infant (*nevus anemicus*) or young child (JXG) with only CAL spots and may become new criteria.

**Systemic Manifestations of Neurofibromatosis.** Other than the CAL spots, learning disability is the most common manifestation of NF1 in children.<sup>374,375</sup> Learning disability, which occurs in 30% to 70% of affected children, includes nonverbal and verbal disability as well as attention-deficit/hyperactivity disorder, which can lead to the poor development of social skills.<sup>376</sup> Diagnostic criteria for autism spectrum disorders have been found in 30% of children with NF1.<sup>377</sup> Another common sign is the occurrence of enhanced intensity of T2 signals in brain MRI examinations in the basal ganglia, brainstem, internal capsule, and cerebellum (unidentified bright objects) (43% to 93%).<sup>378</sup>



**Figure 11-48** Neurofibromatosis type 1. This plexiform neurofibroma is hypertrichotic and was misdiagnosed as a congenital nevus.



**Figure 11-49** Neurofibromatosis type 1. This plexiform neurofibroma of the tongue led to discomfort and difficulty with both speech and mastication. Note the cheek and neck involvement.

The ocular manifestations of NF1 include plexiform neurofibromas, Lisch nodules, optic gliomas, and the recently recognized choroidal nodules. Lisch nodules are asymptomatic yellowish-brown melanocytic hamartomas on the iris that cause no problem with vision. These Lisch nodules are found in more than 90% of affected adults but in only 43% of children under 12 years of age. They are best detected by slit-lamp examination, although larger ones may be seen without magnification as beige spots on a dark iris or darker spots on a light iris. Their presence virtually ensures the diagnosis of NF1, but their absence does not discount the diagnosis. Choroidal nodules are detectable in 71% to 79% of children with NF1 by near-infrared reflectance,<sup>379,380</sup> suggesting that they may be a better criterion for diagnosis in young children.<sup>381</sup> Optic gliomas occur in approximately 15% of children with NF1 and are more indolent than optic gliomas in



**Figure 11-50** Plexiform neurofibroma without neurofibromatosis type 1 (NF1). Occasionally typical plexiform neurofibromas occur in individuals without evidence of NF1; mosaicism should be considered.



**Figure 11-52** Neurofibromatosis type 1. Precocious puberty in a 5-year-old boy with an optic chiasm/hypothalamic glioma.



**Figure 11-53** Neurofibromatosis type 1. Bilateral tibial bowing without evidence of pseudoarthrosis in an affected infant.



**Figure 11-51** Juvenile xanthogranuloma (JXG) in neurofibromatosis type 1 (NF1). JXGs are seen in up to 37% of affected children, are usually multiple (mean of three per patient), occur with a mean age of onset of 24 months of age, and tend to clear about 2 years later. Some have suggested that having both JXGs and café-au-lait spots should allow a definitive diagnosis of NF1.

individuals without NF1. Precocious puberty has been described in up to 40% of patients with gliomas of the posterior chiasm and hypothalamic areas (Fig. 11-52).<sup>382</sup> Overall, only 33% of patients with optic gliomas develop symptoms or signs such as decreased visual acuity or visual-field defects, proptosis, strabismus, and/or optic-nerve pallor. A total of 35% of those with symptomatic optic gliomas eventually require treatment, specifically for their progressive loss of vision, gross disfigurement (e.g., from proptosis), or poor weight gain with diencephalic syndrome. Chemotherapy with carboplatin and vincristine is the treatment of choice. Surgical resection is used for cosmetic palliation, and radiation therapy is avoided because of the risk of second malignancy treatment.<sup>383,384</sup> Progression in optic gliomas usually occurs by 6 to 7 years of age, suggesting that annual eye examinations can thereafter be spaced to every 2 years until adulthood. Although

routine baseline MRIs are not necessary, imaging should be performed if abnormalities are found on ophthalmologic evaluation or in the face of signs of a problematic optic glioma.<sup>384</sup> Spontaneous regression of optic gliomas may occur.<sup>385</sup>

Brain tumors may lead to neurologic abnormalities. Other than optic pathway gliomas, brainstem gliomas (pilocytic astrocytomas) are the most common intracranial neoplasms<sup>386</sup> but usually behave less aggressively than histologically identical tumors patients who do not have NF1. Owing to the indolent nature of these tumors, conservative management with close follow-up monitoring is recommended. A total of 23% of meningiomas have been noted in individuals with NF1.<sup>387</sup> More severe developmental delay occurs in only 5% of patients and has been associated with total deletion of the neurofibromin gene<sup>388</sup>; these patients also have facial dysmorphisms and large numbers of neurofibromas.

Skeletal manifestations are most commonly bone dysplasias, pectus deformity, and scoliosis. Even without osseous abnormalities, children and adolescents with NF1 have decreased bone mineral density.<sup>389</sup> Although not among the diagnostic criteria, spinal deformities, particularly scoliosis or kyphosis, may occur in at least 10% of patients, and pectus deformities occur in approximately 24% of patients.<sup>390,391</sup> The dystrophic form of scoliosis almost always develops before 10 years of age and then progresses, usually involving the lower cervical and upper thoracic spine, and is associated with dysplastic changes of the vertebral bodies. Tibial dysplasia (congenital bowing), pathognomonic for NF1, presents as anteromedial bowing of the tibia (Fig. 11-53), usually during the first year of life and has been described in about 1% to 4% of affected children. The cortex of the bone is thinned,

and the medulla is sclerotic.<sup>392</sup> Fractures may occur at the site, leading to pseudoarthrosis. Sphenoid wing dysplasia occurs in 3% to 7% of children with NF1 and may manifest as pulsating exophthalmos. Nonossifying fibromas have also been described in association with multiple CAL spots (Jaffe–Campanacci syndrome); this group of patients has a high risk of recurrent fractures and significant resultant deformity and disability.<sup>393</sup>

Other features of NF1 that may be seen during childhood are short stature (10%), frequent headaches (30% to 40%), macrocephaly (24%), and rarely hypertension (1%). Short stature most often occurs without evidence of neuroendocrine problems.<sup>394,395</sup> The macrocephaly is usually not associated with hydrocephalus, although aqueductal stenosis has rarely been reported. In children, hypertension usually relates to renal artery stenosis, a form of NF1 vasculopathy<sup>396</sup>; in adults with hypertension and NF1, pheochromocytoma should be suspected. Stenosis or occlusion of several other arteries may occur, leading to cerebral vascular accidents, aneurysms, and even sudden cardiac death.<sup>397,398</sup> Small telangiectatic vessels often form around the stenotic area of the cerebral arteries, leading to a “puff of smoke” (moyamoya) on cerebral angiography. Watson syndrome is an allelic variant of NF1 with associated pulmonic stenosis, and NF1-Noonan syndrome combines the features of Noonan syndrome (ocular hypertelorism, low-set ears, downslanting palpebral fissures, webbed neck, and pulmonic stenosis) with NF1, usually with mutations in neurofibromin but not *PTPN11*, the gene usually associated with Noonan syndrome.

NF1 is associated with a 5% lifetime risk of developing malignancy. In addition to the development of MPNSTs, nonlymphocytic leukemias, rhabdomyosarcoma, and lymphoma are described with increased incidence in affected children. Although JXGs have been described in association with juvenile chronic myelogenous leukemia, few patients with NF1 and JXGs have leukemia.<sup>399</sup>

**Therapy of Neurofibromatosis Type 1.** The current management for most children with NF1 is anticipatory guidance, genetic counseling, and surveillance for potential complications. If available, referral to a multidisciplinary clinic that specializes in seeing individuals with NF1 is optimal. Baseline screening tests, except for ophthalmologic examinations, are not recommended. Monitoring and early intervention for learning disabilities is important. Complete physical examinations should be performed at least twice yearly, including measurements of height, weight, head circumference, and blood pressure; careful palpation for tumors; and assessment for scoliosis or other bony deformities. Methylphenidate has been shown to be helpful for the attention-deficit issues in children with NF1.<sup>400</sup>

Dermal neurofibromas may be excised, but plexiform neurofibromas usually cannot be removed in their entirety.<sup>401</sup> Surgical debulking may be undertaken for tumors that are disfiguring, interfere with function, or are subject to irritation, trauma, or infection. Mitogen-activated protein kinase kinase (MEK) inhibition has been shown to decrease both neurofibroma and MPNST size and prolong survival in preclinical studies<sup>402</sup>; decreased tumor size was noted in all 11 children treated with selumetinib, a MEK1/2 inhibitor.<sup>403</sup> Mast cells appear to play a critical role in the initiation and progression of plexiform neurofibromas, and imatinib has led to an at least 20% decrease in tumor size within 6 months in 26% of patients.<sup>404,405</sup> Treatment with sirolimus (mTOR inhibitor) improved pain associated with pediatric plexiform neurofibromas but caused no shrinkage.<sup>406</sup>

Genetic counseling is another important aspect of treatment, because there is a 50% chance of transmitting NF with each pregnancy. Mutations can be found by multistep mutation detection in more than 95% of individuals with NF1.<sup>345,407</sup> Mosaicism with postzygotic mutation in neurofibromin, however, is not uncommon.<sup>408,409</sup> Affected patients may show mosaic-generalized NF1, which is indistinguishable clinically from germ-line mutations with generalized manifestations or mosaic-localized NF1. Patients with mosaic-localized or “segmental NF1” show typical features of NF1 limited to a specific body segment. Although CAL spots are the most common manifestation of segmental NF1 in children, other cutaneous manifestations (freckling, dermal and plexiform neurofibromas) or noncutaneous manifestations (pseudoarthrosis, sphenoid wing dysplasia, optic glioma, Lisch nodules) in the localized area may also occur.<sup>410</sup>

Individuals with mosaic forms of NF1 who also have germ-line involvement (more common with mosaic-generalized NF1) may have offspring with full NF1 with an up to 50% probability with each pregnancy. A national support group, the National Neurofibromatosis Foundation ([www.nfnetwork.org](http://www.nfnetwork.org) and [www.ctf.org](http://www.ctf.org)), offers patient information and support.

## ERYTHEMA DYSCHROMICUM PERSTANS

Erythema dyschromicum perstans (ashy dermatosis) is an acquired chronic, progressive bluish to ash-gray hyperpigmentation that can affect individuals of both sexes from childhood through adulthood. Although more common in darker-skinned individuals, several light-skinned affected children have been described.<sup>411,412</sup> The cause of erythema dyschromicum perstans remains unknown. Lesions usually begin as slate-gray macules (Fig. 11-54) but occasionally show a transient, slightly raised erythematous border. Generally seen on the trunk and upper limbs, lesions may also occur on other areas, with the exception of the scalp, mucous membranes, palms, and soles. Lesions vary from a few millimeters to many centimeters in diameter and often cover extensive areas. Lesions are usually distinct but can be confluent. Multiple linear lesions of erythema dyschromicum perstans have been described that follow the lines of Blaschko,<sup>413</sup> and lesions may be unilateral.<sup>414</sup>

This disorder must be differentiated from the postinflammatory hyperpigmented lesions of tinea versicolor, pityriasis rosea, and fixed-drug eruption, which usually show brown rather than grayish pigmentation. Idiopathic eruptive macular pigmentation is differentiated by the development of brown (rather than grayish) nonconfluent macules of the trunk, neck, and proximal extremities; the absence of preceding inflammation; the lack of exposure to a medication; and basal cell hyperpigmentation without damage to the keratinocytes and without dermal mast cells in biopsy sections. Histologic features of erythema dyschromicum perstans depend on the stage of the lesion. Older lesions show pigment incontinence, but early lesions may show hydropic degeneration of epidermal cells and a lichenoid infiltrate of lymphocytes.



**Figure 11-54** Erythema dyschromicum perstans. Oval slate-gray macules, all oriented along the same axis, on the trunk of this otherwise healthy boy. In children with erythema dyschromicum perstans, the hyperpigmented macules often clear spontaneously after years.

The dermatosis is asymptomatic but chronic. There are frequent exacerbations with extension into previously uninvolved areas. There is no known effective therapy, but most cases in children clear spontaneously within a few years.<sup>411,415</sup>

### POSTINFLAMMATORY HYPERPIGMENTATION

Post-inflammatory hyperpigmentation is one of the most common causes of hyperpigmentation, and is characterized by an increase in melanin formation following cutaneous inflammation.<sup>416,417</sup> Ordinary post-inflammatory hyperpigmentation is of relatively short duration and tends to persist for several months after the original cause has subsided. Examples include the pigmentation following physical trauma, friction, primary irritants, eczematous eruptions, lichen simplex chronicus, acne vulgaris and dermatoses such as pityriasis rosea, psoriasis, fixed drug eruptions, photodermatitis, and pyoderma. Individuals with dark complexions and those who tan easily following UV light exposure show the greatest degree and longest persistence of this form of post-inflammatory hyperpigmentation. In cases in which the dermal–epidermal junction and basal layer become disrupted (lupus erythematosus, lichen planus, lichenoid drug eruptions) melanin incontinence occurs (Figs. 4-43 and 4-51). The melanin tends to drop from its normal epidermal position and passes into melanophages of the dermis, leading to more pronounced and persistent discoloration. If areas of postinflammatory hyperpigmentation can be protected from further UV light exposure, fading gradually occurs over a period of months to years. Most patients do not respond to topical agents or resurfacing procedures as well as patients with melasma (see below).<sup>418,419</sup> Topical anti-inflammatory medications are appropriate if inflammation is ongoing.

### Retention Hyperkeratosis

Because melanin is transferred to epidermal cells, thickened epidermis often appears hyperpigmented. Focal patches of hyperpigmentation and mild skin thickening are not uncommonly seen at fold areas (such as the ankle) and on the neck and represent retention hyperkeratosis (sometimes called *scurf*) (Fig. 11-55). These persistent patches can be removed easily by gently scrubbing with an alcohol pad.

### MELASMA

*Melasma* is a term applied to a patchy dark-brown to black hyperpigmentation located primarily on the cheeks, the forehead, and occasionally the temples, upper lip, and neck.<sup>417,420</sup> Seen in up to 20% of women, including adolescents, who take anovulatory drugs or who are pregnant, this disorder has been termed the *mask of pregnancy*. Typical melasma also can occur in males and in females who are



**Figure 11-55** Retention hyperkeratosis. Persistent focal patches of hyperpigmentation and mild skin thickening, especially on the neck and near joints represent retained scale and can be removed easily by gently scrubbing with an alcohol pad. Parents often erroneously consider this a sign of inadequate cleansing.

neither pregnant nor taking oral contraceptives. Occasionally it may also appear in patients of both sexes taking phenytoin (Dilantin) or its derivatives. Overall 10% of affected individuals are male. Once melasma has developed, it tends to persist for a long time, and treatment is generally not very satisfactory. Melasma of pregnancy usually clears within a few months after delivery only to recur with subsequent pregnancies. Oral contraceptive-induced melasma may persist for up to 5 years after discontinuation of the medication.

Because sun exposure tends to trigger and intensify this hyperpigmentation, the disorder characteristically becomes more prominent in the summer months.<sup>421</sup> Both UVA and visible light have been implicated, emphasizing the need for physical sunscreen use and use of sun-protective clothing. In addition, treatment of melasma consists of discontinuation of potentially responsible medications and the use of bleaching agents.<sup>418,419</sup> Topically applied hydroquinones have been the gold standard of treatment, but their safety has recently been questioned, leading to the search for alternatives. Hydroquinones inhibit tyrosinase and are most effective when compounded with tretinoin (0.05% to 0.1%) and mild topical steroids. Twice-daily application of azelaic acid 15% to 20% is less efficacious but causes less irritation.<sup>422</sup> Other topical agents that have been used are tranexamic acid (also used orally), kojic acid, plant extracts (such as licorice or orchid extracts, soy, arbutin, and silymarin), ascorbic acid, N-acetylglucosamine, and niacinamide.<sup>419</sup> Chemical peels (e.g., with tretinoin or trichloroacetic acid) and laser therapy, especially with Q-switched neodymium:yttrium-aluminum-garnet (Nd:YAG), may also be helpful. These preparations often require 3 to 4 months before a therapeutic effect is achieved. Concurrent sun protection is critical to prevent further hyperpigmentation in patients using hydroquinones. Because continuous use of hydroquinone bleaching creams or lotions can result in excessive pigmentary loss or ochronosis-like hyperpigmentation, once the desired degree of depigmentation is achieved, hydroquinone therapy should be discontinued.

### METABOLIC CAUSES OF HYPERPIGMENTATION

Cutaneous changes often are helpful in the diagnosis of several endocrine disorders, including Addison disease (see Figs. 23-6, and 23-7), hyperthyroidism (see Fig. 23-2), hypothyroidism, acromegaly, and Cushing syndrome (see Chapter 23). More than two-thirds of patients with chronic hepatic disease (cirrhosis or prolonged bile-duct obstruction) also have some degree of cutaneous hyperpigmentation. Of these, diffuse darkening of the skin is perhaps the most common. Blotchy areas of brown hyperpigmentation occasionally may be seen, and accentuation of normal freckling and areolar hyperpigmentation may appear. Progressive, diffuse blotchy hyperpigmentation in addition to hair lightening has been described with cobalamin (vitamin B<sub>12</sub>) deficiency from homozygous mutations in *ABCD4*, which encodes a transporter involved in processing cobalamin.<sup>423</sup> Polycystic kidney disease and other chronic renal disease may be accompanied by diffuse yellowish-brown skin discoloration, especially on the face and hands. Although urinary chromogens and carotenemia may be present, melanin pigmentation also has been implicated.

### Hemochromatosis

Hemochromatosis is a familial iron storage disorder characterized by cutaneous hyperpigmentation that usually manifests between 40 and 60 years of age. However, type 2 or the juvenile form of hemochromatosis presents during childhood. An autosomal recessive disorder, the two subtypes are caused by mutations in *HJV*, encoding hemojuvelin (HFE2A), or *HAMP*, encoding hepcidin (HFE2B).<sup>424,425</sup> Hemojuvelin and hepcidin are involved in iron metabolism. Hyperpigmentation is seen in almost every patient with hemochromatosis and in conjunction with abdominal pain, is often the presenting sign. The increased pigmentation is produced by melanin and not by the deposition of iron in the skin. It appears initially in the exposed areas before it becomes diffuse and is most intense in the skin of the face, arms, body folds, and genitalia. Mucous membranes (the gums, palate, and buccal mucosa) and sometimes the conjunctivae are involved in 15% to 20% of affected persons. The skin is soft, dry, thin, shiny, and of fine texture. Spider angiomas are present in 60% to 80% of affected individuals, and palmar erythema is common. Facial, axillary, thoracic, and pubic

hairs are scant or absent. Cardiomyopathy, evidence of hypogonadism, and reduced glucose tolerance are seen by young adulthood. The hepatic cirrhosis characteristic of adult-onset hemochromatosis, however, is less clinically relevant in type 2 hemochromatosis, and icterus is unusual.<sup>426</sup>

Secondary hemochromatosis (hemosiderosis) with associated hyperpigmentation may be seen in patients with anemia who receive numerous blood transfusions. In such instances visceral fibrosis is unusual, diabetes mellitus is uncommon, and hypogonadism is not present.

The diagnosis of metabolic hemochromatosis is suggested by the presence of cutaneous hyperpigmentation in patients with hepatic cirrhosis and a history of diabetes mellitus. Elevated levels of serum ferritin and transferrin saturation confirm the diagnosis.<sup>427</sup> The demonstration of parenchymal iron distribution by skin, liver, and gastric biopsies and the presence of hemosiderin in urinary sediment are helpful. Skin biopsies show increased melanin in the basal layer and deposition of iron in the upper cutis (especially in macrophages, endothelial cells of capillaries, and the propria of eccrine glands).

The clinical course of untreated hemochromatosis is characterized by tissue destruction, malfunction of involved organs, and eventual death. Symptomatic treatment of the diabetes, liver dysfunction, and cardiac symptoms and quarterly phlebotomies, when initiated early, commonly result in clinical and pathologic improvement. Dietary restriction of iron is impractical, and chelating agents to date have been of little value.

### Ochronosis

Alkaptonuria (ochronosis) is an inborn error of tyrosine metabolism in which homogentisic acid, an intermediate product in the metabolism of phenylalanine and tyrosine, accumulates in the tissues and is excreted in the urine because of a lack of homogentisic acid oxidase. This autosomal recessive disorder usually first becomes manifest in the third decade with scleral blue-black pigmentation (Osler sign). Affected children rarely show Osler sign, and the characteristic dark urine is usually not noted because the color change only occurs with sitting for 1 to 2 h, especially in an alkaline environment.<sup>428,429</sup> Dark urine in the diaper may be the first sign in infants. Skin pigmentation first becomes visible around the fourth decade of life, especially on ear cartilage, eyelids and other facial areas, intertriginous areas, and over tendons. Nails may be stained brown. Around this time, the ochronotic arthropathy from pigment deposition also starts to develop and involves the weight-bearing joints (spine, knees) most commonly. The mean age of joint replacement is 55 years, of development of renal stones 64 years, of cardiac valve involvement 54 years, and of coronary artery calcification 59 years. The diagnosis can be confirmed by alkalinizing the urine (e.g., with sodium hydroxide), which leads to the typical black color; the homogentisic acid is detected by enzymatic spectrophotometry or gas liquid chromatography. Treatment with ascorbic acid twice daily may reduce the connective tissue damage, and affected children have also been placed on a low-protein diet. Nitrofurantoin therapy may decrease homogentisic acid production.<sup>430</sup> Endogenous ochronosis has recently been improved by erbium-doped YAG laser resurfacing and deep focal point treatment to remove areas of residual deep pigment.<sup>431</sup>

Exogenous ochronosis is clinically and histologically similar to its endogenous counterpart but is not hereditary and has no internal manifestations. The condition usually occurs in African-American patients from exposure to hydroquinones and is characterized by asymptomatic hyperpigmentation of the face, neck, back, and extensor surfaces of the extremities. Less commonly, exogenous ochronosis has been described after exposure to antimalarials or products containing resorcinol, phenol, mercury, or picric acid.<sup>432</sup>

### HYPERPIGMENTATION CAUSED BY HEAVY METALS

The systemic absorption of chemicals can also cause discoloration of the skin. Although the incidence of hyperpigmentation owing to exogenous heavy metals has decreased in recent years, limited exposure to such preparations still occurs, and metallic hyperpigmentation may still be seen in children as well as adults.

Argyria occurs after long-term ingestion or excessive application of silver preparations and presents as localized or widespread bluish-gray or slate-colored discoloration of the skin produced by the deposition of silver within the dermis. The condition is more pronounced on exposed parts of the body—namely the face, forearms, and hands—but may also occur in the sclerae, oral mucous membranes, and lunulae of the nails. Argyria has been increasingly described because of the promotion of colloidal silver-based products for their immunostimulant, antimicrobial, and anti-inflammatory properties. The antimicrobial properties are proportional to the bioactive silver ion released and its availability to interact with bacterial or fungal cell membranes.<sup>433</sup> These “health food” products deliver primarily inactive metallic silver, not the antimicrobial ionized form. Colloidal silver and silver sulfadiazine cream, for example, have high levels of silver release with relatively low levels of ionized silver.<sup>434</sup> Ionized silver dressings have more recently been introduced for wound care<sup>433</sup>; they occasionally cause local dermal argyria<sup>435</sup> but show very low local silver levels. On the other hand, temporary superficial silver staining of the stratum corneum is a common side effect of these dressings. An adolescent girl with osteosarcoma who had limb salvage and placement of a silver-coated megaprosthesis developed intense blue-gray pigmentation along the surgical incision line 1 year after surgery from slow release of the silver.<sup>436</sup>

Cases with more extensive hyperpigmentation have been described after chronic ingestion of silver-containing water<sup>437</sup> or colloidal silver<sup>438</sup> or widespread topical application of silver sulfadiazine<sup>439,440</sup> or colloidal silver. Localized staining can be seen periorbitally and on the eyes from ophthalmic preparations containing silver at acupuncture sites<sup>441,442</sup> or after exposure to silver earrings<sup>443,444</sup> but most commonly is now reported at burn or wound sites after use of silver sulfadiazine or colloidal silver when used as antibacterial agents, for example, for patients with burns or epidermolysis bullosa.<sup>440,445</sup>

The diagnosis of argyria is based on clinical examination and history of exposure and may be confirmed by cutaneous biopsy of affected areas, which shows fine, small round refractive silver granules throughout the dermis, especially around eccrine glands. Increased amounts of melanin may be seen in the basal layer of the epidermis and also within macrophages in the upper dermis. Treatment of argyria depends on recognition of the disorder, discontinuation of the use of the silver-containing preparation, and avoidance of sunlight exposure. The dermal hyperpigmentation is usually irreversible.

Chrysiasis (gold-induced hyperpigmentation) is a rare cutaneous disorder induced by the administration of gold salts followed by exposure to UV light.<sup>446,447</sup> The pigmentation is bluish gray or purplish and is similar to that seen in argyria except that the hyperpigmentation is more prominent around the eyes, is limited to areas of sunlight exposure, and does not affect the sclerae and oral mucous membranes. Hyperpigmentation may develop after treatment with a Q-switched laser after systemic gold treatment.<sup>448</sup> Other cutaneous manifestations are seen in up to 20% of individuals on gold therapy, which is most commonly administered for rheumatoid arthritis. These include morbilliform, eczematous, urticarial, bullous, purpuric, lichen planus-like, and pityriasis rosea-like eruptions. The histopathologic features of gold-induced hyperpigmentation consist of small, black, round or oval, irregularly shaped gold particles located in a perivascular distribution and in dermal histiocytes.

Chronic exposure to mercury systemically may result in acrodynia (pink disease), a disorder of infants and young children characterized by leg cramps; headaches; hypertension; excessive perspiration; itching; swelling; redness and peeling of the hands, feet, and nose; weakness of the pectoral and pelvic girdles; and nerve dysfunction in the lower extremities. However, exposure to topically applied mercury may lead to slate-gray pigmentation in areas of topical application. The discoloration is exaggerated in the areas of skin folds and is permanent.<sup>449</sup>

### DRUG-INDUCED HYPERPIGMENTATION

Hyperpigmentation may be induced by chronic exposure to medication and tends to be worsened by sun exposure. The diagnosis of a drug eruption is based almost entirely on history and physical

examination. The main drugs implicated in causing skin pigmentation are nonsteroidal anti-inflammatory drugs, minocycline, antimalarials,<sup>450</sup> amiodarone, diltiazem,<sup>451</sup> cytotoxic drugs, heavy metals (see Hyperpigmentation Caused by Heavy Metals section), clofazimine, imipramine,<sup>452,453</sup> and chlorpromazine. Clinical features are variable according to the triggering molecule and have a large range of patterns and shades. Bluish-gray discoloration is most common and especially prominent at sites of exposure to UV light. The condition is most commonly seen in the pediatric population in adolescents who have been taking minocycline for acne, with the blue discoloration usually notable at sites of acne scarring and on the oral mucosae and shins (Fig. 11-56).<sup>454</sup> Three subgroups have been described based on clinical appearance and histopathologic correlates: type I (blue-gray pigmentation in scars); type II (blue-gray pigmentation in previously normal skin, especially of the shins); and type III (brown discoloration at sun-exposed sites).<sup>455</sup> Biopsy specimens tend to show pigmentation within dermal macrophages, often localized to vessels and adnexal structures. Treatment involves interruption of therapy and sun avoidance, although laser, particularly the alexandrite 755 nm laser, may be useful.<sup>456,457</sup> These measures are often followed by fading of lesions, but pigmentation may persist for a long time or even be permanent.<sup>458</sup>

The plaques of fixed drug eruptions are circumscribed, usually round or oval, often edematous and sometimes bullous, usually pruritic, and reddish-purple. Drug-induced hyperpigmentation tends to recur in the same location after the readministration of certain drugs, particularly sulfonamides, tetracyclines, acetaminophen, phenolphthalein, barbiturate derivatives, and antineoplastic agents such as cyclophosphamide. Histopathologic examination of lesions of the hyperpigmented phase of fixed drug eruptions reveals an increase in the amount of melanin in the basal layer of the epidermis and within macrophages of the upper dermis and is helpful in confirming the diagnosis.

### Carotenemia

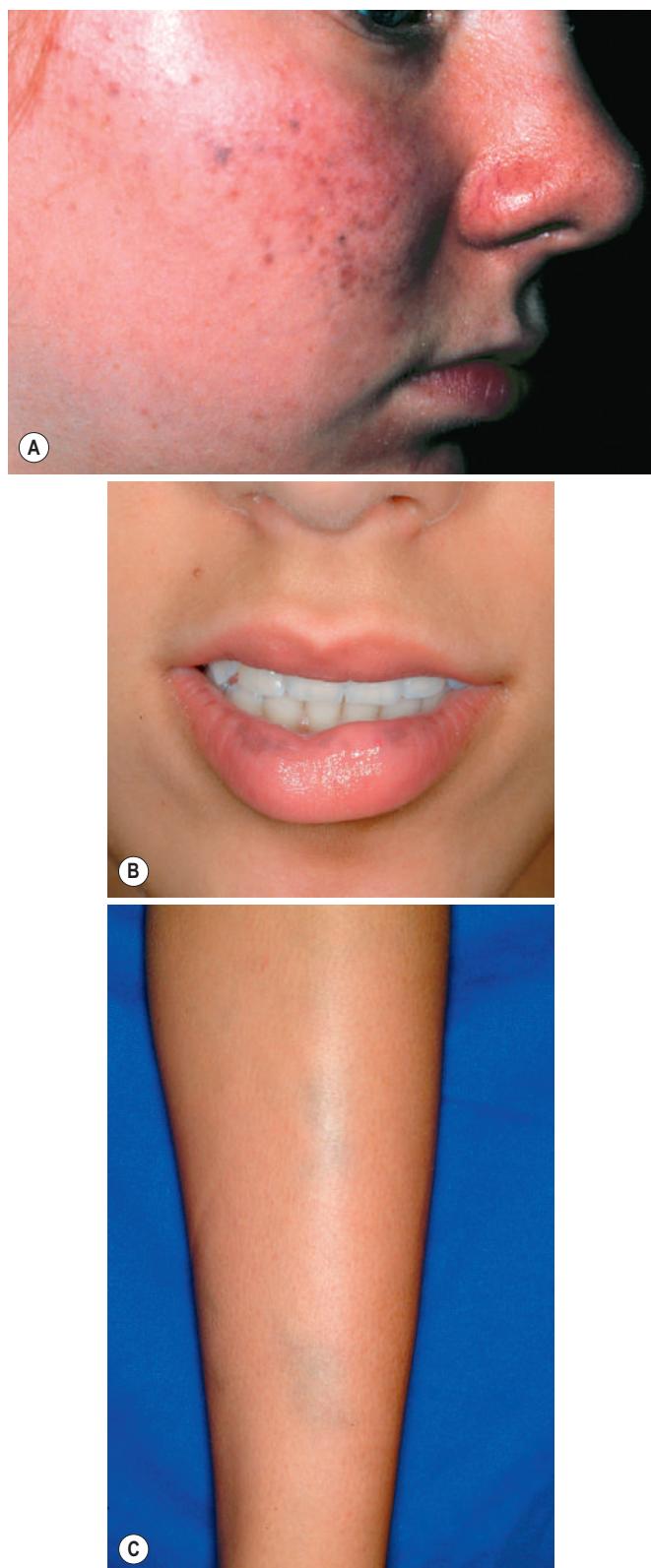
Carotenemia (sometimes called *carotenoderma*) is a yellowish-orange discoloration of skin caused by the ingestion of excessive quantities of carotene-containing foods, particularly carrots, squash, pumpkin, yellow turnips, sweet potatoes, peaches, apricots, papayas, mangos, egg yolk, and even green beans.<sup>459–461</sup> The condition is seen primarily in infants and occasionally in older children and adults.<sup>462</sup> The color is most prominent on the palms and soles, in the nasolabial grooves, on the forehead, chin, upper eyelids, postauricular areas, and anterior axillary folds, and over areas of pressure such as the elbows, knees, knuckles, and ankles (see Fig. 23-3). Lack of involvement of the sclerae and mucous membranes coupled with the absence of pruritus and lack of color change in the urine or stool helps rule out the presence of hepatic or biliary jaundice. Lycopene, a red-colored carotenoid pigment found in fruits and vegetables, especially ripened tomatoes, beets, chili beans, and various fruits and berries, may cause a reddish-yellow discoloration of the skin (lycopenemia).

Carotenemia is a benign disorder in infants, and no intervention is required. Rarely carotenemia may be a sign of systemic disease, especially hypothyroidism, weight-loss diets or anorexia, or diabetes. The diagnosis of carotenemia is confirmed by the presence of high carotene levels in the presence of normal serum bilirubin. If the coloration is problematic, reduction of dietary intake of carotene-containing foods to normal levels or correction of the underlying disorder usually results in gradual improvement within 4 to 6 weeks. Rarely children will show a genetic defect in the metabolism of carotenoids that is more recalcitrant to dietary intervention.<sup>463,464</sup>

### DERMAL MELANOCYTOSES

#### Mongolian Spots

Mongolian spots are flat, deep brown to slate gray or blue-black, often poorly circumscribed, large macular lesions generally located over the lumbosacral areas, buttocks (Fig. 11-57), and occasionally the lower limbs, back, flanks, and shoulders of normal infants. They are seen in 75% to 90% of individuals of African descent and Native-American babies; 62% to 86% of Asians<sup>465–468</sup>; 70% of the Hispanic population,



**Figure 11-56** Drug-induced hyperpigmentation. Bluish-gray discoloration on the cheeks at sites of acne scarring (**A**) on the oral mucosae (**B**) and on the shin (**C**) of adolescents administered minocycline for acne.



**Figure 11-57** Mongolian spots. Large blue-gray patches over the lumbosacral area and buttocks of an African-American baby. These spots often fade or clear within the first few years of life.

and 10% of Caucasian infants. Mongolian spots are present at birth, tend to fade during the first 2 to 3 years of life, and only occasionally persist into adulthood. Extrasacral location, multiple Mongolian spots, large size ( $>10$  cm in diameter), and darker color are associated with persistence beyond 1 year.

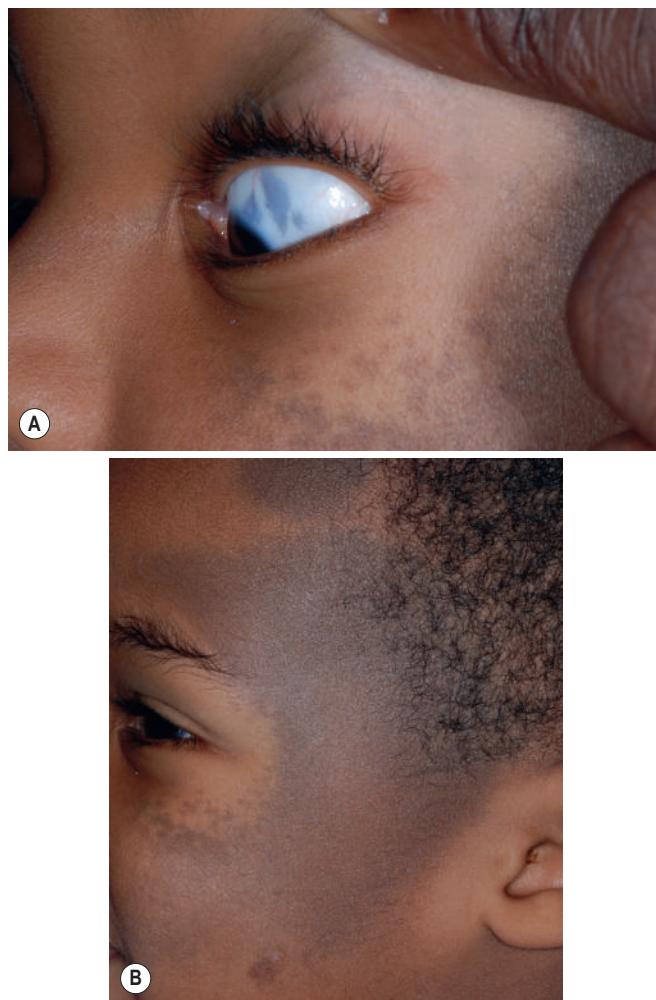
Mongolian spots may be single ( $\approx 50\%$  of babies) or multiple and vary from a few millimeters to 10 cm or more in diameter. They represent collections of spindle-shaped melanocytes located deep in the dermis, probably as the result of arrest during their embryonal migration from the neural crest to the epidermis. The slate blue to blue-black color depends on the Tyndall effect (a phenomenon in which light passing through a turbid medium such as the skin is scattered as it strikes particles of melanin). Long-wavelength light rays (red, orange, and yellow) tend to be less scattered and therefore continue to pass downward into the lower levels of the skin; colors of shorter wavelengths (blue, indigo, and violet) are scattered to the side and backward to the skin surface, thus creating the blue-black or slate-gray discoloredation.

Because Mongolian spots are benign, therapy is unnecessary. However, large and numerous Mongolian spots may be seen in lysosomal storage disorders, among them GM1 gangliosidosis type 1, Hunter syndrome, and Hurler syndrome.<sup>469-473</sup> In these children, the Mongolian spots often fade but not until at least the second decade of life.<sup>473</sup> Large and extensive Mongolian spots can be seen with phakomatoses pigmentovascularis and phakomatosis pigmentopigmentalis, on association with vascular malformations, and other pigmented lesions, respectively.<sup>474</sup>

### Nevus of Ota and Nevus of Ito

The nevus of Ota (nevus fuscoceruleus ophthalmomaxillaris) represents a usually unilateral, irregularly patchy, blue to bluish-gray to brown discoloredation of the skin of the face supplied by the first and second divisions of the trigeminal nerve.<sup>475,476</sup> It typically involves the periorbital region, the temple, the forehead, the malar area, and the nose (Fig. 11-58). About two-thirds of patients with this disorder have a patchy bluish discoloredation of the sclera of the ipsilateral eye (see Fig. 11-58) and occasionally, the conjunctiva, cornea, and retina. Palatal involvement has been described in up to 18% of affected individuals.<sup>477</sup> In about 5% of cases the nevus of Ota is bilateral rather than unilateral, and in rare instances the lips, pharynx, and nasal mucosa are similarly affected.

Although most commonly seen in Asians, nevus of Ota is not uncommonly seen in persons of African descent. Unlike Mongolian spots, which tend to disappear with time, the cutaneous coloration of nevus of Ota generally persists and often shows a speckled rather than a uniform discoloredation. Approximately 50% of lesions are congenital; the remainder usually appear during the second decade of life. Scleral



**Figure 11-58** Nevus of Ota. Unilateral, irregularly patchy, brownish-gray discoloredation of the sclera (A) and periorbital region (B) in an African-American boy.

melanocytosis alone is a much more common finding, which can progress and then recede with advancing age. In a study of Chinese children, only 4% to 5% were found to have scleral melanocytosis during the first year of life, but that number increased to 45% by 6 years of age with 78% of cases bilateral<sup>478</sup>; only 12% of the children continued to show evidence of scleral melanocytosis by 18 years of age.

The nevus of Ito (nevus fuscoceruleus acromiodeltoideus) has the same features as the nevus of Ota except that the pigmentary changes tend to involve the shoulder (Fig. 11-59), supraclavicular areas, sides of the neck, and upper arm, scapulae, and deltoid regions. It may occur alone or may be seen in conjunction with the nevus of Ota.

Similar to Mongolian spots, biopsy sections of the nevus of Ota and nevus of Ito show elongated dendritic melanocytes scattered among the collagen bundles. The melanocytes, however, often appear to be situated somewhat higher in the dermis than those seen in ordinary Mongolian spots.

Although these lesions do not disappear spontaneously, changes in color may occur. Darkening of lesions has been noted during and after puberty. These disorders are generally benign. However, glaucoma has been described in 10%<sup>479</sup> and melanoma, most commonly of the eye (choroid, orbit, iris, ciliary body, and/or optic nerve), but also of the skin, brain and meninges, has rarely been reported.<sup>479-483</sup> Long-term dermatologic and ophthalmologic follow-up monitoring is needed.

Laser therapy may improve the appearance of nevus of Ota, especially the Q-switched alexandrite laser and fractionated Nd:YAG.<sup>484,485</sup>



**Figure 11-59** Nevus of Ito. Blue patch on the shoulder.



**Figure 11-60** Blue nevus. Acquired navy blue papule on a girl's nose.

Multiple sessions are required, but resultant scarring is rare. One complication in individuals with darker skin types is postinflammatory hypopigmentation; vigorous sun protection is imperative, and pre-treatment with hydroquinone is sometimes used. Involvement on the zygomatic arch or frontal forehead regions responds better than peri-orbital pigmentation.<sup>486–488</sup> Cosmetic cover-up may also be used.

Nevus of Ota and nevus of Ito may be seen in association with vascular malformations (nevus flammeus or cutis marmorata telangiectatica congenita most commonly) in a disorder called *phakomatosis pigmentovascularis* (see Chapter 12).<sup>489</sup> The condition may be associated with Sturge–Weber syndrome or Klippel–Trénaunay syndrome when the nevus flammeus is on the forehead or limbs, respectively. Occasionally, a nevus spilus is seen in association as well.<sup>490</sup> Sturge–Weber syndrome has been shown to result from somatic mutations in *GNAQ*<sup>491</sup> and Klippel–Trénaunay syndrome in *PI3KCA* (phosphoinositide-3-kinase, catalytic, alpha), suggesting that these mutations, when occurring in melanocytes, may cause nevus of Ota or nevus of Ito.<sup>491,492</sup>

## BLUE NEVI

Blue nevi are a heterogeneous group of congenital and more often acquired melanocytic tumors.<sup>493</sup> Most often seen are common blue nevi and cellular blue nevi, although there may be histologic overlap between these types.<sup>494</sup> The nevi appear blue-gray clinically because of the deep (dermal) location of the melanin pigment and the Tyndall effect (selective absorption of longer wavelength components of light by melanin with reflection of the shorter blue components). Blue nevi are thought to result from the arrested embryonal migration of melanocytes bound for the dermal–epidermal junction. It is thus possible that the blue nevi, Mongolian spots, and the nevi of Ota and Ito are closely related and possibly represent different stages of the same physiologic process.

The common blue nevus (also called the *classic* or *dendritic blue nevus*) presents as a small, round or oval, dark blue or bluish-black, smooth-surfaced, sharply circumscribed, slightly elevated dome-shaped papule, nodule, or plaque (Fig. 11-60). Most common blue nevi range from 2 or 3 mm to 10 mm (<1 cm) in diameter. Although usually single, they may be multiple. Lesions may be present at birth but may appear at any age. Although common blue nevi may occur on any part of the body, areas of predilection include the buttocks, dorsal aspect of the hands and feet, scalp, and the extensor surfaces of the forearms. They also may occur on the face, bulbar conjunctiva, mucous membranes, and the hard and soft palates.

Once a common blue nevus appears, it usually remains static and persists throughout life. Although fading of color and some degree of flattening may occur with time, malignant degeneration of this form of blue nevus is rare. When a diagnosis of malignant melanoma is

considered, the common blue nevus can be differentiated from it by the presence of normal skin markings over the lesion, in contrast to the loss of such markings in lesions of malignant melanoma, the homogeneity of coloration and the smooth borders on routine examination, and the presence of a bluish-gray homogeneous lesion by dermoscopic evaluation.<sup>495</sup>

Cellular blue nevi tend to be larger and generally measure more than 1 cm in diameter. They are usually located on the scalp, buttocks, sacrococcygeal areas, and occasionally the dorsal aspect of the hands and feet. The plaque-type variant of blue nevus is a subset that is present at birth or develops during early childhood, occurs most commonly on the scalp, and may enlarge during puberty. The cellular blue nevus carries a higher risk of malignant transformation than the common blue nevus, but malignant transformation is still rare. Malignant blue nevi are locally aggressive but spread to regional lymph nodes in about 5% of individuals.

The classification of other forms of blue nevi is controversial.<sup>496</sup> Blue nevi may be hypochromic (sclerotic, hypomelanotic, and amelanotic forms), eruptive (particularly after sunburn on the upper central chest, shoulders, and “V” of the neck), or targetoid (preferentially on the back of the hands or feet, leading to a misdiagnosis of melanoma). Many show clinical and histologic features of more than one form, particularly combinations of variants of blue nevi with common and/or Spitz nevi (see Chapter 9). The deep penetrating nevus (usually has its onset after the first decade of life), epithelioid blue nevus (most commonly seen in individuals with Carney complex), and pigmented epithelioid melanocytoma show features of both blue nevi (intradermal location, pigmentation) and Spitz nevi (epithelioid morphology).<sup>497</sup> Molecular studies are likely to refine classification. *GNAQ* is mutated in about 83% of blue nevi.<sup>492</sup> However, deep penetrating nevi show *HRAS* mutations as seen in Spitz nevi rather than *GNAQ* or *GNA11* mutations,<sup>498</sup> suggesting reclassification of deep penetrating nevi with Spitz nevi.

Benign-appearing blue nevi do not require excision. If the diagnosis is in question, biopsy can be performed. Histopathologic examination of common blue nevi reveals greatly elongated spindle-shaped melanocytes, mainly in the middle and lower thirds of the dermis, which results in the blue coloration. In addition to spindle-shaped melanocytes, cellular blue nevi also have nodular islands of melanocytes.

The complete list of 498 references for this chapter is available online at <http://expertconsult.inkling.com>.



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## Classification of Vascular Lesions

Vascular birthmarks, or congenital vascular anomalies, are common lesions that may present in a variety of fashions. There has traditionally been a significant amount of confusion regarding the nomenclature of these lesions, and the term *hemangioma* has been widely used in the medical literature in reference to a variety of different vascular anomalies.<sup>1,2</sup> In 1982, Mulliken and Glowacki proposed a classification system for vascular birthmarks based on clinical and cellular features.<sup>3</sup> This classification was further refined 6 years later in a book,<sup>4</sup> and in 1996 it was adopted as the official classification system for vascular anomalies by the International Society for the Study of Vascular Anomalies (ISSVA). This nomenclature revolutionized the classification of vascular lesions, and is the basis for continued study into the causes of these lesions and their therapy.

According to this classification system (Box 12-1), vascular birthmarks are divided into the categories of tumors and malformations. Vascular tumors are neoplasms of the vasculature. This category includes hemangioma of infancy (the most common vascular tumor), kaposiform hemangioendothelioma (KHE), tufted angioma, and pyogenic granuloma (PG). Vascular malformations represent anomalous blood vessels without any endothelial proliferation or cellular turnover. In distinction to infantile hemangioma (IH), these lesions tend to be present immediately at birth and persist for a lifetime. Vascular malformations are further classified according to their predominant components, i.e., capillary malformation (port wine stain [PWS], salmon patch), venous malformation (VM), lymphatic malformation (LM), and arteriovenous malformation (AVM). Figure 12-1 pictorially demonstrates the different natural histories of IHs and vascular malformations.

This chapter includes discussion of vascular tumors and tumor syndromes, vascular malformations and malformation syndromes, disorders associated with vascular dilation, and a few miscellaneous disorders of the cutaneous vasculature.

## Vascular Tumors and Tumor Syndromes

### INFANTILE HEMANGIOMA

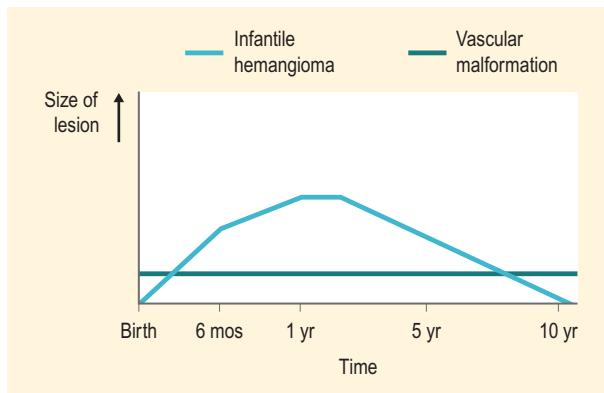
IH, or hemangioma of infancy, is the most common benign soft-tissue tumor of childhood. Although estimates vary, it occurs in around 2% to 12% of infants.<sup>5-9</sup> Female infants are three times more likely to have IHs than male infants, and the incidence is increased in premature neonates. Although they occur in all races, IHs appear to be less common in those of African or Asian descent.<sup>10</sup> Multiple gestation pregnancy, advanced maternal age, placenta previa and preeclampsia also appear to be risk factors for IH.<sup>11</sup> Although they are traditionally considered to be sporadic lesions, autosomal dominant segregation within families has been described.<sup>12</sup> These lesions vary considerably in their appearance and significance, related to their size, depth, location, growth pattern, and stage of evolution. Older descriptive terms for IH include *strawberry*, *cavernous*, and *capillary hemangiomas*. These terms are no longer useful and should not be used in the era of more specific vascular lesion nomenclature, as discussed earlier and shown in Box 12-1. Although IHs may occur on any part of the body, they most commonly involve the head and neck regions. Facial hemangiomas have been noted to have a nonrandom distribution, with the majority of lesions occurring on the central face at sites of development fusion.<sup>13</sup> Four primary segments of facial IH distribution have been identified, as shown in Table 12-1.<sup>14</sup>

The pathogenesis of IH is not yet completely understood. Positive endothelial-cell staining with erythrocyte-type glucose transporter (GLUT)-1 protein has been noted in lesions during all of the growth phases.<sup>15</sup> It is absent in other vascular lesions such as vascular malformations and hemangioendotheliomas. This protein is normally expressed in the microvascular endothelia of blood–tissue barriers such as the brain, retina, placenta, and endoneurium.<sup>16</sup> As such it has been suggested that IH may originate from invading angioblasts that have differentiated toward a placental cell type or from embolized placental cells, although some data refute a placental trophoblastic origin for these lesions.<sup>16</sup> Further evidence of a potential relationship between human placenta and IH includes the high level of transcriptome similarity between these tissues<sup>17</sup> and the higher incidence of pathologic placental findings observed from pregnancies resulting in a child with IH compared with those resulting in healthy infants without IH.<sup>18</sup> Other endothelial-cell markers shared between IH and placental tissue include Lewis Y antigen, FcγRII, and merosin. Recently, the Wilms tumor 1 (WT1) gene was found to also stain proliferative vascular tumors, including IH.<sup>19,20</sup> Aside from the placental embolization theory of pathogenesis, other hypothesized etiologies for IH development include a somatic mutation in a gene-mediating endothelial-cell proliferation or hypoxia-induced stimulation of endothelial progenitor cells.<sup>21</sup>

Hemangiomas may occur as superficial, deep, or mixed lesions representing their soft-tissue depth. The clinical appearance of the lesion depends on the type of hemangioma present. Superficial IHs, when well formed, present as bright red to scarlet, dome-shaped to plaque-like to lobulated papules, plaques, and nodules (Figs. 12-2 through 12-6). They may partially blanch with pressure and are rubbery or noncompressible on palpation. Deep IHs usually present as subcutaneous, partially compressible nodules and tumors, often with an overlying blue hue, prominent venous network, or telangiectasias (Figs. 12-7 through 12-9). These lesions may be warm to palpation. Combined IHs have both a superficial component and a deep component and occur in up to 25% to 30% of patients.<sup>22</sup> They present with both the superficial, bright red component and a deeper, blue nodular component (Figs. 12-10 and 12-11). Hemangiomas may also be divided into subtypes based on their anatomic configuration. Focal lesions are discrete, usually round lesions that appear to arise from a single focal point. Segmental lesions (see below) involve a more broad anatomic unit that may be determined by embryonic placodes. Indeterminate lesions are difficult to classify into one of the preceding two subtypes.

Hemangiomas may present with a variety of precursor lesions, and in up to 50% of affected infants these premonitory marks may be evident at birth.<sup>10</sup> They include areas of telangiectasias (Fig. 12-12), pallor, ecchymotic macules (Fig. 12-13), and even ulceration (Figs. 12-14 and 12-15).<sup>23</sup> Fully formed IHs may occasionally present at birth and are termed *congenital hemangiomas*. These lesions are discussed in more detail later.

The natural history of IH is characteristic. It is notable for a period of growth (the proliferative phase), a period of stability (the plateau phase), and a period of spontaneous regression (the involutorial phase). The majority of IHs first become evident at 2 to 3 weeks of life, with potential continued growth until around 9 to 12 months of age. The majority of growth, however, occurs during the first 5 months of age, and in those that continue to grow beyond this age, the growth rate is markedly slower.<sup>24</sup> Occasional lesions have a proliferative phase that lasts for longer than 1 year, sometimes as long as 18 to 24 months. Deep IHs tend to exhibit both a delayed onset of growth as



**Figure 12-1** Natural history of infantile hemangioma and vascular malformation.

#### Box 12-1 Contemporary Classification of Vascular Birthmarks

##### Vascular tumors

Hemangioma of infancy

Tufted angioma

Kaposiform hemangioendothelioma

Pyogenic granuloma

Hemangiopericytoma

##### Vascular malformations

Capillary (CM) (i.e., port wine stain, salmon patch)

Venous (VM)

Lymphatic (LM)

Arterial (AM)

Arteriovenous (AVM)

Complex/combined (i.e., capillary-lymphatic-venous or capillary-venous)



**Figure 12-2** Hemangioma, superficial: forehead.



**Figure 12-3** Hemangioma, superficial: trunk.

**Table 12-1** Distribution Patterns of Facial Infantile Hemangiomas

Segment Number/ Name	Distribution	Comment
1 Frontotemporal segment	Lateral forehead Anterior temporal scalp Lateral frontal scalp Upper eyelid	Potentially greater risk of associated brain anomalies when PHACES syndrome present
2 Maxillary segment	Lateral cheek Upper lip Spares philtrum, preauricular area	
3 Mandibular segment	Preauricular area Mandible Chin Lower lip	Potentially greater risk of cardiac defects when PHACES syndrome present
4 Frontonasal segment	Medial frontal scalp/forehead Nasal bridge Nasal tip/ala Philtrum	

Modified from Haggstrom AN, Lammer EJ, Schneider RA, et al. Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. *Pediatrics* 2006;117(3):698–703.

PHACES, posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, eye anomalies, and sternal defects.



**Figure 12-4** Hemangioma, superficial. Note the patchy nature of this lesion, which eventually became confluent.



**Figure 12-5** Hemangioma, superficial: leg.



**Figure 12-6** Hemangioma, superficial. Note the early ulceration of the lateral inferior portion.



**Figure 12-7** Hemangioma, deep. Note the subtle blue hue and surface telangiectasias.



**Figure 12-8** Hemangioma, deep. This larger lesion shows the characteristic deep-blue hue and surface telangiectasia.



**Figure 12-9** Hemangioma, deep. This small, deep lesion resulted in mechanical ptosis, necessitating therapy out of concern for light-deprivation amblyopia. Note the overlying surface telangiectasias.



**Figure 12-10** Combined hemangioma. Note the larger, deep component and the bright red, superficial component of this combined lesion.



**Figure 12-11** Combined hemangioma. This lesion is predominantly deep, with studding of the surface with small, superficial components.



**Figure 12-14** Hemangioma precursor, ulceration. This 2-day-old newborn had this perianal ulceration; at 3 weeks of age, the ulceration was healing and the lesion had the classic appearance of a superficial hemangioma.



**Figure 12-12** Hemangioma precursor, telangiectasias. This lesion might initially be diagnosed as a port wine stain; within 4 weeks it was thickening, with eventual ulceration of the lip.



**Figure 12-15** Hemangioma precursor, ulceration. This perianal lesion presented at 1 week of age as a vascular plaque with ulceration.



**Figure 12-13** Hemangioma precursor, ecchymosis. This bruise-like appearance may be seen before hemangioma proliferation occurs.

well as a sustained, longer growth phase.<sup>24</sup> The onset of the involutional phase, which is difficult to predict in any given patient, is marked by a color change from bright red to dull red, purple, or gray (for superficial lesions) (Figs. 12-16 and 12-17). It may be more difficult to appreciate early involution in deep IH, but with time these lesions become smaller, more compressible, and less warm. It is estimated that completed involution of IH occurs at a rate of 10% per year, such that 30% have involuted by 3 years of age; 50% by 5 years of age; 70% by 7 years of age, and more than 90% by 9 or 10 years of age.<sup>10,22,25,26</sup> However, it should be remembered that involution does not necessarily imply totally normal skin. Possible residual changes after IH involution include telangiectasias (Fig. 12-18), atrophy (Fig. 12-19), scarring (Fig. 12-20), or fibrofatty masses (Figs. 12-21 and 12-22). These possibilities must be explained thoroughly to the parents of patients with IH.

Treatment decisions regarding an IH must incorporate many factors. These include the size and location of the lesion or lesions (see below), the age of the patient and growth phase of the hemangioma, associated findings, and the perceived potential for psychosocial distress both for parents and for the patient later in life. The latter is quite difficult to predict but must be seriously considered in the patient with a conspicuous IH, especially if it is facial. These lesions may be associated with parental disbelief, fear, mourning, and social stigmatization.<sup>27</sup> A hemangioma severity scale has been developed and validated and incorporates the factors above, as well as risk for



**Figure 12-16** Hemangioma, involution phase. Note the patchy vascular appearance in this involuting lesion in a 2-year-old boy.



**Figure 12-17** Hemangioma, involution phase. The redness has largely resolved and the lesion flattened in this 3-year-old female.



**Figure 12-18** Hemangioma, involuted. This lesion demonstrates the residual telangiectasias that may persist after involution of the hemangioma.



**Figure 12-19** Hemangioma, involuted. This hemangioma was very large with complete obstruction of the visual axis and secondary ulceration. After involution, atrophy and scarring are both evident.



**Figure 12-20** Hemangioma, involuted. Residual scarring and atrophy are evident in this fully involved lesion.



**Figure 12-21** Hemangioma, involuted. The cheek of this 4-year-old boy shows the residual fibrofatty tissue that may remain after involution.



**Figure 12-22** Hemangioma, involuted. This philtrum lesion has involuted, but fibrofatty residua remain.

#### Box 12-2 Hemangiomas: Considerations for Evaluation, Referral, and/or Therapy

- Life-threatening
- Function threatening
  - Periocular
  - Nasal tip
  - Ear (extensive)
  - Lips
  - Genitalia, perineum
  - Airway
  - Hepatic
- Large facial
- Large anogenital/perineal
- "Beard" distribution\*
- Ulcerating
- Lumbosacral
- Multiple

\*See text for discussion.

associated structural anomalies, complications, pain, and likelihood of disfigurement.<sup>28</sup> The major goals of management should be to prevent or reverse life- or function-threatening complications; prevent disfigurement; minimize psychosocial stress; avoid overly aggressive procedures; and adequately prevent or treat ulceration in order to minimize infection, pain, and scarring.<sup>29</sup> Treatment decisions can be challenging and must include parental input and a thorough risk-to-benefit analysis. Hemangiomas for which further evaluation, referral to a specialist, and/or therapy should be considered are listed in **Box 12-2**. (These are discussed in more detail under Clinical Variants and Associated Syndromes.)

Treatment options for IH are listed in **Table 12-2**. Probably the most useful principle in the treatment of these lesions is that of active non-intervention. This term implies that the physician inquires about the parents' knowledge of the condition, offers education regarding natural history and therapeutic indications, and offers anticipatory guidance and support. Active nonintervention is an appropriate "therapy" for the majority of IHs, and can be offered by the pediatrician or primary care physician in most instances. Serial photography may be useful for parents of children with hemangiomas in order to document the gradual spontaneous involution, which may be subtle and underappreciated by them.<sup>22</sup> Referral to support groups and informational resources, such as the Hemangioma Investigator Group ([www.hemangiomaeducation.org](http://www.hemangiomaeducation.org)), Vascular Birthmarks Foundation ([www.birthmark.org](http://www.birthmark.org)), or the National Organization of Vascular Anomalies ([www.novanews.org](http://www.novanews.org)), is useful for parents of these children.

**Table 12-2** Treatments for Infantile Hemangioma\*

Treatment	Comment
Active nonintervention	Emotional support and guidance; distribution of patient education materials and referral to informational and support networks
Local wound care	When ulcerated: topical antibiotic, nonstick wound dressings, compresses, becaplermin gel
Oral antibiotics	When secondary infection present
Pain control	When ulcerated: may require temporary use of narcotic analgesics
Topical corticosteroids	Potent formulations; may be useful for localized, superficial IH
Intralesional corticosteroids	Usually triamcinolone; localized lesions; caution with periocular IH
Oral corticosteroids	Traditional gold standard for systemic therapy; prednisone or prednisolone, 2–4 mg/kg per day
Topical β-blockers	Most often timolol gel-forming ophthalmic solution, 0.1%–0.5%, applied 2–4 times daily; may be useful for smaller, localized and/or superficial IH
Oral β-blockers	Usually propranolol 2 mg/kg per day; risks include bradycardia, hypotension, hypoglycemia, bronchospasm, hypothermia, nightmares
Interferon α	Subcutaneous injection; severe, treatment-resistant, or life-threatening IH; risk of spastic diplegia
Laser therapy	Usually PDL; mainly useful for ulcerated IH or residual surface vascularity (i.e., telangiectasias) persisting after involution
Vincristine	Severe, treatment-resistant or life-threatening IH; requires venous access; risks include myelosuppression, peripheral neuropathy, extravasation necrosis
Surgical excision	Useful in select situations, i.e., incomplete resolution, disfiguring facial lesions, smaller complicated IH refractory to medical therapy

IH, Infantile hemangioma; PDL, pulsed-dye laser.

\*See text for more discussion.

Corticosteroids are the traditional mainstay of therapy for IHs requiring treatment. They are most often used in the oral form, although both intralesional and topical preparations may be useful. Intralesional corticosteroids are useful for localized lesions. Several injections may be necessary, and periocular lesions should be treated only by a physician experienced in their administration, given the possibility of embolization of corticosteroid particles and permanent vision loss.<sup>30,31</sup> Topical corticosteroid therapy with clobetasol (a potent, class 1 topical steroid) may be useful for localized IH.<sup>32,33</sup> In the authors' experience, this therapy is most useful for macular or very thin plaque hemangiomas in the early proliferative stage. This medication should be used cautiously with attention to the risks of atrophy, ocular toxicity, and adrenal suppression.

Oral corticosteroids were at one time considered the gold standard for treatment of complicated IHs, and their mechanism of action is poorly understood.<sup>6,34</sup> They are most useful during the proliferative phase and are generally administered in dosages ranging from 2 to 4 mg/kg per day of prednisolone or prednisone. Some authors advocate doses up to 5 mg/kg per day.<sup>22,34</sup> This therapy is usually continued for several months, with gradual tapering as tolerated. If corticosteroids are tapered too quickly, rebound growth and adrenal suppression may occur. The goals of decreased IH growth or partial shrinkage

must be balanced by the risks of long-term therapy. Common side effects include irritability, weight gain, hypertension, and gastrointestinal (GI) upset. Because the immune response is suppressed in patients receiving systemic corticosteroids, live-virus vaccinations should not be given during (or within 1 month after discontinuation of) therapy. Although decreased linear growth velocity may occur in treated patients, catch-up growth usually occurs after their discontinuation.<sup>6,10,35</sup> Adrenal axis suppression is rare, and when it occurs, tends to be reversible.<sup>35,36</sup> Many experts treat concomitantly with H2 blockers (i.e., ranitidine) to diminish the potential for symptomatic steroid-associated gastritis or worsening of gastroesophageal reflux. *Pneumocystis carinii* pneumonia has been rarely reported, which has prompted some experts to recommend trimethoprim-sulfamethoxazole prophylaxis during systemic steroid therapy.<sup>37,38</sup> In the more recent era of β-blocker therapy for IH, oral corticosteroids are used significantly less often.

Interferon α-2a or -2b, a potent inhibitor of angiogenesis, has been used successfully in patients with IH refractory to corticosteroid therapy.<sup>39</sup> This medication is administered as a daily subcutaneous injection, in a dose of 1 to 3 million units/m<sup>2</sup>. Common side effects include fever, irritability, and malaise. Neutropenia, anemia, and elevation of hepatic transaminases may also occur. However, the most concerning toxicity of this therapy is neurologic in origin, most notably spastic diplegia, which may occur in up to 20% of treated patients.<sup>40,41</sup> Because of this risk, interferon therapy should be reserved for patients with severe life- or function-threatening lesions that are recalcitrant to other therapies, and neurologic evaluation before and during therapy should be performed.<sup>42</sup> The chemotherapeutic agent vincristine is also occasionally used for steroid-resistant, life-threatening IHs.<sup>43-45</sup>

The current standard of care for IH requiring systemic therapy is propranolol. This nonselective β-blocker, which is traditionally used for cardiac indications such as hypertension or arrhythmia, was incidentally noted to result in marked shrinkage of IHs when administered in two children who had a cardiac indication and who also happened to have hemangiomas.<sup>46</sup> Subsequently these effects were confirmed in several more patients reported by the same authors as well as in several other open-label series, prospective studies, and retrospective reviews.<sup>47-53</sup> In the years after the initial report, propranolol has evolved to become the therapy of choice for most clinicians with expertise in the treatment of IH. A multicenter, prospective, international, placebo-controlled study of oral propranolol for IH has been completed and culminated in the recent approval of propranolol for treating IH by the US Food and Drug Administration as well as the European Medicines Agency.<sup>54</sup> The mechanism of action of propranolol in this setting is unclear, although most attribute the effects to some combination of vasoconstriction, inhibition of proangiogenic growth factors (including vascular endothelial growth factor, basic fibroblast growth factor, and matrix metalloproteinase-9), and induction of apoptosis.<sup>55</sup> It is most often started at around 0.5 to 1 mg/kg per day, with the dosage gradually titrated up to 2 to 3 mg/kg per day divided into two to three doses daily. Potential side effects include hypotension, bradycardia, bronchospasm, hypoglycemia, hypothermia, and nightmares, and this agent should be administered under close supervision with attention to these possible toxicities.<sup>56</sup> Rebound growth or recurrence of IH after propranolol therapy has been increasingly recognized and may occur in 6% to 19% of patients.<sup>57,58</sup> The time between cessation of therapy and notation of rebound is typically 3 to 6 months, and most lesions respond well to a second course of propranolol. Although propranolol therapy tends to be most effective during the early proliferative phase of IH (i.e., first 6 months), lesions in the post-proliferative phase may also respond to treatment.<sup>59</sup>

Hypoglycemia has surfaced as one of the most relevant (and preventable) potential toxicities of oral propranolol therapy, and the highest risk period for this effect is in the morning after the overnight fast that occurs during sleep.<sup>60</sup> The mechanism for the development of hypoglycemia is likely related to β-blocker-mediated inhibition of gluconeogenesis and glycogenolysis, mandatory components of physiologic glucose homeostasis. Measures to decrease this risk include always giving propranolol with food, holding therapy during periods of illness or decreased oral intake, and the avoidance of fasting for longer than 8 hours (which may require nighttime awakenings for

feeding).<sup>61,62</sup> Parents should be taught to recognize early warning signs of hypoglycemia, including shakiness, sweating, anxious appearance, and coldness. Table 12-3 list some guidelines for the use of propranolol in the treatment of IH.

After the discovery of propranolol's efficacy in treating IH, several investigators reported the use of a topical nonselective β-blocker timolol for small, uncomplicated superficial hemangiomas. Topical timolol maleate gel-forming ophthalmic solution is classically used for the treatment of glaucoma, but increasing reports have described its efficacy in subsets of patients with these smaller IH.<sup>63-67</sup> Most often used in concentrations of 0.1%, 0.25%, or 0.5%, it is applied two to four times daily to the surface of the IH and rubbed in well. Most small, superficial IHs and even some combined (superficial and deep) lesions respond to the treatment, which in general is very well tolerated. Systemic β-blocker side effects have been noted to occur only rarely, although adequate parent education about these potential toxicities (see previous discussion of propranolol) is warranted.<sup>68</sup> Topical timolol

**Table 12-3** Guidelines for Use of Propranolol in the Treatment of Infantile Hemangioma

Guideline	Comment
Consider contraindications	Cardiogenic shock, sinus bradycardia, hypotension, heart block (>1st degree), heart failure, bronchial asthma, hypersensitivity to propranolol
Perform ECG for patients at risk	At-risk category includes: HR below normal for age, family history of congenital heart conditions or arrhythmias, maternal history of connective tissue disease, personal history of arrhythmia or one noted during examination
Patients with PHACES syndrome: thorough imaging evaluation of head, neck, and cardiac arterial anatomy should be performed before initiation of therapy	If imaging findings place patient into higher risk for stroke, consult/comanage with neurologist during therapy; use lowest effective dose possible
Inpatient initiation of therapy recommended for infants ≤8 weeks' gestationally corrected age, with comorbid conditions, or with poor social support	Outpatient initiation of therapy appropriate for infants >8 weeks' gestationally corrected age, with adequate social support, and lack of comorbid conditions
Typical dosing is 1 mg/kg per day (initiation) and 2–3 mg/kg per day (maintenance), divided three times daily	BP and HR checks recommended at baseline, 1 and 2 hours after initial dose, and repeated with each dose increase of >0.5 mg/kg per day (until maintenance dose reached); dose may be increased every 3–7 days until goal dosage is reached
Always dose propranolol with food and avoid prolonged fasting	Discontinue during illness or periods of decreased oral intake; awaken baby to feed at night as needed to prevent sleeping longer than 8 hours without eating
Hold propranolol during illness that includes wheezing	β-blockers may worsen bronchospasm

Modified from Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics 2013;131:128–40, and Martin K, Blei F, Chamlin SL, et al. Propranolol treatment of infantile hemangiomas: anticipatory guidance for parents and caretakers. Pediatr Dermatol 2013;30(1):155–9. BP, Blood pressure; ECG, electrocardiography; HR, heart rate; PHACES, posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, eye anomalies, and sternal defects.



**Figure 12-23** Hemangioma, ulcerated. This arm lesion, which was in the proliferative phase, reveals superficial ulceration with crusting.



**Figure 12-25** Hemangioma, ulcerated. This ulcerated labial hemangioma was very painful and responded to topical wound care and laser therapy.



**Figure 12-24** Hemangioma, ulcerated. This lower-lip lesion ulcerated with permanent scarring the result.



**Figure 12-26** Hemangioma, ulcerated. This anterior neck hemangioma ulcerated and healed with marked cribiform scarring.

ophthalmic solution is a reasonable consideration for small, primarily superficial, uncomplicated, and functionally insignificant IH.

Ulcerated IH deserves special mention, as this is the most common complication in these lesions, occurring in up to 16% of patients.<sup>69,70</sup> Ulceration usually occurs during the proliferative phase (Fig. 12-23) and is especially common in areas of recurrent trauma such as the lips (Fig. 12-24), genitals (Fig. 12-25), perineum/perianal region, or in moist intertriginous sites such as the neck (Fig. 12-26).<sup>70</sup> Tissue breakdown results in bleeding, secondary infection, pain, and permanent scarring. Local wound care with compresses, topical antibiotics (i.e., bacitracin, mupirocin, or metronidazole), and nonstick wound dressings (i.e., petrolatum-impregnated gauze) are useful. Oral antibiotics should be considered if persistent or deep ulceration, drainage, or exudate is present and should be guided by the results of culture and sensitivity testing. Pain management with acetaminophen or acetaminophen with codeine may be indicated. Topical lidocaine may be helpful for pain control but should be used with extreme caution given the risks of absorption and possible systemic toxicity. Bevacizumab gel, a recombinant human platelet-derived growth factor approved for topical therapy of lower-extremity diabetic neuropathic ulcers in patients 16 years of age and older, has been used off-label for the treatment of ulcerated IH with good success.<sup>71,72</sup> Ulcerated IHs that do not improve with the above treatments usually warrant systemic therapy.

Pulsed-dye laser (PDL; the word *laser* is an acronym for *light amplification by stimulated emission of radiation*) therapy may be useful in the

treatment of ulcerated IH. This laser emits a wavelength of light specific for oxyhemoglobin, thus imparting specificity for vascular structures (selective photothermolysis). Because the light penetrates only 1 mm of depth in the skin, this modality is generally not helpful for nonulcerated, elevated, or nodular lesions. With ulcerated lesions, though, it is useful in accentuating reepithelialization and decreasing pain.<sup>6,10,73</sup> The choice of PDL therapy must be individualized to the patient, and occasionally patients may show no response or even worsening with this modality.<sup>74</sup> PDL therapy may also be useful for residual surface vascularity after IH involution. Although PDL is the most commonly utilized form of laser therapy for IH, other lasers such as the neodymium-doped yttrium aluminum garnet (Nd:YAG) laser or the alexandrite laser may offer some benefit but carry a higher risk of scarring.<sup>21</sup>

### CLINICAL VARIANTS AND ASSOCIATED SYNDROMES

Hemangiomas in certain locations may suggest a higher probability of complications or associated findings. Hemangiomas involving various portions of the face may be quite problematic. Periorbital IHs may be relatively insignificant when small, but larger lesions (Fig. 12-27) may result in a variety of ocular complications. In addition, any periorbital IH may be indicative of deeper, retrobulbar involvement, which may or may not present with unilateral proptosis. Light-deprivation amblyopia may result from visual axis obstruction, most



**Figure 12-27** Hemangioma, periocular. This large hemangioma was obstructing the visual axis secondary to its size and location.

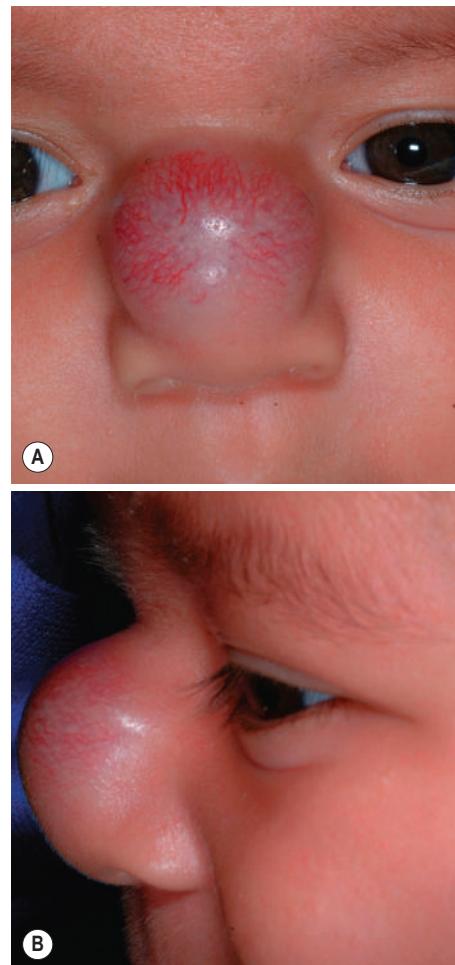


**Figure 12-28** Hemangioma, periocular. Superior eyelid hemangiomas may result in ptosis, with a risk for light-deprivation amblyopia.

commonly in the setting of significant upper eyelid lesions that result in mechanical ptosis (Fig. 12-28). Astigmatism may occur if the IH compresses the globe and may result in permanent amblyopia.<sup>10</sup> Rarely, IH situated near a tear duct may block the drainage system and result in matting and conjunctivitis.<sup>31</sup> Because of these concerns, any child with a periorbital IH should undergo ophthalmologic examination. If there are functional or anatomic ophthalmologic concerns, systemic therapy is usually indicated.

Nasal tip/bridge IHs (Fig. 12-29) often require specialist consultation because of their propensity to distort the nasal anatomy (Fig. 12-30), resulting in permanent disfigurement. Slow involution of these lesions may pose significant psychosocial distress to the older child, and the splaying of nasal cartilage combined with redundant fibrofatty tissue after involution may result in the "Cyrano" nasal deformity (Fig. 12-31). The nasal crease sign is a linear, gray atrophic crease in the inferior columella that may occur with segmental facial IH involving the nose (Fig. 12-32) and that may portend imminent cartilage destruction and nasal collapse.<sup>75</sup> It is for reasons such as these that therapy is often indicated for nasal IH.

Hemangiomas located on the lips tend to involute slowly and are more prone to ulceration and bleeding. These changes may in turn contribute to increased pain, feeding difficulties, and permanent

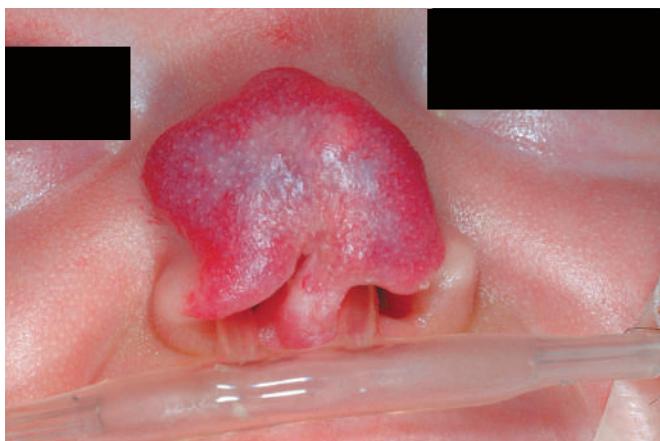


**Figure 12-29** Hemangioma, nasal bridge. This large lesion of the nasal bridge (**A**) results in significant bulbous distortion of the nose (**B**) and is likely to leave residual deformity.

scarring. Ear IHs may also be cosmetically disfiguring, and when large may obstruct the auditory canal and result in conductive hearing loss.

Hemangiomas that involve the neck, lower lip, chin, preauricular, and mandibular areas (beard lesions) (Fig. 12-33) are clinically important because of the increased risk of associated airway lesions in these patients. In one study, patients with more extensive IHs in this location had up to a 63% incidence of subglottic or upper-airway hemangiomatosis.<sup>76</sup> Airway IH may also occur in the absence of cutaneous IH. Infants with symptoms are usually brought for treatment within the first few months of life with croup-like cough, hoarseness, and biphasic stridor. Any infant with extensive IH in this distribution and/or symptoms of upper-airway obstruction should be immediately referred for direct visualization of the airway with laryngoscopy. Treatment options in this setting may include tracheotomy, propranolol, corticosteroids, interferon  $\alpha$ , surgical excision, and laser therapy.

Parotid IHs often present as mixed superficial and deep lesions with a prominent deep component of swelling with an overlying blue hue (Fig. 12-34). These lesions tend to grow significantly and may involute more slowly than IHs in other locations. They may have a poorer response to pharmacologic therapy, although propranolol has been demonstrated to be effective in many patients.<sup>77-80</sup> Genital (Fig. 12-35) and perineal IHs are problematic because of ulceration, with the concomitant risks of bleeding, infection, permanent scarring, and pain. When these lesions are larger and/or segmental, the possibility of associated developmental anomalies of the external genitalia, anorectal region, genitourinary tract, spine and spinal cord must be



**Figure 12-30** Hemangioma, nose. This large nasal lesion resulted in destruction of nasal cartilage and erosion of the columella in this extremely premature infant female.



**Figure 12-31** Hemangioma, nasal tip. Large nasal tip lesions like this one may leave significant fibrofatty residua, resulting in a "Cyrano" deformity.

considered (see PELVIS Syndrome). Hepatic IHs may be associated with significant morbidity and mortality and are discussed further in the Diffuse Neonatal Hemangiomatosis section.

Lumbosacral IHs (Fig. 12-36) are important, because they may signal underlying occult spinal dysraphism or spinal cord defects. Tethering of the spinal cord is one of the more common associations,<sup>81</sup> and this anomaly may result in permanent neurologic sequelae without release. Other common findings include spinal lipoma, intraspinal hemangioma, and sinus tracts.<sup>82</sup> In a prospective study of 41 patients with lumbosacral IHs who underwent magnetic resonance imaging (MRI) examination, intraspinal abnormalities were detected in 21 patients, with a positive predictive value of IH for spinal dysraphism of 51.2%. An increased risk for spinal anomalies correlated with IH ulceration and the presence of additional cutaneous anomalies (including gluteal cleft asymmetry or deviation, sacral dimple, skin appendage, lipoma, dermal melanocytosis, dermal sinus, and aplasia cutis). Importantly, 35% of patients with an isolated lumbosacral IH had spinal dysraphism. Also important, 42% of children with normal ultrasound scans who then underwent MRI evaluation had spinal anomalies, highlighting the potential risk of relying on ultrasonography as a screening tool for high-risk infants.<sup>83</sup> In addition to spinal anomalies, sacral IH may also be associated with various congenital anorectal or urogenital anomalies, as discussed with genital and perineal lesions.<sup>84</sup> This association is discussed in more detail below (see PELVIS syndrome). Any infant with a lumbosacral IH, especially when it is large or of the segmental type or when other cutaneous stigmata



**Figure 12-32** Hemangioma, nasal crease sign. This infant girl had a segmental facial hemangioma involving the left forehead, periorbital region, glabella, nasal bridge, and nose. At 11 days after noting this linear gray atrophic crease (A) she returned to clinic with complete destruction of the nasal septum and columella and nasal collapse (B).



**Figure 12-33** Hemangioma, beard distribution. Lesions involving the lower lip, chin, neck, or mandibular regions have a greater risk of airway involvement, as was seen in this female infant.



**Figure 12-34** Hemangioma, parotid. This large subcutaneous tumor with a blue hue and surface telangiectasias was characteristic for a parotid infantile hemangioma. These lesions tend to grow significantly and regress more slowly, and often require systemic therapy.



**Figure 12-36** Hemangioma, lumbosacral. This large segmental lesion would have an increased risk of association with underlying spinal dysraphism or spinal cord defects. MRI in this child was normal.



**Figure 12-37** Hemangioma, segmental. This superficial hemangioma occupied a large surface area of the distal arm and proximal forearm.



**Figure 12-35** Hemangioma, genital. This labial lesion is at increased risk for surface breakdown given its location.

are present, should be considered for MRI to assess for underlying abnormalities.

Segmental hemangiomas are lesions that involve a broad anatomic region (see Fig. 12-36; Fig. 12-37) or a recognized developmental unit.<sup>85</sup> They are often unilateral and sharply demarcated at the midline, although exceptions occur. Segmental IHs are most commonly located on the face. They seem to have a higher rate of complications and entail a greater risk for functional compromise and associated abnormalities such as urogenital anomalies or the posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, eye anomalies, and sternal defects (PHACES) syndrome (see the following paragraph).<sup>85</sup> In addition, they are more often complicated by ulceration.<sup>13</sup> The association of segmental IH with GI (typically lower GI) bleeding has been highlighted and appears to occur most often in the setting of PHACES syndrome with aortic dysplasia.<sup>86</sup>

The PHACES syndrome or PHACES association (Online Mendelian Inheritance in Man, 606519) is a constellation of clinical findings associated with extensive facial IH. Table 12-4 outlines the various

features seen in this syndrome. The majority of patients with PHACES syndrome are female.<sup>87,88</sup> Although the pathogenesis of this syndrome is unclear, it appears to be a developmental “field defect” that arises around the seventh to tenth week of gestation.<sup>89</sup> The facial IHs in patients with PHACES syndrome are usually large and segmental (Fig. 12-38) and may be unilateral or bilateral. They usually follow an aggressive growth pattern, and ulceration is common.<sup>87</sup> There may be a dermatomal distribution, although these dynamic lesions should not be confused with the static vascular malformations (PWSs) associated with Sturge–Weber syndrome (see below). When there is “beard” area involvement, airway hemangiomatosis should be considered. Hemangiomas may also occur in other nonfacial locations in the setting of PHACES syndrome, most notably the upper torso and extremities.<sup>90</sup> Patients with large facial IHs, especially in the presence of ventral developmental defects such as sternal clefting or abdominal raphe, should be screened for this syndrome with MRI of the brain, echocardiography, ophthalmologic examination, and close neurologic and head circumference examinations. Direct airway visualization should be considered if the infant has extensive involvement in the beard area or symptoms of upper airway obstruction.

Anomalies of the cervical and cerebral vasculature are commonly noted in PHACES syndrome, and these patients appear to have a progressive arterial vasculopathy with risk of arterial ischemic stroke (AIS).<sup>91</sup> Regressive changes in the vascular anomalies have also been noted in some patients.<sup>92</sup> Common central nervous system (CNS) structural abnormalities include Dandy–Walker malformation, cerebellar hemisphere hypoplasia (ipsilateral to the hemangioma), and arachnoid cysts.<sup>93,94</sup> Aortic arch anomalies, especially aortic coarctation, are the most commonly noted cardiac abnormalities in PHACES

**Table 12-4** PHACES Syndrome

Manifestation(s)	Comment
P Posterior fossa malformations	Dandy–Walker malformation; cerebellar atrophy; hypoplasia or agenesis of various CNS structures; may also have intracranial hemangioma, midline anomalies, neuronal migration disorder
H Hemangioma	Extensive facial; plaque-like; segmental; occasional airway involvement
A Arterial anomalies	Mainly head and neck; aneurysms, anomalous branches, aberrancy, hypoplasia, absence, stenosis, kinking, looping, tortuosity; increased risk of AIS
C Cardiac anomalies and aortic coarctation	PDA, VSD, ASD, PS, TF, others; in addition to aortic coarctation, may have dysplasia, aneurysm, aberrant origin of the subclavian artery with or without vascular ring
E Eye abnormalities	Microphtalmia, optic-nerve dysplasia, persistent fetal vasculature, morning-glory disc anomaly; also Horner syndrome, retinal vascular abnormality, cataract, coloboma
S Sternal clefting and supraumbilical abdominal raphe	Ventral midline developmental defects; may also include hypopituitarism, ectopic thyroid (with risk of hypothyroidism)

AIS, Arterial ischemic stroke; ASD, atrial septal defect; CNS, central nervous system; PDA, patent ductus arteriosus; PHACES, posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, eye anomalies, and sternal defects; PS, pulmonary stenosis; TF, tetralogy of Fallot; VSD, ventricular septal defect.



**Figure 12-38** Hemangioma, facial. Giant lesions like this one may be associated with the PHACES (posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, eye anomalies, and sternal defects) syndrome.

syndrome and tend to be complex and anatomically atypical. These anomalies may remain asymptomatic in the first days of life until the ductus arteriosus closes, at which time they may result in severe hemodynamic consequences.<sup>95</sup> Box 12-3 lists the recommended evaluation for the infant deemed to be at risk for PHACES syndrome. Diagnostic criteria for PHACES syndrome have been published.<sup>96</sup>

PELVIS syndrome has been used to describe infants with perineal IH in association with a variety of other malformations involving the genitourinary and GI tracts, lumbosacral spine, and spinal cord.<sup>97</sup> The acronym PELVIS stands for **p**erineal hemangioma, **e**xternal genitalia malformations, **I**lipomyelomeningocele, **v**esicorectal abnormalities, **i**mperforate anus, and **s**kin tag. This association has also been known as **SACRAL** syndrome, standing for **s**pinal dysraphism, **a**nogenital anomalies, **c**utaneous anomalies, and **r**enal and urologic anomalies

### Box 12-3 Recommended Evaluation of the Infant at Risk for PHACES Syndrome

#### Baseline

Thorough physical examination, including:

Cutaneous (including assessment for ventral developmental defects)

Cardiac (including pressure measurements in all four extremities)

Respiratory (i.e., for stridor, hoarseness of cry, tachypnea)

Neurologic (i.e., for hypotonia, developmental delay)

Abdominal (i.e., for hepatomegaly, abdominal bruit)

MRI/MRA of the brain and neck

Echocardiography

Ophthalmologic evaluation

Thyroid function testing

#### If Indicated

MRI/MRA of the chest

Other endocrine evaluations (i.e., for growth hormone deficiency, hypopituitarism, diabetes insipidus)

Airway evaluation/direct laryngoscopy

*MRI*, Magnetic resonance imaging; *MRA*, magnetic resonance angiography; PHACES, posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, eye anomalies, and sternal defects.

associated with **angioma** of **lumbosacral** localization.<sup>98</sup> More recently this phenotype has been expanded to include IHs involving not only the perineum but also the lumbosacral region, genitalia, and/or lower extremity by a group that suggested the terminology of **LUMBAR association**, for lower body IH and other cutaneous defects, **urogenital anomalies/ulceration**, **myelopathy**, **bony deformities**, **anorectal malformations/arterial anomalies**, and **renal anomalies**.<sup>99</sup> In this series, the IHs were noted to often be segmental as well as of the “minimal growth” phenotype (Fig. 12-39; also see below). Other cutaneous findings that may be present include lipoma, skin tag, caudal appendix, hair tuft, and sacral dimple. **PELVIS/SACRAL/LUMBAR** syndrome has been likened to PHACES syndrome, although it affects the lower half of the body and should be considered in any infant with a segmental IH (including those with minimal growth) affecting the anogenital, lumbosacral, or lower-extremity regions.

**Abortive hemangiomas** refers to IHs that exhibit very little (if any) proliferation during the period of expected growth. These lesions typically present as reticulated vascular patches, often with fine telangiectasias, occasionally as grouped telangiectases overlying normal-appearing skin, or as blue patches with a peripheral halo.<sup>100</sup> Small foci of typical bright red, superficial IH may be present around the periphery (Fig. 12-40). Other terms that have been used to describe these lesions include **plaque-telangiectatic hemangiomas**, **macular hemangioma with PWS-like appearance**, **reticular IH**, **minimal-growth hemangiomas**, and **IHs with minimal or arrested growth (IH-MAGs)**.<sup>101,102</sup> Several authors have confirmed these lesions to be IH in origin via positive GLUT-1 immunostaining of biopsies. IH-MAGs tend to present more commonly than typical IHs on the lower half of the body and may be associated with ulceration, especially when occurring in the anogenital area.<sup>102</sup>

Congenital IHs are lesions that are fully formed at birth. These lesions may follow the typical time course of IH, may have a more accelerated involution phase, or may persist unchanged. Noninvoluting congenital hemangioma (NICH) is a specific subtype of IH also known as a **congenital nonprogressive hemangioma**. These lesions may be diagnosed *in utero*, are fully formed at birth, and do not show the postnatal proliferation characteristic of IH.<sup>103</sup> Clinically NICH lesions are round to ovoid, pink to purple tumors with overlying prominent telangiectasias and peripheral pallor (Fig. 12-41).<sup>104</sup> Importantly, these lesions also do not undergo the spontaneous involution typical of IH and hence appear to be a distinctive type of vascular lesion. Interestingly, NICH lesions also have a different histologic appearance and are not immunoreactive for GLUT-1.<sup>103</sup>

**Rapidly involuting congenital hemangioma (RICH)** is the term used to describe a congenital IH that undergoes rapid involution early in life. These tumors may present similar to an NICH or they may have the appearance of a typical IH. They may also present as small to large



**Figure 12-39** PELVIS (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag) syndrome. This infant has an infantile hemangioma with minimal growth involving the perineum (**A**) buttocks, and lumbosacral back (**B**). His history was also notable for imperforate anus, tethered spinal cord, and a filar lipoma. Note the midline lumbosacral scar related to his cord-untethering surgery.



**Figure 12-40** Abortive hemangioma (infantile hemangioma with minimal or arrested growth). This telangiectatic vascular patch presented on the medial calf of this 5-month-old boy. Note the scattered brighter red vascular macules and papules around the periphery, a classic feature in some of these lesions.

tumors with a red, violaceous, or gray appearance that may mimic other vascular (i.e., KHE, see [Kaposiform Hemangioendothelioma](#) section) or malignant (i.e., rhabdomyosarcoma, fibrosarcoma) neoplasms. They often involute completely by 12 to 15 months of age ([Fig. 12-42](#)) and may leave behind dermal and subcutaneous atrophy.<sup>105</sup>



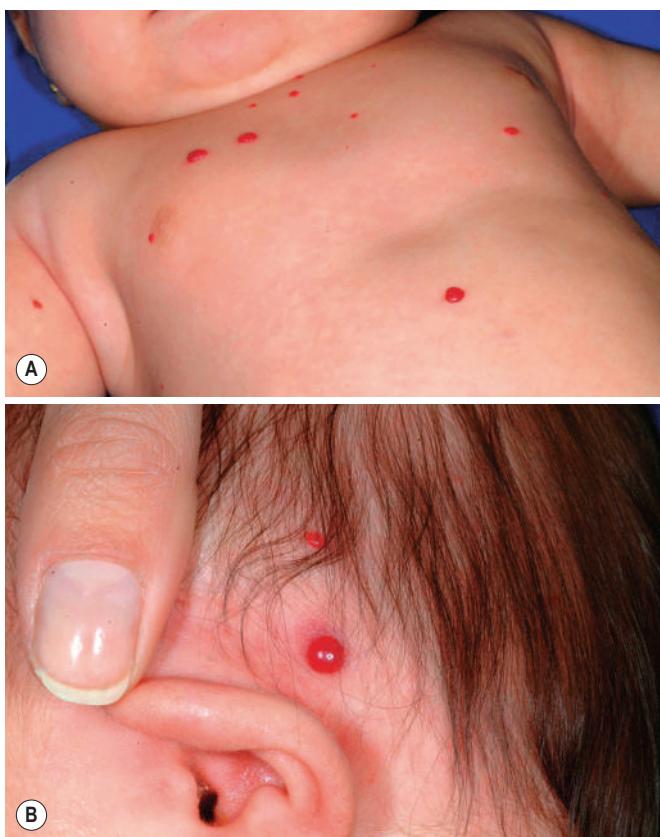
**Figure 12-41** Hemangioma, noninvolving congenital. Characteristic features include prominent surface telangiectasias and a peripheral rim of pallor.



**Figure 12-42** Hemangioma, rapidly involuting congenital. This hemangioma was fully formed at birth (**A**) and involuted completely by 1 year of age (**B**).

### Diffuse Neonatal Hemangiomatosis

Diffuse neonatal hemangiomatosis (disseminated neonatal hemangiomatosis) describes patients with multiple cutaneous lesions in conjunction with extracutaneous organ involvement. It must be differentiated from benign neonatal hemangiomatosis, in which the infant has multiple cutaneous lesions without any symptomatic visceral lesions or complications.<sup>106,107</sup> Patients with either type of hemangiomatosis may have only a few or up to hundreds of cutaneous IHs ([Figs. 12-43](#) and [12-44](#)). Some authors advocate for the terminology



**Figure 12-43** Hemangiomatosis, diffuse. This infant had multiple small lesions as shown on the trunk (**A**) and scalp (**B**) and no internal involvement.



**Figure 12-44** Hemangiomatosis, diffuse. This infant had variably sized lesions and liver hemangiomatosis.

*multipifocal IH with or without extracutaneous disease*, noting that many cases reported in the literature as diffuse neonatal hemangiomatosis may actually represent other entities such as multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT) (see later this chapter).<sup>108</sup>

Although past data suggested that the risk of internal involvement could be predicted by the number of cutaneous IHs, the traditional

recommendation for internal imaging in patients with five or more lesions was more anecdotal than evidence-based. Recently, however, in a prospective study comparing 151 infants with five or more IHs to 50 infants with between one and four IHs, hepatic hemangiomas were identified on hepatic ultrasound in 16% (24) of the infants with five or more cutaneous IHs and in none of the control group with one to four cutaneous IHs. The study also revealed that preterm (<37 weeks' gestational age) delivery, multiple gestation, lower birth weight, *in vitro* fertilization, placental anomalies, and preeclampsia each occurred more often in infants with more than five cutaneous IHs, but on multivariate analysis only preterm delivery and lower birth weight were associated with having five or more cutaneous IHs. Of the 24 infants with hepatic hemangiomas, only two required therapy specifically for this finding.<sup>109</sup> This study helps to confirm that infants with five or more IHs are at greater risk for hepatic hemangiomas (and should be evaluated with liver ultrasound) and that the majority of those with hepatic involvement remain asymptomatic and do not require therapy.

Although the most common extracutaneous site for IH in patients with diffuse hemangiomatosis is the liver, multiple other organs can be involved, including the intestine, brain, eyes, spleen, oral mucosa, kidney, and lungs.<sup>110,111</sup> The diagnosis of hepatic hemangiomatosis is usually made clinically and radiographically, because liver biopsy is undesirable owing to the risk of bleeding. Liver lesions may be asymptomatic or present with hepatomegaly and congestive heart failure, the latter of which is believed to be the result of arteriovenous (AV) shunting, which leads to increased venous return and increased cardiac output. Occasionally anemia or thrombocytopenia is present.

Three patterns of liver hemangiomatosis have been proposed: focal, multifocal, and diffuse.<sup>112</sup> Focal lesions are well defined and solitary on imaging and are most often clinically asymptomatic. They usually are not accompanied by cutaneous lesions and tend to involute rapidly. Multifocal liver hemangiomas present as multiple spherical tumors, which may be asymptomatic or can result in high-output cardiac failure secondary to AV shunting. These lesions involute after the same course as seen with cutaneous IH. Diffuse lesions are extensive, may result in near-total replacement of hepatic parenchyma, and may be associated with serious complications including vessel compression, respiratory decompensation, abdominal compartment syndrome, and multiorgan system failure.<sup>112</sup> These lesions may also be associated with severe hypothyroidism.

Abdominal ultrasonography with Doppler studies is the diagnostic modality of choice, although MRI or computed tomography (CT) may occasionally be necessary. Treatment options may include optimization of cardiac function, corticosteroids, propranolol, interferon  $\alpha$ , vincristine, cyclophosphamide, embolization, hepatic artery ligation, hepatic resection, and liver transplantation.<sup>10,112</sup> Propranolol has been increasingly reported as an effective therapy for hepatic IH, and in most patients improvement in the liver lesions correlates with resolution of heart failure and improvement or resolution in the associated hypothyroidism, when present.<sup>113,114</sup> Infants with diffuse liver hemangiomas should undergo thyroid hormone monitoring and replacement as necessary. Most visceral hemangiomas, like the cutaneous lesions, grow during infancy and in surviving children regress during early childhood. Other evaluations that may be useful in the investigation for diffuse hemangiomatosis include complete blood cell counts, stool examinations for occult blood, liver function studies, urinalysis, echocardiography, electrocardiography, and CNS imaging when clinically indicated.

#### KASABACH–MERRITT PHENOMENON

Kasabach–Merritt phenomenon (KMP; also known as *Kasabach–Merritt syndrome*) is characterized by thrombocytopenia (owing to platelet trapping), coagulopathy, and microangiopathic hemolytic anemia in association with a rapidly enlarging vascular lesion. It was traditionally felt to be a complication of IH but is now known to be associated with vascular tumors other than IH, namely KHE and tufted angioma.<sup>115</sup> These lesions have characteristics that clinically distinguish them from hemangiomas (see below). KMP occurs most often within the first few weeks of life and presents with sudden enlargement of the vascular lesion, ecchymosis, prolonged bleeding,



**Figure 12-45** Kasabach–Merritt phenomenon. Note the deep purple color of this vascular tumor, which suddenly enlarged and became firm, with accompanying thrombocytopenia.



**Figure 12-47** Tufted angioma. This vascular plaque was mildly indurated to palpation. (Courtesy of Annette Wagner, MD.)



**Figure 12-46** Kaposiform hemangioendothelioma. These tumors are characteristically deep purple in color and may be associated with Kasabach–Merritt phenomenon.

epistaxis, hematuria, or hematochezia.<sup>116</sup> The cutaneous lesions show purpura, edema, induration, and an advancing ecchymotic margin (Fig. 12-45).<sup>117</sup> In addition to thrombocytopenia, other laboratory findings include anemia, hypofibrinogenemia, elevated D-dimers, fragmentation of erythrocytes on manual smear, and prolonged coagulation studies. The mortality rate is high, from 10% to 30%.

#### Kaposiform Hemangioendothelioma

Kaposiform hemangioendothelioma (KHE) is a locally aggressive vascular tumor, so named because of the histologic resemblance to Kaposi sarcoma. It presents as a firm, subcutaneous nodule or plaque that expands rapidly and often has a violaceous discoloration (Fig. 12-46).<sup>22,118</sup> Although KHE usually presents in infancy, it may appear months to years later.<sup>119</sup> In addition to involvement of the skin, KHE may involve the deep soft tissues and the bone.<sup>120</sup>

#### Tufted Angioma

Tufted angioma is actually named after its histologic appearance, which reveals groups of dermal capillary tufts. These lesions present clinically as erythematous, annular nodules, or plaques, often with induration (Fig. 12-47).<sup>121,122</sup> Although these lesions may spontaneously involute over years, they tend to persist or gradually progress in most patients. Both KHE and tufted angioma are usually easily distinguished clinically from IH, although in some patients either of the former two may mimic the latter.

Treatment for KMP is challenging. Multiple different regimens have been reported without randomized studies to support or refute their efficacy. It seems clear that a multidisciplinary approach is optimal, including medical and surgical components of diagnosis and therapy.<sup>117</sup> Hematologic therapies include red blood cell transfusions and administration of fresh frozen plasma and cryoprecipitate. Many experts recommend minimization of platelet transfusions given the risks of further platelet trapping and further expansion of the tumor. High-dose corticosteroids, antifibrinolytics, interferon  $\alpha$ , vincristine, sirolimus, cyclophosphamide and antithrombotics have been advocated.<sup>123–125</sup> Vincristine was demonstrated useful in a retrospective study of 15 patients with KMP based on increased platelet count and fibrinogen level and decreased size of the tumor.<sup>126</sup> Four of these patients had a relapse and were again treated successfully with the agent.<sup>126</sup> Vincristine in combination with corticosteroids is considered first-line treatment for many experts.<sup>123,125</sup> Combination vincristine and ticlopidine, without or with aspirin (vincristine-aspirin-ticlopidine [VAT] therapy), has been reported useful in several patients with KMP.<sup>127,128</sup> Early surgical intervention with full resection has been advocated for smaller lesions where this modality is feasible.<sup>116</sup> Other reported treatments include embolization, compression, and radiation therapy.<sup>129–133</sup> Propranolol was associated with clinical response in only 25% of patients with KMP in one series, suggesting the need for further study of this agent.<sup>134</sup>

#### PYOGENIC GRANULOMA

Pyogenic granuloma (PG) is a common acquired vascular lesion of the skin and mucous membranes in infants and children. It presents as a bright red to red-brown, raised, slightly pedunculated or sessile papulonodule (Figs. 12-48 and 12-49). The base of sessile lesions may reveal a peripheral collarette of scale (Fig. 12-50). Although its appearance is usually solitary, PG may occasionally present as several lesions. In addition, secondary PG-like proliferations may occasionally occur on the surface of an existing PWS (Fig. 12-51), usually in the older child or young adult. Multiple, or “agminated,” PG lesions have been reported in the setting of preexisting congenital vascular stains as well as in areas of preceding scalding burns.<sup>135,136</sup> PG is prone to superficial ulceration and bleeding, which usually brings the patient to medical attention. The pathogenesis of PG is unknown. Despite the name, the lesions are not considered infectious. Although they may occur on any skin surface, they most commonly appear in areas subject to trauma, especially the hands, fingers, forearms, face, and occasionally the mucosal surfaces of the mouth. They have been described on the penile shaft after circumcision.<sup>137</sup> Although histologic evaluation is usually not necessary for diagnosis, pathologic examination reveals changes similar to those of a well-circumscribed IH.

The traditional therapy for PG is simple shave excision followed by treatment of the base with electrodesiccation, which achieves hemostasis and seems to help prevent recurrence. PDL therapy may be useful for the treatment of smaller lesions,<sup>138</sup> and the continuous



**Figure 12-48** Pyogenic granuloma. An acquired, vascular papule.



**Figure 12-49** Pyogenic granuloma. This lesion is multilobulated.



**Figure 12-50** Pyogenic granuloma. This lesion demonstrates the calurette of skin around the base of the lesion.

wave/pulsed carbon dioxide ( $\text{CO}_2$ ) laser has also been demonstrated effective.<sup>139</sup> Topical imiquimod cream, an immune response modifier, may be helpful in some patients.<sup>140</sup>

### BACILLARY ANGIOMATOSIS

Bacillary angiomatosis (BA) is an exanthem characterized by cutaneous vascular lesions in association with *Bartonella* (previously *Rochalimaea*) infections. *Bartonella* species also cause cat-scratch disease, prolonged fever, hepatosplenomegaly, and ocular manifestations (includ-



**Figure 12-51** This young girl with Klippel-Trenaunay syndrome has multiple, pyogenic granuloma-like papules overlying a port wine stain of her lower extremity.

ing Parinaud oculoglandular syndrome), encephalopathy, hemolytic anemia, osteomyelitis, endocarditis, glomerulonephritis and pulmonary disease.<sup>141</sup> BA occurs primarily in immunocompromised individuals and was originally described (and once seen quite commonly) in patients with acquired immunodeficiency syndrome (AIDS).<sup>142</sup> It has been rarely documented in immunocompetent children.<sup>143,144</sup> BA is caused by *B. henselae* and *B. quintana*, and transmission is via the body louse, a cat scratch, or cat fleas. The lesions may involve various tissues, including brain, bone, lymph nodes, GI tract, respiratory tract, and bone marrow. Osseous lesions are most commonly seen with *B. quintana* infection, and visceral involvement is caused almost solely by *B. henselae*.<sup>145</sup> However, skin lesions are the most common manifestation, may be caused by both species, and present as disseminated red to purple papules generally no larger than 1 to 2 cm in diameter. The clinical differential diagnosis may include PG and Kaposi sarcoma. Occasionally, BA may present with ulcerative lesions.<sup>146</sup> Liver peliosis is a similar condition affecting the liver and lymph nodes and usually caused by *B. quintana*.

The diagnosis of BA is confirmed by tissue biopsy with histologic examination, which reveals vascular proliferation and plump endothelial cells with the infecting bacilli identified on Warthin-Starry stain. The possibility of human immunodeficiency virus (HIV) infection should be considered if BA is diagnosed. The disorder usually responds to antibiotic therapy with erythromycin, doxycycline, trimethoprim-sulfamethoxazole, or rifampin.

### GLOMUS TUMOR

Glomus tumor (glomangioma, glomuvenuous malformation) is a benign vascular lesion that usually presents as a blue papule or nodule. It represents a relatively uncommon hamartoma of the glomus body, which is a temperature-regulating AV shunt that bypasses the usual capillary bed of the dermis. The glomus cell, which proliferates in this disorder, is a modified smooth-muscle cell. Rarely seen in infants, these lesions may be solitary or multiple and occur in children as well as adults. Occasionally, nodular or plaque-like lesions may also occur.

Solitary glomus tumors, which represent 90% of all lesions,<sup>147</sup> do not appear to have a familial tendency. They are characterized by the clinical triad of paroxysmal pain, local tenderness, and cold sensitivity. Solitary lesions present as a blue-red nodule (Fig. 12-52) from 1 mm to several centimeters in size. They most often appear on the upper extremities, particularly the nailbeds, and occasionally on the lower extremities, head, neck, or penis. Although the etiology is unknown, some lesions appear to be associated with previous trauma. The differential diagnosis of a solitary glomus tumor includes VM, blue nevus, melanoma, dermatofibroma, and leiomyoma. If occurring in an infant, hemangioma of infancy may also be in the differential.

In contrast to the solitary type, multiple glomus tumors (often referred to as *glomuvenuous malformations*) are often dominantly transmitted, may be painful or painless, and vary from a few lesions to several hundred. The familial nature may not be obvious, because



**Figure 12-52** Solitary glomus tumor. (Courtesy of Sarah Chamlin, MD.)



**Figure 12-53** Multiple glomus tumors. This patient had multiple blue papules and papulonodules.

family members may have small lesions and never seek treatment.<sup>148</sup> They are relatively more common in children than adults, and although they can occur anywhere on the cutaneous surface, the majority involve the lower extremities. They may be regionally distributed or generalized, and segmental patterns of presentation have been reported.<sup>149,150</sup> Affected individuals usually have truncating mutations in the glomulin (*GLMN*) gene.<sup>151</sup> Multiple glomus tumors appear as blue-purple, flat to dome-shaped papules, plaques, and nodules (Fig. 12-53) that vary from a few millimeters to several centimeters in size. The differential diagnosis of multiple glomus tumors includes leiomyomas, diffuse hemangiomatosis, and blue rubber-bleb nevi. Multiple glomus tumors involving the fingers and toes have been reported in some individuals with neurofibromatosis type 1.<sup>152</sup>

A congenital variant of glomus tumor has been described and is characterized by a blue-red, nodular plaque that may be painful and tends to grow proportionate with the child's growth.<sup>147</sup> Congenital facial plaque-like glomus tumors may mimic VMs and can be quite disfiguring.<sup>153</sup>

Treatment of glomus tumors consists primarily of surgical excision, although this is not a feasible option for patients with multiple lesions and recurrence tends to be common. Sclerotherapy has been used with some success, as have CO<sub>2</sub> lasers.<sup>154</sup> Subungual glomus tumors are usually treated successfully with periungual or transungual surgical excision, although residual nail deformities may result.<sup>155</sup>

### HEMANGIOPERICYTOMA

Hemangiopericytoma is a rare tumor that occurs in both an adult and a childhood form, although children account for fewer than 10% of all cases.<sup>156</sup> Congenital lesions are occasionally observed.<sup>157,158</sup> This

tumor arises from pericytes, which are smooth-muscle cells that surround capillaries and postcapillary venules. Skin, subcutaneous, and muscular tissues maybe involved, and any part of the body can be affected, the most common location being the lower extremities. Some experts question whether a majority of lesions previously called *hemangiopericytomas* actually represent solitary fibrous tumors (originating from fibroblasts).<sup>159</sup>

Hemangiopericytoma may present in a variety of fashions without a distinctive or pathognomonic appearance. It often presents as a deep soft-tissue mass with slow growth. It may be flesh-colored or have a blue-red hue. Multicentric lesions have been described in infants and tend to behave in a fashion similar to their solitary counterparts.<sup>160</sup> The diagnosis of hemangiopericytoma is based on the cellular and architectural features on tissue histology.

The prognosis of this tumor in childhood is variable. It appears that children younger than 1 year of age (in which case, it is termed *infantile hemangiopericytoma* or the *congenital/infantile form of hemangiopericytoma*) have a better prognosis with a high response to chemotherapy. In children older than 1 year of age, the tumor behaves more similarly to those in adults and may be more aggressive.<sup>156</sup> Treatment consists of complete surgical resection when feasible, as well as radiotherapy and rarely chemotherapy.<sup>159</sup>

### ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA

Angiolymphoid hyperplasia with eosinophilia (ALHE) is an uncommon vascular proliferation disorder occurring most commonly in young adult women and only rarely in children. It presents as a subcutaneous mass of the head and neck region, especially around the ears or on the scalp. Regional lymph node enlargement and eosinophilia may be present, and treatment is usually by surgical excision, although observation, cryotherapy, laser ablation, steroids, radiation, and chemotherapy have been reported.<sup>161</sup>

Kimura disease is a closely related, yet distinct, chronic inflammatory disorder that occurs primarily in young Asian males. It is characterized by the triad of painless subcutaneous nodules in the head or neck region, blood and tissue eosinophilia, and elevated serum immunoglobulin (Ig)E levels.<sup>162</sup> Clinically, the lesions of Kimura disease present as solitary or multiple, purple-red papules, nodules, or deep swellings. The parotid and submandibular glands may be involved,<sup>163</sup> as may the oral mucosa, scalp, ears, or orbit. Unilateral cervical lymphadenopathy is commonly present. Laboratory evaluation consistently reveals eosinophilia and increased IgE.<sup>164</sup> Pediatric Kimura disease may be associated nephritic syndrome, urticaria, and eczema.<sup>165</sup>

ALHE and Kimura disease may be confused with a variety of other entities, most commonly malignancies such as lymphoma, salivary gland tumors, or histiocytosis. These disorders histologically reveal vascular proliferation with eosinophils and mast cells, and their etiology remains unclear. Treatment options for Kimura disease include surgical excision (although recurrence is common), steroids, chemotherapy, and radiation.

### Vascular Malformations and Malformation Syndromes

#### SALMON PATCH

The salmon patch (nevus simplex) is the most common vascular lesion of infancy. It occurs in 30% to 40% of all newborns and appears as a flat, dull pink, macular lesion on the posterior neck and scalp (Fig. 12-54), glabella (Fig. 12-55), forehead, upper eyelids, and occasionally the nose or nasolabial regions. When seen on the nape of the neck, it is commonly referred to as a *stork bite* and when on the forehead/glabella, as the *angel kiss*. Although the salmon patch represents the most common form of capillary malformation, it is felt by many to be a form of persistent fetal circulation rather than a true malformation. Although older nomenclature may include salmon patch under the category of PWS, this terminology should not be used because these lesions have distinct natural histories and differing significance in



**Figure 12-54** Salmon patch. Faint, vascular macules of the occipital scalp.



**Figure 12-56** Inflammatory nuchal salmon patch. This young girl developed dermatitis overlying her congenital salmon patch. Note the central purulence, which represented secondary bacterial superinfection. The dermatitis resolved after treatment with topical steroids and oral antibiotics.



**Figure 12-55** Salmon patch. This blanchable vascular patch of the glabella and forehead becomes more prominent with crying or increased body temperature. Note the associated stain over the left superior eyelid.



**Figure 12-57** Port wine stain: arm/hand.

terms of potential syndrome associations. Salmon patches are usually isolated lesions without other associated findings. Nuchal or occipital stains may occasionally develop an associated overlying dermatitis (Fig. 12-56), which may respond to topical corticosteroids or PDL treatment, if necessary.<sup>166</sup>

No treatment is usually necessary for salmon patches, because 95% of facial lesions fade within the first 1 to 2 years of life. Lesions on the posterior neck or scalp (also known as *Unna nevus*) may fade, although some of these persist indefinitely. Since they are usually covered by hair, these lesions do not typically pose a cosmetic problem. Parents should be educated regarding the common finding of “reappearance” or accentuation of facial lesions during episodes of crying, breath-holding, straining with defecation, or physical exertion.

## NEVUS FLAMMEUS/PORT WINE STAIN

Nevus flammeus, or PWS, is a congenital capillary malformation that may occur as an isolated lesion or in association with a variety of syndromes. These lesions present as macular (nonpalpable) stains with a pink (Fig. 12-57) to dark red (Fig. 12-58) color. Although an early PWS may be indistinguishable from an IH, these lesions are usually distinguished by their congenital presence and their static nature without the rapid proliferation and thickening that characterizes hemangiomas during the first months of life. PWS may darken progressively over many years, and occasional lesions develop secondary proliferative (PG-like) vascular blebs on their surface (see Fig. 12-51). They may also become somewhat thickened and raised later in life. PWSs are often, but not always, unilateral and the most



**Figure 12-58** Port wine stain: face/scalp.

#### Box 12-4 Port Wine Stain-Associated Syndromes

- Sturge–Weber syndrome
- Klippel–Trénaunay syndrome
- Parkes Weber syndrome
- Phakomatosis pigmentovascularis
- Proteus syndrome
- CLOVES syndrome
- Macrocephaly-capillary malformation (M-CM) syndrome
- Capillary malformation-arteriovenous malformation (CM-AVM) syndrome
- Cobb syndrome
- Bannayan–Riley–Ruvalcaba syndrome
- Beckwith–Wiedemann syndrome
- Von Hippel–Lindau disease
- Rubinstein–Taybi syndrome
- Wyburn–Mason syndrome
- Roberts syndrome
- Coat disease

**CLOVES**, Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal and spinal anomalies.

common site of involvement is the face, although they may occur on any cutaneous surface.

The significance of PWS is two-fold: the potential cosmetic impact of the lesion (especially facial PWS) on the developing child, and the potential for syndrome associations. **Box 12-4** lists the various congenital syndromes that may have PWS as a component. Several of these will be discussed later.

PWS lesions show little tendency toward spontaneous improvement or involution, and traditional therapy was limited to the use of tinted “cover-up” cosmetics (such as Covermark or Dermablend). Laser therapy has revolutionized the treatment of these lesions, and the flashlamp-pumped tunable PDL is the most accepted laser for PWS treatment.<sup>167</sup> PDL allows the targeting of short bursts of energy at intravascular hemoglobin (because of the specific wavelength of the emitted light) within the lesional vessels while sparing other tissue components and thus allowing for precise therapy. The absorbed light is converted into thermal energy, which leads to the coagulation of blood vessels. Treatment of PWS with PDL is usually performed in conjunction with local or general anesthesia, depending on the size and location of the lesion and the age of the patient. Some smaller lesions can be treated in the clinic setting without the need for anesthesia. PDL therapy is usually performed over several sessions separated in time by 6 to 8 weeks and can be quite effective in lightening these lesions, thereby minimizing their cosmetic and psychosocial significance. Although there may be psychological benefits of PDL therapy of facial PWS early in life,<sup>168</sup> studies evaluating efficacy as a function of patient age have yielded mixed results. Some authors have reported optimal treatment response in patients younger than 1 year of age, whereas others have found no evidence that treatment during



**Figure 12-59** Port wine stain. This lesion involves both the V1 and V2 trigeminal dermatomes in this infant with Sturge–Weber syndrome. (Courtesy of Annette Wagner, MD.)

early childhood is more effective than treatment at a later age.<sup>169,170</sup> In general, lesions over bony areas of the face (i.e., the forehead), lateral cheeks, chest, and proximal arms seem to respond best to PDL therapy, whereas those over the midface and distal extremities respond less well.<sup>167</sup> PWS of the central face may not respond as well, given the deeper vessels that may escape the effect of the PDL.<sup>171</sup> When PDL is being considered for PWS, it is important for the patient/parents to understand that complete clearance is rare, and 20% to 30% of PWSs are resistant to the treatment.<sup>172</sup>

#### Sturge–Weber Syndrome

Sturge–Weber syndrome (SWS; encephalofacial or encephalotrigeminal angiomas) is a neuroectodermal syndrome characterized by a PWS in the distribution of the first (ophthalmic) branch of the trigeminal nerve (V1) in association with leptomeningeal angiomas (presenting usually with seizures) and glaucoma. There are rare reports of patients with classic brain and ophthalmic findings of SWS in the absence of a facial PWS.<sup>173–176</sup> A somatic activating mutation in GNAQ (specifically, a single-nucleotide variant c.548G>A, p.Arg183Gln) was recently identified as the etiology behind SWS and has also been found in a significant number of individuals with non-syndromic PWS.<sup>177–179</sup>

Patients with SWS have a PWS in a V1 distribution (Fig. 12-59) and may also have multidermatomal or more extensive cutaneous involvement. Overall it appears that around 8% of patients with a trigeminal PWS have associated glaucoma and/or seizures.<sup>180</sup> Involvement of the V1 dermatome seems to be consistent in all patients.<sup>176</sup> Involvement of the other trigeminal dermatomes may be useful in predicting the risk of SWS. In one study, involvement of V1, V2, and V3 was associated with an increased incidence of SWS, as was bilateral trigeminal involvement.<sup>176,180</sup> Another study comparing unilateral to bilateral facial PWS found a higher incidence of glaucoma and leptomeningeal angiomas with bilateral involvement and greater risk of CNS involvement when there was complete (vs. incomplete) involvement of V1.<sup>181</sup> Although the exact innervation of the lower eyelid is controversial (V1 vs. V2), it seems that involvement of both upper and lower eyelids portends a significantly higher risk of SWS.<sup>176,180</sup> When PWS lesions are unilateral, there is usually a sharp demarcation at the midline.

CNS disease is another component of SWS. Seizures are the most common CNS feature and often have their onset during the first year of life. The seizures of SWS may be difficult to control, and both

early onset and increased seizure intensity are associated with future developmental and cognitive delay.<sup>176,182,183</sup> Headaches (including migraines), stroke-like episodes, focal neurologic impairments, cognitive deficits, and emotional and behavioral problems including depression, violent behavior, and self-inflicted injury are also more common in SWS.<sup>176,184</sup> Low self-esteem is common in relation to the facial PWS.

Leptomeningeal angiogenesis is a classic component of the syndrome, and lesions are commonly ipsilateral to the cutaneous vascular stain. Cerebral atrophy is a common radiologic finding, as is enlargement of the choroid plexus and venous abnormalities. MRI is the modality of choice for identifying these changes, although CT scans are better at detecting the classic cortical calcifications, which are also seen.<sup>185</sup> These calcifications follow the convolutions of the cerebral cortex and are characterized by double-contoured parallel streaks of calcification ("tram lines"). Intracerebral calcifications may be visible during early infancy and can often help confirm the diagnosis before other characteristic features are present. Diffusion MRI, postcontrast fluid-attenuated inversion recovery (FLAIR) imaging, and high-resolution blood oxygen level-dependent (BOLD) magnetic resonance venography may be useful in the imaging of suspected SWS.<sup>184</sup> Electroencephalography (EEG) is a good option for assessing abnormal brain activity in young children and may be useful in identifying patients at risk for future neurologic symptoms. However, a concerning EEG should always be followed by appropriate radiographic imaging.<sup>186</sup>

Ocular involvement occurs in around 60% of patients with SWS.<sup>176</sup> Glaucoma is the most common ocular finding, and it may present at any time between birth and the fourth decade. It may be unilateral or bilateral, with the latter being more common in patients with bilateral facial PWS. Vascular malformations of the eye in patients with SWS may involve the conjunctiva, episclera, choroid, and retina.<sup>187</sup> Other eye findings include nevus of Ota, buphthalmos, and blindness.<sup>188</sup>

Care of the child with SWS should be multidisciplinary. Dermatologic, neurologic, and ophthalmologic follow-up care is indicated, and the primary care provider must provide anticipatory guidance and support. Other specialty services may become necessary, including plastic surgery, neurosurgery, interventional radiology, and physical and occupational therapy. Referral to support organizations is useful. The Sturge-Weber Foundation ([www.sturge-weber.org](http://www.sturge-weber.org)) provides education and support to individuals with this condition and other disorders associated with PWS.

The primary aim of treatment in SWS is the minimization or elimination of seizure activity. Although the primary management for seizures is with pharmacologic agents, surgical therapy may become necessary. Visually guided lobectomy with excision of the angiomatic cortex is considered the primary surgical approach in a patient with focal lesions.<sup>189</sup> Hemispherectomy is often advised for patients with intractable seizures and unihemispheric involvement. This radical therapy is often successful, with decreased seizure activity and in some patients, cognitive and behavioral improvement.<sup>190,191</sup> Presymptomatic therapy with low-dose aspirin has been advocated by some for young children before the onset of seizures or strokes in an effort to decrease the incidence of these complications.<sup>186,192</sup> The modified Atkins diet and ketogenic diet have been used in some patients to help control seizures.<sup>186,193</sup>

### Phakomatosis Pigmentovascularis

*Phakomatosis pigmentovascularis* (PPV) is a term used to describe the association of a nevus flammeus (PWS) with a pigmented nevus or in some cases, a nevus anemicus. PPV has traditionally been classified into four types. More recently, a fifth type of PPV has been proposed as the concomitant findings of cutis marmorata telangiectatica congenita (CMTC) and mongolian spots.<sup>194</sup> The classification of PPV is shown in Table 12-5, and the cause of this disorder remains unclear. Nevus anemicus is a distinct vascular birthmark characterized by blanching of cutaneous blood vessels, hence presenting as a "white" (actually vasoconstricted) patch of skin (Fig. 12-60) that becomes unnoticeable when the surrounding skin is blanched with a glass slide (diascopy). These lesions may occur as part of PPV (types II, III, and IV) but may also be seen as sporadic lesions.

The most common form of PPV is type II, consisting of nevus flammeus and dermal melanocytosis (i.e., mongolian spots, nevus of Ota)

**Table 12-5** Classification of Phakomatosis Pigmentovascularis

Type*	Findings
I	Nevus flammeus + epidermal nevus
II	Nevus flammeus + dermal melanocytosis ± nevus anemicus
III	Nevus flammeus + nevus spilus ± nevus anemicus
IV	Nevus flammeus + dermal melanocytosis + nevus spilus ± nevus anemicus
V	Cutis marmorata telangiectatica congenita + dermal melanocytosis

\*Further subdivided into: *a*, skin abnormalities only; *b*, skin abnormalities and systemic abnormalities.



**Figure 12-60** Nevus anemicus. Note the well-demarcated patch of hypovascular blanching on this infant's upper chest. This area became more prominent with crying, as during this photograph.



**Figure 12-61** Phakomatosis pigmentovascularis type II. This infant has port wine stains in combination with dermal melanocytosis (mongolian spot, nevus of Ito).

(Fig. 12-61). Without extracutaneous involvement, the subtype designation *a* is used (i.e., PPV type IIa). When systemic involvement is present, the subtype designation *b* is used (i.e., PPV type IIb). Systemic involvement usually consists of similar changes to those seen in SWS or Klippel-Trénaunay (KT) syndrome.<sup>195</sup> This involvement is usually related to the body surface area affected by the vascular lesion.<sup>196</sup> In one series, nevus of Ota was a common associated finding.<sup>197</sup> Neurologic involvement in PPV may include psychomotor retardation,



**Figure 12-62** Klippel-Trénaunay syndrome. Lower extremity port wine stain with mild hemihypertrophy.



**Figure 12-63** Klippel-Trénaunay syndrome. This patient has the characteristic triad, including port wine stain, hemihypertrophy, and venous varicosities. (Courtesy of Sarah Chamlin, MD.)

seizures, cerebral atrophy, and hydrocephalus, and ophthalmologic associations include conjunctival melanocytosis, episcleral vascular malformations, and glaucoma.<sup>198,199</sup>

Therapy for the cutaneous lesions of PPV is generally not necessary, although PDL treatment may be useful for the nevus flammeus. Lesions of dermal melanocytosis may or may not fade spontaneously with time.

#### Klippel-Trénaunay and Parkes Weber Syndromes

Klippel-Trénaunay (KT) syndrome is a sporadic disorder characterized by the triad of vascular malformation, venous varicosity, and hyperplasia of soft tissue and bone. The vascular malformation is most often a capillary malformation of the Parkes Weber Syndromes (PWS) type. The various lesions of KT syndrome are usually distributed on the same extremity, although other areas may be involved. The lower extremity is the most common location affected. When AVMs are also present, patients have been invariably referred to as having Klippel-Trénaunay–Weber (KTW) syndrome or Parkes Weber syndrome.<sup>200</sup>

Patients with KT syndrome exhibit a capillary malformation that may vary from fairly localized, faint lesions to extensive, bright red or purple stains (Figs. 12-62 and 12-63). These lesions are usually present at birth or become evident during early infancy. Prominent superficial veins may be present, and venous varicosities often develop with aging, being present in nearly all patients over 12 years of age.<sup>200</sup> These lesions may become quite large and tortuous and may predispose patients to episodes of thrombophlebitis. Hypertrophy of the affected body part is another component of the syndrome and usually presents with increased limb girth and length (Fig. 12-64). The majority of this hypertrophy is related to soft-tissue and fat overgrowth, although bony hypertrophy is also observed.<sup>200</sup> Although the cause of this overgrowth is unknown, local hyperemia and augmented arterial flow related to the vascular abnormalities are hypothesized etiologic factors. Digital anomalies may also be present in patients with KT syndrome and include macrodactyly, syndactyly, ectrodactyly, clinodactyly, and camptodactyly.<sup>201</sup>

Lymphatic disease seems to be more common than originally thought in patients with KT syndrome. This component may be manifested as lymphangiectasia, large LMs, lymphedema, vascular blebs (Fig. 12-65), and pseudoverrucous papules. Patients with sharply demarcated and “geographic” vascular stains may have an increased likelihood of lymphatic involvement.<sup>202</sup>

Complications of KT syndrome, in addition to occasional thrombo-phlebitis as mentioned previously, include coagulopathy, congestive heart failure (in the presence of hemodynamically significant AVM), pulmonary embolism, stasis dermatitis, cutaneous ulcerations, and bleeding. Vascular malformations may occasionally involve the GI tract, liver, spleen, genitourinary tract, and heart, and life-threatening GI bleeding has been reported.<sup>203</sup> Orthopedic difficulties related to the overgrowth include compensatory scoliosis and hip dislocation. Facial involvement may result in premature dental eruption, facial asymmetry, and malocclusion.<sup>204</sup> Pain is a potentially debilitating problem for patients with KT syndrome and may be related to multiple causes including superficial or deep thrombosis, cellulitis, calcifications, arthritis, and neuropathic origins.<sup>205</sup> Treatments for KT syndrome are primarily supportive and may include compression garments, chronic pain therapy, laser therapy for the cutaneous stain, and vascular/orthopedic surgical procedures as needed. The clearest indication for surgical therapy is leg-length discrepancy, which is projected to exceed 2 cm at skeletal maturity and which can be treated with epiphysiodesis in the growing child.<sup>206</sup> Physical and occupational therapy should be considered, and referral to the Klippel-Trénaunay Support Group ([www.k-t.org](http://www.k-t.org)) is strongly encouraged. In addition, there are a variety of resources available for individuals who require different shoe sizes (including [www.oddshoe.org](http://www.oddshoe.org), [www.oddshoefinder.com](http://www.oddshoefinder.com), and the National Shoe Retailers Association at [www.nsra.org](http://www.nsra.org)).

#### Proteus and CLOVES Syndromes

Proteus syndrome is a rare and sporadic disorder characterized by postnatal segmental overgrowth of multiple tissues. This overgrowth may involve the skin and subcutis, connective tissues, CNS, and



**Figure 12-64** Klippel–Trénaunay syndrome. This young girl has massive hemihypertrophy, and her vascular malformation reveals multiple small thromboses, which are often quite painful. (Courtesy of Annette Wagner, MD.)



**Figure 12-65** Klippel–Trénaunay syndrome with vascular blebs. Note the purple, translucent papules overlying the vascular stain on the lower extremity of this young boy.

viscera.<sup>207</sup> The involvement characteristically occurs in a patchy (mosaic or segmental) and asymmetric pattern. Proteus syndrome was named after the Greek god Proteus, who had the ability to assume various forms to avoid capture.<sup>208</sup> Joseph Merrick, whose life was characterized in the story *The Elephant Man*, is believed to have had Proteus syndrome, although he was originally thought to have had neurofibromatosis type 1. A mosaic activating mutation in *AKT1*, which encodes the AKT1 kinase, has recently been identified in several individuals with Proteus syndrome.<sup>209</sup> Previously some reports suggested a potential association with somatic mutations in the tumor suppressor gene *PTEN* (see Chapter 9), although some now designate this cohort as having the segmental overgrowth, lipomatosis, AVM, and epidermal nevus (SOLAMEN) syndrome.<sup>210</sup> It is possible that both of these disorders are part of a related family of disorders that involve dysfunction of the PI3K-AKT pathway.

Cutaneous manifestations of Proteus syndrome include connective tissue hamartomas that primarily involve the palms and soles and result in cerebriform hyperplasia (Fig. 12-66). Lipomas and extensive fatty hyperplasia may be found in the subcutaneous tissues as well as more diffusely, at times involving body cavities, muscles, and limbs, and regional absence of fat may also occur. Epidermal nevi are common. A variety of cutaneous and subcutaneous vascular malformations may occur, including capillary, venous, and LMs. Patchy hypoplasia of the dermis may occur, resulting in prominent cutaneous venous structures.<sup>211</sup>



**Figure 12-66** Proteus syndrome, cerebriform palmar hyperplasia.



**Figure 12-67** Proteus syndrome, macrodactyly. Note overgrowth of the second toe.

Other features of Proteus syndrome include disproportionate overgrowth that may involve the extremities, hands, feet, digits (macrodactyly, Fig. 12-67), skull (macrocephaly exostoses), vertebrae, external auditory meatus, and viscera.<sup>212</sup> Dysmorphic facial features are occasionally present and include dolichocephaly, elongated facies, low nasal bridge, downslanting palpebral fissures, and wide or anteverted nares. Adenomas of the ovaries or parotid glands may occur with increased incidence in patients with Proteus syndrome. Hemimegalencephaly is the most common CNS finding, and ocular manifestations may include strabismus, nystagmus, high myopia, cataracts, and retinal pigmentary abnormalities.<sup>213,214</sup>

Diagnostic criteria for Proteus syndrome, which include general/nonspecific criteria (mosaic distribution of lesions, sporadic occurrence, and progressive course) as well as multiple specific criteria, may be useful both clinically and in the research arena.<sup>215</sup> Evaluation and management of the patient with Proteus syndrome may include skeletal survey, MRI of clinically affected areas, and consultation with dermatology, genetics, and orthopedic specialists when necessary. Both the medical and emotional aspects of the disorder must be considered. Supportive counseling and referral to the Proteus Syndrome Foundation ([www.proteus-syndrome.org](http://www.proteus-syndrome.org)) are useful.

*CLOVES* syndrome refers to an overgrowth syndrome characterized by congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal and spinal anomalies. Originally termed *CLOVE syndrome* by Sapp et al., the suggestion for expanding the acronym to *CLOVES* was made by Alomari 1 year later based on observations of associated spinal and skeletal involvement.<sup>216,217</sup> Patients with this disorder are often born with lipomatous masses

involving the thoracic and abdominal regions among other areas. They may have slow-flow vascular malformations but may also have spinal or paraspinal fast-flow lesions consistent with AVMs, and these lesions may result in spinal-cord injury including myelopathy.<sup>218</sup> Musculoskeletal defects often involve the hands and feet but may also include scoliosis, spina bifida, vertebral anomalies, congenital hip dysplasia, pectus excavatum, and rib defects. Neurologic manifestations may include tethering of the spinal cord, spasticity, paresis, and neural tube defects.<sup>219</sup> Although there is some significant overlap in the clinical features of CLOVES and Proteus syndromes, there are several distinguishing features, including the lack of cerebriform connective tissue hamartomas of the palms and soles, the progressive enlargement (and recurrence after resection) of the lipomatous masses, and the presence of paraspinal high-flow vascular lesions seen in the patients with CLOVES syndrome.<sup>219</sup> CLOVES syndrome has been ascribed to postzygotic mutations in PIK3CA, a gene involved in the PI3K-AKT growth-signaling pathway. Various segmental overgrowth disorders have been described in association with mutations in this gene and have been termed *PIK3CA-related overgrowth spectrum*.<sup>220</sup>

### **Macrocephaly-Capillary Malformation Syndrome**

The combination of CMTC-type skin changes and macrocephaly, occurring along with other findings such as abnormal somatic growth, craniofacial and skeletal anomalies, developmental delay, neurologic abnormalities with abnormal findings on neuroimaging, mental retardation, and connective tissue abnormalities, was originally termed *macrocephaly-CMTC*.<sup>221,222</sup> Subsequently, however, it was suggested that the vascular lesions seen in this setting are more consistent with reticulate PWSs and that this constellation is more appropriately termed *macrocephaly-capillary malformation (M-CM) syndrome*.<sup>223,224</sup> Centrofacial capillary malformations seem to be common in patients with this syndrome and most notably involve the nose, glabella, and philtrum.<sup>223,224</sup> The most common findings on neuroimaging include ventriculomegaly, cavum septum pellucidum, cerebellar tonsillar herniation, megalecephaly, and cerebral and/or cerebellar asymmetry.<sup>225,226</sup>

### **Capillary Malformation-Arteriovenous Malformation Syndrome**

Capillary malformations occurring in a familial fashion were demonstrated to be associated with the *CMC1* locus on chromosome 5q in 2002 and subsequently shown to be associated with inactivating mutations in the gene *RASA1*.<sup>227,228</sup> These individuals were also shown to have a predisposition toward the development of AVMs (see *Arteriovenous Malformation* section), AV fistulae, or Parkes Weber syndrome, and this autosomal dominant disorder was subsequently named *capillary malformation-arteriovenous malformation (CM-AVM) syndrome*. The hallmark skin lesions are capillary malformations that are typically multiple (Fig. 12-68); occur in a haphazard distribution; may reveal pink, red, brown or gray coloration; and occasionally have an associated white halo.<sup>229,230</sup> They are often present at birth but may continue to develop during childhood, a key feature that should suggest the need to consider this diagnosis.

The AVMs in CM-AVM syndrome may be cutaneous, subcutaneous, intramuscular, intraosseous, or cerebral, and arteriovenous fistulae (AVFs) may also be present. Occasionally one patient may have two or more AVMs or AVFs. Aneurysmal malformation of the vein of Galen has been described.<sup>230</sup> Spinal AVMs or AVFs have more recently been recognized in association with CM-AVM syndrome and *RASA1* mutation,<sup>231</sup> highlighting the importance of both brain and spine imaging (as well as mutation analysis) for patients in whom the disorder is suspected.<sup>232</sup>

### **Bannayan–Riley–Ruvalcaba Syndrome**

Bannayan–Riley–Ruvalcaba syndrome (BRRS) is an autosomal dominant, multiple hamartoma syndrome caused by mutations in the *PTEN* gene. This syndrome is one of the so-called *PTEN hamartoma tumor syndromes*, which also include Cowden syndrome (see Chapter 9), Lhermitte–Duclos syndrome, and some cases of Proteus syndrome. The hallmarks of BRRS are macrocephaly, lipomas, penile lentigines (involving the glans penis), developmental delay, and vascular malformations. The latter have been inconsistently described in the literature

as “hemangiomas” or “angiomas” but are actually vascular malformations usually of the capillary type. AVM has also been described in patients with BRSS.<sup>233</sup> Cowden syndrome and BRSS are considered allelic disorders and share several clinical features, possibly including the predisposition to malignant tumors known to exist in the former.<sup>234,235</sup> Some consider these two disorders to be one condition with variable expression and age-related penetrance.

### **Cobb Syndrome**

Cobb syndrome (cutaneomeningospinal angiomyomatosis) consists of the association of a cutaneous vascular malformation with a vascular malformation (often an AVM) involving the same metamere of the spinal cord. The cutaneous and spinal-cord lesions usually correspond within a segment or two of the involved dermatome.<sup>236</sup> The skin lesions present as a dermatomal capillary malformation with or without a deeper vascular component and occasionally with hyperkeratosis of the surface suggestive of an angiokeratoma. The importance of recognizing this cutaneous lesion lies in the resultant ability to image the spine and refer a patient for neurosurgical therapy before symptoms ensue. Neurologic symptoms related to the spinal-cord vascular malformation may include root pain, motor dysfunction, paresthesias, and spastic paralysis.<sup>236,237</sup>

Evaluation of the patient with a dermatomal capillary malformation should include MRI of the corresponding region of the spinal cord with consideration for spinal angiography. Treatment options may include surgery (when feasible), endovascular embolization, radiation, and steroid therapy, and the goal of therapy is to minimize neurologic sequelae by reducing mass effect, venous hypertension, and vascular steal.<sup>238</sup>

### **Beckwith–Wiedemann Syndrome**

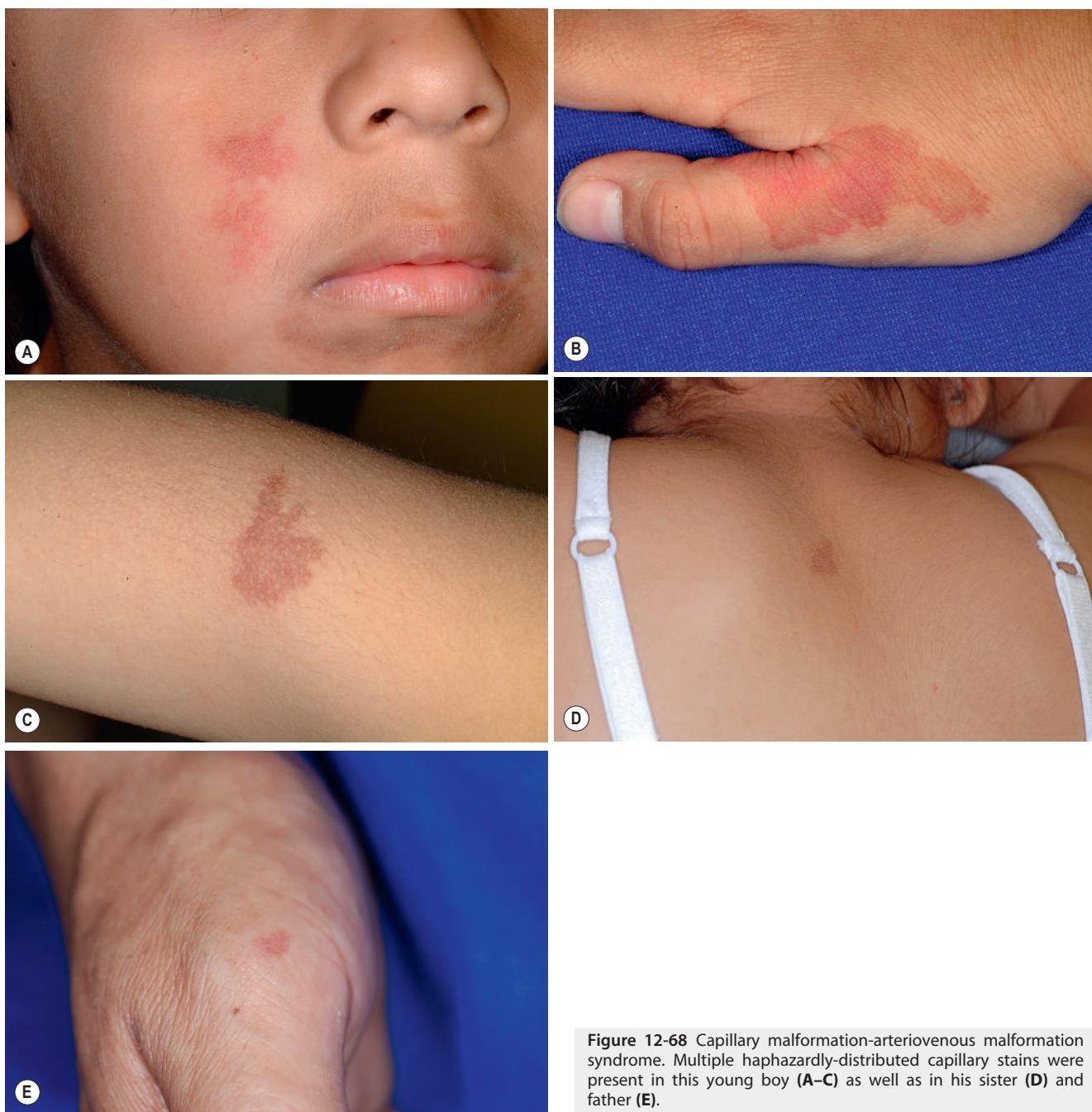
Beckwith–Wiedemann syndrome (BWS) is a genetic overgrowth syndrome characterized most classically by visceromegaly, macroglossia, various developmental defects, and neonatal hypoglycemia. It is the most common of the overgrowth syndromes.<sup>239</sup> BWS is a multigenic disorder with dysregulation of the expression of imprinted genes residing in the 11p15.5 region.<sup>240</sup> The inclusion of BWS in this section relates to the common occurrence of a facial capillary malformation involving the midforehead, glabella, and upper eyelids. This malformation may extend to involve the nose and upper lip in some patients.

Clinical features of BWS, which are variable, include omphalocele, macrosomia, and macroglossia. Overgrowth may be generalized or limited to specific body regions and may be associated with an advanced bone age. In addition to omphalocele, other abdominal-wall defects include umbilical hernia, prune-belly sequence, and inguinal hernia. Visceromegaly may involve the kidneys, liver, spleen, and pancreas. Hypoglycemia is the most common laboratory finding and tends to regress during early infancy. Patients with BWS have an increased risk of malignant tumors including Wilms tumor, adrenocortical carcinoma, and hepatoblastoma.<sup>241</sup> Perinatal features include prematurity, polyhydramnios, enlarged placenta, distended abdomen, and large fetal size.<sup>239</sup> Prenatal ultrasound may be useful in detecting the latter four features, enabling an early diagnosis of the syndrome.<sup>239</sup>

## **VENOUS MALFORMATION**

Venous malformation (VM) is a fairly common slow-flow type of vascular malformation present at birth. Various inaccurate names have been used to describe these lesions in the literature, including *venous angioma*, *cavernous angioma*, and *cavernous hemangioma*. It should be remembered that VM, like all vascular malformations, is a nonproliferative collection of abnormal vessels distinct from IH and other proliferative vascular tumors. They usually grow with the child. Although these lesions are present at birth, they occasionally may not become obvious until later in life. In addition, VM may rapidly enlarge after trauma, and occasionally this may be the initial presentation.

VM tends to present as blue to purple nodules in the skin (Fig. 12-69). Surrounding veins maybe prominent, and calcified phleboliths may be present within the lesion. These are the result of spontaneous local venous thrombosis within the malformation. Most VMs are asymptomatic, although they may occasionally become painful in association with their gradual enlargement and pressure on



**Figure 12-68** Capillary malformation-arteriovenous malformation syndrome. Multiple haphazardly-distributed capillary stains were present in this young boy (**A-C**) as well as in his sister (**D**) and father (**E**).

surrounding structures. Although most VMs are isolated, they may occur in association with other syndromic features such as in Maffucci syndrome and blue rubber bleb nevus syndrome (BRBNS) (see below). VM can occur in any body location, although head and neck lesions tend to be the most extensive.<sup>242</sup>

The diagnosis of VM can be confirmed with CT, MRI (with or without venography), or Doppler ultrasonography. Plain radiographs may reveal the calcifications associated with phleboliths (which present as painful, firm nodules). Other complications of VM (in addition to thromboses) include disfigurement with psychosocial distress (Fig. 12-70), pain, limitation of motion, bleeding coagulopathy (usually localized intravascular coagulopathy [LIC]), and functional compromise related to location of the lesion. LIC typically presents with pain, elevation of the D-dimer and variable fibrinogen levels.<sup>243</sup> Treatment for VM is difficult and may include compression with elastic stockings (which helps to limit swelling, decrease pain, and decrease the risk of coagulopathy in extremity lesions), surgery,

physical therapy, and percutaneous sclerotherapy. Low-dose aspirin therapy or low molecular-weight heparin may be useful in patients prone to thrombotic changes/LIC within the lesions. A multidisciplinary approach to therapy is desirable, with the goals of improving cosmesis, decreasing pain, limiting bony deformities, and maintaining function.

#### Maffucci Syndrome

Maffucci syndrome is a rare, congenital, nonhereditary disorder characterized by the combination of dyschondroplasia and vascular malformations. The cutaneous lesions in this disorder are compressible, red-blue papules and nodules most consistent with VMs. They may develop thrombi and phleboliths, with the associated calcifications visible on plain radiography.<sup>244</sup> These vascular malformations may occur anywhere on the skin surface but are often more extensive on one side of the body and have a preference for the hands and feet.<sup>245</sup> In addition to these lesions, LM<sup>246</sup> and spindle-cell



**Figure 12-69** Venous malformation. Note venous prominence of the medial and plantar surfaces and the swelling of the dorsal foot.



**Figure 12-71** Blue rubber bleb nevus syndrome. This patient has multiple blue-purple, compressible papules and papulonodules.



**Figure 12-70** Venous malformation. This blue nodular plaque involved the right medial cheek and lateral nose, and became more disfiguring as this young boy grew older, posing a psychosocial concern.

hemangioendothelioma<sup>247</sup> (a proliferative vascular tumor) are occasionally present. The vascular malformations of Maffucci syndrome may involve extracutaneous sites in some patients, including mucosal regions, bones, the respiratory tract, and the GI tract.

In addition to the vascular malformations, patients with Maffucci syndrome have enchondromas, which are the result of a developmental abnormality in cartilage formation (dyschondroplasia). These lesions start to develop during early infancy in conjunction with the vascular anomalies. They present as hard nodules over areas of long bones, hands, fingers, and feet. Occasionally they may enlarge and become so numerous as to result in grotesque deformity. Radiographically, enchondromas appear as irregular cystic lucencies. Other progressive skeletal abnormalities (marked bony deformities, pathologic fractures) may occur, as may neurologic deficits related to cerebral encroachment of skull enchondromas.

A significant risk in patients with Maffucci syndrome is that of malignancy, especially chondrosarcoma, which tends to arise from preexisting enchondroma lesions (up to 40% of which may transform into chondrosarcomas).<sup>248</sup> Other malignancies may also occur with increased incidence in these patients. Intracranial chondrosarcoma may rarely occur.<sup>249</sup> Maffucci syndrome has been shown to be caused by somatic mosaic mutations of *IDH1* and *IDH2*.<sup>250</sup>

#### Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus syndrome (BRBNS; also called *Bean syndrome*) is a rare disorder characterized by the presence of cutaneous and GI

VMs. Other visceral organs may occasionally be involved. Although usually a sporadic disorder, autosomal dominant inheritance has been reported.<sup>251</sup>

Patients with BRBNS have signs at birth or during early childhood of numerous blue to purple, soft, compressible nodules (Fig. 12-71). The lesions range in size from a few millimeters to 4 cm. Any area of the skin may be involved, as well as mucosal surfaces of the mouth and genitalia. With time, the lesions increase in both size and number. One of the diagnostic features is the ability to compress the nodules, leaving an empty wrinkled sac that then refills rapidly upon withdrawal of the pressure. GI involvement is characterized by hematemesis or melena with chronic anemia. The small bowel is the most common site of GI tract involvement, but lesions can occur anywhere from the mouth to the anus.<sup>251</sup> Blood loss may at times be severe, necessitating transfusion, and intestinal intussusception may occur.<sup>252</sup> Various orthopedic complications owing to adjacent VMs may occur and include bowing and pathologic fractures. CNS involvement with vascular malformations may also be a component of the syndrome.<sup>253,254</sup>

BRBNS may be diagnosed based on the clinical presentation, although other diagnostic studies may be necessary and may include CT, MRI, barium studies, skin biopsy, and upper and lower GI tract endoscopy. Capsule endoscopy and intraoperative enteroscopy have been reported as useful for thorough investigation of the small bowel.<sup>255</sup> Treatment of the condition is primarily supportive and may include iron replacement, transfusions, endoscopic sclerotherapy, band ligation or laser photocoagulation, and resection of severely involved portions of the GI tract. The response to pharmacologic agents is variable. Subcutaneous octreotide, a somatostatin analog used to decrease splanchnic blood flow in patients with GI bleeding, may be useful in decreasing the need for blood transfusion.<sup>256</sup> Other reported agents include corticosteroids, interferon  $\alpha$ , and vincristine.<sup>257</sup>

#### ARTERIOVENOUS MALFORMATION

Arteriovenous malformations (AVMs) are rare fast-flow vascular malformations consisting of both arterial and venous components with AV shunting. These lesions may vary in their clinical presentation, from macular erythema to thin vascular plaques to larger pulsating nodules or masses with an audible bruit. They typically range from stage I (pink patches or macules that may mimic a capillary malformation) to stage IV (larger lesions characterized by the presence of cardiac compromise). A bruit may be appreciated upon auscultation or with bedside Doppler ultrasonography and supports the diagnosis. AVMs may display aggressive growth patterns and result in functional or cosmetic deformity and in some patients, cardiovascular compromise related to increased blood flow. They are the most endangering type of vascular anomaly. Potential associations with AVMs include CM-AVM syndrome, Parkes Weber syndrome, Cobb syndrome, and



**Figure 12-72** Macrocytic lymphatic malformation.

hereditary hemorrhagic telangiectasia (HHT) (all are discussed elsewhere in this chapter). Diagnostic confirmation of an AVM may involve ultrasound with color Doppler study, CT or MRI evaluation, or arteriography. Treatment is notoriously challenging and includes surgical excision, embolization, and amputation. Multidisciplinary management is advisable when available.

## Disorders of Lymphatic Vessels

The lymphatic system is a complex network of thin-walled vessels responsible for carrying tissue fluid to the venous system.<sup>258</sup> Anomalies of the lymphatic system may include lymphedema and LMs. Lymphedema occurs as a result of aplasia or hypoplasia of lymphatic channels or obstruction of lymphatic pathways. LMs are slow-flow malformations that occur as a result of hyperplasia of the lymphatic network. Older terminologies for LMs are common in the literature, including *lymphangioma*, *cavernous lymphangioma*, *lymphangioma circumscriptum*, and *cystic hygroma*. These malformations are probably best described in accordance with the modern classification as LMs and further classified as macrocytic, microcystic, or combined.

LMs are composed of interconnected lymphatic channels and present differently depending on the size of these aberrant vessels. LMs may remain undiagnosed for years and may initially present after trauma with resultant enlargement, hemorrhage, or secondary infection.

Macrocytic LMs are composed of large interconnected lymphatic channels and cysts. They have been most commonly referred to as *cystic hygromas* or *cavernous lymphangiomas* in the literature. They may occur in any location, although the head, neck, axilla, and chest are the most common sites. Although macrocytic LM was once considered a diagnostic sign of Turner syndrome, it is now known that these lesions may be associated with other karyotypic abnormalities and malformation syndromes.<sup>258</sup> Other potential associations include Down syndrome, trisomy 18, trisomy 13, and Noonan syndrome. Teratogens may also be associated with macrocytic LM. These lesions are typically present at birth, and may be recognized antenatally on prenatal ultrasound.<sup>259</sup>

Macrocytic LM presents as a large, somewhat translucent mass lying under normal-appearing skin (Fig. 12-72). It enhances with transillumination. Acute hemorrhage within an LM may result in swelling, tenderness, and purple discoloration. Diagnostic confirmation can be made with ultrasound, CT, or MRI examination. Prenatal and neonatal complications include lymphedema, facial deformity, and effusions (pleural, pericardial, abdominal). Hydrops fetalis, heart failure, respiratory compromise, and intrauterine demise may occasionally occur. Treatment options for macrocytic LM include surgical excision; serial aspirations; and sclerosing therapy with bleomycin, OK-432 (Picibanil), ethanol, sodium tetradecyl sulfate (STS) or doxycycline.<sup>259–263</sup> Oral sildenafil, which selectively inhibits phosphodiesterase-5 and is normally utilized for pulmonary hyper-



**Figure 12-73** Microcystic lymphatic malformation. Note the multiple flesh-colored, translucent papules with hemorrhagic changes in some of the lesions.



**Figure 12-74** Combined microcystic/macrocytic lymphatic malformation with hemorrhage. There are numerous surface blebs (microcystic component), many of which reveal hemorrhage. This young boy also had a large underlying macrocytic lymphatic malformation. Note the surgical scars from past excisions.

tension and erectile dysfunction, resulted in marked reduction in size in three young children with large LMs and is being further studied.<sup>264</sup>

Microcystic LMs are a more common form of LM, representing microscopic aggregations of small lymphatic channels. These lesions usually present as cutaneous plaques or nodules with superimposed changes in the overlying skin. These surface changes consist of erythematous to flesh-colored papules that may be somewhat translucent (Fig. 12-73), accounting for the traditional analogy with frog spawn. The differential diagnosis of the superficial component of microcystic LM may include warts, molluscum contagiosum, herpes simplex, herpes zoster, and epidermal nevus. Perianal lesions may be misdiagnosed as anogenital condylomata.<sup>265</sup> Hemorrhage may occur within the superficial component (Fig. 12-74), and intermittent swelling or bruising may be a feature. Other complications include intermittent leakage of lymph fluid, inflammation, and secondary infection.

Microcystic LMs often present during infancy and may involve any area of the skin or mucosa. Oral lesions are quite common, most often involving the tongue (Fig. 12-75) or cheek. Microcystic LM is often (but not always) treatable by surgical excision.

## LYMPHEDEMA

*Lymphedema* refers to a set of conditions characterized by interstitial accumulation of lymphatic fluid and may be primary or secondary



**Figure 12-75** Microcystic lymphatic malformation of the tongue. This boy has extensive involvement of his tongue with translucent papules, several of which reveal hemorrhage. The white color of some lesions relates to maceration from the moist environment of the mouth.



**Figure 12-76** Congenital lymphedema. Note the fullness of the dorsal aspect of the foot in this infant male.

**Table 12-6** Classification of Lymphedema

Type	Comment
<b>PRIMARY</b>	
Congenital lymphedema	Single extremity or multiple limbs
Lymphedema praecox	Pubertal or postpubertal females
Lymphedema tarda	Usually after 35 years of age
Milroy disease	AD form of congenital familial lymphedema; linked most commonly to mutations in <i>FLT4</i> gene ( <i>VEGFR3</i> )
Lymphedema-distichiasis	AD; lymphedema in association with distichiasis (supplementary row of eyelashes); linked to mutations in <i>FOXC2</i> gene
Hypotrichosis-lymphedema-telangiectasia	AD; linked to mutation in <i>SOX18</i> gene
<b>SECONDARY</b>	
<b>Lymphedema Occurring after Disruption of Lymphatic Pathways by:</b>	
Disease	Filariasis
Surgery	Lymph node dissection
Radiation therapy	
Burns	
Pregnancy	
Large/circumferential wounds to the extremity	

Modified from Rockson SG. Lymphedema. Am J Med 2001;110(4):288–95, Rockson SG. Diagnosis and management of lymphatic vascular disease. J Am Coll Cardiol 2008;52:799–806, and Murdaca G, Cagnati P, Gulli R, et al. Current views on diagnostic approach and treatment of lymphedema. Am J Med 2012;125:134–40.

AD, Autosomal dominant.

(Table 12-6). Primary lymphedema is related to anatomic abnormalities in the lymphatic system, which may include hypoplasia of vessels, absence of lymphatic valves, and/or impaired contractility of the structures. Secondary lymphedema, which results in disruption or obstruction of lymphatic pathways, arises as a consequence of disease, surgery, or radiotherapy.<sup>266,267</sup> Primary lymphedema most often involves the lower extremities, whereas upper-extremity involvement is more common in secondary lymphedema.

Lymphedema presents as edema of the affected extremity. Early in the course the involved region is puffy (Fig. 12-76), whereas later in



**Figure 12-77** Lymphedema. This 10-year-old girl had long-standing, nonpitting edema of her feet bilaterally.

the course the area becomes more fibrotic and indurated. Secondary cutaneous changes may be present, including a “peau d’orange” appearance of the overlying skin, pigmentary changes, and recurrent episodes of cellulitis. When a lower extremity is involved, swelling of the dorsal aspect of the foot (Fig. 12-77) is common with a characteristic blunt, “squared off” appearance of the digits.<sup>266</sup> The staging system for lymphedema includes stages 0 or Ia (subclinical state without appreciable swelling) through III (lymphostatic elephantiasis with or without pitting and with trophic skin changes including acanthosis, deposition of fat and fibrosis, and warty overgrowths).<sup>268</sup>

Congenital lymphedema may involve a single extremity (upper or lower) or multiple limbs, and the changes are present at birth. Lymphedema praecox, which usually occurs in females around the time of puberty, presents as edema of the foot or ankle or rarely with upper extremity involvement.<sup>269</sup> Milroy disease is an inherited form of lymphedema, usually occurring with an autosomal dominant pattern of transmission, most commonly resulting from mutations in *FLT4/VEGFR3* (see Table 12-6). Limb swelling in all extremities is

possible, although bilateral lower-extremity lymphedema is most typical.<sup>270</sup>

The diagnosis of lymphedema is usually a clinical one. Useful findings include edema, fibrosis, *peau d'orange* appearance of the skin, and a positive Stemmer sign (inability of the examiner to tent the skin at the base of the digits in the involved extremity).<sup>267</sup> In cases where further diagnostic confirmation is necessary, available options include indirect radionuclide lymphoscintigraphy, lymphangiography, MRI or CT imaging, and Doppler ultrasonography. Therapy for lymphedema includes massage (manual lymphatic drainage), elevation, compression garments, physical therapy/exercise, and meticulous skin care in an effort to prevent skin breakdown and infection. Intermittent pneumatic compression may be useful. Surgical approaches are reserved for patients with severe disease who have failed conservative measures and include excision of lymphedematous tissues, use of a lymphatic collector or interposition vein segment to restore lymphatic continuity, or lymphaticovenous anastomoses. Pharmacologic therapy is of limited use but may include diuretics, benzopyrones (including rutosides and bioflavonoids), and antimicrobial agents (as needed).

### GORHAM SYNDROME

Gorham syndrome (Gorham–Stout disease, disappearing bones, vanishing bone disease, massive osteolysis) is a rare condition of unknown origin characterized by progressive bony destruction with intramedullary proliferation of thin-walled vascular structures. Many affected patients have cutaneous vascular lesions as well. Although there is no consensus on the nature of these vascular elements, several authors have proposed that they represent lymphatic vessels.

Patients with Gorham syndrome are usually children or young adults, and they show pathologic fractures and/or bone pain. Nearly any bone may be involved, but most common are the ribs, scapula, clavicle, humerus, pelvis, spine, femur, skull, and mandible.<sup>271,272</sup> It may occur in a focal fashion with spread to contiguous bony structures and occasionally with multicentric, widespread involvement. Nonskeletal manifestations include respiratory distress, pleural effusions, ascites, and chylothorax. Chylothorax is an uncommon but often fatal complication of Gorham syndrome and may be associated with malnutrition, lymphocytopenia, and infection.<sup>271</sup> The diagnosis of Gorham syndrome is confirmed by the finding of osteolytic changes on radiography without reparative bone formation and in the absence of soft-tissue mass and by histologic evaluation of biopsied material.<sup>273</sup>

The natural history of Gorham syndrome is variable, and therapy is difficult. Surgical resection, bone grafting, fractionated radiation therapy, and chemotherapy have all been used with variable results.

### MULTIFOCAL LYMPHANGIOENDOTHELIOMATOSIS WITH THROMBOCYTOPENIA

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT; also known as *cutaneovisceral angiomyomatosis with thrombocytopenia*) is a condition characterized by multifocal, congenital, and progressive vascular papules and nodules involving the skin and GI tract in association with severe GI bleeding and thrombocytopenic coagulopathy.<sup>274</sup> Histologically these vascular lesions reveal collections of ectatic, thin-walled vessels lined by hobnailed endothelial cells and express markers such as CD31 and LYVE-1, which suggest they are consistent with lymphatic differentiation.

Clinically MLT presents with multiple vascular lesions that are red to brown to purple macules (Fig. 12-78), papules, and nodules varying in size from a few millimeters to several centimeters. They may number in the hundreds, may have a scaly surface, and may be indurated, suggesting deeper dermal or subcutaneous involvement. GI tract bleeding may be severe, and endoscopy reveals diffusely distributed mucosal vascular lesions in the stomach and the small and large intestines. Thrombocytopenia is usually present with normal to slightly elevated coagulation studies (prothrombin and partial thromboplastin times) and variable values for fibrinogen and D-dimer in patients reported to date. Other organs of potential involvement include the lungs, synovium, muscle, bone, eye, bone marrow, spleen, and brain.

Treatment for MLT is challenging, and therapies reported to date (with variable response) have included corticosteroids, interferon  $\alpha$ ,



**Figure 12-78** Multifocal lymphangioendotheliomatosis with thrombocytopenia. This neonate had multiple cutaneous vascular macules as well as multiple GI lesions with severe bleeding and thrombocytopenia. (Courtesy of Beth A. Drolet, MD.)



**Figure 12-79** Angiokeratoma. This was an isolated lesion in an otherwise-healthy 14-year-old female.

blood-product transfusions, octreotide, aminocaproic acid, thalidomide, propranolol, intravenous immunoglobulin, bevacizumab, suture ligation of GI tract lesions, and colectomy.<sup>274–277</sup>

### ANGIOKERATOMAS

Angiokeratomas are skin lesions characterized by ectasia (dilation) of the superficial vessels of the dermis and hyperkeratosis of the overlying epidermis. They present as hyperkeratotic, dark red to purple or black papules (Fig. 12-79) measuring between 1 mm and 10 mm in diameter. Several types of angiokeratoma are recognized, and although these lesions usually occur sporadically, they may occasionally be associated with potentially serious metabolic disease.

#### Solitary or Multiple Angiokeratomas

These usually occur on the lower extremities of young adults. They are blue to black in color and may sometimes be confused with malignant melanoma. These lesions may be related to preceding trauma or injury.

### Angiokeratoma Circumscriptum

This presents as a plaque composed of multiple, clustered red to purple papules. These lesions may be present at birth or develop during childhood.

### Angiokeratoma of Mibelli

This occurs on the dorsal fingers or toes or in interdigital spaces. These lesions appear during childhood or adolescence, are more common in females, and are inherited in an autosomal dominant fashion.

### Angiokeratoma of Fordyce

This is a condition that presents with numerous red to purple papules on the scrotum or vulva of adults. Scrotal lesions may be seen in association with varicocele or inguinal hernia.

Although these forms of angiokeratoma occur in the absence of associated serious abnormalities, the lesions may occasionally be seen in the setting of potentially serious metabolic disorders.

### Angiokeratoma Corporis Diffusum

Angiokeratoma corporis diffusum (ACD) is the name used to describe lesions that present as numerous dark red to black papules distributed primarily on the abdomen (Fig. 12-80), genitals, buttocks, and thighs ("bathing-trunk" distribution). The most common disorder associated with ACD is Fabry disease (FD; also known as *Anderson–Fabry disease*), a rare X-linked recessive disorder caused by deficient  $\alpha$ -galactosidase A. The genetic cause is a mutation in the *GLA* gene (encoding  $\alpha$ -galactosidase A), most often point mutations but occasionally small and large deletions or insertions.<sup>278</sup> Males with FD have an accumulation of glycosphingolipids, which results in dysfunction of the heart, kidneys, and nervous system. Acral paresthesias and acral and/or abdominal pain occur, often within the first decade of life, and may respond to treatment with carbamazepine. Other findings in FD include corneal and lenticular opacities, hypohidrosis, progressive neuropathy, progressive renal and heart failure, and cerebral artery thrombosis.<sup>279</sup> The angiokeratomas of FD may number in the thousands and tend to cluster in the iliosacral areas, on the scrotum, and around the umbilicus. The first lesions commonly appear on the scrotum and must be differentiated from angiokeratoma of Fordyce. A majority of patients have pinpoint macular purplish spots on the lips, particularly near the vermillion border of the lower lip. These lesions are smaller than those on the skin. The tongue is generally not affected, but hemoptysis and epistaxis have been reported with involvement of the buccal and nasal mucosae. In addition to the typical cutaneous lesions, fine telangiectasias have been described in the axillae and on the upper chest. Enzyme replacement therapy (ERT) with recombinant  $\alpha$ -galactosidase A (available as agalsidase  $\alpha$  and agalsidase  $\beta$ ) is available for treatment of FD, although it may not lead to complete resolution of symptoms in all patients. When started early

in life, however, ERT may halt and even reverse the progressive multi-organ deterioration seen in patients with FD and improve quality of life.<sup>280,281</sup>

There are other inherited lysosomal storage diseases that may have associated angiokeratomas of the skin. Fucosidosis is an autosomal recessive lysosomal storage disease in which deficiency of  $\alpha$ -fucosidase results in multisystem accumulation of oligosaccharides and glycosphingolipids.<sup>282</sup> This disorder is characterized by progressive neuromotor deterioration, seizures, coarse facial features, dysostosis multiplex, visceromegaly, and growth retardation. Recurrent respiratory infections may also occur. The predominant cutaneous feature of fucosidosis is ACD, which may resemble that seen in FD. In distinction to the lesions of FD, however, the angiokeratomas associated with fucosidosis tend to occur earlier in life, usually around 5 years of age and display a more generalized distribution. Other dermatologic features reported in fucosidosis include hypohidrosis or hyperhidrosis, cutaneous vascular abnormalities, and transverse nail bands.<sup>282</sup> Fucosidosis is caused by a mutation in the *FUCA1* gene.

Other metabolic disorders that may be associated with ACD include GM1 gangliosidosis, galactosialidosis,  $\beta$ -mannosidosis, sialidosis, Schindler disease type II and aspartylglycosaminuria. All of these conditions are inherited in an autosomal recessive fashion, and the diagnosis is made by urine oligosaccharide analysis or enzyme assay.

## Disorders Associated with Vascular Dilation

### LIVEDO RETICULARIS

Livedo reticularis is a mottled or reticulated, blue-red discoloration of the skin that occurs predominantly on the lower extremities (Fig. 12-81) and less commonly on the trunk or upper extremities. Ulceration may occasionally occur. Although the pathogenesis of livedo reticularis is unclear, the changes seem to be related to slow blood flow and decreased oxygen tension. Exposure to cold environments usually intensifies this vascular pattern. The distinction between livedo reticularis and cutis marmorata may be clinically difficult, although cutis marmorata tends to disappear with rewarming and may be seen as a normal finding in up to 50% of infants.

The significance of livedo reticularis lies in its possible association with a variety of systemic disorders (Box 12-5; see Chapter 22). Associated disorders may include coagulopathies, autoimmune diseases (including systemic lupus erythematosus, dermatomyositis, rheumatoid arthritis, and scleroderma), systemic vasculitides (including polyarteritis nodosa, granulomatosis with polyangiitis (formerly Wegener granulomatosis), and Churg–Strauss syndrome), arterial occlusive disease, and antiphospholipid antibody syndrome. Sneddon syndrome is characterized by the association of livedo reticularis and cerebral ischemic arterial events such as stroke or transient ischemic attack.<sup>283,284</sup> These patients may have associated antiphospholipid



**Figure 12-80** Angiokeratoma corporis diffusum in Fabry disease. This 19-year-old male had multiple lesions involving the trunk, groin, and thighs.



**Figure 12-81** Livedo reticularis.

### Box 12-5 Associations with Livedo Reticularis

- Autoimmune diseases
- Coagulation disorders
- Hematologic aberration or malignancy
- Hormone-secreting tumors
- Arterial occlusive diseases
- Sneddon syndrome (cerebral ischemic arterial disease)
- Antiphospholipid antibody syndrome
- Systemic vasculitis
- Paraproteinemia
- Drugs

antibodies. Moyamoya disease, a rare chronic cerebrovascular occlusive disease involving the circle of Willis, has also been reported in conjunction with cutaneous livedo reticularis in a child.<sup>285</sup> In rare instances, recurrent small ulcerations may develop on the lower legs and feet in adults with idiopathic livedo reticularis and has been termed *livedo vasculitis* or *livedoid vasculitis*. Mild hypertension and edema of the legs, ankles, and feet may occur in this setting. A variant of this disorder (atrophie blanche) is characterized by white atrophic areas, hyperpigmentation, and ulceration with telangiectatic vessels at their periphery. Atrophie blanche usually occurs on the ankles and dorsal feet in young to middle-aged women but may also occasionally occur in children.

Although there is no specific treatment for livedo reticularis, therapeutic options include avoidance of cold, anticoagulant therapy (especially for patients with ulceration), and treatment of the underlying associated condition.

### FLUSHING AND THE AURICULOTEMPORAL NERVE SYNDROME

Flushing, a transient diffuse erythema of the blush areas (the face, neck, and/or adjacent trunk), is caused by dilation of superficial cutaneous blood vessels mediated by neural mechanisms or the direct action of a vasodilator substance on vascular smooth muscles. Flushing can be caused by emotion; the ingestion of alcoholic or hot beverages; food additives such as sulfites, nitrites, and monosodium glutamate (MSG) in what has been termed the "Chinese restaurant syndrome"; calcium channel blockers such as nifedipine; disulfiram (Antabuse); carcinoid syndrome (a disorder caused by a neoplasm that produces large amounts of serotonin and bradykinin); and other tumors that produce catecholamines such as neuroblastoma, renal-cell carcinoma, or ganglioneuroma.

The auriculotemporal nerve (Frey) syndrome is a phenomenon characterized by unilateral (rarely bilateral) flushing, sweating, or both in the distribution of the auriculotemporal nerve. These changes usually occur in response to gustatory or olfactory stimuli. Frey syndrome is believed to be related to increased irritability of the cholinergic fibers and possibly to misdirected regeneration of fibers during the healing that comes after trauma. It may result after parotid surgery, CNS disease (cerebellopontine angle tumors), cervical sympathectomy, and radical neck dissection.<sup>286</sup> When it occurs in one of these settings, it is usually in an adult.

Frey syndrome in infants and children is less common and is most often noted after the introduction of solid food.<sup>287</sup> It may occasionally be misdiagnosed as a food allergy reaction,<sup>287,288</sup> although the unilaterality of the eruption in most cases should distinguish it from an allergic process. Table 12-7 lists some features that help to distinguish food allergy from pediatric Frey syndrome. In children, the presentation of Frey syndrome is often limited to facial flushing (without sweating), and these changes occur most often after ingestion of fruits (especially citrus fruits and apple), candy, or a favorite food. Perinatal birth trauma from forceps-assisted delivery with subsequent damage to the auriculotemporal nerve may be responsible in many pediatric cases. In those with no history of trauma to the parotid area, congenital aberration of the auriculotemporal nerve pathway between parasympathetic and sympathetic fibers is suspected. The gustatory flushing of Frey syndrome has also been observed in patients with type 1 neurofibromatosis and facial plexiform neurofibromas.<sup>289</sup> The

**Table 12-7** Useful Features for Distinguishing Food Allergy from Pediatric Frey Syndrome

	Food Allergy	Frey Syndrome
Laterality	Often bilateral	Usually unilateral (occasionally bilateral)
Distribution	Patchy and irregular; often	Segmental distribution within areas generalized innervated by auriculotemporal nerve (usually a stripe from mouth angle toward frontotemporal scalp); limited to face
Skin lesions	Urticaria	Flushing (typically without sweating in children)
Pruritus	Present	Absent
Angioedema	May be present	Absent
Other findings	May have respiratory or GI symptoms, anaphylaxis	None
Implicated foods	Commonly cow's milk, egg, soy, wheat, peanuts, tree nuts, fish, shellfish	Commonly citrus fruits, green vegetables, candy (especially sour), child's favorite foods
History	May have associated personal or family history of atopy	May have history of forceps-assisted delivery

Modified from Sethuraman G, Mancini AJ. Familial auriculotemporal nerve (Frey) syndrome. Pediatr Dermatol 2009;26(3):302–5. GI, Gastrointestinal.

clinical presentation is that of bright erythema extending in a patch from the corner of the mouth toward the preauricular cheek and as far as the frontotemporal scalp (Fig. 12-82) that occurs within a few seconds after ingestion of the responsible food. The changes resolve spontaneously over 30 to 60 minutes, and therapy is unnecessary. Spontaneous resolution may occur after a period of time and often is the case in children with Frey syndrome. In adults with severe forms of the disorder, treatments have included topical antiperspirants or anticholinergic ointments and botulinum toxin injections.

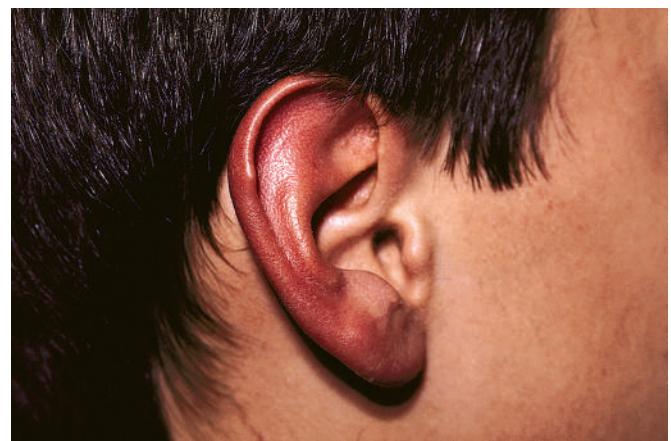
### ERYTHROMELALGIA

Erythromelalgia (also known as *erythermalgia*) is a rare condition characterized by paroxysmal intense burning pain, erythema, and warmth of the skin. It most often involves the distal limbs, especially the feet but also the hands. It may occur in primary or secondary forms and is quite uncommon in childhood. When it does occur in children, it is usually idiopathic.<sup>290,291</sup> Secondary erythromelalgia has been reported in association with various disorders including hematologic diseases (i.e., polycythemia, malignancy, spherocytosis, and thrombotic thrombocytopenic purpura), embolic disease, cardiovascular disease, connective tissue disorders (including lupus erythematosus, rheumatoid arthritis, and vasculitis), infectious diseases, neurologic disease, and musculoskeletal disease, and as a drug-induced condition.<sup>292</sup> In patients with an associated myeloproliferative disorder, the findings of erythromelalgia may precede the diagnosis by months to years.<sup>293</sup> Inherited erythromelalgia has been demonstrated to be caused by gain-of-function mutations in SCN9A, which encodes the voltage-gated sodium channel protein Na<sub>v</sub>1.7.<sup>294,295</sup> These channels are preferentially expressed in primary sensory neurons of the dorsal root and trigeminal ganglion and sympathetic ganglion neurons.<sup>296</sup>

Erythromelalgia presents with striking erythema and warmth of the affected distal extremity that is worsened by heat and relieved by cooling and elevation. The affected skin may have a purple hue. It is



**Figure 12-82** Auriculotemporal nerve (Frey) syndrome. Facial flushing extended from the mouth angle to the frontotemporal scalp in this young girl just seconds after ingestion of solid foods (in this instance, fruit snacks).



**Figure 12-83** Red ear syndrome. This young boy had recurrent episodes of painful burning and redness of the ear.



**Figure 12-84** Cutis marmorata telangiectatica congenita. The reticulate mottling was limited to the chest in this newborn male.

most often bilateral, although it may occasionally be unilateral. Occasionally proximal extension of the warmth and redness up the extremity are noted. Less often the face, ears, or nose may be affected.<sup>297</sup> When severe, erythromelalgia may have a profound effect on quality of life and sleep quality and may disrupt work and social functioning.<sup>292</sup> In a review of 32 pediatric patients with erythromelalgia, physical activity was limited in 66%, with 13% of patients becoming wheelchair-bound as a result of the condition, and school attendance was adversely affected in 34% of the patients.<sup>297</sup> Multiple therapies have been utilized for erythromelalgia with variable (and usually minimal) success. These include cooling, topical anesthetic agents (including lidocaine patches), aspirin, serotonin-reuptake inhibitors, tricyclic antidepressants, anticonvulsants, calcium channel blockers, sympathetic blocks, sympathectomies, intravenous lidocaine, mexiletine, and psychotherapy.<sup>291,292,298,299</sup>

Red ear syndrome (erythromelalgia of the ears, auricular erythromelalgia) deserves mention here. This entity presents with a painful, burning, bright red ear (Fig. 12-83) that occurs paroxysmally and is usually unilateral. Both ears may occasionally be involved. Some have termed this presentation *otomelalgia* given its similarity in presentation to erythromelalgia. Red ear syndrome may represent a migraine variant and in fact may be associated with classic symptoms of migraine headache.<sup>300</sup> Other potential associations include irritation of the third cervical root, temporomandibular joint dysfunction, or thalamic syndrome.<sup>301</sup> Patients with this presentation may respond to therapies directed at migraine headache or a tricyclic antidepressant.<sup>302</sup> Cool compresses of the ears often relieves discomfort acutely during an episode.<sup>303</sup>

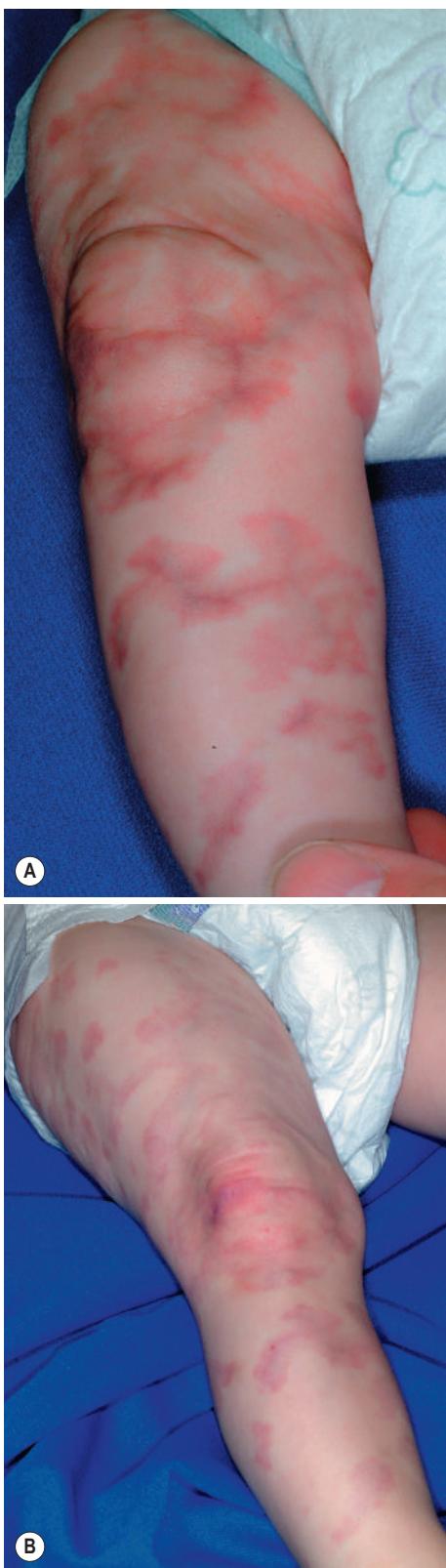
### CUTIS MARMORATA TELANGIECTATICA CONGENITA

CMTC (congenital generalized phlebectasia) is a condition characterized by either localized or generalized reticulate erythema. Although the clinical findings may resemble physiologic cutis marmorata, the changes of CMTC do not disappear with rewarming and may be associated with other abnormalities.

Patients with CMTC exhibit skin changes either at or shortly after birth. Clinical examination reveals red to violaceous, reticulate,

mottled, or mottled patches (Figs. 12-84 and 12-85). The nature of the skin changes may include prominent veins, telangiectasias, and atrophy. The changes may be limited to a localized region of the body or an extremity or may show a diffuse pattern of involvement. When localized, the distribution tends to be segmental with a sharp demarcation at the midline.<sup>304</sup> The skin changes are accentuated by a decrease in the ambient temperature. CMTC lesions may resemble livedo reticularis as well as cutis marmorata, and occasionally ulceration may be present. The color of the skin lesions may vary from light pink to dark purple.

Additional anomalies may occasionally be present in patients with CMTC. A common finding is body asymmetry, especially limb hypoplasia on the affected side.<sup>305,306</sup> Limb hyperplasia may also occasionally occur.<sup>307</sup> Other vascular anomalies may be present in patients with CMTC, most commonly PWS and less often IH.<sup>304,305,308</sup> SWS has been reported in some patients. Ophthalmologic abnormalities include glaucoma, retinal pigmentation, and retinal detachment. Neurologic abnormalities may include macrocephaly, seizures, hydrocephalus, and psychomotor retardation.<sup>221,305,306</sup> Adams–Oliver syndrome is a genetically heterogeneous disorder characterized by CMTC in association with distal transverse limb defects and aplasia cutis congenita of the scalp. Despite the potential associations, most patients with CMTC have only minor associated anomalies or disease limited to the skin. The incidence of associated findings is unclear and varies in the literature from 18% to 89%.<sup>305,307,309</sup> In the authors' experience, the majority of patients do not have associated anomalies. The syndrome previously referred to as *macrocephaly-CMTC* was subsequently renamed *M-CM syndrome* once it was recognized that the vascular



**Figure 12-85** Cutis marmorata telangiectatica congenita. **(A)** This blue-purple, reticulate mottling on the leg of this 2-month-old male does not disappear with rewarming, which distinguishes it from typical cutis marmorata. **(B)** Marked fading was noted at 2 years of age.



**Figure 12-86** Spider angioma. Note lesions on the nasal bridge and the right upper lip.

stains in this condition are actually reticulate PWSs (and not CMTC). This entity is discussed in more detail earlier in this chapter.

The pathogenesis of CMTC is unclear. Histologic examination, when skin biopsy has been performed, reveals dilated capillaries and veins in the dermis. Vascular proliferation analogous to that seen with IH has been reported.<sup>310</sup> The clinical diagnosis of CMTC is usually straightforward. The differential diagnosis may include reticulate PWS, KT syndrome, and disorders with pronounced cutis marmorata such as homocystinuria, Down syndrome, Divry–Van Bogaert syndrome, and Cornelia de Lange syndrome.<sup>304,311</sup> It is important to recognize that CMTC-like lesions may also occur in the setting of neonatal lupus erythematosus.<sup>312</sup> Diffuse genuine phlebectasia (Bockenheimer syndrome) is a rare disorder characterized by large venous ectasias usually limited to an extremity. This disorder is unlikely to be confused clinically with CMTC.

The natural history of CMTC is notable for gradual fading of the cutaneous lesions in most patients. When improvement occurs it tends to be within the first several years of life.<sup>308</sup> Treatment is unnecessary, and in fact PDL therapy seems less effective for these lesions than it is for capillary malformations (i.e., PWSs). Ophthalmologic evaluation is probably unnecessary in most patients but should be considered when there is facial involvement with the vascular process. Referral to a neurologist should be made if neurologic symptoms or features of a complex, multiorgan syndrome are present.

## TELANGIECTASES

Telangiectases are permanent dilations of capillaries, venules, or arterioles in the skin that may disappear on diascopy (gentle pressure with a microscope slide). Many processes affecting the blood vessel endothelium and its supporting structure can lead to the development of this common vascular lesion. Some of these are primary disorders of the blood vessels themselves for which the cause is unknown. Others are secondary and are related to a known disturbance, such as aging, sun exposure, radiation, or a systemic disorder in which they may serve as a useful diagnostic clue. Although telangiectases are usually a sporadic finding without associated underlying abnormalities, a benign hereditary form has also been described. Medical intervention is usually unnecessary, but PDL therapy may be considered for cosmetic purposes.

### Spider Angioma

The spider angioma (nevus araneus) is the best-known type of telangiectasia. It is characterized by a central vascular papule with symmetrically radiating thin branches ("legs") (Fig. 12-86). Spider angiomas appear most commonly on exposed areas of the face, upper trunk, arms, hands, and fingers, and occasionally on the mucous membranes of the lip and nose. They usually blanch with diascopy only to refill and reappear once the glass slide is removed. The central body is an arteriole that at times may reveal pulsations with diascopy.



**Figure 12-87** Angioma serpiginosum.

Although spider angiomas can be associated with liver disease, pregnancy, and estrogen therapy, they are commonly idiopathic and may occur in up to 15% of normal children and young adults. The etiology of spider angiomas in patients with liver disease is unclear, but they seem to be related to alcoholism and impaired liver function.<sup>313</sup>

Whereas some spider angiomas may regress spontaneously, in many individuals they tend to persist indefinitely. Treatment options, when desired, include electrocoagulation or PDL therapy.

### Angioma Serpiginosum

Angioma serpiginosum is a rare condition that manifests as multiple punctate erythematous lesions. It seems to represent a vascular malformation, although vascular proliferation has been reported. The condition is reported most often in young females.

Angioma serpiginosum presents as pinpoint red to violaceous macules that often extend in a serpiginous pattern (Fig. 12-87).<sup>314</sup> There is often some background erythema. The lesions may occasionally appear purpuric and may be confused with various purpuric dermatoses.<sup>315</sup> The disorder is usually localized, and the most common distribution is on the lower extremities, although more extensive involvement may be seen.<sup>314</sup> Angioma serpiginosum tends to be asymptomatic.

Individual puncta of angioma serpiginosum may disappear, but complete spontaneous clearing of lesions is rare. Treatment with the PDL therapy often leads to improvement or resolution.<sup>316,317</sup>

### Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT; also called *Osler–Weber–Rendu syndrome*) is an autosomal dominant vascular disorder characterized by mucocutaneous telangiectases and a bleeding diathesis, as well as vascular malformations in the lungs, liver, GI tract, and CNS. It has been estimated to affect approximately 1 in 5000 to more than 10,000 individuals.<sup>318–321</sup> Two molecular subtypes of HHT are recognized: HHT1 and HHT2. HHT1 is known to be caused by mutations in the endoglin gene, and HHT2 by mutations in the activin receptor-like kinase 1 (*ALK1/ACRV1*) gene.<sup>322,323</sup> Mutations in *SMAD4* give rise to juvenile polyposis/HHT (JPHT).<sup>319</sup> Although there is significant overlap between the clinical findings in HHT1 and HHT2, there appears to be a difference in the rates of underlying vascular anomalies.

Patients with HHT most commonly experience epistaxis and anemia, the latter usually being the result of GI blood loss. The epistaxis may begin in early childhood (an estimated 50% report having nosebleeds by 10 years of age), but the characteristic mucocutaneous telangiectases often do not appear until 5 to 30 years after the epistaxis, often during adolescence or even later.<sup>320</sup> These vascular lesions have a predisposition for certain anatomic sites, including the lips, ears, oral cavity (especially tongue and palate), palms, fingers, soles, and nasal mucous membranes. Lesions may be present under the nails. The telangiectases in HHT are often described as *punctate* or

*macular* (vs. the more classic spider variety with a central core and peripheral radiating vessels). Epistaxis occurs spontaneously on more than one occasion, and nighttime bleeds are particularly suspicious for HHT.<sup>324</sup> Other mucous membranes may also be involved, and hemorrhage may occur from any involved mucosal site. Although the distribution of lesions and associated bleeding diathesis are clinically suggestive of HHT, it may occasionally be difficult to distinguish the cutaneous lesions from those seen in benign disorders such as generalized essential telangiectasia. In addition, the classic distribution of HHT-associated telangiectases may not be observable until the third or fourth decade of life,<sup>318</sup> further compounding the challenge of rendering an early diagnosis.

AVMs may occur in patients with HHT and may be responsible for significant morbidity and even death. Pulmonary and cerebral AVMs are the most classically recognized lesions, although hepatic and spinal AVMs may also occur. Previously “silent” lesions in the lung or brain may hemorrhage, and pulmonary lesions are particularly worrisome because of the risks of hypoxemia or embolism of particulate matter through right-to-left shunts, with neurologic sequelae.<sup>325</sup> Pulmonary AVMs appear less common in HHT2 than in HHT1.<sup>318</sup> Catastrophic intracranial hemorrhage has been reported in infants and children with HHT who were not suspected of having the disease despite family histories of the syndrome.<sup>325</sup> Screening for pulmonary and cerebral AVMs, when clinically indicated, may include chest radiography, pulse oximetry, blood-oxygen determination, and high-resolution CT, MRI, and magnetic resonance angiography (MRA). Transthoracic contrast echocardiography with agitated saline contrast (echo bubble study) appears to be a sensitive test for pulmonary AVMs and is being increasingly utilized as an initial screen for HHT. Hepatic AVMs in patients with HHT do not appear to pose the same risk for catastrophic events as compared with pulmonary or cerebral lesions.<sup>318</sup> Patients may also be prone to vascular lesions in the primarily upper GI tract, which may lead to GI bleeding.

The diagnosis of HHT generally relies on history, clinical examination, and review of family history.

Deoxyribonucleic acid (DNA) diagnostic testing is technically difficult and costly, but testing is available for diagnosis of an affected individual and for prenatal diagnosis. Newborn screening by endoglin protein expression and mutation analysis of umbilical-vein endothelial cells may allow early identification of affected newborns.<sup>326</sup> Treatment of HHT is dictated by the extent of mucocutaneous and organ involvement. Therapies for epistaxis include embolization, laser ablation, and septal dermoplasty, as well as some pharmacologic alternatives such as estrogens, desmopressin (DDAVP), and antifibrinolytic agents. GI tract bleeding is treated with surgical or medical therapies, including hormones, danazol, iron replacement, and octreotide. Treatments for lung, cerebral, and hepatic AVMs depends on the extent of involvement and may include medical therapies, surgery, embolization, and transplantation.

### Unilateral Nevoid Telangiectasia

Unilateral nevoid telangiectasia is a condition characterized by multiple telangiectases in a dermatomal distribution. The condition may be congenital or acquired and may be sporadic or associated with medical conditions (such as chronic liver disease), physiologic states (i.e., puberty, pregnancy), or medications (usually estrogen hormonal therapy).<sup>327,328</sup> Although the etiology is controversial, it may be related to an increased level of estrogen receptors in involved skin.<sup>328</sup>

The condition presents with numerous skin telangiectases in a unilateral distribution, especially involving the upper body or extremities (Fig. 12-88). A dermatomal distribution may or may not be evident. Unilateral nevoid telangiectasia occurs most often in females during pregnancy or puberty. When it occurs in adult males, it is often in association with alcoholic cirrhosis. It has also been reported in association with hepatitis C virus.<sup>328</sup> Treatment is unnecessary, although PDL therapy has been demonstrated to be useful.<sup>329</sup>

### Ataxia-Telangiectasia

Ataxia-telangiectasia (A-T; or Louis–Bar syndrome) is a multisystem autosomal recessive disorder characterized by oculocutaneous telangiectases, cerebellar ataxia, a profound humoral and cellular immunodeficiency, and a predisposition toward hematologic malignancy.



**Figure 12-88** Unilateral nevoid telangiectasia. These telangiectatic macules were limited to the hand, forearm, and upper arm.

A-T is caused by a mutation in the A-T mutated (*ATM*) gene, which maps to chromosome 11q. The protein product of this gene is a nuclear protein involved in the early recognition and response to double-stranded DNA breaks.<sup>330</sup>

There is considerable phenotypic variability in patients with A-T, and patients may differ significantly in their rate of progression or appearance of features.<sup>331</sup> The initial clinical manifestation is often truncal ataxia, which may present as early as infancy.<sup>332</sup> Other neurologic features include choreoathetosis, dysarthria, myoclonic jerks, and oculomotor abnormalities. Affected patients may display drooling; peculiar eye movements; a sad, mask-like facies; and a stooped posture with drooping shoulders and the head tilted forward and to the side. Confinement to a wheelchair by the second decade is not unusual.

The mucocutaneous telangiectases are a variable feature of A-T but not uncommonly help lead to the correct clinical diagnosis. They usually appear around 3 to 5 years of age, most often on the medial and lateral bulbar conjunctivae. Skin telangiectases develop primarily on sun-exposed sites including the ears, cheeks, neck (Fig. 12-89), arms, and upper chest. Other body regions may be affected, and occasionally the cutaneous telangiectases are quite subtle. Other cutaneous findings may include subcutaneous fat loss, progeroid (premature aging) changes of skin and hair, and diffuse hair graying. Segmental, patchy hypopigmentation and hyperpigmentation have been observed,<sup>333</sup> and patients without the telangiectases have been reported.<sup>334</sup> Noninfectious cutaneous granulomas (Fig. 12-90), which present as erythematous plaques, nodules, and ulcers, are a fairly common cutaneous feature in patients with A-T.<sup>335,336</sup> They are usually located on the extremities, with the second most common site being the face. The granulomas less commonly involve the trunk.<sup>337</sup> These lesions tend to be persistent but may be improved by intralesional injections of triamcinolone or short courses of oral corticosteroids (which must be used cautiously given the underlying risk of infection). Some have suggested that these noninfectious lesions are caused by immune dysregulation and its effects on wound healing and tissue repair.<sup>337</sup>

Chronic sinopulmonary infections occur in the majority of patients with A-T. Bronchiectasis with respiratory failure may occur and is the most common cause of death. Growth failure and mental retardation may also occur. Several immunologic defects have been reported in patients with A-T, including decreased IgA, IgE, and IgG and multiple defects in cell-mediated immune responses. Decreased thymic output and skewed T- and B-cell receptor repertoires have been observed.<sup>338</sup>

Lymphoid malignancies occur with markedly increased incidence in patients with A-T. These include Hodgkin disease, non-Hodgkin lymphoma, and leukemia. There appears to be a four- to fivefold increased rate of T-cell tumors compared with B-cell tumors in patients who have A-T.<sup>339</sup> In those with Hodgkin disease there is a reduced survival compared with Hodgkin disease in the general



**Figure 12-89** Ataxia-telangiectasia, telangiectasias. (Reproduced with permission from Bolognia JL, Jorizzo JL, Rapini RR. Dermatology. Philadelphia: Mosby; 2003.)



**Figure 12-90** Ataxia-telangiectasia, granulomas. These granulomatous skin lesions are very resistant to therapy.

population.<sup>340</sup> Of the non-Hodgkin lymphomas, diffuse large B-cell lymphomas account for the majority, and T-cell acute lymphoblastic leukemia is the most common form of leukemia.<sup>339,341</sup>

The diagnosis of A-T usually rests on the clinical findings. Elevated levels of  $\alpha$ -fetoprotein and carcinoembryonic antigen support the diagnosis. Molecular diagnosis and prenatal diagnosis are possible but not readily available, and the familial mutation must be known. Treatment for A-T is largely supportive, including antimicrobial therapy for infection, early therapy for bronchiectasis, neurodevelopmental follow-up care and therapy, and aggressive surveillance for malignancy. Vigorous photoprotection is vital, because A-T patients have a lowered threshold for the development of skin malignancies, and radiation use for treatment of hematopoietic malignancy should be minimized, when feasible. Death is usually the result of chronic bronchiectasis with pulmonary insufficiency and/or pneumonia (55%) or malignancy (15%).



**Figure 12-91** Generalized essential telangiectasia. This patient had a widespread distribution of telangiectases without any bleeding diathesis.

### Generalized Essential Telangiectasia

Generalized essential telangiectasia is a disorder of multiple cutaneous telangiectases without a bleeding diathesis. The condition is notable for a widespread distribution of lesions (Fig. 12-91), progression and/or permanence of the telangiectases, accentuation by dependent positioning, and absence of other epidermal or dermal skin changes (i.e., atrophy, purpura, or dyspigmentation).<sup>342</sup> The most common site of involvement is the lower extremities, and the disorder is more common in females. Oral mucosal and conjunctival telangiectases have occasionally been reported. Although the etiology of generalized essential telangiectasia is unknown, some have suggested a possible autoimmune diathesis.<sup>343</sup> Treatment for this condition is unnecessary. In patients who desire therapy for cosmesis, pulsed-dye or Nd:YAG laser treatments appear effective.

## Pigmented Purpuric Eruptions

Pigmented purpuric eruptions (PPEs; pigmented purpura, pigmented purpuric dermatosis, progressive pigmented purpura) comprise a group of dermatoses characterized by cutaneous petechiae, purpura, and often a yellow-brown pigmentation. Histologically these disorders all reveal inflammation of the superficial dermal capillaries (capillaritis) without frank vasculitis. Table 12-8 lists the five different subtypes of PPE. The etiology of PPE is unknown, and although they occur primarily in adults, they may also occur in children. Proposed associations with PPE include capillary fragility, cell-mediated immune responses, hepatitis B and C infection, and medication reactions.<sup>344–346</sup> The vast majority of children with PPE are healthy and have no associated medical condition.

Schamberg disease is the prototype for PPE, being the most common type and the most common to present in children. Although rare, it may even occur in infants.<sup>347</sup> The primary lesion is a red-brown punctate macule, and multiple such lesions ("cayenne pepper spots") occur at the border of red-brown patches (Fig. 12-92).<sup>345,348</sup> The most common location is the lower extremities, although more widespread involvement may occur. Schamberg disease has been associated with the ingestion of several medications, including aspirin and acetaminophen. In addition there are rare reports of an association

**Table 12-8** Subtypes of Pigmented Purpuric Eruptions

Type	Comment
Schamberg disease	Red-brown patches with petechiae ("cayenne pepper spots"); mainly lower extremities
Majocchi disease	Also called <i>purpura annularis telangiectodes</i> ; punctate, perifollicular, telangiectases present; tend to become annular and hyperpigmented
Lichen aureus	Rust-yellow lichenoid papules and papules; often linear or along Blaschko lines; fairly common in children
Eczematid-like purpura of Doucas and Kapetanakis	Generalized; eczematous, with lichenification and pruritus present
Pigmented purpuric lichenoid dermatitis of Gougerot and Blum	Red-brown, lichenoid papules and plaques; very rare in children



**Figure 12-92** Pigmented purpuric eruption, Schamberg disease. Pin-point, petechial macules coalesce and are superimposed on faint, red-brown patches.

between pigmented-purpura-like eruptions and progression to cutaneous T-cell lymphoma (mycosis fungoides).<sup>349,350</sup> Although seemingly rare, these reports highlight the need to consider this diagnosis in patients (especially adults) with unusually persistent PPE.

Majocchi disease is an annular variant of PPE, presenting with punctuate, perifollicular petechiae, telangiectases, and hyperpigmented annular patches (Fig. 12-93). It occurs primarily in adolescents and younger adults and occurs on the lower extremities as well as the trunk and upper extremities.

Lichen aureus is a unique type of PPE in its presentation. Patients have lichenoid papules that coalesce to form plaques, often with a linear distribution or in some cases, distribution along the lines of Blaschko. The color of the lesions varies from pink to rust-yellow (Fig. 12-94) to purple, and again the lower extremities are the favored site of involvement.

Eczematid-like purpura of Doucas and Kapetanakis is usually a generalized form of PPE with eczematous changes and pruritus. Lichenification (skin thickening with accentuated skin markings) occurs as a result of frequent scratching. Pigmented purpuric lichenoid dermatitis of Gougerot and Blum presents with red-brown, polygonal lichenoid papules with telangiectases.

There are no satisfactory treatments for PPE. In cases where a drug reaction is possible, withdrawal of the offending agent may induce regression. Treatments utilized with variable success have included



**Figure 12-93** Pigmented purpuric eruption, Majocchi disease. Pink-tan patches with petechiae and mild central clearing were present on the lower legs of this adolescent boy.



**Figure 12-94** Pigmented purpuric eruption, lichen aureus. These golden-tan macules and patches distributed in a linear fashion revealed pinpoint petechial macules with diascopy (viewing through a glass slide while applying pressure).

topical and systemic corticosteroids, antihistamines, and psoralens and ultraviolet A (PUVA) light therapy. Therapy with ascorbic acid (vitamin C) and bioflavonoids (specifically rutoside) as well as narrowband ultraviolet B (UVB) phototherapy has also been reported as useful in open-label studies.<sup>351–354</sup> Two young adults with extensive PPE responded to pentoxifylline therapy.<sup>355</sup>

#### Box 12-6 Etiologic Associations with Purpura Fulminans

##### Severe Acute Infection

- Neisseria meningitidis*
- Staphylococcus aureus*
- Streptococcal infections (including invasive pneumococcal)
- Plasmodium falciparum*
- Others

##### Postinfectious

- Varicella
- Streptococcal infections
- Others

##### Inherited Disorders of Coagulation

- Homozygous protein C deficiency (neonatal PF)
- Homozygous protein S deficiency (neonatal PF)
- Factor V Leiden mutation

##### Medication-Related

- Coumarin-induced skin necrosis

##### Other

- Sepsis
- Disseminated intravascular coagulation
- Trauma
- Malignancy
- Obstetric complications
- Hepatic failure
- Immunologic reactions

Modified from Chalmers E, Cooper P, Forman K, et al. Purpura fulminans: recognition, diagnosis and management. *Arch Dis Child* 2011;96:1066–71; Price VE, Ledingham DL, Krumpel A, Chan AK. Diagnosis and management of neonatal purpura fulminans. *Semin Fetal Neonatal Med* 2011;16:318–22, and Thornsberry LA, LoSicco KJ, English JC. The skin and hypercoagulable states. *J Am Acad Dermatol* 2013;69:450–62. PF, Purpura fulminans.

## Purpura Fulminans

Purpura fulminans (PF) is a rare condition characterized by acute, rapidly progressive hemorrhagic necrosis of the skin and disseminated intravascular coagulation. The potential etiologic associations with PF are listed in Box 12-6. It occurs most often in association with severe bacterial (especially meningococcal and *Staphylococcus aureus* septicemia) or viral infection or as a postinfectious syndrome after infections such as varicella or scarlet fever.<sup>356,357</sup> In the latter instance, it usually occurs 10 days to 1 month after the infection. PF has also been described in association with invasive pneumococcal infection.<sup>358</sup> It may also be associated with congenital deficiencies of proteins C or S, which are vitamin K-dependent glycoproteins with antithrombotic properties. In fact, infection-associated PF may be partly the result of acquired deficiencies in these proteins.<sup>359,360</sup> Factor V Leiden, which is a mutated version of factor V, has been shown to be associated with activated protein C resistance, an increased risk of thrombotic events, and exacerbated PF in patients with meningococcal disease.<sup>356,361</sup> PF is associated with significant morbidity and is occasionally fatal, especially in the presence of concomitant meningococcal disease.

PF presents with erythematous macules that progress rapidly into purpura and ecchymoses, often with sharp irregular borders. The lesions are tender, enlarge rapidly, and coalesce with the development of central necrosis, hemorrhagic blebs (Fig. 12-95), and a raised edge with surrounding erythema. The ecchymotic lesions are most commonly distributed on the lower extremities and buttocks, with occasional involvement of the trunk and upper extremities. Deep extension with muscle necrosis and bone involvement may occur. Mucous membranes are usually spared. Chills, fever, tachycardia, anemia, and prostration are common. Visceral involvement is less common but may include CNS and retinal vessel thrombosis, hematuria, and GI hemorrhage. Adrenal gland thrombosis may result in Waterhouse–Friderichsen syndrome. Skin and muscle necrosis may be severe enough to require grafting, and digital or limb ischemia may necessitate amputation. Epiphyseal growth plate necrosis in a growing child



**Figure 12-95** Purpura fulminans. Ecchymotic patches and plaques with necrosis and a hemorrhagic bulla over the knee.

may result in limb foreshortening.<sup>362</sup> Newborn infants with protein C or S deficiency or factor V Leiden have clinical features of PF within 24 hours after birth and are at high risk for widespread thrombosis of capillaries and venules.<sup>363</sup> Children under 4 years of age and those with the factor V Leiden mutation appear to be at increased risk for severe disease and amputation.<sup>357</sup>

Laboratory evaluation in the patient with PF reveals decreased fibrinogen and thrombocytopenia. The prothrombin time and partial thromboplastin time are prolonged, and fibrin degradation products are increased. Protein C, protein S, and antithrombin III levels are decreased. Histologic evaluation of the skin lesions reveals dermal vascular thrombosis and hemorrhagic necrosis.<sup>362</sup>

The treatment for PF depends upon the underlying disorder and/or associated infection. Initial management consists of fluid resuscitation, ventilatory and inotropic support, and antibiotic administration when indicated.<sup>364</sup> Administration of proteins C and S (i.e., in the form of fresh frozen plasma or protein C concentrate) may prevent progression of lesions that are not yet necrotic.<sup>359,365</sup> Repeated infusions may be necessary because of the short half-life of protein C.<sup>359</sup> Antithrombin III concentrate has been administered to some patients. Concomitant heparin has been advocated by some (but not by others), especially when there is evidence for large vessel venous thrombosis. Long-term administration of oral anticoagulants is often necessary in patients with congenital protein C or S deficiency. Packed red blood cell transfusion, platelet transfusion, and cryoprecipitate may each need to be considered in certain patients. Surgical modalities include debridement, autologous skin grafting, tissue and muscle flaps, amputation, skin allografts, and tissue-engineered skin.<sup>366,367</sup>

## Gardner-Diamond Syndrome

Gardner-Diamond syndrome (autoerythrocyte sensitization syndrome, painful bruising syndrome, psychogenic purpura) is a rare disorder characterized by painful bruising and usually seen in patients with emotional or psychiatric disturbance. Historically the disorder was ascribed to a sensitization reaction to the patient's own erythrocytes, hence the alternative nomenclature *autoerythrocyte sensitization syndrome*.<sup>368</sup> The majority of patients with Gardner-Diamond syndrome are adolescent or adult females, with only occasional reports of involved males.

The disorder is characterized by recurrent episodes of spontaneous, painful ecchymoses that are often precipitated by emotional stress. The lesions may vary in size and may involve any part of the cutaneous surface. Most patients report a burning sensation initially. The lesions of Gardner-Diamond syndrome tend to resolve over weeks only to recur again with time. The etiology of this condition remains unclear. In the original reports, patients were noted to have a positive reaction to intradermal injection of their own erythrocytes, which resulted in an ecchymosis.<sup>369</sup> The significance of this finding has been

questioned in subsequent reports, and the immune nature of the condition remains speculative. A number of psychiatric disorders have been observed in association with the cutaneous findings, including depression, anxiety, impulse-control issues, hypochondriasis, hysterical and borderline personality disorders, and obsessive-compulsive behavior.<sup>368</sup> There is no effective treatment for Gardner-Diamond syndrome, which has a chronic unremitting course, and psychiatric evaluation is usually advisable.<sup>370</sup> Psychotropic medications, hypnotherapy, and psychotherapy have been successfully used in some patients.<sup>371</sup>

## Scurvy

Scurvy, which is caused by vitamin C deficiency, is relatively rare in developed countries, although there are several cases described in the literature in children with an inadequate dietary intake of this vitamin.<sup>372</sup> Clinicians caring for children and adolescents must therefore be aware of this disease and its clinical presentation.

Vitamin C (ascorbic acid) is a vital component of the human diet because of the inability of humans to derive it from glucose via gluconolactone oxidase.<sup>373</sup> Ascorbic acid is found primarily in fresh fruits, vegetables, and vitamin supplements. When deficiency of this vitamin occurs in a developed country, it is usually in the elderly, indigent, drug- or alcohol-abusing, or food-faddism populations or those with GI disorders or poor dentition.<sup>373,374</sup> Children at risk include those in neglectful social situations, those with neurodevelopmental disabilities or psychiatric illnesses, those with severe food allergies or GI disease, and those with unusual dietary habits or with parents who are food faddists.<sup>372-377</sup> There are several reports of scurvy in children with autism.<sup>378-381</sup> Because ascorbic acid is a cofactor in the synthesis of collagen and collagen is a vital component of the pericapillary network in the skin, capillary fragility results from deficiency of this nutrient.

Clinical manifestations of scurvy include fatigue, petechiae, ecchymoses, purpura, and perifollicular hemorrhages. The latter finding is considered pathognomonic for the condition. In addition, follicular hyperkeratosis and "corkscrew hairs" may be noted. Purpura often occurs on the lower extremities but may also involve other body regions. Gingival findings include swelling, bleeding, and loosening of teeth. Bony fractures appear to be more common in pediatric patients when compared with adults, and arthralgias, joint swelling and hemarthrosis may occur. Other findings include GI bleeding, conjunctival and intraocular hemorrhage, alopecia, and epistaxis. In some patients, musculoskeletal pain and weakness may be presenting features.<sup>373,376,377</sup> Cardiovascular manifestations of scurvy may include cardiac hypertrophy, postural hypotension, syncope, and possibly hypertension.<sup>373</sup>

Scurvy is usually diagnosed clinically, with the differential diagnosis including hematologic malignancy, vasculitis, infection, coagulopathy, child abuse, and factitial disorder.<sup>372</sup> A serum ascorbic-acid level is usually confirmatory (when <11 µmol/L), although this value may be normal if the patient has had recent intake of vitamin C. Concomitant vitamin deficiencies (especially calcium, vitamin B<sub>12</sub>, or iron) may also be present.<sup>374</sup> The clinical symptoms usually respond promptly to vitamin C replacement, with dosages for infants and children ranging from 100 to 300 mg/day.

The complete list of 381 references for this chapter is available online at <http://expertconsult.inkling.com>.

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Blisters or bullae are rounded or irregularly shaped lesions of the skin or mucous membranes that result from the accumulation of fluid between the cells of the epidermis, the epidermis and stratum corneum, or the epidermis and dermis. The term *bullae* refers to blistering lesions 0.5 to 1 cm in diameter or larger; those smaller than 0.5 cm in diameter are called *vesicles*. The classification of bullous or vesiculobullous disorders is based on clinical morphology and examination of biopsied specimens of lesional or perilesional skin by light microscopy, immunofluorescence analysis, and electron microscopy. It is well recognized that the skin of infants and children is more susceptible to blister formation than that of adults.

## Hereditary Blistering Disorders

### EPIDERMOLYSIS BULLOSA

The term *epidermolysis bullosa* (EB) refers to a group of inherited disorders characterized by bullous lesions that develop spontaneously or as a result of varying degrees of friction or trauma.<sup>1–3</sup> The various subtypes of inherited EB result from mutations in 18 different genes and have recently been reclassified. These phenotypes are divided into four major inherited forms based first on the level of skin cleavage (Fig. 13-1) (the traditional subtypes of EB: simplex, junctional, dystrophic, and Kindler syndrome, a mixed EB type). Subsequent classification is based on the clinical phenotype including distribution of lesions and presence of scarring, the relative severity of cutaneous and extracutaneous involvement, the mode of inheritance, and if available, molecular analysis. In the new classification, the only eponyms that remain are Kindler syndrome and EB simplex (EBS)-Ogna (for lack of better suggested names).

In EBS (epidermolytic EB) the blister cleavage occurs within the epidermis, and healing occurs without scarring. In junctional EB (JEB) the skin separates in the lamina lucida of the dermal–epidermal junction, and blistering leads to atrophic scarring. In dystrophic (dermolysis) EB (DEB) the blister forms in the papillary dermis below the basement membrane, and patients form scars and milia. EB with congenital absence of skin (formerly called *Bart syndrome*) can be seen at birth with any of the major forms of EB (Fig. 13-2), although it most commonly is seen with dystrophic forms of EB. Neonates most commonly show congenital localized absence of skin of the lower extremities. EB acquisita (EBA) is an acquired immune-mediated blistering disorder that can resemble DEB (see *Epidermolysis Bullosa Acquisita* section).

Skin biopsy samples for immunofluorescence mapping have traditionally been used to confirm the diagnosis of EB and to determine the subtype based on the level of cleavage from localization of known antigens in the skin and the presence of structural proteins associated with EB. Biopsies are ideally performed at the edge of a lesion freshly induced by rotating the skin with a moist Q-tip. Light microscopic evaluation of biopsy sections is generally not useful except for rare types (such as lethal acantholytic EB). Although whole exome sequencing has been shown to be more cost effective and efficient for detecting EB gene mutations than sequencing of individual genes suspected to be mutated,<sup>4</sup> at this time immunomapping studies can still be performed much more quickly, providing the family with some prognostic information.

The overall incidence of EB is 1 in every 50,000 births, although the simplex forms comprise the majority of cases. A national EB registry was established in the United States and has generated data beneficial to many families who have children with EB. The Dystrophic Epidermolysis Bullosa Research Association (DEBRA), a national

([www.debra.org](http://www.debra.org)) and international ([www.debra-international.org](http://www.debra-international.org)) group, is dedicated to research and support for patients with all forms of EB and their families.

### EPIDERMOLYSIS BULLOSA SIMPLEX

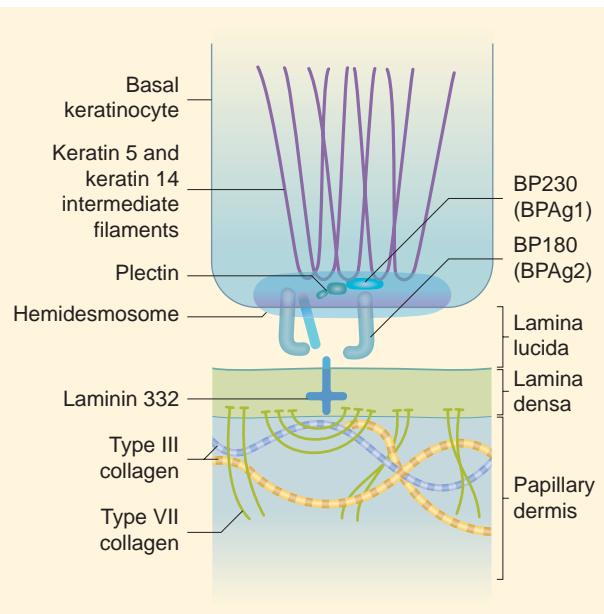
EBS is characterized by blisters that develop in areas of trauma and most commonly results from defective keratin filaments.<sup>5,6</sup> Because the blister cleavage is intraepidermal, lesions tend to heal without scarring. The most common form is basal EBS, which includes localized EBS (formerly called *Weber–Cockayne disease*), generalized intermediate EBS (formerly called *Koebner type*), and generalized severe EBS (formerly called *Dowling–Meara EBS* or *EBS herpetiformis*) (Table 13-1).<sup>3</sup> The vast majority of patients with EBS show autosomal dominant inheritance, although rare autosomal recessive forms have been described.<sup>7,8</sup> Suprabasal EBS includes a variety of autosomal recessive forms with absence of desmosomal components (for example, desmoplakin [DSP] in lethal acantholytic EB).

#### Generalized Severe Epidermolysis Bullosa Simplex

Generalized severe EBS (formerly Dowling–Meara) is the most severe form of EBS from keratin gene mutations (Table 13-2). During the newborn period, the generalized blisters tend to be large and may be difficult to distinguish from those of the severe dystrophic or junctional forms of EB despite the relatively good overall prognosis of babies with this form (Fig. 13-3).<sup>9</sup> Many young infants also show a significant inflammatory reaction in association with blistering and the formation of transient milia at sites of healed blisters, a finding usually characteristic of the dystrophic forms. The characteristic small, clustered (herpetiform) blisters may be seen in neonates, especially on the proximal extremities or trunk, but are more commonly noted during infancy and later childhood (Fig. 13-4). Blistering tends to decrease during later childhood and adulthood, and hyperkeratosis of the palms and soles may develop by 6 or 7 years of age, especially in those younger children with significant palmoplantar blistering (Fig. 13-5). During the neonatal period and early infancy, the extensive blistering may prove life-threatening. After this period, however, the blistering is rarely a threat to life. Nail involvement with sloughing is common in the generalized severe form, but the nails regrow without dystrophy. Similarly, oral and esophageal mucosal blistering may occur and cause problems with feeding and obtaining adequate nutrition, especially with the markedly increased caloric needs of more severely affected infants and younger children. Ocular mucosal blistering is less common, but natal teeth have been described.

#### Generalized Intermediate Epidermolysis Bullosa Simplex

Generalized intermediate EBS (formerly Koebner EBS) is characterized by generalized blistering of skin, most notable at sites of friction (see Table 13-2). Extensive blistering in the neonatal period and early infancy increases the risk of sepsis and may be life-threatening. In general the tendency toward blistering tends to improve with advancing age, particularly by teenage years. Hyperhidrosis is common, and mild to moderate hyperkeratosis of the soles is often present. Although erosions of the mucous membranes may be seen in the newborn as a result of vigorous sucking, mucosal involvement is generally mild and the nails are rarely affected, in contrast to the generalized severe form. Involvement of the conjunctiva and cornea has rarely been described. Migratory circinate EBS results from mutations in the tail domain of *KRT5*, and is characterized by small blisters on the hands, feet, and legs with migratory circinate erythema (Fig. 13-6) and often postinflammatory hyperpigmentation.<sup>10</sup> There is no mucosal or nail involvement.



**Figure 13-1** Schematic of the structural elements of the basal keratinocytes, basement membrane zone, and upper dermis.



**Figure 13-2** Epidermolysis bullosa (EB). Congenital localized absence of skin, also known as *Bart syndrome*, is now known to be a pattern seen in any of the three major subsets of EB. This baby with Bart syndrome has a form of junctional EB, but denudement at birth is most often seen in babies with dystrophic EB and occasionally EB simplex.

### Localized Epidermolysis Bullosa Simplex

Localized EBS (formerly Weber–Cockayne EBS) is the most common clinical variant (see Table 13-2). A relatively high threshold of frictional trauma is required to induce blister formation. Bullae are usually confined to the hands and feet (primarily the palms and soles; Fig. 13-7); they are often first seen in infants but may not appear until adolescence or early adulthood. The bullae are usually associated with trauma, occur more readily in hot weather with sweating of the feet, and do not tend to be seriously debilitating, although activities that involve trauma to the feet are often restricted. Hyperhidrosis is common, and hyperkeratosis of the palms and soles, although often present, is usually mild. Lesions heal rapidly without scarring, nail involvement rarely occurs, and the mucous membranes do not tend to be involved. In young children, blisters may develop on the knees from the frictional trauma of crawling. In adolescents and young adults, blisters often occur on the feet after long hikes or dancing or on the hands after a game of tennis or golf. EBS with mottled pigmentation is characterized by a mottled, reticulated pigmentation (Fig. 13-8), particularly of the trunk and neck, in association with mild

**Table 13-1** Classification and Affected Genes in Epidermolysis Bullosa Simplex

Type	Inheritance	Affected Gene
EBS, suprabasal, acantholytic	AR	DSP/desmoplakin
EBS, suprabasal, acantholytic	AR	JUP/plakoglobin
EBS, suprabasal, skin fragility—plakoglobin deficiency	AR	JUP/plakoglobin
EBS, suprabasal, skin fragility—woolly hair	AR	DSP/desmoplakin
EBS, suprabasal, skin fragility—ectodermal dysplasia	AR	PKP1/plakophilin-1
EBS, suprabasal, acral peeling skin syndrome	AR	TGM5 (see Ch. 5) Transglutaminase 5
EBS, suprabasal; EBS superficialis	AD or AR	?
EBS, basal, generalized severe (formerly Dowling–Meara)	Usually AD	KRT5, KRT14/ keratins 5, 14
EBS, basal, generalized intermediate (formerly Koebner)	Usually AD	KRT5, KRT14/ keratins 5, 14
EBS, basal, localized (formerly Weber–Cockayne)	Usually AD	KRT5, KRT14/ keratins 5, 14
EBS, basal, with mottled pigmentation	AD	KRT5 > KRT14
EBS, basal, migratory circinate	AD	KRT5, C-terminal
EBS, basal, Ogna type	AD	PLEC1/plectin
EBS, basal, with muscular dystrophy	AR	PLEC1/plectin
EBS, basal, with pyloric atresia	AR	PLEC1/plectin
EBS, basal, BP230	AR	DST-e/dystonin-e
EBS, basal, exophilin 5	AR	EXPH5/exophilin

AD, Autosomal dominant; AR, autosomal recessive; EBS, epidermolysis bullosa simplex.

acral blistering (see Table 13-2). Patients often show small verrucous papules of the hands and feet and palmoplantar keratoderma.<sup>11</sup>

### Genetic Basis of Dominant Forms of Basal Epidermolysis Bullosa Simplex

Basal EBS most commonly results from mutations in the genes encoding keratin 5 and keratin 14 (the keratins expressed in basal cells). Keratins are the most abundant proteins of epidermal keratinocytes, and keratin pairs are critical for the filamentous network that provides integrity to epidermal cells. When a point mutation occurs in one of the keratin alleles, resulting in a change in one amino acid, the abnormal keratin protein is still able to form filaments, but these filaments are abnormal. The abnormal filaments do not provide adequate structural integrity to the cell, and as a result, the cell lyses. Cytolysis of epidermal basal cells is the essential histologic feature of all forms of EBS resulting from keratin gene mutations. Electron microscopic examination shows cleavage through the basal layer (above the periodic acid–Schiff-positive basement membrane of the epidermis). In the severe generalized form, clumping of tonofilaments and displacement of nuclei are seen ultrastructurally. The risk of cell lysis and the trauma required to elicit the blistering depend on the site of the mutation and how critical that gene region is for resultant keratin function. The sites of mutations in the most severe generalized form are most critical for keratin function (end-terminal rod domains), whereas the sites mutated in the localized type are least critical. The mutations that lead to EBS with mottled pigmentation tend to be at the head region

**Table 13-2** Characteristics of Major Forms of Epidermolysis Bullosa Simplex, Basal

Type	Clinical Manifestations
EBS, localized (formerly Weber–Cockayne)	Easy blistering on palms and soles May be focal keratoderma of palms and soles in adults ≈25% show oral mucosal erosions Rarely show reticulated pigmentation, especially on arms and trunk and punctate keratoderma (EBS with mottled pigmentation)
EBS, generalized, intermediate (formerly Koebner)	Generalized blistering Variable mucosal involvement Focal keratoderma of palms and soles Nail involvement in 20% Improves with advancing age
EBS, generalized, severe (formerly Dowling–Meara)	Most severe in neonate, infant; improves beyond childhood Large, generalized blisters; later, smaller (herpetiform) blisters Mucosal blistering, including esophageal Nails thickened, shed but regrow May have natal teeth
EBS with mottled pigmentation	Reticulated hyperpigmentation, especially on arms and trunk Punctate keratoses and keratoderma

EBS, Epidermolysis bullosa simplex.



**Figure 13-3** Generalized severe epidermolysis bullosa (EB) simplex. During the infantile periods the blistering is often severe and generalized, making distinction clinically from other forms of EB difficult. Note the thickening and sloughing of nails.



**Figure 13-4** Generalized severe epidermolysis bullosa (EB) simplex. With advancing age the blisters often become smaller and more clustered (herpetiform) in this form of EB. Blisters may be hemorrhagic and quite inflamed.



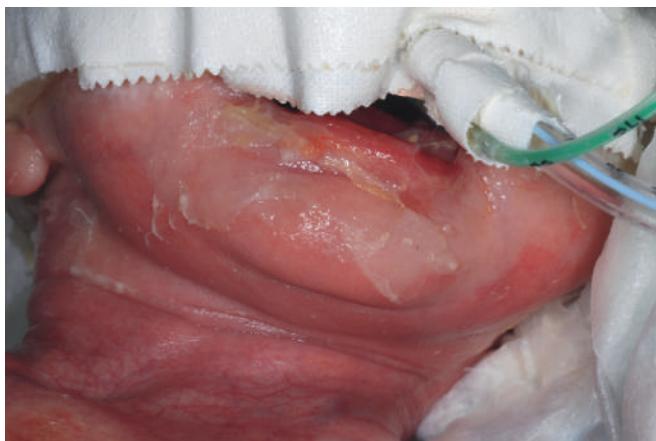
**Figure 13-5** Generalized severe epidermolysis bullosa simplex. Blistering on the palms and soles may be severe, but palms and soles show thickening with advancing age that is likely protective.



**Figure 13-6** Generalized intermediate epidermolysis bullosa simplex, migratory circinate form. This boy had a mutation near the tail of KRT5.



**Figure 13-7** Localized epidermolysis bullosa simplex. Note the superficial blistering with both intact bullae and denuded skin. This form tends to be limited to the palms and soles.



**Figure 13-9** Suprabasal acantholytic epidermolysis bullosa simplex. Note the sheet-like peeling of skin on the chin. This baby, who died as a neonate, had total body denudement, extensive mucosal sloughing, and complete alopecia from a mutation in *DSP*.



**Figure 13-8** Epidermolysis bullosa simplex with mottled pigmentation. The reticulated pigmentation may be bothersome to affected individuals, but the mild blistering, as seen proximal to the knee, is not.

of *KRT5* or *KRT14* (most often a mutation that changes the twenty-fifth amino acid of keratin 5),<sup>12,13</sup> suggesting that this site on the keratin protein is vital for the transfer of pigment from melanocytes to keratinocytes. The migratory circinate form has been linked to mutations in the tail region of *KRT5*.

#### Recessive Forms of Basal Epidermolysis Bullosa Simplex

Basal EBS less commonly is autosomal recessive, including with biallelic mutations in *KRT5* or *KRT14* (which can phenotypically show localized or generalized blistering). Three clinically distinct forms of EBS result from mutations in the gene-encoding plectin (*PLEC1*): EBS-Ogna, EBS with muscular dystrophy, and EBS with pyloric atresia.<sup>14,15</sup> EBS-Ogna, the only disorder with abnormal plectin that is autosomal dominant, mainly shows acral blistering, although more generalized blistering has been described; affected individuals characteristically bruise easily and may show onychogryphosis. EBS with muscular dystrophy presents in the neonatal or infantile period with generalized blisters, but the onset of muscular dystrophy varies from infancy to adulthood. Patients may show ptosis, granulation tissue with stenosis of the respiratory tract, and focal keratoderma. EBS with pyloric atresia presents with the same widespread congenital absence of skin (especially on the extremities), generalized blistering and pyloric atresia as in JEB with pyloric atresia. Malformed pinnae and nasal alae, joint contractures, and cryptorchidism are other shared features.

Plectin interacts with  $\alpha 6\beta 4$  integrin, providing a rationale for similar clinical manifestations. The mutations of EBS with muscular dystrophy cluster in exon 31, which is spliced out in one of the two isoforms of plectin, explaining the much milder phenotype of EBS with muscular dystrophy.<sup>16</sup> Two mild recessive forms have also been more recently described. EBS with autosomal recessive BP230 deficiency (EBS-AR BP230) results from mutations in encoding dystonin-e (DST-e), the epidermal isoform of bullous pemphigoid (BP) antigen (BPAG1e or BP230).<sup>17,18</sup> Affected individuals experience localized lifelong blistering and erosions beginning in infancy, but lesions are primarily localized to the ankles and feet. EBS with autosomal recessive exophilin 5 deficiency (EBS-AR exophilin 5) results from mutations in *EXPH5*, encoding exophilin-5 (or *SLAC2-B*), which is a protein involved in vesicle transport.<sup>19</sup> Small, localized erosions and bleeding primarily affect site of trauma, primarily the lower back, knees, and ankles. Ultrastructural studies of biopsies provide the clue to diagnosis, showing keratin filament clumping and acantholysis (as can be seen in EBS) but also typical perinuclear cytoplasmic vesicles.

#### Suprabasal Epidermolysis Bullosa Simplex

To date, biallelic mutations in four genes (*DSP*, *PKP1*, *JUP*, and *TGM5*) can lead to autosomal recessive suprabasal forms of EBS. The lethal acantholytic form of EB (LAEB) presents at birth with generalized denudement and absence of hair and nails.<sup>20,21</sup> Frank blisters are not seen, but the skin peels in sheets (Fig. 13-9). Mucosal sloughing is severe, and affected neonates may be born with teeth. All babies to date have died in the neonatal period. Cardiomyopathy is usually associated. Mutations have been described in the C-terminal domain of *DSP*. Less deleterious mutations in *DSP* also cause skin fragility and woolly hair syndrome (see Chapter 7), characterized by superficial erosions and crusting with woolly hair, palmoplantar keratoderma, and cardiomyopathy. Acantholytic EBS from mutations in *JUP*, encoding plakoglobin, manifests at birth as generalized erythroderma with superficial peeling and erosions. Patients have alopecia, dystrophic nails, and recurrent infections and generally die in the neonatal period, but there are no cardiac issues.<sup>22</sup> As with other mutations in desmosomal components, a milder form allows survival but the development of generalized erosions, sparse woolly hair, and focal keratoderma. Plakophilin deficiency (skin fragility and ectodermal dysplasia syndrome) results from mutations in *PKP1*, the gene encoding plakophilin-1.<sup>23-26</sup> Affected patients show generalized erythroderma at birth with blistering. The soles are often most disabling, with palmoplantar keratoderma and painful fissures. Superficial erosions and crusting are prominent in the perioral area, and tongue fissures have been described. The hair tends to be short, sparse and woolly, and the nails are thickened and dystrophic. Affected individuals show variable hypohidrosis, blepharitis, and growth retardation.<sup>24</sup> Plakophilin-1 is a

**Table 13-3** Classification and Causes of Major Forms of Junctional Epidermolysis Bullosa

Type	Inheritance	Gene Defect
JEB, generalized severe (formerly Herlitz)	AR	<i>LAMA3</i> , <i>LAMB3</i> , <i>LAMC2</i> /laminin 332
JEB, generalized, intermediate (formerly non-Herlitz)	AR	Mild mutation: laminin 332
JEB, generalized, intermediate (formerly non-Herlitz)	AR	<i>COL17A1</i> /type XVII collagen
JEB, generalized with pyloric atresia	AR	<i>ITGA6</i> , <i>ITGB4</i> /integrin $\alpha 6$ or $\beta 4$
JEB, generalized, late onset	AR	<i>COL17A1</i> /type XVII collagen
JEB, generalized, with respiratory and renal involvement	AR	<i>ITGA3</i> /integrin $\alpha 3$
JEB, localized	AR	<i>COL17A1</i> /type XVII collagen <i>ITGA6</i> , <i>ITGB4</i> /integrin $\alpha 6\beta 4$ laminin 332
JEB with pyloric atresia	AR	<i>ITGA6</i> , <i>ITGB4</i> /integrin $\alpha 6$ or $\beta 4$
JEB, localized, inversa	AR	<i>COL17A1</i> /type XVII collagen
LOC syndrome	AR	Laminin 332, $\alpha 3$ chain

AR, Autosomal recessive; JEB, junctional epidermolysis bullosa;  
LOC, laryngooxychocutaneous syndrome.

structural component of the desmosomes that allows cell–cell adhesion; biopsies of affected skin show acanthosis, acantholysis, widening of the space between keratinocytes, and few poorly formed desmosomes.<sup>27</sup> Acral peeling skin syndrome, which results from mutations in *TGM5*, the gene encoding transglutaminase 5, involves subcorneal cleavage and can be confused with localized EB on the hands and feet.<sup>28</sup> Of note, peeling skin syndrome in an acral or generalized distribution can also result from mutations in other genes (see Chapter 5). EBS superficialis involves cleavage of the upper epidermis and stratum corneum in which superficial erosions occur and one can easily induce sheet-like peeling of skin. The mode of transmission and genetic basis remain unclear, but it is classified with the suprabasal forms of EBS.<sup>29</sup>

### JUNCTIONAL EPIDERMOLYSIS BULLOSA

Junctional EB (JEB) is a group of mechanobullous disorders in which the cleavage plane occurs in the lamina lucida at the junction of the epidermis and dermis (Table 13-3).<sup>30,31</sup> Encompassing a spectrum from severe life-threatening disease to relatively mild involvement, various subtypes of this disorder have been described, each transmitted in an autosomal recessive manner (Table 13-4). Autosomal dominant disorders (mutation on one allele) with only dental manifestations from a missense mutation in *LAMB3*,<sup>32</sup> dental issues and blistering from a missense mutation in *COL17A1*,<sup>33</sup> or the corneal erosions from a missense mutation in *COL17A1* (termed *epithelial recurrent erosion dystrophy* [ERED])<sup>34</sup> have been described.

Early diagnosis of the subtype of JEB is critical and is based on immunomapping (including detection of level of cleavage and lamina lucida proteins) and if available, genotyping. Immunomapping studies of sections from skin adjacent to a freshly induced blister show cleavage at the lamina lucida level. Electron microscopic evaluations reveal markedly reduced or absent hemidesmosomes, anchoring structures that span the lamina lucida of the basement membrane of skin and mucosae.

**Table 13-4** Characteristics of Major Forms of Junctional Epidermolysis Bullosa

Type	Clinical Manifestations
JEB, generalized severe (formerly Herlitz)	50% of patients die by 2 years old Blisters heal with atrophic scarring but no milia Periungual and fingerpad blistering, erythema Blistering of oral and esophageal mucosae Laryngeal and airway involvement with early hoarseness Later, perioral granulation tissue with sparing of lips Anonychia Dental enamel hypoplasia, excessive caries Growth retardation Anemia
JEB, generalized, intermediate (formerly non-Herlitz)	Less severe, but similar manifestations to Herlitz type, including dental, nail and laryngeal involvement Granulation tissue is rare Perinasal cicatrization Less mucosal involvement Alopecia Anemia but not as severe as JEB, generalized severe
JEB, localized	Localized blisters without residual scarring or granulation tissue Minimal mucosal involvement Dental and nail abnormalities as in JEB, generalized severe
JEB, generalized with pyloric atresia	Usually lethal in neonatal period Generalized blistering, leading to atrophic scarring May be born with large areas of cutis aplasia No granulation tissue Nail dystrophy or anonychia Pyloric atresia, genitourinary malformations Rudimentary ears Dental enamel hypoplasia (survivors) Variable anemia, growth retardation, mucosal blistering

JEB, Junctional epidermolysis bullosa.

In the severe generalized form of JEB (formerly called JEB-Herlitz), blistering begins at birth and death occurs in 45% by 1 year of age and 54% by 2 years of age.<sup>35</sup> Survival into adulthood is common for most other forms of JEB but has been occasionally described for individuals with the severe generalized type of JEB.

Severe generalized JEB is characterized by the generalized distribution of blisters and large erosions mainly on the buttocks, perioral area, trunk, and scalp. Blistering is almost always present at birth (see Fig. 13-2). Blistering of the fingertips with sloughing of the nails (Fig. 13-10) and perioral involvement (Fig. 13-11) with sparing of the lips are important if not diagnostic features of the junctional forms of EB. Granulation tissue, especially of the perioral region, is characteristic of this severe form (and laryngooxychocutaneous [LOC] syndrome), and is usually present by a few years of age. Sites of healing tend to be atrophic but show far fewer milia than the dystrophic forms. The mucous membranes are affected, especially the oral mucosae. Hoarseness and laryngeal involvement are common, and airway involvement may lead to death. The genitourinary and gastrointestinal tracts are often affected as well. The teeth are dysplastic, and a cobblestone appearance to the dental enamel is characteristic. Severe growth retardation and recalcitrant anemia are common. Mutations in this severe generalized form always affect a gene encoding one of the three chains of laminin 332 (*LAMA3*, *LAMB3*, and *LAMC2* encoding  $\alpha 3$ ,  $\beta 3$ , and  $\gamma 2$  chains, respectively).



**Figure 13-10** Generalized severe junctional epidermolysis bullosa (JEB). Blistering of the fingertips with periungual erythema and sloughing of the nails is characteristic of JEB.



**Figure 13-12** Junctional epidermolysis bullosa, pyloric atresia type. The rudimentary ears and extensive denudement of the extremities is typical of this type of epidermolysis bullosa. This baby had a mutation in the gene encoding integrin  $\beta 4$ .



**Figure 13-11** Generalized severe junctional epidermolysis bullosa. Perioral blistering with formation of granulation tissue is characteristic. Note that the lips are relatively spared, but the teeth show enamel dysplasia.

Generalized intermediate or localized JEB, may also result from less deleterious mutations in one of the laminin 332 genes. Mutations in the  $\alpha 3$  chain of laminin 332 can lead to the localized form, LOC syndrome (Shabbir syndrome).<sup>36,37</sup> LOC syndrome occurs most often in the Punjab region of India and Pakistan. It features excessive granulation tissue of the larynx (leading to hoarseness and potentially airway obstruction), conjunctival granulation tissue (leading to symblepharon, corneal scarring, and potentially blindness), and erosive blisters most commonly on the face and neck. Death is common because of respiratory-tract involvement. JEB inversa presents with blisters predominantly in intertriginous areas (axillary areas and groin). Mucosal blistering tends to be variable in extent but less than in the generalized forms. A rare form, JEB with respiratory and renal involvement, shows limited skin blistering on the legs and buttocks but congenital nephrotic syndrome and severe neonatal respiratory distress with interstitial pneumopathy. The disorder results from biallelic mutations in the gene encoding integrin  $\alpha 3$ , and affected infants die within the first months of life.

Generalized intermediate JEB (previously called *non-Herlitz* JEB or *generalized atrophic benign EB* [GABEB]) most commonly affects the gene encoding BP180 (collagen XVII; COL17A1) but occasionally reflects at least one missense mutation in a gene encoding laminin 332. In general, the features tend to be less severe than in the severe generalized form, but granulation tissue is rarely seen and EB nevi are

common. EB nevi are dark, irregular hyperpigmented patches that may be worrisome dermoscopically<sup>38</sup> but show benign nevi or increased basal pigment deposition histologically<sup>39,40</sup> and clear spontaneously during the subsequent months to years. Diffuse alopecia (scarring or nonscarring) is a key feature of this form, and narrowing of the nares is often seen. Squamous cell carcinoma (SCC) occasionally occurs in affected areas later in life; the occurrence of these features that are not typically seen in the severe generalized form may reflect the greater lifespan in this form.

JEB with pyloric atresia results from mutations in either  $\alpha 6$  integrin (*ITGA6*) or its hemidesmosome partner,  $\beta 4$  integrin (*ITGB4*).<sup>16</sup> Blistering is generalized at birth, often with large areas of cutis aplasia. Other features in addition to pyloric atresia are rudimentary and malformed ears (Fig. 13-12) and genitourinary tract malformations, attesting to the important role of  $\alpha 6\beta 4$  integrin in the development of the ears, pylorus, and genitourinary tract. Less commonly, EB with pyloric atresia results from plectin abnormalities. A late-onset form of JEB has been described with onset in young adulthood or later; nails are dystrophic or absent and dental enamel is hypoplastic, but blistering is milder than in other junctional forms. Patients may have hyperhidrosis and absent dermatoglyphics.

### Dystrophic Epidermolysis Bullosa

The scarring (dystrophic) types of EB are predominantly divided into dominant dystrophic epidermolysis bullosa (DDEB) and recessive dystrophic epidermolysis bullosa (RDEB) forms with varying degrees of severity (Tables 13-5 and 13-6). The recessive forms have been further subdivided into the severe generalized and generalized other forms. In general, the dominant forms are considerably less severe; affected individuals are generally healthy, are of normal stature, and show limited blistering of the skin. The severe generalized form of RDEB, conversely, is severe and incapacitating. Functional deformities of the hands and feet result from extensive scarring, growth and development are retarded, and profound anemia and hypoalbuminemia are standard. All forms of DEB affect anchoring fibrils, critical elements for epidermal–dermal cohesion, and result from mutations in type VII collagen.<sup>41–43</sup>

### Dominant Dystrophic Epidermolysis Bullosa

Generalized dominant dystrophic epidermolysis bullosa (DDEB) usually presents at birth or shortly thereafter, although mild cases may not show blistering or nail changes until adulthood. The blisters and resultant scars and milia formation primarily involve the extensor areas of the extremities and the dorsum of the hands (see Fig. 13-15). Nail thickening, dystrophy, or complete nail destruction are seen in 80% of cases (Fig. 13-13).<sup>44</sup> Although mucous membrane lesions appear in 20% of cases, they tend to be mild and not problematic. The teeth and hair are generally not affected, and physical development is normal. Some forms of DDEB are localized, including localized to the

**Table 13-5** Classification and Cause of Major Forms of Dystrophic Epidermolysis Bullosa

Type	Inheritance	Gene Defect
Dominant		
DDEB, generalized	AD	<i>COL7A1/collagen VII</i>
DDEB, rare types: acral, pretibial, pruriginosa, nails only, bullous dermolysis of newborn	AD	<i>COL7A1/collagen VII</i>
RDEB, generalized severe	AR	<i>COL7A1/collagen VII</i>
RDEB, generalized intermediate	AR	<i>COL7A1/collagen VII</i>
RDEB, inversa	AR	<i>COL7A1/collagen VII</i>
RDEB, rare types: localized, pretibial, pruriginosa, centripetalis, bullous dermolysis of the newborn	AR	<i>COL7A1/collagen VII</i>

AD, Autosomal dominant; AR, autosomal recessive; DDEB, dominant dystrophic epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa.

**Table 13-6** Characteristics of Major Forms of Dystrophic Epidermolysis Bullosa

Type	Clinical Manifestations
Dominant dystrophic	Onset at birth to early infancy Blistering predominates on dorsum of hands, elbows, knees, and lower legs Milia associated with scarring Some patients develop scar-like lesions, especially on the trunk 80% have nail dystrophy
Recessive dystrophic, severe generalized	Present at birth Widespread blistering, scarring, milia Deformities: pseudosyndactyly, joint contractures Severe involvement of mucous membranes, nails; alopecia Growth retardation, poor nutrition Anemia Mottled, carious teeth Osteoporosis, delayed puberty, cardiomyopathy, glomerulonephritis, renal amyloidosis, IgA nephropathy Predisposition to squamous cell carcinoma in heavily scarred areas
Recessive dystrophic, generalized intermediate	Generalized blisters from birth with milia, scarring Less anemia, growth retardation, mucosal but more esophageal issues with advancing age

IgA, immunoglobulin A.

nails (DDEB, localized, nails only) or acral areas and/or hands and feet. The pretibial form of DDEB shows lichenoid or atrophic papules and plaques on the pretibial areas but also hand, foot, and nail involvement. DEB pruriginosa (DEB-Pr) is a poorly understood form of DEB (usually dominant) with the onset of severe associated pruritus and prurigo-like, scarred vesicles and papules primarily of the pretibial areas that is often delayed until adolescence or adulthood.<sup>45-48</sup> Bullous dermolysis of the newborn (DEB-BDN; formerly called *transient BDN*) shows skin blistering, often extensive, at birth or in early infancy (Fig. 13-14). However, blistering dramatically improves during the first months to 2 years of life, and beyond mild residual atrophy, scarring,



**Figure 13-13** Dominant dystrophic epidermolysis bullosa (DDEB). Nail dystrophy, especially of the toenails, is commonly seen in individuals with DDEB.



**Figure 13-14** Transient bullous dermatolysis of the newborn. After extensive blistering of the lower extremity at birth, no further blisters developed. Immunomapping showed the split to be in the upper dermis, and staining for type VII collagen was reduced.

and nail dystrophy and an increased risk of dental caries, ongoing blistering is not a problem. The disorder results from mild mutations in *COL7A1* and can be inherited in a dominant or recessive manner.

### Severe Generalized Recessive Dystrophic Epidermolysis Bullosa

Children with severe generalized RDEB (formerly called the *Happleau-Siemens type*) have a severe life-altering bullous disease characterized by widespread dystrophic scarring and deformity and by severe involvement of mucous membranes. RDEB may manifest as a less severe form (generalized intermediate RDEB) with less severe blistering of the skin and mucosae that may be mistaken for DDEB (Fig. 13-15); individuals with this form often begin to have problems with esophageal function in adolescence. Two other forms of RDEB have more localized cutaneous involvement. Blistering in RDEB inversa tends to involve the intertriginous axial, lumbosacral, and acral sites in addition to extensive mucosal involvement, including esophageal strictures and external auditory canal stenosis. RDEB centripetalis is a rare RDEB form that starts with limited involvement (hands, feet, nail dystrophy) but progresses with an advancing border to involve most of the extremities by mid-adulthood; face, truncal, and mucosal involvement never occur.<sup>49</sup>

Although any area of the skin may be involved in infants with generalized severe RDEB, the most commonly affected areas are the hands, feet, buttocks, scapulae, face, occiput, elbows, and knees. In older children the hands, feet, knees, elbows, and posterior neck and/



**Figure 13-15** Generalized intermediate recessive dystrophic epidermolysis bullosa. This boy and his brother had mild involvement of the hands, feet, and legs with nail dystrophy. The sites and appearance of lesions resembled dominant dystrophic epidermolysis bullosa, but the involvement in his brother and subsequent genotyping showed the biallelic mutation in *COL7A1*.



**Figure 13-16** Recessive dystrophic epidermolysis bullosa (RDEB). This young girl demonstrates the “shawl sign” of RDEB. Despite haircuts, dressings, and vigorous protection, this area has continued to be blistering and open for the past 5 years.

or upper mid-back (Fig. 13-16) are most commonly involved. Bullae may be hemorrhagic, and large areas, especially on the lower extremities, may be completely devoid of skin. When a blister ruptures or its roof peels off, a raw painful surface is evident. The Nikolsky sign (production or enlargement of a blister by slight pressure or the production of a moist abrasion by slight pressure on the skin) is often positive. Fluid contained in bullae, although at first sterile, may become secondarily infected, which can lead to sepsis; *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most common organisms.

Bullae are often followed by atrophic scars and varying degrees of hyperpigmentation or hypopigmentation. Milia overlying the scars are characteristic. EB nevi are common (see above). The hands and lower aspects of the legs are particularly susceptible to severe blistering and scarring. The fingers and toes may become fused, with resultant pseudosyndactyly in which the digits become bound together by a glove-like epidermal sac, with resulting claw-like clubbing or mitten-like deformities (Fig. 13-17). The fingers and toes become immobile (usually during the first years of life), and the wrists, elbows, knees, and ankles may become fixed in a flexed position from contractures, leading to immobility and often confinement to a wheelchair.

Oral mucosal involvement occurs soon after birth (Fig. 13-18), leading to dysphagia and limiting the ability to suck well. Erosions of the esophagus may at times result in segmental stenosis (most



**Figure 13-17** Recessive dystrophic epidermolysis bullosa. Pseudosyndactyly or mitten deformity of the foot in this young boy with extensive atrophic scarring.



**Figure 13-18** Recessive dystrophic epidermolysis bullosa. Oral mucosal blistering in a neonate.

often in the upper third) with consequent difficulty in swallowing. Gastroesophageal reflux disease often occurs, especially presenting as effortless vomiting. Constipation is common and may be related to anal fissuring, inadequate dietary fiber, and administration of iron. Affected children are reluctant to eat and often fail to thrive, given their increased nutritional needs owing to loss of protein and other nutrients through wounds. As the child grows older there is a tendency for the disease to become less severe, but the affected individual soon learns to avoid hot drinks, rough foods, and large particles that might produce blistering of the mouth, pharynx, or esophagus. Typically, patients show microstomia owing to intraoral scarring and a frenulum that is bound down. The eyes may develop blisters with associated ocular inflammation and later corneal scarring, potentially leading to visual impairment.<sup>50</sup> Hoarseness, aphonia, and even laryngeal stenosis may result from laryngeal blistering and scarring. Bone mineralization is low in patients with EB, particularly those with RDEB, probably owing to a combination of insufficient nutrition, reduced physical activity, and chronic inflammation.<sup>1,51</sup>

The teeth in RDEB are particularly susceptible to early and commonly severe caries. The progressive intraoral scarring leads to microstomia and decreased salivation.<sup>1,52</sup> Even routine dental care may cause the eruption of bullae and erosions on the lips, gingivae, and oral mucosa. The nails may show severe dystrophy or complete absence of nails. Scalp and body hair may be sparse, and there may be patches of cicatricial alopecia.<sup>53</sup>

In patients with the severe generalized form of RDEB, death may occur during infancy or childhood as a result of septicemia,

pneumonia, or renal failure. Patients with RDEB (and rarely DDEB) have an increased risk of glomerulonephritis, renal amyloidosis, and immunoglobulin (Ig) A nephropathy.<sup>1,54–56</sup> The tremendous loss of fluid, blood, and protein through the skin coupled with malnutrition can lead to hypoalbuminemia and anemia. Dilated cardiomyopathy is an uncommon complication (4.5% by 20 years of age)<sup>57</sup> but may be fatal, especially in the presence of concurrent chronic renal failure. The cause of the cardiomyopathy may be multifactorial, including from transfusion-associated iron overload, viral myocarditis, and deficiency of selenium and carnitine. Other complications of RDEB include erosions and scarring of the anal area (often resulting in severe discomfort, chronic constipation, or soiling), urethral stenosis, urinary retention, hypertrophy of the bladder, and occasionally hydronephrosis.<sup>2,54</sup>

Patients with RDEB (and to a lesser extent JEB but not DDEB) show a progressively increasing risk of developing cutaneous SCCs (7.5%, 68%, 80%, and 90% by 20, 35, 45, and 55 years of age, respectively)<sup>58</sup> in heavily ulcerated and scarred areas of skin.<sup>59</sup> These lesions are predominantly over joints and on the distal extremities and present as nodular lesions or nonhealing ulcers.<sup>60,61</sup> Suspicious masses should be biopsied to distinguish SCCs from benign lesions such as verruciform xanthoma.<sup>62,63</sup> *MMP13* expression is strongly positive in SCC but is negative in benign hyperkeratotic lesions.<sup>64</sup> Cutaneous carcinomas tend to be locally aggressive, often requiring amputation, and tend to metastasize, leading to death.

Death during childhood is most common with JEB (median age 4 to 6 months).<sup>35</sup> Sepsis, failure to thrive, and respiratory failure are the major causes of death during childhood. Children with RDEB generally survive the neonatal and infantile periods but succumb to infection later during childhood or to aggressive cutaneous carcinomas during adulthood.

### KINDLER SYNDROME

Kindler syndrome is characterized by generalized progressive poikiloderma, congenital acral skin blistering, diffuse cutaneous atrophy (Fig. 13-19), skin fragility, webbing of the fingers and toes with digital tapering, nail dystrophy, oral mucosal lesions, and photosensitivity, sometimes within minutes after exposure.<sup>65,66</sup> Other features are hyperkeratosis of the palms and soles; leukokeratosis; ectropion; red friable hyperplastic gums; constipation and sometimes severe colitis; esophageal, laryngeal, anal, vaginal and urethral meatal stenosis; and phimosis.<sup>67</sup> Although the photosensitivity and the blister formation seem to decrease with age, the atrophic scarring and poikiloderma increase. The incidence of SCC of the acral skin or mouth is increased after the age of 30 years. Because the blistering arises at multiple levels within and/or beneath the basement membrane zone, Kindler syndrome has been classified as mixed EB. Treatment of this disorder requires the avoidance of trauma and the proper use of emollients, appropriate sun protection, and the judicious use of antibiotics to

prevent secondary infection. Regular dental care and surveillance for early malignancies are important, as are iron replacement if the patient is anemic and management of the stenoses and colitis. The gene mutated in Kindler syndrome is *FERMT1* (formerly called *KIND-1*), which encodes fermitin family homolog 1 (FFH1) protein or kindlin-1, a focal adhesion protein that regulates keratinocyte cell adhesion, motility, and stem cell homeostasis.<sup>68–71</sup>

### Treatment of Epidermolysis Bullosa

As in any inherited disorder, it is the responsibility of the physician to inform parents of the risks of transmitting genetic abnormalities.<sup>72</sup> When the condition is determined by a dominant gene (as in DDEB)<sup>73,74</sup> and a parent is affected, the risk of the disorder in siblings is 50%. In a family in which a child manifests abnormalities because of a recessive gene (as in RDEB), parents risk a 25% possibility with each pregnancy of the disorder occurring in future offspring. Appropriate genetic counseling, however, depends on accurate diagnosis. Since the clinical course of many forms of EB is variable, especially during the neonatal and infantile periods, it is recommended that patients be carefully evaluated as early as possible with immunofluorescent mapping, monoclonal antibody studies, and deoxyribonucleic acid (DNA) analysis if appropriate in an effort to establish the correct diagnosis. Prenatal diagnosis of all forms of EB is now available using molecular techniques, but is easiest if the gene defect is known in that family.<sup>75</sup> The current availability of whole exome sequencing has allowed concurrent investigation of several types of EB for a fraction of the price of sequencing any one individual gene.<sup>4</sup> Preimplantation diagnosis has been performed and is an option that utilizes *in vitro* fertilization to ensure a normal fetus without the risk of abortion.<sup>76,77</sup>

The psychosocial effects of EB, especially the more severe forms, on the affected individual and family are among the most dramatic of any skin disease.<sup>72</sup> Affected children are concerned about having itchy skin, being in pain, having difficulty with participation, failing to understand others, and feeling different.<sup>78</sup> Parents of affected children worry about the child being different, the child suffering pain, feeling uncertain about the future, restrictions on employment and leisure, problems with organizing care, being constantly on duty, family problems, the ignorance and lack of skills of alternative care providers, and resistance by the child to care.<sup>79</sup> These problems should be discussed and psychological support for patients and their families offered as part of optimal care.

The treatment of EB is largely palliative, with protection from friction or overheating, avoidance of abrasion and constriction, control of secondary infection, nutritional supplementation, and pain control.<sup>80,81</sup> Because blisters result from mechanical injury, measures should be taken to relieve pressure and prevent unnecessary trauma. Clothing should be soft and worn inside out. Labels that may rub the skin should be removed. Velcro closures are less traumatizing than other traditional closures. Mittens can be worn to minimize self-induced trauma. Shoes should be soft and fit well; leather shoes with leather linings, ideally with external seams (e.g., moccasins), are usually recommended.<sup>72</sup> During the summer, canvas shoes and jelly sandals are the best choices. Shoes should be large enough to accommodate dressings and minimize friction. Insoles can be made from cooling gel, sheepskin, or protective dressings. Affected babies can be lifted and moved on a soft pad, and the bathtub can be lined with a thick towel. A cool environment and lubrication of the skin to decrease surface friction are helpful in the reduction of blister formation. When blisters occur, extension may be prevented by aseptic aspiration of blister fluid. The roofs of blisters should be left intact whenever possible to protect the underlying skin.

Keeping palms and soles with EBS cool and dry helps to minimize blistering, especially during hot weather. Hyperhidrosis is often a concomitant feature, and measures to minimize the increased blistering associated with hyperhidrosis can be helpful. These include applying 20% aluminum chloride hexahydrate at night and gently drying the area with a cool hair dryer, wearing socks that absorb moisture,<sup>72</sup> and sprinkling of affected areas with absorbent powder such as Zeasorb. For extreme cases and in older patients with the localized form of EBS, injections of botulinum toxin A have been advocated.<sup>82</sup> Silver-impregnated socks can decrease infections and increase foot comfort.



**Figure 13-19** Kindler syndrome. This boy shows poikiloderma, cutaneous atrophy, webbing of the fingers, and nail dystrophy.



**Figure 13-20** Recessive dystrophic epidermolysis bullosa (RDEB). Non-adherent dressings should be placed between the fingers and toes of children with RDEB to reduce the risk of pseudosyndactyly. Note the scarred skin and anonychia.

A water mattress and a soft fleece covering will help to limit friction and trauma. Daily baths and topical application of protective petrolatum to eroded areas or, especially if slightly crusted, antibiotic ointments (usually bacitracin, mupirocin, or gentamicin) are helpful. Protective dressings that do not adhere to wounds should be applied to eroded areas to promote healing but prevent further denudation when dressings are changed (e.g., petrolatum-impregnated gauze, Telfa, Mepilex, Mepilex Transfer, Mepitel, Restore).<sup>83</sup> In children with RDEB, dressings should be carefully placed between the digits, although the ameliorative effect of this practice to decrease the risk of pseudosyndactyly (Fig. 13-20) has not been tested. Sterile precautions must be taken when changing dressings to reduce the risk of bacterial infection. Tape and any significant pressure to skin must be avoided. Dressings can be held in place by rolled gauze (such as Kerlix) or loose self-adherent wraps) with tape only applied to the dressing itself or by stockinette (such as Surgifix or Spandage). Dressings with silver have helped patients with recurrent infections, but application of silver sulfadiazine has been associated with argyria.<sup>84,85</sup> Families need to weigh the antiinfective benefits with the risk of potentially high blood levels of silver.<sup>86</sup> Bacteriostatic dressings with methylene blue and crystal-violet dyes (such as Hydrofera blue) and medical-grade honey<sup>87</sup> are also available. Crusted or purulent areas should be cultured and treated based on the sensitivity of organisms. Topical application of mupirocin and/or gentamicin ointments may be useful for limited areas of crusting (see mention of *readthrough* with gentamicin ointment below). More extensive involvement requires administration of systemic antibiotics. Excessive usage of systemic antibiotics, however, should be avoided because of the high risk of development of resistance. Gentamicin soaks (480 mg/L saline), acetic-acid soaks (diluted white vinegar), and addition of small amounts of bleach to the bathwater (e.g.,  $\frac{1}{4}$  to  $\frac{1}{2}$  cup per tub) have been used to decrease the overgrowth of *Pseudomonas* and staphylococcal organisms. The risk of sepsis with cutaneous infection is high in neonates and infants, and patients should be monitored carefully. Topical and systemic steroids are generally not useful for patients with EB and should be avoided in view of their promotion of infection and other side effects. However, limited application of potent topical steroid, or oral thalidomide has been helpful for the granulation tissue of laminin 332 defects.<sup>88</sup>

Pain control is an important component of EB care, especially in affected infants. The changing of dressings at blistered sites is excruciatingly painful for patients yet must be performed from a few times weekly to up to twice daily, depending on the extent of drainage and the presence of infection. In one study, saltwater baths led to a significant reduction in pain and pain medication use in 91% and 66%, respectively, of 16 children with primarily RDEB.<sup>89</sup> Methadone and liquid cough suppressants with dextromethorphan have been used to relieve discomfort in infants. For older children, acetaminophen with

codeine, oral midazolam, or morphine has been used before dressing changes and baths to improve tolerance. Amitriptyline and cognitive behavioral techniques have also been suggested to relieve the chronic pain and discomfort.<sup>90</sup>

Overall 85% of patients with EB complain of pruritus, which can be more problematic on a five-point Likert scale than pain.<sup>91</sup> The itch is less problematic with EBS than with the more severe JEB and DEB types and can interfere with sleep. Exacerbants are healing wounds, a hot environment, infection, high humidity, and stress. Antihistamines and topical creams and ointments are of limited value,<sup>80,92</sup> but short-term courses of mid-potency topical steroids and as second-line agents, low-dose gabapentin or pregabalin can be considered.<sup>80</sup>

Nutritional supplementation is critical for patients with the more severe forms of EB to prevent failure to thrive, which has been linked to mortality in 20.5% of patients with generalized severe JEB by 2 years of age. The loss of protein, iron, and blood through the open areas of skin leads to hypoalbuminemia and deficiency of iron and trace minerals. Furthermore, the chronic disruption of the epithelial lining of the small intestine leads to gross malabsorption of nutrients, and the pain with ingestion of food decreases intake. Consultation with a nutritionist is important to maximize caloric and protein intake and provide specific nutrients and vitamins such as iron, zinc and vitamin D<sub>3</sub>. Oral iron may be poorly tolerated by the gastrointestinal tract, and constipation is a potential issue; intravenous administration of iron or blood transfusions may be needed to maintain a hemoglobin (Hgb) level of at least 8 g/dL in severely affected children. Soft nipples such as the Haberman feeder should be used, with the opening enlarged to minimize the need for sucking. The lips should be protected with petrolatum before initiating feeding. In general, nasogastric-tube feeding should be avoided, or if necessary, a tube suitable for long-term feeding should be used. Placement of a button gastrostomy tube should be considered in infants who start to drop off of their growth curve, as a means of supplemental feeding to increase caloric intake and as an alternative route to oral feeding; early gastrostomy placement should be considered for severe generalized forms of JEB and RDEB. Regular dental intervention is essential to decrease caries; teeth can be cleaned with soft, moist gauze and rinses of chlorhexidine<sup>93</sup>; some advocate use of MI Paste for the teeth. Endosseous implants have been placed successfully in patients with EB.<sup>94</sup>

Dysphagia is the major symptom of esophageal involvement in RDEB.<sup>95,96</sup> It may result from a reversible inflammatory reaction or from a permanent stricture. Barium studies demonstrate esophageal lesions; endoscopy, however, is not recommended. Softening of the diet for several weeks may result in modest to marked improvement of symptoms. If conservative management fails to result in proper nourishment, esophageal dilation, ideally through fluoroscopic guidance, should be performed and may be repeated if stenosis recurs. Esophageal perforation is the most serious complication of dilation. Surgery is an alternative, through colonic interposition and resection of localized strictures with end-to-end anastomosis, but the procedures carry a high risk. Gastroesophageal reflux may be exacerbated by esophageal dilation but responds to medical management with thickening of the milk, histamine 2 receptor (H2)-blockers, proton pump inhibitors, or promotility agents. Constipation is usually managed by maintaining adequate fluid intake and dietary fiber and by administering laxatives such as polyethylene glycol 3350 (MiraLax). Restoration of function in severe fusion and flexion deformities of the hands and feet can often be helped by physiotherapy and appropriate plastic surgery, especially to separate the thumb and straighten digits.<sup>97</sup> However, partial recurrence is the norm, especially on the nondominant hand. Healing in these “degloving” procedures may be facilitated by application of biologic dressings with the tissue-engineered skin substitutes and autologous epidermal grafts to the wounds (Fig. 13-21).<sup>98-100</sup> Anesthesia management for procedures is complicated, but may include mask anesthesia, endotracheal tube, intravenous sedation, and local anesthetic blocks.<sup>101,102</sup>

With repeated blistering, ulceration, and scar formation, SCCs may sometimes develop on the involved skin or mucous membrane, particularly in RDEB and to a lesser extent generalized JEB. Wounds that fail to heal or appear atypical, especially in affected adults, deserve biopsy to consider the possibility of SCC. SCCs rarely appear on the



**Figure 13-21** Biologic dressings for epidermolysis bullosa. Biologic dressings can be used selectively to promote healing of denuded areas.

tongue or esophagus. The accumulative risk in RDEB is 13% by 20 years of age, 57% by 35 years, and 87% by 45 years of age.<sup>2</sup> Melanoma may arise in children with RDEB, and the risk of developing basal cell carcinomas seems to be increased in adults with generalized severe EBS. Early intervention using full-thickness excision with wide margins is key.<sup>103,104</sup> Mohs surgery offers no long-term benefit in decreasing local recurrence, metastases or death. Amputation is required in 42% of patients with RDEB and SCC, with approximately equal outcomes on the hands and legs. Surgical debulking and radiation therapy are palliative to reduce pain or bleeding. Recently, cetuximab (epidermal growth factor receptor [EGFR] antagonist) has controlled SCC metastasis in a patient.<sup>80,105,106</sup>

During the past few years, considerable research has shown the value of protein and gene replacement for the recessive forms of EB in animal models.<sup>107</sup> Intradermal injection of allogeneic fibroblasts temporarily stimulates increased expression of type VII collagen from the patient (not donor) fibroblasts, especially in patients who have RDEB with less severe disease.<sup>108–110</sup> Recombinant type VII collagen, whether intralesional, intravenous, or topical, has been shown to home to the dermal–epidermal junction of wounded skin in mouse models and decrease blistering.<sup>111–114</sup> Intradermally injected recombinant type VII collagen is currently approved for early human trials; studies with intravenous and topical administration are planned. One potential concern is that overexpression of type VII collagen in RDEB SCC cell keratinocytes increased cell invasion,<sup>115</sup> raising the caution that giving high concentrations of type VII collagen may increase cancer-associated risks. In patients with null mutations, it is possible that topical gentamicin may lead to “readthrough,” essentially skipping the stop codon and allowing full-length gene expression, as has been demonstrated *in vitro*.<sup>116</sup>

Stem cell transplantation, more recently with the use of mesenchymal stem cells and reduced-intensity conditioning regimens, has led to the transfer of cells producing collagen VII to the basement membrane and clinical improvement in patients with RDEB<sup>117</sup> and severe generalized JEB. Two commercially available drugs, AMD3100 and tacrolimus, have recently been shown in combination to mobilize stem cells to skin wounds, leading to the possibility of mobilizing more stem cells toward EB wounds after transplantation with this combination.<sup>118,119</sup> Transplantation of viral vector gene-corrected cultured epidermal stem cells from a patient with non-Herlitz JEB led to persistent, normal-appearing skin (now almost 7 years later).<sup>120,121</sup> In an effort to avoid the risk of insertional mutagenesis with viral vectors, transcription activator-like effector nuclease (TALEN) technology has been used *in vitro* to target specific mutations in *COL7A1* for nuclelease-induced double-stranded DNA break and homologous recombination with the normal gene sequence.<sup>122</sup> More recently, cells from a patient with RDEB were made into induced pluripotent stem cells (iPSCs), corrected by adenovirus-associated genome editing, and after removal of any cells with mutations predisposing to cancer, allowed to differentiate into keratinocytes.<sup>123</sup>

Individuals with EB may have “revertant mosaicism,” in which a second gene change in a localized area leads to functional and clinical normalization (Fig. 13-22)<sup>124,125</sup> or nonrevertant mosaicism, in which



**Figure 13-22** Recessive dystrophic epidermolysis bullosa with revertant mosaicism. Note that the right side of the back shows no blistering, in contrast to the extensively blistered and scarred left side of the back. This clear area of revertant mosaicism only became visible for assessment after years of blistering and residual inflammation and scarring.

a gene change in some but not all somatic cells either leads to a mosaic dominant disorder (one allele affected) or converts a carrier state into a recessive disorder (both alleles affected) at the involved sites, as has recently been described for RDEB.<sup>126</sup> Detection of normal-appearing skin sites, which are most common in generalized intermediate JEB because of mutations in *COL17A1*, allows an unlimited source of cultured keratinocytes, fibroblasts, or even iPSCs for stem cell transplantation or for grafting.<sup>125,127</sup>

## Immune-Mediated Blistering Disorders

The chronic nonhereditary bullous diseases of childhood are a group of largely autoimmune disorders with autoantibodies directed against structural components of the skin. Diagnosis is based on clinical characteristics and histologic and immunofluorescent features of skin biopsy specimens.<sup>128</sup> Treatment of autoimmune blistering disorders (which tend to be quite rare overall in children) usually requires systemic immunosuppressive agents. In general, pemphigus, mucous membrane pemphigoid, and EBA are more challenging to manage.

### PEMPHIGUS

*Pemphigus* is a term applied to a group of severe, chronic, sometimes fatal blistering disorders characterized by flaccid bullae that develop on normal-appearing skin and mucous membranes. Pemphigus can be classified into pemphigus vulgaris, pemphigus foliaceus, IgA pemphigus, drug-induced pemphigus, and paraneoplastic pemphigus. The blister formation in pemphigus results from acantholysis, which is loss of cohesion between epidermal cells owing to intercellular edema and the disappearance of intercellular bridges in the lower epidermis. The structural components against which autoantibodies are generated in pemphigus are all components of desmosomes.

#### Pemphigus Vulgaris

Pemphigus vulgaris is a potentially life-threatening chronic vesiculobullous disease characterized by flaccid bullae and persistent erosions with a predilection for middle-aged individuals. An extremely uncommon disorder of childhood, the prognosis is better in children than in adults.<sup>129</sup> The cutaneous lesions of pemphigus vulgaris favor the seborrheic areas (the face, scalp, neck, sternum, axillae, groin, and periumbilical regions) and pressure areas of the feet and back (Fig. 13-23). The oral mucosae are affected in 95% of patients and are the initial site in the majority of patients, often months before the appearance of skin lesions. Intact blisters are rarely seen on the oral mucosa, because they rupture soon after formation, leaving raw denuded painful erosions that heal slowly. Other mucosal surfaces, the



**Figure 13-23** Pemphigus vulgaris. The cutaneous bullae and erosions are uncommon in children. The most common manifestation of pemphigus vulgaris is oral mucosal blistering. (Courtesy of Moise Levy, MD.)

anogenital areas, conjunctivae,<sup>130</sup> vermillion borders of the lips, pharynx, and larynx may be similarly involved. Pemphigus in children can involve the esophagus and ileum, leading to protein-losing enteropathy.<sup>131</sup> Because a majority of patients with proven pemphigus vulgaris have painful oral erosions for weeks to months before they develop the characteristic bullous eruption (and the disease may be limited to mucosae), children with severe recurrent mucocutaneous lesions or chronic erosive mucous membrane disease should be examined carefully.<sup>132</sup> Mucosal biopsy should be performed if skin lesions are not present.

The primary cutaneous lesions of pemphigus vulgaris appear as vesicles or bullae that arise on erythematous plaques or normal-appearing skin. The initial lesions may remain localized to one area of the skin or mucous membrane for weeks or months before other areas of the skin are involved. With the onset of new lesions, the patient may experience some pruritus, burning, or local discomfort. Blisters generally measure 1 cm or less at onset but may increase by peripheral extension to several centimeters in diameter. Lateral pressure applied to the normal-appearing skin at the periphery of a lesion results in lesional extension and shearing of skin (the Nikolsky sign). This phenomenon, a manifestation of defective epidermal cohesion, is not pathognomonic of pemphigus, since the Nikolsky sign may also be seen in patients with superficial forms of EB, BP, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Vertical pressure may also produce peripheral extension of lesions. The blisters rupture easily, and the resultant erosions are painful, bleed easily, and heal slowly. Scaling and crusting are common, and patients commonly are misdiagnosed as having impetigo or infected seborrheic dermatitis.

A variant of pemphigus vulgaris, pemphigus vegetans, is differentiated by the hypertrophic granulomatous tissue (vegetations) after healing and the tendency for predilection for the face, flexural, and intertriginous areas. Patients commonly show small pustules at the periphery of ruptured bullae.<sup>133</sup>

Routine histologic evaluation, as well as direct immunofluorescent (DIF) and indirect immunofluorescent (IIF) assays and enzyme-linked immunosorbent assay (ELISA) provide complementary studies to diagnose and monitor the course of pemphigus vulgaris. The earliest histologic change is intercellular edema with loss of cohesion between epidermal cells, resulting in the formation of clefts and bullae in a suprabasal location. The basal cells, although separated from one another, remain attached to the dermis with a resultant "row of tombstones" appearance. A rapid Tzanck smear will show acantholytic cells.<sup>134</sup> DIF tests on biopsied samples show IgG and complement bound to intercellular areas of the epidermis. IIF studies of the serum of patients with pemphigus vulgaris show IgG antibodies binding to the intercellular spaces. The targeted structural antigen in patients with only mucosal pemphigus is desmoglein 3, a desmosomal component expressed in the mucosa and lower region of the epidermis, and the presence of antibody can be tested by ELISA. Desmoglein 1 can



**Figure 13-24** Pemphigus foliaceus. Children with pemphigus foliaceus are often thought to have impetigo and treated unsuccessfully with courses of antibiotics as a result; the target of this immunobullous disorder, desmoglein 1, is the same target as the exfoliatin produced by *S. aureus* infection.

compensate for desmoglein 3, and antibodies against both desmogleins must be present for both mucosal and skin blistering to occur in pemphigus. Increases in antidesmoglein antibody titers may precede clinical flares and decreases in titer correlate with clinical responses. ELISA assays with anti-desmoglein 1 and to a lesser extent, anti-desmoglein 3 antibodies have correlated with disease activity better than indirect immunofluorescence assays in some studies.<sup>135-138</sup>

A transient form of pemphigus vulgaris, neonatal pemphigus vulgaris, may be seen in neonates of pregnant women with circulating anti-desmoglein 3 antibodies, even without active mucocutaneous disease. Blistering subsides in affected neonates within a few weeks, concomitant with the catabolism of maternal antibodies.<sup>139-142</sup>

### Pemphigus Foliaceus

Pemphigus foliaceus (superficial pemphigus) is a more superficial form of pemphigus.<sup>143</sup> The disease most commonly affects middle-aged persons and although rare in children, is more common than pemphigus vulgaris in prepubertal children. The disorder in children is more benign than that in adults, and the course is milder than that of pemphigus vulgaris.

Bullae, when seen, are usually small and flaccid. They rupture easily, and because of their superficial location leave shallow erosions. Slowly spreading crusted plaques thought to be impetigo but resistant to oral antibiotics are the most common presenting manifestation (Fig. 13-24). Patients often show an arcuate configuration to lesions. Common areas of erosive involvement include the scalp,<sup>144</sup> face, upper chest, abdomen, and back. Bullae are more likely to be intact if located on the lower extremities. Patients generally are not severely ill but may rarely complain of pruritus, pain, and burning. At times, however, the clinical picture may progress to resemble that of a severe generalized exfoliative dermatitis. Oral lesions are rarely seen in pemphigus foliaceus and when present, usually consist of small, superficial, often inconspicuous erosions.

Histologic findings in pemphigus foliaceus are similar to those of pemphigus vulgaris and demonstrate epidermal bullae and intercellular acantholysis of the epidermis. The acantholysis seen in pemphigus foliaceus, however, is more superficial and occurs in the upper epidermis, usually in the granular layer or just beneath it, with resultant formation of clefts in a superficial, often subcorneal, location. DIF shows an intracellular deposition of IgG and C<sub>3</sub> that is indistinguishable from that of pemphigus vulgaris. The targeted antigen is desmoglein 1, a desmosomal component localized to the suprabasal keratinocytes, which is also the target of bacterial exfoliative toxins in patients with bullous impetigo and staphylococcal scalded skin syndrome (see Chapter 14).<sup>145</sup> Although desmoglein 1 is also found in the mucosa, desmoglein 3 at this location provides stabilization, and patients with pemphigus foliaceus, as a result, do not tend to have oral

mucosal lesions.<sup>146</sup> Neonatal pemphigus has not been observed in infants born to mothers with active fogo selvagem (IgM and IgG4 do not cross the placenta<sup>147</sup>) but has been described in babies of mothers with sporadic pemphigus foliaceus and high titers of anti-desmoglein 1 antibodies.<sup>148–150</sup>

Pemphigus erythematosus (Senear–Usher syndrome) is a variant of pemphigus foliaceus in which lesions often localize to the butterfly area of the face, the scalp, upper chest, and back. Patients may show detectable antinuclear antibodies.<sup>151,152</sup> Fogo selvagem (endemic pemphigus; Brazilian pemphigus) is a variant of pemphigus foliaceus found in tropical regions but is clinically and immunologically indistinguishable from sporadic pemphigus foliaceus.<sup>153</sup> Certain human leukocyte antigen (HLA) alleles and exposure to certain blood-sucking insects are risk factors. Patients with fogo selvagem show pathogenic anti-desmoglein 1, IgG4, and IgM autoantibodies,<sup>154,155</sup> which may develop as a result of antigenic mimicry initiated by an environmental stimulus in predisposed persons.<sup>156</sup> Endemic in Brazil and to a lesser extent in other South American countries, 15% of patients are children. The striking distribution of lesions on sun-exposed skin, its burned appearance, and the painful burning sensation in lesions (more so than in sporadic pemphigus foliaceus) are responsible for the name *fogo selvagem* (Portuguese, meaning *wildfire*). In chronic cases hyperpigmentation, hyperkeratosis, and loss of hair over the scalp and body are prominent features of this disorder.

### Drug-Induced Pemphigus

Drug-induced pemphigus is particularly rare in children. The most commonly implicated agents are penicillamine and captopril (both thiol drugs), but other drugs have also been implicated (Box 13-1). Sulfhydryl groups are thought to interact with the sulfhydryl groups in desmogleins 1 and 3, thus modifying the antigenicity of the desmoglein. In contrast to other types of drug reactions, drug-induced pemphigus often requires several months of exposure to the medication before onset. Initially a nonspecific morbilliform, annular, or urticarial eruption may be seen, eventually evolving after a variable latency period into the blistering process. The disorder typically resembles pemphigus foliaceus more often than pemphigus vulgaris. Oral lesions are rare.

### Immunoglobulin A Pemphigus

Immunoglobulin A (IgA) pemphigus, characterized by the intercellular deposition of IgA rather than IgG autoantibodies, has been divided into the subcorneal pustular dermatosis form and intraepidermal neutrophilic IgA dermatosis based on the subcorneal or intraepidermal localization of the blister histologically. Both conditions clinically show vesicles, small bullae, and pustules overlying well-circumscribed erythema. IgA pemphigus resembling pemphigus vegetans has also been described.<sup>157</sup> The youngest reported patient was 1 month of age.<sup>158</sup> The autoantigen for the subcorneal pustular dermatosis form has been shown to be the desmosomal protein desmocollin 1.<sup>159</sup> Although circulating antibodies against either desmoglein 1 and desmoglein 3 have been identified in patients with intraepidermal neutrophilic IgA dermatosis, other patients have shown no identifiable autoantigen.<sup>160–162</sup>

The pustular form may be the same disorder as subcorneal pustular dermatosis (Sneddon–Wilkinson disease), a condition that rarely occurs in children, although it has been described in individuals as young as 7 weeks of age.<sup>163</sup> The disease generally begins with small pustules or vesicles on an erythematous base. Occasionally only vesicles may be present, but these soon change into sterile pustules. The

pustules tend to appear in crops and spread to large parts of the body, forming large circinate or gyrate patterns that coalesce to form serpiginous patterns, especially on the abdomen, axillae, and groin. Individual lesions tend to last for periods of 5 days with new lesions appearing as others disappear. As the pustules resolve they are replaced by a superficial leafy scale or crust. After the eruption resolves, a faint blotchy brown hyperpigmentation without atrophy or scarring remains. The condition is benign and is characterized by remissions and exacerbations that may last for 5 to 8 years. Histopathologic examination of an intact lesion of subcorneal pustular dermatosis reveals a subcorneal blister filled almost entirely with neutrophilic polymorphonuclear leukocytes, but immunofluorescence analysis shows no immunodeposits.

### Paraneoplastic Pemphigus

Paraneoplastic pemphigus, a rare autoimmune disorder associated with malignancy, has been described occasionally in children.<sup>164,165</sup> The majority of pediatric patients have underlying Castleman disease, a lymphoproliferative disorder characterized by massive growth of lymphoid tissue usually located in the retroperitoneum or mediastinum.<sup>166,167</sup> Sarcoma, T-cell lymphoblastic lymphoma, and myofibroblastic tumor may also underlie paraneoplastic pemphigus; occasionally no underlying tumor is detected.

All patients tend to show intractable stomatitis, particularly involving the labial mucosa and resembling the labial manifestations of Stevens–Johnson syndrome. Two-thirds of patients show conjunctival involvement sometimes leading to symblepharon and visual impairment. Skin changes can be bullous and/or may resemble lichen planus or erythema multiforme. The trunk and extremities are most commonly involved. Palmoplantar involvement and paronychial inflammation, which may result in nail shedding, are commonly seen. Mucosae of the tracheobronchial system are also involved, and respiratory involvement with the development of bronchiolitis obliterans may be fatal.<sup>168</sup>

Biopsies show intraepithelial acantholysis, keratinocyte dyskeratosis, and basal cell vacuolar changes, combining the histologic features of pemphigus and Stevens–Johnson syndrome. Direct immunofluorescence is often negative, but immunoblots show several circulating autoantibodies directed against a variety of epidermal proteins, particularly of the desmogleins and plakin family (BP antigen 1, DSP, envoplakin, and periplakin).

Paraneoplastic pemphigus must be distinguished from Stevens–Johnson syndrome, toxic epidermal necrolysis, pemphigus vulgaris, bullous and cicatricial forms of pemphigoid, lichen planus pemphigoides, and mucosal infections from herpes or candida. Once the diagnosis is suspected in a child or adolescent, evaluation for malignancy should be initiated. Complete physical examination, particularly of the liver, spleen, and lymph nodes; complete blood count; serum protein electrophoresis; and computerized tomographic scans of the chest, abdomen, and pelvis should be performed to seek evidence of malignancy.

### Treatment of Pemphigus

A support group for patients with pemphigus can be accessed at [www.pemphigus.org](http://www.pemphigus.org). The treatment of choice for pemphigus vulgaris has been systemic corticosteroid therapy given either as high doses orally (1 to 2 mg/kg per day) or as intravenous pulses.<sup>169</sup> In one study, intervention led to complete recovery in only 18% of children, although partial improvement with minor relapses in 79%.<sup>170</sup> The majority of children with pemphigus developed serious side effects from their immunosuppression, including cushingoid features in 65% and growth retardation in 50%, stressing the need for steroid-sparing agents.<sup>171–173</sup> Rituximab (monoclonal anti-CD20 antibody) has now been used as an alternative off-label agent for children as young as 18 months of age<sup>174</sup> with dramatic clinical results and long-term remission.<sup>175,176</sup> In one study with 10 children, complete remission was achieved with single-agent rituximab by a mean of 21 weeks; relapses occurred in about half of the children, but a repeat cycle led to good response when used.<sup>175</sup> Infusion reactions are the most common side effect. Other steroid-sparing agents for pemphigus vulgaris are dapsone,<sup>177</sup> mycophenolate mofetil (600 to 1200 mg/m<sup>2</sup> per day),<sup>178,179</sup> cyclosporine (5 mg/kg per day), methotrexate,<sup>180</sup> azathioprine (2 to

#### Box 13-1 Causes of Drug-Induced Pemphigus

- β-blockers
- Captopril
- Ceftazidime
- Penicillamine
- Penicillin
- Progesterone
- Rifampin
- Sulfasalazine

4 mg/kg per day),<sup>181</sup> or high-dose intravenous immunoglobulin,<sup>182,183</sup> and can be added to allow the corticosteroid to be tapered, although each of these agents has significant potential side effects.

Pemphigus foliaceus is a milder disorder. Suprapotent topical corticosteroids may be effective in some patients, but often treatment with dapsone with or without systemic corticosteroids (initially 1 mg/kg per day) may be required for clearance. In all forms of pemphigus, therapy should be tapered gradually as tolerated when improvement is noted, which may require several months in severe cases.<sup>184</sup> Although patients with Brazilian pemphigus (*fogo selvagem*) may respond to antimalarial therapy (quinine or quinacrine), systemic corticosteroids continue to be the treatment of choice. Once the disease has cleared, pemphigus foliaceus has a lesser tendency to recur than pemphigus vulgaris.

Drug-induced pemphigus usually clears with treatment of the pemphigus and withdrawal of the offending medication. IgA pemphigus in children usually responds to treatment with dapsone or sulfapyridine within 24 to 48 hours but tends to be more difficult to control with steroids and other systemic anti-inflammatory agents. Oral retinoids have been used in patients with IgA pemphigus who do not respond to systemic administration of corticosteroids and dapsone.<sup>185</sup>

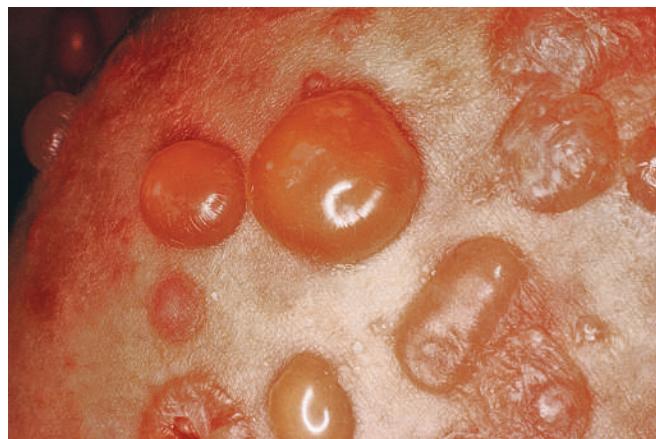
Patients with paraneoplastic pemphigus often have their conditions clear or improve significantly with surgical removal of the Castleman disease, but not until 6 to 18 months after tumor removal. The prognosis is much worse with malignant neoplasms. The majority of patients succumb within months of the diagnosis, usually to respiratory failure or secondary infection. Aggressive treatment of the malignancy coupled with immunosuppressive therapy such as the combination of systemic corticosteroids and cyclosporine should be initiated but may not affect the prognosis. Plasmapheresis has been used in conjunction with corticosteroids and tumor resection.<sup>186</sup>

## BULLOUS PEMPHIGOID

BP is a blistering disorder characterized by large, tense, subepidermal bullae that appear on normal-appearing or erythematous skin.<sup>187</sup> Although usually seen in elderly persons, BP may also occur occasionally in infants<sup>188</sup> and children,<sup>189–192</sup> the youngest reported being a 1-month-old infant.<sup>191,193</sup> Several infantile cases have been described after vaccination<sup>194–198</sup> or primary varicella infection.<sup>199</sup> Childhood BP has been described as a manifestation of chronic renal allograft rejection.<sup>200</sup>

The disorder often starts as mild to moderate pruritus with urticarial or erythematous plaques that evolve over weeks to months into large, tense, sometimes hemorrhagic bullae. Lesions may appear on normal skin or on an erythematous base. The blisters commonly occur at the periphery of annular or polycyclic erythematous plaques. Bullae typically measure 0.25 to 2 cm in diameter. The lower abdomen, anogenital region (including the vulva), and flexural areas of the arms and legs are most often involved, although bullae not uncommonly occur on the face in children. The Nikolsky sign is characteristically absent, and blisters do not extend or increase in size as they do in patients with pemphigus vulgaris. Blistering of the palms and soles is seen in virtually all affected infants,<sup>193</sup> whereas penile involvement is more common in older children.<sup>188,191,201,202</sup> The bullae tend to be more tense and inflamed than those of pemphigus vulgaris (Fig. 13-25), and the course of BP is more indolent than that of pemphigus vulgaris. Blisters resolve without scarring. Oral lesions are seen in approximately 25% of patients, especially in older children.

Variants include cicatricial pemphigoid, which affects mucosal surfaces, and a localized form (chronic pemphigoid of Brunsting-Perry) that is generally limited to the head and neck. The predominant localization of blisters in cicatricial pemphigoid is mucosal<sup>203</sup> (Fig. 13-26), with only 25% of patients showing skin involvement, particularly on the face, neck, and upper chest. Recurrent bullae are seen in the oral mucosa, conjunctivae, and other mucous membranes such as those of the nasopharynx, esophagus, larynx, genitalia,<sup>204</sup> and anus.<sup>205</sup> Oral involvement often takes the form of a desquamative gingivitis,<sup>206</sup> and ocular involvement may not occur until many years after the onset of the condition. Eye involvement often presents as dryness of the eyes with a feeling of chronic, intractable conjunctival irritation. Conjunctival involvement can lead to entropion, trichiasis (ingrowing



**Figure 13-25** Bullous pemphigoid. Large, tense bullae are seen on the lower region of the abdomen in this 13-year-old boy.



**Figure 13-26** Cicatricial pemphigoid. This 3-year-old boy showed blistering of the oral and ocular mucosae. Early diagnosis is critical to prevent the scarring and permanent blindness. The minority of patients with this condition show cutaneous involvement.

eyelashes), symblepharon, dryness of the cornea, corneal ulceration, and in 25% of patients, blindness. Esophageal lesions may result in stricture formation. Laryngeal lesions, when present, can be life-threatening. Adhesions of the genitourinary region may lead to phimosis in boys and narrowing of the vaginal opening in affected girls. Lichen planus pemphigoides is an overlap disease in which the lichen planus develops first<sup>207</sup>; most cases respond to dapsone (see Chapter 4).

Biopsy specimens of cutaneous lesions show subepidermal blister formation generally without papillary microabscesses (an important diagnostic feature of dermatitis herpetiformis [DH]). Eosinophils are often seen in sections, and peripheral eosinophilia is common. DIF reveals deposition of C<sub>3</sub> and IgG at the lamina lucida of the basement membrane zone. Although indirect testing of serum for circulating IgG anti-basement membrane zone antibodies (IIF) is positive in 72% of children, antibody titers do not correlate with clinical disease activity. These circulating immune deposits bind to the roof of salt-split skin, in which the cleavage runs through the lamina lucida of basement membrane. Antibodies are most commonly directed against the NC16A domain of BP180 antigen (collagen XVII) but may be directed against BP230.<sup>201</sup> ELISA assays have been shown to be more sensitive and just as specific as IIF.<sup>208</sup>

Potent topical corticosteroids may be effective for localized areas of involvement and in patients who are mildly affected.<sup>209</sup> In general, systemic corticosteroids are the mainstay of treatment (1 to 2 mg/kg per day). Sulfapyridine (60 to 150 mg/kg per day), dapsone (1 to 2 mg/kg per day), azathioprine, mycophenolate mofetil,<sup>210</sup>



**Figure 13-27** Pemphigoid gestationis. Cutaneous involvement of the newborn has been noted in about 10% of infants born to mothers with this disorder. In the neonate the condition subsides within several weeks as maternal antibodies wane. (Courtesy of Moise Levy, MD.)

intravenous immunoglobulin,<sup>194</sup> and rituximab<sup>174</sup> have been used as steroid-sparing agents and in steroid-resistant cases.<sup>211</sup> Erythromycin (50 mg/kg per day) with or without nicotinamide (25 to 40 mg/kg per day) has been beneficial in some children, presumably owing to its anti-inflammatory effects. Omalizumab, which targets IgE, has been effective as a steroid-sparing agent.<sup>212,213</sup> Rarely plasma exchange and extracorporeal photochemotherapy have been used for childhood BP.<sup>214</sup> The disorder remits in most children within a year and has an excellent prognosis.

### Pemphigoid Gestationis

Pemphigoid gestationis (formerly called *herpes gestationis*) usually presents during the second or third trimester of pregnancy or in the immediate postpartum period.<sup>215</sup> It occurs in 1:50,000 pregnancies. Maternal skin lesions often start at the umbilical area and spread to the abdomen and thighs. Before the development of bullae, initial lesions may be pruritic, eczematous, or erythema multiforme-like erythematous papules and plaques. The disorder can start for the first time with any pregnancy but then tends to recur in subsequent pregnancies. Although the eruption tends to clear in the majority of patients within a few days of delivery, it can persist for many months after delivery. Mild recurrences occasionally have been noted to appear at the time of menstruation, in women who take oral contraceptives, and in women with choriocarcinomas and hydatidiform moles. Cutaneous involvement of the newborn has been noted in about 10% of infants born to mothers with this disorder (Fig. 13-27); on the basis of immunofluorescent findings, a high percentage of newborns have been noted to have subclinical forms of pemphigoid gestationis as well.

The immunopathologic hallmark of pemphigoid gestationis is deposition of C<sub>3</sub>, with or without IgG, distributed in a linear band along the basement membrane. The targeted antigens in skin are BP180 and less commonly, BP230.<sup>216</sup>

The course of pemphigoid gestationis is characterized by alternating exacerbations and remissions. Systemic corticosteroids are the most reliable mode of therapy, and with certain precautions are generally considered safe for both mother and fetus, especially after the first trimester of pregnancy. Alternate-day dosage, if possible, is preferable to daily treatment. To avoid fetal adrenal suppression, dosages should be reduced to a minimum during the final weeks of pregnancy. The cutaneous lesions in infants with this disorder generally remit within several weeks and do not require therapy. Although there may be an increased risk of prematurity or intrauterine growth restriction, pemphigoid gestationis does not result in an increased mortality risk for the mother or the fetus.

### DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis (DH; Duhring disease) is characterized by an intensely pruritic papulovesicular and sometimes bullous eruption that responds dramatically to orally administered doses of sulfones or

sulfapyridine.<sup>217</sup> Although the disorder may affect infants and children, DH generally occurs during the second to fifth decades of life. It is most common in individuals of Northern European descent and is rare in African-Americans. DH is considered the cutaneous form of celiac disease and affects about 5% to 17% of patients with celiac disease.<sup>218,219</sup>

Diagnosis of this disorder cannot be based solely on the morphologic aspects and distribution of lesions but on the constellation of clinical appearance, histopathologic characteristics, immunofluorescent findings, serologic testing, and response to therapy. The major environmental trigger is ingested gluten and particularly its gliadin component. IgA antibodies develop against gliadin but also two structurally homologous autoantigens, tissue transglutaminase (tTG; widely distributed; most important for celiac disease) and epidermal transglutaminase (eTG or transglutaminase 3; epidermis-specific and most important for DH).<sup>220-223</sup> Virtually all patients with DH have intestinal sensitivity to gluten, but the minority show gastrointestinal symptoms. Of children with DH, 16% have chronic diarrhea, 10% have iron-deficiency anemia, and growth retardation is rare.<sup>224,225</sup>

DH tends to affect the extensor surfaces: the elbows, knees, sacrum, buttocks, and shoulders, and occasionally the face, eyelids, facial hairline, posterior nuchal area, and scalp. Lesions are usually grouped and symmetrical in distribution with centrifugal extension and vesicles predominantly at the periphery. In association with the onset of intense pruritus or burning, erythematous and at times, urticarial lesions may develop. Characteristic of this disorder are minute, clear, relatively tense vesicles that measure from 0.3 to 4 mm in diameter. These vesicles rupture easily, either spontaneously or when scratched. Not uncommonly, the grouped ("herpetiform") vesicles and papules are seen amid excoriated papules and postinflammatory hypopigmentation and hyperpigmentation. The palms, flexor fingers, and soles may show hemorrhagic, purpuric, or petechial lesions with active DH,<sup>226-228</sup> found in 64% in one pediatric study.<sup>229</sup> Palmoplantar hyperkeratosis, chronic urticaria, and prurigo have been described in atypical cases. The general course of this disorder is chronic (often lasting 5 to 10 years or more) with frequent exacerbations and remissions.

Childhood DH can be confused with arthropod bites, dermatitis, urticaria, scabies, and pityriasis lichenoides et varioliformis acuta. Serum IgA anti-transglutaminase 3 levels have been proposed as a screening test for DH, although confirmation of the diagnosis requires lesional biopsy for routine histologic evaluation and most importantly, perilesional biopsy (within 1 cm away) for immunofluorescent analysis. Subepidermal microabscesses with accumulations of neutrophils and eosinophils are found at the tips of the dermal papillae by routine histology. IgA is seen at the tips of the dermal papillae in a granular pattern by immunofluorescent microscopy of perilesional skin.<sup>230</sup> Patients should be eating a gluten-containing diet for biopsy or any serologic testing, or false-negative results may occur. If the DIF testing on biopsy sections is negative but the clinical presentation is typical, then serologic testing showing antibodies against tTG and endomysial antibodies (or, even better, the more sensitive anti-eTG or deamidated anti-gliadin if available) can allow a provisional diagnosis and lead to a trial of medical and dietary intervention.

Sulfones (dapsone) and sulfapyridine are effective in relieving the symptoms and suppressing the eruption of DH in children as well as adults. Dramatic relief from the use of these agents, often as early as 24 to 48 hours after initiation, is often helpful in making the diagnosis. The recommended initial dosage for dapsone is 0.5 mg/kg per day. If no response is seen in a week, the dosage can be increased by 0.5 mg/kg per day to a maximum of 2 mg/kg per day, assuming blood counts are normal before each dosage increase. Once existing lesions have been suppressed, the dosage may be tapered to a minimal level (usually 12.5 to 50 mg/day). Baseline blood counts and glucose-6-phosphate dehydrogenase (G6PD) levels are important before initiating therapy. Blood counts should be repeated at least monthly for the first 6 months. Side effects are uncommon but can include hemolytic anemia (especially seen in patients with G6PD deficiency, a contraindication to use), agranulocytosis, methemoglobinemia (manifested most commonly by headache and fatigue but sometimes by bluish discoloration of the face, mucous membranes, and nails), nausea, vomiting, headache, giddiness, tachycardia, psychoses, anemia, leukopenia, fever, exfoliative dermatitis, liver necrosis, lymphadenitis, and



**Figure 13-28** Chronic bullous disease of childhood. Clear or hemorrhagic bullae are commonly found on the legs, as well as the face, lower part of the trunk, and genitalia.

peripheral neuropathy. If at all possible, a gluten-free diet should be instituted. By gluten-free diet alone, children experience remission in approximately 11 months, and clearance of IgA deposits can take years. Reintroduction of gluten leads to rapid clinical deterioration. Adherence for at least 5 years to a gluten-free diet is also thought to lower the increased risk of developing lymphoma (most commonly involving the gastrointestinal system and non-Hodgkin lymphoma). Adherence is particularly difficult, however, in affected adolescents. Support and information about DH and gluten-free diets can be found online (<http://celiac.org/celiac-disease/dermatitis-herpetiformis/>; [www.gluten.net](http://www.gluten.net); [www.dermatitisherpetiformis.org.uk](http://www.dermatitisherpetiformis.org.uk)).

#### LINEAR IMMUNOGLOBULIN A BULLOUS DERMATOSIS

Linear immunoglobulin A (IgA) bullous dermatosis of childhood (chronic bullous disease of childhood) is a subepidermal blistering disease that may be indistinguishable both clinically and histologically from BP.<sup>231-233</sup> Its onset is usually in the first decade of life, particularly during preschool years. Spontaneous remission usually occurs after several months to 3 years and almost always before the onset of puberty. IgA nephropathy is a rare complication.<sup>234</sup> It can follow an infection or represent a manifestation of drug hypersensitivity, especially to antibiotics such as vancomycin, amoxicillin-clavulanate, and trimethoprim-sulfamethoxazole, generally 1 to 13 days after the first dose.<sup>235-237</sup>

The eruption is characterized by large, tense, clear or hemorrhagic bullae measuring 1 to 2 cm in diameter on a normal or erythematous base. The eruption is widespread, and areas of predilection include the face, scalp, lower part of the trunk (including the genitalia and pubis), buttocks, inner thighs, legs, and dorsal aspect of the feet (Fig. 13-28). The bullae may form characteristic annular or rosette-like lesions composed of sausage-shaped blisters resembling a cluster of jewels surrounding a central crust, the string-of-pearls sign (Fig. 13-29). Mucous membrane lesions occasionally occur. Pruritus is a variable feature and may be mild to moderate, intense and distressing, or completely absent.

Histologically, chronic bullous disease of childhood is characterized by subepidermal bullae with edema of adjacent dermal papillae and a dermal infiltrate of polymorphonuclear leukocytes, eosinophils, and mononuclear cells. The immunofluorescent findings of linear IgA deposits in the lamina lucida zone of the dermal–epidermal junction obtained from perilesional skin confirm the diagnosis; occasionally children show both IgA and IgG antibodies.<sup>238,239</sup> Circulating IgA basement membrane-zone antibody is found in up to 80% of patients and usually binds the epidermal side of salt-split skin. Antibodies are most commonly directed against a 120 kDa fragment of BP180 (also called linear IgA disease antigen-1 [LAD-1]) and less commonly, a 97 kDa fragment that is generated from the 120 kDa fragment.<sup>240</sup>



**Figure 13-29** Chronic bullous disease of childhood. The bullae may form characteristic annular or rosette-like lesions resembling a cluster of jewels surrounding a central crust, the string-of-pearls sign.



**Figure 13-30** Epidermolysis bullosa acquisita (EBA). This disorder may resemble dystrophic epidermolysis bullosa (DEB). Note the scarring, milia, and nail dystrophy. The immunodeposits in patients with EBA are directed against collagen VII, the same protein missing or dysfunctional in patients with DEB.

Some children with clinically typical chronic bullous disease of childhood show “mixed immunobullous disease of childhood,” in which both IgG and IgA autoantibodies are detected.

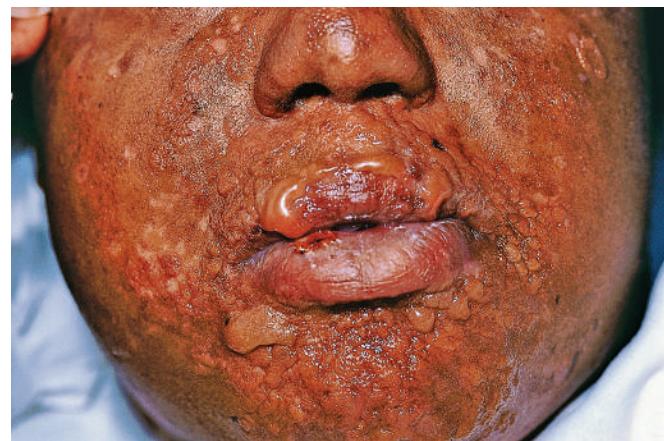
Response to therapy is generally favorable.<sup>241</sup> Dapsone, as in DH, is the drug of choice, although patients have responded to administration of erythromycin, dicloxacillin, or sulfonamides.<sup>242-245</sup> Responses to antibiotics, however, are often transient, and their use has been advocated initially while awaiting results of diagnostic tests or in patients unable to take dapsone and sulfapyridine.<sup>246</sup> If response to dapsone or antibiotics is inadequate, sulfapyridine, systemic corticosteroids, and mycophenolate mofetil are alternative therapies.

#### EPIDERMOLYSIS BULLOSA ACQUISITA

Epidermolysis bullosa acquisita (EBA; acquired EB) is a subepidermal blistering disorder that usually takes on one of two forms: a generalized inflammatory eruption clinically indistinguishable from BP and a noninflammatory acral blistering disorder that results in scarring and milia formation (Fig. 13-30) reminiscent of DDEB. Approximately 40 cases in children have been described.<sup>247</sup> A neonate with EBA from transplacental transfer of antibody has been described (Fig. 13-31).<sup>248</sup> Blisters may be hemorrhagic or serous and tend to be localized to sites



**Figure 13-31** Epidermolysis bullosa acquisita (EBA). This baby developed EBA by transplacental passage of maternal antibodies against type VII collagen. Tense blisters resulted in neonatal denudement and subsequent milia formation, as in dystrophic epidermolysis bullosa.



**Figure 13-32** Bullous systemic lupus erythematosus. Pruritic vesicles and tense bullae develop and may leave intense postinflammatory hypopigmentation or hyperpigmentation. This adolescent responded to the combination of prednisone, azathioprine, and dapsone.

of trauma or pressure, especially on the extensor areas of the extremities. Oropharyngeal mucous membrane erosions are commonly seen; the conjunctival, esophageal, and anogenital mucous membranes are less commonly involved, although blindness may result. The nails may be dystrophic, and scarring alopecia may be seen.

The condition results from the deposition of IgG and less commonly IgA,<sup>249,250</sup> autoantibodies directed against type VII collagen (see Fig. 13-1). Type VII collagen is a structural component of anchoring fibrils that is missing or abnormal in children with RDEB or DDEB, respectively. Immunofluorescence examination shows the linear deposition of IgG and sometimes C<sub>3</sub> at the lower lamina densa or sublamina densa zones of the basement membrane. IIF shows IgG binding to the dermal side of salt-split skin (e.g., beneath the lamina lucida). Immunoblotting analysis shows binding to a 290 kDa protein that corresponds to type VII collagen and recognition primarily of the NC1 noncollagenous domain of type VII collagen; however, children may show antibodies directed against additional domains, particularly children with EBA younger than 10 years of age with the inflammatory phenotype.<sup>251</sup>

EBA has a chronic course with flares but seems to have a better prognosis in children than in adults. Dapsone and corticosteroids are first-line therapy and often lead to remission within about 2 years; mycophenolate mofetil may be steroid-sparing. Rituximab is now also used for treatment-resistant EBA.<sup>252,253</sup> Childhood IgA-mediated EBA has responded to mycophenolate mofetil.<sup>250</sup> Colchicine, infliximab, photophoresis,<sup>254</sup> rituximab,<sup>255</sup> and intravenous immunoglobulin have been helpful for some patients.<sup>256</sup> The recent demonstration that T cells are critical in initiation of EBA suggests that T cell-directed immunomodulatory strategies may be effective in the future.<sup>257</sup>

## BULLOUS SYSTEMIC LUPUS ERYTHEMATOSUS

Similar to patients with EBA, patients with systemic lupus erythematosus (SLE) who manifest immune-mediated bullae show antibodies directed against type VII collagen.<sup>258–261</sup> However, the clinical manifestations more closely resemble those of BP or DH. African-American adolescents and young women are most often affected, with a mean age of onset of 22 years.<sup>262</sup> Occasionally bullous SLE is the presenting sign of lupus,<sup>263–265</sup> but more typically it develops in a patient with known SLE (see Chapter 22). Typical lesions are pruritic vesicles and tense bullae with occasional erythematous macules and papules

(Fig. 13-32).<sup>266</sup> Lesions tend to leave postinflammatory hypopigmentation or hyperpigmentation. Sun-exposed areas are most commonly involved, but flexor and extensor skin surfaces, as well as oral mucosae, may be affected. Bullous SLE in a linear pattern following Blaschko lines has been described in a child.<sup>267</sup>

Immunofluorescence examination shows deposition of IgG and sometimes IgM, IgA, or C<sub>3</sub> at the basement membrane and upper dermis. Granular, linear, and mixed patterns have all been described. Prognosis is usually favorable and is largely determined by the course of the associated SLE. Most patients generally respond quickly to dapsone therapy (in contrast to EBA), but rituximab has also been used in refractory cases.<sup>268</sup> Administration of systemic corticosteroids with or without additional immunosuppressive agents (e.g., methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, or cyclosporine) has led to variable response.

The complete list of 268 references for this chapter is available online at <http://expertconsult.inkling.com>.

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The normal skin of healthy infants and children is resistant to invasion by most bacteria, because the cutaneous surface provides a dry mechanical barrier from which contaminating organisms are constantly removed by desquamation. Under normal conditions the skin is sterile at delivery and for a short period thereafter. During the process of vaginal birth it acquires organisms from the birth canal, which gradually increase in number during the first 10 days of life. If the newborn is delivered by cesarean section, however, the cutaneous surface remains sterile until after delivery but soon becomes exposed to bacteria from human contactants and fomites.

Almost any organism may live on the cutaneous surface under appropriate conditions. A complete list of transient organisms accordingly would include virtually all microorganisms found in the human environment. The number of species composing the resident flora, however, is relatively small and consists predominantly of Gram-positive organisms and a few Gram-negative species, including *Propionibacterium acnes* (normally found in high concentrations about the pilosebaceous follicles of the face and less commonly the axillae and forearms), aerobic diphtheroids (*Corynebacterium minutissimum* and *Corynebacterium tenuis*), *Staphylococcus epidermidis* micrococci, and anaerobic Gram-positive cocci. Others include Gram-negative bacilli (*Escherichia coli*, *Proteus*, *Enterobacter*, and *Pseudomonas*, among others) found uncommonly on normal skin except in the moist intertriginous areas of the groin, axillae, and toe webs and *Staphylococcus aureus*, a common pathogen that appears to usually be seeded from the carrier state in the anterior nares.

Because the cutaneous surface is continuously exposed to microorganisms, it is most helpful to distinguish among transient, resident, and pathogenic flora. The transient flora consists of multiple organisms that are deposited on the skin from the environment, presumably do not proliferate, and are removed easily by washing or scrubbing of the affected area. The resident flora consists of a smaller number of organisms that are found more or less regularly in appreciable numbers on the skin of normal individuals, multiply on the skin, form stable communities on the cutaneous surface, and are not easily dislodged. Pathogenic bacteria, not ordinarily a regular part of this flora, persist on the skin if there is continuous replacement from some internal or external source or if the integrity of the skin is disrupted by injury or disease. It should be noted that the mere presence of potentially pathogenic bacteria in a cutaneous lesion does not necessarily prove the demonstrable organism to be a cause of bacterial infection.

Children have a more varied cutaneous flora than adults and often harbor soil bacteria on their skin. Prepubertal children lack sebum and accordingly have fewer diphtheroid organisms than adults. It is estimated that 10% to 30% of individuals are nasal carriers of *S. aureus* and that 70% to 90% are transient carriers.<sup>1,2</sup> Such coagulase-positive staphylococci are not considered part of the normal cutaneous flora of glabrous skin in adults but are common transients acquired from carrier sites such as the anterior nares and perineum. In a recent 1-year study of 333 healthy preschool children ages 3 to 6 years, 34% of nasal swab samples yielded *S. aureus* from 185 (55%) carriers, and based on consecutive genotype analysis, 15% of the children were classified as persistent carriers (the remaining were considered to be intermittent carriers).<sup>3</sup>

The introduction of a vast array of antibiotics and chemotherapeutic agents has affected striking changes in the management of bacterial infections. With increased use of these agents the focus of attention has shifted to identifying the specific bacterial cause and its antimicrobial sensitivity pattern when feasible, permitting the appropriate choice of antibacterial agent(s). In purulent skin infections it is

relatively easy to obtain adequate specimens for examination and culture. With dry or crusted lesions, the yield will be greatest if the crust is gently lifted off and cultures are obtained from the moist underlying surface. In nonpurulent infections like erysipelas or cellulitis, past recommendations were for aspiration of the most active zone (not the surrounding area of erythema) with a 25-gauge needle attached to a syringe containing sterile saline without added preservatives. This procedure, unfortunately, has a very high false-negative rate, and often the clinician in this setting is forced to rely on clinical features or other diagnostic findings.

## Bacterial Infections

### IMPETIGO

Impetigo is a common, contagious superficial skin infection caused by streptococci, staphylococci, or both. Although seen in all age groups, the disease is most common in infants and children. Lesions may involve any body surface but occur most often on the exposed parts of the body, especially the face, hands, neck, and extremities.

There are two classic forms of impetigo: bullous and nonbullous (or crusted). Nonbullous impetigo accounts for more than 70% of cases.<sup>4</sup> It begins with a 1- to 2-mm erythematous papule or pustule that soon develops into thin-roofed vesicle or bulla surrounded by a narrow rim of erythema. The vesicle ruptures easily with release of a thin, cloudy, yellow fluid that subsequently dries, forming a honey-colored crust, the hallmark of nonbullous impetigo (Fig. 14-1). The infection is easily spread by autoinoculation (Fig. 14-2) through fingers, towels, or clothing, with resultant satellite lesions in either adjacent areas or other parts of the body. Individual lesions may extend peripherally with central clearing, resulting in annular or gyrate morphologies. Nonbullous impetigo historically was caused primarily by group A β-hemolytic streptococci (GABHS) but now appears to be most commonly caused by *S. aureus*.<sup>4,5</sup> Anaerobic organisms may also be recovered from lesions of nonbullous impetigo.<sup>5</sup>

Bullous impetigo, which is nearly always caused by *S. aureus*, presents as flaccid, thin-walled bullae or more commonly, tender, shallow erosions surrounded by a remnant of the blister roof (Figs. 14-3 and 14-4). Common locations include the diaper region (Fig. 14-5), face, and extremities. Lesions of bullous impetigo can be thought of as a localized form of staphylococcal scalded skin syndrome (SSSS) (see *Staphylococcal Scalded Skin Syndrome* section), the characteristic lesions being the result of the same exfoliative toxin as implicated in that condition. Neonatal pustulosis (see Chapter 2), another condition favoring the diaper region and other fold areas in infants, is usually caused by *S. aureus* and presents with small pustules on an erythematous base that rupture easily upon swabbing.

Fever and regional lymphadenopathy may occur later in the course of impetigo but appear to be more common with the nonbullous type caused by GABHS. Potential complications of both bullous and nonbullous impetigo include sepsis, osteomyelitis, septic arthritis, lymphadenitis, and pneumonia.<sup>4</sup> Cutaneous streptococcal disease may be associated with guttate psoriasis, scarlet fever, and poststreptococcal glomerulonephritis when a nephritogenic strain of GABHS is implicated.

An important reservoir for staphylococci is the upper respiratory tract of asymptomatic persons. Asymptomatic nasal carriage occurs in 20% to 40% of normal adults and up to 80% of patients with atopic dermatitis. The perineum is another common site of carriage, albeit not as common as the nares. These carriers spread the agent to the skin of infants and young children, probably with their hands. The



**Figure 14-1** Nonbullous (crusted) impetigo. Erythematous papules with honey yellow-colored crusting.



**Figure 14-2** Nonbullous (crusted) impetigo. These multiple lesions have spread as a result of autoinoculation.



**Figure 14-3** Bullous impetigo. Multiple tender, erythematous patches with a peripheral collarette, representing remnants of the blister roof.

reservoir for streptococci involved in skin infections appears to be skin lesions of other individuals, not the respiratory tract of affected or asymptomatic persons. Factors such as trauma and insect bites probably contribute to the pathogenesis of this infection.

Treatment for impetigo depends on the clinical presentation. Untreated, the disorder may last for 2 to 3 weeks with continuous spread and development of new lesions. In severe cases there may be



**Figure 14-4** Bullous impetigo. Thin-walled vesicles and shallow erosions with peripheral collarettes and mild crusting on the buttock and posterior thigh.



**Figure 14-5** Bullous impetigo. Inguinal and suprapubic involvement in an infant female. Lesions of bullous impetigo have a preference for this location in diapered infants.

large, crusted vegetations with deep extension and ulceration. Gentle cleansing, removal of crusts, and drainage of blisters and pustules may help prevent local spread of disease. If crusts are firmly adherent, warm soaks or compresses are useful.

Topical antibiotics may be useful in the treatment of mild, localized disease caused by *S. aureus*. With streptococcal or more severe staphylococcal infections, however, systemic antibiotics produce a swifter response and fewer failures. Bacitracin, polymyxin, gentamicin, and erythromycin are all effective topical agents and are relatively nonallergenic. Bacitracin, however, is a potential contact allergen, and this should be remembered in patients treated with this agent who develop worsening erythema and evidence of contact dermatitis.<sup>6,7</sup> In addition, treatment failures are common when bacitracin is used for impetigo.<sup>8</sup> Neomycin is another effective topical agent, although reports of contact allergy have traditionally appeared to be more common with this agent than with other topical antimicrobials (see Chapter 3). Mupirocin exerts a high level of bactericidal activity against a broad spectrum of Gram-positive organisms including *S. aureus* and GABHS and has little or no potential for irritation, side effects, or cross-reaction with other antibiotics. It is effective against methicillin-resistant *S. aureus* (MRSA), although some resistance to mupirocin has emerged

in recent years, especially after prolonged use.<sup>9–12</sup> Some studies have demonstrated equal or greater effectiveness of topical mupirocin over oral erythromycin in the treatment of impetigo in children.<sup>13,14</sup> Mupirocin is typically applied three times daily for 7 to 10 days.<sup>15</sup> Nasal carriage of *S. aureus* may be reduced with the use of intranasal mupirocin, which should be considered in known carriers with recurrent impetigo or in the setting of epidemic outbreaks. Retapamulin, a newer pleuromutilin-class topical antibiotic for the treatment of skin and skin-structure infections, has been demonstrated effective against both *S. aureus* and GABHS and is another treatment option for localized impetigo.<sup>16,17</sup> Retapamulin is also active against MRSA and many anaerobes, including *Propionibacterium* species, *Bacteroides* species, and *Clostridium* species.<sup>15</sup> The benefits of retapamulin include its lower propensity toward the development of resistance and twice daily dosing.<sup>18</sup>

Oral therapy for impetigo should be with an agent that covers both *S. aureus* and GABHS, because distinguishing between these etiologies clinically is often not possible. In areas with a low prevalence of erythromycin-resistant *S. aureus*, erythromycin ethylsuccinate or erythromycin estolate are reasonable options. If known erythromycin resistance is present in the community, alternative oral agents with a good track record include a penicillinase-resistant penicillin (i.e., cloxacillin or dicloxacillin), amoxicillin plus clavulanic acid, a first- (i.e., cephalexin) or second- (i.e., cefprozil) generation cephalosporin, clindamycin, or in some cases, other macrolide antibiotics (i.e., clarithromycin or azithromycin). Oral therapy is used by most clinicians when the involvement is more widespread and/or severe.

In severe or recalcitrant cases, skin swab for bacterial culture and sensitivity testing should be performed. The evolving epidemiology of community-associated MRSA (CA-MRSA) (see below) infection must be considered in this setting, as highlighted by multiple observations of the increasing prevalence of this pathogen. These patients often lack traditional risk factors for MRSA, and the isolates may be more susceptible to clindamycin and trimethoprim-sulfamethoxazole.<sup>19,20</sup>

A review of the National Ambulatory Medical Care Survey data on office visits for impetigo from 1997 to 2007 revealed that a majority of the 4 million patients were treated by nondermatologists (pediatricians, internists, emergency room and family physicians), and systemic antibiotics were the most commonly prescribed therapy, followed by topical antibiotics.<sup>21</sup> A recent Cochrane review found that topical mupirocin and topical fusidic acid (not available in the United States) were equally or more effective than oral treatment in the studies that met their inclusion criteria.<sup>22</sup> This highlights a potential opportunity for physician education, because increased utilization of topical therapy for patients with more limited impetigo could decrease the morbidity associated with oral antibiotic treatment, in line with the principles of antibiotic stewardship.

Lesions of impetigo caused by GABHS are shallow and usually heal well, and rheumatic fever does not occur after streptococcal skin infection. In contrast, acute glomerulonephritis and scarlet fever can occur after cutaneous streptococcal infection. As in the case of nephritis after streptococcal pharyngitis, only certain serologic types, different from those producing nephritis as a sequel of streptococcal pharyngitis, appear to result in this complication of cutaneous infection.<sup>16</sup> This complication is uncommon except for certain epidemics resulting from nephritogenic strains of streptococci. Although systemic antibiotics help eliminate cutaneous streptococci, they do not appear to prevent glomerulonephritis caused by streptococcal impetigo. In general, however, with the changing bacteriology and the fact that staphylococci are a more common cause of both types of impetigo, concerns about postimpetigo glomerulonephritis have been greatly reduced.

## METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS INFECTIONS

The epidemiology of *S. aureus* skin and soft-tissue infections has changed over the last decade, with an increasing prevalence of CA-MRSA infections observed in both the United States and elsewhere. Since the initial descriptions of children lacking predisposing risk factors with CA-MRSA infection in the late 1990s, marked increases in *S. aureus* isolates with this characteristic were observed,

both in endemic and epidemic forms. By the mid-first decade of the twenty-first century, up to 50% of community-associated *S. aureus* infections in many US centers were being identified as MRSA.<sup>23</sup> Increases in the number of children hospitalized with MRSA infections have also been observed, but fortunately the mortality rate for these children remains low.<sup>24</sup>

MRSA originated after the introduction of a mobile genetic element, staphylococcal chromosomal cassette (SCC) carrying the *mecA* gene, into strains of methicillin-sensitive *S. aureus* (MSSA). This gene encodes an altered penicillin-binding protein.<sup>25</sup> In distinction to hospital-associated MRSA, CA-MRSA is generally classified as such when there is no history of prior MRSA infection or colonization, when the positive culture was obtained in the outpatient setting or isolated within 48 hours of hospitalization, and when the patient lacks an exposure history (i.e., to a healthcare facility, chronic care facility, or indwelling catheter).<sup>23,25</sup> Molecular characteristics of the isolate are also useful in distinguishing the strains. Many CA-MRSA strains produce Panton–Valentine leukocidin (PVL), a toxin that kills neutrophils, although this toxin is also produced by some of the other more-sensitive strains of *S. aureus*.<sup>26,27</sup> The exact role of PVL in CA-MRSA infections remains controversial, although it appears to be increasingly associated with follicular infections (see Furunculosis section).

CA-MRSA infections seem to disproportionately affect children, young adults, and individuals from ethnic minority and low socioeconomic groups.<sup>28</sup> Spread is facilitated by crowding, skin-to-skin contact, skin compromise, and shared personal hygiene items. Cutaneous CA-MRSA infections are common in athletes, most notably collegiate football players.<sup>29,30</sup> The potential clinical manifestations associated with CA-MRSA infection are listed in Box 14-1. The constellation of disorders caused by infection with CA-MRSA have been grouped under the designation of *skin and soft-tissue infections* (SSTIs). Empiric outpatient therapy decisions for CA-MRSA infections should incorporate the type and site of infection, prevalence of the organism in the community, and local antibiotic susceptibility patterns.<sup>28</sup> Abscesses (including furuncles and carbuncles), which are collections of pus within the dermis and deeper skin layers, are a common manifestation of CA-MRSA infection (Figs. 14-6 and 14-7) and are most commonly located on the buttocks.<sup>31</sup> Incision and drainage of abscesses is often useful and sometimes sufficient as monotherapy for purulent uncomplicated infections. However, better studies are required to determine

### Box 14-1 Clinical Associations with Community-Associated MRSA Infection

- Skin/soft-tissue infections
- Folliculitis
- Furuncles
- Carbuncles
- Impetigo
- Pustulosis (neonates)
- Cellulitis
- Abscesses
- Paronychia
- Staphylococcal scalded skin syndrome
- Necrotizing fasciitis/myositis
- Pneumonia/empyema
- Lymphadenitis
- Otitis media/externa
- Osteomyelitis
- Thrombophlebitis
- Septic arthritis
- Bacteremia
- Pyelonephritis
- Toxic shock syndrome
- Endocarditis
- Epidural abscess

Modified from Miller LG, Kaplan SL. *Staphylococcus aureus*: a community pathogen.

*Infect Dis Clin N Am* 2009;23:35–52; Paintsil E. Pediatric community-acquired methicillin-resistant *Staphylococcus aureus* infection and colonization: trends and management. *Curr Opin Pediatr* 2007;19:75–82, and Kirkland EB, Adams BB. Methicillin-resistant *Staphylococcus aureus* and athletes. *J Am Acad Dermatol* 2008;59:494–502.

MRSA, Methicillin-resistant *S. aureus*.



**Figure 14-6** Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). This 1-year-old girl exhibited an acute onset of multiple tender, fluctuant nodules. Incision and drainage revealed exudate that grew MRSA.



**Figure 14-7** Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). This 6-year-old female with a history of atopic dermatitis had an acute onset of a painful, fluctuant nodule over the thumb. Culture of the drainage revealed MRSA, and the infection cleared with an appropriate systemic antibiotic.

the role of antibiotics in treating abscesses that have been adequately drained.<sup>32</sup>

The most commonly utilized oral antibiotics in the United States are: trimethoprim-sulfamethoxazole, clindamycin, doxycycline, linezolid, rifampin, and the fluoroquinolones. Fusidic acid is also utilized in the United Kingdom, Australia, and other countries.<sup>33</sup> Inducible clindamycin resistance has increased in recent years and should be considered when testing reveals clindamycin susceptibility and erythromycin resistance. In these instances, a "D test" should be performed and used to guide the choice of therapy. Management of colonization has been attempted with intranasal mupirocin and skin disinfection (i.e., with chlorhexidine washes), with variable success.<sup>34</sup> Recently it was shown that persistent colonization with MRSA in outpatients is associated with increased household colonization pressure (colonization of household contacts).<sup>35</sup> In addition, MRSA colonization and infection has been increasingly observed in companion animals, especially cats and dogs, and may serve as reservoirs for human infection.<sup>36–38</sup>

## ECTHYMA

Ecthyma is a deep or ulcerative type of pyoderma commonly seen on the lower extremities and buttocks of children, and caused most often by GABHS. It may occur as small punched-out ulcers or a deep spreading ulcerative process. The disorder begins in the same manner as



**Figure 14-8** Ecthyma. Well-demarcated, punched-out ulcers on the thigh of this 10-year-old male.



**Figure 14-9** Ecthyma gangrenosum. These hemorrhagic, necrotic skin lesions were accompanied by *Pseudomonas aeruginosa* bacteraemia in this immunosuppressed child being treated with chemotherapy.

impetigo, often occurring after infected insect bites or minor trauma, but penetrates through the epidermis to produce a shallow ulcer. The initial lesion is a vesiculopustule with an erythematous base and firmly adherent crust. Removal of the crust reveals a lesion deeper than that seen in impetigo with an underlying saucer-shaped ulcer and raised margin (Fig. 14-8). The lesions are painful and heal slowly over a few weeks, often with scar formation. When multiple, lesions of ecthyma may be confused with child abuse related to cigarette burns. *S. aureus* (including MRSA) may occasionally be cultured from the lesions, and epidemic outbreaks have been reported, occasionally in association with poststreptococcal glomerulonephritis or other systemic sequelae.<sup>39,40</sup> Treatment consists of warm compresses and the appropriate systemic antibiotic.

Ecthyma gangrenosum is a cutaneous finding that may be seen in patients with *Pseudomonas aeruginosa* bacteraemia. Most of the affected individuals have an underlying immunodeficiency (either congenital or acquired) or a history of cancer chemotherapy. There are reports of ecthyma gangrenosum in apparently healthy, immunocompetent children (often with diaper-area involvement), but the diagnosis should prompt a thorough investigation for occult immunodeficiency.<sup>41,42</sup> Neutropenia may be a risk factor for ecthyma gangrenosum. The characteristic lesions are hemorrhagic papules with a pink or violaceous rim (Fig. 14-9) that progress to bullae, ulcers, and necrotic plaques. Eschar formation eventually occurs (Fig. 14-10), and old lesions heal with scarring. The diagnosis can be confirmed by Gram stain and bacterial culture of lesions or blood cultures, which are positive for *P. aeruginosa*. Treatment with appropriate



**Figure 14-10** Ecthyma gangrenosum. This child with congenital immunodeficiency developed thick eschars, which required a diverting colostomy and eventual skin grafting.



**Figure 14-12** Bacterial folliculitis. Erythematous follicular papules and papulopustules on the buttocks of a young boy. This is the most common location for bacterial folliculitis in children.



**Figure 14-11** Bacterial folliculitis. Erythematous, follicular papulopustules.

antipseudomonal therapy (i.e., aminoglycoside and an antipseudomonal penicillin) should be instituted early.

## FOLLICULITIS

The term *folliculitis* refers to an infection of hair follicles. The clinical appearance varies according to the location and depth of follicular involvement. Deeper follicular infections (furuncles and carbuncles) are discussed later. Superficial folliculitis (Bockhart impetigo), an infection of the follicular ostium, begins with superficial small, yellow-white pustules, often with a narrow red areola (Fig. 14-11) and a hair shaft protruding from the center of the lesion. It occurs most commonly in children and usually is seen on the buttocks (Fig. 14-12) and extremities, especially the thighs. Most lesions are painless, occur in crops, and heal over 7 to 10 days with postinflammatory hyperpigmentation. *S. aureus* is by far the most common pathogen; other possible etiologies include streptococci, Gram-negative organisms, and even dermatophytes. In immunocompromised children, commensal organisms may cause folliculitis, including *Pityrosporum* and *Demodex* (see Chapter 18). Superficial folliculitis is not always infectious in origin. "Sterile folliculitis" may be seen after skin contact with oil or other occlusive products and results in follicular plugging and inflammation. A classic example of sterile folliculitis is the scalp pustulosis occasionally associated with application of hair oils.

Superficial folliculitis usually responds to gentle cleansing with antibacterial soaps and the application of topical antibiotics such as clindamycin, erythromycin, or mupirocin. More extensive or resistant



**Figure 14-13** Folliculitis barbae. Follicular papules, pustules, and crusting with autoinoculation and caused by shaving.

cases should be treated with a systemic antibiotic (a penicillinase-resistant penicillin or cephalosporin, depending on local resistance patterns). In such instances, bacterial culture should be obtained before the initiation of systemic therapy. Sodium hypochlorite (bleach) baths or washes on a twice to three-times weekly basis may be useful for individuals or families with recurrent folliculitis or furunculosis (see below). The recommended concentration for bleach baths is  $\frac{1}{2}$  cup of bleach (around 5% to 6% sodium hypochlorite) dissolved in a full bathtub (around 40 gallons) of water, or approximately 1 mL/L (final concentration approximately 0.005%).

### Folliculitis Barbae

*Folliculitis barbae* (*sycosis barbae*) is a term used to describe a deep-seated folliculitis of the beard area involving the entire depth of the follicle and perifollicular region (Fig. 14-13). A pruritic papule is usually the initial lesion, with the process spreading from one follicle to another by trauma from scratching and/or shaving. The disorder is



**Figure 14-14** Pseudomonal (hot-tub) folliculitis. Erythematous, follicular papules and papulopustules of the thighs, correlating with areas covered by the swim garment.

characterized by follicular papules and pustules and with progression, erythema, crusting, and boggy infiltration of the skin. Although occasionally other bacteria may be isolated, the etiology is usually *S. aureus*. The use of an electric rather than traditional razor or complete avoidance of shaving can sometimes be helpful in prevention and treatment of this condition. Warm compresses and topical antibiotics are often sufficient to control minor forms of sycosis barbae. If the condition is severe or recurrent, several weeks of systemic antibiotics may be necessary.

#### Pseudofolliculitis Barbae

Pseudofolliculitis barbae (PFB) (see Chapter 7) is a common, noninfectious inflammatory disorder of the pilosebaceous follicles of the beard that may be confused with sycosis barbae. PFB (commonly referred to as *razor bumps*) is caused by shaved hairs that curve inward with resultant penetration of the skin followed by an inflammatory foreign body reaction. This form of folliculitis is seen particularly in African-Americans and individuals with curly hair. Mild cases may be managed by careful shaving and occasionally by changing from a traditional to an electric razor. Discontinuation of shaving is quite effective but not always acceptable to the patient. Close shaving, which promotes oblique penetration of hairs into the skin, should be avoided whenever possible. Other treatment options include chemical depilatory creams, topical retinoids or glycolic acid, topical steroids, benzoyl peroxide, and topical antibiotics. Epilation laser therapy (see Chapter 7) has also been demonstrated to be effective for the condition.<sup>43,44</sup>

#### Pseudomonal Folliculitis (Hot-Tub Folliculitis)

Pseudomonal folliculitis is a form of folliculitis caused by *P. aeruginosa* that occurs after exposure to poorly chlorinated hot tubs, whirlpools, or swimming pools. It has also been reported in association with a contaminated water slide,<sup>45</sup> a contaminated loofah sponge,<sup>46</sup> swimming in a children's pool filled with well water,<sup>47</sup> and after shower/bath exposure.<sup>48,49</sup> It is characterized by erythematous, follicular pustules and vesiculopustules that occur most often on the trunk, buttocks, and legs (Fig. 14-14), especially in sites occluded by swimming garments. Lesions usually develop within 1 to 2 days after exposure. Mild constitutional symptoms may be present, including fever, malaise, headache, and arthralgias. More serious associations, including urinary tract infection and pneumonia, have also been reported.<sup>50,51</sup> Lesions of hot-tub folliculitis generally subside spontaneously over 7 to 10 days. Antipseudomonal antibiotic therapy (i.e., with ciprofloxacin) may be necessary in severe cases. Preventive measures include maintenance of appropriate chlorination, frequent water changes, and thorough scrubbing of whirlpool baths and hot tubs with each water change. Importantly, 21% of 108 water and swab samples of hot tubs and indoor swimming pools were positive for *P. aeruginosa* in one study, and 96% of these isolates were multidrug resistant.<sup>52</sup> The Centers for Disease Control and Prevention recommend maintaining



**Figure 14-15** *Pseudomonas* hot foot syndrome. Tender papules and papulopustules on the plantar foot. Culture of a swab from one of the pustules grew out *P. aeruginosa*. (Courtesy of John J. Van Aalst, MD.)

the concentration of free chlorine in swimming pools to between 1 and 3 ppm and the pH at 7.2 to 7.8.<sup>53</sup>

*Hot hand-foot syndrome* (also known as *Pseudomonas* hot foot syndrome) presents with painful, erythematous palmoplantar nodules (Fig. 14-15) after exposure to water containing a high concentration of *P. aeruginosa* and may be seen in conjunction with hot-tub folliculitis.<sup>54</sup> When pustules are present, the organism can be easily cultured from skin swab material. An epidemic occurred in children exposed to the same community wading pool with a floor that was coated with abrasive grit and which, along with the inlets and a drain, yielded *P. aeruginosa* on culture.<sup>55</sup> This disorder may be related to (or the same condition as) idiopathic palmoplantar hidradenitis of childhood (see Chapter 20). Similar palmoplantar inflammatory lesions have been reported in otherwise healthy children infected with *Mycobacterium abscessus*, also in association with exposure to public swimming pools (see Nontuberculous ["Atypical"] Mycobacterial Infection section).

#### Eosinophilic Pustular Folliculitis/Eosinophilic Folliculitis of Infancy

Eosinophilic pustular folliculitis (EPF; Ofuji disease) is a dermatosis of unknown cause characterized by erythematous patches with follicular papules and pustules, often in an annular or serpiginous arrangement, with occasional peripheral eosinophilia and leukocytosis. It was classically reported in Japanese individuals, although it may be seen in people of diverse ethnic backgrounds, and men appear to be affected more than women.<sup>56</sup> Although this disorder is not bacterial in origin, it is included here because it is in the differential diagnosis of folliculitis. EPF may involve any surface area, including the face, trunk, and extremities. A form of EPF is recognized as an extremely pruritic dermatosis in adult patients with human immunodeficiency virus (HIV) infection, usually presenting late in the course of infection.<sup>57</sup>

A distinct form of EPF occurs in otherwise healthy infants and toddlers and has been called *eosinophilic folliculitis of infancy*. It presents with recurrent crops of itchy follicular pustules of the scalp (most commonly; Fig. 14-16), trunk, and extremities with eventual spontaneous involution (see Chapter 2). The outbreaks occur in a cyclical fashion and may last from 3 months to 5 years, occasionally longer. Peripheral eosinophilia may be present.<sup>58</sup> Whereas adults tend to have annular, serpiginous, or polycyclic lesions, the prominent scalp involvement and failure to form annular rings appear to distinguish the infantile form. Occasionally, eosinophilic folliculitis of infancy may be a presenting feature of the hyperimmunoglobulin-E (hyper-IgE) syndrome (see Chapter 3).<sup>59</sup>

Treatment options for EPF include topical corticosteroids, oral erythromycin, dapsone, indomethacin, colchicine, topical tacrolimus,



**Figure 14-16** Eosinophilic folliculitis of infancy. This 8-week-old female had recurrent, pruritic, follicular papules and papulopustules on the scalp in conjunction with a peripheral eosinophilia. She was ultimately diagnosed with hyper-IgE syndrome.



**Figure 14-17** Furuncle. This tender, fluctuant papulonodule was located on the thigh in the same patient with folliculitis shown in Figure 14-12.

antihistamines, and ultraviolet B (UVB) phototherapy, which have each been used with variable success. The majority of patients respond to treatment with the former two agents; in one study of 51 patients treated with low- to medium-potency topical steroids, 46 (90%) responded well.<sup>60</sup> The other treatments have been demonstrated successful but carry a greater risk of adverse effects.

## FURUNCLES AND CARBUNCLES

Furuncles (or “boils”) are painful, deep infections of the hair follicle in which purulent material extends into the dermis and subcutaneous tissues, forming perifollicular abscesses (see above). These lesions have a tendency toward central necrosis and suppuration. They are caused by *S. aureus* and are seen most often in older children and adults. They usually develop from a preceding folliculitis with deeper extension into the dermis and subcutaneous tissue. Chronic carriers of *S. aureus* are particularly predisposed,<sup>61</sup> and familial spread of PVL-producing MSSA isolates has been observed and may be associated with greater numbers and more intensely erythematous lesions.<sup>62</sup> Furuncles caused by CA-MRSA infection are increasing in incidence in the United States and are strongly related to production of the PVL virulence factor.<sup>63</sup> Furuncles are most common in areas of skin that are hairy and subject to friction and maceration, particularly the back, axillae, thighs, buttocks, and perineum. They present as tender red nodules (Fig. 14-17) that gradually become fluctuant and if untreated,



**Figure 14-18** Carbuncle. Large, tender, erythematous nodule on the lateral trunk of this 14-year-old obese male. Note the adjacent, smaller furuncle.

### Box 14-2 Predisposing Factors for Furuncles and Carbuncles

- Diabetes mellitus
- Obesity
- Alcoholism
- Scabies
- Hematologic disorders
- Immunodeficiencies, including hyper-IgE syndrome
- Malnutrition
- Chemotherapy
- Corticosteroid therapy
- Local skin trauma (abrasions, cuts, excoriations)
- Debilitated state

may have a purulent blood-tinged discharge. There is a high rate of contagion in patients with furunculosis.

Carbuncles are larger, deep-seated staphylococcal abscesses composed of aggregates of interconnected furuncles that drain at multiple points on the cutaneous surface (Fig. 14-18). They are usually seen in males on the posterior neck, back, thighs, and buttocks and extend into the deeper dermis and subcutaneous tissues, reaching a larger size than furuncles (up to 10 cm in diameter). They undergo necrosis and suppuration more slowly than furuncles and may present with severe pain and constitutional symptoms. Several factors predispose to the development of furuncles and carbuncles (Box 14-2).

The treatment of furuncles and carbuncles depends on the extent and location of lesions. The mainstay of therapy is systemic anti-staphylococcal antibiotics with incision and drainage of fluctuant lesions. Cultures with sensitivity testing should be considered, especially in geographic areas with an increasing prevalence of staphylococcal resistance. Lesions caused by MRSA may respond (as discussed) to incision and drainage alone. Topical antibiotics (as discussed for impetigo and folliculitis) are not sufficient for the treatment of furuncles and carbuncles, given the depth of the process. The triple regimen of chlorhexidine skin disinfection (21 days), mupirocin applied to the nares (5 days), and oral clindamycin (21 days) was found to be very effective with a prolonged remission in nearly 90% of patients in an open-label study that included patients with both MSSA and MRSA furunculosis.<sup>64</sup> Many practitioners recommend sodium hypochlorite baths or washes for patients with recurrent disease (see *Folliculitis* section). Lastly, attention to predisposing factors with appropriate treatment or modification (as feasible) is indicated.

## CELLULITIS

Cellulitis is an acute infection of the skin, particularly the subcutaneous tissues, characterized by erythema, swelling, and tenderness. The



**Figure 14-19** Cellulitis. Erythematous patches and plaques with edema involving the arm of this 18-month-old male. Note the multifocal nature and partial clearing as a result of parenteral antibiotic therapy.

borders of cellulitis are not elevated or sharply defined, which helps to contrast it from the more superficial form called *erysipelas* (see *Erysipelas* section).

Cellulitis usually occurs after some form of skin trauma including puncture wounds, lacerations, dermatitis, burns, varicella, or dermatophyte infections. It presents with markedly red, tender, warm swelling of the skin with an infiltrated appearance (Fig. 14-19), and the most common location is the lower extremities. Constitutional symptoms including malaise and fever are often present. The most common causes of cellulitis are *S. aureus* and GABHS, although occasionally other bacterial agents may be implicated. MRSA appears to be a rare cause of nonsuppurative cellulitis when extrapolated from staphylococcal patient-colonization data, although colonization may not be a primary risk factor in the pathogenesis of this infection.<sup>65</sup> In young children, particularly those under 2 years of age, *Haemophilus influenzae* type b (Hib) was traditionally implicated in a facial cellulitis termed *buccal cellulitis*, although this form is now less common since licensure of the conjugated Hib vaccine.<sup>66</sup> Buccal cellulitis characteristically reveals a dusky red to blue discoloration of the involved skin. Children with *H. influenzae* cellulitis may be quite toxic, with accompanying upper respiratory tract symptoms and bacteremia or septicemia. *Streptococcus pneumoniae* is another potential etiology of facial cellulitis in children, occurring especially in those under 36 months of age who are at risk for pneumococcal bacteremia. Because 96% of the serotypes (in one large series of *S. pneumoniae* facial cellulitis) are included in the heptavalent-conjugated pneumococcal vaccine now licensed in the United States, this cause of cellulitis will likely become significantly less relevant in years to come.<sup>67</sup> Lastly, in children younger than 3 months of age, cellulitis is most commonly caused by group B streptococci (GBS) and is more likely to be associated with invasive disease, including bacteremia and meningitis.<sup>68</sup> These children require blood, urine and cerebrospinal fluid (CSF) sampling and cultures as part of their initial evaluation.

Periorbital cellulitis is a unique form of cellulitis that deserves special mention here, given the potential confusion with orbital cellulitis and the associated complications. Periorbital (preseptal) cellulitis is a form of the disease that presents with erythema and swelling of the periorbital tissues. It may appear after skin trauma, in which case it is usually caused by *S. aureus* or GABHS infection or may result from cutaneous spread of pathogens from the paranasal sinuses or bloodstream, where it may result from Hib or *S. pneumoniae* infection. If the infection traverses the orbital septum (a continuation of the periosteum of the bony orbit to the margins of the upper and lower eyelids), it may result in orbital cellulitis, a more serious condition that may be complicated by abscess formation or cavernous sinus thrombosis.<sup>69</sup> Patients with orbital cellulitis may experience proptosis, ophthalmoplegia, and decreased visual acuity in addition to the cutaneous findings. Computed tomography (CT) and ophthalmologic examina-

tions are indicated if orbital cellulitis is suspected. The microbiology of periorbital and orbital cellulitis has also changed with the advent of Hib immunization, and Hib is now a very uncommon cause of these disorders, being supplanted by streptococcal species (including *S. pneumoniae* and GABHS) and *S. aureus*.<sup>70-72</sup>

Treatment of cellulitis depends on the clinical presentation and knowledge (and identification, when possible) of the affecting organisms. The diagnosis of cellulitis is generally a clinical one, although fine-needle aspiration with Gram stain and bacterial culture may be helpful when unusual organisms are suspected (i.e., the immunocompromised host).<sup>61</sup> Antibiotic therapy that covers for GABHS and *S. aureus* will be appropriate in most cases of routine, nonfacial cellulitis. In geographic areas with high rates of CA-MRSA, antibiotic selection should include coverage against this organism. There is no consensus on the choice between oral and intravenous antibiotics, although blood cultures, intravenous antibiotics, and hospitalization have traditionally been recommended for children at high risk for cellulitis. In recent years, short-course intravenous antibiotic therapy has been increasingly used in emergency department (ED) settings but may be associated with a higher failure rate and longer ED stay.<sup>73</sup>

In children with facial or periorbital cellulitis, the possibility of *S. pneumoniae* and Hib infection should be considered in conjunction with the patient's age and immunization status, and antibiotics should be chosen accordingly. Imaging (most often contrast-enhanced CT or diffusion-weighted magnetic resonance imaging [MRI]) is recommended in these patients to define the extent of involvement and help guide appropriate therapy.<sup>74</sup> In infants younger than 3 months of age with cellulitis, GBS should be presumed as a potential etiologic agent, and in these infants, as well as the patient with periorbital or orbital cellulitis who is young, toxic, or shows signs of meningeal irritation, laboratory evaluation for sepsis and meningitis should be performed. Hospitalization with parenteral antibiotic therapy (and ophthalmologic consultation in those with orbital cellulitis) is indicated in these latter settings.

## ERYSIPelas

Erysipelas is a superficial cellulitis of the skin with marked lymphatic involvement, resulting in most cases from GABHS. The organism usually gains access by direct inoculation through a break in the skin, but occasionally hematogenous infection may occur. The initial lesion begins as a small area of erythema that gradually enlarges to reveal a characteristic warm, painful, shiny, bright red infiltrated plaque with a distinct and well-margined border. The face, scalp, and hands are the most common sites of involvement, although erysipelas may involve any skin surface. Penicillin, or a macrolide antibiotic in patients with penicillin allergy, is the drug of choice for therapy. In occasional patients, *S. aureus* may be a copathogen, in which case antimicrobial therapy directed against this organism is necessary.

## PERIANAL STREPTOCOCCAL DERMATITIS

Perianal streptococcal dermatitis (PSD, also known as *perianal dermatitis*, *perianal cellulitis*, *perianal streptococcal cellulitis*, and *streptococcal perianal disease*) is a well-defined entity that may be often overlooked. It presents as sharply circumscribed perianal erythema with occasional fissures, purulent discharge, and/or functional disturbances.<sup>75</sup> GABHS is the etiology in most cases of PSD, although *S. aureus* and coliform bacteria have also been recovered.<sup>76,77</sup> An epidemic outbreak in a daycare center has been reported.<sup>78</sup> In a recent series of 26 patients with perianal dermatitis, *S. aureus* was the most common isolate and clinically was notable for concurrent papules and pustules of the buttocks and extension of the erythema to the adjacent buttock skin.<sup>79</sup>

The skin findings in PSD are variable, from a dry pink appearance to bright red erythema (Fig. 14-20) with a wet surface and occasionally the presence of a white pseudomembrane.<sup>80</sup> The surface is often tender to touch, and associated symptoms include rectal itching or discomfort, painful defecation, blood-streaked stools, and constipation. In males, balanoposthitis or in females, vulvovaginitis may be present.<sup>81</sup> Fever is notoriously rare in patients with PSD. Streptococcal

**A****B**

**Figure 14-20** Perianal streptococcal dermatitis. Bright red erythema with a moist, tender surface (**A**) and pink maceration with mild exudate or pseudomembrane (**B**). Both patients were tender to palpation and had painful defecation.

pharyngitis may concomitantly be present in patients with PSD, but the exact associations between pharyngitis, PSD, and streptococcal colonization is unclear.<sup>80</sup> There is some suggestion that specific GABHS isolates may have a tropism for perineal tissues, but the mechanism of infection is not yet clear.<sup>81</sup> Guttae psoriasis (see Chapter 4), which is classically associated with streptococcal pharyngitis, may also be associated with PSD, and in any patient with new-onset guttate psoriasis, a thorough anogenital examination should be performed.

The differential diagnosis of PSD is broad and includes psoriasis, candidiasis, seborrheic dermatitis, cutaneous Crohn disease, pinworm infestation, and sexual abuse. The diagnosis can be confirmed by bacterial culture of a perianal swab, but when performing cultures to confirm the diagnosis of PSD, it is important to notify the laboratory of the microbe (GABHS) in question, because several labs utilize media selective for enteric pathogens with rectal swabs. Treatment with oral penicillin V, amoxicillin, a first-generation cephalosporin, or a macrolide or azalide (i.e., erythromycin, clarithromycin, or azithromycin) for patients allergic to penicillin is usually effective, with or without concomitant topical mupirocin. Some have suggested, however, that the risk of clinical recurrence is greater in patients treated initially with penicillin or amoxicillin.<sup>82</sup> Oral cefuroxime was demonstrated more effective than penicillin in one study and is another reasonable option.<sup>83</sup> If staphylococcal infection seems more probable clinically or is isolated in culture, the antibiotic regimen should be adjusted accordingly.



**Figure 14-21** Blistering dactylitis. Edema and a tense bulla on the thumb of this 7-year-old girl. Culture of the blister fluid yielded *Staphylococcus aureus* rather than the more commonly seen group A  $\beta$ -hemolytic streptococci.

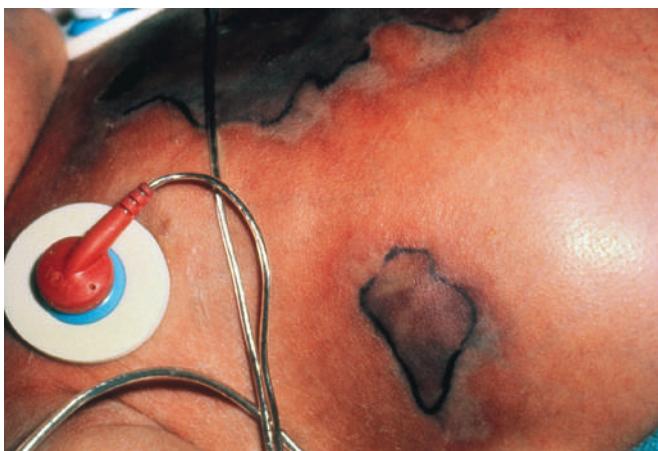
### BLISTERING DACTYLITIS

Blistering dactylitis (also known as *blistering distal dactylitis*) is a unique bullous manifestation of GABHS infection or only occasionally, other bacteria including *S. aureus* and GBS.<sup>84–86</sup> It is rarely reported in association with MRSA infection.<sup>87</sup> In its classic form, blistering dactylitis presents as a painful, tense, superficial blister on an erythematous base (Fig. 14-21) most often located over the volar fat pad of the distal phalanx of a finger or several fingers. It is most common in children between the ages of 2 and 16 years, although it is also reported in adults, most notably immunocompromised ones. The blisters may occasionally extend to involve the dorsal surfaces of the fingers. Systemic manifestations including fever are rare. The differential diagnosis of blistering dactylitis includes bullous impetigo, herpetic whitlow, traumatic blistering, burns, and epidermolysis bullosa. Coexistent whitlow and blistering dactylitis have been reported.<sup>88</sup> The diagnosis is confirmed by Gram stain and culture of blister fluid. If herpes infection is suspected, Tzanck smear, direct fluorescent antibody testing, or viral culture should be performed. Streptococcal blistering dactylitis is successfully treated with penicillin or erythromycin, but given recognition of the increasing role that staphylococci may play in the etiology, empiric antimicrobial therapy to cover for both organisms is recommended.

### NECROTIZING FASCIITIS

Necrotizing fasciitis is a rapidly progressive, potentially fatal, necrotizing infection of the skin and subcutaneous tissues commonly associated with severe systemic toxicity. Over the years it has been known by several different names, including *hospital gangrene*, *acute infective gangrene*, *streptococcal gangrene*, *gangrenous erysipelas*, *synergistic necrotizing cellulitis*, and *Meleney ulcer*. A popular term in the lay media is *flesh-eating bacteria disease*. Although usually caused by GABHS, necrotizing fasciitis may be polymicrobial in nature and has been reported in association with other streptococci, *P. aeruginosa*, *S. aureus*, *Klebsiella* species, *E. coli*, *Enterobacter cloacae*, *Serratia* species, *Proteus* species, *Enterococcus*, a variety of anaerobic agents including *Clostridium* species and *Bacteroides* species, and even *Vibrio* species.<sup>89–93</sup> CA-MRSA has been described as a potential monomicrobial cause of necrotizing fasciitis.<sup>94</sup> The disorder is most common in individuals with decreased local resistance (skin trauma, surgery, varicella), malnutrition, or chronic disease. Necrotizing fasciitis is rare in children. In neonates, it has been observed in association with omphalitis, balanitis, mammatitis, fetal scalp monitoring, and postoperative complications, with omphalitis being the most common.<sup>95,96</sup>

Necrotizing fasciitis most commonly presents on an extremity and is characterized by pain, edema, and erythema with exquisite



**Figure 14-22** Necrotizing fasciitis. Erythema and necrosis of the abdominal wall are seen in this severely ill toddler.

tenderness to palpation. These changes quickly progress through several sequential stages including ecchymosis, bullae, necrosis (Fig. 14-22), gangrene, and with deep and extensive infection, overlying skin anesthesia.<sup>90</sup> The inflammation extends deeply along fascial planes, highlighting the importance of rapid diagnosis and surgical exploration. Laboratory findings include leukocytosis, elevated serum creatine kinase level, hyponatremia, coagulopathy, and bacteremia. Fever, shock, and altered mental status typically develop within 48 hours. The most serious complication of necrotizing fasciitis is streptococcal toxic shock syndrome (TSS) (see below), which is characterized by hypotension, renal impairment, coagulopathy, liver abnormalities, respiratory distress, and a diffuse erythematous cutaneous eruption. Clinical clues that suggest necrotizing fasciitis over cellulitis include intense pain (often out of proportion to the clinical examination), rapid progression, bullae, necrosis, and lack of a rapid response to antibiotic therapy. Imaging studies may be useful in confirming the diagnosis, especially if soft-tissue gas is present, although this is not a consistent finding. MRI may be useful in distinguishing necrotizing fasciitis from uncomplicated infective fasciitis.<sup>97</sup> Confirmation of infection can be accomplished with Gram stain and culture of blister fluid, lesion discharge or tissue, blood culture, and polymerase chain reaction (PCR) analysis for pyrogenic exotoxin B on tissue biopsy specimens.<sup>91</sup>

Prompt thorough surgical debridement of necrotic tissue is of prime importance in the management of patients with this disorder, because without exploration and debridement, the mortality rate approaches 100%.<sup>98</sup> Additionally, greater delays in time to initial surgical debridement are associated with increased mortality in children, as in adults with similar infections.<sup>99</sup> Antimicrobial therapy should be initiated immediately, and the chosen agents should have activity against Gram-positive, Gram-negative, *Clostridium*, and anaerobic organisms.<sup>90,93</sup> Clindamycin in particular seems to be quite effective as part of the antimicrobial regimen, given its ability to suppress both toxin and M protein synthesis.<sup>92</sup> Antimicrobial therapy should be adjusted based on the results of Gram stain and bacterial cultures of the surgical specimen. In addition to these specific therapies, fluid resuscitation and blood pressure/blood product support are often indicated. The roles of hyperbaric oxygen therapy and intravenous immunoglobulin (IVIG) remain controversial, the latter being used primarily in the setting of GABHS infection with TSS.

## NOMA

Noma (cancrum oris, necrotizing ulcerative stomatitis) is a rare, progressive destructive infection usually involving the soft and hard tissues of the oral and paraoral structures. Most reported cases of noma are in children who are severely malnourished or chronically debilitated, and the disease tends to be most common in sub-Saharan Africa, South America, and Asia. The peak ages of incidence are

between 1 and 4 years.<sup>100</sup> The triad of malnutrition, poor oral hygiene, and periodontal disease contributes to the increased incidence in these locations.<sup>101</sup> It is usually caused by anaerobic organisms, including *Fusobacterium* species, *Prevotella intermedia*, *Actinomyces* species, *Pestotreptococcus micros*, and *Borrelia* species and is characterized by a gangrenous, ulcerative infection of the gingivae, buccal mucosa, and eventually the cheeks and jaw.

The initial stage of noma is characterized by a painful, small purple-red lesion that becomes indurated and progresses to edema, necrosis, and ulceration. With expansion, underlying bone involvement occurs with resultant loss of dentition. Bony sequestrations of the mandible or maxilla may occur. Patients may also have fever, tachycardia, tachypnea, and anorexia, and their medical history may reveal recurrent fevers, diarrhea, and history of parasitic and/or viral infections.<sup>102</sup> Treatment of noma includes antibiotics, wound care, and debridement with eventual surgical reconstruction. Without treatment, the mortality rate is 70% to 90%, and survivors suffer the long-term sequelae of orofacial mutilation and functional impairment.<sup>103</sup> Rehydration, attention to electrolyte balance, and nutritional rehabilitation to correct protein and micronutrient deficiencies are other important aspects of therapy.<sup>102</sup>

Noma neonatorum is a gangrenous process of the nose, eyelids, oral cavity, and anogenital region in low-birthweight infants and usually caused by *P. aeruginosa*. Most patients also have *Pseudomonas* sepsis, and the mortality rate without antimicrobial therapy is extremely high. Noma neonatorum, which is also more common in developing countries, was so named because of the clinical and histologic similarity to noma. However, there is significant overlap with the clinical presentation of ecthyma gangrenosum. Although some of the reported infants had immunodeficiency, it was either absent or not tested for in the majority of published cases. Noma neonatorum may represent a neonatal form of ecthyma gangrenosum.<sup>104</sup>

## MENINGOCOCCEMIA

Meningococcal infection, caused by the Gram-negative diplococcus *Neisseria meningitidis*, is a major world health problem in children under 5 years of age and is the leading cause of bacterial meningitis in children. Three serogroups of *N. meningitidis*, A, B, and C, account for more than 90% of cases of meningococcal disease, and along with groups Y and W-135 are implicated most commonly worldwide as causes of invasive disease.<sup>105,106</sup> Person-to-person spread of *N. meningitidis* usually occurs through inhalation of droplets of infected nasopharyngeal secretions by direct or indirect oral contact.<sup>107</sup> Meningococcal disease typically presents between 1 and 14 days after nasopharyngeal acquisition of *N. meningitidis*.<sup>108</sup>

Acute meningococcemia may present in a variety of ways, from transient fever to fulminant disease. After an upper respiratory prodrome, patients develop high fever and severe headache. If meningitis develops, stiff neck, nausea, vomiting, and coma may be present. Up to two-thirds of patients develop a skin eruption, most classically a petechial rash of the skin and mucous membranes. Other cutaneous morphologies include macular, morbilliform, and urticarial eruptions, as well as a gray-colored acrocyanosis. The petechiae are usually small, stellate, and gray-purple with a raised border and slightly depressed, vesicular, or pustular center.<sup>109</sup> The trunk and lower extremities (especially ankles and wrists) are common sites of predilection, whereas the palms, soles, and head tend to be spared. Mucosal surfaces including the palpebral and bulbar conjunctivae may be involved.<sup>105</sup> More extensive hemorrhagic lesions are seen in fulminant meningococcal infections, and a progressive increase on all areas of the body may be followed by coalescence of lesions to form large purpuric patches with sharply marginated borders (Fig. 14-23). These may progress to bullae, necrosis with sloughing, and eventual eschar formation. Autoamputation related to digital ischemic necrosis is a potential complication. Consumptive coagulopathy may be present and when occurring in the setting of progressive cutaneous hemorrhage and necrosis, is termed *purpura fulminans*.<sup>110</sup> This finding is felt to portend a poor prognosis for the patient with meningococcemia. Three important clinical features that are suggestive of early acute meningococcal disease are leg pain, cold hands and feet, and abnormal skin color.<sup>111</sup>



**Figure 14-23** Meningococcemia. Erythematous macules and papules with petechiae, purpura, and early skin necrosis.

Chronic meningococcemia is a rare form of meningococcal infection that is unusual in children. It is characterized by intermittent episodes of skin lesions in conjunction with fever, joint pain, myalgia, and episcleritis. The cutaneous lesions seen in the majority of patients appear in crops coincident with or after the fever. Individual lesions are usually macular and occasionally purpuric or pustular. Because of potential confusion with other infectious or collagen vascular illnesses, a high index of suspicion is necessary.<sup>112</sup> Patients with complement deficiencies, especially of the terminal complement system (C5-9), have an increased risk of both acute and chronic meningococcal infections.<sup>113</sup>

The differential diagnosis of meningococcemia includes gonococcemia, Henoch–Schönlein purpura, rickettsial diseases, enteroviral infections, erythema multiforme, atypical measles, hypersensitivity vasculitis, and other bacterial septicemias or meningitides. The diagnosis is confirmed by culture of the blood and CSF. Isolation of meningococci from the nasopharynx is presumptive but not diagnostic, because asymptomatic carriage is not uncommon.<sup>105</sup> Petechial lesions can be smeared and examined for the presence of Gram-negative diplococci and may be cultured for organisms. Serologic assays that can detect *N. meningitidis* capsular polysaccharide antigen in CSF, urine, serum, and other bodily fluids are also available. A serogroup-specific PCR test to detect *N. meningitidis* is used routinely in the United Kingdom and may be useful in patients who receive antimicrobial therapy before cultures have been obtained.<sup>106</sup> The diagnosis of chronic meningococcemia is best confirmed by blood culture taken during a febrile episode, although several cultures may be necessary.<sup>114</sup>

Meningococcal disease is treated with penicillin G, but at the time of presentation the initial choice of antimicrobials should be based on the clinical differential diagnosis and local antibiotic susceptibility patterns. Antibiotics with more expanded coverage such as cefotaxime or ceftriaxone are often used initially in patients with sepsis or meningitis until the diagnosis is confirmed.<sup>105</sup> In patients with a history of anaphylaxis to penicillin, chloramphenicol is recommended.<sup>106</sup> Supportive therapy with fluid, pressor, and blood product support as indicated is vital. Chemoprophylaxis of close contacts of patients with invasive meningococcal disease is recommended within 24 hours of diagnosis of the index case. Selective immunization is recommended for children 2 years of age and older in high-risk groups (asplenia, terminal complement deficiencies, or travel to endemic or epidemic areas). Routine immunization with the licensed quadrivalent vaccine is recommended for adolescents at the 11- to 12-year visit and at high school entry or 15 years of age (whichever comes first), as well as students entering college who plan to live in dormitories and military recruits. However, routine childhood immunization is not recommended because of the low incidence of disease, the poor response in young children, the short-lived immunity, and the potential impaired response to subsequent vaccine doses in some serogroups.<sup>106,115</sup>



**Figure 14-24** Gonococcemia. Hemorrhagic, erythematous papules and nodules involve the distal digits in this 17-year-old female with disseminated gonococcal infection and underlying systemic lupus erythematosus.

## GONOCOCCEMIA

Gonococcemia is associated with cutaneous lesions similar to those of meningococcemia and presents with fever, chills, arthralgia, and myalgia in patients with gonococcal septicemia. Symptoms of sexually transmitted gonococcal infection may or may not be present, including vaginitis, pelvic inflammatory disease, urethritis, proctitis, or pharyngitis. Hematogenous spread of *Neisseria gonorrhoeae* occurs in up to 3% of untreated persons with mucosal gonorrhea.<sup>116</sup> Skin lesions develop within 3 to 21 days of contact, are located primarily over joints of the distal extremities, and usually appear as petechiae, small erythematous or hemorrhagic papules, or vesiculopustules (Fig. 14-24). They usually heal spontaneously in 4 to 6 days.

The causative agent, *N. gonorrhoeae*, is a Gram-negative diplococcus and may be demonstrated by smear, culture, or immunofluorescence studies of skin lesions or by culture of the blood, anogenital tract, pharynx, or joint fluid on Thayer–Martin medium (chocolate agar with the addition of antibiotics to inhibit normal flora and nonpathogenic neisserial organisms). Nucleic acid amplification studies (i.e., PCR) are also available and have a high sensitivity and specificity when performed on urethral or cervicovaginal swabs.<sup>116</sup>

The treatment of choice for gonococcemia is parenteral ceftriaxone or cefotaxime. Alternatives for individuals with β-lactam allergy include ciprofloxacin, ofloxacin, or spectinomycin. If concomitant infection with *Chlamydia trachomatis* is suspected, initial therapy should also include erythromycin, doxycycline, or azithromycin.

## STAPHYLOCOCCAL SCALDED SKIN SYNDROME

SSSS is a term used to describe a blistering skin disease caused by the epidermolytic (or exfoliative) toxin (ET)-producing *S. aureus*. It was previously known as *Ritter disease* or *pemphigus neonatorum* and tends to occur most often in neonates and young children. Its severity may range from mild, localized blistering to widespread exfoliation. Mild cases are probably more common yet less often reported.<sup>117</sup>

The pathogenesis of SSSS relates to the production of ETs, of which there are two serotypes affecting humans, ETA and ETB. These toxins have high sequence homology and are both capable of cleaving the epidermis at the superficial level of the stratum granulosum. The pathogenic mechanisms of ETA and ETB have been clearly elucidated, and they have been shown to target desmoglein 1, a cell–cell adhesion molecule found in desmosomes of the superficial epidermis.<sup>118–120</sup> Desmoglein 1 is the same molecule targeted in the autoimmune blistering disease, pemphigus foliaceus (PF) (see Chapter 13).<sup>118</sup> Once it was determined that antibodies against desmoglein 1 cause PF, astute researchers hypothesized and eventually proved that the target of the staphylococcal exfoliative toxin was also desmoglein 1.<sup>121</sup> There are two main theories for the observation that SSSS preferentially affects



**Figure 14-25** Staphylococcal scalded skin syndrome. Periorbital and perioral erythema and erythema of the neck folds and upper trunk in this 4-year-old boy with early infection.

neonates and children: lack of protection from antitoxin antibodies and decreased renal excretion of the toxin.<sup>122</sup> In adults, SSSS is quite rare and usually occurs in the setting of immunosuppression, malignancy, heart disease, or diabetes.<sup>123</sup>

Outbreaks of SSSS have been reported in neonatal intensive care units and well-baby nurseries. In these settings, asymptomatic or clinically infected healthcare workers often act as carriers of the epidemic strain of *S. aureus*, and given the potential severity of infection in the premature infant, prompt recognition with institution of strict infection-control strategies is vital to prevent further nosocomial spread.<sup>124,125</sup> In a series of 39 neonates with SSSS, pneumonia was the most common complication, followed by myocarditis.<sup>126</sup>

SSSS generally begins with localized infection of the conjunctivae, nares, perioral region, perineum, or umbilicus. Separation of perioral crusts often leaves behind radial fissures around the mouth, resulting in the characteristic facial appearance of SSSS (Figs. 14-25 and 14-26). Other infections that may serve as the initial nidus for SSSS include pneumonia, septic arthritis, endocarditis, or pyomyositis. Fever, malaise, lethargy, irritability, and poor feeding subsequently develop, and the generalized eruption begins. The rash is characterized by erythema that progresses to large, superficial fragile blisters that rupture easily, leaving behind denuded, desquamating, erythematous, and tender skin (see Fig. 14-26; Fig. 14-27). The eruption is most marked in flexural creases but may involve the entire surface area of skin. The Nikolsky sign (progression of the blister cleavage plane induced by gentle pressure on the edge of the bulla) is positive. With extensive denudation of skin, patients may have decreased thermoregulatory ability, extensive fluid losses, and electrolyte imbalance and are at serious risk for secondary infection and sepsis. With appropriate management the skin heals without scarring, given the superficial cleavage plane of the blisters.

SSSS is usually diagnosed based on the clinical presentation. The main differential diagnosis is toxic epidermal necrolysis (TEN), a severe exfoliative condition that is usually drug-induced and has a high mortality rate. The most helpful distinguishing feature of TEN is mucosal involvement, including of the mouth, conjunctivae, trachea, and genital mucosa, which is lacking in SSSS.<sup>122</sup> Other less common differential diagnoses include scalding burns, epidermolysis bullosa, graft-versus-host disease, nutritional deficiency dermatosis, and bullous ichthyosis (in the neonate). The diagnosis of SSSS is confirmed by isolation of *S. aureus*. It must be remembered that the majority of blisters in SSSS are sterile, because they are caused by the hematogenous dissemination of the bacterial toxin and not the bacteria itself. The organism is most easily recovered from pyogenic (not exfoliative) foci on the skin, conjunctivae, nares, or nasopharynx. When the diagnosis remains in question, differentiation from TEN can be made by microscopic examination of a skin snip of the blister roof or a skin



**Figure 14-26** Staphylococcal scalded skin syndrome. Facial and neck-fold erythema with desquamation, crusting, and perioral radial fissures (A) and a distant ruptured bulla on the toe (B) of an infant girl with the disorder.



**Figure 14-27** Staphylococcal scalded skin syndrome. Diffuse peeling and erythema in a 4-week-old African-American infant girl who also had *Staphylococcus aureus* isolated from her blood.

biopsy. In SSSS, cleavage occurs in the superficial epidermis at the level of the granular layer, whereas in TEN the split occurs below the dermal-epidermal junction.

Treatment of SSSS is directed at the eradication of toxin-producing staphylococci, thus terminating toxin production. A penicillinase-resistant penicillin, first- or second-generation cephalosporin, or

clindamycin are all appropriate initial choices, with modification based on sensitivity testing. In patients with MRSA infection, parenteral vancomycin or other agents (as dictated by local resistance patterns) would be indicated. Because SSSS is usually a more mild disease in older children, ambulatory therapy may be an option in this population. In neonates or in infants or children with severe infection, hospitalization is mandatory, with attention to fluid and electrolyte management, infection control measures, pain management, and meticulous wound care with contact isolation. In particularly severe disease, care in an intensive care or burn unit is required. Neutralizing antibodies that inhibit the binding of ETs to desmoglein 1 are under investigation, given concerns about the development of antibiotic-resistant, exfoliative-toxin-producing staphylococci.<sup>127</sup>

### TOXIC SHOCK SYNDROME

TSS is an acute febrile illness characterized by fever, rash, hypotension, and multisystem organ involvement. Although classically described in menstruating women in relation to the use of superabsorbent tampons, TSS is now recognized in both menstrual and nonmenstrual forms, the latter now being more common.<sup>128</sup> Nonmenstrual TSS may occur in association with surgical procedures, nasal packing, the postpartum state, and a variety of *S. aureus* infections.

TSS is caused by toxin-producing strains of *S. aureus*. Manifestations of the disease are mediated primarily by the TSS toxin (TSST-1) and staphylococcal enterotoxins (SEA, SEB, SEC). These toxins are capable of widespread polyclonal activation of T cells, which results in massive cytokine release and in the clinical picture of TSS. Both TSST-1 and the SEs are considered "superantigens," given their ability to activate T cells without intracellular processing and via specific binding to major histocompatibility complex (MHC) class II molecules.<sup>129,130</sup> MRSA appears to account for a small percentage of TSS cases.<sup>131</sup>

A prodrome of mild constitutional symptoms including malaise, myalgias, and chills often precedes the symptoms of TSS. Eventually fever develops along with lethargy, diarrhea, chills, nausea, and altered mental status. Symptoms of hypovolemia including hyperventilation, palpitations, and orthostatic dizziness may be present.<sup>132</sup> Physical findings include high fever, hypotension, a diffuse rash, and pharyngitis with hyperemia of mucous membranes. The cutaneous eruption is a diffuse, macular erythroderma that is occasionally reminiscent of the rash of scarlet fever. Accentuation of the eruption in skin folds is a common finding, and in rare cases the inguinal or perineal regions may be the only skin surfaces involved.<sup>133</sup> Edema of the hands, feet, and face may be present, and desquamation of the affected skin surfaces (Fig. 14-28) eventually ensues. The nails may be shed, and telogen effluvium may occur up to several months later. Oral examination often reveals a strawberry tongue (Fig. 14-29), and palatal petechiae may be present. Diffuse myalgia is almost always present, and many patients complain of exquisite skin or muscle tenderness when they are touched or moved.

In addition to the fever, desquamating rash, and hypotension, evidence of multiorgan involvement is present. To meet the case definition of TSS, three or more of seven other organ systems must be involved (Box 14-3).<sup>134</sup> The diagnosis of TSS generally rests on clinical criteria, although isolation of *S. aureus* from a normally sterile site, especially if toxin production can be demonstrated, is supportive. Histopathologic findings on skin biopsy are not pathognomonic. The differential diagnosis of TSS includes streptococcal TSS (see below), Kawasaki disease, scarlet fever, drug reaction, atypical measles, Rocky Mountain spotted fever, and other exanthematous illnesses. The presence of shock and multiorgan involvement is unusual in the other entities, except for streptococcal TSS, which usually has some distinguishing features.

A neonatal TSS-like disease has been reported, and in some of these patients MRSA was recovered.<sup>135</sup> When studied, several of these MRSA isolates were positive for TSST-1 production. Most of the reported neonates had a mild course with a fairly rapid recovery.<sup>135</sup>

Since the late 1980s a disease similar to TSS yet with some distinguishing features has been recognized. This disorder is associated with toxin-producing GABHS and is referred to as *streptococcal TSS*. Although the pathogenic mechanisms are not entirely clear, streptococcal pyrogenic exotoxins (SPEA, SPEB, SPEC), mitogenic factor, and



**Figure 14-28** Desquamation in toxic shock syndrome. Mild perineal (A) and digital (B) desquamation in a 3-year-old female with toxic shock syndrome.



**Figure 14-29** Strawberry tongue in toxic shock syndrome. Hyperemia with prominent lingual papillae.

streptococcal superantigen appear to be associated with the clinical findings.

Streptococcal TSS is similarly characterized by the acute onset of shock and multisystem organ failure, but unlike staphylococcal TSS, patients usually have a focal, invasive tissue or blood infection with GABHS (Box 14-4). Most patients with streptococcal TSS have pain localized to an extremity in association with necrotizing fasciitis or myonecrosis. This pain is usually out of proportion to the clinical findings on physical examination. Varicella is a particularly important risk

### Box 14-3 Case Definition of Toxic Shock Syndrome

- Temperature  $>38.9^{\circ}\text{C}$  ( $102^{\circ}\text{F}$ )
- Diffuse macular erythroderma
- Desquamation, 1 to 2 weeks after onset, particularly of the palms and soles
- Hypotension
- Multisystem involvement (3 or more of the following):
  - Gastrointestinal (vomiting, diarrhea)
  - Muscular (severe myalgia, increased creatine phosphokinase level)
  - Mucous membrane (vaginal, oropharyngeal, or conjunctival) hyperemia
  - Renal (elevated serum urea nitrogen or serum creatinine level more than twice the upper limit of normal, or urinary sediment with  $>5$  WBC per field in absence of UTI)
  - Hepatic (total bilirubin, AST or ALT greater than twice the upper limit of normal)
  - Hematologic (platelet count  $\leq 100,000/\text{mm}^3$ )
  - Central nervous system (disorientation, altered consciousness without focal neurologic signs when fever and hypotension are absent)
- Laboratory criteria: negative results on the following tests (if obtained):
  - Blood, throat, or CSF cultures (except blood culture may be + for *S. aureus*)
  - Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

Probable disease: meets laboratory criteria and 4 of the 5 bulleted (dark green) findings are present

Confirmed disease: meets laboratory criteria and all 5 of the bulleted (dark green) findings, including desquamation (unless patient expires before desquamation occurs)

Modified from American Academy of Pediatrics. Staphylococcal Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red Book®: 2015 Report of the Committee of Infectious Diseases. American Academy of Pediatrics; 2015. p. 715–32 and Wharton M, Vogt RL, Buehler JW. Case definitions for public health surveillance. MMWR 1990;39(RR-13):1–43.

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CSF, cerebrospinal fluid; UTI, urinary tract infection; WBC, white blood cell.

### Box 14-4 Case Definition of Streptococcal Toxic Shock Syndrome

- Isolation of GABHS:
- From a normally sterile site (i.e., blood, CSF, peritoneal fluid, tissue biopsy)\*
  - OR
  - From a nonsterile site (i.e., throat, sputum, vagina)<sup>†</sup>
  - AND
  - Hypotension or shock
  - AND
  - At least 2 of the following:
    - Renal impairment (creatinine  $>2\text{ mg/dL}$  or  $>\text{twice the upper limit for age}$ )
    - Coagulopathy (DIC or thrombocytopenia)
    - Hepatic involvement (AST, ALT, or total bilirubin  $>\text{twice the upper limit for age}$ )
    - Adult respiratory distress syndrome
    - Generalized erythematous rash with or without desquamation
    - Soft-tissue necrosis (i.e., necrotizing fasciitis or myositis or gangrene)

Modified from American Academy of Pediatrics: Committee on Infectious Diseases. Severe invasive group A streptococcal infections: a subject review. Pediatrics 1998;101(1):136–40, and Wolf JE, Rabinowitz LG. Streptococcal toxic shock-like syndrome. Arch Dermatol 1995;131(1):73–7. © 1995 American Medical Association. All rights reserved.

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CSF, cerebrospinal fluid; DIC, disseminated intravascular coagulopathy; GABHS, group A β-hemolytic streptococcus.

\*Definite case: from a normally sterile site and both bulleted (dark green) findings.

<sup>†</sup>Probable case: from a nonsterile site and both bulleted (dark green) findings.

factor for invasive GABHS infections in children, and in the child with varicella who becomes febrile after having been afebrile or who has any fever beyond the fourth day of illness, GABHS infection should be considered.<sup>136</sup>

A prodromal illness with influenza-like symptoms is present in up to 20% of patients with streptococcal TSS. Subsequently shock

develops rapidly, and often the patients develop renal impairment, disseminated intravascular coagulopathy, and an adult respiratory distress syndrome-like illness. Physical examination reveals a diffuse macular erythroderma and mucous membrane findings similar to those seen in staphylococcal TSS. Examination of the site of primary infection (usually an extremity) reveals localized swelling and erythema with eventual development of vesicles and hemorrhagic bullae.<sup>137</sup> Laboratory aberrations include leukocytosis, anemia, thrombocytopenia, elevation of serum creatinine and creatine phosphokinase, hypocalcemia, abnormal liver function studies, and evidence of disseminated coagulopathy. Streptococcal TSS presenting with purpura fulminans has been reported.<sup>138</sup> In one series of pediatric streptococcal TSS, one-quarter of the patients succumbed to the disease as a result of refractory shock and multiorgan failure; in half of these, death occurred within 24 hours of hospital admission.<sup>139</sup>

Management of TSS is similar for both staphylococcal and streptococcal disease. Supportive therapy (including aggressive fluid management), vasopressors, and antibiotics are the mainstays of therapy. Identification of sites of infection is vital, with appropriate drainage or in the case of streptococcal TSS, aggressive and early surgical exploration and debridement as indicated. Many experts recommend combination antibiotic therapy that includes clindamycin, given its effects on protein (i.e., toxin) synthesis inhibition, although clindamycin should not be used alone.<sup>136</sup> IVIG may be beneficial when used in combination with antibiotics for TSS because IVIG blocks superantigen-induced T-cell activation. Use of IVIG should be considered in patients in whom there has been no clinical response within the first several hours of aggressive supportive therapy.<sup>134,140</sup>

### ERYTHRASMA

Erythrasma is a superficial bacterial infection of the skin caused by *C. minutissimum*. It is characterized by asymptomatic, well-demarcated, reddish-brown, slightly scaly patches in the groin, axillae, gluteal crease, or inframammary regions and less often the interdigital spaces of the feet. Involvement of the vulvar mucosae has been observed.<sup>141</sup> Some 15% of erythrasma cases occur in children between 5 and 14 years of age. Erythrasma is often confused with a dermatophyte infection (i.e., tinea corporis), with which it may occasionally coexist. However, it can be differentiated from tinea infection by the characteristic coral red fluorescence seen when viewed under Wood lamp illumination (because of the production of porphyrins by the corynebacteria). Erythrasma tends to be more common in patients who are overweight, the elderly, and patients with diabetes.<sup>142</sup> Culturing the organism is difficult and requires a special medium. Erythrasma may be treated with topical antibiotics including erythromycin or clindamycin, although there is some evidence of increasing antibiotic resistance to the former.<sup>143</sup> Antibacterial soaps may help prevent recurrence. Oral antibiotic therapy is very effective and classically includes erythromycin, tetracycline, or newer macrolide agents.<sup>144</sup> In one recent series of patients with erythrasma who had cultures and susceptibility testing performed, amoxicillin clavulanate was the systemic agent with the least demonstrated resistance and hence should also be considered as potential systemic therapy when indicated.<sup>143</sup> *C. minutissimum* has rarely been associated with more severe disease, including cellulitis and bacteremia.<sup>145</sup>

### TRICHOMYCOSIS AXILLARIS

Trichomycosis axillaris (trichobacteriosis) is a superficial infection of the axillary and less commonly pubic hairs that results in adherent white or yellow concretions distributed irregularly along the hair shafts. *C. tenuis* is the causative agent for this condition and hence the traditional name *trichomycosis axillaris*, which implies a fungal infection, is a misnomer. The disorder usually occurs after puberty owing to its association with axillary and pubic hair but then occurs with equal incidence in all postpubertal age groups. The most common sign of trichomycosis axillaris is the presence of red-stained perspiration on the clothing, and individuals with hyperhidrosis often complain of a particularly offensive axillary odor. The nodules of trichomycosis axillaris consist of bacterial elements embedded in an amorphous matrix, and Gram stain reveals thread-like Gram-positive bacteria.



**Figure 14-30** Pitted keratolysis. Shallow pits of the plantar great toes in this adolescent boy. Malodor was also present.

Affected areas only rarely fluoresce (as a pale yellow color) under Wood light examination. Treatment consists of shaving the hairs of the affected areas, using antiperspirants (to help decrease hyperhidrosis and growth of Gram-positive flora), and the application of topical antibiotics such as clindamycin or erythromycin. Benzoyl peroxide has also been demonstrated to be useful.

### PITTED KERATOLYSIS

Pitted keratolysis is another superficial corynebacterial infection, in this case involving the plantar feet, lateral aspects of the toes, and occasionally the palms. It is characterized by erythema with shallow round pits (Fig. 14-30), crateriform depressions, or shallow erosions most commonly involving weight-bearing portions of the feet. Malodor is common, and although the condition is usually asymptomatic, painful, plaque-like lesions have been reported in children.<sup>146</sup> Pitted keratolysis is caused by *Corynebacterium (Kytococcus) sedentarius*, which produces extracellular enzymes capable of degrading human keratins.<sup>147</sup> The disorder has worldwide distribution and occurs most commonly in hot, tropical climates and in populations (i.e., homeless individuals, elite athletes) who experience repeated skin exposure to moisture and environmental hazards.<sup>148,149</sup> The diagnosis is fairly straightforward and based on clinical findings, although Gram stain of stratum corneum shavings can be used if necessary. Culture is generally not helpful. Pitted keratolysis is treated with topical erythromycin, clindamycin, or mupirocin. Clindamycin-benzoyl peroxide combination topical gel was very effective in an open-label study of four patients.<sup>150</sup> Treatment of the hyperhidrosis component with prescription-strength aluminum chloride products or 40% formaldehyde in petrolatum ointment is also useful.

### ERYSIPEROID

Erysipeloid is an infection of traumatized skin, particularly the fingers, hands, or arms of individuals who handle meat, raw saltwater fish, shellfish, or poultry and in those who come into contact with certain animals, especially pigs, sheep, rabbits, chickens, turkeys, ducks, emus, pigeons, cows, guinea pigs, cats, dogs, fish, and shellfish.<sup>151</sup> As such, it is most commonly associated with occupations such as animal breeders, veterinarians, slaughterhouse workers, butchers, fishermen, fishmongers, cooks, and grocers.<sup>152</sup> It is caused by *Erysipelothrix rhusiopathiae* (*insidiosa*), a Gram-positive bacillus that can survive for months in soil or decomposed organic material. Human infection with this organism can take one of three forms: the mild cutaneous infection erysipeloid, which may be confused clinically with erysipelas; a diffuse cutaneous form; and a serious systemic infection, usually septicemia or endocarditis.<sup>153</sup> Erysipeloid presents 1 to 7 days after inoculation as a painful, violaceous-red, sharply demarcated patch, usually on the hand or a finger. Burning, pain, or pruritus may be reported by the patient, and constitutional symptoms may occasionally be present.

A diffuse, generalized eruption in regions remote from the site of infection, hemorrhagic vesicles, and regional lymphadenopathy may occasionally occur. Systemic complications are rare and include septicemia, endocarditis, septic arthritis, cerebral infarct, osseous necrosis, and pulmonary effusion. When endocarditis occurs, it tends to involve structurally damaged but native left-sided valves.<sup>154</sup>

The diagnosis of localized cutaneous erysipeloid can be difficult, because the organism does not grow well in culture and tissue biopsy findings are nonspecific. The yield in culture may be increased by using enriched blood culture and incubating with 5% to 10% carbon dioxide. Blood culture may be useful when systemic infection is present. PCR assays are also available to assist in the diagnosis. Although the vast majority of patients with untreated localized erysipeloid tend to recover spontaneously within 3 weeks, antibiotics such as penicillin, cephalosporins, erythromycin, and tetracyclines (among others) have been demonstrated to be effective.

## Nontuberculous (“Atypical”) Mycobacterial Infections

The nontuberculous mycobacteria (NTM), which have traditionally been referred to as *atypical mycobacteria*, include those species different from *Mycobacterium tuberculosis*. These slender, nonmotile, acid-fast organisms have a worldwide distribution and usually are nonpathogenic for humans. Infection tends to occur in immunocompromised individuals or when in the immunocompetent host, after an episode of skin trauma.<sup>155</sup> Six major clinical syndromes have been identified, including lung infection, lymphadenitis, SSTI, disseminated infection, catheter-related infection, and chronic granulomatous infection of bones, joints, and tendon sheaths.<sup>156</sup> Skin infection with NTM usually manifests as skin nodules, abscesses, papulopustules, or ulcers.<sup>157</sup> Systemic spread most often occurs in immunocompromised hosts. The diagnosis of NTM infection is usually confirmed by histology and tissue culture.

The NTM include *Mycobacterium marinum*, *Mycobacterium ulcerans*, *Mycobacterium fortuitum*, *Mycobacterium chelonae*, *M. abscessus*, *Mycobacterium kansassii*, *Mycobacterium avium-intracellulare* (*Mycobacterium avium* complex), and a variety of others that less commonly result in clinical infection. Those that will be discussed in this section are *M. marinum* (swimming pool granuloma), *M. ulcerans* (Buruli ulcer), and *M. fortuitum/M. chelonae/M. abscessus* (the “rapid growers”). Cervical lymphadenitis caused by NTM will also be briefly discussed.

*M. marinum* may result in a skin infection termed *swimming pool granuloma* or *fish-tank granuloma*. The organism resides in stagnant water and seawater as well as in natural pools and some heated pools in temperate climates. Exposure to fish-tank water is a more recently described source for inoculation and seems to be a fairly common mode of infection.<sup>158,159</sup> Abrasions from swimming pools or fish tanks and at times cuts sustained from cleaning fish may become infected with this NTM. *M. marinum* infections, sometimes unusually aggressive ones, are being increasingly reported in patients receiving anti-tumor-necrosis factor therapy, including etanercept and infliximab.<sup>160,161</sup> Most lesions begin on an extremity, hand, or foot after an incubation period of 2 to 3 weeks. In some studies the incubation period may be longer, up to 9 months after inoculation.<sup>162</sup> Infection begins with a nodule or pustule that eventually forms an ulcer or abscess. Multiple secondary lesions develop, often in a linear, lymphatic (sporotrichoid) distribution (Fig. 14-31). Without therapy, the skin lesions resolve over 1 to 3 years with scarring. Potential associated complications include tenosynovitis, arthritis, and osteomyelitis, and in immunocompromised individuals severe disseminated infection may occur. The differential diagnosis includes cellulitis, sporotrichosis, syphilis, cutaneous leishmaniasis, tularemia, foreign-body reaction, cat-scratch disease (CSD), neoplasia, and deep fungal infection. Skin biopsy reveals inflammation with tuberculoid granulomas, and culture of *M. marinum* from tissue confirms the diagnosis. Although purified protein derivative (PPD) skin testing may be positive, it is not diagnostic of *M. marinum* infection.

When a patient has cutaneous lesions suggestive of *M. marinum* infection, a thorough exposure history should be pursued and tissue biopsy performed. Although there is no completely satisfactory



**Figure 14-31** *Mycobacterium marinum* infection. This boy developed nodules that subsequently ulcerated on the dorsal foot (*superior lesion in photograph*) and the medial ankle (*inferior lesion in photograph*). The family had a large fish tank that they routinely cleaned in the bathtub used by the patient.



**Figure 14-32** Nontuberculous mycobacterial cervical lymphadenitis. This fluctuant, violaceous nodule developed in the inferior mandibular region of this otherwise-healthy 3-year-old girl. Occasional drainage had been noted by her parents, and the lesion improved gradually with clarithromycin therapy.

treatment for this infection, options that have been used with variable success include tetracycline, minocycline, doxycycline, clarithromycin, sulfamethoxazole-trimethoprim, linezolid, and rifampin, alone or in combination with ethambutol.<sup>155,158,163,164</sup> Excision, curettage, and warm compresses are traditional treatment modalities that may be helpful for early or small lesions, but recurrences are common.

*M. ulcerans* may result in an ulcerating skin condition called *Buruli ulcer*, which is most common in Africa, Central and South America, and Asia. Buruli ulcer usually begins after a scrape by grass or a thorn and presents initially as a painless nodule that progresses to abscess formation and eventually, a shallow ulcer. The favored site of distribution is a lower extremity. The ulcer persists for months to years and eventually heals spontaneously with scarring and lymphedema.<sup>155</sup> Surgery, hyperthermic therapy, and systemic antimicrobials have all been used with variable success.

*M. fortuitum*, *M. cheloneae*, and *M. abscessus* are all referred to as *rapid growers*, given their distinctive ability to produce colonies in culture as soon as 5 to 7 days. They may result in clinical disease after trauma, the most notable association being abscess formation after surgery, especially within postsurgical scars. Children are more likely to experience infection with *M. fortuitum* than the other two rapidly growing NTMs, which are more commonly isolated from older individuals.<sup>165</sup> There are increasing reports of *M. cheloneae* infection after tattooing, with culture of the organism originating from premixed tattoo inks.<sup>166–168</sup> Inflammatory skin lesions (papules, pustules, and nodules) involving primarily the palms and soles have been observed in children in association with *M. abscessus* infection acquired from public swimming pools. This presentation has been designated by some as “*M. abscessus* hand-and-foot disease,” and may have a prolonged latency (45 to 60 days) between exposure and onset, which is significantly longer than that typically seen with *Pseudomonas* hot foot syndrome (see earlier this chapter).<sup>169,170</sup> Lesions may occasionally occur in other sites including elbows, knees, and trunk, and although this condition is self-limited, recurrences may occur. This observation has led some to recommend therapy with an appropriate agent such as clarithromycin when this diagnosis is suspected or confirmed.<sup>170</sup>

Cervical lymphadenitis resulting from NTM should be mentioned, because it is the most common manifestation of infection with these agents in healthy, immunocompetent children. These patients usually experience nontender, unilateral cervical lymphadenopathy, although other sites may be involved including the inguinal region, axilla, and lower limb.<sup>171,172</sup> There may or may not be a history of preceding local trauma, and the area may reveal overlying erythema (Fig. 14-32), violaceous discoloration, fluctuance, or drainage. The most common of the NTM to cause cervical lymphadenitis is *M. avium-intracellulare*,<sup>171,173</sup> although *Mycobacterium haemophilum* appears to be increasing in incidence as another etiology in some areas.<sup>174,175</sup> Treatment options include surgery, incision and drainage, and antimicrobial therapy including ethambutol, rifampicin, and clarithromycin. Observation alone is another option given the complete resolution seen in most patients within 9 to 12 months.<sup>176</sup> Although surgical excision has long been considered the standard of care for NTM lymphadenitis, more diversified treatment strategies including the increased use of antimicrobial agents is being observed.<sup>177</sup>

## Tuberculosis of the Skin

The incidence of cutaneous tuberculosis was at one time declining owing to the availability of effective antimycobacterial therapy, improvement in living standards, and vigorous preventative and therapeutic programs. However, it has reemerged in areas with a high incidence of HIV infection and multidrug-resistant pulmonary tuberculosis.<sup>178,179</sup> Most published reports of childhood cutaneous tuberculosis are from developing countries, and the prevalence is high in India and Southeast Asia, although the highest prevalence is reported in Pakistan.<sup>180</sup> Cutaneous tuberculosis can be acquired either exogenously or via hematogenous spread of *M. tuberculosis* and may show a wide range of clinical presentations. The majority of cases of cutaneous tuberculosis are related to systemic involvement. In this section, several types of tuberculous skin lesions are reviewed. Of the lesions discussed, scrofuloderma and lupus vulgaris tend to be the most common types of cutaneous tuberculosis to occur in children.<sup>181,182</sup>

Primary tuberculous complex (tuberculous chancre) develops as a result of inoculation of *M. tuberculosis* into the skin (and occasionally the mucosa) of an individual who has not previously been infected or who has not acquired immunity to the organism. This disorder occurs on exposed surfaces at sites of trauma (i.e., abrasion, insect bite, puncture wound, ritual circumcision, ear piercing, tattooing). The cutaneous lesion develops 2 to 4 weeks after inoculation, and the earliest lesion is a brown-red papule that develops into an indurated plaque that may ulcerate. The edges of the ulcer are ragged and undermined, and thick adherent crusts may be present. When viewed through a



**Figure 14-33** Scrofuloderma. A discharging sinus is noted from the tuberculous focus in the underlying bone in this 4-year-old boy. (Courtesy of Venkatesh Ramesh, MD.)

glass slide producing pressure on the lesion (diascopy), these areas may have an “apple jelly” yellow-brown color. Marked regional lymphadenopathy may be associated with the skin lesion<sup>183</sup> and usually develops several weeks after the cutaneous lesion. Healing of the ulcer generally occurs over several weeks, but the regional lymphadenopathy may persist significantly longer and after weeks to months may soften and form sinuses that communicate with the skin surface (scrofuloderma).

*Scrofuloderma* refers to direct extension to the skin from underlying foci of tuberculous infection, and in addition to lymph nodes may occur overlying infection of the bone or joint. It is the most common form of cutaneous tuberculosis in children. Scrofuloderma is manifested most commonly as painless swelling in the parotid, submandibular, supraclavicular, or lateral regions of the neck.<sup>184</sup> As the lesions grow, they may develop ulcers and sinuses (Fig. 14-33). *M. tuberculosis* can be easily identified by Gram stain and culture of the draining exudate. Untreated lesions of scrofuloderma may persist with little change for years and eventually heal with cicatricial bands.

Tuberculosis verrucosa cutis (warty tuberculosis) is an externally acquired, relatively uncommon inoculation type of tuberculosis in individuals who have had previous contact with *M. tuberculosis* and thus have some degree of immunity. The inoculation usually occurs at sites of minor wounds or abrasions, and it occurs most often in adults with occupations that require the handling of patients with tuberculous infections or tuberculous tissues, including pathologists (“prosector’s wart”) and butchers (“butcher’s wart”). Lesions usually occur on the dorsal hands, fingers, or lower extremities. They begin as small violaceous papules that become hyperkeratotic and warty. Multiple lesions may occur, but the majority of lesions of tuberculosis verrucosa cutis are solitary.

Lupus vulgaris is the most common form of cutaneous tuberculosis. It is a chronic, smoldering form of the infection and usually occurs in individuals with a high degree of sensitivity. Although lupus vulgaris can arise at the site of a primary inoculation, in the scar of scrofuloderma, or at the site of a bacillus Calmette-Guérin (BCG) vaccination, it generally appears in previously normal areas of skin. The most common location of involvement is the head and neck, and regional lymphadenopathy may be present in over half of the patients.<sup>182</sup> In children in India, this form of cutaneous tuberculosis most often occurs on the lower extremities and gluteal region.<sup>180</sup> Lupus vulgaris presents as small, soft, brown-red papules that enlarge and coalesce to form larger patches with elevation and intensification of their brownish color. As in tuberculous chancre, the lesion shows a characteristic apple-jelly color on diascopy. The natural history of lupus



**Figure 14-34** Lupus vulgaris. This 7-year-old boy had an enlarging erythematous, infiltrative, scaly plaque of the nasal bridge, cheek, and periorbital region. Note the characteristic central scarring and peripheral activity. (Courtesy of Venkatesh Ramesh, MD.)

vulgaris is marked by slow and limited growth over years or occasionally decades. Ulceration and atrophy may occur.<sup>181,184</sup> When ulceration occurs, it may be complicated by scarring and disfigurement, especially with nose and nasal cartilage involvement (Fig. 14-34). The differential diagnosis of lupus vulgaris includes sarcoidosis, cutaneous lymphoid hyperplasia, lupus erythematosus, halogenoderma, leishmaniasis, leprosy, deep fungal infections, and cutaneous malignancy.

Oriificial tuberculosis is a rare manifestation of cutaneous tuberculosis occurring usually in individuals who are debilitated or immunocompromised. It affects the mucocutaneous junctions of the orifices (nose, mouth, anus, urinary meatus, and genital) and is caused by autoinoculation of tubercle bacilli from secretions. Lesions present as shallow, painful ulcers with a granulating base and undermined edges, with swelling, edema, and inflammation of the surrounding mucosa. Painful ulcers of the mouth or other mucosal membranes in patients with visceral tuberculosis should arouse suspicion of this disorder.

Miliary tuberculosis of the skin (tuberculosis cutis miliaris disseminata) is an extremely rare manifestation of fulminating pulmonary or meningeal tuberculosis. It is quite uncommon in children and in recent times is seen most often in the setting of adult HIV infection.<sup>185,186</sup> When present, the eruption is caused by hematogenous dissemination of *M. tuberculosis* to the skin in addition to multiple internal organs. Cutaneous lesions present as minute, symmetrically distributed, erythematous, red-brown macules, papules, or vesiculopustules. Purpuric lesions may occasionally be present. The course of miliary tuberculosis is usually fulminating, and the mortality rate high.

Diagnostic options for cutaneous tuberculosis include smears, stains, and cultures of skin swabs, aspirates, and biopsy tissue. The Mantoux intradermal tuberculin test is commonly positive, but the reactivity does not correlate with disease activity.<sup>182</sup> Another screening test is the QuantiFERON TB Gold test, which quantifies the release of interferon-γ in whole blood upon stimulation with *M. tuberculosis* antigens. PCR amplification of *M. tuberculosis* deoxyribonucleic acid (DNA) is a rapid, sensitive, and accurate technique for diagnosis and may be applied to paraffin-embedded skin-biopsy tissue.<sup>187,188</sup>

The treatment of all forms of cutaneous tuberculosis is similar to that used for active pulmonary tuberculosis. Current recommendations of the American Academy of Pediatrics include a 6-month regimen consisting of isoniazid, rifampin, ethambutol and pyrazinamide for 2 months followed by 4 months of isoniazid and rifampin (with ethambutol or streptomycin added if drug resistance is a concern) or a 6-month regimen (for hilar adenopathy only) of

isoniazid and rifampin.<sup>189</sup> Tuberculous meningitis is treated with a four-drug regimen for 2 months followed by isoniazid and rifampin for 7 to 10 more months.<sup>189</sup>

## The Tuberculid Disorders

The tuberculid disorders are hypersensitivity reactions to *M. tuberculosis* and classically include erythema induratum, papulonecrotic tuberculid, and lichen scrofulosorum. Originally felt to be related to toxins or an allergic response to tubercle bacilli, they are currently believed to be the result of hematogenous dissemination of organisms from an internal focus to the skin, where they incite a cutaneous inflammatory response. Lupus miliaris disseminatus faciei (formally described as a tuberculid) is probably more aptly described as a granulomatous disorder of the pilosebaceous units (see Chapter 8). A deep nodular form presenting on the lower extremities has been termed *nodular tuberculid* and seems to represent a hybrid between papulonecrotic tuberculid and erythema induratum.<sup>190</sup> Once a tuberculid disorder has been diagnosed, a thorough evaluation for subclinical active tuberculosis should be initiated.<sup>191</sup>

Erythema induratum of Bazin is a chronic, recurring panniculitis (inflammation of the fat) that typically occurs on the calves of girls and young women. Although the association with tuberculosis has historically been controversial, the clinical and histopathologic features, ability to identify *M. tuberculosis* on PCR studies, and response to antituberculosis therapy seem to support a tuberculous etiology.<sup>192–196</sup> Lesions present as symmetrical, tender, deep-seated nodules that develop into red-purple masses that tend to ulcerate. The ulcers are irregular and shallow and heal with an atrophic scar. Erythema induratum tends to be chronic and recurrent; many patients have a personal or family history of tuberculosis. The tuberculin skin test is positive, but mycobacteria are seldom recovered from lesions by standard culture techniques. PCR analysis of skin-biopsy specimens has been found to be rapid and sensitive in the diagnosis of this disorder.<sup>194–196</sup> Treatment of erythema induratum with combination antituberculous therapy is usually successful, although in untreated patients the lesions usually involute spontaneously over a period of years.

Papulonecrotic tuberculid is the most common tuberculid seen in children, although it is rarely seen in the United States. It is characterized by symmetric crops of dusky red, small papules and nodules with central necrosis or ulceration that heal with superficial scarring. Sites of predilection for papulonecrotic tuberculid include the extensor extremities (particularly the knees and elbows), the buttocks, and the lower trunk. Ear involvement may also be common, and pulmonary tuberculosis is usually present.<sup>197</sup> The lesions may clinically resemble those of varicella. As with erythema induratum, recovery of the organism from standard tissue culture is of low yield. Patients usually have a positive intradermal tuberculin skin-test reaction, and gene-amplification PCR performed on skin-biopsy tissue is useful in confirming the diagnosis.<sup>198</sup> Papulonecrotic tuberculid usually responds promptly to antituberculous therapy. Simultaneous occurrence of papulonecrotic tuberculid and erythema induratum has been reported.<sup>199</sup>

Lichen scrofulosorum is characterized by clusters of lichenoid papules on the trunk of children or young adults, usually in association with tuberculosis of lymph nodes and/or other organs. Lesions are firm, 1- to 5-mm, flesh-colored to reddish-brown flat-topped papules. They tend to be asymptomatic and slowly undergo spontaneous involution.

## Leprosy

Leprosy (Hansen disease) is a chronic infectious disorder of worldwide distribution in which the acid-fast bacillus *Mycobacterium leprae* has a special predilection for the skin and nervous system. Although the worldwide incidence of leprosy has decreased significantly, likely in response to multidrug therapy (MDT), widespread BCG vaccination, and public health initiatives, it is still somewhat prevalent in certain areas including India, China, and Southeast Asia. Leprosy is rare in

**Table 14-1** Classification of Leprosy (in Order of Decreasing Host Resistance)

Group	Clinical Features
Tuberculoid (TT) (mildest; high resistance)	A single or few localized anesthetic macules or plaques; hair loss within lesions; few if any organisms; peripheral nerve involvement common
Borderline tuberculoid* (BT)	Lesions similar to TT but more numerous; satellite papules around larger lesions (at times); hair and sensation diminished (but not absent) within lesions; peripheral nerve involvement common
Borderline borderline (BB)	Features of both TT and LL; more lesions than BT; borders more vague; nerve involvement and satellite lesions common; many bacilli usually present
Borderline lepromatos (BL)	Multiple nonanesthetic asymmetrically distributed annular plaques; may be surrounding papules; late neural lesions; leonine facies
Lepromatos (LL) (most severe; low or no resistance)	Generalized involvement (skin, mucous membranes, upper respiratory tract, reticuloendothelial system, adrenal glands, and testes); no neural lesions until late; no sensory or hair growth impairment; many bacilli in tissue
Indeterminate	Small number of hypopigmented macules; no thickened nerves or sensory impairment

\*The three intermediate forms (BT, BB, and BL) are clinically unstable and may pass from milder to more severe states and vice versa.



**Figure 14-35** Lepromatos leprosy. Erythematous, infiltrative patches and plaques that revealed many acid-fast bacilli in the skin-biopsy specimen.

the United States with around 85% of diagnosed cases occurring in immigrants, and the disease may mimic many common dermatological and neurological disorders.<sup>200</sup>

Although there is no universal agreement on the classification of leprosy, the disorder is usually divided into several clinical subtypes depending on the patient's degree of immunity to *M. leprae* (Table 14-1). At one end of the spectrum is the lepromatos (LL) form of the disorder, the disfiguring disease most familiar to the public. In this variant patients are anergic to *M. leprae* and develop widespread disease involving the skin (Fig. 14-35), upper respiratory tract, sensory and motor nerves, eyes (superficial keratitis), testes, lymph nodes, and bone. Many bacilli are present in the tissues. Nodules or diffuse infiltrates, especially on the face and earlobes, produce the characteristic "leonine facies." Loss of eyebrows and eyelashes may also occur. At the opposite pole is tuberculoid leprosy (TT), a form that occurs in patients with a very high degree of immunity against *M. leprae*. In this variant, patients have only a single (or occasionally a few) large

well-defined macule(s) or infiltrative plaques that show hypopigmentation and loss of sensation. The peripheral nerves, most commonly the ulnar, external popliteal, and great auricular nerves, are thickened and palpable, and patients may develop trophic disturbances and paryses. Between these ends of the spectrum, borderline forms of the disorder are seen. Patients with borderline lepromatous leprosy tend to have the most extensive involvement of nerves. Owing to the decreased sensation in affected areas, these patients are at risk for secondary infections and digital ulceration. Blindness occurs in around 5% of patients with leprosy.<sup>201</sup>

The incubation period of leprosy is typically very long and ranges from 3 months to 40 years (average, 2 to 4 years).<sup>200</sup> Early childhood disease often presents with solitary lesions that may occur on any exposed area of the skin, and childhood disease is most commonly indeterminate or at the tuberculoid end of the spectrum. The mode of transmission of leprosy remains unclear, although an upper respiratory route is suggested.

Leprosy should be suspected in any patient from a leprosy-endemic area (or immigrants from such regions) who has chronic hypopigmented or infiltrative skin lesions, skin anesthesia, thickened nerves, or eye complaints. The diagnosis is confirmed by the identification of acid-fast bacilli in skin smears or biopsy material, and the histologic picture reveals a granulomatous infiltrate containing large foamy histiocytes (lepra cells) in the epidermis. Treatment should be directed by a clinician experienced in the care of patients with leprosy and preferably in a Hansen-disease center where feasible. Although therapeutic recommendations of the past called for monotherapy with dapsone, given increasing resistance to this approach MDT is now recommended and includes other agents such as rifampin and clofazimine. In treated patients, 95% of all nerve function impairment develops within 2 years, supporting a decreased frequency for neurologic follow-up examination in patients without neurologic findings by that time.<sup>202</sup>

Leprosy reactions are fairly commonplace during treatment for the disease and are related to immune-mediated inflammation. These reactional states, which include reversal reactions and erythema nodosum leprosum (ENL), may result in worsening of neural and skin lesions and significant tissue damage. These reactions are often treated with systemic corticosteroids and in the case of ENL, thalidomide is a very effective agent.<sup>203</sup> Although there is no effective vaccination for leprosy, BCG vaccination has been demonstrated to be effective at protecting some populations from infection.<sup>200,204</sup>

## Anthrax

Anthrax, an infection caused by the Gram-positive *Bacillus anthracis*, is occasionally transmitted to humans through contact with infected animals or animal products such as hides or wool. Whereas this mode of infection usually results in cutaneous anthrax, inhalation disease ("woolsorters' disease") has occurred in settings such as factories where processing of these products takes place.<sup>205</sup> Anthrax has long been considered a potential agent of biologic warfare, the significance of which was magnified by the events of September 11, 2001, and the following apparent bioterrorism involving the spread of *B. anthracis* via bioengineered spore-containing letters within the US postal system. These events highlight the importance of adequate education in and recognition of this infection and other potential biologic weapons of mass destruction.

Clinical infection with *B. anthracis* usually takes one of three forms: inhalational, cutaneous, or gastrointestinal. The cutaneous form (malignant pustule) is responsible for 95% of the cases in the United States and is usually an occupational disease of farmers, butchers, veterinarians, and individuals who process animal products.<sup>206</sup> The spore is introduced via an abrasion or cut in the skin and develops into the primary lesion, which is a painless, pruritic papule. This papule progresses to develop small surrounding vesicles surrounded by a brawny, nonpitting edema. The vesicles rupture with the development of necrosis, and eventually a black eschar forms (Fig. 14-36) and overlies an ulcer. Nonnecrotic ulcerations may also be the presenting feature, as was observed in a patient affected by the 2001 terrorism attacks, and lesions may be solitary or multiple.<sup>207</sup> Low-grade fever,



**Figure 14-36** Cutaneous anthrax in a child. Erythematous plaque with necrosis and eschar formation in a 7-month-old male. Anthrax bacilli were detected in biopsy tissue. (Reprinted with permission from Roche KJ, Chang MW, Lazarus H. Images in clinical medicine: cutaneous anthrax infection. N Engl J Med 2001;345(22):1611. © 2001, Massachusetts Medical Society. All rights reserved.)

malaise, and headache are often present, and regional lymphadenopathy early in the course is common. Without therapy, this form is fatal in 20% of cases.<sup>208</sup> Cutaneous anthrax is rare in children and may be accompanied by anthrax meningitis or systemic spread of disease. Microangiopathic hemolytic anemia, hyponatremia, and coagulopathy were reported in a 7-month-old infant with cutaneous infection.<sup>209</sup>

Gastrointestinal anthrax forms after ingestion of undercooked meat from infected animals. In this case, the characteristic eschar forms in the gastrointestinal tract, usually the terminal ileum or cecum, and patients experience fever, nausea, vomiting, and anorexia. Severe abdominal pain (presenting as an acute abdomen), bloody diarrhea, sepsis, and death may ensue, with a mortality rate greater than 50%.

Inhalational anthrax is the most severe form of infection and is traditionally associated with a very high (>95%) mortality rate. Patients initially experience flu-like symptoms and progress to dyspnea, stridor, fever, and cyanosis. Meningitis, coma, and death may ensue.

The diagnosis of anthrax can be confirmed by Gram stain and culture of a skin lesion, CSF, or blood. Confirmatory studies are usually performed in a reference laboratory. Nasal swabs are used epidemiologically but are not a reliable method of diagnosis.<sup>205,208</sup> Serologic testing is useful only from a retrospective standpoint and requires acute and convalescent samples. A variety of real-time PCR assays exist for detection of *B. anthracis*.<sup>210</sup> Histopathologic examination of a skin-biopsy specimen may also be useful, especially with the concomitant use of a tissue Gram stain.

Penicillin has been the drug of choice for anthrax for many decades, with penicillin resistance found only rarely in naturally occurring strains. Other antimicrobials with good activity against *B. anthracis* include ciprofloxacin, tetracyclines, macrolides, clindamycin, and cephalosporins. Some of these other agents may be more concentrated in the phagocyte and therefore may be more desirable.<sup>211</sup> The treatment of choice for bioterrorism-associated anthrax, however, is ciprofloxacin, even in children.<sup>212</sup> Postexposure prophylaxis is recommended in situations where there is a credible threat of exposure to spores, and ciprofloxacin (alternative doxycycline) is recommended for a full 60 days in this setting.

## Cat-Scratch Disease

Cat-scratch disease (CSD) is an acute, self-limited infection of children and young adults caused by the pleomorphic Gram-negative bacillus *Bartonella henselae*. *Bartonella* species, which are Gram-negative bacilli,



**Figure 14-37** Cat-scratch disease. Axillary lymphadenopathy in a 2-year-old boy with a crusted red papule at the primary inoculation site on the chest.

result in a variety of diseases in humans, including Carrión disease, prolonged fever of unknown origin, encephalopathy, ocular disease, trench fever, and endocarditis. CSD is a benign cause of lymphadenitis in children and is usually transmitted from infected kittens to humans by means of a scratch or bite that is often recalled only in retrospect.<sup>213</sup> The domesticated house cat is the most important natural reservoir for *B. henselae*, and stray cats and kittens are more likely to be infected than are pet or adult cats, respectively.<sup>214</sup> It is estimated that up to half of domestic cats have antibodies to *B. henselae*, testing seropositive for the bacteria.<sup>215</sup> This organism has also been linked to bacillary angiomatosis (see Chapter 12), a vascular proliferative disease seen most commonly in individuals infected with HIV. CSD is most common in areas with warm climates and occurs most often in the fall and winter.<sup>216</sup>

The most common clinical presentation of CSD is lymphadenopathy. However, the infection usually begins with a small papule or nodule within the original cat-scratch line 3 to 10 days after the trauma. Over the following 1 to 2 weeks, the regional lymph nodes draining the region begin to enlarge (Fig. 14-37), reaching the point of maximal enlargement around 1 month after the initial injury.<sup>217</sup> Often the initial wound at the site of contact with the animal has resolved by the time the patient pursues medical care. The enlarged lymph nodes gradually decrease in size over a period of a few months in the absence of therapy. In up to 10% of patients, lymph nodes become erythematous and fluctuant, occasionally requiring needle aspiration.<sup>216</sup> In 85% of patients, there is only a single lymph node involved.<sup>215</sup> Common locations for the lymphadenopathy of CSD include the neck, axillary, and inguinal regions.<sup>218</sup> In one large series, the most common sites of lymphadenopathy (in order of decreasing incidence) were the axilla, epitrochlear region, cervical region, submandibular region, and groin.<sup>219</sup> Biopsy of lymph nodes, when performed, reveals granulomas with multiple microabscesses.

Other features that may be present in patients with CSD include fever, headache, and malaise. Parinaud oculoglandular syndrome consists of unilateral granulomatous conjunctivitis with concomitant ipsilateral preauricular lymphadenopathy at the site of inoculation and represents the most common form of atypical CSD. This presentation appears to occur as a result of indirect inoculation of the organism into the eye rather than by direct contact through a cat scratch as is typical of CSD. Other less common associations include neuroretinitis (presenting as acute-onset unilateral vision loss), encephalopathy, endocarditis, seizures, generalized lymphadenopathy, or prolonged fever. Bony involvement may present with osteomyelitis and may include lytic lesions of the cortex and/or inflammation of the marrow.<sup>220</sup> Immunocompromised individuals with *B. henselae* infec-

tion may develop a disseminated, invasive form of infection that involves multiple organs. *Bacillary peliosis* is the term used to describe reticuloendothelial organ involvement including the liver (peliosis hepatitis), spleen, abdominal lymph nodes, and bone marrow.<sup>216</sup>

CSD is usually diagnosed based on the characteristic clinical presentation in combination with a history of recent contact with a cat. Diagnostic confirmation is provided by positive serologic studies for antibodies to *B. henselae* (either >1:64 antibody titer or a fourfold titer elevation between acute and convalescent sera). Serology remains the most practical diagnostic tool for the laboratory detection of *B. henselae* infection.<sup>215</sup> Blood and tissue can be cultured, but the organism is slow growing and may be difficult to isolate. Identification of the organism in tissue samples stained with the Warthin-Starry silver stain lends further support to the diagnosis and may be useful in some settings. The most sensitive test available is *B. henselae* DNA sequence detection via PCR, but this modality is not readily available.<sup>217</sup>

Treatment of CSD in the immunocompetent host with uncomplicated disease is not always necessary, as it is a self-limited disease and studies demonstrating a significant advantage of therapy are lacking. However, treatment may shorten the period of symptomatic illness and may promote more rapid resolution of the clinical abnormalities.<sup>217</sup> *B. henselae* has been demonstrated to be susceptible to a variety of antimicrobial agents, including azithromycin (the recommendation of many clinician-researchers), clarithromycin, rifampin, doxycycline, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole. Disease in immunocompromised patients may be more serious, and thus therapy is usually recommended with a macrolide, rifampin, or doxycycline for at least 6 weeks.<sup>213</sup> Surgical removal of lymph nodes is generally not indicated except in rare patients in whom the diagnosis is in doubt, in whom repeated aspirations fail to relieve pain, or in whom the inflammatory process persists without involution.

## Disorders Resulting from Fungus-like Bacteria

Actinomycosis and nocardiosis are disorders caused by actinomycetes, which are Gram-positive organisms that may resemble fungi both microscopically and macroscopically. Although these infections can occur at any age, they most often occur in adults. Although primary skin infection is rare, involvement of the cutaneous and subcutaneous tissues may result from contiguous spread from other sites or secondary infection of traumatized or injured skin, particularly in debilitated or immunodeficient individuals.

### ACTINOMYCOSIS

Actinomycosis is a chronic suppurative infection caused by *Actinomyces israelii*, an anaerobic Gram-positive saprophyte of the tonsillar crypts, carious teeth, and female genital tract, and rarely by other *Actinomyces* species. Infection is often associated with dental procedures, trauma, or surgery.<sup>221</sup> This disorder is clinically characterized by the production of “sulfur granules” from multiple draining sinuses. It tends to occur in one of three areas: the cervicofacial region (most common), lungs, or intestinal tract. Some patients have mixed-organ involvement that may include the skin, brain, pericardium and extremities.<sup>222</sup> Cervicofacial actinomycosis, seen most often in individuals with poor oral hygiene and carious teeth, begins when the infecting organism invades a traumatized oral mucous membrane. This form presents as soft-tissue swelling, usually over the mandibular region. It increases to form a brawny, erythematous nodule that discharges serosanguineous or purulent material through multiple sinus tracts, from which the characteristic sulfur-yellow granules consisting of masses of organisms can be demonstrated. Destruction of bone with periostitis and osteomyelitis may occur, and absence of regional lymph node involvement is characteristic.

Aspiration of the organism causes pulmonary infection that progresses through the pleura, causing draining sinus tracts of the chest wall. It may occur after esophageal disruption during surgery or non-penetrating trauma or may occur as a manifestation of extension of cervicofacial infection.<sup>223</sup> The abdominal form develops from the ileum, cecum, or appendix (in association with appendicitis) and is

seen as draining sinuses, tracts, or subcutaneous abscesses extending to either the abdominal wall or the perineum. Primary infection of other body sites may affect the urinary tract, CNS, bones, and joints. A localized form, known as *mycetoma*, occurs most commonly on the feet or ankles of individuals who walk around barefoot (see Chapter 17).

Actinomycosis is diagnosed by isolation and identification of the causative organism in anaerobic culture. It may also be confirmed by observation of the highly characteristic sulfur granules (groups of delicate filaments, often with club-shaped ends) in purulent or biopsied materials. The course of actinomycosis is prolonged and characterized by closure of one sinus tract and the opening of another. Treatment is with intravenous penicillin G for 4 to 6 weeks followed by oral penicillin in high doses for 6 to 12 months.<sup>223</sup> Surgical incision and drainage of abscesses and excision of fibrotic, avascular tissue are occasionally necessary. Alternative antibiotics for patients allergic to penicillin include tetracyclines, erythromycin, or clindamycin.

## NOCARDIOSIS

Nocardiosis is a severe, primarily pulmonary infection caused by an aerobic Gram-positive, partially acid-fast fungus-like organism, *Nocardia asteroides*. It is less often caused by *Nocardia brasiliensis* or other species. Nocardiosis primarily affects men in the 30- to 50-year-old age group, although it has been increasingly recognized in infants and children. Disseminated disease has a significant morbidity and mortality and is more likely in immunosuppressed hosts.

Nocardiosis may occur with several different presentations, including pulmonary, systemic, CNS, and cutaneous/subcutaneous forms. It generally occurs through inhalation of contaminated dust, and the clinical picture is usually that of a primary pulmonary disease that resembles tuberculosis in its clinical and radiographic findings. These primary pulmonary infections may result in blood-vessel erosion with subsequent hematogenous dissemination to other organs, including the skin. In those instances in which the skin is involved (<15% of cases), the most common lesions are abscesses of the chest wall with granulomatous lesions surrounding draining sinuses.<sup>224</sup> Primary cutaneous or subcutaneous nocardiosis is usually the result of traumatic implantation of foreign objects into the skin and often presents in immunocompetent hosts.<sup>221,225</sup> Once inoculated into the skin, it may present in a lymphocutaneous syndrome mimicking sporotrichosis, as a cellulitis-like picture, or as a mycetoma (large, draining mass).<sup>226</sup> Disorders that may predispose an individual to invasive disease include chronic granulomatous disease, organ transplantation, HIV infection, or diseases requiring long-term systemic steroid therapy.<sup>227</sup>

Nocardiosis should be considered in obscure pulmonary and meningeal syndromes and chronic suppurative disorders of the bones or skin. The diagnosis is established by the presence of organisms in smears or cultures of sputum, aspirated material collected from lesions, or biopsy material. Unfortunately, the diagnosis is seldom established until the disease is far advanced. The cornerstone of therapy for nocardiosis is sulfonamides and trimethoprim-sulfamethoxazole. Imipenem, third-generation cephalosporins, amoxicillin clavulanate, amikacin, minocycline, and fluoroquinolones maybe other options.<sup>226</sup> The overall mortality rate of nocardiosis is around 25% and is highest in those patients who have pulmonary involvement and those with immunocompromise.<sup>228</sup>

## Treponemal Infections

### SYPHILIS

Syphilis is an infectious disease caused by the spirochetal organism *Treponema pallidum*. It is transmitted primarily by sexual contact, with the next most common mode being vertical transmission across the placenta, which may result in congenital syphilis (see Chapter 2). After a steady decline in the number of cases of syphilis in the early 1970s, the incidence of syphilis has fluctuated with peaks and troughs occurring in approximately 10-year cycles, with the overall trend being toward increasing rates, especially in men who have sex with men.<sup>229,230</sup> Syphilis continues to be an important health problem

throughout the world and left untreated may result in long-term neurologic, cardiovascular, and other systemic sequelae, as well as congenital syphilis in offspring of infected mothers. Some 15% to 40% of untreated patients develop recognizable late complications.<sup>229</sup> Currently more than 60% of new cases of syphilis occur in men who have sex with men, and the HIV coinfection rate is high (up to 60% in some geographic locations) among patients with syphilis in the United States.<sup>230–232</sup> Importantly, syphilis infection increases the likelihood of acquiring and transmitting HIV.

Untreated acquired syphilis is characterized by a series of clinical stages that are summarized in Table 14-2. There may be considerable overlap of symptoms in the various stages, and the early stages may pass by undiagnosed. The incubation period for syphilis ranges from 5 to 90 days. Patients with early syphilis (primary, secondary, and the first year of latent syphilis) are considered infectious. The late latent (after the first year) and late stages, conversely, are considered noninfectious, rarely relapse, and tend to be destructive and scarring.

Primary syphilis usually manifests as a single, painless genital papule or, more commonly, ulcer (chancre), occurring on the labia or vaginal wall in females and the glans penis (Fig. 14-38) in males. In

**Table 14-2** Clinical Stages of Syphilis

Stage	Clinical Manifestations	
<b>Primary</b>	Painless papule or ulcer at site of inoculation Regional lymphadenopathy	
<b>Secondary</b>	Generalized macular/papular rash, involves palms/soles Condyloma lata in intertriginous areas Mucous patches Constitutional symptoms Occasional aseptic meningitis	
<b>Latent</b>	No symptoms, but specific antibody tests positive	
<b>Tertiary</b>	Cardiovascular Neurosyphilis Gumma	Aortic aneurysm CVA, paresis, psychiatric symptoms, ataxia, autonomic dysfunction, cranial nerve palsies, optic neuritis Inflammatory infiltrates in multiple organs

CVA, Cerebrovascular accident.



**Figure 14-38** Primary syphilis. Eroded chancre of the glans penis in a male with primary infection.



**Figure 14-39** Secondary syphilis. Crusted, hyperkeratotic, erythematous papules and plaques on the palms.

homosexual men, anorectal ulcers are most common. Chancres may occasionally be multiple, painful, purulent, or destructive.<sup>233</sup> Painless regional lymphadenopathy is often present, although there may occasionally be tenderness to palpation. The differential diagnosis of the primary syphilitic chancre includes other sexually transmitted diseases, including herpes simplex virus infection and chancroid (caused by *Haemophilus ducreyi*), which both tend to be differentiated by painful ulcers. Extraprofessional ulcers occur rarely in primary syphilis and when present occur most commonly on the fingers, tongue borders, or anus. If left untreated, the ulcer of primary syphilis heals spontaneously over 4 to 6 weeks.

Secondary syphilis develops 2 to 8 weeks after exposure in untreated individuals and is more common in females given the increased number of asymptomatic or undiagnosed primary lesions compared to men.<sup>234</sup> The primary chancre may still be present at the time of diagnosis of secondary syphilis. The classic cutaneous findings of this stage are characterized by a widespread macular and papular skin eruption that may occasionally be follicular or pustular. Examination reveals pink to erythematous, slightly scaly macules and papules that often involve the palms and soles, as well as flanks and arms. In dark-skinned individuals the lesions tend to be hyperpigmented. The palm and sole lesions may appear as macular or hyperkeratotic red-brown papules or plaques (Fig. 14-39) and are often helpful in the differentiation between secondary syphilis and the primary differential diagnosis, pityriasis rosea. Other entities in the differential diagnosis include drug eruption, lichen planus, acute exanthems, tinea versicolor, sarcoidosis, Mucha-Habermann disease (pityriasis lichenoides), nummular eczema, and psoriasis.

Other mucocutaneous lesions seen in secondary syphilis include alopecia, mucous patches, and condyloma lata. Patchy alopecia may be present in up to 7% of patients and classically has a "moth-eaten" appearance. Mucous patches occur on the tongue, buccal mucosa, and lips and present as erythematous patches, often with associated erosion and a silvery-gray membrane. Condyloma lata are smooth, gray plaques found in warm and moist intertriginous zones in up to 20% of patients. These lesions are highly infectious and must be differentiated from genital warts (condylomata acuminata).

Systemic symptoms may also be present and include fever, headache, malaise, pharyngitis, and arthralgias. Ocular inflammatory conditions (including episcleritis, keratitis, and uveitis) may occur, as may aseptic meningitis, painless lymphadenopathy (especially epitrochlear), and hepatitis. A particularly aggressive form, termed *lues-maligna*, has been observed most often in the population infected with HIV.<sup>235</sup>

Cutaneous lesions of secondary syphilis usually heal without scarring, even in the absence of therapy, within 2 to 10 weeks. Residual hyperpigmentation or hypopigmentation may be present. Residual

hypopigmentation on the skin of the neck has been termed the *necklace of Venus* (leukoderma collis).

Latent syphilis is a stage of the disease during which there are no clinical signs or symptoms or during which there are mild but generally unrecognized nonspecific symptoms such as malaise, anorexia, headache, sore throat, arthralgia, and low-grade fever. A diagnosis of latent syphilis is usually established on the basis of a positive serologic test after other stages of syphilis have been ruled out by physical and CSF examination. This stage is arbitrarily divided into early latent syphilis (occurring within 1 year of infection) and late latent syphilis (occurring after 1 year). Patients with early latent syphilis are considered to be infectious.

Tertiary syphilis is divided into late benign syphilis (gumma), neurosyphilis, and cardiovascular syphilis (see Table 14-2). It appears in around 10% to 40% of untreated patients and after a latent period of 3 to 30 years or longer. Tertiary syphilis is extremely rare in children.

The hallmark lesions of late benign syphilis are the "gummas," and the skin is one of the most common organs of involvement, other common sites being the bone and liver. The cutaneous lesions present as superficial nodules or nodoulcerative plaques that may result in punched out ulcers. Common sites of involvement include the extremities, face, scalp, sternum, and the sternoclavicular joints. Upon healing, hyperpigmentation and atrophic scarring may persist. When the palate or nasal mucosa is affected, destruction is often pronounced and may lead to perforation of the affected areas. Large gummas may have several perforations, and as the intervening bridges of skin break down and necrose, lesions tend to produce arched or scalloped margins with arciform and geographic patterns. Bone lesions occurring in this stage are marked by periostitis involving the cranial bones, tibia, and clavicle and present with nocturnal pain and local swelling.<sup>229</sup>

The diagnosis of syphilis depends on the combined findings from history, clinical examination, tissue examination, and serologic studies. *T. pallidum* cannot be cultured. Dark-field microscopy is the gold-standard diagnostic method for primary syphilis, although it is not always readily available. Direct fluorescent antibody testing for *T. pallidum* has also been described for the diagnosis of primary syphilis. Both of these approaches, however, have been supplanted by serologic diagnostic methods, which are also the mainstay of laboratory diagnosis for secondary, latent, and tertiary syphilis.

Serologic tests, which provide only indirect evidence of infection, are divided into nontreponemal and treponemal categories. The nontreponemal tests detect an antibody against cardiolipin that is present in the sera of many patients with syphilis. These examinations include the Venereal Disease Reference Laboratory (VDRL) slide test and the Rapid Plasma Reagins (RPR) card test. These examinations are inexpensive, rapid, and convenient but may result in false-positive reactions (i.e., with advanced age, malignancies, Lyme disease, chronic liver disease, pregnancy, systemic lupus erythematosus, and some viral or bacterial infections) and are limited in their sensitivity. The treponemal tests include fluorescent treponemal antibody absorption (FTA-ABS), the microhemagglutination test for antibodies to *T. pallidum* (MHA-TP), the *T. pallidum* enzyme immunoassay (TP-EIA), and *T. pallidum* particle agglutination (TP-PA) tests.<sup>236</sup> Treponemal tests measure specific antibodies formed by the host in response to infection with *T. pallidum*. They have a higher sensitivity and specificity than nontreponemal tests and are used as confirmation of diagnosis. Treponemal tests establish the high likelihood of a treponemal infection either at the present time or at sometime in the past.<sup>237</sup>

Parenteral penicillin G is the mainstay of treatment for all forms of syphilis, with dosing regimens and duration of therapy varying based on stage of disease and the clinical manifestations that are present.<sup>236</sup> In patients with penicillin allergy, doxycycline or tetracycline are the preferred alternatives. Azithromycin has been investigated for its utility in treating patients with early disease.<sup>238</sup> The treatment of choice for congenital syphilis or neurosyphilis is aqueous crystalline penicillin G.<sup>236</sup> Patients under therapy for syphilis are generally assessed for response to therapy by serial quantitative nontreponemal tests. Patients with neurosyphilis require very close follow-up clinical and intermittent CSF examinations for at least the first 2 years after diagnosis.

## PINTA

Pinta, a nonvenereal treponemal infection caused by *T. pallidum* subspecies *carateum*, occurs almost exclusively among the dark-skinned population of Central and South America and Cuba. It is transmitted by direct contact and is often seen in children of affected parents. Although transmission by insects is possible, this mode of exposure is considered to be exceedingly rare. Pinta is the only spirochetal disease that results in purely cutaneous manifestations.

There are three basic forms of pinta, termed *primary*, *secondary*, and *late*. The primary stage, seen on uncovered areas such as the face, arms, and legs, begins 1 to 8 weeks after inoculation as red papules that enlarge into oval or round erythematous scaly plaques measuring up to 10 cm in diameter. Small papules often become surrounded by satellite macules or papules that coalesce to form configurative patterns. Regional lymphadenopathy is common. After several months to years, secondary lesions (referred to as *pintids*) appear as small, scaly papules that coalesce into large, scaly plaques. Their color is initially red to violaceous, with progression to a slate-blue, brown, gray, or black hue.<sup>239</sup> In this stage, widespread involvement is present with coalescence of lesions. The differential diagnosis may include psoriasis, eczema, tinea corporis, syphilis, or leprosy. Lesions of primary and secondary pinta are highly infectious.

The late phase develops in 3 to 10 years and is characterized by irregular pigmentation with a range of different shades (correlating with the site of deposition of melanin in the dermis), resulting in a spotted and highly characteristic appearance. These lesions have an insidious onset, usually during adolescence or young adulthood, and are eventually replaced by depigmented patches closely resembling vitiligo. The most common sites of involvement are the bony prominences including the wrists, elbows, and ankles. Periarticular skin atrophy and extensor surface hyperkeratosis is also common during this phase.<sup>240</sup>

The diagnosis of pinta is made by identification of *T. carateum* on dark-field examination or more commonly, serologic testing. The serologic studies utilized for the diagnosis of pinta are the same as those utilized for venereal syphilis, and these diseases are immunologically and serologically indistinguishable.<sup>241</sup> Penicillin is the treatment of choice, with options similar to those of syphilis for patients with penicillin allergy.

## YAWS

Yaws, caused by *Treponema pallidum* subspecies *pertunue*, is a nonvenereal treponemal disease endemic in many tropical regions that typically begins in childhood (usually before puberty). It is also transmitted by direct skin contact (nonsexual) and has been divided into primary, secondary, and tertiary stages. The primary stage is characterized by an erythematous papule that occurs within 2 to 4 weeks at the site of inoculation (the “mother yaw”), usually the legs, feet, or buttocks. It enlarges and becomes confluent with surrounding satellite nodules with eventual ulceration. This stage is occasionally accompanied by constitutional symptoms, arthralgias, and lymphadenopathy. Spontaneous healing of the skin lesion eventually occurs with scarring, although it may take up to 6 months.<sup>242</sup>

Weeks to months after the primary lesion, secondary yaws occurs, presenting as smaller, widespread cutaneous papules (“daughter” yaws or framboesias) that tend to occur adjacent to body orifices. These lesions ulcerate and secrete infectious treponemes. This stage is characterized also by palmoplantar lesions, bone involvement, lymphadenopathy, and occasional neurologic and ophthalmologic abnormalities. Hyperkeratotic involvement of the palms and soles with painful fissuring is common. The latter may cause patients to walk on the sides of their feet, producing a characteristic gait known as *crab yaws*. If not treated in its early stages, yaws may become a chronic infection with frequent relapses and severe disfigurement with permanent bony deformities.<sup>243</sup>

Although the disorder generally terminates with the secondary stage, 10% of patients develop a late tertiary stage in which gummatous lesions occur. These lesions, which present 5 to 10 years after inoculation, may be locally destructive and lead to skin ulceration as well as deforming bone and joint sequelae. Late neurologic or ophthal-

mologic manifestations may occasionally present during the tertiary stage but are not typical.

Yaws is usually diagnosed based on the characteristic clinical findings in an endemic region combined with dark-field microscopy or serologic studies. Again, the same serologic examinations used to diagnose venereal syphilis and pinta are utilized. Treatment options include long-acting penicillin (benzathine penicillin), azithromycin, and tetracycline.

## LYME DISEASE

Lyme disease is the most common vector-borne disease in the United States. It was first recognized in southeastern Connecticut in 1975 and is an immune-mediated multisystem disorder caused by the spirochete *Borrelia burgdorferi*. Lyme disease is transmitted by *Ixodes* species ticks, primarily *Ixodes scapularis* (the deer tick) in the United States. It occurs most commonly in areas where deer ticks are abundant and *B. burgdorferi* carriage is common, especially the coastal northeastern, mid-Atlantic, and northern central regions of the United States, as well as much of Europe and Northern Asia.<sup>244</sup> Lyme disease is rare in the Pacific states because of the low infection rate of *Ixodes pacificus* (the Western black-legged tick) with *B. burgdorferi*.<sup>245</sup> When cases occur in the western states, they are most common in northern California and Oregon. In Europe, the vector is most often *Ixodes ricinus*, and the pathogenic *Borrelia* species are *Borrelia afzelii* and *Borrelia garinii*.<sup>246</sup> There is a bimodal age distribution of Lyme disease, with the initial peak occurring in children between the ages of 5 and 14 years.<sup>247</sup>

There are several factors associated with the risk of transmission of *B. burgdorferi* from ticks to humans. Because organisms often remain dormant in the tick until multiplication and migration occur during feeding, the risk of transmission is low if the tick is removed within 24 hours of attachment. In addition, the proportion of infected ticks varies according to geographic location, and hence the risk of disease is low outside of endemic regions. The highest probability of transmission of infection occurs 48 to 72 hours after the onset of attachment.<sup>248</sup>

The clinical findings of Lyme disease were originally described as occurring in three stages, although now they are generally divided into two stages: early (divided into early localized or early disseminated) and late (Table 14-3). These correspond to the traditional stages I, II, and III. The onset of clinical manifestations usually occurs from 3 days to 4 weeks after the tick bite. However, because of the small pencil-point size of the *Ixodes* tick, only about 30% of patients recall having had a tick bite.

**Table 14-3** Clinical Manifestations of Lyme Disease

Stage of Disease	Clinical Findings
Early localized (stage I)	Erythema migrans (single) Constitutional symptoms (headache, myalgias, arthralgias, fatigue, fever) Lymphadenopathy
Early disseminated (stage II)	Erythema migrans (multiple) Lymphadenopathy Constitutional symptoms (headache, myalgias, arthralgias, fatigue, fever) Neurologic: facial palsy, meningitis, other neuropathies Cardiac: atrioventricular conduction defects, congestive heart failure, myocarditis Rheumatologic: arthritis
Late (stage III)	Neurologic: encephalopathy, encephalomyelitis, peripheral neuropathy Rheumatologic: arthritis Cutaneous: lymphocytoma cutis, acrodermatitis chronica atrophicans



**Figure 14-40** Erythema migrans of Lyme disease. Expanding, erythematous, annular patch of early localized Lyme disease. A small red papule is seen centrally at the site of the tick bite.



**Figure 14-41** Erythema migrans, multiple lesions. Multiple erythematous macules and patches were present in this child with early disseminated Lyme disease.

### Early Localized Lyme Disease (Stage I)

The earliest manifestation of Lyme disease is usually a single skin lesion termed *erythema migrans* (EM). It is felt that at this stage the spirochetal infection is restricted to the skin in most patients. EM begins with a red papule at the site of the bite and progresses to become a flat, erythematous patch. With peripheral expansion, there may be central clearing (although not always), resulting in an annular patch (Fig. 14-40). This lesion usually is nonpalpable, and it is most commonly asymptomatic. Occasional variations include vesicular, urticarial, scaly, and purpuric presentations.<sup>249</sup> Systemic symptoms may be present and include fatigue, fever, chills, headache, myalgias, and arthralgias. Lymphadenopathy may also occur. Although EM may occur anywhere on the cutaneous surface, the thighs, groin, and axillae are particularly common sites of involvement. The lesions can be differentiated from those of *tinea corporis* and *nummular eczema* by rapid peripheral expansion, lack of scaling, and lack of pruritus. The eruption of EM resolves spontaneously over several weeks even without therapy. Multiple EM lesions may be seen and usually correlate with spirochetemia and disseminated disease (see the following section).

### Early Disseminated Lyme Disease (Stage II)

As the organism disseminates, patients may show additional signs or symptoms, including multiple lesions of EM (Fig. 14-41). The individual lesions are similar to the original EM lesion, although they tend to be less inflamed and do not extend as aggressively.<sup>250</sup> Multiple EM lesions occur in around 25% of infected children in the United States.<sup>245</sup> Constitutional symptoms are common during this stage of infection. Neurologic manifestations of early disseminated Lyme disease include peripheral neuropathy (especially cranial nerve VII palsy) and lymphocytic meningitis. Facial palsy is the most characteristic neuropathy and is reported in 40% to 50% of patients with neurologic involvement. Bilateral facial palsy, a quite rare presentation, should be highly suspicious for Lyme disease, especially when occurring in an endemic area. The facial palsy of Lyme disease usually resolves in 2 to 8 weeks with or without treatment. Other cranial and peripheral mononeuropathies are possible, albeit more common in adults than children,<sup>249</sup> and a Guillain–Barré-like syndrome has been reported. Because Lyme meningitis is fairly common in endemic regions between April and December, clinicians should include this on the differential diagnosis for children presenting with undifferentiated aseptic meningitis and CSF pleocytosis in this scenario.<sup>251</sup> Migratory arthralgia or frank arthritis may also occur, as may cardiac involvement. The latter is marked by first-, second-, or third-degree atrioventricular conduction defects or bundle branch blocks and less commonly carditis or congestive heart failure.<sup>249</sup> In children with early disseminated Lyme disease, predictive variables for carditis include older age, presence of arthralgias, and cardiopulmonary symptoms.<sup>252</sup>

### Late Lyme Disease (Stage III)

The primary features of late Lyme disease, which occurs in 60% of untreated cases, are arthritis and neurologic disease. Fortunately, with better and earlier recognition of this disorder, manifestations of late disease have become much less common.<sup>244</sup> Cutaneous manifestations during late disease include lymphocytoma cutis and acrodermatitis chronica atrophicans (ACA) (see below). The arthritis is usually monoarticular or oligoarticular and tends to involve the knees most commonly, although migratory and small-joint involvement may be seen. The presentation may simulate that of juvenile rheumatoid arthritis or an acute septic arthritis, and confusion with the latter may be compounded by the finding of markedly elevated joint-fluid leukocyte counts.<sup>253</sup> The most common neurologic sequelae of late disease are encephalopathy, encephalomyelitis, and sensorineural peripheral neuropathy, although late neurologic disease tends to be rare in children.

Other cutaneous manifestations that have been potentially linked to *B. burgdorferi* infection include linear morphea, lichen sclerosis et atrophicus, and lymphocytoma cutis (cutaneous lymphoid hyperplasia). In Europe, *B. burgdorferi* infection has also been associated with Ban-nwarth syndrome (localized radicular pains accompanied by motor or sensory changes and occasionally lymphocytic meningitis), atrophoderma of Pasini and Pierini, eosinophilic fasciitis, and progressive facial hemiatrophy. ACA is reported primarily in Europe as a late manifestation of disease. It is characterized early by violaceous plaques followed by induration, hyperpigmentation, and atrophy of the skin on the distal extensor extremities and may be associated with concurrent arthritis and neuropathy.<sup>250</sup> This Lyme complication is associated primarily with infection by *B. afzelii*.<sup>254</sup>

Chronic Lyme disease (also known as *posttreatment chronic Lyme disease*) is a challenging and controversial entity from both a diagnostic and therapeutic standpoint. Two syndromes to occur in this context have been reported. The first consists of patients who continue to have symptoms similar to the pretreatment period despite appropriate therapy, especially joint complaints. The second syndrome to occur in this setting is similar to chronic fatigue syndrome or fibromyalgia, and patients present with complaints of extreme fatigue, myalgias, headache, polyarthralgias, and mood disturbances. Some patients are more symptomatic than others, possibly reflecting some sort of genetic influence, and although the disease does not tend to be destructive or progressive, its effects can be quite debilitating.<sup>255</sup> Chronic Lyme disease may be overdiagnosed as a result of equivocal test results, unreliable tests, or the misdiagnosis of associated psychiatric comorbidities.<sup>256,257</sup>

The diagnosis of Lyme disease relies upon clinical findings suggestive of the disease in combination with confirmatory laboratory testing. Antibody determinations are the most commonly utilized diagnostic examinations, and include indirect immunofluorescence

assays and enzyme-linked immunosorbent assays (ELISAs). Both can assess for IgM and IgG antibodies to *B. burgdorferi*. It must be remembered that patients with early localized Lyme disease are commonly seronegative for antibodies, and hence the diagnosis in that setting requires astute clinical judgment. Serologic studies may also be limited by cross-reactivities with other organisms and high rates of seropositivity among asymptomatic persons in endemic areas.<sup>258</sup> Immuno-blotting or Western blotting allows for more specific detection of antibodies and may be used in conjunction with the previously mentioned assays. Culture of *B. burgdorferi* is possible from tissue or fluid but it is slow and difficult and requires special media that are not readily available. PCR studies for Lyme disease have been applied to a variety of tissues and fluids but in general are neither approved nor widely available for this purpose and may result in false positive results. Lyme urinary antigen capture tests are unreliable and should not be used.

The treatment of Lyme disease depends on the type of presentation and the age of the patient. In patients in whom the diagnosis of early Lyme disease is strongly suspected, treatment is initiated based on clinical findings, given the potential delays in laboratory confirmation. Doxycycline for 14 to 21 days is the treatment of choice for early localized disease in children older than 8 years of age. For those younger than 8 years of age, amoxicillin or cefuroxime for the same period is indicated.<sup>259</sup> Alternatives include erythromycin or clarithromycin.<sup>249</sup> Early disseminated disease and late disease are treated with the same oral regimen but for 21 days. Persistent or recurrent arthritis, carditis, meningitis, or encephalitis are treated with parenteral ceftiraxone or penicillin for 14 to 28 days.<sup>259</sup> Occasionally, patients may develop intensification of symptoms during the first 24 hours of antibiotic therapy (a Jarisch–Herxheimer-like reaction), presumably caused by the host immune response to dying organisms. This reaction usually disappears in 1 to 2 days and is not an indication for discontinuation of therapy.

The hallmark of prevention for Lyme disease is tick avoidance. Simple measures to this end include avoidance of tick-infested areas, tucking pant legs into socks, and inspection for ticks after high-risk activities or exposures in endemic areas. The judicious use of chemical repellents such as N,N-diethyl-3-methylbenzamide (DEET), picaridin, or permethrin (see Chapter 18) on skin or clothing is also helpful. Because the *Ixodes* tick must be attached to the skin for at least 24 hours before infection is transmitted, daily inspection should be performed on individuals after exposure to potentially infested areas, and prompt tick removal by grasping the tick with a forceps, tweezers, or gloved fingers will help prevent transmission of the disease.<sup>260</sup> Removal should be performed without crushing the tick, and an effort should be made to leave no body parts behind. The bite site should be washed with soap and water to prevent secondary infection. Maintaining household pets as tick-free will also decrease the chance of transmission of tick-borne diseases.

Most experts recommend against serologic testing or prophylactic antibiotic therapy after a tick bite, especially for patients who have had ticks attached for less than 24 hours.<sup>244</sup> Most deer ticks, even in highly endemic areas for Lyme disease, are not infected with *B. burgdorferi*, and the overall risk of infection after a recognized deer-tick bite in such an area is only around 1.4%.<sup>261</sup> A vaccine for Lyme disease was available and approved by the US Food and Drug Administration for individuals between 15 and 70 years of age but was withdrawn in 2002 and is no longer available.

## Protozoal Disorders

### LEISHMANIASIS

The term *leishmaniasis* refers to three different diseases caused by the protozoan parasite of the genus *Leishmania*: cutaneous leishmaniasis (oriental sore, Delhi boil, Balkh sore), mucocutaneous leishmaniasis, and visceral leishmaniasis (kala-azar). These infections are characterized by diversity and complexity, and the majority of cases occur in Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, and Syria (in the “Old World”) and Brazil and Peru (in the “New World”).<sup>262</sup> *Leishmania* is present in most tropical and subtropical countries owing to characteristics of the sandfly vector (see below). In the United States,

leishmaniasis is primarily seen in foreign travelers, immigrants, and military personnel returning from countries where it is endemic.<sup>263</sup> Travelers can become infected even after short stays in *Leishmania*-endemic areas,<sup>264</sup> and the increase in travel to endemic regions of South and Central America has led to an increase in the number of cases diagnosed in the United States.<sup>265</sup> Although there may be overlap in clinical presentations caused by specific species, in general Old-World cutaneous leishmaniasis is caused by *Leishmania tropica* or *Leishmania major*; New World cutaneous disease by *Leishmania braziliensis* or *Leishmania mexicana*; mucocutaneous disease by *Leishmania braziliensis*; and visceral disease by *Leishmania donovani*. There are, however, multiple other less common species of *Leishmania* as well.

Leishmaniasis is transmitted by the sandfly (*Phlebotomus* or *Lutzomyia* species), which lives in dark and damp places. Sandflies fly silently and are most active in the evening and at night. The infection is transmitted to humans (an accidental host) by the bite of the sandfly, which itself becomes infected after a blood meal from infected mammals (primarily rodents and dogs).<sup>262,266</sup> An important epidemiologic observation of recent note is the increasing incidence of visceral leishmaniasis among patients with acquired immunodeficiency syndrome (AIDS) in southern Europe and a few other endemic areas.<sup>266,267</sup> *Leishmania* species are obligate intracellular parasites of macrophages, by which they are phagocytosed after inoculation into the skin. They subsequently replicate within macrophages and spread throughout the reticuloendothelial system of the host.

Cutaneous leishmaniasis has a variety of clinical presentations, although the most common is an indolent skin ulcer. There are an estimated 1.5 million new cases of cutaneous disease each year, and the incidence may be increasing.<sup>268</sup> The incubation period after the bite of the sandfly is usually 1 to 12 weeks, and occasionally the infection may remain subclinical. The initial lesion is a papule that enlarges to form a painless ulcer with a raised margin and necrotic base (Figs. 14-42 and 14-43). Most often there are one to two lesions, although multiple lesions have been observed, and some patients may show a lymphangitic distribution similar to that of sporotrichosis.<sup>264</sup> Regional lymphadenopathy and secondary bacterial infection may occur, the latter of which is often associated with pain.<sup>262</sup> Most lesions of cutaneous leishmaniasis heal over months to years, leaving an atrophic scar.

Other presentations of cutaneous leishmaniasis include a dry ulcerative form that appears as a brown nodule that ulcerates more slowly and reveals an adherent crust; leishmaniasis recidivans, which is manifested by red to yellow-brown papules that appear in or close to a scar of an old lesion of cutaneous leishmaniasis; and a nonulcerating generalized form that may resemble lepromatous leprosy. Patients



**Figure 14-42** Cutaneous leishmaniasis. An erythematous crusted plaque in a 4-year-old child. (Courtesy of William Burrows, MD.)



**Figure 14-43** Cutaneous leishmaniasis. Multiple erythematous papules and plaques with necrosis and crusting were present in this 2-year-old female. *Leishmania tropica* was confirmed by PCR analysis. (Courtesy of Ayelet Shani-Adir, MD.)

with this form of leishmaniasis present a public health hazard, because the skin is heavily infested and may act as a reservoir for transmission by the *Phlebotomus* fly.

The differential diagnosis of cutaneous leishmaniasis includes foreign-body reactions, tropical or traumatic ulcers, superinfected insect bites, myiasis, impetigo, fungal and mycobacterial infections, sarcoidosis, and neoplasms.<sup>262,264</sup> The diagnosis of leishmaniasis is usually made on the basis of the typical lesion(s) combined with a history of exposure or travel to an endemic region. Confirming the diagnosis can be challenging. Tissue biopsy for culture, smear, and histologic evaluation is useful. An impression smear is made by gently pressing the fresh biopsy tissue against a glass microscope slide, staining with Giemsa or hematoxylin and eosin (H&E) stain, and examining for amastigotes (intracellular organisms). Tissue specimens for culture must be plated on special culture, and the organisms can be typed by isoenzyme analysis in a reference laboratory, although the procedure is quite time consuming.<sup>268</sup> Alternative methods for diagnosis include needle aspirates, slit-skin smears, monoclonal antibody tissue stains, and molecular techniques based on kinetoplast (a small portion of extranuclear material) DNA analysis. Serologic studies, which may be helpful in visceral or disseminated cutaneous disease, are usually of no value for localized cutaneous leishmaniasis. PCR-based diagnosis is also possible and is particularly useful in cases with a low parasite load (i.e., mucosal leishmaniasis).

Mucocutaneous leishmaniasis results from hematogenous or lymphatic dissemination of organisms from skin to the nasopharyngeal mucosa. It often manifests years after resolution of cutaneous lesions of leishmaniasis.<sup>264</sup> Mucocutaneous leishmaniasis presents with chronic nasal symptoms and is followed by progressive nasopharyngeal destruction. Secondary bacterial infections with regional adenitis and lymphangitis are common, and occasionally the mucocutaneous lesions may be nodular and vegetative. Destruction of the nasal septum and nasopharynx may result in soft-tissue and cartilage erosion, with resultant deformities of the nose, lips, cheeks, pharynx, larynx, and palate that are often cosmetically debilitating.<sup>269</sup>

Visceral leishmaniasis may present with varied clinical findings and severity of illness. It infects an estimated 500,000 new individuals in

less-developed countries each year and may occur in large-scale epidemics, especially in east Africa and India.<sup>270,271</sup> The classic kala-azar syndrome, caused by *L. donovani*, results in fever, cachexia, hepatosplenomegaly, pancytopenia, and progressive deterioration. If left untreated, visceral leishmaniasis is often fatal. A common complication after therapy for kala-azar is "post-kala-azar dermal leishmaniasis." This disorder is characterized by macular, papular, and nodular skin lesions that usually begin around the mouth and subsequently generalize.<sup>272</sup>

Treatment of leishmaniasis depends upon the clinical presentation, and in fact there is no single optimal therapy for all forms. When considering treatment for cutaneous disease, it is important to remember that this form of leishmaniasis tends to heal spontaneously, but that *L. braziliensis* has the potential to progress to mucocutaneous disease.<sup>268</sup> Therefore any patient with *L. braziliensis* confirmed as the etiologic agent or with a history of contracting the infection in an area endemic for this organism should receive adequate systemic therapy. The goals of therapy are to reduce scarring and prevent parasite dissemination.

Pentavalent antimonial drugs such as sodium stibogluconate (Pentostam) and meglumine antimoniate (Glucantime) remain the mainstay of systemic therapy. These agents are generally administered in the hospital, although controlled outpatient management is an acceptable alternative in some situations. Pentostam is available in the United States from the Drug Service of the Centers for Disease Control and Prevention. Potential toxicities related to the antimonial agents include electrocardiographic abnormalities, hepatic toxicity, pancreatitis, and pneumonitis. Amphotericin B and its lipid formulations have shown efficacy in the treatment of leishmaniasis, especially in India where antimonial resistance has been an increasing concern.<sup>266,270</sup> Other treatments utilized with varying degrees of success have included cryosurgery, surgical excision, topical paromomycin ointment, intralesional sodium stibogluconate, and pentamidine. High-dose oral fluconazole was demonstrated useful in the treatment of cutaneous leishmaniasis caused by *L. braziliensis*.<sup>273</sup> Other potentially promising treatments for visceral leishmaniasis that have been studied include the anticancer alkylphosphocholines milt eosine, edelfosine, and ilmofosine.<sup>274,275</sup>

The complete list of 275 references for this chapter is available online at <http://expertconsult.inkling.com>.

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Viruses are ultramicroscopic organisms that grow only within living cells. The antigenic material responsible for viral immunologic reactions is present in the outer protein membrane (capsid) of the virus. The nucleoprotein core is composed of either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). Lacking ribosomes, viruses depend on the use of the host cells' enzyme systems, blending with metabolic material of the host cell and often remaining undetected until some stimulus incites the production of new viral particles.

Viral infections of the skin may present with varied morphologies, including papules, vesiculobullous lesions, ulcers, and tumors. This chapter will include a discussion of herpes simplex virus (HSV) infections, herpes zoster (HZ), viral-like disorders of the oral mucosa, and warts. Some poxvirus infections will be discussed, including molluscum contagiosum (MC), cowpox, pseudocowpox ("milker's nodules"), orf, and smallpox. Although human immunodeficiency virus (HIV) infection does not result in primary skin disease, a brief discussion of acquired immunodeficiency syndrome (AIDS) in children and its skin disease associations is included. Neonatal herpes infection is discussed in Chapter 2.

## Herpes Simplex Virus Infection

The herpesvirus family includes HSV, Epstein–Barr virus (EBV), cytomegalovirus (CMV), varicella-zoster virus (VZV), and human herpesviruses (HHV) 6 through 8. Aside from HSV, the other herpesviruses are implicated primarily in exanthematous illnesses. HSV infections are quite prevalent in both children and adults. HSV-1 and HSV-2 are double-stranded DNA viruses that primarily infect the epidermis or mucosal surfaces. After acute infection, the virus rapidly replicates and establishes latent infection in regional nerve ganglia, from which it occasionally reactivates.<sup>1,2</sup> These viruses rely on the host-cell nucleus for DNA replication, and hence when microscopic evaluations are performed on samples with infection, the characteristic cytologic inclusions are located within the nucleus.<sup>3</sup>

HSV-1 is primarily associated with oral and labial lesions and HSV-2 with anogenital lesions, although the predilection of a specific viral serotype to a particular anatomic site appears to be changing.<sup>4</sup> Primary HSV-1 infection is largely a childhood disease that affects the oral mucosa, pharynx, lips, and occasionally the eyes.<sup>2</sup> HSV-2 is primarily implicated in genital-tract disease, with spread occurring via sexual contact or most commonly in neonates by passage through an infected birth canal (see Chapter 2). Although the mucocutaneous lesions caused by HSV-1 and HSV-2 are clinically indistinguishable, differentiation between the two serotypes can be made by viral culture, Western blot serologic testing, HSV-antigen detection with monoclonal anti-HSV antibodies, or polymerase chain reaction (PCR) studies. The Tzank smear is a rapid and cost-effective diagnostic test but is dependent on the experience of the examiner and cannot distinguish between HSV and VZV infections. Transmission of HSV is accomplished via exposure to infected mucous membranes or skin with active lesions or to mucosal secretions from an individual with active infection but can also be transmitted via exposure to secretions from an asymptomatic person who is shedding the virus.<sup>5</sup>

Infection with HSV is classified as primary or recurrent. Primary infections occur in individuals without circulating antibodies and result from direct contact with infected secretions or actual mucocutaneous lesions. After an incubation of days to weeks, they may present as subclinical infection, characterized only by the development of antibodies, as a localized or generalized cutaneous eruption,

or as a serious systemic infection with central nervous system or disseminated involvement. Most primary HSV infections are asymptomatic. Recurrent HSV infection occurs in individuals who were previously infected either clinically or subclinically. It is characterized by repeated episodes of mucocutaneous lesions at the same site or sites.

Topical and systemic antiviral agents commonly used to treat HSV infections are summarized in Table 15-1.

### HERPETIC GINGIVOSTOMATITIS

Herpetic gingivostomatitis most commonly occurs in children between the ages of 10 months and 5 years, although it may occur at any age. It presents with small vesicles on an erythematous base that evolve into painful, shallow gray erosions and ulcerations (Fig. 15-1). The lesions most often involve the palate, tongue, and gingivae. Gingival swelling and easy bleeding may occur. Perioral lesions involving the lips, cheeks, and chin (Fig. 15-2) occur in up to three-quarters of patients.<sup>6</sup> Other common features include fever, drooling, eating and drinking difficulties, foul breath odor, and irritability. Cervical and submandibular lymphadenopathy is also quite common. Secondary bacteremia with group A β-hemolytic streptococci, *Staphylococcus aureus*, or other organisms may occasionally be a complication.<sup>7</sup> Associated hepatitis has been observed, most often in neonates and immunosuppressed patients with acute primary HSV-1 infection, but also rarely in immunocompetent children.<sup>8</sup>

The differential diagnosis of herpetic gingivostomatitis in a child includes herpangina, hand-foot-and-mouth disease, aphthous stomatitis, Behcet syndrome, pemphigus vulgaris, and Stevens–Johnson syndrome. The diagnosis can be confirmed by viral culture or direct fluorescent antibody studies when necessary. Although gingivostomatitis is usually caused by HSV-1, HSV-2 may cause a similar syndrome that usually occurs in adolescents and young adults who engage in oral–genital contact.<sup>1</sup> Such primary HSV-2 infection results in similar symptoms of gingivostomatitis and pharyngitis, which in some patients may be difficult to differentiate from bacterial pharyngitis. Adolescents and young adults may also have primary HSV-1 gingivostomatitis.<sup>9,10</sup>

Although herpetic gingivostomatitis tends to be self-limited over 10 days to 2 weeks, dehydration may result from poor oral intake and excessive fluid losses, especially in younger children. In some patients, hospitalization may be required for intravenous hydration and pain control. Ambulatory treatment measures include supportive therapy with fluids and use of topical analgesics, anesthetics, or coating agents, including lidocaine, diphenhydramine, milk of magnesia, Maalox, or Kaopectate.<sup>11</sup> Specific antiviral therapy with acyclovir is advocated by some, seems most effective when started within 3 days of disease onset, and may reduce the number of oral lesions, prevent the development of new lesions, diminish difficulties with eating and drinking, and reduce the rates of hospitalization in young children.<sup>12–14</sup>

### OCULAR HERPES INFECTION

Primary HSV infection of the eye can result in a severe purulent conjunctivitis with edema, erythema, and vesiculation with superficial erosion or ulceration of the cornea (epithelial keratitis). Ocular HSV infection is a leading cause of recurrent keratoconjunctivitis with associated corneal opacification and one of the chief causes of corneal blindness in the United States.<sup>1,11</sup> This infection results from recurrent viral shedding from the trigeminal nerve reactivation and is more often caused by HSV-1. Patients with keratoconjunctivitis present

**Table 15-1** Topical and Oral Antiviral Medications Used for Herpes Simplex Virus Infections\*

Drug	Formulation	Regimen	Indication/Comment
<b>TOPICAL</b>			
Acyclovir	5% cream (2 g, 5 g) 5% ointment (15 g, 30 g)	Apply 5 times/day Apply 6 times/day	Recurrent HL; A: ≥12 years; 4 days; Rx Initial GH, localized HSV; A: adults; 7 days; Rx
Penciclovir	1% cream (1.5 g, 5 g)	Apply q. 2 h (awake)	Recurrent HL; A: ≥12 years; 4 days; Rx
Docosanol	10% cream (2 g)	Apply 5 times/day	HL; A: ≥12 years; treat until healed; OTC
<b>ORAL (ALL RX)</b>			
Acyclovir	200 mg capsule 400 mg, 800 mg tablet 200 mg/5 mL susp		A: ≥2 years
		200 mg 5 times/day 200 mg 5 times/day 400 mg 2 times/day	Initial GH; 10 days Recurrent GH; 5 days Suppression, recurrent GH; up to 12 months, then reevaluate
Famciclovir	125, 250, 500 mg tablet	1500 mg single dose 1000 mg 2 times/day 250 mg 2 times/day	A: ≥18 years Recurrent HL Recurrent GH; 1 day Suppression, recurrent GH; up to 12 months
Valacyclovir	500 mg, 1 g caplet	1 g 2 times/day 500 mg 2 times/day 500 mg–1 g once daily 2 g 2 times/day	A: adults, and ≥12 years for HL Initial GH; 10 days Recurrent GH; 3 days Suppressive GH HL; 1 day; both adults and children ≥12 years

A, Approved; GH, genital herpes; HL, herpes labialis; HSV, herpes simplex virus; Rx, by prescription; OTC, over-the-counter.

\*Approved indications and regimens listed; often used off-label.



**Figure 15-1** Herpetic gingivostomatitis. Multiple erosions with crusting. Note the associated lesions involving the chin.



**Figure 15-2** Herpetic gingivostomatitis. Lip erosions with multiple perioral herpetic lesions.

with pain, photophobia, lacrimation, and eye discharge. There may also be involvement of the eyelid (blepharitis). Deeper involvement of the cornea (stromal keratitis) or anterior uvea (iritis) may occur, and both are more serious and associated with a greater risk of visual loss. Children with HSV keratitis may have poorer visual outcomes than adults, are more often misdiagnosed, and are susceptible to amblyopia.<sup>15</sup> Ocular HSV infections may be unilateral or bilateral; patients with bilateral involvement tend to have a more protracted clinical course, and recurrences are more common.<sup>16</sup> Bacterial superinfection of herpetic keratoconjunctivitis is common. Acute retinal necrosis has rarely been reported in children.<sup>17</sup>

The diagnosis of herpetic keratoconjunctivitis can be confirmed with viral culture. Nested PCR studies, where available, seem to be superior to culture and can be performed on tear film or corneal scrapings.<sup>18</sup> The immunochromatographic assay (ICGA) kit utilizes a monoclonal antibody against HSV glycoprotein D and has high specificity (but lower sensitivity) when applied to corneal scrapings.<sup>19</sup> Ophthalmology referral is indicated, and treatment includes topical antiviral ophthalmic ointments or solutions and oral antiviral agents. Topical antiviral agents include trifluridine, vidarabine, and idoxuridine. In a series of 53 pediatric patients with HSV eye infections, 79%

of those with keratitis had corneal scarring and 26% experienced vision impairment, highlighting the importance of prompt referral and therapy.<sup>20</sup>

### HERPES LABIALIS

*Herpes labialis* refers to herpetic infections occurring on the lips, most often the vermillion border. This is the most common type of recurrent herpes infection and represents the classic “cold sore.” As with other types of recurrent infection, it occurs after reactivation of latent HSV in the cells of the trigeminal ganglia. Herpes labialis often presents initially with prodromal symptoms such as tingling, burning, or itching. After 1 to 2 days the cutaneous eruption appears as a localized cluster of small vesicles or erosions on an erythematous base (Fig. 15-3). Occasionally other areas of the face may be involved, and in immunocompromised individuals oral mucosal and/or severe involvement (Fig. 15-4) may be noted (see below). Topical and oral antiviral agents are useful in treating herpes labialis, especially when initiated within 1-2 days of the disease onset. Prophylaxis with oral agents is advocated by many for patients with a history of multiple recurrences of herpes labialis.



**Figure 15-3** Herpes labialis. Erythematous erosions clustered on the right lower lip in a patient with labial herpes. This young girl also had herpes-associated erythema multiforme (see Chapter 20).



**Figure 15-4** Herpes labialis. Severe crusting and lip edema in a patient receiving cancer chemotherapy.

## GENITAL HERPES

Genital herpes (herpetic vulvovaginitis, herpes progenitalis) is one of the most widespread sexually transmitted diseases (STDs) in the developed world and has an increasing incidence.<sup>21,22</sup> HSV-2 is primarily responsible for genital-tract herpetic infections, and seroprevalence studies reveal rates as high as 60% to 90% in developing countries and 20% to 22% of the general population in developed countries.<sup>2,23</sup> The proportion of HSV-1 isolates in genital herpes is also increasing, especially in young adults and college students.<sup>24</sup> Risk factors that directly correlate with HSV-2 infection include race (higher risk in African-Americans and Hispanics), age, years of sexual experience, lower family income, lower education level, number of sexual partners, and other STDs.<sup>2</sup> The diagnosis of genital HSV in a child should raise the suspicion of sexual abuse.<sup>25</sup> Maternal-fetal transmission of HSV may result in neonatal herpes, which is discussed in Chapter 2.

The majority of HSV-2 infections are subclinical and go unrecognized by the host.<sup>11</sup> Symptomatic primary genital herpes presents with lesions 2 to 8 days after contact with an infected individual. In distinction, first episode, nonprimary genital herpes (i.e., the initial episode



**Figure 15-5** Genital herpes. Vesicles on an erythematous base involving the right labia minora in a childhood victim of sexual abuse.

of genital herpes in a host with a past history of nongenital herpes) may not present with signs or symptoms for several months.<sup>22</sup> The lesions of primary genital HSV are painful vesicles clustered on an erythematous base (Fig. 15-5) and distributed on the vulva, labia, vagina, perineum, penile shaft, glans penis, urethra, and less often the scrotum. In females, cervical involvement, intense soft-tissue swelling, and severe pain may be present. The vesicles rupture rapidly, leaving behind painful erosions or ulcers that may be associated with pruritus, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy. Pustules may occasionally be present. Systemic signs and symptoms may include fever, malaise, headache, and myalgias. Herpetic sacral radiculomyelitis with urinary or fecal retention and neuralgias may occur, as may aseptic meningitis.<sup>1,11</sup> Less common features of HSV infection include endometritis and salpingitis in women and prostatitis in men. The symptoms of genital HSV usually improve over 5 to 7 days, and the cutaneous lesions heal over 2 to 4 weeks without therapy.

Genital herpes may show a heterogeneous clinical spectrum. Extra-genital involvement may be seen, with lesions most commonly involving the buttocks, anal region, thighs, mouth, and fingers (see below).<sup>2,21</sup> Atypical morphologies may also be present, including deep and tender ulcers, single erosions, erosive urethritis, vulvar fissure, and penile edema.<sup>21</sup> A high index of suspicion must be maintained, especially in the immunocompromised host or in patients with features of other STDs. The differential diagnosis for genital herpes includes syphilis, chancroid, lymphogranuloma venereum, condylomata acuminata, Behcet syndrome, HZ, erosive candidiasis, and lichen sclerosis. Acute infection with EBV may also present with acute genital ulceration (see Chapter 16).

Recurrent genital HSV infection is characterized by less severe cutaneous lesions that are usually preceded by a prodrome of pain, tenderness, itching, tingling, or paresthesia. The vesicles are fewer in number, and recurrent disease may be less common with HSV-1 versus HSV-2 disease. Triggering factors for recurrent disease may include physical or emotional stress, febrile illness, and menstruation. Recurrence rates tend to be highest for the first years after the initial infection.<sup>26</sup> Asymptomatic (subclinical) HSV shedding is another feature of genital herpes and among women with genital HSV-2 infection, occurs on an average of 2% of days.<sup>27</sup> The risk of subclinical shedding increases with the rate of symptomatic recurrences.

The diagnosis of genital herpes can be confirmed by viral culture, Tzanck preparation (cannot distinguish between HSV-1 and HSV-2), direct fluorescent antibody testing, Western blot serologic testing, or PCR. Treatments for genital herpes include supportive care and anti-viral therapy (see Table 15-1). Supportive measures include warm sitz baths, topical anesthetics, topical antibacterial ointments to prevent secondary infection, and oral analgesics. Education regarding the nature and risks of HSV infection and safe sex practices should be offered, and evaluation for other STDs should be considered when appropriate. An effective vaccine against HSV is highly desirable, and

research toward this end is ongoing. Experimental vaccines contain recombinant glycoprotein subunits, attenuated or replication-defective virus vaccines, and those composed of plasmids expressing glycoprotein subunits. Vaccine development has been challenging given the poor understanding of the mechanisms by which host immune responses fail to control HSV.<sup>28–30</sup>

The choice of antiviral therapy depends on the host immune status and the nature of the infection (primary or recurrent). Oral acyclovir, famciclovir, and valacyclovir may all help to speed healing, decrease symptoms, and decrease viral shedding. Long-term suppressive therapy in patients with frequent recurrences is useful in reducing both the rate and duration of flares. Although topical acyclovir ointment may offer some benefit for initial genital herpes infections, it offers little in recurrent infections.

### CUTANEOUS HERPES AND ECZEMA HERPETICUM

Cutaneous HSV infection can occur on any body surface area. Involvement of the finger (herpetic whitlow) is discussed in the next section. Nonorolabial, nongenital involvement presents in a similar fashion, with clustered vesicles or erosions on an erythematous base (Figs. 15-6 and 15-7). The lesions may be misdiagnosed as impetigo or HZ. Occasionally, recurrent cutaneous HSV may present only with prodromal symptoms followed by skin erythema and edema but without the characteristic vesiculation. In some instances, patients with recurrent cutaneous HSV may develop associated secondary bacterial infection or lymphangitis.



**Figure 15-6** Cutaneous herpes. Resolving vesicles and crusted papules overlying an erythematous base on the left cheek.



**Figure 15-7** Cutaneous herpes. Coalescing vesicles on a red base over the distal nose.

Eczema herpeticum (EH, or Kaposi varicelliform eruption; see Chapter 3) is a severe, disseminated HSV infection that occurs in individuals with atopic dermatitis or other chronic skin disease, including pemphigus, Darier disease, burns, and others.<sup>31</sup> Although the etiology of EH has not been clearly established, the impaired skin barrier associated with these diseases is believed to create a more permissive environment for viral invasion and binding to cellular receptors,<sup>31</sup> leading to a higher prevalence of EH with greater dermatitis severity.<sup>32</sup> Despite the high prevalence of atopic dermatitis in the general population and frequent exposure to HSV, EH is quite rare, possibly relating to a requirement for multiple additional host and environmental factors.<sup>33</sup> Single nucleotide polymorphisms in the interferon regulatory factor 2 (*IRF2*) gene have been demonstrated to confer a greater risk of EH, possibly reflecting an abnormal immune response to HSV.<sup>34</sup> Patients with EH usually experience an abrupt onset of fever, malaise, and a widespread eruption of monomorphous vesicles and erosions (Figs. 15-8 and 15-9; see Chapter 3, Figs. 3-28 and 3-29). The lesions are



**Figure 15-8** Eczema herpeticum. This toddler with chronic atopic dermatitis had an explosive onset of fever and widespread vesicles with crusting in eczematous areas. Note the monomorphic nature and clustering of these crusted papules with a few intact small vesicles on the dorsal hand.



**Figure 15-9** Eczema herpeticum. These coalescing vesicles progressed rapidly in this young girl with atopic dermatitis.

most prominent in areas of active dermatitis but especially tend to involve the head, neck, and trunk.

Complications of EH include keratoconjunctivitis, secondary bacterial superinfection, fluid loss, and viremia. The mainstay of treatment for EH is systemic antiviral therapy, which for the majority of patients is most appropriately administered via intravenous delivery in the hospital. Early initiation of therapy is preferable, and delays in starting acyclovir therapy appear to be associated with increased length of hospital stay.<sup>35</sup> Other treatment considerations include hydration with attention to electrolyte balance, antibiotic therapy for secondary bacterial infection, and pain control. Meticulous skin care should be performed, with bland emollients applied during the early phase of barrier recovery, as well as the application of anti-inflammatory agents for the underlying dermatitis. The timing of the latter remains controversial; although some have suggested that use of topical corticosteroids during active EH may adversely affect prognosis, a review of more than 1300 children admitted for treatment revealed no increase in length of stay when these agents were started at the time of admission.<sup>36</sup> Ophthalmologic evaluation is indicated when facial involvement is present. More extensive EH at presentation may be an indicator of an increased rate of repeated episodes.<sup>37</sup>

Erythema multiforme (see Chapter 20), an acute, self-limited reactive skin disease, has been associated with HSV infection in both children and adults. In prepubertal children with erythema multiforme, especially the recurrent type, HSV DNA was detected by PCR studies on skin biopsy specimens taken from the target lesions.<sup>38,39</sup> This finding was noted both in patients with a known history of HSV and in those without any such history. Prophylactic acyclovir may thus be useful in abrogating recurrences of erythema multiforme in children.

### HERPETIC WHITLOW

Herpetic whitlow is a unique form of HSV infection involving the pulp of the distal phalanx (or multiple phalanges). It is seen most often in physicians, dentists, dental hygienists, and nurses who have contact with the mouth or genital regions of patients with herpetic lesions. It may also occur as a result of autoinoculation in patients with herpes labialis, herpes stomatitis, or genital herpes.<sup>40</sup> The virus is inoculated onto the skin of one or more fingers, resulting in a deep-seated, painful vesicular or bullous eruption with erythema (Fig. 15-10). Spontaneous resolution usually occurs over 3 weeks if the condition is left untreated. The differential diagnosis of herpetic whitlow may include blistering dactylytis, burns, and impetigo. The diagnosis is confirmed by viral culture or direct fluorescent antibody testing, and treatment with oral acyclovir or other antiviral agents may result in alleviation of pain and more rapid healing.



**Figure 15-10** Herpetic whitlow. Clustered, tender, deep-seated vesicles of the distal phalanx.

### HERPES GLADIATORUM

*Herpes gladiatorum* is a term used to describe a widespread primary inoculation HSV infection occurring in contact sports enthusiasts such as wrestlers or rugby players. It may occur at some time in up to one-third of wrestlers and is characterized by grouped vesicles on an erythematous base. It has also been observed after shared use of boxing gloves believed to be contaminated by HSV-1, with lesions occurring over the knuckles.<sup>41</sup> The most common locations for herpes gladiatorum are the head, neck, and upper extremities.<sup>42,43</sup> In addition to widespread cutaneous lesions, affected individuals may have fever, malaise, sore throat, anorexia, headache, weight loss, and regional lymphadenopathy. The cutaneous lesions of herpes gladiatorum may occasionally lack classic vesicles, in which case the differential diagnosis may include tinea corporis gladiatorum, impetigo, and atopic dermatitis.<sup>43</sup>

Herpes gladiatorum can be effectively treated with oral acyclovir, famciclovir, or valacyclovir. The duration of therapy necessary before allowing the athlete to return to competition is controversial, and evidence-based recommendations do not exist. Sharing of equipment and towels should be discouraged and appropriate cleaning of wrestling mats encouraged. Seasonal antiviral prophylaxis has been advocated by some in an effort to suppress recurrent outbreaks and reduce the risk of spread to susceptible teammates or opponents.<sup>44,45</sup>

### HERPES IN THE IMMUNOCOMPROMISED HOST

Severe, chronic, and recalcitrant HSV infections may be seen in the setting of immunodeficiency. These settings include individuals with hematologic malignancy, those with a history of bone marrow or solid-organ transplantation, and those with HIV infection. Although these patients may develop common forms of HSV infection, their lesions may be more widespread and extensive. Persistent or recurrent ulcers are a common manifestation of HSV infection in patients with AIDS.<sup>1</sup> Large, persistent ulcers in patients infected with HIV should arouse suspicion for HSV, although the differential diagnosis may include syphilis and chancroid. Less common locations such as the buttocks and back are also more likely to be involved in these patients.<sup>21</sup> HSV lesions in immunocompromised hosts may also be verrucous, pustular, markedly crusted (Fig. 15-11), necrotic (Fig. 15-12), or exophytic.

In addition to cutaneous lesions, disseminated HSV may be noted in this patient population. Oropharyngeal involvement, esophagitis, tracheobronchitis, pneumonitis, hepatitis, pancreatitis, adrenal necrosis, and gastrointestinal-tract and bone marrow involvement may occur.<sup>1</sup> These severe and/or disseminated infections may be caused by either HSV-1 or HSV-2.



**Figure 15-11** Herpes in the immunocompromised host. This large, crusted plaque was culture-positive for *Herpes simplex* in this 6-year-old female receiving chemotherapy for leukemia.



**Figure 15-12** Herpes in the immunocompromised host. Vesicles rapidly progressed to necrotic plaques in this young girl status post-bone marrow transplantation.



**Figure 15-13** Herpes zoster. Confluent vesicles and crusted vesicles with erythema in a dermatomal distribution on the left thigh. This boy was otherwise healthy with no identifiable underlying predisposition.



**Figure 15-14** Herpes zoster. Edema with erythema and vesiculation, distributed in a V1 and partial V2 distribution. Corneal involvement may occur with this presentation.

## Herpes Zoster

HZ (also called *zoster* or *shingles*) is an acute vesicular eruption caused by reactivation of a latent infection with VZV in the sensory ganglia. Although it is most often seen in elderly or immunosuppressed individuals, it may also occur in children. Although pediatric zoster is most common in immunocompromised children or those who had a primary intrauterine infection or acute varicella within the first year of life,<sup>40</sup> it may occasionally occur in children without any of these risk factors. Neonatal HZ has rarely been reported, presumably in association with exposure to varicella zoster *in utero*. Due to licensure of the live attenuated Oka strain varicella vaccine, it has become clear that HZ may be caused by reactivation of the latent vaccine virus, even in children.<sup>47,48</sup> Studies of HZ incidence since implementation of the vaccination program in 1995 have yielded conflicting results, showing both increased incidence and no increase, and suggesting that there may be other unidentified risk factors for HZ that are changing over time.<sup>49</sup> In a review of 322 children with HZ, the incidence in vaccinated children (either wild-type or vaccine-strain) was 79% lower than in unvaccinated children (wild-type only).<sup>50</sup>

HZ is characterized by vesicles and erythema clustered in a dermatomal distribution of one or more sensory nerves (Fig. 15-13). The most commonly affected dermatomes are the second cervical to second lumbar nerves (C2 to L2) and the fifth (Fig. 15-14) and seventh cranial nerves. Patients often complain of hyperesthesia, pain, and tenderness to light touch in the affected area(s), usually before any cutaneous findings are present. Although the eruption is usually unilateral with a sharp demarcation at the midline, occasional contralateral involvement is seen. It is not unusual to see a few randomly scattered vesicular lesions beyond the primary dermatomal involvement, and such scattered lesions do not necessarily constitute disseminated zoster.

Successive crops of new lesions with extension of the process may occur for up to 1 week, followed by crusting of the vesicles and healing over 1 to 2 weeks. In children the disorder tends to be milder, and healing often occurs rapidly, within a few days to 1 week.<sup>51</sup> In addition, in otherwise healthy children, postherpetic neuralgia (PHN, a delayed phenomenon of chronic pain and paresthesias in an area previously affected by HZ) is rare. PHN is more common in elderly patients and in those with a history of ophthalmic HZ (see below).<sup>52</sup>

Immunocompromised children with HZ may have more extensive involvement with a higher risk of viremia and visceral dissemina-

tion.<sup>51</sup> This may include pneumonia, encephalitis, hepatitis, and disseminated intravascular coagulopathy.<sup>51,53</sup> These patients may also have disseminated cutaneous involvement that presents in a fashion more typical of acute varicella and with no obvious dermatomal component.<sup>53</sup> The intensity of chemotherapy may affect the risk of HZ; in one series, more than half of the children with acute lymphoblastic leukemia receiving chemotherapy on high-risk protocols developed HZ during their course of treatment.<sup>54</sup> *Abdominal zoster* refers to the presentation of HZ as severe abdominal pain that precedes the development of cutaneous lesions. These patients are often explored surgically, and the condition is associated with a high incidence of abdominal visceral involvement. Children infected with HIV may have chronic or relapsing HZ, or HZ with unusual cutaneous lesions (i.e., hyperkeratotic papules, ulcers, or necrotic plaques).

Infection associated with the ophthalmic branch of the fifth (trigeminal) nerve may involve the cornea with keratitis and uveitis and may lead to permanent damage. This presentation (termed *HZ ophthalmicus*) occurs when the nasociliary branch is involved and accordingly presents with cutaneous involvement of the nasal tip (Hutchinson sign).<sup>55</sup> This important sign should not be overlooked and should prompt rapid diagnosis, referral, and institution of therapy.

**Table 15-2** Systemic Antiviral Medications Used for Herpes Zoster\*

Drug	Formulation	Regimen	Indication/Comment
Acyclovir	200 mg capsule 400 mg, 800 mg tablet		A: ≥2 years
	200 mg/5 mL susp	800 mg 5 times/day	Adult dose; 7–10 days Pediatric HZ dosing: NE
	50 mg/1 mL IV	60 mg/kg per day	IC <12 years; divide every 8 hours; 7 days
		30 mg/kg per day	IC ≥12 years; divide every 8 hours; 7 days
Famciclovir	125, 250, 500 mg tablet	500 mg 3 times/day	A: ≥18 years; 7 days
Valacyclovir	500 mg, 1 g caplet	1 g 3 times/day	A: adults; 7 days

A, Approved; HZ, herpes zoster; NE, not established; IC, immunocompromised; IV, intravenous preparation.

\*Approved indications and regimens listed; often used off-label.

HZ of the maxillary division of the trigeminal nerve produces vesiculation of the palate, uvula, and tonsillar area. Involvement of the mandibular division produces vesicular involvement of the anterior aspects of the tongue, floor of the mouth, lips, and buccal mucous membranes. Involvement of the geniculate ganglion produces lesions on the tongue, ear, and skin of the auditory canal. When accompanied by Bell palsy and disturbances of hearing and equilibrium, it is part of the Ramsay Hunt syndrome.

The diagnosis of HZ is often a clinical one, and in typical cases further evaluations are generally unnecessary. In patients in whom diagnostic confirmation is indicated, direct detection with fluorescent antibody stains of vesicle-base scrapings is useful. Viral culture can be used, but VZV may take up to 1 week to induce cytopathic changes. PCR studies are not available on a widespread basis for clinical use, and serologic studies are generally not useful in this setting.

Treatment for HZ consists of symptomatic measures and specific antiviral therapy (Table 15-2). Symptomatic care includes wet compresses, drying lotions (i.e., calamine), antihistamines, and analgesics. High-dose acyclovir decreases vesicle formation, time to crusting, and days of pain when instituted within 72 hours of onset of the exanthem. Acyclovir should be administered via the intravenous route in immunocompromised patients, given their greater severity of disease, or in any patient with disseminated or severe infection. Other antiviral options in immunocompetent patients or those with uncomplicated HZ include valacyclovir and famciclovir. An HZ vaccine is approved for adults 50 years of age and older, with widespread vaccination desirable to help in the prevention of HZ and PHN in this population and in reducing the health and financial costs of HZ.<sup>56,57</sup> This vaccine is nearly identical to the varicella vaccine, except that the HZ vaccine contains 14 times as many virus particles.<sup>58</sup>

## Viral-Like Disorders of the Oral Mucosa

### APHTHOUS STOMATITIS

Recurrent aphthous stomatitis (RAS; aphthous ulcers, canker sores) is one of the most common painful diseases affecting the oral mucosa of children. It has been reported in 5% to 25% of the general population, and there may be a genetic predisposition.<sup>59,60</sup> The etiology is not well understood, and treatment has traditionally been symptomatic. Aphthous stomatitis presents with single or multiple shallow erosions



**Figure 15-15** Aphthous stomatitis. Multiple shallow erosions of the labial mucosa.

or ulcerations (Fig. 15-15) on the labial and buccal mucosae, gingivae, tongue, floor of the mouth, palate, or pharynx. Before the onset of the lesions, a tingling sensation may be present. After 24 to 48 hours, a focal erythema develops, followed soon thereafter by tiny, superficial gray-white erosions. Usually there are 1 to 3 lesions (minor RAS; 80% to 85% of cases), and the area of erosion increases and evolves into one or more sharply defined shallow ulcers covered by gray membranes and surrounded by sharp borders and slightly elevated, bright red areolae. Lesions usually measure 3 to 6 mm in diameter, and if left untreated, persist for 8 to 12 days (sometimes longer) and heal without scarring. Occasionally patients develop larger ulcerations, up to several centimeters in size with prolonged pain, fever, and healing with scarring. This variant has been termed *major RAS* (10% of cases; formally known as Sutton disease) and may be associated with dysphagia, malaise, and HIV infection.<sup>61</sup> Another form of aphthae, herpetiform RAS, occurs in 5% to 10% of patients with aphthous lesions and presents as clusters of pinpoint ulcers that simulate but are not caused by infection with HSV.<sup>62</sup>

Aphthous stomatitis is believed to be multifactorial in origin and may occur in response to a variety of triggering factors, including stress, trauma, hormonal changes, and infection. Cytokines are felt to play an important role, and polymorphisms in the genes for interleukins (ILs) 1b and 6 may increase a patient's individual risk of RAS.<sup>63</sup> Human leukocyte antigen (HLA) B52 and HLA-B44 antigens were found to be strongly associated with RAS in Israeli Arab youths.<sup>64</sup> Drug-induced RAS has also been suggested, especially in association with nonsteroidal anti-inflammatory drugs and β-blockers.<sup>65</sup> Both EBV and CMV have been hypothesized as potential infectious causes of RAS.<sup>66,67</sup> In the vast majority of cases, the etiology remains unknown.

The differential diagnosis (and/or potential associations) of RAS includes Behcet syndrome (see Chapter 25), inflammatory bowel disease (see Chapter 25), cyclic neutropenia, gluten-sensitive enteropathy, herpes simplex infection, candidiasis, vitamin/nutritional deficiencies (iron, folic acid, zinc, and vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, and B<sub>12</sub>), and the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA, Marshall syndrome) (see Chapter 25). PFAPA syndrome is characterized by high fevers (up to 41°C), aphthous ulcers, pharyngitis (which is usually culture-negative), and cervical adenitis. Associated symptoms include headache, nausea, vomiting, and abdominal pain.<sup>62,68</sup> The syndrome usually occurs in patients younger than 5 years of age, and flares recur at 21- to 42-day intervals. The fevers resolve over 24 to 48 hours spontaneously and often drop dramatically after even a single dose of oral corticosteroids. Other reportedly effective therapies have included cimetidine and tonsillectomy.<sup>68</sup> Overall, patients with PFAPA syndrome do well with spontaneous resolution of the episodes within 3 to 5 years and without any long-term sequelae.

Treatments for RAS include primarily topical corticosteroids and topical and/or oral analgesics. Topical clobetasol, a potent corticosteroid, in a denture paste or oral analgesic base and applied two to three times daily often results in remission and symptomatic relief.<sup>69</sup> Mixtures of diphenhydramine elixir and Kaopectate or Maalox have been

used successfully, as have a variety of medical mouthwashes (i.e., chlorhexidine [Peridex] antibacterial oral rinse). Patients with severe manifestations of RAS may respond to the oral corticosteroids (usually short course) colchicine, thalidomide, or dapsone. Multivitamin administration has not been demonstrated useful in reducing the frequency or duration of RAS episodes.<sup>70,71</sup>

### ACUTE NECROTIZING GINGIVITIS

Acute necrotizing gingivitis (acute necrotizing ulcerative gingivitis, trench mouth, Vincent stomatitis, Vincent angina) is a painful ulcerative disorder that chiefly affects adolescents and young adults. A related disorder termed *noma* (see Chapter 14) occurs when the infection spreads beyond the gingiva to involve other oral mucosal surfaces. Although acute necrotizing gingivitis was formerly common in schools and military establishments, it is quite rare in the United States and Western Hemisphere, perhaps owing to improved oral and dental care. The cause of acute necrotizing gingivitis is often a mix of bacterial pathogens, including *Fusobacterium*, *Prevotella*, *Actinomyces*, and *Bacteroides* species and spirochetes. The condition occurs most commonly in patients with predisposing conditions such as malnutrition, poor oral hygiene, ethanol or tobacco use, or immunosuppression.

Clinical findings consist of painful gingivae that bleed easily and an inflamed, eroded, hemorrhagic oropharynx. Ulcerations are most common at the gingival margins and interdental papillae. The ulcers are covered by a grayish-white slough or pseudomembrane that can be removed, leaving behind a raw bleeding surface. Single or multiple papillae may be involved, and the ulceration can be very extensive. Associated features include lymphadenopathy, pain, bleeding of the gums, fever, and a foul breath odor.<sup>72</sup> Treatment of acute necrotizing gingivitis consists of debridement by a dentist or periodontist and broad-spectrum antibiotic therapy, usually penicillin, clindamycin, or erythromycin. Chlorhexidine or saltwater oral rinses may help alleviate discomfort. Attention to good oral hygiene and nutritional rehabilitation (where indicated) are important steps in prevention.

## Warts

Warts (verrucae) are a common viral infection of the skin and mucosae caused by the human papillomavirus (HPV). These benign intraepidermal tumors most commonly occur in children and young adults, and their incidence has been estimated at 10%.<sup>73,74</sup> However, in a recent cross-sectional study of 1465 primary schoolchildren, 33% had warts, so this figure may be an underestimate.<sup>75</sup> Although harmless and often self-involving over years, warts are occasionally painful and may carry a negative social stigma. In addition, HPV may be associated with cutaneous and genital oncogenesis, particularly in immunosuppressed individuals.

There are four basic types of warts: verruca vulgaris, verruca plana, verruca plantaris, and condyloma acuminatum. Each of these will be discussed individually in the following sections. Most warts occur on the hands, fingers, elbows, and plantar surfaces of the feet. Patients with warts commonly autoinoculate themselves inadvertently with the subsequent appearance of multiple secondary lesions. A classic feature of cutaneous warts is that of koebnerization, whereby a linear constellation of lesions develops along the path of excoriation (Fig. 15-16).

HPV is transmitted via skin-to-skin contact or from fomites, where recently shed viruses may survive if the environment is warm and moist (i.e., locker room floors, pool decking, showers). The entry site is often an area of recent trauma or a skin region with subclinical abrasion or fissuring. Recently it has been shown that important environmental risk factors include having family members with warts and wart prevalence in classrooms, suggesting that preventive recommendations should perhaps focus on these sources more than public places.<sup>75,76</sup> The incubation period from inoculation to development of the wart may range from 1 to 6 months or more. Although the duration of warts is variable, one study documented that two-thirds of lesions resolve spontaneously within 2 years.<sup>77</sup> The most important mechanism in wart regression appears to be cell-mediated immunity, with cytokines released by keratinocytes or immune-system cells and inducing an immune response against HPV.<sup>78</sup>



**Figure 15-16** Warts with koebnerization. Multiple small, verrucous papules with a linear clustering (Koebner phenomenon) were present on this child's forehead.

Over 130 HPV types comprise this family of small double-stranded DNA viruses, and the various HPV types have been divided into two groups: cutaneous and mucosal.<sup>79,80</sup> Mucosal types are recovered mainly in the genital tract, although other mucosae may be infected, including the respiratory tract, nose, conjunctiva, and mouth. Although the same HPV virus can cause various types of warts, there is often a correlation between the virus type and the clinical/morphologic characteristics of the lesions it causes. For instance, HPV types 1, 2, 4, and 7 are often associated with common warts (verrucae vulgaris); type 1 with deep palmar and plantar warts; types 3, 10, 28, and 41 with flat warts; types 5, 8, 17, and 20 (among others) with the autosomal recessive disorder epidermodysplasia verruciformis (EV) (see later); and types 6 and 11 with respiratory, conjunctival, and genital infection.<sup>79</sup> In addition, HPV types associated with a high risk for cervical cancer include 16, 18, 31, 33, 35, 39, and 45, among others. HPV types 16 and 18 are the most common high-risk types found in the female anogenital system and are seen in up to 70% of women with cervical cancer. In a study of HPV types and their relationships to patient characteristics, the most distinct clinical profile was noted with HPV 1, which was associated with infection in children younger than 12 years of age, plantar location, a duration of less than 6 months, and patients with fewer warts.<sup>81</sup> Laboratory diagnosis of HPV skin infection is usually unnecessary, and the diagnosis usually straightforward. In instances where identification of the HPV type is necessary, options include nuclear-acid hybridization assays via Southern blotting, dot blots, RNA and DNA probes, and PCR studies. HPV genotyping on swabs of the overlying skin using a novel PCR assay was shown to be a simple and highly sensitive approach to typing.<sup>82</sup>

### VERRUCAE VULGARIS

Verrucae vulgaris (common warts) occur predominantly on the dorsal surface of the hands or periungual regions but may be seen anywhere on the cutaneous surface. Occasionally they may also occur on the oral mucosa. Common warts may occur as single or multiple lesions. They clinically present as flesh-colored, verrucous (rough surfaced) papules that may be dome-shaped (Fig. 15-17), exophytic (Fig. 15-18), or filiform (i.e., having a stalk; Fig. 15-19). Individual lesions may coalesce into larger plaques (Fig. 15-20). "Ring warts" may occur after overly aggressive therapies and are another example of koebnerization (Fig. 15-21). Oral lesions present as small, pink-white, soft papules and plaques of the labial, lingual (Fig. 15-22), buccal, or gingival mucosa. In Heck disease, multiple verrucous papules occur in a similar mucosal distribution (Fig. 15-23).

Periungual and subungual verrucae (Figs. 15-24 and 15-25) occur around and beneath nailbeds, particularly on the fingers of cuticle pickers and nail biters. These lesions, because of their location and susceptibility to trauma, often become irritated, infected, or tender



**Figure 15-17** Common warts. A dome-shaped lesion of the lateral nose and a filiform lesion of the columella.



**Figure 15-18** Common wart. This lesion demonstrates the exophytic type of *verruca vulgaris*.



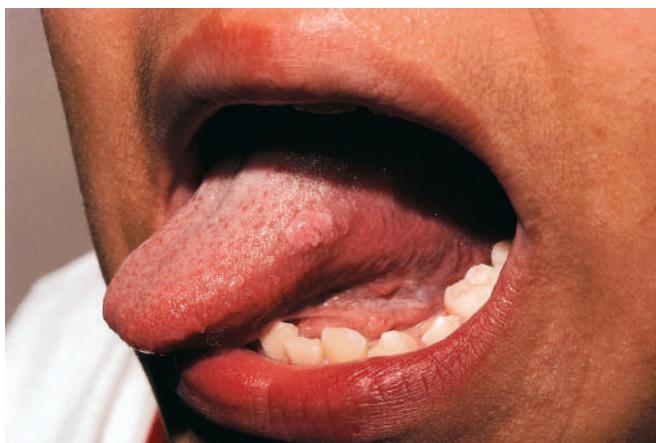
**Figure 15-19** Common wart. This lesion has a stalk, and is termed a filiform wart.



**Figure 15-20** Common warts. Multiple lesions coalesce into a mosaic plaque on the plantar surface.



**Figure 15-21** Ring warts. This annular plaque composed of small verrucous papules developed after a marked blister response to therapy of a single wart above the upper lip.



**Figure 15-22** Common warts affecting mucosa. This tongue lesion presented as a soft, verrucous papule.



**Figure 15-23** Heck disease. Multiple soft, pink verrucous papules of the inner lip mucosa.



**Figure 15-26** Wart with thrombosed capillaries. Note the multiple black dots within this large mosaic plantar wart.



**Figure 15-24** Periungual warts. Verrucous papules of the lateral nail-fold. Note adjacent subungual hemorrhage.



**Figure 15-27** Flat warts. Flat, verrucous papules.



**Figure 15-25** Subungual warts. Verrucous papules of the distal thumb and index finger with extension under the nail plate.



**Figure 15-28** Flat warts. Multiple disseminated flat papules in a patient infected with human immunodeficiency virus (HIV).

and are often more resistant to therapy. Satellite lesions may appear, particularly near warts that have been irritated, manipulated, or incompletely treated. When the diagnosis of *verruca* is in doubt, gentle paring with a number 15 scalpel blade will reveal characteristic punctate black dots that represent thrombosed capillaries (Fig. 15-26).

### VERRUCAE PLANA

*Verrucae plana* (flat warts) occur primarily on the face, neck, arms, and legs. They are usually seen as smooth, flesh-colored to slightly pink or brown, flat-topped papules measuring 2 to 5 mm in diameter (see Fig. 15-16; Figs. 15-27 and 15-28). They vary from a few lesions



**Figure 15-29** Flat warts with koebnerization. Flat papules on the forehead, with a linear configuration (Koebner phenomenon) at sites of autoinoculation.



**Figure 15-30** Plantar warts. Verrucous papules on the plantar surfaces.

to several hundred in any given individual. They may appear in the bearded areas of men and on the legs of women, because irritation from shaving tends to cause their spread. Contiguous warts may coalesce to form larger, plaque-like lesions. Again, linear arrangements of the papules in areas of scratching (koebnerization) are characteristic (see Fig. 15-16; Fig. 15-29).

#### VERRUCAE PLANTARIS

Verrucae plantaris (plantar warts) occur on the plantar surfaces of the feet and tend to be the most symptomatic type of warts as well as a therapeutic challenge. They usually occur on the weight-bearing areas of the heels, toes, and midmetatarsal areas (Fig. 15-30). Because of the pressure of walking, the lesions often develop an endophytic component and are very painful and tender. Coalescence of multiple lesions may result in mosaic warts (Fig. 15-31). It may occasionally be difficult to differentiate plantar warts from corns or calluses. Corns are localized hyperkeratoses that form over interphalangeal joints as the result of intermittent pressure and friction. Penetrating corns often appear at the base of the second or third metatarsal-phalangeal



**Figure 15-31** Plantar warts, mosaic. Multiple verrucous papules coalesced into this giant, painful verrucous plaque.



**Figure 15-32** Condylomata acuminata. Verrucous, brown papules in a perianal distribution.

joint. They can be distinguished from plantar warts by the lack of thrombosed capillaries after paring and by their characteristic hard core. Soft corns are macerated hyperkeratotic lesions that persist at points of friction and pressure in intertriginous areas. They are usually seen on the lateral aspect of the toes or in the web spaces between the fourth and fifth toes.

Black heel (talon noir, calcaneal petechiae) is a common condition that is often confused with plantar warts. In this disorder, superficial dermal capillaries are ruptured by the shearing action associated with sudden stops in athletic individuals, usually tennis, racquetball, or basketball players. Clinically it is characterized by clusters of brown or blue-black pinpoint petechial macules in the horny layer along the backs or sides of the heels or lateral edges of the feet. Gentle paring of the surface with a number 15 scalpel blade can help differentiate this condition from malignant melanoma, calluses, corns, and plantar warts.

#### CONDYLOMATA ACUMINATA

Condylomata acuminata (anogenital warts, anogenital HPV) are HPV-induced lesions of the anogenital tract and one of the most common STDs. The diagnosis of condylomata acuminata in a child is fraught with anxiety for parents and practitioners alike, and the implications regarding sexual abuse versus benign transmission are controversial and often unclear. Although condylomata often occur after sexual contact, other modes of acquiring the infection include vertical (perinatal) transmission, benign (nonsexual) heteroinoculation, and autoinoculation. In addition, fomite spread is another potential mode of transmission.<sup>83</sup>

Condylomata acuminata present most commonly in the perianal area as flesh-colored, soft, verrucous papules (Fig. 15-32) measuring 1 to 5 mm in diameter. The lesions are usually multiple, and "mirror image" lesions may be noted on each side of the anus. Other areas of involvement include the glans penis, penile shaft, scrotum, and vulva. Vaginal and cervical involvement are appreciable only with internal



**Figure 15-33** Condylomata acuminata. Verrucous papules of the labial surfaces, with a large, vegetative lesion protruding from the vagina. This toddler had been sexually abused.



**Figure 15-34** Infantile perianal pyramidal protrusion. Pyramidal-shaped, fleshy papule of the midline raphe.

examination. Occasionally, lesions may enlarge rapidly and present as large, exophytic, cauliflower-like masses (Fig. 15-33). Childhood condylomata are usually incidentally noted during diaper changes, toileting, bathing, or physical examinations.<sup>84</sup> The lesions are usually asymptomatic, but irritation, bleeding, and pain may occur. The differential diagnosis of condylomata acuminata includes MC, epidermal nevus, skin tag, and pseudoverrucous papules and nodules. Infantile perianal pyramidal protrusion is a pyramid-shaped, flesh-colored to pink soft-tissue swelling (Fig. 15-34) that appears in the medial raphe of girls and may represent a peculiar form of lichen sclerosus et atrophicus.<sup>85,86</sup> The distribution, appearance, and solitary nature of this lesion should distinguish it from condylomata.

The diagnosis of condylomata acuminata in a child should prompt consideration for the possibility of sexual abuse. In one large study of children with evidence of child sexual abuse, genital HPV infection was present in 13.7%.<sup>87</sup> However, it should be remembered that anogenital warts occur in large numbers of children as a result of innocent (nonsexual) or vertical transmission or from autoinoculation. Although HPV DNA typing is occasionally considered, it does not help in the differentiation between the various modes of transmission.<sup>83,84</sup> Although innocent autoinoculation or heteroinoculation from hand warts is common, and the finding of such hand lesions in an adult contact or caretaker might be reassuring, fondling is a form of sexual abuse commonly seen in younger children and thus the possibility of sexual abuse must still be considered.<sup>88</sup>

**Table 15-3** Findings in a Child with Condylomata that Should Prompt Referral to Child Protective Services

Finding	Comment
Abuse suspected by parent(s)	Includes history of access to the child by a known sexual offender
Abuse disclosed by child	If child appropriately aged for interview (usually 3 to 4 years)
Child's behaviors suggestive	Includes nightmares, advanced sexual knowledge for age, acting out sexually with peers
Suggestive physical examination	Acute or chronic trauma (petechiae, bruising to the hymen, anal tears, absent hymen, anogenital scarring)
Findings of other sexually transmitted infection	May include gonorrhea, <i>Chlamydia</i> , <i>Trichomonas</i> , human immunodeficiency virus, hepatitis B and C, syphilis
Child older than 4 years	Some experts recommend routine referral

Modified from Sinclair KA, Woods CR, Sinal SH. Venereal warts in children. *Pediatr Rev* 2011;32(3):115–21.

When a child is diagnosed with anogenital condylomata, a directed history should include the age of onset, history of maternal infection (genital warts or abnormal Papanicolaou [Pap] smear), and personal or family history of warts, as well as inquiries about the child's social environment and all caregivers.<sup>88</sup> Physical examination should be focused on findings suggestive of sexual abuse, and laboratory evaluation for other STDs should be performed if noninnocent HPV transmission is suggested. A behavioral and social assessment by a skilled professional should be considered. A summary of findings that should prompt referral to child protective services is shown in Table 15-3. The literature contains significant disagreement with regard to the prevalence of sexual abuse in children with condylomata, with estimates ranging variably from 4% to 91%.<sup>84</sup> Although sexual transmission of HPV may occur at any age, the risk seems greater in children over 3 to 4 years of age.<sup>89,90</sup> The Committee on Child Abuse and Neglect of the American Academy of Pediatrics (AAP) considers the presence of anogenital warts in children “suspicious” and recommends reporting to a child protective agency.<sup>25</sup>

The authors' personal approach is to consider nonsexual transmission of HPV if the child is under 3 years of age; if lesions developed within the first year of life; if the patient has other nongenital warts; if warts are present in close contacts, especially genital warts (or history of abnormal Pap smear) in the mother; and when there are no findings to suggest sexual abuse. If there is any suspicion of sexual abuse, referral to child protective services is initiated. In patients in whom there is uncertainty or where the situation is ambiguous, a social worker from the protective-services team should be enlisted early on in the evaluation for a formal structured interview. Although the diagnosis of sexual abuse must never be missed, “reflexive reporting” to child welfare authorities should be avoided given the emotional devastation and destruction that may result. Practitioners need to balance the risk of missing a case of sexual abuse (if they do not report) against the decision to report the family, with the parents or caregivers potentially suffering false accusation and its ramifications, which in some cases may include losing parental custody.<sup>91</sup> If the practitioner evaluating the patient is uncomfortable in performing such an evaluation, referral should be made to a clinician with expertise for further evaluation.<sup>84</sup>

Treatment of condylomata acuminata in children (see the following section) is challenging for many reasons. In an interesting study of the natural history of these lesions in children, spontaneous resolution occurred in 54% of patients within 5 years of the diagnosis, suggesting that nonintervention is a reasonable initial approach to managing this condition.<sup>92</sup> Precise identification of the rate of spontaneous involution is challenging, however, because the majority of infected children receive some form of therapy.<sup>93</sup>

**Table 15-4** Treatments for Warts and Condylomata Acuminata in Children

Treatment	Comment
<b>WARTS</b>	
Watchful waiting	Especially appropriate in young children
Topical salicylic acid	Available OTC; may be more effective when combined with duct-tape occlusion
Cryotherapy	Both in-office and OTC available
Manual paring or filing	May minimize pain from plantar warts
Immunotherapy:	
Oral	Cimetidine; OL use (see text)
Topical	Imiquimod (home use; OL); SADBE, DCP
Laser therapy	Pulsed dye laser potentially useful; CO <sub>2</sub> laser useful but scarring may result
Photodynamic therapy	Rarely utilized in children
Injection therapy	<i>Candida</i> /mumps antigens, bleomycin, interferon; rarely utilized in children
Curettage, electrocautery	Rarely utilized in children
Topical retinoids	May be useful for flat warts; OL
Topical chemotherapy:	
5% 5-fluorouracil	OL use; may be useful for facial flat warts
2% 5-fluorouracil + 17% salicylic acid	Available OTC from compounding pharmacy; useful for plantar warts; applied nightly with tape occlusion
Antiviral therapy:	
Cidofovir	OL use; typically used IV to treat CMV retinitis in immunocompromised patients; has been compounded as 1% topical cream for refractory warts
<b>CONDYLOMATA</b>	
Watchful waiting	Especially appropriate in young children
Chemovescicants	Podophyllin, TCA, podofilox
Immunotherapy:	
Oral	Cimetidine; OL use (see text)
Topical	Imiquimod; OL if <12 years
Cryotherapy	
Sinecatechins	Green tea extracts; 15% ointment approved for anogenital warts ≥18 years
Laser therapy	Rarely used for this indication in children
Surgery	Rarely used for this indication in children

CMV, Cytomegalovirus; CO<sub>2</sub>, carbon dioxide; DCP, diphenylcyclopropenone; IV, intravenous; OL, off-label; OTC, over-the-counter; SADBE, squaric acid dibutylester; TCA, trichloroacetic acid.

### Treatment of Common Warts and Condylomata Acuminata

No specific antiviral therapy exists for HPV infections, and most wart treatments rely on destruction of the affected area of epidermal proliferation. Some newer methods of therapy are immunomodulatory in nature. Because spontaneous involution of warts may occur, watchful waiting is an appropriate consideration, especially in younger patients in whom destructive therapies are traumatic and poorly tolerated. When considering therapy for warts, every effort should be made to avoid overly aggressive or scarring therapies. **Table 15-4** lists some of the treatment options for common, plantar, and planar warts and for condylomata acuminata. Several are discussed here in more detail.

Patients and parents must be reminded that even with apparent “cures” of warts or condylomata, latent HPV infection in grossly normal appearing squamous epithelium beyond the areas of treatment may persist and results in a fairly high risk of recurrence.

Whether warts should be treated depends on the patient's and parents' desires and the nature of the lesions. Those patients with warts that are painful, extensive, enlarging, subject to trauma, or cosmetically objectionable are most likely to be interested in therapy. If treatment is to be given, it should be harmless to the child, and if a painful therapy is being utilized, the child should be old enough to consent to the therapy. Parents occasionally request painful therapies (i.e., cryotherapy) for young children; this decision should be made only after a thorough discussion of the therapy, the pain involved, and its risk-to-benefit ratio. It should be emphasized that some modalities used for the treatment of warts in adults are neither feasible nor desirable for the treatment of warts in children. The choice of therapy will depend on the age, personality, and developmental status of the patient and the number, size, and location of the lesions.

Salicylic acid is available commercially under a variety of brand names and generics. It comes as liquids, gels, plasters, and pads. Salicylic acid preparations are applied directly to the wart surface and may be left on continuously or overnight. An effective form of combination therapy is to apply a salicylic acid liquid to the wart(s) and after drying occurs (5 minutes) to occlude the surface with duct tape. This treatment is placed on at bedtime, and the duct tape is removed the next morning. With removal of the tape, gradual debridement of the wart is performed, and the application is repeated nightly until the warts have resolved. Salicylic-acid therapy may take from 2 to 12 weeks for complete wart resolution. A potential side effect of this therapy is maceration and irritation of the skin surrounding the wart. If this occurs, therapy should be held for 2 to 3 days to allow for resolution and then it is resumed. A compounded product of 17% salicylic acid and 2% 5-fluorouracil (Wart PEEL, NuCara Pharmacy, Coralville, IA) is available and quite effective when applied to plantar warts nightly under tape occlusion.

Cryotherapy is a highly effective therapy for warts, albeit one that is painful and that may be unacceptably traumatic for younger patients. The most effective cryogen appears to be liquid nitrogen, which has a vaporization temperature of -196° C.<sup>88</sup> Other agents such as dimethyl ether and propane (Histofreezer) and chlorodifluoromethane (Verruca-Freeze) achieve temperatures in the range of -40 to -80° C and appear to be less effective.<sup>94</sup> Liquid nitrogen is applied to the wart with a cotton-tipped applicator or via a spray gun, for 10 to 20 seconds. The number of applications per treatment session depends on multiple factors, including the size of the wart, its location, past responses, and the style of the physician. The goal is to induce blister formation above the dermal–epidermal junction without causing a deep ulcer or significant necrosis to surrounding tissue. Therapy is often repeated at 3- to 4-week intervals and may be more effective when preceded by gentle debridement of warty tissue with a number 15 scalpel blade. Cryotherapy may be extremely uncomfortable, and some children will not accept this mode of therapy. Although the child can be held down for the procedure, this is an undesirable approach in most instances, and alternative treatments should be considered. Several over-the-counter cryotherapy wart removal products (i.e., Wartner, Compound W Freeze Off, Dr Scholl's Freeze Away) are available and use the combination of dimethyl ether and propane to freeze to -57° C. The cryogen is delivered by a foam pad attached to an applicator, and held on the wart for 10 to 20 seconds.

Immunologic forms of wart therapy rely on the host immune system to mount a response against the HPV-induced lesions. Although these forms of therapy are not uniformly efficacious, they offer another option in the treatment of patients with warts. The most common form of oral immunotherapy is treatment with cimetidine, which is believed to possess immunomodulatory activity including the ability to inhibit suppressor T-cell function, activate T helper (Th) 1 cells, and stimulate production of IL-2 and interferon-γ.<sup>95,96</sup> In one study, 32 children with warts were treated with cimetidine, 25 to 40 mg/kg per day divided into three or four doses, with an 81% clearance rate after 2 months of treatment.<sup>95</sup> Other studies of cimetidine and warts have shown conflicting results.<sup>97–100</sup> When utilized, most experts recommend 30 to 40 mg/kg per day divided into twice daily doses. However, the treatment is usually well tolerated with few if any side effects, and when effective, recurrences are rare.

Imiquimod is a topical immune-response modifier approved for the treatment of genital and perianal warts in patients 12 years of age or

older. It is marketed in a 5% and 3.75% creams (Aldara and Zyclara, respectively) and is applied to those lesions thrice weekly (on nonconsecutive days) to daily. Imiquimod has its therapeutic effect via induction of interferon- $\alpha$  and other cytokines in the skin.<sup>101,102</sup> Studies have suggested that the off-label use of this agent with more frequent application schedules (once daily for 5 weeks to twice daily applications), may be useful in the treatment of common warts.<sup>103,104</sup>

Topical immunotherapy with squaric acid dibutylester (SADBE) is another option in the treatment of recalcitrant warts. Topical immunotherapy was initially described with dinitrochlorobenzene (DNCB) and subsequently with diphenylcyclopropenone (DCP). These agents are less desirable because of mutagenicity associated with the former and local side effects associated with the latter.<sup>105</sup> With SADBE immunotherapy, sensitization of (unaffected) skin is followed by the application of the solution to nonfacial warts. The therapy is painless and often effective, with complete clearance rates ranging from 58% to 84% in open-label studies.<sup>105–107</sup> Although in-office application has been traditionally utilized for topical immunotherapy, experience with at-home application of SADBE has demonstrated safety and high patient acceptance.<sup>105</sup>

Side effects of this treatment include allergic contact dermatitis (at either sensitization or treatment sites) and rarely urticaria. The hypothesized mechanism of action of this form of immunotherapy is generation of a delayed-type hypersensitivity reaction at the site of the wart and possibly a systemic antiviral effect, because even untreated lesions at distal sites may occasionally resolve.<sup>105</sup>

Pulsed-dye laser therapy is another option for the treatment of recalcitrant warts. This laser, which is most often utilized in the treatment of vascular birthmarks, works by selectively destroying the blood vessels found within warts.<sup>108</sup> This therapy has a large advantage over carbon-dioxide laser therapy in that it is nonscarring and the period of postoperative recovery is significantly shorter. Pulsed-dye laser therapy has been demonstrated to be quite effective in the treatment of warts including common, plantar, and periungual types.<sup>73,108,109</sup> Its use, however, is best limited to lesions that are recalcitrant and have failed other therapeutic modalities.

Flat warts may be treated with a variety of modalities, although their small size, common location on the face, and occurrence in groups make aggressive therapies impractical. Treatment options for these lesions include light cryotherapy, imiquimod, topical retinoids (i.e., tretinoin or adapalene cream), oral cimetidine, topical chemotherapy (i.e., 5-fluorouracil cream) or topical immunotherapy.

Therapies for condylomata acuminata have been poorly studied in children. As mentioned, a significant portion of anogenital warts in the pediatric population may spontaneously involute over several years, and thus watchful waiting is an appropriate consideration. When therapy is desired, a commonly used regimen is that of either podophyllin or trichloroacetic acid (or the two in combination), which are applied in the office. These agents cause cytotoxic effects with resultant necrosis of the affected cells, and their use may be limited by local irritation. Podofilox solution or gel (Condylx) is a closely related compound marketed for application in the home setting. Podofilox, which is approved for use in adult patients, is applied twice daily for three consecutive days, although more limited regimens (i.e., once daily) are often recommended for children to try and avoid local irritation. Self-treatment with podofilox has shown greater efficacy and cost-effectiveness than office therapy with podophyllin.<sup>110</sup> Imiquimod, applied three times weekly on nonconsecutive days, is another option that has been demonstrated effective in the treatment of external genital and perianal warts.<sup>111</sup> This treatment is also occasionally limited by local irritation. Other treatments used occasionally for condylomata acuminata include cryotherapy, laser therapy,<sup>112,113</sup> oral cimetidine, topical immunotherapy,<sup>114</sup> 5-fluorouracil cream, and surgical ablation. The pain of cryotherapy often precludes its use for warts in this location for children.

Prevention of anogenital HPV infection is the goal of HPV vaccination. Two vaccines are available in the United States, including a quadrivalent (types 6, 11, 16, and 18; Gardasil, Merck & Co) vaccine initially approved for use in females 9 to 26 years of age and a bivalent (types 16 and 18; Cervarix, GlaxoSmithKline) vaccine initially approved for use in females 10 to 25 years of age.<sup>115</sup> These vaccines have subsequently been demonstrated useful in preventing related

cervical precancerous lesions in females, anal precancerous lesions in males, and genital warts in both males and females.<sup>116</sup> The current recommendation of the AAP and the Advisory Committee on Immunization Practices is for routine immunization (with either vaccine) of females 11 or 12 years of age and those 13 to 26 years of age not previously immunized. The quadrivalent vaccine is also recommended for routine immunization of males 11 or 12 years of age and those 13 to 21 years of age not previously immunized.<sup>117</sup> Vaccination is also recommended for men who have sex with men and those who are immunocompromised through 26 years of age.<sup>115</sup> It is important to emphasize that these vaccines do not provide benefit for established HPV infections, and they are most effective when administered before the first sexual contact.<sup>118</sup>

## EPIDERMODYSPLASIA VERRUCIFORMIS

EV is a rare autosomal recessive disorder characterized by a genetically determined susceptibility to widespread and persistent infection of the skin with specific HPV types.<sup>119</sup> Infections begin in early childhood, and malignant transformation (nonmelanoma skin cancer) occurs in approximately half of patients during adulthood. The predisposition to HPV infection is believed to be the result of an immunogenetic defect associated with generation of cytokines, which downregulate cell-mediated immunity, and possibly with low levels of IL-10.<sup>120</sup> The role of environmental factors (most notably UV irradiation) also appears to be important in the pathogenesis of the HPV-associated malignancies.<sup>121</sup> EV has been found to be caused by inactivating mutations in two adjacent, related genes, EVER1/TMC6 and EVER2/TMC8. These genes encode transmembrane proteins located in the endoplasmic reticulum.<sup>122,123</sup> EV may represent a primary deficiency of intrinsic immunity to the EV-specific HPVs ( $\beta$ -papillomaviruses), in innate immunity, or in both.<sup>123</sup> There is also an acquired form of EV, which has been rarely reported, usually in the setting of HIV infection or other forms of immunosuppression.<sup>124–126</sup>

Patients with EV seek treatment during childhood with widespread tinea versicolor-like, hypopigmented macules and/or flat verruca plana-like papules. These papules are red to red-brown and may coalesce into larger plaques. The most common locations for the warty lesions are the hands, extremities, and the face, whereas the tinea versicolor-like lesions occur predominantly on the trunk.<sup>121</sup> When skin malignancy (usually squamous cell carcinoma) develops during adulthood, it is most often at sun-exposed sites, and these tumors are most often associated with HPV types 5 and 8. There is no specific therapy for EV. Protection from UV radiation with protective clothing and sunscreens and sun avoidance are vital. Close clinical surveillance for squamous cell carcinoma is recommended, with early surgical excision as needed. Experimental therapies have included interferon, imiquimod, cimetidine, photodynamic therapy, and systemic retinoids.<sup>121,127</sup>

## RECURRENT RESPIRATORY PAPILLOMATOSIS

Recurrent respiratory papillomatosis (RRP; laryngeal papillomatosis) is a disorder of HPV-associated benign tumors of the larynx and at times other portions of the aerodigestive tract. RRP is the most common benign neoplasm of the larynx in children and is usually caused by HPV types 6 and 11, which are both common genital-tract HPV types.<sup>128</sup> Although the exact method of HPV acquisition in patients with RRP is not well established, it is most likely caused by maternal-fetal transmission (ascending *in utero* infection or direct contact in the birth canal), and less likely via postnatal acquisition.<sup>129,130</sup> However, even given the potential links among cervical HPV, vaginal delivery, and RRP, the utility of elective cesarean sections in mothers with genital-tract HPV infection as a preventive measure remains controversial.<sup>130–132</sup> A maternal history of condylomas during pregnancy appears to be a risk factor for more severe RRP.<sup>133</sup> Fortunately, very few children overall who are exposed to genital HPV at birth develop symptoms of RRP.

Although the tumors of RRP are benign, significant morbidity may result from obstruction of the airway and potential malignant degeneration. RRP is usually diagnosed before the age of 5 years, and the clinical presentation often includes the triad of stridor, progressive

hoarseness, and respiratory distress.<sup>128</sup> Other symptoms may include dyspnea, chronic cough, recurrent upper respiratory infections, pneumonia, dysphagia and failure to thrive.<sup>134</sup> Patients may be initially diagnosed with asthma, croup, or bronchitis. In some, the condition may go undiagnosed until frank respiratory distress develops with the resultant need for emergent tracheotomy. The condition is diagnosed with direct airway endoscopy, and the mainstay of therapy for RRP is surgery or laser therapy. Adjuvant treatments include interferon, photodynamic therapy, and antiviral therapy. Intralesional cidofovir in combination with surgery has been advocated as an effective therapeutic combination, although efficacy has been questioned by some, and weight-based dosing limits are recommended.<sup>135–138</sup> It also appears that aggressive control of gastroesophageal reflux disease, when present, is vital, because it may contribute to the severity of RRP.<sup>128,139</sup>

## Molluscum Contagiosum

MC is a common cutaneous viral infection in children caused by a member of the poxvirus family (*Molluscum contagiosum* virus, or MCV). Although MC is often an STD or associated with immunodeficiency (especially HIV infection) in adults, childhood disease tends to lack these associations. There has been a dramatic increase in MC over recent decades in the United States, with an 11-fold increase in patient visits for the disorder reported for one 18-year period.<sup>140</sup> In children, the infection is also becoming more prevalent, because the spread of virus through skin-to-skin contact and fomites is rapid and easy. MC occurs most often in school-aged children and especially those under 8 years of age. Although controversy still exists, epidemiologic data suggest that MC may be transmitted via swimming pools as well as via fomites such as sponges and towels and in beauty parlors.<sup>141–144</sup>

Autoinoculation of the virus is a common mode of spread in affected patients. MC lesions tend to spread more rapidly in children with atopic dermatitis, possibly related to suppressed Th-cell responses. Congenital MC have been reported and likely represents vertical transmission of MCV.<sup>145</sup>

MC presents as pearly, flesh-colored to pink papules that often appear translucent (Figs. 15-35 through 15-37). The range in size is from 2 to 8 mm. A small central dell or depression may or may not be evident, and occasionally excrescences protrude from this central region (Fig. 15-38). Although single lesions may occur, MC most often presents with numerous clustered papules, and linear configurations (from koebnerization) may be present (Fig. 15-39). Although MC lesions may occur on any area of the skin surface, they are most common in areas of skin rubbing or moist regions, including the axillae, popliteal fossae, and groin. Genital and perianal lesions are also common, even in children, in whom the disorder is nearly always transmitted in a benign (nonsexual) fashion. Lesions may develop significant erythema (Fig. 15-40), which usually represents a host immune response against MCV and often heralds spontaneous involution. Occasionally, childhood MC may be marked by very high numbers



**Figure 15-35** Molluscum contagiosum. Solitary, dome-shaped pearly papule. Note the capped white plug.



**Figure 15-36** Molluscum contagiosum. Multiple pearly, translucent papules in the popliteal fossa. Note erythema and flattening of some lesions, representing the host immune response and early involution.



**Figure 15-37** Molluscum contagiosum. Pearly, umbilicated papules around the knee.



**Figure 15-38** Molluscum contagiosum. This solitary lesion with surrounding dermatitis demonstrates the central excrescence that may be present in some mollusca.



**Figure 15-39** Molluscum contagiosum with koebnerization. Linear configuration of lesions along a line of autoinoculation.



**Figure 15-41** Molluscum contagiosum in an immunocompromised host. This young boy receiving cancer chemotherapy had disseminated mollusca contagiosa, including multiple recalcitrant lesions in the groin.



**Figure 15-40** Molluscum contagiosum with host immune response. The bright red appearance of several of the lesions is typical once an immune response is being mounted by the host. The inflamed lesions usually resolve over 2 to 3 weeks.



**Figure 15-42** Giant molluscum contagiosum. These two nodular plaques of the scalp turned out to be giant molluscum lesions. This pattern of presentation may be confused with other causes of cutaneous pseudolymphoma (see Chapter 10).

of lesions (Fig. 15-41) or a giant size (Fig. 15-42). The latter may occasionally be confused with cutaneous pseudolymphoma (see Chapter 10), although MC is also considered to be one potential cause of pseudolymphomatous skin infiltration (and may be associated with CD30-positive lymphoid infiltrates).<sup>146</sup>

Surrounding dermatitis around MC lesions (“molluscum dermatitis”) is common (Fig. 15-43), is considered one form of an id reaction, and may be misdiagnosed as eczema.<sup>147</sup> Importantly the presence of molluscum dermatitis, if untreated, may propagate the cycle of infection when the patient scratches and subsequently autoinoculates the virus onto other regions. Complications of MC are rare but include secondary bacterial infection (Fig. 15-44), which is often secondary to scratching-induced impetiginization. In some patients with eyelid lesions, chronic conjunctivitis or superficial punctate keratitis may develop. Gianotti-Crosti syndrome-like reactions have been observed in some patients with MC and present with an eruption of monomorphic papules on the extensor extremities primarily and occasionally on the face, buttocks, or trunk. When this pattern presents, the papules are distinct from the underlying molluscum lesions (Fig. 15-45).<sup>148</sup>

Spontaneous clearing of MC often occurs over years, but parents and patients may request therapy for several reasons. These include the cosmetic significance of the lesions, pruritus, and epidemiologic concerns of other parents, teachers, or school nurses. In addition, in

patients with an underlying atopic diathesis, the lesions may be more extensive and autoinoculation more significant given the extensive pruritus. Traditional therapies (and those utilized in adults), such as curettage or cryotherapy, rely on destructive measures and may be traumatic for pediatric patients. Although curettage is not a preferred method of the authors, the pain of the procedure may be reduced by pretreatment of the lesional areas with topical anesthetic (lidocaine or lidocaine/prilocaine) cream. Care must be exercised, however, given reports of the latter (lidocaine/prilocaine, eutectic mixture of local anesthetics [EMLA]) cream in association with adverse events including methemoglobinemia, hypoxemia, and seizures.<sup>149,150</sup> In these reports, however, the topical anesthetic had been applied in excess of the recommended use. The maximum dose and application area recommendations suggested by the manufacturer of EMLA cream are listed in Table 15-5.

A highly effective and well-tolerated therapy for MC is the in-office application of cantharidin. Cantharidin is an extract from the blister beetle, *Cantharis vesicatoria*, and is known to induce vesication of the epidermis upon application to human skin.<sup>151</sup> Although concerns regarding the safety of cantharidin therapy have tempered its use for some, with appropriate application and patient education it is usually very well tolerated and effective.<sup>151–153</sup> Among pediatric dermatologists surveyed, 92% reported satisfaction with cantharidin’s efficacy in treating MC.<sup>154</sup> Although a prospective, blinded, placebo-controlled



**Figure 15-43** Molluscum contagiosum with molluscum dermatitis. Note the intensely erythematous, scaly plaque surrounding multiple mollusca in the antecubital fossa.



**Figure 15-44** Molluscum contagiosum with secondary bacterial infection. This patient with mollusca developed an associated dermatitis and eventual secondary infection with *Staphylococcus aureus*.

study of cantharidin did not demonstrate superiority of cantharidin over placebo during a 2-month observation period,<sup>155</sup> favorable results are often noted clinically, and this therapy continues to be a top choice for practitioners who treat these lesions.

A concentration of 0.7% or 0.9% cantharidin is usually used, and guidelines for the safe and effective use of this agent for treatment of MC are listed in Box 15-1. Treatment results in blister formation within 24 to 48 hours, with healing over several days to 1 week. The extent of blistering is minimized by having the patient (or parent) rinse treated areas after a specified time after application, usually 2 to 6 hours.<sup>153</sup> Treatment of perioral or periocular facial lesions, mucosal



**Figure 15-45** Molluscum contagiosum and Gianotti–Crosti syndrome-like reaction. This 2-year-old boy had numerous lesions of molluscum, several of which were becoming inflamed (**A**) in conjunction with monomorphic papules on the extensor surfaces of the upper (**B**) and lower (**C**) extremities, suggestive of Gianotti–Crosti syndrome.

sites, or occluded areas (i.e., diaper region) with this agent is not generally recommended. Cantharidin should be applied in the office only and by a physician or other qualified and well-trained health professional and should never be dispensed for home application.<sup>156</sup> If molluscum dermatitis is present, it should be cleared by use of a topical corticosteroid ointment before commencing with cantharidin therapy. Access to cantharidin is difficult in some regions of the United States given recent critical reevaluation of pharmacy-compounding practices by the US Food and Drug Administration. When available, however, cantharidin is considered by many practitioners to be a first-line treatment for this common condition.

**Table 15-5** Maximum Recommended EMLA Dose and Application Areas

Age and Body Weight*	Maximum Total Dose of EMLA (g)	Maximum Application Area (cm <sup>2</sup> )	Maximum Application Time (h)
0–3 months or <5 kg	1	10	1
3–12 months and >5 kg	2	20	4
1–6 years and >10 kg	10	100	4
7–12 years and >20 kg	20	200	4

EMLA, Eutectic mixture of local anesthetics, lidocaine/prilocaine.

\*If patient is older than 3 months of age and does not meet minimum weight requirement, the maximum total dose of EMLA should be based on the patient's weight.

### Box 15-1 Guidelines for Treatment of Molluscum Contagiosum with Cantharidin

Patient and parent education (handouts useful)

Avoid treating lesions in the following sites:<sup>\*</sup>

- Facial
- Mucosal
- Occluded

Treat 20 to 30 lesions maximum per treatment session

Application of cantharidin (0.7% or 0.9%):

- Vigorously shake bottle several times before opening to ensure even dispersal of cantharidin crystals within collodion base
- Use applicator stick or blunt (wooden) end of cotton-tipped applicator
- Apply single small droplet (sufficient to cover lesion) to each molluscum
- Avoid "painting"
- Let area dry for 3 to 5 minutes before patient gets dressed
- Do not occlude treated sites
- Treat initial lesion in a location that can be easily visualized by patient (to calm anxiety about the therapy)
- Have patient bathe/rinse off all treated sites in 2 to 6 hours (may vary based on past response; 4 hours good starting point with first treatment; may rinse sooner if significant discomfort or if vesiculation is noted)
- Acetaminophen or ibuprofen may be administered by parent, if needed, for pain
- Bacitracin ointment applied to blisters twice daily until areas heal
- Therapy repeated at 3- to 4-week intervals as needed

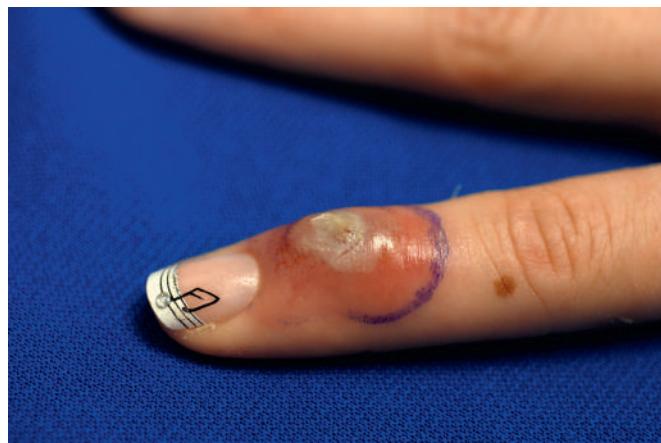
\*Treatment of facial (but not periorbital) lesions can be considered on a case-by-case basis once the patient's initial response to cantharidin application has been assessed.

Other methods of therapy that have been reported for MC include imiquimod cream, topical tretinoin cream, salicylic acid,  $\alpha$ -hydroxy acids, tape stripping, pulsed-dye laser therapy, 5% potassium hydroxide, topical cidofovir, oral cimetidine, and silver nitrate paste.<sup>103,141,151,157–166</sup>

Imiquimod cream has been used off-label with different treatment regimens, from three times weekly to application on a daily basis, with variable results. Two unpublished randomized controlled trials failed to show superiority of imiquimod over vehicle, although some smaller trials and observational studies have suggested potential efficacy.<sup>167</sup> Topical tretinoin cream is a commonly used method (also off-label) for treating facial MC, although its use may be limited by its irritation potential.

## Cowpox and Pseudocowpox

Cowpox is a rare zoonotic infection caused by a DNA orthopoxvirus that is similar to the vaccinia and smallpox viruses. It is transmitted by contact with infected animals, which may include cattle (from whom it may be transmitted as an occupational infection) and wild



**Figure 15-46** Orf. An inflammatory nodule with superficial vesiculation and oozing on the distal index finger of a 16-year-old female. She had been bitten by a goat 3 weeks before while visiting a petting zoo.

rodents, which serve as its natural reservoir.<sup>168</sup> After an incubation period of 1 to 3 weeks, a localized crusted nodule with ulceration or vesiculation forms and evolves through several stages to ultimately heal with a scar over several weeks. Flu-like symptoms may occasionally be present, and lymphadenopathy is common. Immunocompromised hosts may develop severe generalized infection. Although there is no accepted standard for therapy, cidofovir and some novel antiviral agents have been studied for patients with severe involvement, and measures to prevent secondary bacterial infection (i.e., wound care, topical and oral antibiotics) are recommended.<sup>168</sup>

Pseudocowpox (milker's nodule, paravaccinia) is a parapox virus infection seen worldwide and usually occurring in dairy farmers and new milkers. The infection is acquired from contact with the teats of cattle infected with the virus, and children may occasionally acquire it. Clinically, pseudocowpox is characterized by a single or several papules on the hands or fingers that progress through several stages: a macular or papular lesion becomes a vesicular lesion; then subsequently it progresses to a nodular stage with weeping; then it moves to a papillomatous or verrucous (warty) stage; and finally a dry crust develops, and healing occurs over 4 to 8 weeks. Typically, no scarring results. Secondary bacterial infection may occur in some patients. Occasionally, an erythema multiforme-like secondary eruption may occur.<sup>169</sup> Treatment is similar to that discussed for cowpox.

The diagnosis of cowpox or pseudocowpox is usually made by the combination of the history of exposure and clinical examination. The differential diagnosis may include herpetic whitlow or other poxvirus infections (i.e., orf). If confirmation of the diagnosis is necessary, virus isolation and serologic studies may be useful. In addition, light or electron microscopic examination of skin biopsy tissue is useful, the latter showing characteristic brick-shaped viral particles.<sup>168,170</sup>

## Orf

Orf (ecthyma contagiosum, contagious ecthyma) is another parapox virus infection that normally infects sheep and goats (scabby mouth, sore mouth, contagious pustular dermatosis) and occasionally humans. Transmission is via contact with infected lesions in animals or fomites, including barn doors, fences, troughs, and shears.<sup>170</sup> More recently, human orf has been associated with household meat processing and animal slaughter, often in the setting of ethnic religious celebrations.<sup>171</sup> Clinically, orf usually presents with a solitary lesion (Fig. 15-46), although several lesions may be present. The onset usually follows a 3- to 7-day incubation period after exposure. The clinical stages of the skin lesions are identical to those described previously for cowpox and pseudocowpox. Associations include secondary bacterial infection, lymphadenopathy, lymphangitis, erythema multiforme-like eruptions, and recurrences in immunocompromised hosts.<sup>172,173</sup> Giant lesions of orf are occasionally reported.<sup>174</sup>



**Figure 15-47** Smallpox. Multiple, tense pustules of the face in a patient from Ghana with smallpox. (Courtesy of the CDC, Dr J Noble Jr.)

Diagnostic modalities are the same as those for discussed above, and in addition, a PCR method for diagnosis has been described<sup>175</sup> (see **Cowpox and Pseudocowpox** section) and is available through the Centers for Disease Control and Prevention (CDC) or state health departments. Treatment is supportive, and the lesions involute spontaneously over 4 to 8 weeks without scarring. Antibiotics should be given if secondary bacterial infection is present.

## Smallpox

Smallpox (variola major) is an exanthematous disease but is included here with other poxvirus infections. The last case of endemic smallpox occurred in Somalia in 1977, and the disease was declared eradicated in 1980.<sup>176</sup> Variola virus, the etiologic agent of smallpox, has been maintained since that time in two high-security laboratories, the CDC in Atlanta and the Vektor Institute in Novosibirsk, Russia. However, concerns that some virus may exist outside of these laboratories and that it could potentially be used for a widespread bioterrorism attack remain. Routine vaccination for smallpox ended after the eradication declaration in 1980, and as such, a large population of susceptible persons now exists. The remaining protection of individuals who have received vaccination is unclear.

Smallpox begins with entry of the virus from respiratory droplets via the respiratory tract. It then travels to regional lymph nodes, where replication occurs. Viremia develops, and after an incubation period of 7 to 17 days, symptoms develop. These include high fever, malaise, severe headache, and backache. The temperature may be as high as 40°C. An enanthem precedes the exanthem and presents as erythematous macules on the oral mucosae, including the palate, tongue, and pharynx. The characteristic exanthem begins 1 to 2 days later with erythematous macules that progress to papules, then vesicles, and eventually pustules (Fig. 15-47) over 4 to 7 days. All lesions tend to be in the same stage of development, which is a useful feature in distinguishing smallpox from varicella (see Chapter 16) (Table 15-6). Skin lesions begin on the face and extremities with subsequent spread to the rest of the body and eventual widespread involvement. Crusting then begins around day 8 or 9 and is followed by healing with scarring. Complications of smallpox include secondary bacterial infection (usually associated with a second fever spike during the exanthem phase), pneumonia, arthritis, encephalitis, and death. Mortality in the past was as high as 30%, although it would probably be lower in developed countries with the availability of modern-day medical

**Table 15-6** Distinguishing Features of Smallpox and Varicella

	Smallpox	Varicella
Prodrome	High fever, headache, backache, malaise	Mild fever, constitutional symptoms
Skin examination	Centrifugal distribution; pustules all in same stage of development; deep involvement	Central distribution; vesicles and crusted papules in different stages at one time; superficial
Scarring	Common; often severe	Occasional; usually mild (unless secondary bacterial infection)
Complications	Bacterial infection, pneumonia, arthritis, encephalitis, blindness, death	Bacterial infection; rarely pneumonia, encephalitis, arthritis

intervention. In survivors, blindness may occur because of viral keratitis or bacterial eye infection.

Variants of smallpox include hemorrhagic and malignant forms. In the hemorrhagic form, which is uniformly fatal, patients have high fever, abdominal pain, and then petechiae and hemorrhage of skin and mucous membranes.<sup>177</sup> The malignant form is similar but without progression of the rash from vesicles to pustules. Variola minor (alastrim) is a less severe variant of smallpox with fewer lesions and a milder course occurring in individuals with partial immunity.<sup>177</sup> These patients have a longer incubation period, milder prodrome, and lower mortality rate.<sup>178</sup>

Rapid diagnosis of smallpox is vital, because a single confirmed case could result in an international epidemic. State health officials should be contacted, and the tissue should be submitted to a Biological Safety Level 4 laboratory for processing.<sup>176</sup> The CDC should also be notified. Airborne and contact precautions should be strictly followed. Vesicular or pustular fluid, crusts (scabs), blood samples, and throat swabs should be collected as directed by regional or national health authorities. Methods for confirming the diagnosis of smallpox include cell culture, PCR, electron microscopy, serologies, and immunohistochemical stains. Collection of epidemiologic data is vital, and contacts must be identified so that a vaccine can be administered. The administration of a vaccine within 4 days of exposure may diminish the severity of the illness.

Therapy for smallpox consists first and foremost of isolation of the patient, who will remain infectious until approximately 10 days from the onset of the rash. Vaccination should be given, and meticulous skin and eye care, as well as hydration and nutrition support, is vital. No specific antiviral therapy exists for smallpox, although cidofovir has shown some benefit in the postexposure prevention of other poxvirus infections.<sup>179,180</sup>

The issue of smallpox vaccination has received much attention with the resurgence of interest in this disease. A vaccinia virus (*Orthopoxvirus vaccinia*) vaccine has been used to prevent infection with the smallpox virus. Concern about the variola virus potentially being used as a biological weapon has resulted in the United States and some other countries deciding to stockpile live vaccinia virus vaccine (ACAM2000) and to vaccinate military personnel. There is also an attenuated vaccine (IMVAMUNE) that has been investigated for individuals who cannot safely receive ACAM2000.<sup>181</sup> In light of world events in the twenty-first century, several groups of individuals have received smallpox vaccination, including physicians from the CDC and eligible first responders and healthcare workers. New production of a smallpox vaccine has again been initiated, this time in tissue-cell culture. The current recommended vaccination strategy is known as *ring vaccination* and also is referred to as surveillance and containment. In this strategy, if a single case of smallpox occurs, infected patients would be immediately isolated, and contacts would be identified and immunized by specially trained (and vaccinated) healthcare teams.



**Figure 15-48** Eczema vaccinatum. Extensive umbilicated papulopustules involving the chest and nipples of a 2-year-old hospitalized male. He had a history of atopic dermatitis and was exposed to vaccinia virus via household contact with a relative who had recently received the smallpox vaccination. (Courtesy of Sarah Stein, MD.)

Complications of smallpox vaccination include local vaccination-site reactions and more widespread reactions such as fever, generalized vaccinia, urticaria, erythema multiforme, encephalitis, and rarely death. Local reactions are common and include pustules at the vaccination site, bacterial superinfection, and lymphadenitis. In addition, pustular reactions at sites distant from the vaccination site occasionally occur from autoinoculation.

Eczema vaccinatum is a serious, potentially life-threatening side effect of smallpox vaccination occurring in individuals with atopic dermatitis or less commonly other skin disorders. It is caused by widespread dissemination of vaccinia and can occur in patients with either active or quiescent dermatitis.<sup>182</sup> The barrier disruption in these patients permits viral implantation with subsequent spreading from cell to cell and occasionally a viremic phase.<sup>183</sup> The lesions are similar in appearance to those associated with primary vaccination, but with extensive involvement they may become confluent (Fig. 15-48). Bacterial superinfection, shock, and death may occur, especially without the prompt administration of vaccinia immunoglobulin (VIG). Scarring is common. Because of the risks of eczema vaccinatum, individuals with atopic dermatitis should not receive elective vaccination if there is no risk of exposure to smallpox, and individuals who have regular contact with persons with atopic dermatitis should not receive vaccination unless they can avoid person-to-person contact until the scab separates from the vaccination site.<sup>183</sup> In addition to administration of VIG, patients with eczema vaccinatum may require treatment with cidofovir, ST-246, or other potent antivirals. Importantly, patients with eczema vaccinatum may shed large amounts of virus, and viable vaccinia virus may be present on inanimate objects in their environment, potentially causing inadvertent infection in other susceptible individuals exposed to those items.<sup>184</sup>

Childhood smallpox vaccination is a topic that has received considerable attention as part of the “pre-event” vaccination program. Of concern is the fact that children under the age of 5 years have historically had the highest rates of complications, especially for the most severe reactions.<sup>176</sup> In response to this and other data, the Advisory Committee on Immunization Practices does not recommend routine smallpox vaccination for children and adolescents younger than 18 years of age, and the Committee on Infectious Diseases of the AAP has strongly endorsed further vaccine development and testing in children as well as adults.<sup>178,185</sup>

## Acquired Immunodeficiency Syndrome in Children

Infection with HIV type 1 occurs worldwide in adults and children, with the majority of new pediatric cases occurring in children living

in sub-Saharan Africa (up to 2000 new cases per day). The number of children with AIDS is decreasing in the United States, owing to better prevention of perinatal transmission and the availability of effective therapies.<sup>186</sup> HIV-1 is an RNA retrovirus that infects CD4+ T lymphocytes as well as other cells of the immune system. With the subsequent depletion of CD4+ T cells, progressive immunocompromise occurs, leaving the patient at risk for a wide variety of infections, inflammatory conditions, and malignancies. AIDS is diagnosed when an infected patient has an opportunistic or other unusual or persistent infection as well as a CD4+ T cell count lower than 200 cells/ $\mu$ mL.

More than 90% of infant and childhood HIV-1 infections in the United States are the result of perinatal (mother-to-child) transmission. The remaining children acquire the infection from blood-product exposure, sexual abuse, or unknown sources. It is estimated that in the absence of antiretroviral therapy, approximately 30% of women infected with HIV-1 transmit the virus to their infants.<sup>187</sup> This can occur *in utero*, during delivery, or via breastfeeding after delivery. Maternal plasma viral load is one of the strongest predictors of perinatal transmission.<sup>188</sup> Infection with HSV type 2 or other STDs resulting in cervical or vaginal ulcers also increases the risk of transmission.<sup>189</sup> When infants acquire the infection via breastfeeding, it tends to occur within the first several months of life.<sup>190</sup> Formula feeding, therefore, is a desirable choice in this setting. The availability of treatments and the global commitment to prevent mother-to-child transmission have positively impacted the epidemiology of childhood HIV infection. In the United States, the number of infected infants per year has decreased from approximately 1800 to fewer than 100.<sup>191</sup> Combination antiretroviral drugs administered during pregnancy and labor have drastically reduced transmission rates to under 2%.<sup>192</sup>

Adolescents, on the other hand, are a population with an increasing rate of HIV-1 infection. Some of these patients acquired the infection perinatally and because of improved medical care are living longer than in the past. The number of vertically infected adolescents will increase dramatically in numbers over the years to come.<sup>193</sup> In others, high-risk behaviors such as intravenous drug abuse and unprotected sexual intercourse place them at increased risk. Those at highest risk are homeless youth and those living in poverty, as well as young minority men who have sex with men. Victims of sexual abuse are another population of adolescent youth at high risk for HIV-1 infection. A high index of suspicion of HIV-1 infection should be maintained when an at-risk adolescent presents with a mononucleosis-like illness or persistent adenopathy.<sup>186</sup>

HIV-1 infection may present differently depending upon the child's age. Although a detailed discussion of the clinical features is beyond the scope of this section, a brief review is included. Importantly, cutaneous and/or mucosal findings are often significant in the patient with HIV-1 infection or AIDS. These are listed in Table 15-7.

Acute HIV-1 infection may present with several nonspecific features, known as *acute HIV infection syndrome*. Symptoms may include fever, myalgias, fatigue, pharyngitis, weight loss, and headache, and because of the nonspecific nature of many of these, the infection often goes unrecognized.<sup>194</sup> Dermatologic features that may be seen during acute HIV infection syndrome include a mononucleosis-like, erythematous eruption, desquamation of palms and soles, urticaria, and alopecia. In addition, gastrointestinal symptoms are common during this acute illness and include abdominal pain, vomiting, and diarrhea.

In infants with HIV-1 infection, the most common features include *Pneumocystis carinii* pneumonia (PCP), lymphoid interstitial pneumonitis (LIP), failure to thrive, recurrent infections (especially bacterial and candidal), and encephalopathy.<sup>186</sup> LIP occurs in the setting of EBV infection with chronic lymphoid pulmonary infiltrates and a “honeycomb” pattern on chest radiography. It may represent a unique immune response to coinfection with EBV and HIV,<sup>195,196</sup> and it usually responds to therapy with oxygen and steroids. Patients with LIP have a better prognosis than those with PCP, the latter of which is the most common AIDS-defining illness in children. The acute HIV infection syndrome may be absent in infants with HIV-1 infection.<sup>193</sup> Infants infected with HIV-1 are prone to gastrointestinal infections, enteropathy, and malabsorption. They may also have hepatosplenomegaly and lymphadenopathy. Primary infection with CMV may result in hepatitis, bone marrow failure, pneumonitis, or encephalitis. Perinatal HIV

**Table 15-7** Mucocutaneous Manifestations of HIV-1/AIDS

Class	Type	Comment
Infections	Bacterial	Syphilis <i>Staphylococcus aureus</i> : impetigo, folliculitis, ecthyma, abscess <i>Pseudomonas aeruginosa</i> : folliculitis, ecthyma gangrenosum, abscess <i>Bartonella</i> : bacillary angiomatosis
	Mycobacterial	MAC: nodules, ulcers, pustules, folliculitis TB: scrofuloderma, papules, vesicles, ulcers, nodules, pustules, abscess Atypical mycobacteria: various skin findings
	Viral	HSV: typical or atypical (deep ulcers, thick crusts) VZV: primary varicella, herpes zoster CMV: perianal ulceration, vesicles, purpura, nodules EBV: oral hairy leukoplakia HPV: common warts, condylomata acuminata Molluscum contagiosum: often genitals/face or widespread; recalcitrant <i>Candida albicans</i> : cutaneous, oral, esophageal, vulvovaginal
	Fungal	<i>Pityrosporum ovale</i> : tinea versicolor Dermatophytes: tinea infections, onychomycosis Deep fungal infections: histoplasmosis, cryptococcosis, sporotrichosis, coccidioidomycosis <i>Penicillium marneffei</i> : various skin findings <i>Pneumocystis carinii</i> : occasional skin lesions
	Protozoal	
Infestations	Scabies	Classic findings or severe, crusted (Norwegian) form
	Amoeba	<i>Acanthamoeba</i> , <i>Naegleria</i> species: papules, nodules, ulcers
	Demodicidiosis	<i>Demodex folliculorum</i> : folliculitis (often facial)
Inflammatory	Psoriasis	May be severe, widespread
	Reactive arthritis	NG urethritis, arthritis and skin changes: keratoderma blennorrhagicum, balanitis, oral ulceration
	Seborrheic dermatitis	More severe, more widespread
	Eosinophilic folliculitis	Sterile, pruritic follicular papules and pustules
	Drug eruption	May be severe; most often secondary to trimethoprim/sulfamethoxazole, penicillins, antituberculous medications; include morbilliform eruption, erythema multiforme, SJS; may also develop in response to HAART
	Aphthous ulcers	
Idiopathic	Pruritus	Absence of primary cutaneous findings; may be severe
	Papular eruption	Pruritic, nonfollicular papules
	Ichthyosis	An acquired form of the disorder
	Xerosis	Severe skin dryness
Malignant	Kaposi sarcoma	Skin and mucosal nodules, plaques; may metastasize; mainly homosexual/bisexual men; association with HHV-8
	Cutaneous lymphoma	Usually T-cell, less commonly B-cell, non-Hodgkin lymphoma
	Other skin cancers	Basal cell, squamous cell carcinoma; malignant melanoma

Data from references 194–202 and 204–206.

AIDS, Acquired immunodeficiency syndrome; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HAART, highly-active antiretroviral therapy; HIV-1, human immunodeficiency virus type 1; HHV, human herpesvirus; HPV, human papillomavirus; HSV, herpes simplex virus; MAC, *Mycobacterium avium* complex; NG, nongonococcal; SJS, Stevens–Johnson syndrome; TB, *Mycobacterium tuberculosis*; VZV, varicella zoster virus.

infection may also result in endocrine dysfunction with growth failure and pubertal delay.<sup>197</sup>

In children (i.e., those between 2 and 6 years of age), the most common features of HIV-1 infection are recurrent episodes of otitis media and sinusitis, recurrent bacterial infections, LIP, and encephalopathy. Other serious infections, including meningitis and osteomyelitis, may occur. Invasive disease caused by *Streptococcus pneumoniae* may occur, although this may become less common with the advent of routine pneumococcal immunization. Again, hepatomegaly and lymphadenopathy are common, and problems with weight gain and linear growth may be seen.

In older children and adolescents with HIV-1 infection, the most common signs and symptoms include *Candida* infections (i.e., oral thrush, vulvovaginitis, esophagitis), HZ, recurrent herpes simplex infection, parotitis, cryptosporidiosis, and infections with CMV and atypical mycobacteria. Nonspecific signs after acute HIV infection are common and may simulate those of EBV infection. Poor growth, pubertal delay, and HIV-associated wasting may all occur.

There are multiple other associations with HIV-1 infection. Metabolic disturbances may result in hyperlipidemia, body-fat redistribution (with resultant lipodystrophy or lipoatrophy), insulin resistance, and hyperglycemia. Lipodystrophy appears to be propagated by the use of combination antiretroviral therapy (cART) (see below), which contributes to altered lipid metabolism.<sup>198</sup> Ocular manifestations include retinopathy, keratoconjunctivitis, keratitis, iridocyclitis, and retinal

microvasculopathy. Infectious retinitis may be caused by CMV, VZV, *Toxoplasma*, or other agents. Cardiac manifestations of HIV-1 infection include effusion, myocarditis, endocarditis, dilated cardiomyopathy, and pulmonary hypertension. In addition to HIV-associated encephalitis, or AIDS encephalopathy, other neurologic complications include aseptic meningitis, peripheral neuropathy, Guillain–Barré-like syndrome, and myelopathy. Patients may also have genitourinary, rheumatologic, gastrointestinal, and hematologic manifestations and have an increased risk of malignancy, especially non-Hodgkin lymphoma. Tuberculosis occurs with increased incidence in patients infected with HIV-1 and has important epidemiologic significance both within the community and for the world at large. In fact, the incidence of tuberculosis worldwide has been increasing, owing primarily to the incidence of HIV infection.<sup>198</sup> Psychological effects of HIV infection can be profound and may relate to the degree of illness, the threat of death, the association with substance abuse, and the social stigma associated with the disease.<sup>199</sup>

The diagnosis of HIV infection is based on clinical, immunologic, and serologic findings, and the exclusion of other causes of immunodeficiency. Antibody-based tests include enzyme-linked immunosorbent assays (ELISAs), second-generation ELISAs, and confirmatory Western blotting. Direct detection assays include p24 antigen capture ELISA and DNA/RNA assays via PCR, *in situ* hybridization, or other hybridization assays. In infants under 18 months of age, anti-HIV antibody may be transplacental and therefore is not diagnostic of HIV

infection (although a negative result suggests that the infant is uninfected). The diagnostic method of choice in infants, therefore, is HIV DNA PCR on peripheral blood lymphocytes.<sup>193</sup> Other laboratory tests that may be useful in the evaluation for HIV infection include complete blood cell counts with platelets, CD4+ lymphocyte counts, serum chemistries, and urinalysis. Plasma HIV RNA (viral load) studies are useful in monitoring response to therapy and are the best indicator of risk for disease progression in children.<sup>200</sup>

The mainstays of therapy for patients with HIV infection are a combination of medications encompassing one to three main categories. These categories include nucleoside analog reverse transcriptase inhibitors (NRTIs) and nucleotide analog reverse transcriptase inhibitors (NtRTIs) including zidovudine or ZDV (formerly azidothymidine [AZT]), didanosine (ddI), stavudine (d4T), lamivudine (3TC), abacavir (ABC), emtricitabine, and tenofovir; nonnucleoside analog reverse transcriptase inhibitors (NNRTIs) including nevirapine, efavirenz, delavirdine, and etravirine; and HIV protease inhibitors (PIs) including atazanavir, darunavir, fosamprenavir, nelfinavir, ritonavir, indinavir, saquinavir, tipranavir, and lopinavir.<sup>186,201</sup> Fusion inhibitors (enfuvirtide, maraviroc) interfere with the penetration of HIV into the target cells (maraviroc via binding to the chemokine receptor [CCR] type 5 receptor on CD4 Th cells), and integrase inhibitors (raltegravir) block the viral integrase and insertion of the DNA copy of the viral genome into the host-cell chromosome.<sup>201</sup> In addition, HIV vaccines intended to boost immunity toward the virus have been studied,<sup>202</sup> and adjunctive therapies such as intravenous immune globulin and cytokine therapy are occasionally utilized. The challenge of developing an HIV vaccine has been compounded by the poor host immune response to HIV infection.<sup>203</sup>

Special considerations in treating young children infected with HIV include differences in body size, composition, and drug metabolism, distribution, and elimination. (Updated treatment guidelines for pediatric HIV infection can be found at [www.aidsinfo.nih.gov/guidelines](http://www.aidsinfo.nih.gov/guidelines).) In infants the best outcome is seen when antiretroviral therapy is

immediately initiated after diagnosis. In older children or adolescents, the decision to start therapy is based on the viral load, CD4+ lymphocyte count, and clinical status. Survival in children infected with HIV has improved notably with the introduction of cART, with a decrease in disease progression and mortality.<sup>204</sup> However, children seem to be more likely than adults to develop metabolic side effects of therapy, including lipodystrophy, dyslipidemia, insulin resistance, mitochondrial toxicity with lactic acidemia, and decreased bone-mineral density. Interestingly, HIV-associated growth retardation, manifested by muscle wasting and decreased linear growth, appears to be minimized with the use of cART in children, although the long-term significance of these findings is unclear.<sup>205</sup>

The complete list of 206 references for this chapter is available online at <http://expertconsult.inkling.com>. 

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# 16 Exanthematous Diseases of Childhood

Several viral and bacterial illnesses may be accompanied by localized or generalized skin eruptions called *exanths*. These eruptions may be the first manifestation of a disorder and often are the reason for parents and patients to pursue medical evaluation. Prompt recognition and diagnosis of exanths is desirable and may dictate that other examinations be performed to assess for systemic associations. Although identification of the exact infectious agent is not always practical or possible, knowledge of the most common causes of the various exanths is important from an epidemiologic perspective. For instance, when diagnosing a child with a parvovirus B19-related exanthematous disease, consideration of at-risk contacts (i.e., gravid females, individuals with hemolysis or conditions resulting in decreased red blood cell production) is vital.

The majority of childhood exanths are caused by viruses and less often by bacterial or rickettsial agents. Most childhood exanths are diagnosed and managed by primary care providers, and thus a thorough familiarity with both classic and atypical exanths is desirable for the pediatric primary care practitioner. When evaluating the patient with an exanthem, several features should be considered, including the morphology of individual lesions, the distribution pattern, prodromal and concurrent symptoms, known exposures, associated exanthem (eruption of the mucous membranes), local epidemiology, and the findings of a thorough review of systems and physical examination. Whereas some exanthematous processes present with a characteristic patterning of lesion morphology and distribution, others may reveal no pathognomonic features, and the cutaneous findings must be taken into consideration along with the overall presentation of the patient. Exanths may be divided into erythematous, vesicular, and papular forms and have also been invariably described as *morbilloform* ("measles-like"), *rubelliform* ("rubella-like"), *scarlatiniform* ("scarlet fever-like"), or urticarial.<sup>1</sup> Pustular and petechial changes may occasionally be noted.

The classic childhood exanths are listed in Table 16-1. These disorders were originally classified with a numeric designation in the early 1900s. Since then much has been learned about the etiologic agents of the classic exanths, and several newer exanthematous disorders have been described. This chapter includes a discussion of the classic exanths: varicella, infectious mononucleosis (IM), and exanths caused by enteroviruses, *Mycoplasma*, and rickettsial agents. In addition, nonspecific viral exanths are discussed, as are some atypical exanths including papular acrodermatitis of childhood, unilateral laterothoracic exanthem (ULE), and papular-purpuric gloves-and-socks syndrome (PPGSS). Kawasaki disease, which may have clinical overlap with multiple exanthematous disorders, is discussed in Chapter 21. Acute generalized exanthematous pustulosis (AGEP), another exanthematous disorder, is discussed in Chapter 20.

## Varicella (Chickenpox)

Varicella-zoster virus (VZV) is a member of the herpesvirus family, and the causative agent of both varicella (chickenpox) and herpes zoster (shingles, see Chapter 15). Varicella results from primary infection with VZV and is a highly communicable human disease. Once acquired, VZV becomes permanently established in the sensory ganglia in a latent form with intermittent reactivation in a dermatomal distribution, resulting in herpes zoster.<sup>2</sup> Although acute varicella is usually a self-limited infection, before extensive use of the varicella vaccine most children had upward of 250 to 500 skin lesions,

approximately 9000 to 11,000 children were hospitalized annually, and up to 100 individuals per year died of the disease or its complications.<sup>3,4</sup>

VZV is found worldwide, and annual epidemics occur most often during late winter and spring.<sup>5</sup> Varicella is highly contagious and is usually spread between the prodrome and the first 3 days of the skin eruption.<sup>6</sup> VZV is transmitted via respiratory droplets, then enters regional lymph nodes, and eventually a viremia ensues with more widespread dissemination. Primary infection elicits a humoral immune response with production of immunoglobulin (Ig)A, IgM, and IgG anti-VZV antibodies, the latter of which help protect against reinfection.<sup>5</sup> Patients are considered contagious until at least 5 days after onset of the rash or until all existing lesions are dry and crusted.

A live attenuated varicella vaccine (Oka strain) was introduced in 1995, and in 1996 the Advisory Committee on Immunization Practices (ACIP) recommended universal one-dose vaccination of all children at age 12 to 18 months, with catchup vaccination of all susceptible children before age 13 years.<sup>4</sup> The ACIP and the American Academy of Pediatrics (AAP) have expanded their recommendations to include use of the vaccine for postexposure prophylaxis and for some immunocompromised children.<sup>3</sup> The vaccine is also indicated in adults who are susceptible to varicella. The vaccine has been quite effective in decreasing the overall incidence of varicella, and in vaccinees who develop breakthrough disease, the disease tends to be milder with fewer lesions that may remain papular rather than becoming vesicular.<sup>3</sup> In a 6-year case-control study of the effectiveness of the varicella vaccine over time, the effectiveness in the year after vaccination (97%) was greater than in years 2 through 8 after vaccination (84%), although most cases of breakthrough disease in vaccinees were mild.<sup>7</sup> Another study of the effectiveness of a one- versus two-vaccination regimen revealed high vaccine efficacy over 10 years for both groups (94.4% and 98.3%, respectively), and again, breakthrough disease was mild.<sup>8</sup> A decline in varicella-related hospitalizations for invasive group A  $\beta$ -hemolytic streptococcus (GABHS) infections has been documented between the period of the prevaccine era and that of widespread vaccine use.<sup>9</sup> Although some studies have demonstrated lower effectiveness of the varicella vaccine than expected, overall the data appear to support its universal use. In 2006, because of insufficient population immunity to prevent community transmission, the ACIP and AAP changed the varicella vaccine policy, recommending a universal two-dose vaccination program.<sup>10</sup>

The varicella vaccine is available as a monovalent vaccine (Varivax, Merck & Co, Kenilworth, NJ) and as part of a quadrivalent measles-mumps-rubella-varicella vaccine (MMRV; ProQuad, Merck & Co). Postlicensure studies have suggested a slightly increased risk of febrile seizures among children aged 12 to 23 months who received MMRV for their initial dose (versus separate MMR and varicella vaccines). A personal or family history of seizures is considered a precaution for use of MMRV, and unless a parent expresses strong preference for this vaccine, it is recommended that the first dose be administered as separate measles-mumps-rubella (MMR) and varicella vaccines.<sup>11</sup> For the second dose at any age or the first dose at ages 48 months and older, the combination MMRV vaccine is recommended.<sup>12</sup>

Primary varicella begins with a prodrome of fever, chills, malaise, headache, arthralgia, and myalgia. After 24 to 48 hours, the earliest skin lesions become evident, initially as red macules or papules (Fig. 16-1) that progresses rapidly to a vesicular phase. The fully developed lesion has been likened to a "dewdrop on a rose petal" (Fig. 16-2). Varicella lesions present initially on the scalp, face, or trunk and then spread to the extremities. Older lesions crust over, and new lesions

**Table 16-1** Classic Childhood Exanthems

Numerical Designation	Name(s)	Agent(s)	Comment
1	Measles, rubella	Measles virus (paramyxovirus)	Declining incidence with vaccination; occasional epidemics of imported cases and cases in unimmunized individuals in United States
2	Scarlet fever, scarlatina	GABHS	Toxin-mediated
3	German measles, rubella	Rubella virus (togavirus)	Rare with vaccination
4	Filatow-Dukes disease	?SA	No longer considered a distinct entity
5	Erythema infectiosum, fifth disease, slapped cheek disease	Parvovirus B19	Patients not contagious once rash is present
6	Exanthem subitum, roseola infantum, sixth disease	HHV-6 and HHV-7	Diffuse rash appears after abrupt defervescence

GABHS, Group A  $\beta$ -hemolytic streptococcus; HHV, human herpesvirus; SA, *Staphylococcus aureus*.



**Figure 16-1** Varicella. Note the early lesions consisting of erythematous macules and papules and the well-developed vesicular lesion.



**Figure 16-3** Varicella. Various stages are present in this patient with human immunodeficiency virus (HIV) infection and varicella, including vesicles and crusted papules.



**Figure 16-2** Varicella. These well-developed lesions demonstrate why they have been likened to "dewdrops on a rose petal."



**Figure 16-4** Varicella scarring. Hypopigmented macules and scars are present in this patient with a history of varicella.

continue to develop, resulting in the pathognomonic finding of lesions in various stages being present at the same time (Fig. 16-3). New lesions continue to develop for 3 to 4 days, and by day 6, most lesions have crusted over. Patients with sunburn or dermatitis may develop a more severe exanthem. An associated enanthem may be present and consists of painful erosions in the oropharynx, conjunctivae, or vaginal mucosae. The lesions of varicella heal with hypopigmentation (Fig. 16-4) and scarring (Fig. 16-5), especially at sites of the initial lesions.

Varicella tends to be a mild, self-limited disease in most immunocompetent hosts. Complications, however, may occur. The most

common complication is secondary bacterial superinfection, usually the result of *Staphylococcus aureus* or GABHS.<sup>13</sup> Invasive GABHS infections, including streptococcal toxic shock syndrome and necrotizing fasciitis, may rarely occur. Secondary bacterial infection usually presents as isolated secondary fever or localized symptoms, such as bulla (large blister) formation or cellulitis. Varicella gangrenosa is diagnosed when an area reveals rapidly progressing erythema, induration, and pain.<sup>5</sup> Peripheral gangrene may occur in the distal extremities.<sup>14</sup> Other skin-related complications include deep ulcerative lesions (Fig. 16-6), subcutaneous abscesses, and regional lymphadenitis. Patients under the age of 5 years who live in a household with older children seem



**Figure 16-5** Varicella scarring. Large, deep scars are present in this patient who had secondary bacterial infection of her primary varicella lesions.



**Figure 16-6** Varicella, complicated. Deep, ulcerative lesions occurred in this young girl with underlying immunodeficiency and secondary infection of the skin with *Streptococcus pyogenes*.

to be at greatest risk for bacterial complications.<sup>13</sup> In patients who develop secondary bacterial infection, bacteremia may occur, as may pneumonia, arthritis, or osteomyelitis.

Second to bacterial superinfection, the most common complication in patients with primary varicella is neurologic involvement. This may present as encephalitis, meningoencephalitis, cerebellar ataxia, transverse myelitis, or Guillain–Barré syndrome. Reye syndrome was a fairly common complication of varicella before the association with salicylates was identified. Reye syndrome (acute encephalopathy and fatty degeneration of the viscera) presents with decreased level of consciousness, vomiting, and abnormalities in liver function. The incidence of this complication has fallen dramatically over recent years. Varicella pneumonia is the most common serious complication in adults but is rare in healthy children.<sup>2,5</sup> When it occurs during the course of childhood varicella, it is usually bacterial in origin. Severe pulmonary deterioration may occur, and it may occasionally be

fatal.<sup>15</sup> Thrombocytopenia, arthritis, uveitis, nephritis, myocarditis, pancreatitis, and hepatitis may also occasionally occur. When arthritis occurs in this setting, it may be bacterial (*Streptococcus pyogenes* or *S. aureus*) or aseptic ("varicella arthritis") in origin. The latter is typically confined to a single joint, most commonly the knee, ankle, shoulder, or foot.<sup>16</sup> Purpura fulminans is a rare and life-threatening complication of varicella, and disseminated intravascular coagulopathy may occasionally occur.<sup>17</sup>

Immunocompromised hosts with varicella, including those with leukemia, lymphoma, or human immunodeficiency virus (HIV) infection; those receiving corticosteroids; and those with a history of organ or bone marrow transplantation may have more serious disease and a higher incidence of complications. These individuals have an increased risk of disseminated varicella, lung disease, thrombocytopenia, and other organ involvement. Bacterial superinfection may also occur with increased incidence, and hemorrhagic complications of the disease are more common. Varicella during pregnancy poses an increased risk of serious disease to both the mother and the fetus (see Chapter 2). Pregnant females have a higher incidence of varicella pneumonia, and mortality from the disease is increased.

The diagnosis of primary varicella is usually based on the history and clinical findings. Laboratory confirmation, when desired, can be performed by either virologic or serologic methods. Virologic methods include direct and indirect immunofluorescence studies, which are performed on tissue (i.e., cells scraped from the base of a fresh vesicle or organ biopsy tissue in patients with disseminated disease). These studies have the advantages of being both rapid and sensitive.<sup>18,19</sup> Tzanck smears on skin scrapings identify multinucleated giant cells and confirm the diagnosis of herpesvirus infection but are not specific for VZV. Cell culture is unequivocally confirmatory but not ideal for VZV given the prolonged time necessary for cytopathic effects to appear. Other virologic methods include hybridization and polymerase chain reaction (PCR) assays. Serologic studies for diagnosing VZV infection include acute and convalescent IgM and IgG antibody titers.

The treatment of varicella in otherwise-healthy children is usually symptomatic, with the goals being control of pain and pruritus and prevention of secondary superinfection. Supportive therapies include oral antihistamines for pruritus, acetaminophen for fever or pain, and topical care. Useful topical regimens may include cool compresses, oatmeal baths, and application of topical products such as bacitracin ointment, calamine lotion, pramoxine-containing preparations, or menthol-camphor (Sarna) lotion. Antibiotics should be given if secondary bacterial infection is present.

The decision regarding the use of antiviral therapy for primary varicella depends on several factors, including host immune status, the extent of the infection, and timing of the diagnosis. In general, routine use of antiviral agents for varicella in otherwise-healthy children is not recommended. Acyclovir, famciclovir, and valacyclovir are antiviral agents licensed for treatment of VZV infections, although famciclovir is not approved for primary varicella. Oral acyclovir has been suggested in some studies to decrease the severity of primary VZV infection, including a decrease in the days of fever, number of days of new lesion formation, total number of lesions, and pruritus. In a review of published studies on acyclovir treatment of varicella in otherwise-healthy children and adolescents, a reduction in the number of days with fever was noted, but the results were inconsistent with respect to the number of days to no new lesions, maximum number of lesions, and number of days to relief of itching.<sup>19</sup> In addition, no differences in the incidence of varicella complications between acyclovir and placebo groups were consistently noted.<sup>20</sup> Oral antiviral therapy should be considered, however, for healthy individuals who are at risk for moderate or severe disease, such as those over 12 years of age (especially unvaccinated), those with chronic skin or lung disorders, and those receiving therapy with salicylates (long-term courses) or corticosteroids (short, intermittent, or aerosolized courses).<sup>21</sup> When used in the treatment of varicella in otherwise-healthy patients, antiviral therapy should be started within 24 hours of the appearance of the rash. The use of oral antivirals for pregnant females with uncomplicated varicella remains controversial, although some experts recommend its use for those who develop it during the second or third trimesters. Intravenous acyclovir is recommended for pregnant females with serious complications of varicella.<sup>21</sup>

### Box 16-1 Indications for Varicella-Zoster Immune Globulin (VarizIG)

- Types of exposure to varicella-zoster:
- Residing in same household as infected patient
  - Playmate: face-to-face indoor play
  - Hospital: varicella in roommate; face-to-face contact with infected staff member or patient; visit by a person deemed contagious with varicella; intimate contact with person deemed contagious with zoster
  - Newborn: onset of varicella (not herpes zoster) in mother from 5 days or less before delivery or within 48 hours after delivery
- Candidates for VarizIG:
- Immunocompromised child without history of varicella or varicella immunization
  - Susceptible pregnant female (no evidence of immunity)
  - Newborn infant whose mother develops varicella (see above)
  - Hospitalized premature infant:
    - ≥28 weeks' gestation, if mother lacks reliable history of varicella or serologic evidence of antibodies
    - <28 weeks' gestation or birthweight 1000 g or less, regardless of maternal history of varicella or serologic status

Modified from American Academy of Pediatrics, et al. Varicella zoster infections. In: Pickering LK, Red book. 29th ed. 2012 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2012. p. 774-89.

In immunocompromised children, intravenous antiviral therapy with acyclovir should be administered and is most effective when initiated early in the course of the disease (preferably within 24 hours of the onset of the rash). Some experts endorse high-dose oral acyclovir in selected immunocompromised individuals who are perceived to be at a lower risk for severe disseminated varicella. In 2008 valacyclovir was also approved for treatment of primary varicella in children 2 to under 18 years of age; some experts have used this agent for treating selected immunocompromised patients.<sup>21</sup> In susceptible individuals with a known exposure to VZV, options include administration of varicella-zoster immune globulin (VarizIG) or varicella vaccine. VarizIG is a high-titer preparation of VZV IgG that is given via the intramuscular route. It is recommended for susceptible individuals at high risk for infection and pregnant females who have been exposed to VZV (Box 16-1). VarizIG is best given within 48 hours of the exposure, but the United States Food and Drug Association (FDA) recently extended the approved period for which it can be given to up to 10 days.<sup>5,21,22</sup>

## Rubeola (Measles)

In the prevaccine era, more than 500,000 cases of measles, or rubeola, were reported annually in the United States. After introduction of a live-virus vaccine in 1963, a significant reduction in the incidence of infection was noted. The MMR vaccine has been distributed in excess of 575 million doses and is one of the most widely used combination viral vaccines in the world.<sup>23</sup> However, a dramatic resurgence occurred from 1989 to 1990, and during this period the highest mortality since 1977 was noted.<sup>24,25</sup> Those affected most during the measles resurgence were preschool-age children from the inner-city areas, especially those who were unvaccinated and from low-income families. A majority of the deaths occurring from measles infection during this period occurred in children aged 5 years or younger.<sup>25</sup> Other target populations during the measles resurgence included vaccinated school-age children and college students, probably owing to the insufficiency of a single vaccine dose and waning immunity.

In response to the measles resurgence of the 1980s, the Committee on Infectious Diseases of the AAP and the ACIP recommended an amendment to the previous vaccination schedule and suggested two doses of measles vaccination rather than one.<sup>25,26</sup> The current recommendation for measles vaccination calls for a two-dose schedule, with the first given at 12 to 15 months and the second at 4 to 6 years of age, and revaccination of children 11 to 12 years of age or older who received only one previous dose of measles vaccine.<sup>27</sup> Changes in



**Figure 16-7** Koplik spots. Gray-white papules of the buccal mucosa in a patient with measles.

the measles vaccination strategy resulted in a markedly diminished incidence of the disease in the United States, with 100 cases reported in 1999.<sup>28</sup> Although the incidence in the United States declined to extremely low levels compared with the prevaccine era, measles continues to be a major health problem worldwide, with the World Health Organization estimating around 700,000 deaths per year from the disease.<sup>29</sup> Of the 100 cases reported in the United States in 1999, 33% were imported from other countries.<sup>28</sup> In developing countries, infants under 9 months of age who are too young to have received vaccination have a high incidence of measles with more multisystem involvement and a greater risk of death.<sup>29</sup> Importantly, sporadic epidemics of primarily importation-associated measles in the United States continue to occur. During January through July 2008, 131 measles cases were reported to the Centers for Disease Control and Prevention (CDC), and these occurred primarily in unvaccinated school-aged children.<sup>30</sup> The majority of these children were eligible for vaccination but had parents who chose not to have them vaccinated. In 2011, 222 measles cases were reported to the CDC, the majority of which were associated with importations from other countries and more than 85% of cases occurring in individuals who were unvaccinated or had unknown vaccination status.<sup>31</sup> In 2014, measles cases in the United States had risen to 644.<sup>32</sup> In early 2015 the United States experienced a large, multistate outbreak of measles infection linked to an amusement park in California. Among 110 of the earliest patients in this outbreak, 45% were unvaccinated, 5% had received only one dose of the vaccine, and 43% had unknown or undocumented vaccination status. Of the unvaccinated patients, 67% were intentionally unvaccinated because of personal beliefs (65% of these were children under the age of 18 years).<sup>33</sup> Given such observations, maintaining high vaccination coverage and index of suspicion for measles and ensuring a rapid public-health response at times of outbreaks are critical in the attempt to maintain measles elimination in the United States.<sup>34,35</sup>

Measles is caused by a single-stranded ribonucleic acid (RNA) virus in the family *Paramyxoviridae*. Infection begins in the nasopharyngeal epithelium and less commonly through the conjunctivae. Transmission of measles is primarily via respiratory droplets and less commonly by small particle aerosols.<sup>36</sup> The incubation period is around 10 to 14 days. From the initial site of infection, the virus enters the lymph nodes and lymphatics and multiplies within the reticuloendothelial system with a subsequent viremia.<sup>29</sup> The virus is then disseminated to multiple lymphoid tissues and other organs, including the skin, liver, and gastrointestinal tract.<sup>37</sup> Measles immunity includes cell-mediated, humoral, and mucosal responses. Measles antibodies are responsible for protection from future infection or reinfection.<sup>29</sup>

Measles classically presents with fever and the three Cs: cough, coryza, and conjunctivitis. The pathognomonic enanthem, Koplik spots, usually occurs during this prodromal period and presents with punctuate, gray-white to erythematous papules distributed on the buccal mucosa (Fig. 16-7). These lesions were recently found to be



**Figure 16-8** Rubeola (measles). Erythematous macules and patches of the face early in the course of the disease.



**Figure 16-9** Rubeola (measles). Intensely erythematous patches of the face with cephalocaudal spread onto the trunk and extremities.

highly predictive of confirmed measles.<sup>38</sup> The skin eruption of measles usually begins 2 to 4 days after the prodrome, which may intensify several days before the onset of rash. It begins on the face (Fig. 16-8), especially the forehead, hairline, and behind the ears, and spreads downward onto the trunk (Fig. 16-9) and extremities. The lesions are erythematous to purple-red macules and papules that may become confluent and fade in the same order as their appearance, leaving behind coppery macules and desquamation.

Complications of measles include pneumonia, laryngotracheobronchitis, otitis, gastroenteritis, myocarditis, and encephalitis. Pneumonia may be caused by the measles virus itself or be related to secondary bacterial or viral infection. Keratoconjunctivitis is common, especially in children with vitamin A deficiency, in which case it may result in blindness.<sup>36</sup>

Modified measles is measles occurring in a previously vaccinated individual. In this situation the prodrome is milder and of shorter duration, the exanthem is less prominent, and Koplik spots may be absent.<sup>39</sup> This presentation of measles may pose a diagnostic challenge given the nonpathognomonic presentation. Atypical measles occurs rarely in contemporary times and is seen in individuals exposed to natural measles after vaccination with the killed measles vaccines. These vaccines were utilized for a short period in the 1960s in the United States and for more variable periods of time in other countries including Canada and Sweden.<sup>39</sup> It has occasionally been reported in children who received the live attenuated vaccine.<sup>40</sup> Atypical measles presents with high fever, headaches, and myalgias and eventually the measles rash and often pneumonia. Hemorrhagic features may be present, and the exanthem may be confused with Rocky Mountain spotted fever (RMSF). Subacute sclerosing panencephalitis (SSPE) is a delayed neurodegenerative disease characterized by seizures, personality changes, coma, and death within 5 to 15 years of the measles diagnosis. It classically occurs many years later in 1 in 100,000 patients with measles but fortunately has been dramatically decreased in incidence with widespread vaccination strategies.<sup>36,41</sup>

The diagnosis of measles is traditionally made based upon clinical presentation with laboratory confirmation. Acute and convalescent serologic studies documenting a fourfold increase in titer confirm the diagnosis of measles.<sup>42</sup> PCR and semiquantitative real-time PCR assays have been developed, the latter being quite sensitive and specific and potentially useful in situations where early and rapid diagnosis is vital.<sup>43</sup> The treatment of uncomplicated measles is largely supportive, because specific antiviral therapies do not exist. Ribavirin, a synthetic nucleoside analog useful in the treatment of other paramyxovirus (i.e., respiratory syncytial virus) infections, has been utilized in severely ill or immunocompromised patients.<sup>41,44</sup> Antibiotics are useful in patients with secondary bacterial infections such as otitis media or bacterial pneumonia. Vitamin A supplementation has been recommended by the World Health Organization and the United Nations International Children's Emergency Fund for children with measles who reside in areas where vitamin A deficiency is a recognized problem or where the measles case fatality rate is 1% or greater.<sup>45</sup> In these instances, vitamin A appears to reduce mortality and ameliorate the severity of diarrhea, possibly through a protective action on the epithelial lining of the gastrointestinal tract, increased mucus secretion, and enhanced local barriers to infection.<sup>46</sup> Hospitalized patients with measles should be kept in respiratory isolation for 4 days from the onset of the rash. Most patients will recover completely without sequelae and have lifelong immune protection against reinfection.

## Scarlet Fever

Scarlet fever (scarlatina) is a bacterial exanthem that may at times be confused with a variety of viral exanthematous diseases. It is caused by GABHS and is primarily a disease of children between the ages of 1 and 10 years. It is very rarely diagnosed in infants. Transmission of GABHS is usually via respiratory secretions. Epidemiologic changes over time in the types of streptococcal pyrogenic exotoxin (SPE) produced by the organism have been associated with changes in the severity of this disease. The shift from SPE-A- to SPE-B- and SPE-C-producing strains, which was seen early in the twentieth century, has paralleled the decrease in morbidity and mortality from scarlet fever, as well as the decline in incidence and severity of rheumatic fever (RF) in the United States.<sup>47</sup> However, RF and rheumatic heart disease (RHD; progressive valve damage) continue to burden many low- and middle-income countries, as well as some populations in higher-income countries. Immigration from countries where RF and RHD are endemic to higher-income areas have resulted in an increased prevalence in some regions where they were once believed to be eliminated.<sup>48</sup> In the United States, the incidence of RF is generally lower than in developing countries, but there have been some regional outbreaks, including an outbreak in Utah in the 1980s whereby the incidence in children aged 3 to 17 years approached 12 per 100,000.<sup>49</sup>



**Figure 16-10** Scarlet fever. Diffuse erythema with small, punctate papules. This eruption has a sandpapery texture to palpation.



**Figure 16-11** Scarlet fever in dark-skinned patient. The rash in this patient resembles "goose flesh." Note the early desquamation at some sites.

Scarlet fever presents with fever, throat pain, headache, and chills along with cutaneous findings. It is less commonly associated with streptococcal skin infection rather than pharyngitis. The primary distinction between streptococcal pharyngitis and scarlet fever is the accompanying exanthem present in the latter. Oropharyngeal inspection reveals tonsillopharyngeal erythema, exudates, and petechial macules of the palate. During the first few days of illness, the tongue may reveal a white coating with red and edematous papillae projecting through (white strawberry tongue). By the fourth or fifth day, the coating peels off, leaving behind a red, glistening tongue studded with prominent papillae (red strawberry tongue).

The differential diagnosis of streptococcal pharyngitis includes infection with viral agents (especially mononucleosis), *Mycoplasma*, *Chlamydia*, and *Arcanobacterium haemolyticum*. In adolescents the differential diagnosis should include groups C and G *Streptococcus* species and *Neisseria gonorrhoeae*,<sup>50</sup> and in developing countries *Corynebacterium diphtheriae* may be implicated. *A. haemolyticum*, formerly known as *Corynebacterium haemolyticum*, is a Gram-positive bacillus that most often infects adolescents and young adults and may result in a syndrome of pharyngitis and a scarlatiniform exanthem.<sup>51</sup> The pharyngitis in these patients is usually severe (occasionally mistaken for diphtheria), and the exanthem may also occasionally mimic toxic shock syndrome, measles, urticaria, or erythema multiforme.<sup>52,53</sup> Infection with *A. haemolyticum* can occasionally be associated with bacteremia, severe sepsis, and soft-tissue infections (especially in patients with concomitant diabetes mellitus).<sup>54,55</sup> Lemierre syndrome, a condition characterized by pharyngitis, bacteremia (usually with anaerobic organisms including *Bacillus* and *Fusobacterium*), and thrombophlebitis of the internal jugular vein, has also been reported in association with this organism.<sup>56</sup>

Tender anterior cervical adenopathy is commonly present in patients with scarlet fever, and rhinorrhea and cough are usually absent. Some experts argue that presence of the latter two findings is a negative factor for the diagnosis of GABHS infection.<sup>50</sup> The exanthem of scarlet fever presents as a fine, erythematous, macular and papular eruption (Fig. 16-10) that has been described as "sandpaper." It involves the trunk and extremities and may be accentuated in flexural areas with a petechial component (Pastia lines). In darker-skinned individuals, the exanthem of scarlet fever may be more difficult to recognize and may consist only of punctate papules resembling cutis anserina ("goose flesh") (Fig. 16-11). Circumoral pallor may be a useful clinical sign and is visualized as a rim of pallor encircling the perioral area. The exanthem generally resolves over 4 to 5 days and may heal with thick sheets of desquamation, especially over the hands, feet, toes, and fingers (Fig. 16-12). An interesting observation is that the SPEs produced by GABHS contribute to the exanthem by their ability to stimulate a delayed-type hypersensitivity response that requires prior exposure of the host to the organism.<sup>57</sup>



**Figure 16-12** Post-scarlet fever desquamation. Extensive peeling of the hands and digits occurred in this patient after treatment for scarlet fever.

Scarlet fever is diagnosed based on the clinical presentation in conjunction with results of laboratory testing. The gold standard laboratory examination is throat culture with growth of GABHS. Rapid antigen detection (rapid strep testing), when properly performed, has a high sensitivity and specificity.<sup>50</sup> In addition, antistreptococcal serologies may occasionally be useful. Complications of scarlet fever include pneumonia, pericarditis, meningitis, hepatitis, glomerulonephritis, and RF. Although the symptoms of streptococcal pharyngitis and scarlet fever will often improve spontaneously, treatment more rapidly alleviates symptoms and more importantly is the primary mode of prevention for the subsequent occurrence of RF. The prevailing theory regarding RF prevention is that antimicrobial therapy should be started within 9 days from the onset of symptoms of GABHS pharyngitis.<sup>50,58</sup>

The drug of choice for treatment of scarlet fever is penicillin V. Although amoxicillin and ampicillin are commonly used, they have no microbiologic advantage over penicillin.<sup>58</sup> In patients allergic to penicillin, erythromycin or another macrolide (i.e., clarithromycin or azithromycin) or clindamycin may be utilized. Other options include a first-generation cephalosporin (although the possibility of cross-reaction in patients with penicillin allergy must be considered) or intramuscular penicillin G, which has the advantage of not being compliance-dependent but the disadvantage of being painful during administration.<sup>58</sup>

## Rubella (German Measles)

Rubella, or German measles, is a viral exanthematous disease with a worldwide distribution. The incidence of rubella has greatly decreased since widespread rubella vaccination began in the United States in 1969. Before that time, epidemics occurred every 6 to 9 years, and major epidemics or pandemics occurred every 10 to 20 years.<sup>59</sup> The primary goal of the rubella vaccination program was to prevent fetal infection, which may have various effects including miscarriage, stillbirth, and congenital rubella syndrome (CRS) (see Chapter 2). Although reported rubella cases in the United States are now quite low, outbreaks still occur, primarily among Hispanic adults, most of whom were born outside of the country and are unvaccinated.<sup>60</sup> As of 2013, goals for rubella elimination had been established in two World Health Organization regions, the Americas (by 2010) and the European region (by 2015), and accelerated control of rubella and prevention of CRS have been established for the Western Pacific region.<sup>61,62</sup> In Japan, rubella outbreaks significantly increased in 2012 and 2013 with a corresponding increase in CRS. The effects of such outbreaks can be far-reaching given the possibility of disease importation into other countries and serves as a reminder of the need to maintain high levels of vaccination coverage and infectious-disease surveillance.<sup>61</sup>

Rubella is caused by an RNA virus in the *Togaviridae* family. Humans are the only source of infection, and postnatal disease is spread through direct or droplet contact from nasopharyngeal secretions. Up to 50% of cases of rubella are asymptomatic, and mild, self-limited disease is common. The incubation period ranges from 14 to 23 days.

Prodromal symptoms may occur, especially in adolescents and adults, and include low-grade fever, headache, malaise, eye pain, myalgias, sore throat, rhinorrhea, and cough. The prodrome usually presents 2 to 5 days before the exanthem appears. The skin eruption consists of erythematous to rose-pink macules and papules (Fig. 16-13) that tend to become confluent and most commonly involve the face and trunk. The eruption spreads in a cephalocaudad manner and begins to involute after 1 to 3 days, fading in the same order in which it appeared. After severe rubella eruptions, a fine flaky desquamation may be observed in areas of maximum involvement.

Generalized lymphadenopathy often occurs, especially in the suboccipital, postauricular, and cervical regions. Although this pattern of lymph node enlargement is highly characteristic of rubella, it is not pathognomonic and may occur in other disorders including measles, varicella, adenovirus infection, and mononucleosis. Arthralgias and arthritis are common, especially in females in whom they occur up to 52% of the time.<sup>63</sup> The most common joints affected are those of the fingers, wrists, and knees. Complete resolution of the joint symptoms may take up to several weeks, and chronic arthritis occasionally develops. A characteristic exanthem, Forschheimer spots, may be present in patients with rubella and presents with erythematous and petechial



**Figure 16-13** Rubella. Nonspecific rose-pink macules and papules on the trunk of an adolescent male with German measles.

macules on the soft palate.<sup>64</sup> Other complications of rubella include encephalitis (which occurs in 1 in 6000 patients), myocarditis, pericarditis, and hepatitis.<sup>42</sup> Anemia, neutropenia, and thrombocytopenia may also occur, as may hemolytic uremic syndrome.

A clinical diagnosis of rubella is difficult to make given the potential overlap with multiple other exanthematous diseases. Serologic tests are most useful in confirming the diagnosis of rubella. The presence of rubella-specific IgM antibody indicates recent infection, as does a fourfold or greater increase in titer between acute and convalescent serum taken 1 to 2 weeks apart.<sup>42,65</sup> The virus can be isolated from nasal specimens plated onto appropriate cell-culture media. The treatment of postnatal rubella is generally supportive. Hospitalized patients require contact isolation (and nonhospitalized children should be excused from school or day care) for 7 days after onset of the rash.

The ongoing efforts of global rubella eradication campaigns will hopefully result in eventual worldwide elimination of the disease. Continued efforts to ensure the immunity of women of child-bearing age will help to decrease the incidence of vertical transmission and CRS.

## Filatow–Dukes Disease

In 1900, Dukes described what was believed to be a unique exanthem and contrasted it from rubella and scarlet fever.<sup>66</sup> This disorder was termed *fourth disease* and subsequently became known as Filatow–Dukes disease given a similar description by Filatow 15 years earlier. The exanthem was described as bright red papules with a diffuse distribution, skin tenderness, and fever, and there was significant overlap with other exanthematous diseases, including staphylococcal scalded skin syndrome, scarlet fever, and rubella. Significant controversy followed the initial descriptions of fourth disease, and some authors propose that a distinct disorder never existed.<sup>67</sup> The possibility that epidermolytic toxin-producing staphylococci were the etiologic agent for the disorder described in the original reports has been suggested.<sup>68</sup> In general, researchers and practitioners alike have abandoned the idea of Filatow–Dukes disease representing a distinct entity.

## Erythema Infectiosum

Erythema infectiosum (EI; fifth disease) is a common childhood exanthematous illness caused by parvovirus B19 (referred to as *B19*). Although parvoviruses are ubiquitous in nature and may cause significant disease in a wide range of animals, B19 is the only one resulting in human disease.<sup>69</sup> Several disorders have been linked to B19 infection in humans (Box 16-2), including EI, arthritis, aplastic crises, and fetal hydrops. B19 infection is common in most countries, and in the United States 60% of adults are seropositive for the virus.<sup>70</sup> Infection is most common in school-age children. In immunocompromised hosts, persistent bone marrow suppression may occur, resulting in

### Box 16-2 Clinical Associations with Parvovirus B19 Infection

- Asymptomatic infection
- Exanthematous disorders
  - Erythema infectiosum (fifth disease)
  - Poplar-purpuric gloves-and-socks syndrome
  - Asymmetric periflexural exanthem
  - "Bathing trunk" exanthem
  - Petechial exanthems
- Other disorders
  - Arthritis
  - Transient aplastic crises
  - Chronic anemia
  - Refractory anemia after solid-organ or stem-cell transplantation
  - Hemophagocytic lymphohistiocytosis
  - Myelodysplastic syndrome
  - Fetal hydrops
  - Vasculitis
  - Neurologic disease
  - Rheumatologic disease



**Figure 16-14** Erythema infectiosum. Erythema of the bilateral cheeks, which has been likened to a "slapped cheeks" appearance.

severe cytopenias that may be misinterpreted as being related to malignancy relapse or drug reactions.<sup>71</sup>

In patients with classic EI, B19 infection is transmitted via the respiratory tract and is followed by a viremia that ends after 5 to 7 days with the production of IgM anti-B19 antibody. Prodromal symptoms such as headaches, fever, and chills are common during the viremic phase.<sup>72</sup> Respiratory symptoms may also be present. IgG antibody appears during the third week of illness and coincides with the appearance of the rash and arthralgias, and hence patients with the cutaneous findings of EI are not considered infectious. Outbreaks of EI occur primarily during the winter and spring.

EI is the most recognizable B19-associated manifestation. It is also known as "slapped cheek" disease given the characteristic fiery-red facial erythema (Fig. 16-14) that occurs 2 to 3 days after the prodromal symptoms. The cheeks are most prominently affected, with the nasal bridge and perioral areas usually being spared. This phase of the illness has been termed the *first stage*, and is subsequently followed by stages two and three. The differential diagnosis of the initial eruption of EI includes phototoxic reaction and systemic lupus erythematosus.

During stage two, the patient develops a lacy, reticulated eruption on the extremities and trunk 1 to 4 days after the facial rash. This eruption may be pruritic and is often evanescent. It often begins with a confluent pattern followed by central clearing, which results in the lacy and reticulated appearance (Figs. 16-15 and 16-16). The palms and soles are usually spared. The rash of the second stage of EI tends to fade over 2 to 3 weeks but may intermittently recur in response to environmental stimuli including sunlight, warm temperatures (i.e., a hot bath), or physical activity. This intermittent waxing and waning represents the third stage of EI, and the duration is variable, usually 1 to 3 weeks.

Joint symptoms occur in 8% to 10% of children with EI but in up to 60% of adults with primary B19 infection, especially females.<sup>69,73,74</sup> The most commonly involved joints include the metacarpophalangeal joints, proximal interphalangeal joints, knees, wrists, and ankles. For most patients, the joint symptoms are transient and self-limited. Occasionally, affected children develop a chronic arthritis.<sup>75</sup> Some experts have suggested a potential association between B19 infection and rheumatic arthritis or other connective tissue diseases, although the strength of this association remains unclear.

B19 has a remarkable affinity for erythroid precursors, binding to a receptor known as *P antigen (globoside)*.<sup>76</sup> Direct infection of the red blood cell precursors results in a transient arrest in red blood cell production and resultant transient anemia. Transient aplastic crises may occur in patients suffering from disorders of decreased red blood cell production or increased red blood cell destruction or loss. Predisposing disorders include iron-deficiency anemia, spherocytosis, sickle cell disease, thalassemia, glucose-6-phosphate dehydrogenase defi-



**Figure 16-15** Erythema infectiosum. Reticulate erythema on the upper arm of a patient with erythema infectiosum.



**Figure 16-16** Erythema infectiosum. Patchy erythema with reticulate changes of the inner thigh in a patient with erythema infectiosum.

ciency, and pyruvate kinase deficiency. Although these episodes may be asymptomatic with spontaneous recovery, severe involvement may result in chills, pallor, weakness, fatigue, vasoocclusive crises, or congestive heart failure. Treatment with red blood cell transfusions may be indicated and for some patients is life-saving.

Because B19 can cross the placenta, fetal infection is possible in nonimmune females with acute infection. With time it has become clear that B19 may result in a variety of fetal effects, occasionally even death. This epidemiologic consideration is important in caring for pediatric patients with B19-associated disorders. Fetal effects of B19 infection may include anemia (ranging from mild and self-limited to severe), high-output congestive heart failure, hydrops fetalis (generalized edema with ascites, pleural effusions, and polyhydramnios), and intrauterine fetal demise. Neonatal encephalopathy, encephalitis, cerebral migratory abnormalities, and meningitis have rarely been reported. The majority of pregnant women with B19 infection are asymptomatic, which makes the true incidence of fetal involvement difficult to determine.<sup>72,77</sup> It is estimated that 30% to 66% of adult females are immune to B19 infection,<sup>77-80</sup> and therefore their fetuses



**Figure 16-17** Papular-purpuric gloves-and-socks syndrome. Petechial purpura of the palms in a patient with parvovirus B19 infection.



**Figure 16-18** Papular-purpuric gloves-and-socks syndrome. Erythema and petechiae of the plantar feet were accompanied by pruritus and sore throat in this young girl with parvovirus B19 infection.

are not at risk. In the majority of fetuses who acquire acute infection *in utero*, the infection is self-limited and the infants are delivered asymptomatic and at term.<sup>81</sup> The greatest risk appears to be when infection is acquired before 20 weeks' gestation, and the majority of fetal losses occur between 9 and 28 weeks' gestation, mostly between 20 and 24 weeks.<sup>77,82,83</sup> The overall risk of B19-related fetal loss in pregnancies complicated by B19 infection is estimated around 1% to 9%.<sup>77,80,84</sup> Surviving infants tend to be healthy with normal development and neurologic outcome.<sup>84,85</sup> B19-related teratogenicity has only rarely been reported.<sup>85,86</sup> The diagnosis of B19 infection during pregnancy can be confirmed by maternal B19 IgM and IgG antibodies or PCR assay (see below). These studies are usually corroborated with findings on prenatal ultrasonography, most often evidence of fetal anemia and hydrops.<sup>87</sup> PCR assays on fetal cord blood or amniotic fluid samples have also been utilized for diagnosis.<sup>88</sup> Management of severely afflicted fetuses with B19 infection includes fetal digitalization and *in utero* blood transfusions.

B19 may be associated with a variety of purpuric or petechial exanthems, including PPGSS (see below) and more generalized presentations. In one outbreak of petechial rashes, B19 was confirmed in 76% of 17 children, and the petechiae were widely distributed, often with accentuation in the axillary and inguinal regions as well as the distal extremities.<sup>89</sup> Some authors have suggested the terminology *parvovirus B19-associated purpuric-petechial eruption* for these polymorphous presentations that appear to correspond to the viremic phase of primary infection.<sup>90</sup>

## PAPULAR-PURPURIC GLOVES-AND-SOCKS SYNDROME

Papular-purpuric gloves-and-socks syndrome (PPGSS) is another viral exanthematous illness that in many (but not all) cases has been documented to be caused by B19. This rare disorder presents most often in young adults and less often in children and is usually diagnosed during the spring and summer months.<sup>91,92</sup> Patients with PPGSS present with the acute onset of rapidly progressive, symmetric swelling and erythema of the hands and feet, often with a petechial or purpuric component (Figs. 16-17 and 16-18). Bullous lesions are rarely present.<sup>93</sup> The eruption has a sharp demarcation at the wrists and ankles and is usually quite pruritic. A more diffuse, papular exanthem may occur elsewhere on the body. An associated enanthem consisting of hyperemia, petechiae, and erosions is often present and affects the soft and hard palate, pharynx, tongue, and inner lips.<sup>91,94</sup> The symptoms of PPGSS tend to be milder in children and adolescents when compared with adults.<sup>95</sup>

Associated symptoms include fever, arthralgias, malaise, and respiratory or gastrointestinal complaints. Hematologic complications including leukopenia and thrombocytopenia are rarely observed.<sup>91,94,96,97</sup> Mononeuritis multiplex has been described in asso-

ciation with perineuritis noted on skin biopsy.<sup>98</sup> PPGSS resolves spontaneously over 1 to 2 weeks, and recurrences are rare. Importantly, the antibody response to B19 seen in PPGSS may differ from that observed in patients with EI, such that patients with the exanthem of PPGSS may still be viremic and therefore infectious.<sup>91,94</sup> The B19 VP2 structural protein has been demonstrated in the endothelial lining of dermal blood vessels in skin biopsies from patients with PPGSS.<sup>99</sup>

The diagnosis of B19 infections is often made clinically in patients presenting with classic EI. In immunocompetent children who are otherwise well, laboratory confirmation of B19 infection is usually unnecessary. Instances in which such confirmation may be indicated, however, include atypical presentations, immunocompromised hosts, individuals with hematologic diseases, and those who have been exposed to gravid females. Serologic studies including enzyme immunoassays and radioimmunoassay are useful in detecting anti-B19 IgM and IgG antibodies, and other useful tests include direct hybridization with deoxyribonucleic acid (DNA) probes, *in situ* hybridization, and PCR studies.<sup>69,76,100</sup> In a pregnant female who has been exposed to B19, serologic testing for IgM and IgG antibodies should be performed, and if acute infection is documented, serial fetal ultrasonography is usually indicated. As mentioned, maternal and fetal serum PCR techniques may be useful, especially when serologic study results are unclear,<sup>101</sup> and B19 antigen detection in amniotic fluid samples has also been described.<sup>102</sup>

## Roseola Infantum

Roseola infantum (exanthem subitum, sixth disease) is a common childhood disease caused by human herpesvirus (HHV) type 6 or 7. HHV-6 and HHV-7 are ubiquitous members of the *Herpesviridae* family. These DNA viruses preferentially infect activated T cells, resulting in enhancement of natural killer cell activity and induction of numerous cytokines.<sup>103</sup> As with other herpesviruses, they become latent after primary infection and may reactivate during times of altered immunity.<sup>104</sup> Serologic studies have demonstrated that most children have been infected with HHV-6 before 3 years of age and with HHV-7 by 6 to 10 years of age.<sup>103-105</sup>

Transmission of HHV-6 and HHV-7 is believed to be primarily via saliva, and horizontal transmission between mother and child is well documented.<sup>104</sup> Persistent or intermittent excretion of HHV-6 in saliva and stool has been documented in parents of children who had documented primary infection.<sup>106</sup> Although most newborns have transplacentally acquired antibodies, by 6 months nearly all have become seronegative and are therefore susceptible to infection.<sup>103</sup> HHV-6 has been divided into two variants, HHV-6A and HHV-6B. Most childhood infections are ascribed to the HHV-6B variant, and HHV-6A may be more commonly implicated in immunocompromised hosts.<sup>107</sup> The

**Table 16-2** Some Clinical Associations with HHV-6 and HHV-7 Infection

Condition	HHV-6, HHV-7, or Both	Comment
Roseola infantum	Both	HHV-6 more common
Fever	Both	Infants mainly
Febrile seizures	Both	In young infants
Otitis media	6	
Meningitis	6	
Encephalitis	Both	
Encephalopathy	6	Basal ganglia/white matter abnormalities on brain MRI
Hepatitis	Both	
Lymphadenopathy	Both	
Lymphoproliferative disease	6	Proposed but unproven
Infections in patients who have had transplants	6	Viral reactivation
Hemophagocytic syndrome (macrophage activation syndrome)	6	Especially in patients who have had transplants
Drug hypersensitivity syndrome	Both, but mainly 6	Proposed as complex interplay between drug reaction and HHV infection
HIV-1 cofactor	Both	Proposed but unproven
Pityriasis rosea	7	Controversial
Mononucleosis	Both	In adults
Multiple sclerosis	6	In adults; controversial

Data from references 103, 105, 107, 111, 112, 113, 114, 115.

HHV, Human herpesvirus; HIV, human immunodeficiency virus;

MRI, magnetic resonance imaging.

diagnosis of these infections can be made via virus isolation in peripheral blood mononuclear cell (PBMC) cultures, serologic studies, qualitative PCR, reverse transcriptase-PCR (RT-PCR), and real-time quantitative PCR. PCR-based diagnosis has been applied to a variety of body fluids and tissues including plasma, whole blood, saliva, urine, cervical swabs, placenta and PBMCs. RT-PCR can detect messenger RNA (mRNA), which is present only during active replication and hence may be useful in distinguishing between primary infection and past or latent infection.<sup>108–110</sup>

A broad range of conditions has been potentially linked to infection with HHV-6 and HHV-7 (Table 16-2).<sup>103,105,107,111–115</sup> By far, however, the best-recognized association for both agents is that of roseola infantum. Roseola is a mild exanthematous illness that most often occurs in children under 3 years of age. The classic presentation is that of high fever (38 to 41°C [101 to 106°F]) that lasts for 3 to 5 days in an otherwise-well infant. With normalization of the temperature, the classic exanthem appears, initially on the trunk and eventually spreading to involve the extremities, neck, and face. The skin eruption is composed of fairly nondescript, erythematous, blanchable macules and papules (Fig. 16-19) that occasionally display a peripheral halo of vasoconstriction. The exanthem usually resolves over 1 to 3 days.

Associated signs and symptoms may include irritability, diarrhea, bulging fontanel, cough, cervical lymphadenopathy, and edematous eyelids.<sup>116</sup> Periorbital edema is quite common and when present in a febrile but otherwise well-appearing child may be a useful clue to the diagnosis during the preexanthematous stage. Nagayama spots are erythematous papules involving the mucosae of the soft palate and uvula and represent the enanthem that occurs in up to two-thirds of patients.<sup>107,116</sup> The differential diagnosis of the skin eruption in roseola infantum may include measles and rubella, although the temporal



**Figure 16-19** Roseola infantum. (A) Erythematous, blanchable macules and papules in an infant who had a high fever for 3 days preceding the skin eruption. (B) On closer inspection, some lesions reveal a subtle peripheral halo of vasoconstriction.

characteristics (rash after abrupt defervescence) are usually suggestive of roseola.

Primary HHV-6 infection may also be asymptomatic or may present in a manner distinct from classic roseola infantum. Nonspecific fever in infants with or without otitis media may often be the result of HHV-6 infection.<sup>117,118</sup> First febrile seizures in young children may also commonly be associated with primary HHV-6 infection.<sup>117,119</sup> Other potential central nervous system complications include encephalopathy and encephalitis, which tend to occur during the preexanthematous stage and may be associated with long-term neurologic morbidity.<sup>115,120</sup> HHV-6-associated encephalitis has occurred in both immunocompetent and immunocompromised individuals. The

prognosis is variable in these patients and ranges from complete recovery to severe neurologic sequelae or death.<sup>121,122</sup> Solid-organ and bone marrow transplant recipients are at increased risk of reactivation disease, which may be asymptomatic or present with rash, fever, encephalitis, pneumonitis, hepatitis, or bone marrow suppression.<sup>123,124</sup> In some patients, the clinical presentation of HHV-6 reactivation may mimic that of acute graft-versus-host disease.

Treatment for roseola infantum is unnecessary, and the illness usually spontaneously resolves without long-term sequelae. Although *in vitro* studies or clinical observations have suggested anti-HHV activity of ganciclovir, foscarnet, and cidofovir, these agents are rarely used clinically for patients with HHV-6 or HHV-7 infection. However, further research to identify effective treatment options is desirable given the wide array of complications that may be associated with severe infection or infection in the immunocompromised host.

## Other Viral Exanthems

### NONSPECIFIC VIRAL EXANTHEMS

Although several exanthematous eruptions may present with characteristic features such as lesion morphology or distribution, the majority are somewhat nonspecific and may be difficult to distinctly categorize. These eruptions may be hard to distinguish from drug reactions or in some younger patients, miliaria rubra (prickly heat). Unique defining characteristics such as an associated exanthem or symptom complex may be absent. Most nonspecific exanthems fall into the erythematous and/or papular categories, presenting with blanchable red macules and papules with a diffuse distribution (Fig. 16-20). Associated symptoms, which are generally nonspecific as well, may include fever, headache, myalgias, fatigue, and respiratory or gastrointestinal complaints.<sup>125</sup> Most nonspecific exanthems resolve without treatment over 1 week without long-term sequelae.

Common causes of nonspecific exanthems include nonpolio enteroviruses (see below) and respiratory viruses (i.e., adenovirus, rhinovirus, parainfluenza virus, respiratory syncytial virus, influenza virus). Other potential agents include Epstein–Barr virus (EBV), HHV-6 and HHV-7, and parvovirus B19, although these agents more often result in distinct exanthematous illnesses as discussed elsewhere in this chapter. In general, the majority of nonspecific exanthems occurring in the winter months are caused by the respiratory viruses and those

occurring during the summer months are most often caused by the enteroviruses.

Petechial exanthems, in particular, may pose a diagnostic dilemma to clinicians (given their potential association with life-threatening infections) and are associated with increased rates of hospitalization and diagnostic testing. Multiple viral organisms may be associated with a petechial exanthem, including parvovirus, respiratory syncytial virus, influenza and parainfluenza viruses, rhinovirus, EBV, cytomegalovirus (CMV), adenovirus, and enteroviruses. In a prospective study of children (0 to 18 years of age) who had petechiae and signs or symptoms of infection, real-time PCR was utilized to identify a variety of viruses in nasopharyngeal aspirates. Of 58 patients with a petechial rash, 67% were positive for a viral pathogen, and 41% were notable for viral coinfections (two or more pathogens).<sup>126</sup> The most common pathogens in this study were CMV and EBV (each 18% of the patients), followed by enteroviruses and rhinovirus (each 14% of the patients). Influenza A H1N1 and human bocavirus were also noted fairly often (9% each of the patients). Distinguishing clinically between viral and bacterial processes may be challenging. The ability to rapidly diagnose viral infection via quantitative PCR, however, may help minimize unnecessary antibiotic therapy, invasive diagnostics, and hospitalizations.<sup>126</sup>

### GIANOTTI–CROSTI SYNDROME

Gianotti–Crosti syndrome (GCS; papular acrodermatitis of childhood) was initially described in 1955 by Gianotti as an erythematous papular eruption symmetrically distributed on the face, buttocks, and extremities of children. A subsequent description by Crosti and Gianotti was made in 1956, and since then the disorder has been commonly known as Gianotti–Crosti syndrome. A viral etiology was suspected early on after the description of the disorder, and subsequently the notion of hepatitis B virus as a cause was hypothesized. It is currently well accepted that GCS is a distinct viral exanthem that may occur after infection with any of several viral agents, with hepatitis B being one possible (but uncommon) cause in certain parts of the world, especially Italy and Japan.<sup>127</sup>

GCS occurs predominantly in children between the ages of 1 and 6 years. Before the appearance of the exanthem, upper respiratory symptoms, fever, and lymphadenopathy may be present. The eruption is characterized by edematous, erythematous, monomorphic papules and occasionally papulovesicles distributed symmetrically over the face, buttocks (Fig. 16-21), and extensor surfaces of the upper (Fig. 16-22) and lower (Fig. 16-23) extremities. Occasionally the papules coalesce into larger, erythematous plaques (Fig. 16-24). Hemorrhagic changes or localized purpura (Fig. 16-25) may occasionally be present. The trunk is usually (but not always) spared in patients with GCS.<sup>128</sup> In most patients the skin eruption is asymptomatic, although mild pruritus may be present.



**Figure 16-20** Nonspecific viral exanthem. Nondescript erythematous macules and papules in an infant with a nonspecific symptom complex.



**Figure 16-21** Papular acrodermatitis of childhood. Erythematous, edematous papules symmetrically distributed on the bilateral buttocks.



**Figure 16-22** Papular acrodermatitis of childhood. Monomorphous, erythematous papules of the dorsal hands in a young girl who had similar lesions on the face and the extensor surfaces of her arms and legs.



**Figure 16-23** Papular acrodermatitis of childhood. Erythematous, edematous papules of the thighs and knees in a patient with Gianotti-Crosti syndrome.

A viral etiology has long been suspected as the cause of GCS. In 1970 two independent groups confirmed the association with hepatitis B infection.<sup>129,130</sup> In these patients, the exanthem was accompanied by acute anicteric hepatitis. In patients with hepatitis-associated GCS, hepatitis B surface antigen subtype ayw has been most classically implicated. Another term, *papulovesicular acrolocated syndrome* (PVAS), was traditionally used to describe a similar presentation with a more vesicular component. It was once believed that this presentation was distinct based on the presence of pruritus and the lack of both hepatitis and a hepatitis B association. In a review of 308 cases of Gianotti-Crosti syndrome in Italy, however, distinction between GCS and PVAS was not clinically possible, nor was there a significant difference in the presentation or course as related to the etiologic agent (i.e., hepatitis B versus other viruses).<sup>131</sup>

Subsequently multiple viral agents have been implicated in causing GCS. These include EBV, which is believed to be the most common etiology in the United States, as well as CMV, Coxsackie viruses, respiratory viruses (adenovirus, respiratory syncytial virus, parainfluenza virus), parvovirus B19, rotavirus, and HHV-6.<sup>127,131-138</sup> A possible association with immunizations has also been suggested. Vaccination reports have included MMR, *Haemophilus*, oral polio, diphtheria-pertussis-tetanus, Japanese B encephalitis, varicella, and hepatitis B vaccines.<sup>139-145</sup> Recurrence of the eruption and accentuation of lesions at the site of vaccination have been observed.<sup>146</sup> There is also a report of GCS occurring in association with primary HSV-1 gingivostomatitis in a 3-year-old boy.<sup>147</sup> GCS-like reactions have been observed



**Figure 16-24** Papular acrodermatitis of childhood. Erythematous papules coalesced into larger, edematous plaques in this patient.



**Figure 16-25** Papular acrodermatitis of childhood. Localized purpura of the ear lobe occurred in this patient with Gianotti-Crosti syndrome.

in some patients with molluscum contagiosum (see Chapter 15, Fig. 15-44, A)<sup>148</sup>; GCS seems to be a distinct exanthem occurring in response to a variety of viral agents and possibly vaccinations, with hepatitis B being an extremely rare cause in the United States.

Treatment for GCS is supportive. Although the eruption is self-limited, it may take 8 to 12 weeks to resolve completely. Postinflammatory hypopigmentation (Fig. 16-26) may occasionally persist for several months after resolution of the exanthem. Routine laboratory studies for hepatitis are generally not warranted. However, a thorough history (including potential risk factors for hepatitis) and physical examination (with attention to the presence or absence of hepatosplenomegaly and lymphadenopathy) should be performed. Hepatitis serologies and liver function studies should be performed only in patients in whom there is a clinical suspicion.



**Figure 16-26** Papular acrodermatitis of childhood, postinflammatory hypopigmentation. These postinflammatory changes are most common in patients with darker native complexions.



**Figure 16-28** Unilateral laterothoracic exanthem. Early involvement shows localization to the lateral trunk, axilla, and proximal inner arm in this patient.



**Figure 16-27** Unilateral laterothoracic exanthem. Erythematous macules and papules of the lateral trunk. The eruption eventually generalized.



**Figure 16-29** Unilateral laterothoracic exanthem. The thigh was the initial site of involvement in this patient whose lesions demonstrate an erythema infectiosum-like morphology. (Courtesy of Dr. Sarah Chamlin.)

### UNILATERAL LATEROTHORACIC EXANTHEM

Unilateral laterothoracic exanthem (ULE; asymmetric periflexural exanthem of childhood) was initially described by Bodemer and de Prost in 1992 as a distinct exanthem presenting initially in a unilateral, localized fashion.<sup>149</sup> It was probably described years earlier when Brunner et al. described a “new papular exanthem of childhood” in 1962,<sup>150</sup> and in 1986 when Taieb et al. reported five children with a “localized erythema” similar to that described in ULE.<sup>151</sup>

ULE is most common in patients between 1 and 5 years of age. It usually occurs during the winter or spring, although it has been described year round.<sup>150,152,153</sup> In most patients, onset of the skin eruption is unilateral and on the trunk (Fig. 16-27), often with extension toward the axilla (Fig. 16-28) and less often around the inguinal region or on an extremity (Fig. 16-29). The lesions spread in a centrifugal fashion and often become bilateral, although they maintain a predominance on the initial side of involvement. The skin lesions in ULE may show various morphologies, including macules, papules,

eczematous changes, and morbilliform, scarlatiniform, annular, or reticulate patterns. Some have described early lesions as consisting of a red papule surrounded by a pale halo.<sup>152</sup> Pruritus occurs in around 50% of patients. Vesicles and purpuric changes are rare. Desquamation is common during the healing stage, and postinflammatory pigment changes may also be present. Although skin biopsy is usually unnecessary, when performed it has revealed a lymphocytic infiltrate with notable clustering around the dermal eccrine ducts.<sup>152,154</sup> The most common initial misdiagnosis is that of contact dermatitis. The clinical differential diagnosis of ULE may also include nonspecific exanthem, pityriasis rosea, scarlet fever, miliaria, EI, tinea, and papular acrodermatitis of childhood.

Associated features may include a prodrome consisting of low-grade fevers and respiratory or gastrointestinal symptoms. Fatigue and conjunctivitis may also be present. Enlarged axillary and/or inguinal lymph nodes are occasionally noted, and hepatosplenomegaly is generally absent. An associated exanthem has not been described with ULE.

The etiology of ULE remains unclear, although most favor a viral etiology. Early reports suggested *Spiroplasma* infection,<sup>151</sup> although this has not been confirmed in subsequent studies. In a prospective case-controlled study using throat, stool, blood, and skin samples, several microbiologic investigations were performed for viral and bacterial infection. No differences between cases and controls were noted, and no consistent etiologic agent was identified.<sup>155</sup> Although parainfluenza virus and adenovirus infection were diagnosed in six patients in one series, confirmation of a causal role is lacking.<sup>153</sup> ULE was observed in a 1-year-old girl who also had positive EBV PCR in peripheral blood, suggesting a possible association.<sup>156</sup> The appearance of ULE after the onset of molluscum contagiosum has also been reported, similar to GCS (see above).<sup>157</sup> ULE appears also to be a distinct presentation pattern in response to a variety of potential infectious agents.

The lesions of ULE resolve spontaneously, but similar to those of papular acrodermatitis of childhood, they may be delayed. Most often ULE resolves over 3 to 4 weeks, although in some patients it may take up to 8 weeks. Treatment is supportive.

## ENTEROVIRAL EXANTHEMS

Enteroviruses, a subgroup of the picornaviruses, may cause a variety of clinical syndromes with associated exanthems. Human enteroviruses are small, single-stranded RNA viruses that include echovirus (31 serotypes), Coxsackievirus A (23 types), Coxsackievirus B (six types), enteroviruses 68 through 71 (four types), and polioviruses (three types).<sup>158</sup> The majority of enterovirus infections seen in practice are benign and manifested by fever alone or distinct syndromes, including hand-foot-and-mouth disease (HFMD), herpangina, hemorrhagic conjunctivitis, and pleurodynia.<sup>159</sup> However, severe or life-threatening infections may also result from enteroviral infection, including meningitis, encephalitis, myocarditis, neonatal sepsis, and polio. Infections in neonates are often disseminated and may be difficult to differentiate from bacterial processes.<sup>160</sup> Nonpolio enteroviruses are the leading cause of viral meningitis.<sup>159,161</sup> Spread of enteroviruses occurs person-to-person via the fecal-oral route and occasionally common source exposure (i.e., swimming pool water).<sup>162</sup> Enteroviral infections tend to predominate during the summer and fall, although sporadic cases may be seen throughout the year.

Nonspecific exanthems resulting from nonpolio enteroviruses are common and may present as macular and papular nonpruritic eruptions with or without petechiae. When a petechial component is present, the clinical presentation may be confused with that of more serious infections such as meningococcemia. This diagnostic confusion may be exacerbated by the concomitant presence of aseptic meningitis, which may accompany enterovirus, Coxsackievirus, or echovirus infections.<sup>39</sup> Other exanthem patterns may include urticarial, scarlatiniform, zosteriform, and vesicular forms.<sup>158</sup> Table 16-3 lists some exanthem/enanthem associations with the nonpolio enteroviruses.<sup>163-173</sup> Several are discussed in the following paragraphs in more detail.

HFMD is the best-recognized enteroviral exanthem. It is a disorder of young children, most commonly affecting those between 1 and 4 years of age. HFMD has been linked to several nonpolio enteroviruses, including Coxsackieviruses A5, A6, A7, A9, A10, A16 (most common), B1, B2, B3, and B5; echovirus 4<sup>174</sup>; and enterovirus 71.<sup>125</sup> Patients have fever, malaise, and the characteristic exanthem, which consists of gray-white, vesicular lesions on the palms (Fig. 16-30) and soles (Fig. 16-31) and less often involving the dorsal or lateral surfaces of the hands and feet. A less specific macular and papular erythematous eruption may be present on the buttocks, thighs, and external genitalia. Occasionally a more diffuse vesicular eruption with lesions in areas other than the palms and soles may be present (Fig. 16-32). The exanthem of HFMD consists of vesicles and erosions of the buccal surfaces, palate, tongue (Fig. 16-33), uvula, gingivae, and anterior tonsillar pillars. These lesions are painful and lead to anorexia and

**Table 16-3** Some Reported Exanthem/Enanthem Associations with Enteroviruses

Exanthem	Comment
Hand-foot-and-mouth disease	Most common; Coxsackievirus A or B, enterovirus 71; atypical form with high numbers of vesicles on extremities, palms, soles, face and buttocks may occur, especially in association with epidemics of Coxsackievirus A6 infection
Herpangina	Oral lesions and fever; Coxsackievirus A or B
Eczema coxsackium	Accentuation of erosions and vesicles in areas of skin previously or currently affected with AD
Hemorrhagic conjunctivitis	Eyelid edema, lacrimation, pain; Coxsackievirus A24 and enterovirus 70
Nonspecific exanthem	Any enterovirus
Gianotti-Crosti syndrome	Coxsackievirus A or B
Henoch-Schönlein purpura	Coxsackievirus B1
Still-like disease	Coxsackievirus B4
Zoster-like eruption	Echovirus 6
El-like eruption	Echovirus 12
Congenital skin lesions	Coxsackievirus B3
Eruptive pseudoangiomatosis	Echovirus
AGEP	Coxsackievirus B4
Nail matrix arrest	Patients with preceding hand-foot-and-mouth disease

Data from references 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173. AD, Atopic dermatitis; AGEP, acute generalized exanthematous pustulosis; El, erythema infectiosum.



**Figure 16-30** Hand-foot-and-mouth disease. Deep-seated vesicles with erythema involving the palmar surface of the fingers.

occasionally dehydration. Cervical and submandibular lymphadenopathy may occasionally be present in patients with HFMD.

Although the course of HFMD is most often benign and treatment is supportive, epidemics of enterovirus 71 infection in Asia highlight the potential seriousness of the infection. In these epidemics, severe disease was seen most often in children under 5 years of age, with the majority of deaths occurring secondary to pulmonary edema or pulmonary hemorrhage.<sup>175</sup> Other complications included encephalitis,



**Figure 16-31** Hand-foot-and-mouth disease. Erythematous deep-seated and superficial vesicles involved the plantar surface in this infant with erosions of the palate and uvula.



**Figure 16-32** Hand-foot-and-mouth disease. Red to purple vesicles involved the knees and elbows in this patient with classic lesions involving the mouth, palms, and soles.



**Figure 16-33** Hand-foot-and-mouth disease. A painful erosion of the lateral aspect of the tongue.

aseptic meningitis, acute flaccid paralysis, myocarditis, and cardiopulmonary collapse.<sup>175–177</sup> The neurotropism of enteroviruses is demonstrated by the common finding of brain (especially brain stem) involvement on autopsy specimens from children who died of severe HFMD.<sup>178</sup>



**Figure 16-34** Atypical enterovirus exanthem. This 3-year-old girl had fever and the acute onset of a vesicular eruption on her upper (**A**) and lower (**B**) extremities and her face with a perioral accentuation. Her manifestation coincided with a local Coxsackievirus A6 epidemic.

Atypical forms of HFMD may occur, highlighted over recent years in the setting of epidemics of Coxsackievirus A6 infection.<sup>179–181</sup> In these patients, extensive numbers of vesicles and erosions may occur on the extremities (Fig. 16-34), perioral face, groin, and buttocks, in addition to the more classic locations. In addition, in patients with atopic dermatitis, accentuation of the blistering process may be noted in areas previously or concurrently affected with eczematous lesions. This observation has been termed *eczema coxsackium*,<sup>179</sup> and these patients may be mistakenly diagnosed as having *eczema herpeticum* (see Chapter 3). A similar accentuation of the viral exanthem may be seen in other areas of skin inflammation or injury, including sunburn, irritant dermatitis, tinea infection, or lacerations. Post-HFMD nail matrix arrest with onychomadesis (nail shedding), initially reported in five children in 2000,<sup>171</sup> is now a well-recognized postinfectious association. It may present as Beau lines (transverse depressions in the nail plate) or complete separation of the nail plate from the nail matrix (Fig. 16-35). Although this observation has been seen after infection with a variety of enteroviruses, Coxsackieviruses A6, A10, B1, and B2 have been the most commonly confirmed.<sup>182–186</sup> The changes tend to occur around 30 to 40 days after the onset of HFMD and are followed by spontaneous regrowth of normal nail plates.

Herpangina is a characteristic enanthem that may be caused by a variety of nonpolio enteroviruses, especially Coxsackieviruses A and



**Figure 16-35** Nail matrix arrest after hand-foot-and-mouth disease. Transverse ridging and eventual nail shedding occurred in this 5-year-old male 2 months after having the enteroviral infection. The nails spontaneously grew back normally within several months.



**Figure 16-36** Eruptive pseudoangiomatosis. This teenaged girl sought treatment in the summer with the acute onset of small, hemangioma-like papules. Note the surrounding halo of vasoconstriction surrounding each lesion. (Courtesy of Dr. Andrew Sagan.)

B. It presents with fever, sore throat, and malaise, usually in children between 3 and 10 years of age. Inspection of the oral mucosa reveals gray-white vesicles and erythematous erosions involving the palate, uvula, and tonsillar pillars. Although it may occasionally be confused with acute herpetic gingivostomatitis, labial and skin involvement is much more common with HSV infection. Treatment for HFMD or herpangina consists of pain control and ensurance of adequate fluid intake in order to prevent dehydration. The lesions spontaneously resolve over 1 week. Hand-washing by preschool-aged children and their caregivers was demonstrated to have a significant protective effect against community-acquired HFMD and herpangina during an enterovirus 71 outbreak in China.<sup>187</sup>

Echovirus exanths have been variably described with a number of presentations and morphologies. Some of these include macular, vesicular, urticarial, and petechial eruptions, erythema multiforme, HFMD, and roseola-like exanths.<sup>39</sup> Echovirus 6 has been associated with a dermatomal, vesicular eruption mimicking herpes zoster.<sup>163</sup> Echovirus type 9 infection may result in an illness with aseptic meningitis and a petechial eruption that may mimic meningoococcemia.<sup>188</sup> Echovirus 16 was classically associated with a roseola-like exanthem referred to as *Boston exanthem*, which was one of the initial exanths to be described and virologically confirmed. Approximately one-third of individuals with echovirus infection may develop a rubelliform eruption consisting of discrete pink-red macules that spread from the face and neck to the upper trunk and extremities. Some patients also have yellow or gray-white lesions on the oral mucous membranes that may resemble Koplik spots. Other symptoms that may be associated with echovirus infection include fever, gastrointestinal complaints, upper respiratory symptoms, and conjunctivitis.

Eruptive pseudoangiomatosis is an exanthem consisting of the acute onset of hemangioma-like lesions and possibly related to echovirus infection.<sup>189</sup> Cherry et al., in 1969, originally described four children with acute echovirus infection (two with echovirus 25 and two with echovirus 32) who developed such lesions with resolution occurring over 2 to 6 days.<sup>164</sup> Other affected children were subsequently described, all of whom presented with the acute onset and spontaneous resolution of angioma-like papules during the course of a viral illness.<sup>165,190</sup> The disorder has also been observed in adults.<sup>191,192</sup> The angiomatous papules in eruptive pseudoangiomatosis are often surrounded by a rim of blanching (Fig. 16-36), and histopathologic evaluation, when performed, has revealed dilated dermal blood vessels and plump endothelial cells without any increase in the number of blood vessels.<sup>165,193</sup> Associated symptoms have included fever, malaise, headache, diarrhea, and respiratory complaints. Although echoviruses have not been confirmed as the etiology by other investigators, a viral cause continues to seem most likely. Recurrence of eruptive pseudoangiomatosis has occasionally been observed.<sup>194</sup>

### Box 16-3 Some Disease Associations with Epstein–Barr Virus

- Asymptomatic infection
- Infectious mononucleosis
- Lymphoproliferative disorders:
  - X-linked lymphoproliferative syndrome
  - EBV-associated hemophagocytic syndrome
  - Lymphoproliferative disorders in immunocompromised patients
- Gianotti–Crosti syndrome
- Chronic EBV infection
- Acute genital ulceration
- Oral hairy leukoplakia
- Neoplastic disorders:
  - Burkitt lymphoma
  - Nasopharyngeal carcinoma
  - B- or T-cell lymphoma (including AIDS-associated B-cell lymphomas)
  - Extranodal NK/T-cell lymphoma, nasal type
  - Hodgkin disease
  - Hepatocellular carcinoma

AIDS, Acquired immunodeficiency syndrome; EBV, Epstein–Barr virus; NK, natural killer.

## INFECTIOUS MONONUCLEOSIS

IM is a common infection occurring during adolescence and is usually associated with EBV infection. Although most cases of IM are related to EBV infection, not all primary EBV infections manifest as IM.<sup>195</sup> The spectrum of disorders linked to EBV infection is shown in Box 16-3. Other etiologic agents of IM-like illness include CMV, hepatitis A, adenovirus, GABHS, *A. haemolyticum*, HHV-6, rubella virus, HIV, and *Toxoplasma gondii*.<sup>196,197</sup> Malignancy and drug reactions may also result in IM-like illnesses.<sup>195</sup>

Confirmation of EBV as the major cause of IM occurred in the late 1960s.<sup>195,197</sup> EBV is a member of the *Herpesviridae* family and as such is a large, DNA-containing virus with the ability to become latent after primary infection and with the potential for subsequent reactivation. The virus has tropism for both lymphocytes (especially B cells) and epithelial cells, with infection beginning in the oropharyngeal epithelial cells, which may shed the virus for up to 18 months after primary acquisition.<sup>197,198</sup> The primary transmission route is via saliva. Natural EBV infection occurs only in humans and results in lifelong infection.<sup>199</sup> It is estimated that more than 95% of adults are infected with EBV worldwide.

Primary EBV infection in infancy is mostly asymptomatic or presents with very mild, nonspecific symptoms such as upper respiratory tract symptoms, pharyngitis, lymphadenopathy, and fever.



**Figure 16-37** Infectious mononucleosis. A diffuse, erythematous macular and papular eruption occurred in this adolescent male after receiving amoxicillin therapy.

Epidemiologic studies suggest that most children have acquired EBV by 5 years of age in underdeveloped countries or lower socioeconomic classes, whereas primary infection occurs later in life (i.e., between 10 and 30 years) in developed countries and higher socioeconomic classes.<sup>195,200</sup> Older children and adolescents are more likely to develop clinical symptoms of IM after an incubation period of 2 to 7 weeks.

IM is generally a benign, self-limited illness characterized by fever, exudative tonsillopharyngitis, and lymphadenopathy. Malaise, fatigue, and headache are also common. The temperature may reach 40°C (104°F) and is often prolonged, lasting for 1 to 2 weeks. Physical examination may reveal splenomegaly, hepatomegaly, periorbital edema, palatal petechiae, jaundice, and a skin eruption. The lymphadenopathy is typically nontender and involves both the anterior and posterior cervical chains. Diffuse adenopathy is occasionally present. Historically, IM was divided into three syndromes: anginose, characterized by the classic triad of fever, pharyngitis, and lymphadenopathy; typhoidal, characterized by prolonged high fever; and glandular, characterized by mild pharyngitis, low-grade fever, and marked lymphadenopathy.

The skin eruption of IM is nonspecific, occurs in around 5% of patients, and may present as a macular, petechial, scarlatiniform, urticarial, or erythema multiforme-like rash.<sup>197,200</sup> After the administration of ampicillin or amoxicillin, however, 90% to 95% of patients develop an erythematous macular and papular eruption (Fig. 16-37) that may be related to ampicillin-antibody immune complexes resulting from B-cell activation.<sup>201</sup> This reaction occurs about 5 to 9 days after starting the antibiotic and does not appear to represent a true drug allergy.

Useful laboratory evaluations in patients with IM include hematologic and hepatic panels and serologic analysis. Complete blood cell counts often reveal an absolute lymphocytosis, often with more than 10% atypical lymphocytes (representing activated T cells). Other aberrations may include anemia, thrombocytopenia, and neutropenia, the latter developing 1 to 2 weeks into the illness. Autoimmune hemolytic anemia is uncommon, occurring in around 3% of cases.<sup>201</sup> Mild hepatitis may be manifested by elevations in the hepatic transaminases, alkaline phosphatase, and L-lactate dehydrogenase (LDH). Coagulopathy is usually absent. The most useful confirmatory examination is the

**Table 16-4** Epstein–Barr Virus-Specific Serology Interpretation

Status	VIRAL CAPSID ANTIGEN (VCA)			EBNA
	IgG	IgM	Early Antigen	
No past infection	—	—	—	—
Acute IM	+	+	±	—
Convalescent IM	+	±	±	±
Past infection	+	—	Low + or —	+
Reactivated/chronic	++	±	++	±

Data from Peter J, Ray CG. Infectious mononucleosis. *Pediatr Rev* 1998;19(8):276–9. Godshall SE, Kirchner JT. Infectious mononucleosis: complexities of a common syndrome. *Postgrad Med* 2000;107(7):175–86, and Jenson HB. Acute complications of Epstein–Barr virus infectious mononucleosis. *Curr Opin Pediatr* 2000;12:263–8.

EBNA, Epstein–Barr virus nuclear antigen; Ig, immunoglobulin; IM, infectious mononucleosis.

serologic assay for heterophile antibodies. These IgM antibodies can be readily measured with a variety of rapid test kits (i.e., monospot) and have high specificity. Although up to 15% of patients with IM may initially be negative for heterophile antibodies, many become positive on repeat testing performed during the second or third week of the illness.

Virus-specific serologies can help confirm a definitive diagnosis of EBV infection and should be used to diagnose IM in children under 4 years of age (who are often heterophile antibody negative), patients with atypical presentations, or those with severe or prolonged illness.<sup>197</sup> EBV serology interpretations are shown in Table 16-4. Detection methods for EBV-related proteins or DNA are also available. Real-time PCR and measurements of EBV viral load seem particularly useful in diagnosing acute IM when the serologic studies are inconclusive.<sup>202</sup>

Complications of IM include splenic rupture, upper airway obstruction, hematologic issues (hemolytic anemia, thrombocytopenia, aplastic anemia, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, and disseminate intravascular coagulation), chronic fatigue, and neurologic findings. Subcapsular splenic hemorrhage with rupture is fortunately quite rare (<0.5% of cases in adults). It presents as an abrupt onset of left upper-quadrant abdominal pain and may be treated by splenectomy or nonoperative management. Upper airway obstruction may result from tonsillar hypertrophy and is treated as an inpatient with close observation, maintenance of the airway, hydration, and occasionally systemic corticosteroids.<sup>201</sup> Neurologic complications include cranial nerve palsies, Guillain–Barré syndrome, meningoencephalitis, aseptic meningitis, optic neuritis, and seizures. Other less common complications include pneumonia (which is often related to coinfection with a bacterial or another viral agent), electrocardiographic abnormalities, rhabdomyolysis, and chronic liver disease.<sup>197,201</sup> EBV is the most common infectious trigger of hemophagocytic lymphohistiocytosis (see Chapter 10).

Chronic fatigue syndrome (CFS) may follow IM in both adolescents and adults, with 13% of adolescents (mainly females) meeting criteria 6 months after IM in one study.<sup>203</sup> CFS is defined as at least 6 months of severe fatigue and disabling musculoskeletal and cognitive symptoms without any other explanation. In the aforementioned cohort, the figures for CFS in this group decreased to 7% at 12 months and 4% at 24 months after IM. It appears that female gender and greater fatigue severity are predictors for the development of CFS in adolescents with IM.<sup>204</sup>

The management of IM is primarily supportive. Adequate rest, fluids, and analgesics (acetaminophen, nonsteroidal anti-inflammatory agents) are commonly recommended. Patients with splenomegaly are counseled to avoid strenuous exercise and contact sports to prevent the complication of splenic rupture. These activities should

be avoided for the duration of splenomegaly, usually 1 month after onset of symptoms.<sup>195</sup> Most splenic ruptures occur within 3 weeks of the diagnosis, but it has been reported as late as 7 weeks after the diagnosis.<sup>205</sup> Amoxicillin and ampicillin should be avoided in patients with suspected IM. Corticosteroids are generally recommended only for patients with complications such as marked tonsillar hypertrophy with the potential for airway obstruction, massive splenomegaly, myocarditis, hemolytic anemia, or hemophagocytic syndrome.<sup>206</sup> Acyclovir, which may show *in vitro* activity against EBV, is of no proven value in the treatment of EBV-associated IM or lymphoproliferative syndromes, although antiviral agents may benefit immunocompetent patients when used in adjunct with corticosteroids.<sup>195,202,206</sup>

Acute genital ulceration (AGU; *ulecus vulvae acutum*; Lipschütz ulcer) is another potential presentation of primary EBV infection, presenting most commonly in teenaged girls. The initial report of this observation is credited to Lipschütz, who in 1913 proposed a classification of AGU into three categories, the third type being the sudden onset of genital ulcers in non-sexually active girls and young women.<sup>207</sup> This presentation may be associated with several possible infectious agents, but one of the most common appears to be EBV. Other reported agents may include CMV, *Mycoplasma pneumonia*, and influenza A virus.

AGU associated with EBV infection presents with painful genital ulcers, often bilateral (and occasionally in a "kissing pattern") and involving the labia minora or majora (or both). Edema is often present and may at times be severe. Tissue necrosis may occur, rarely necessitating surgical debridement. Other clinical features may include pharyngitis, lymphadenopathy, fever, and fatigue, but these classic symptoms of IM may not develop until later in the course (and in some patients may not develop at all).<sup>208</sup> The primary differential diagnosis is infection with HSV, and viral culture or PCR studies are often necessary, as are serologic studies for EBV. Seroconversion for EBV may be observed weeks after the initial presentation, with initially negative testing. EBV PCR testing on blood or genital tissue (when biopsy is performed) may be positive, although *in situ* hybridization and EBV RNA and protein staining in tissue samples suggests that AGU is most likely related to inflammatory events rather than direct viral cytopathic effects.<sup>207,209</sup> AGU caused by EBV infection is usually treated supportively, and the lesions tend to heal over 3 to 6 weeks; systemic corticosteroids have been recommended by some authors. This infectious cause of AGU is likely underrecognized and should be strongly considered in young females who have acute painful ulcers and who deny genital or oral sexual activity.<sup>210</sup>

## Exanthems Associated with *Mycoplasma pneumoniae* Infection

*Mycoplasmas* are a distinct class of bacteria that lack rigid cell walls and are thus insensitive to antibiotics that inhibit cell-wall synthesis such as penicillins. The best-recognized agent in this class is *M. pneumoniae*, a prominent etiology of atypical pneumonia in school-age children, adolescents, and adults. This infection generally presents with the insidious onset of fever, malaise, headache, and cough, and may be associated with skin findings in up to one-third of patients.<sup>211</sup> A variety of cutaneous eruptions have been potentially linked to *M. pneumoniae* infection. Some of these include nonspecific erythematous macular and papular eruptions,<sup>212–214</sup> erythema nodosum,<sup>211</sup> urticaria,<sup>211</sup> erythema multiforme minor,<sup>215</sup> GCS,<sup>216</sup> leukocytoclastic vasculitis,<sup>217</sup> bullous PPGSS,<sup>218</sup> Stevens–Johnson syndrome,<sup>219,220</sup> and subcorneal pustular dermatosis.<sup>221,222</sup> Stevens–Johnson syndrome is the most significant cutaneous association with *M. pneumoniae* infection and is discussed in detail in Chapter 20.

## Rickettsial Diseases

Although the use of molecular technology has resulted in some reclassifications of agents included in the order Rickettsiales, these organisms are all included in this section. These genus groups include *Bartonella*, *Coxiella*, *Ehrlichia*, *Anaplasma*, and *Rickettsia*. Table 16–5 is a summary of several rickettsial organisms and their disease

**Table 16-5** Some Rickettsial Organisms and Their Disease Associations

Organism	Disease Association(s)	Vector
<b>BARTONELLA</b>		
<i>Bartonella henselae</i>	Bacillary angiomatosis, CSD, endocarditis, bacillary peliosis	?Cat flea
<i>Bartonella quintana</i>	Trench fever, bacillary angiomatosis, endocarditis, bacillary peliosis	Human body louse
<b>COXIELLA</b>		
<i>Coxiella burnetii</i>	Q fever, endocarditis	Tick
<b>EHRLICHIA</b>		
<i>Ehrlichia chaffeensis</i>	Human monocytic ehrlichiosis	Lone Star tick
<i>Anaplasma phagocytophilum</i>	Human granulocytic ehrlichiosis (anaplasmosis)	Deer tick, dog tick
<b>RICKETTSIA</b>		
<i>Rickettsia akari</i>	Rickettsialpox	House-mouse mite
<i>Rickettsia conorii</i>	Mediterranean spotted fever	Dog tick
<i>Rickettsia prowazekii</i>	Epidemic typhus	Human body louse
<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever	Wood tick, dog tick
<i>Rickettsia typhi</i>	Endemic typhus	Rat flea
<i>Rickettsia tsutsugamushi</i>	Scrub typhus	Trombiculid mite

CSD, Cat-scratch disease.

associations. Bacillary angiomatosis caused by *Bartonella henselae* and *Bartonella quintana* is discussed in Chapter 12. Cat-scratch disease, caused by *B. henselae* is discussed in Chapter 14. Some other rickettsial disorders are discussed here.

Rickettsial infections are arthropod-borne diseases caused by microorganisms that occupy an intermediate position between bacteria and viruses. Spread by blood-sucking insects such as the body louse, fleas, and ticks, the various rickettsial diseases that occur in the United States include endemic or murine typhus, rickettsialpox, RMSF, and Q fever. Human granulocytic ehrlichiosis (HGE) (now also known as *anaplasmosis*) and human monocytic ehrlichiosis (HME) cases have also been reported with an expanding geographic distribution.

## ENDEMIC TYPHUS

Endemic (murine) typhus is caused by *Rickettsia typhi* and is transmitted by the rat flea *Xenopsylla cheopis*. It occurs worldwide, especially in warm climates with heavy populations of rats or opossums.<sup>223</sup> Although endemic typhus occurs most often in developing nations, it continues to occur in the United States, especially in Gulf Coastal areas and Texas.<sup>224</sup> Adults are most often affected, but children have constituted up to 75% of infections in some outbreaks.<sup>223</sup> Clinical manifestations most commonly include fever and headache, with rash occurring in around two-thirds of patients. The eruption is variably characterized as macular, papular, and occasionally petechial. Other features may include nausea, vomiting, malaise, myalgias, diarrhea, arthralgia, lymphadenopathy, conjunctivitis, and pneumonitis. Effective treatments include doxycycline and chloramphenicol. Endemic typhus should be considered in the child with prolonged fever and a rash, especially those residing in southern California, southern Texas, and Hawaii.<sup>225</sup>

## RICKETTSIALPOX

Rickettsialpox, caused by *Rickettsia akari*, is transmitted to humans by the house-mouse mite *Liponyssoides sanguineus*. Although rickettsialpox is rarely reported or diagnosed, it remains endemic in certain regions of the United States, particularly New York City.<sup>226</sup> The disorder begins with the bite of an infected mite, which results in a black eschar and subsequently other symptoms. The classic triad of rickettsialpox consists of fever, eschar, and rash. The skin eruption presents as numerous, monomorphic red papules with a small, central vesicular component. Although it may occasionally be confused with varicella, the rash of rickettsialpox is characterized by fewer lesions, less pruritus, monomorphic nature, and presence of an eschar at the site of the original bite of the mite.<sup>226</sup> Other features include myalgias, gastrointestinal symptoms, arthralgias, and lymphadenopathy. Although rickettsialpox is self-limited over 7 to 10 days, treatments of choice include doxycycline or chloramphenicol.

## ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii* and is the most common rickettsial illness in the United States. In one 4-year period during the mid-1990s, the average annual RMSF incidence was 2.2 cases per million persons, with the highest incidence confirmed among children 5 to 9 years of age (3.7 per million).<sup>227</sup> Of 4800 cases reported to the CDC between 1990 and 1998, 20% of cases and 15% of reported deaths were in children under 10 years of age.<sup>228</sup> During 2000 through 2007, the annual reported incidence of RMSF increased to 7 cases per million persons, the highest rate ever recorded, and children ages 5 to 9 years appeared to have the highest risk of a fatal outcome.<sup>229</sup> Among children living in the southeastern and south central United States, 12% had positive *R. rickettsii* antibody titers in one serologic survey, and hence exposure to the agent may be more common than indicated by reports of disease.<sup>230</sup> Because of the rapid progression of disease and the high mortality rate that may be seen without appropriate therapy, prompt diagnosis and initiation of specific treatment is vital in children with RMSF. Despite the name of this disease, it has been reported throughout the continental United States except for in Maine and Vermont.<sup>228,231</sup> The highest incidence is in Oklahoma, Tennessee, Arkansas, and the South Atlantic region; the most important factor in transmission of the disease is the prevalence of infected ticks.<sup>232,233</sup>

RMSF is transmitted by the bite of the wood tick (*Dermacentor andersoni*) in the Western United States and Canada and the dog tick (*Dermacentor variabilis*) in the Eastern United States. Most cases occur during the spring and summer months. Even in areas considered to be highly endemic for the disease (i.e., Virginia, North Carolina, Oklahoma), only a small fraction of ticks are infected with *R. rickettsii*.<sup>234</sup> Up to 40% of individuals diagnosed with RMSF do not recall a history of tick bite.<sup>234</sup> Importantly, ticks may attach to any body site (some of which are difficult to observe), often have a painless bite, and commonly go unnoticed.<sup>232</sup>

Patients with RMSF usually report symptoms within 14 days of the tick bite. The initial prodromal symptoms include headache, gastrointestinal symptoms, malaise, and myalgias. These are followed by fever and rash. The classic triad of RMSF consists of fever, headache, and rash, but many patients with the disease do not show symptoms in this classic fashion. Headache is a very prominent feature, may be severe, and is usually accompanied by severe myalgias. Patients with gastrointestinal complaints may have nausea, vomiting, and generalized or focal abdominal pain, occasionally mimicking an acute abdomen.<sup>234</sup> Neurologic findings may include meningismus or impaired level of consciousness (which occur in approximately one-third of cases),<sup>235</sup> seizures, and psychiatric complaints. Photophobia may also be present.

An exanthem occurs in up to 90% of patients with RMSF and usually appears around day 3 to 5 of the illness. It begins as discrete erythematous blanching macules and papules, which begin in a peripheral fashion and spread centrally (centripetally). Common locations for early lesions include the ankles, wrists, palms, and soles. With time, the skin lesions evolve into petechial macules and papules



**Figure 16-38** Rocky Mountain spotted fever. Erythematous macules and petechiae involving the hand and forearm.

(Fig. 16-38). Occasionally they become hemorrhagic, and focal areas of necrosis may occur. Larger areas of purpura may be present, and in some patients the skin eruption mimics that of meningococcemia. Skin necrosis and gangrene may occasionally result. Some patients have a delayed appearance of the rash, and in up to 10% the rash is completely absent ("spotless" RMSF).<sup>234</sup> These patients seem to have the same course as patients with a rash, and the index of suspicion must be higher in them, incorporating clinical and epidemiologic clues when present. Other mucocutaneous features may include hyperpigmentation, jaundice, and mucosal erosions.

Laboratory findings in RMSF may include a left shift with a normal to low white blood cell count, thrombocytopenia, liver function abnormalities, and decreased serum sodium. A lymphocytic cerebrospinal fluid pleocytosis is often noted. The differential diagnosis of RMSF includes other rickettsial diseases, meningococcal disease, Kawasaki disease, drug reactions, measles, and other viral exanthems. The diagnosis is usually made on a clinical basis, and if the disease is even remotely suspected, prompt institution of a tetracycline-class antibiotic should occur. Biopsy of skin lesions reveals endothelial-cell damage with a perivascular and interstitial mononuclear-cell infiltrate and small-vessel vasculitis, as well as extravasation of red blood cells and fibrin thrombi within vessels.<sup>236,237</sup> The indirect fluorescent antibody (IFA) test is the most widely used diagnostic examination and detects anti-*R. rickettsii* IgM and IgG antibodies, which are usually present 10 to 14 days after acute infection. Enzyme-linked immunosorbent assay (ELISA) testing has also been utilized.<sup>238</sup> PCR-based diagnosis is typically available only in specialized laboratories. Skin biopsy with immunohistochemical staining is highly specific but may not be available in all locales; when necessary, skin specimens can be submitted to the CDC via state health departments.<sup>239</sup>

The treatment of choice for RMSF is doxycycline, which is preferable to other tetracycline agents because of its reliable absorption, twice-daily dosing schedule, and broader spectrum of coverage for other tick-borne diseases.<sup>232,234</sup> If RMSF is strongly suspected, treatment should be promptly initiated and not delayed while waiting for laboratory confirmation.<sup>239</sup> Chloramphenicol is also effective but is generally used only for patients in whom a contraindication to doxycycline is present (i.e., pregnancy). In an analysis of risk factors for fatal RMSF, evidence for the superiority of tetracyclines was demonstrated even when compared with chloramphenicol therapy.<sup>240</sup> It should be noted that the risk of dental staining, which may be associated with doxycycline therapy in children under 8 years of age, is generally far outweighed by the risk of RMSF going untreated. Doxycycline therapy is recommended by the AAP and by the CDC as the treatment of choice in both RMSF and ehrlichiosis (see below).<sup>241</sup> Dental staining appears to be dose- and duration-related and is unlikely to occur in children treated with short courses of tetracyclines.<sup>233,242</sup> Therapy should be continued until the patient demonstrates clinical improvement and is afebrile for at least 3 days. Most patients are treated for 7 to 10 days.

Useful measures in preventing RMSF include wearing long clothing when outdoors (especially when in high-risk areas for tick bites), use of insect repellents effective against ticks (see Chapter 18), and frequent inspection for ticks with tweezers removal when necessary. It seems that transmission of the organism probably cannot occur until after 24 hours of tick attachment.<sup>243</sup>

## Q FEVER

Q fever, caused by the rickettsia *Coxiella burnetii*, is a worldwide zoonosis affecting domestic animals, birds, and arthropods.<sup>244</sup> It is transmitted to humans through contact with infected domestic animals including cattle, sheep, goats, or the products of these animals.<sup>236</sup> The primary route of human infection appears to be via inhalation of contaminated aerosols, and because the organism has a low respiratory infective dose, there is concern over its potential use as an agent of biologic warfare.<sup>244</sup> Tick bites, ingestion of unpasteurized milk or dairy products, and human-to-human spread are unusual sources of transmission of *C. burnetii* to humans.

The presentation of Q fever in humans is variable, and because the symptoms are so variable, it is likely underreported and underdiagnosed.<sup>245</sup> It may present as a nonspecific flu-like illness, atypical pneumonia, or hepatitis. Other clinical manifestations may include fever, myocarditis, pericarditis, osteomyelitis, and central nervous system infection.<sup>246</sup> Malaise is common and may persist for months after the acute symptoms have disappeared. Rash is reported in up to 20% of patients overall but has a higher prevalence in children (up to 50%) and does not appear to have distinguishing features. Erythematous macules, petechiae, purpura, urticaria, vesicles, livedo reticularis, and erythema nodosum have been reported.<sup>236</sup> Subcutaneous nodules representing necrotizing granulomatous inflammation have also been observed.<sup>247</sup> The diagnosis of Q fever is confirmed by serologic studies or PCR, and treatment in children consists of doxycycline for 14 days, or if the disease is mild and uncomplicated, for 5 days followed by additional treatment with trimethoprim/sulfamethoxazole if fever persists.<sup>245</sup> In some patients, Q fever is a self-limited disease that is diagnosed retrospectively.<sup>244</sup> A history of recent contact with farm animals and pets in the presence of consistent clinical findings should prompt investigation for *C. burnetii*.<sup>246</sup>

## EHRLICHIOSIS

*Ehrlichia* are obligate intracellular bacteria that belong to the family *Rickettsiaceae*. The two forms of disease of most concern in the United States are human monocytic (monocytotropic) ehrlichiosis (HME) and human granulocytic (granulocytotropic) ehrlichiosis (HGE), both of which are transmitted by tick bites and have similar clinical manifestations.

HME is caused by *Ehrlichia chaffeensis*, and occurs primarily in the southeastern and south central United States. States with the highest reported incidences are Mississippi, Oklahoma, Tennessee, Arkansas, and Maryland.<sup>248</sup> The most common vector is the Lone Star tick (*Amblyomma americanum*), and the distribution of disease closely parallels the endemic regions for this arthropod.<sup>249</sup> Most cases of HME occur during late spring and summer.

HGE, also known as human granulocytic anaplasmosis (HGA), is caused by *Anaplasma phagocytophilum*, which was previously known as "the agent of human granulocytic ehrlichiosis."<sup>250</sup> This infection is caused by bites from infected deer ticks or dog ticks and is seen with a broader geographic distribution in the United States. The highest annual incidence rates have been reported in Connecticut, Wisconsin, and New York.<sup>248</sup> Most cases of HGE occur between the months of April and September.

There may be considerable overlap of the clinical manifestations in patients with HME and HGE, although HME tends to be a more severe disease. Nonspecific symptoms of both disorders include fever, fatigue, headache, malaise, chills, myalgia, nausea, and rash (which is more common in pediatric patients). Hematologic aberrations may include

progressive leukopenia, thrombocytopenia, and anemia, and hemophagocytic lymphohistiocytosis has been seen in the setting of *E. chaffeensis* infection.<sup>251</sup> Some patients have elevation of liver transaminases, alkaline phosphatase, and lactate dehydrogenase, and hyponatremia may also be present. Hepatosplenomegaly and systolic murmur are common examination findings in patients with HME.<sup>249</sup> Shock necessitating pressor support and mechanical ventilation has been reported in patients with HME.<sup>252</sup> Neurologic features may include meningitis or meningoencephalitis (especially in HME) and peripheral nerve manifestations such as brachial plexopathy, cranial nerve palsies, facial nerve palsy, and demyelinating neuropathy (primarily in HGE).

The incidence of rash in patients with HME or HGE is not well established but seems to occur less often than that seen in patients with RMSF. It has been described as macular, papular, or petechial. Other less commonly reported patterns include vesicular, nodular, purpuric, vasculitic, erythrodermic, and ulcerated types.<sup>236</sup> The distribution is variable, although in the case of HME, it tends to spare the face, palms, and soles. The onset of the cutaneous eruption is most often within the first 3 to 10 days of the illness. The skin lesions seen in patients with HGE may predominate in the vicinity of the tick bite. The differential diagnosis of ehrlichiosis is broad, including septic shock, meningococcemia, thrombotic thrombocytopenic purpura, toxic shock syndrome, RMSF, Lyme disease, murine typhus, tularemia, babesiosis, and other tick-borne fevers.

Diagnostic options for ehrlichiosis include examination of peripheral blood smears, immunohistology, PCR assay, isolation of the organism, and serologic studies.<sup>248,253</sup> The most clinically relevant laboratory study is that of paired serologies (often via indirect immunofluorescence assay), which often need to be performed by a reference laboratory. Western blotting has also been utilized.<sup>254</sup> The treatment of choice for ehrlichiosis is doxycycline, and chloramphenicol is also a useful agent.<sup>236,249,255</sup> As with RMSF, treatment should be promptly initiated if there is a clinical suspicion for the diagnosis. Rifampin has been successfully used in children with HGE and may be another option for patients with non-life-threatening disease.<sup>111</sup> Efforts to reduce contact with ticks are also useful in lowering the risk of ehrlichiosis.

The complete list of 255 references for this chapter is available online at <http://expertconsult.inkling.com>.

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Fungi are a group of simple plants that lack flowers, leaves, and chlorophyll and get their nourishment from dead or living organic matter, thus depending on plants, animals, and humans for their existence. Fungal infections that affect humans may be superficial, deep, or systemic and can occasionally be fatal. Although they do not rank as pathogens with the bacteria or viruses, a number of species once thought to be ubiquitous and harmless have been implicated in various diseases, and with the increasing use of broad-spectrum antibiotics, corticosteroids, and potent cytotoxic agents and the increasing incidence of acquired immunodeficiency, deep mycoses have become increasingly significant.

The pathogenic fungal diseases are divided into superficial and deep infections. The superficial infections are those limited to the epidermis, hair, nails, and mucous membranes. Deep fungal infections are those in which the organisms affect other organs of the body or invade the skin through direct extension or hematogenous spread.

## Superficial Fungal Infections

There are three common types of superficial fungal infection: dermatophytosis, tinea versicolor, and candidiasis (moniliasis). Those caused by dermatophytes are termed *tinea*, *dermatophytosis*, or because of the annular appearance of the lesions, *ringworm*. In addition, *tinea nigra*, a superficial infection of the stratum corneum caused by a yeast-like fungus and often misdiagnosed as a melanocytic lesion, and *piedra*, an asymptomatic infection of the hair shaft, may be noted in both children and adults.

The dermatophytes are a group of related fungi that live in soil (geophilic), on animals (zoophilic), or on humans (anthropophilic). They digest keratin and invade the skin, hair, and nails, producing a diverse array of clinical lesions. Depending on the involved site, the infection may be termed *tinea capitis*, *tinea faciei*, *tinea barbae*, *tinea corporis*, *tinea manuum*, *tinea pedis*, *tinea cruris*, or *tinea unguium* (*onychomycosis*, *tinea* of the nails). The diagnosis and management of fungal diseases of childhood have become easier in the past decade owing to the development of more effective diagnostic techniques and therapeutic agents.

## DIAGNOSIS OF FUNGAL INFECTIONS

Tests for fungal infection are rewarding procedures readily available to all physicians, not merely those trained in dermatology. Diagnosis of ringworm of the scalp may be aided by the presence of fluorescence under a Wood light examination, although the changing epidemiology of this infection in the United States has made this examination clinically irrelevant in most cases. Other diagnostic studies that may be useful include direct microscopic examination of skin scrapings or infected hairs and fungal culture. These tests can be performed simply, inexpensively, and rapidly in the office. Laboratory confirmation of fungal infection is useful in confirming the diagnosis, in detecting the asymptomatic carrier state, and in the case of *tinea capitis*, in demonstrating a mycologic cure when clinical symptoms have resolved. Dermatophyte identification may also provide useful epidemiologic information (i.e., human-to-human vs. animal-to-human transmission) and may help guide the clinician's choice of antifungal therapy. Definitive proof of fungal infection should be considered when prolonged systemic therapy is being considered, in patients with some features but who lack lymphadenopathy (the most predictive clinical finding), and in patients who fail empiric therapy.<sup>1</sup>

### Wood Light Examination

The discovery in 1925 that hair infected by certain dermatophytes would fluoresce when exposed to ultraviolet light filtered by a Wood filter led to a helpful but occasionally improperly used diagnostic tool. When a Wood light examination is performed, it must be remembered that infected hairs, not the skin, fluoresce when exposed to light rays emitted by this lamp. Although the nature and the source of the fluorescent substance in infected hairs are not fully understood, this phenomenon is believed to be the result of a substance, perhaps pteridine, emitted when the fungus invades the hair.

Optimally, a powerful Wood lamp should be used in a completely darkened room. The usefulness of Wood lamp examination depends on the pattern of arthroconidial formation and hair invasion. Organisms that result in ectothrix infection (i.e., *Microsporum audouinii* and *Microsporum canis*) result in brilliant green fluorescence with this examination. However, those organisms associated with endothrix infection (i.e., *Trichophyton tonsurans* and *Trichophyton violaceum*), where organisms are present within the hair shaft, show no fluorescence. *Trichophyton schoenleinii*, the cause of favus (see below), produces a pale green fluorescence on Wood lamp examination. Sources of error in Wood light examinations include an insufficiently darkened room; the blue or purple fluorescence produced by lint, scales, serum exudates, or ointments containing petrolatum; and failure to remember that it is the infected hair and not the skin that fluoresces.

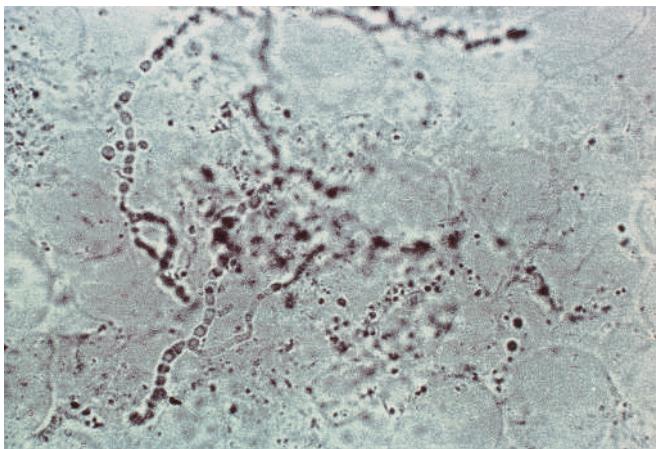
### Potassium Hydroxide Wet-Mount Preparations

Microscopic examination of skin scrapings is an important but commonly overlooked aid in the diagnosis of suspected fungal infection of the skin or hair. This examination will yield rapid results but requires considerable experience, because false-positive interpretations are common. Material for mycologic study should be taken by gently scraping outward from the active border of a suspected lesion with a number 15 scalpel blade or the edge of a glass slide. Moistening the skin with alcohol before performing the scraping may be useful in adhering the skin debris to the blade before it is smeared on a slide. Cut hairs, nail scrapings, subungual debris, and material from the edge of an affected nail may also be used for wet-mount examination. The material is placed on a glass microscope slide with care and spread out flat and evenly in a single layer. A coverslip is applied, and a few drops of 10% to 20% potassium hydroxide (KOH) are added at the side of the coverslip until the entire space between coverslip and slide is filled. Gentle heating of the preparation (with care to prevent boiling of the KOH, because this will cause crystallization) should be performed until the horny cells and debris are rendered translucent. If the KOH solution contains dimethylsulfoxide (DMSO), the slide should not be heated, because heating a DMSO-KOH preparation will dissolve fungi as well as epidermal cells.<sup>2</sup>

After collection and preparation of the specimen, gentle pressure is applied to the coverslip. This will improve the preparation by forcing out trapped air and thinning the specimen, thus allowing better visualization of fungi. The light of the microscope condenser should be dimmed to enhance contrast between branched hyphae and epidermal elements, and the specimen should be viewed under low power. A positive KOH examination reveals branching fungal hyphae with septations (Fig. 17-1).

### Fungal Culture

Although direct microscopic examination of skin scrapings will often confirm the suspicion of *tinea*, definitive identification rests on



**Figure 17-1** KOH examination in tinea. Note the septated fungal elements (hyphae). (Courtesy of Alfred W. Kopf, MD.)

isolation of the fungus by the gold standard, fungal culture. There are several types of fungal culture media, but the most popular are Sabouraud dextrose agar or mycobiotic agar (Mycosel) containing cycloheximide and chloramphenicol, which suppress growth of common saprophytic and bacterial contaminants respectively.<sup>3</sup> Dermatophyte test medium (DTM) agar is another commonly used media that also contains antibiotics (cycloheximide, gentamicin, and chlortetracycline), which inhibit saprophytic fungi and bacteria. DTM also contains a color indicator that changes from yellow to orange to red in the presence of dermatophytes. This medium is particularly useful for physicians who lack detailed knowledge of fungus-colony morphology and simply require confirmation of dermatophyte infection. However, one disadvantage of DTM is that the addition of the color indicator precludes laboratory identification of the exact dermatophyte, because it may obscure some colonial features used to distinguish these organisms.

Specimens for fungal culture may be obtained via a variety of collection procedures. Traditional methods include plucking broken hairs or scraping scale, but these procedures may be frightening or painful for younger children. Other modalities include use of a sterile toothbrush, wet gauze, cytobrushes, and adhesive tape. Use of a cytobrush has demonstrated very high sensitivity when compared with the traditional method of scraping the scalp.<sup>4</sup> The simplicity and reliability of the cotton swab technique has also been confirmed.<sup>5</sup> In this method, a sterile cotton-tipped applicator moistened with tap water (or Culturette swab in transport medium) is rubbed vigorously and rotated over the affected area of the scalp and then inoculated onto the appropriate fungal medium. This technique isatraumatic, readily available, and both sensitive and specific, even with delays between collection and plating of the sample.<sup>5</sup>

Trichoscopy (which refers to dermoscopy of the hair) has been recently reported as a useful diagnostic modality in the diagnosis of various hair disorders including tinea capitis.<sup>6</sup> A dermatoscope is a device composed of a magnifier attached to a nonpolarized light source utilized primarily by dermatologists. As such, this methodology is likely less applicable to the primary care provider. When utilized in tinea capitis, trichoscopy reveals comma-shaped and corkscrew hairs, black dots, and broken (not tapered) hairs.<sup>6,7</sup>

## THE DERMATOPHYTOSES

### Tinea Capitis

Tinea capitis, the most common dermatophytosis of childhood, is a fungal infection of the skin and hair of the scalp characterized by scaling and patchy alopecia. It is generally a disease of prepubertal children, especially those between the ages of 3 and 7 years, although infants and adults are occasionally affected. Neonatal tinea capitis has been reported.<sup>8,9</sup> In a prospective, cross-sectional surveillance study

**Table 17-1** Clinical Manifestations of Tinea Capitis in Children

Clinical Feature	Comment
<b>SCALP</b>	
Alopecia	One or multiple patches; may simulate alopecia areata
Scaling	May be minimally inflammatory; may mimic seborrheic dermatitis
Erythema	Localized or widespread
Pustules	Differential diagnosis includes sterile folliculitis or bacterial folliculitis
"Black dots"	Alopecia with hair shafts broken off at surface of skin; may simulate trichotillomania
Kerion	Boggy, tender plaque with pustules and purulent discharge; represents a vigorous host immune response
Scarring	Rarely seen when untreated; usually follows kerion
Favus	Yellow, cup-shaped crusts around the hair
<b>OTHER</b>	
Lymphadenopathy	Common; cervical or occipital
Id reaction	Widespread, papular or papulovesicular eruption; extremity-predominant; usually seen after initiation of therapy; must be recognized as distinct from true drug reaction

of children in kindergarten through fifth grade in a large U.S. metropolitan area, 6.6% of children overall had positive cultures for *T. tonsurans*, and the infection rates at participating schools ranged from 0% to 19.4%, with African-American children demonstrating the highest rates of infection (12.9%).<sup>10</sup>

A variety of dermatophytes may cause tinea capitis, especially *T. tonsurans* (the most common etiology in the United States, where it causes >90% of infections), *T. violaceum*, *M. canis*, and *M. audouinii*. Across Europe, *M. canis* remains the most common organism, although shifts toward *T. tonsurans* are being observed, especially in the United Kingdom.<sup>11</sup> These organisms may be anthropophilic (spread from humans, i.e., *T. tonsurans* and *T. violaceum*); zoophilic (spread from animals, i.e., *M. canis* and *M. audouinii*); or geophilic (spread from soil). Dermatophytes have a short incubation period (generally 1 to 3 weeks) and infect boys more commonly than girls. Predisposing factors for tinea capitis include large family size, crowded living conditions, and low socioeconomic class.<sup>3</sup> In addition to transmission from other humans or animals, dermatophyte spread via fomites (hairbrushes, combs, hats, and contaminated grooming instruments) is well documented. The reason for increased resistance to tinea capitis infection after puberty is unknown, but may be related to a higher content of fungistatic fatty acids in the sebum of postpubertal individuals. Hair-care practices (styling, frequency of washing, use of oils or grease), traditionally believed to play a significant role in the acquisition of tinea capitis, appear to not play a major role.<sup>12</sup>

Asymptomatic scalp carriage of dermatophytes varies and tends to correlate with the amount of tinea capitis in a community.<sup>13</sup> Such carriers constitute a major reservoir for transmission of the organisms causing the disease. Asymptomatic carriage is most common with the anthropophilic organisms *T. tonsurans* and *T. violaceum*, and most carriers are African-American, Afro-Caribbean, or black children in Africa.<sup>3</sup> Household contacts may be a significant source of asymptomatic carriers, and cosleeping and comb sharing seem to be important factors in the spread of disease in this setting.<sup>14</sup> Varied treatment options have been suggested for the carrier state, although there is a paucity of well-designed clinical studies.

The clinical manifestations of tinea capitis are varied and are summarized in Table 17-1. It may present in a "seborrheic dermatitis" pattern, with diffuse scaling and minimal inflammation (Fig. 17-2).



**Figure 17-2** Tinea capitis. Diffuse scaling with minimal erythema and patchy alopecia.



**Figure 17-3** Tinea capitis. Multiple patches of alopecia with erythema and scaling. Note the presence of pustules.

One or multiple patches of alopecia may be present (Fig. 17-3), and at times tinea capitis may present in a fashion similar to alopecia areata. “Black dot” tinea presents with alopecic areas with small black dots within them, representing the ends of broken off hair shafts (Fig. 17-4). This form is most commonly seen with endothrix infections such as *T. tonsurans*. It should be noted that the black-dot sign is probably overemphasized and although present may often be relatively inconspicuous.

Scalp pustules may be present (Fig. 17-5) and need to be distinguished from bacterial or sterile folliculitis. Kerion (Fig. 17-6) is a markedly inflammatory presentation of tinea capitis and reveals a boggy plaque with alopecia, pustules, and often purulent drainage from the surface. These lesions represent a vigorous host immune response to the dermatophyte and are caused most often by *M. canis* and *T. tonsurans* (and in rural areas by *Trichophyton verrucosum*). Although kerions may heal spontaneously, aggressive therapy is desirable, because the severe inflammatory response may result in permanent scarring alopecia (Fig. 17-7). Kerion has also been observed in neonates.<sup>15</sup>

Lymphadenopathy, especially cervical or suboccipital, is very common in patients showing symptoms of tinea capitis. In one study, presence of lymphadenopathy was highly suggestive of a positive fungal culture in children who were suspected of having tinea capitis, especially those with the concomitant presence of alopecia or scaling.<sup>16</sup>

Favus, a severe chronic form of tinea capitis rarely seen in the United States, is caused by the fungus *T. schoenleinii*. This disorder is characterized by scaly erythematous patches with yellow crusts or “scutula,” representing hairs matted together with hyphae and keratin



**Figure 17-4** “Black dot” tinea capitis. This well-demarcated patch of alopecia is composed of numerous broken-off hair shafts (black dots).



**Figure 17-5** Tinea capitis. This young girl had multiple pustules throughout her scalp with minimal inflammation, scaling, or alopecia. Culture revealed *Trichophyton tonsurans*.



**Figure 17-6** Kerion. This fluctuant, erythematous, boggy, and crusted plaque was exquisitely tender to palpation. *Trichophyton tonsurans* was isolated in fungal culture.

debris (Fig. 17-8). Such infections often result in scarring and permanent alopecia.<sup>17</sup>

A widespread papular hypersensitivity or dermatophytid (id) reaction may occur in patients with tinea capitis. This usually presents as tiny lichenoid papules on the scalp, trunk, and extremities (Fig. 17-9)



**Figure 17-7** Scarring alopecia after kerion. This patch of alopecia persisted after therapy for a severe kerion.



**Figure 17-8** Favus. This severe form of tinea capitis is caused most often by *Trichophyton schoenleinii*. (Courtesy of Israel Dvoretzky, MD and Benjamin K. Fisher, MD.)

that may be pruritic. This reaction is commonly seen after initiation of antifungal therapy and needs to be differentiated from a drug reaction so as to avoid the unnecessary discontinuation of therapy for the tinea. Although this distinction may not always be straightforward, drug reactions tend to be morbilliform, more widespread, and more erythematous. Id reactions represent an immune response to the dermatophyte and are best treated symptomatically with topical corticosteroid preparations and oral antihistamines as needed.

The differential diagnosis of tinea capitis includes seborrheic dermatitis, psoriasis, alopecia areata, trichotillomania, folliculitis, impetigo, lupus erythematosus, and a variety of less common scalp dermatoses. Confirmation of the diagnosis is desirable, and the gold standard is fungal culture, as discussed earlier. Wood light examination may be useful if the infection cause is an ectothrix organism but this is less common in the United States. Demonstration of the fungus by KOH wet-mount preparations of broken hairs or black dots col-



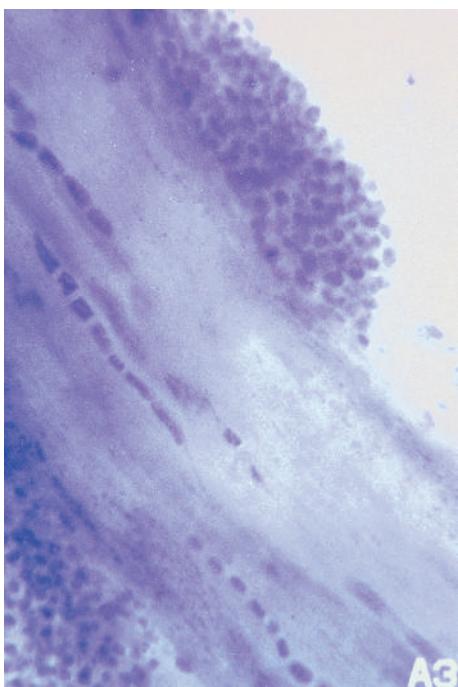
**Figure 17-9** Dermatophytid (id) reaction. These flesh-colored, pruritic papules developed on the extensor extremities (**A**) and face (**B**) after initiating oral therapy for tinea capitis.

lected with a forceps or of skin scrapings from scaly areas may be useful. Microscopic examination of an infected hair (Fig. 17-10) will reveal tiny arthrospores surrounding the hair shaft in *Microsporum* infection (ectothrix infection) and chains of arthrospores within the hair shaft (endothrix infection) in *T. tonsurans* and *T. violaceum* infections.

The color change in a DTM-plated fungal culture may begin within 24 to 48 hours for fast-growing dermatophytes and appears as a pinkish or red zone around the developing colony. The color will intensify as growth proceeds, with full color development for most cultures in 3 to 7 days (Fig. 17-11). When DTM medium is used, however, the culture should not be evaluated for color after 10 days, because contaminant fungal growth may cause color change by that time, thus leading to false-positive results. It must be remembered that fungi grow best at room temperature and require oxygen. Accordingly, the culture media should be left at room temperature, and the tops of the culture tubes or bottles should be left slightly unscrewed (or the tubes maybe covered only with a cotton plug) to allow aeration of the preparation.

Tinea capitis requires systemic therapy, because the drug needs to penetrate the hair follicle. For decades, the treatment of choice for tinea capitis has been griseofulvin, and this drug remained the only agent approved by the US Food and Drug Administration (FDA) for the treatment of this disorder in children until recently. Terbinafine oral granules are now approved by the FDA for treatment of tinea capitis in children 4 years of age and older. Several other agents, including the azole antifungals (fluconazole, itraconazole, and ketoconazole) have been increasingly evaluated as alternative approaches to therapy. Hence, although griseofulvin remains the gold standard, newer treatment options continue to be explored and may, in the near future lead to a modification of the traditional approach to therapy. In some instances, these newer agents may be preferable given similar efficacy to griseofulvin and shorter treatment durations.<sup>18</sup>

Griseofulvin is a well-tolerated and safe drug that has been extensively used worldwide for this indication. Although in the past doses



**Figure 17-10** KOH examination of hair. Note multiple spores surrounding the hair shaft (ectothrix) in this patient with *Microsporum* infection. (Courtesy of Alfred W. Kopf, MD.)



**Figure 17-11** Fungal cultures. Cultures plated on Sabouraud agar (top row, two on left) and dermatophyte test medium (DTM; top row, two on right) reveal fungal growth and color change (yellow to red on DTM), confirming the presence of a dermatophyte.

of 10 mg/kg per day were utilized, most experts currently recommend 20 to 25 mg/kg per day of microsize griseofulvin for 6 to 8 weeks (10 to 15 mg/kg per day if the ultramicrosize form is used). Absorption of griseofulvin is enhanced by a fatty meal, which should be recommended to the patient and parents. Treatment failures are reported and may represent increasing resistance of dermatophytes, although noncompliance with therapy or repeat exposure to infected contacts are probably more common reasons for treatment failure.

Side effects of griseofulvin are rare and include headache, gastrointestinal disturbance, photosensitivity, and rare morbilliform drug reactions. Hematologic and hepatic toxicity is very uncommon, and routine laboratory monitoring is generally not recommended. Although potential cross allergy with penicillins or cephalosporins is often mentioned, in reality this risk is quite low. Concomitant therapy with an antifungal shampoo such as ketoconazole or selenium sulfide

twice to thrice weekly is desirable, because these agents may aid in removing scales and eradicating viable spores, which may help decrease the potential spread of infection.<sup>19,20</sup> This recommendation should be made regardless of the choice of the systemic agent.

Contraindications to griseofulvin therapy include pregnancy, hepatic failure, and porphyria (especially acute intermittent, variegate, and porphyria cutanea tarda). The drug has rarely been implicated in causing exacerbations of lupus erythematosus or lupus-like syndromes.<sup>21</sup> Drug interactions include warfarin-type anticoagulants, barbiturates, and oral contraceptives, and in addition, a disulfiram-like reaction may occur with alcohol ingestion.

Terbinafine is an allylamine antifungal agent that has been demonstrated very effective as therapy for tinea capitis. It is currently approved for onychomycosis and as noted above, was more recently approved for treatment of tinea capitis in children 4 years of age and older (in the oral granules formulation). Comparative studies between terbinafine and griseofulvin have demonstrated that treatment with the former for 4 weeks is at least as effective as griseofulvin for 8 weeks.<sup>22,23</sup> In a comparison of terbinafine oral granules with griseofulvin oral suspension, the former resulted in greater rates of clinical cure and mycologic cure for patients infected with *T. tonsurans* (but not *M. canis*).<sup>24</sup> Metaanalyses of trials comparing griseofulvin to terbinafine have confirmed that the former is superior for infections caused by *M. canis*, whereas terbinafine may be superior for infections caused by *T. tonsurans*.<sup>25,26</sup> Studies have evaluated a variety of terbinafine treatment regimens and durations, including continuous therapy for 1 to 10 weeks (package recommendation for terbinafine granules: 6 weeks) and pulsed dosing, somewhat similar to that described for itraconazole (see below). Suggested dosing regimens for terbinafine include 3 to 6 mg/kg per day or a schedule based on patient weight. According to this schedule, the granules (which come in packets of either 125 mg or 187.5 mg) are dosed as follows: weight less than 25 kg: 125 mg/day; 25 to 35 kg: 187.5 mg/day; greater than 35 kg: 250 mg/day.<sup>27</sup> When the granules are used, they should be sprinkled onto nonacidic food such as mashed potatoes or pudding and swallowed without chewing.<sup>28</sup> Some authors have suggested that the weight-scheduled dosing may underdose individuals at the high-end of the weight range. In a duration-finding study of terbinafine in the treatment of tinea capitis, a 2- or 4-week regimen was found to be clinically superior to a 1-week regimen.<sup>29</sup> If it is used, higher doses of terbinafine or a longer course of therapy may be necessary for *M. canis* infections.<sup>30,31</sup>

Oral terbinafine has an excellent safety profile overall and is the most commonly used systemic antifungal agent in Europe.<sup>32</sup> Side effects related to its use are rare and include gastrointestinal symptoms, dizziness, headache, taste or smell disturbances, depression, and uncommonly, drug reactions (see Chapters 20 and 22). Elevated hepatic transaminases and cytopenias are occasionally seen, and some drugs including cimetidine, terfenadine, and cyclosporine may interact. Laboratory monitoring (complete blood cell count and liver enzymes) at baseline and during therapy is advisable.

Ketoconazole, a broad-spectrum azole antifungal compound, has good activity against dermatophytes, especially *Trichophyton* species. However, given the potential risk of hepatotoxicity and the lack of a liquid formulation, this drug is not a favorable alternative to griseofulvin. Other azole antifungal agents such as fluconazole and itraconazole seem to offer more promise as alternative agents in the treatment of tinea capitis.

Fluconazole, which is currently approved for systemic mycoses, has been demonstrated effective in tinea capitis and as with the other newer agents, may require a shorter treatment duration. It has an excellent safety profile, is usually well tolerated, and is available in a liquid suspension for children (10 and 40 mg/mL). Fluconazole has shown efficacy against both *Microsporum* and *Trichophyton* species. Most studies have evaluated dosing of 3 to 6 mg/kg per day for 2 to 4 weeks.<sup>33-35</sup> Once weekly pulse dosing for 8 to 12 weeks has also been demonstrated effective.<sup>36</sup> Potential adverse effects of fluconazole include gastrointestinal symptoms, headache, drug interactions, and drug reaction. Hematologic and hepatic toxicity may occasionally occur.

Itraconazole is another azole antifungal agent that has been studied for use in tinea capitis, where it has been demonstrated effective in

most (but not all) studies. It is currently approved for onychomycosis and some systemic mycoses, and in studies has shown efficacy against both *Microsporum* and *Trichophyton* species. Itraconazole is effective in a 100-mg capsule and a 10 mg/mL oral solution. The dosing recommended for this agent is 3 to 5 mg/kg per day, with the lower end of the dosing schedule utilized when the oral solution is used. There are numerous studies evaluating itraconazole as a therapy of tinea capitis, and it has been demonstrated effective both in continuous dosing for 2 to 12 weeks and in a variety of pulsed dosing regimens. One such pulsed regimen consists of a daily dose for 1 week followed by repeat pulsing for 1 week given 2 weeks later, and a third pulse given 3 weeks after the second pulse.<sup>37</sup> In this regimen, the decision to administer the second or third pulse was determined by the response of the patient at that point in the therapy. Side effects of itraconazole therapy include headache, gastrointestinal complaints, and occasional hepatic dysfunction. The oral solution seems to be associated with an increased incidence of gastrointestinal side effects. Multiple drug interactions are possible, and hence all concomitantly ingested medications should be carefully referenced before considering itraconazole therapy.

An important consideration in the child with tinea capitis is school attendance and the issue of contagiousness. It is not practical to keep children with tinea capitis out of the classroom, because spore shedding may continue for months, even after adequate therapy.<sup>38</sup> Appropriate therapy should be instituted, and children receiving treatment should be allowed to attend school.<sup>39</sup> Measures should be taken, where feasible, to avoid transmission between susceptible hosts, including no sharing of combs, brushes, hats, or hooded jackets. In patients in whom appropriate therapy has not led to improvement in symptoms, siblings and close contacts should be examined and fungal cultures performed. Haircuts, shaving of the head, or wearing a cap during treatment are unnecessary.<sup>39</sup>

The treatment of kerion (also known as *kerion celsi*) deserves special mention. These markedly inflammatory reactions not uncommonly result in permanent scarring alopecia, and therefore rapid institution of aggressive therapy is indicated. In addition to antifungal therapy, systemic antibiotics should be considered, especially in the presence of significant crusting, because secondary bacterial infection may concomitantly occur. Skin swab for bacterial culture and sensitivity may be useful in this setting to guide the choice of antimicrobial. Oral corticosteroids are recommended by many in the treatment of kerions in a dose of 0.5 to 1 mg/kg per day for 2 to 4 weeks, although good controlled studies are lacking. Anecdotally this approach seems to be associated with more rapid resolution of the inflammation and reduction of pain. However, some authors report excellent outcomes in patients with kerion that was treated with antifungal therapy alone.<sup>40</sup>

### Tinea Faciei

Dermatophyte infection of the face is referred to as *tinea faciei*. Although it often presents in a similar fashion to *tinea corporis* (see below) with annular, scaly plaques (Fig. 17-12), *tinea faciei* may sometimes be quite subtle clinically, especially if topical corticosteroids have been used. In some instances, when the classic annular configuration is absent or the changes are markedly inflammatory, it is referred to as *tinea incognito* (Figs. 17-13 and 17-14), which may also occur in nonfacial areas (Fig. 17-15). *Tinea incognito* typically occurs in patients who have received preceding therapy with topical corticosteroids or calcineurin inhibitors.<sup>41</sup> Although localized mild *tinea faciei* may respond to topical antifungal therapy, systemic treatment (as described for *tinea capitis*) is often required to completely clear these lesions and minimize the rate of recurrence.

### Tinea Barbae

*Tinea barbae* is an uncommon fungal infection of the bearded area and surrounding skin of adolescent and adult males. Because the most common etiologic agents are zoophilic species of *Trichophyton mentagrophytes* and *T. verrucosum* (occasionally *T. violaceum* and *Trichophyton rubrum*), it occurs primarily among individuals from rural areas in close contact with cattle or other domestic animals. Autoinoculation of *T. rubrum* from infected nails (onychomycosis) has been reported in association with *tinea barbae*.<sup>42</sup>

The infection is usually confined to one side of the face and may consist of a solitary lesion or multiple areas of involvement. The



**Figure 17-12** *Tinea faciei*. Annular, erythematous scaly plaques of the face.



**Figure 17-13** *Tinea faciei/incognito*. This markedly inflamed ear had been treated with a variety of topical preparations (including topical corticosteroids, after which the annular border developed) before the diagnosis of *tinea*.

majority of infections are characterized by highly inflammatory purulent papules, pustules, exudate, crusting, and boggy nodules. The hairs within the infected areas are loose or absent, and pus may be expressed through the follicular openings. Spontaneous resolution may occur, or the lesions may persist for months with resultant alopecia and scar formation. Occasionally a less inflammatory superficial variety may occur, characterized by mild pustular folliculitis, erythematous patches with broken-off hairs, and a vesiculopustular border with central clearing similar to that seen in *tinea corporis*.

*Tinea barbae* must be differentiated from bacterial folliculitis of the bearded area (sycosis barbae), contact dermatitis, herpes zoster, or severe herpes simplex. Sycosis barbae is distinguished by the presence of papular and pustular lesions pierced in the center by a hair that is loose and easily extracted. Herpes simplex or herpes zoster usually presents with clusters of vesicles or erosions on an erythematous



**Figure 17-14** Tinea faciei/incipit. This 2-year-old girl was treated with topical antibiotics and steroids before referral. Culture grew *Trichophyton tonsurans*, and the infection cleared with combined oral and topical antifungal therapy.



**Figure 17-16** Tinea corporis. An expanding, erythematous, annular plaque.



**Figure 17-15** Tinea incognito. This impressive dermatitis involving the diaper region ultimately cleared after systemic antifungal therapy. Fungal culture revealed *Trichophyton mentagrophytes*.



**Figure 17-17** Tinea corporis. Multiple annular, erythematous, scaly plaques, with hyperpigmentation of the upper back and shoulders of a teenaged boy.

base, and the diagnosis is confirmed by Tzanck preparation, direct fluorescent antibody examination, or viral culture. Tinea barbae can be confirmed by microscopic examination of a KOH wet-mount of skin scrapings for fungal elements and/or fungal culture.

Treatment of tinea barbae consists of warm compresses (which help to remove crusts) and topical or oral antibiotics for the common secondary bacterial infection. The mainstay of therapy is an oral antifungal agent. With appropriate therapy, resolution occurs over 4 to 6 weeks.

### Tinea Corporis

Superficial tinea infections of the skin are termed *tinea corporis*. Sites of predilection include the nonhairy areas of the face (particularly in children; see *Tinea Faciei*), the trunk, and extremities, with exclusion of ringworm of the scalp (*tinea capitis*), bearded areas (*tinea barbae*), groin (*tinea cruris*), hands (*tinea manuum*), feet (*tinea pedis*), and nails (*onychomycosis*). Contact with other individuals, such as is seen in high school and college wrestlers ("*tinea corporis gladiatorium*"), and domestic animals, particularly young kittens and puppies, is a common cause of the affliction in children. The causative organism in young children is often *M. canis* and occasionally *M. audouinii* or *T. mentagrophytes*. In older children and adults, *T. rubrum*, *T. verrucosum*, *T. mentagrophytes*, or *T. tonsurans* are more likely to be responsible. In children with infection caused by *T. rubrum* or *Epidermophyton floccosum*, parents with tinea infection (especially *tinea pedis* or *onychomycosis*) are commonly the source of infection.

*Tinea corporis* tends to be asymmetrically distributed and is characterized by one or more annular, sharply circumscribed scaly plaques with a clear center and a scaly, vesicular, papular, or pustular border (hence the term *ringworm*) (Figs. 17-16 and 17-17). When multiple lesions are present they may become coalescent, resulting in bizarre polycyclic configurations (Fig. 17-18). Although *tinea corporis* may occur in people of all ages, it is most commonly seen in children, in individuals in warm humid climates, and in patients with systemic diseases such as diabetes mellitus, leukemia, or immunodeficiency. Although extensive *tinea* infection is considered a sign of possible immunodeficiency, it may also occur in otherwise-healthy, immunocompetent children (Fig. 17-19).

*Tinea corporis* is commonly manifested as classic ringworm with annular, oval, or circinate lesions. The pattern may, however, be variable, and it may mimic a variety of other dermatoses, including the herald patch of pityriasis rosea, nummular eczema, psoriasis, contact dermatitis, seborrheic dermatitis, *tinea versicolor*, vitiligo, erythema migrans (Lyme disease), granuloma annulare, fixed drug eruption, and lupus erythematosus. The use of topical corticosteroids may mask the diagnosis by altering the presenting features while the infection persists. Presentations that may occur in this setting include *tinea incognito* (as described) and Majocchi granuloma. This perifollicular granulomatous disorder, which also occurs on the legs of women with *tinea* who shave, is a distinctive variant of ringworm and essentially represents a granulomatous folliculitis and perifolliculitis caused by *T. rubrum* or *T. mentagrophytes*. It presents with erythematous plaques



**Figure 17-18** Tinea corporis. Multiple annular erythematous plaques with confluence and a polycyclic configuration occurred in this immunocompromised patient.



**Figure 17-20** Majocchi granuloma. This annular plaque developed follicular papules after treatment with topical corticosteroids.



**Figure 17-19** Tinea corporis. Extensive involvement was noted in this otherwise healthy, immunocompetent 3-year-old girl. Culture revealed *Trichophyton mentagrophytes*.



**Figure 17-21** Majocchi granuloma. An annular plaque studded with multiple small pustules. This lesion developed after treatment with topical corticosteroids.

or patches that reveal scattered papules, papulonodules, or pustules studding the surface (Figs. 17-20 and 17-21). If observed early in the course of the process, a hair may be noted in the center of the papular or pustular lesions.

Tinea corporis can often be diagnosed based upon the clinical presentation. Diagnostic examinations include KOH wet-mount examination of skin scrapings and fungal culture, as described earlier for tinea capitis. Wood lamp examination is usually not useful for diagnosing tinea corporis.

Confusion often exists among nondermatologists regarding the classification and management of cutaneous fungal infections. By definition, this term incorporates disorders caused by either dermatophyte or *Candida* infection. It must be recognized, however, that dermatophytes and *Candida* are not synonymous, and that although nystatin is an effective agent against candidal infection, it is inappropriate and ineffective in the treatment of tinea (dermatophyte) infections. Conversely, some antifungal preparations that are active against dermatophytes, such as tolnaftate and terbinafine, seem to be minimally effective agents for treating candidal infections.

Topical antifungal therapy is generally effective for superficial or localized tinea corporis. These agents are usually applied twice daily, are well tolerated, and have very few side effects aside from occasional instances of irritant or allergic contact dermatitis. Table 17-2 lists some commonly used topical antifungal agents for dermatophyte infections.<sup>43</sup> Although clinical improvement and relief of pruritus may be seen within the first week of therapy, treatment should be continued for at least 2 to 3 weeks to ensure complete resolution.

If a patient shows no clinical improvement after several weeks of therapy, the diagnosis should be reconsidered or if confirmed and the patient has recalcitrant disease, a course of systemic therapy may be required. In certain situations, systemic antifungal therapy (similar to that described for tinea capitis) may be necessary from the start. These may include disseminated or severe disease, infection in an immunocompromised host, and Majocchi granuloma, in which case the depth of infection within the hair follicle requires the degree of penetration permitted only by a systemic agent.

Combination antifungal/corticosteroid preparations (i.e., 1% clotrimazole/0.05% betamethasone dipropionate) are widely used by nondermatologists in the treatment of superficial fungal infections, but care should be exercised with these products because their use may result in persistent or worsening infection.<sup>44,45</sup> In addition, some of these products contain a fairly potent corticosteroid, and hence their indiscriminate use can result in topical corticosteroid toxicities, including skin atrophy, telangiectasia, striae (Fig. 17-22), or systemic absorption. In some instances, such as severe tinea manuum or tinea pedis, such a combination product may be useful but should be applied for no longer than 2 to 4 weeks. This combination product should never be used in the diaper area, on the face, in fold areas, or under occlusion, and it is not recommended for children younger than 12 years of age.

Tinea corporis gladiatorum, which can impact an individual wrestler's ability to compete, as well as have an effect on entire wrestling squads, may require systemic therapy, especially when extensive. Many have advocated different approaches for prevention, although



**Figure 17-22** Steroid-induced striae. These lesions developed in the axilla of this patient after long-term therapy with betamethasone dipropionate in combination with clotrimazole. (Courtesy of Leonard Milstone, MD.)



**Figure 17-23** Tinea cruris. Scaly, erythematous plaques involving the bilateral medial thighs.

**Table 17-2** Some Commonly Used Topical Antifungal Agents for Tinea

Generic Name	Trade Name (Select)	Type	OTC/Rx
Butenafine	Mentax	C	Rx
Ciclopirox	Loprox, Penlac	C, L, G, NL, Sh	Rx
Clotrimazole	Lotrimin, Mycelex, Desenex	C, L, S, P	Both
Econazole	Spectazole, Ecstatin	C	Rx
Ketoconazole	Nizoral, Nizoral AD	C, Sh	Both
Miconazole	Monistat, Zeasorb AF, Micatin	C, L, P, S	OTC
Naftifine	Naftin	C, G	Rx
Oxiconazole	Oxistat	C, L	Rx
Sertaconazole	Ertaczo	C	Rx
Sulconazole	Exelderm	C, S	Rx
Terbinafine	Lamisil	C, S	Both
Tolnaftate	Tinactin, Zeasorb AF, Fungi Cure	C, G, P, S	OTC

Modified from Lesher J, Woody CM. Antimicrobial drugs. In: Bolognia JL, Jorizzo JL, Rapini RR, et al. editors. Dermatology, London: Mosby; 2003. p. 2007-31.

C, Cream; G, gel; L, lotion; NL, nail lacquer; OTC, over-the-counter; P, powder; Rx, by prescription; S, solution; Sh, shampoo.

well-designed clinical trials have been minimal. In one study, 100 mg of oral fluconazole given once weekly resulted in a significantly decreased incidence of infection when compared with placebo.<sup>46</sup> In a prospective longitudinal study, 100 mg of fluconazole given once daily for 3 days before onset of the competitive wrestling season and again 6 weeks into the season led to a dramatic decrease in the incidence rate of tinea gladiatorum.<sup>47</sup>

### Tinea Imbricata

Tinea imbricata (Tokelau), which is caused by *Trichophyton concentricum*, is a superficial dermatophyte infection seen primarily in tropical regions of the Far East, South Pacific, South and Central America, and parts of Africa. It is characterized by concentric rings of scaling that form extensive patches with polycyclic borders. With time, the lesions spread peripherally and form large plaques that may cover almost the entire skin surface, although the scalp, axillae, palms, and soles are usually spared. When fully developed, the concentric rings are seen as parallel lines of scales overlapping each other, resembling tiles or shingles (*imbrex* means “having overlapping edges,” like a shingle) on

a roof. Diagnosis is based on the characteristic clinical presentation, microscopic demonstration of interlacing septate hyphae, and identification of the organism by fungal culture. Although treatment with a systemic antifungal agent will usually clear the eruption within 2 to 4 weeks, there is a tendency for recurrence when treatment is discontinued. Susceptible individuals tend to carry the disease for their lifetime, given the difficulty in achieving a total cure.<sup>48</sup>

### Tinea Cruris

Tinea cruris (“jock itch”) is an extremely common superficial fungal infection of the groin and upper thighs. It is seen primarily in male adolescents and adults and occurs less commonly in females. Tinea cruris is most symptomatic in hot, humid weather and is most commonly noted in obese individuals or those subject to vigorous physical activity and chafing. Tight-fitting clothing such as athletic supporters, jockey shorts, wet bathing suits, and panty hose may contribute to this condition as well. The three most common dermatophytes to result in tinea cruris are *E. floccosum*, *T. rubrum*, and *T. mentagrophytes*. Tinea pedis is a common coexisting condition, possibly related to autoinoculation of the dermatophyte with clothing that comes into contact with the feet.

Tinea cruris presents as sharply marginated, erythematous plaques with an elevated border of scaling, pustules, or vesicles. It is usually but not always bilaterally symmetric and involves the intertriginous folds near the scrotum, the upper inner thighs (Fig. 17-23), and occasionally the perianal regions, buttocks, and abdomen. The scrotum and labia majora are usually spared, and if they are involved or satellite papulopustules are present, the diagnosis of candidiasis (Fig. 17-24) should be considered. The lesions of tinea cruris may vary in color from red to brown, and central clearing may be present. In chronic infection the redness and scaling may be slight, the active margin may be subtle or ill-defined, and lichenification may be present.

Tinea cruris must be differentiated from intertrigo, seborrheic dermatitis, psoriasis, irritant contact dermatitis, allergic contact dermatitis (generally resulting from therapy), or erythrasma (a superficial dermatosis caused by the diphtheroid *Corynebacterium minutissimum*). A characteristic coral-red fluorescence under Wood light examination is helpful in distinguishing erythrasma (see Chapter 14). The diagnosis of tinea cruris can be confirmed by a KOH wet-mount microscopic examination of cutaneous scrapings or by fungal culture.

Topical therapy (as discussed for tinea corporis) usually suffices for tinea cruris and is applied for 3 to 4 weeks. Other useful measures include reducing excessive chafing and irritation by the use of loose-fitting cotton underclothing, drying thoroughly after bathing or perspiration, and weight loss. The use of an absorbent antifungal powder (i.e., Micatin, Tinactin, or Zeasorb-AF) is sometimes helpful, and oral antifungal therapy is occasionally indicated for severe or recalcitrant disease. Tinea pedis, if present, should also be adequately treated as a preventative measure.



**Figure 17-24** Genital candidiasis. Erythema and scaling of the scrotum with involvement of the adjacent thigh regions. Note the associated satellite papules.



**Figure 17-25** Intertriginous tinea pedis. Scaling, erythema, and maceration of the plantar foot and toe-web spaces.

### Tinea Pedis

Tinea pedis, or “athlete’s foot,” is relatively uncommon in young children but quite common in adolescents and adults, in whom it represents the most prevalent type of ringworm infection. Although children are not completely immune, most instances of athlete’s foot in prepubertal individuals actually represent misdiagnosed cases of foot dermatitis, dyshidrotic eczema, contact dermatitis, or other dermatoses.<sup>49,50</sup> The differential diagnosis of tinea pedis also includes psoriasis, juvenile plantar dermatosis, erythrasma, and secondary syphilis. Associated conditions or complications include onychomycosis (see **Tinea Unguium [Onychomycosis]**), secondary bacterial superinfection, id reaction, and cellulitis.

The etiologic agents most often responsible for tinea pedis are *T. rubrum* and *T. mentagrophytes* and less often *E. floccosum* or (especially in children) *T. tonsurans*. The disorder may present clinically in a variety of different ways. The interdigital type, which is the most common presentation, reveals inflammation, scaling, and maceration in the toe-web spaces (Figs. 17-25 and 17-26), especially the lateral ones. The inflammatory or vesicular type shows inflammation with vesicles (Fig. 17-27) or larger bullae and usually results from *T. mentagrophytes* infection. This type occurs most often in summer, and an immune response to fungal elements may be reflected by a vesicular id eruption on the hands, extremities, and trunk. Moccasin-type tinea pedis presents with erythema, scaling, fissuring, and hyperkeratosis



**Figure 17-26** Tinea pedis. This 6-year-old girl showed erythema and desquamation of the plantar foot and toes (A) and toe-web erythema and maceration (B).



**Figure 17-27** Vesicular tinea pedis. Erythema and scaling are accompanied by intensely pruritic, deep-seated vesicles on the plantar surface.

on the plantar surfaces (Fig. 17-28), often extending to the lateral foot margins. Contrary to the eruption seen in foot eczema, the dorsal aspects of the toes and feet are usually spared, although they may occasionally be involved (Fig. 17-29). This form may be resistant to topical therapy, thus requiring an oral antifungal medication.

The diagnosis of tinea pedis is based upon the clinical picture, with confirmation by KOH examination and fungal culture. Treatment may be challenging, and efforts to protect the feet from commonplace sites of exposure to the organisms (i.e., public showers, gyms, locker rooms,



**Figure 17-28** Moccasin-type tinea pedis. Erythema and scaling with involvement of the lateral foot borders. Note the associated onychomycosis.



**Figure 17-29** Tinea pedis. Involvement of the dorsal surface of the foot is occasionally noted. Note the toe-web involvement.

pool decking) and to keep the feet dry are both important. Such efforts might include thorough drying of the feet after bathing, avoidance of occlusive footwear or nonbreathable socks, and the use of sandals or other footwear in high-risk areas. Absorbent antifungal powders or sprays may be used once or twice daily in individuals prone to these infections, especially after physical exertion and bathing. Those prone to hyperhidrosis can use 6.25% to 20% aluminum chloride (i.e., Certain Dri, Drysol, or Xerac AC) in an effort to decrease recurrent infection.

The usual treatment of choice for tinea pedis is a topical antifungal preparation applied twice daily. Acute vesicular lesions are best treated with wet compresses applied for 10 to 15 minutes two to four times daily in addition to the antifungal therapy. In patients with severely inflammatory disease or those with underlying chronic medical conditions such as diabetes or immunosuppression, oral antifungal therapy should be considered. The choices for oral therapy are similar to those discussed for tinea capitis, and a review of the literature reveals that terbinafine may be one of the more effective agents for this indication.<sup>51</sup>

In instances in which the diagnosis is indeterminate, a topical antifungal agent and a corticosteroid formulation may both be used for a short period (2 to 4 weeks), at which time a fungal culture performed at the initiation of therapy can generally confirm or refute the diagnosis of tinea. If the diagnosis of tinea pedis is confirmed, the topical corticosteroid can be discontinued. Moccasin-type tinea pedis may require the addition of a keratolytic agent (i.e., lactic acid or urea) in addition to the antifungal in order to treat the hyperkeratosis and accentuate penetration of the antimicrobial. Id reactions, when present, are best treated with topical corticosteroids and oral antihistamines (if needed) and generally improve with eradication of the primary infection.

### Tinea Manuum

Ringworm infection of the palmar hand (tinea manuum) is uncommon in childhood and when present is generally seen in postpubertal individuals. When ringworm occurs on the dorsum of the hand, it is referred to as *tinea corporis* rather than *tinea manuum*. Tinea manuum is usually unilateral and is caused by the same fungi responsible for tinea pedis: *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*. It may be seen in association with tinea pedis, and when occurring on only one hand, presents in a fashion that has been termed *two-foot, one-hand syndrome*.

Clinical manifestations include a diffuse hyperkeratosis of the fingers and palm and a less common patchy inflammatory or vesicular reaction. Involvement of the fingernails (onychomycosis, see below) commonly occurs and may be a clue to the diagnosis. When onychomycosis is present, it usually involves some but not all of the nails on the affected hand. Total nail involvement, if present, should suggest the possible diagnoses of psoriasis or lichen planus. The differential diagnosis of tinea manuum includes psoriasis, allergic or irritant contact dermatitis, dyshidrosis, and an id reaction. Unilateral involvement may be another clue to the diagnosis, which can be confirmed by KOH microscopic examination or fungal culture.

The management of tinea manuum is essentially the same as that recommended for tinea pedis, and when the latter infection is simultaneously present, it should be appropriately treated as well.

### Tinea Unguium (Onychomycosis)

*Onychomycosis* is a general term that refers to a fungal infection of the fingernails or toenails. *Tinea unguium* is a term that specifically implies dermatophyte infection of the nails. However, the two terminologies are often used interchangeably in clinical practice, and for the purposes of the discussion, *onychomycosis* will refer to dermatophyte nail infections caused usually by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, and *E. floccosum*. Periungual infection caused by *Candida albicans* is discussed in the section on candidiasis. Onychomycosis is more common in adults, although it does occur in children, often in association with tinea pedis or tinea manuum but also as a primary infection. The overall prevalence of onychomycosis in children has been estimated to be between 0 and 2.6%.<sup>52,53</sup> The lower incidence in children has been attributed to faster nail growth, smaller surface area for invasion, less nail trauma, lower incidence of tinea pedis, and less time spent in environments prone to infected fomites such as locker rooms.<sup>54</sup> The majority of prepubertal children with onychomycosis have a first-degree relative with onychomycosis and/or tinea pedis. Pediatric onychomycosis affects the toenails in two-thirds of patients and the fingernails in one-third.<sup>55</sup>

Onychomycosis is classified into several different patterns, including distal subungual, proximal subungual, and white superficial. The distal subungual type is the most common and is characterized by invasion of the underlying nailbed and inferior portion of the nail plate, which leads to onycholysis (detachment of the nail plate from the nailbed) and thickening of the subungual region, which takes on a discolored yellow-brown appearance<sup>56</sup> (Figs. 17-30 and 17-31). Proximal subungual onychomycosis is relatively uncommon and occurs when the invasion of the nail unit starts at the proximal nail-fold (the area near the cuticle). Clinically, destruction of the proximal nail plate is seen along with similar changes to the distal subungual type (Fig. 17-32). This form of onychomycosis is most common in individuals infected with human immunodeficiency virus (HIV), and it is considered by some to be an early marker for this infection. White



**Figure 17-30** Onychomycosis, distal subungual type. Yellow-white discoloration and thickening with the distal nail surfaces most involved.



**Figure 17-32** Onychomycosis, proximal subungual type. White discoloration of the nail plate with the process originating at the proximal nailfold regions.



**Figure 17-31** Onychomycosis, distal subungual type. (A) Diffuse involvement of the right foot with partial involvement of the left foot was present in this 14-year-old girl with Down syndrome. (B) Note the marked subungual debris and nail-plate destruction. Culture revealed *Trichophyton tonsurans*, a less common cause of onychomycosis.

superficial onychomycosis occurs with superficial infection of the nail plate and presents as well-delineated white plaques on the dorsal nail plate.

The diagnosis of onychomycosis is confirmed by direct microscopy of KOH wet-mount preparations and fungal culture. Material for

examination should be taken from the subungual debris, underside of the nail plate, nail clippings, or nailbed when necessary. Confirmation of the diagnosis is important, because many cases of nail dystrophy are not fungal in origin and are instead the result of another diagnosis such as psoriasis, postdermatitis onychodystrophy, chronic paronychia, trauma, drug-induced onycholysis, pachyonychia congenita, lichen planus, or a variety of other conditions (see Chapter 7). It must be remembered that onychomycosis is seldom symmetrical and that it is common to find involvement of only one, two, or three nails of only one hand or foot. In patients who have involvement of all nails, an alternative diagnosis should be highly suspected. In children diagnosed with onychomycosis, a search for other concomitant mycoses (especially tinea pedis and tinea capitis) should be completed.<sup>57</sup> Importantly, other close contacts with onychomycosis or tinea pedis should also be treated in an effort to end the cycle of transmission.

In general, topical agents tend to be relatively ineffective for the treatment of onychomycosis, in large part because of poor penetration through the nail plate. Topical antifungal therapy, however, is an important consideration as adjunctive therapy when tinea pedis is concomitantly present, in which case it may lower the relapse rate for onychomycosis. In addition, ciclopirox 8% nail lacquer solution has shown promise as an effective topical agent for onychomycosis, occasionally as monotherapy or more commonly, as an adjunctive treatment.<sup>58,59</sup> In a randomized prospective study of 40 children with onychomycosis treated with ciclopirox lacquer monotherapy over 32 weeks, mycologic cure was achieved in 77%.<sup>60</sup> Definitive therapy for onychomycosis in many patients, however, is best achieved with the use of oral antifungal agents. When considering therapy for this condition in children, many factors need to be incorporated into the equation, including the results of diagnostic studies, severity of the infection, age of the patient, and the risk-to-benefit ratios of the treatments being considered. Parents of younger children should be given the appropriate information regarding therapy and be allowed to make an informed decision. In many instances a trial of topical therapy with further consideration of systemic therapy if needed down the road may be a desirable option for parents. A systematic review of published studies on systemic therapy for pediatric onychomycosis revealed cure rates of 70% to 80%, similar to that seen in adults, and very good safety profiles.<sup>61</sup>

Griseofulvin has traditionally been the treatment of choice for systemic therapy of onychomycosis. However, this agent requires long-term administration and is associated with low cure rates and high relapse rates. Newer antifungal agents including fluconazole, itraconazole, and terbinafine appear promising as therapies for this condition, and the latter two medications are FDA-approved for this indication in adults. All of these agents have high affinity for keratin, another advantage over griseofulvin, and all remain concentrated in the nails for months after discontinuation of therapy.<sup>56</sup> In addition, they seem to result in much lower relapse rates.



**Figure 17-33** Tinea versicolor. Hypopigmented, minimally scaly macules and patches of seborrheic areas of the trunk.



**Figure 17-34** Tinea versicolor. Occasional involvement of the face and/or neck is noted, especially in darkly pigmented individuals.

The newer antifungal agents have been dosed in a variety of fashions in studies of onychomycosis. Fluconazole has usually been given as a weekly dose but may require 12 to 26 weeks of treatment.<sup>62</sup> Itraconazole and terbinafine appear to be effective with a more convenient dosing regimen. Itraconazole pulse therapy (given daily for 1 week/month for 3 to 4 months) is a preferred strategy in adults with onychomycosis. This approach has been studied in pediatric patients and appears to be effective and relatively safe,<sup>54,63</sup> although adequately randomized trials are lacking. Terbinafine has demonstrated significant effectiveness in the treatment of onychomycosis. This agent is usually given as a daily dose for 3 to 4 months, and several studies have suggested superior efficacy and cost effectiveness over the other antifungal drugs.<sup>64–66</sup>

### TINEA VERSICOLOR

Tinea versicolor ( pityriasis versicolor ) is an extremely common superficial fungal disorder of the skin characterized by multiple scaling, oval macules, patches, and thin plaques distributed over the upper portions of the trunk, proximal arms, and occasionally the neck or face. It is caused by the yeast forms of the dimorphic fungus *Malassezia furfur*, which are referred to as *Pityrosporum orbiculare* and *Pityrosporum ovale*. This organism is part of the normal cutaneous flora. The disorder occurs worldwide, and the majority of cases present in adolescents, possibly in relation to the lipophilic nature of the organism and the sebum-rich environment of the affected regions. Tinea versicolor only occasionally occurs in prepubertal children. Although *Malassezia* is part of the normal flora, in immunocompromised hosts this yeast may be associated with opportunistic infections, including catheter-related fungemia, peritonitis, septic arthritis, pulmonary infection, and sinusitis.<sup>67</sup>

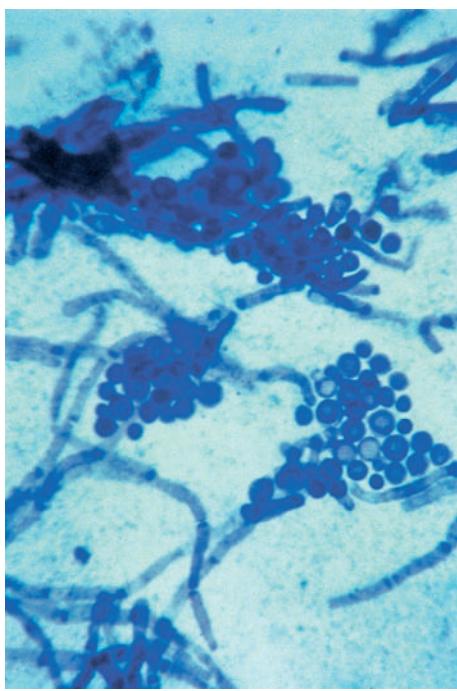
The diagnosis is usually made clinically based on the characteristic presentation. Lesions may be most appreciated during summer months when sun exposure leads to increasing discrepancies in skin pigmentation between affected and unaffected areas. Examination reveals thin, scaly papules and plaques distributed on the chest, back (Fig. 17-33), and less commonly on the face and neck (Fig. 17-34). They may be hypopigmented or hyperpigmented (Fig. 17-35) depending on the patient's complexion and history of sun exposure,



**Figure 17-35** Tinea versicolor. This immunosuppressed teenager with inflammatory bowel disease had hyperpigmented (rather than hypopigmented) scaly papules and plaques.

and sometimes mild erythema is present. Scalloping of the borders is common, and lesions may be so numerous that they coalesce into larger patches. Lower extremities and genitals are rare sites of involvement. Interestingly, azelaic acid is a dicarboxylic acid produced by *M. furfur* that inhibits the dopa-tyrosinase reaction, which may result in the hypopigmentation seen in this disorder. This acid is marketed as an acne therapy product for acne-induced hyperpigmentation (see Chapter 8).

The differential diagnosis of tinea versicolor includes vitiligo, pityriasis alba, postinflammatory hypopigmentation or hyperpigmentation, pityriasis rosea, tinea, psoriasis, and confluent and reticular papillomatosis of Gougerot and Carteaud (see Chapter 23). Distinguishing clinical features are usually sufficient to differentiate these various conditions. Vitiligo presents with depigmentation rather than hypopigmentation, with well-demarcated patches most often localized around orifices and bony prominences. Pityriasis alba presents with



**Figure 17-36** KOH preparation of tinea versicolor. Short, blunt-ended hyphae and clusters of spores are present in the classic “spaghetti-and-meatballs” pattern in scrapings from a patient with tinea versicolor.

hypopigmented patches, but these lesions are usually limited to the face, occur in atopic individuals, and are only rarely as extensive as one would expect for tinea versicolor. The diagnosis can be confirmed by a KOH wet-mount of cutaneous scrapings, which reveals the highly characteristic short fungal hyphae and spores in grape-like clusters (the “spaghetti-and-meatballs” pattern) (Fig. 17-36) on microscopic examination. Fungal culture is generally not useful, because the organism is difficult to grow on culture media and *M. furfur* is part of the normal skin flora.

The treatment options for tinea versicolor are many, although better randomized, placebo-controlled prospective clinical trials investigating their efficacy and safety are needed.<sup>68</sup> Tinea versicolor may respond to a variety of topical preparations. However, because the course of the disorder is usually chronic, recurrences are common, and the pigmentary changes may take months to years to revert, adequate patient education and setting appropriate expectations are vital. Selenium sulfide 2.5% shampoo is a convenient, inexpensive, safe, and relatively effective mode of therapy, especially for younger patients. It is applied in a thin layer for 10 minutes before rinsing for 1 to 2 weeks. Less frequent intermittent applications (i.e., every other week or monthly) are then useful for maintenance. Ketoconazole 2% shampoo has also been recommended and was shown effective when applied as a single application or daily for 3 days.<sup>69</sup> More recently, terbinafine 1% spray has become available and is applied once to twice daily for 1 to 2 weeks. Topical antifungal creams are also effective, but their use is often impractical given the wide surface area of skin usually involved.

Oral therapy is desirable in patients with severe disease or recurrent disease or in those in whom topical therapies have failed. A variety of oral antifungal agents including ketoconazole, fluconazole, itraconazole, and terbinafine have been proposed for this condition. Multiple dosing regimens have been advocated, including continuous, intermittent, and single-dose approaches. A favorite systemic regimen for tinea versicolor is single-dose (400 mg) ketoconazole followed by physical activity to promote secretion of the drug onto the skin via sweating. The patient then delays showering or rinsing for 10 to 12 hours and repeats the therapy in 1 week. Recently, however, the FDA has recommended against ketoconazole as a first-line antifungal therapy, given concerns over potentially severe liver toxicity.

Itraconazole single-dose therapy (400 mg) was compared with a 7-day continuous therapy (200 mg daily dose), and both regimens were found to be equally effective.<sup>70,71</sup> In another randomized prospective study, single- and multiple-dose regimens of ketoconazole and fluconazole were compared, and single-dose (400 mg) oral fluconazole provided the best clinical and mycological cure rates with no relapse during 12 months of follow-up study.<sup>72</sup> In a study of extensive tinea versicolor, single-dose ketoconazole (400 mg) was compared with two doses of fluconazole (300 mg) with a 2-week interval between doses. Similar clinical response was noted in both groups (81.5% improvement for fluconazole, 87.9% for ketoconazole) with no significant adverse events in either group.<sup>73</sup>

There is no current consensus or gold standard of care for systemic therapy of tinea versicolor. If an imidazole antifungal agent is used, however, the potential for drug interactions (especially with itraconazole and ketoconazole), liver toxicity (itraconazole and ketoconazole), congestive heart failure (itraconazole), and other side effects must always be considered and discussed with the patient and/or parent.

### TINEA NIGRA

Tinea nigra is a superficial fungal infection of the stratum corneum caused by the black yeast-like mold *Phaeoannellomyces* or *Hortaea werneckii* (formerly called *Cladosporium* or *Exophiala werneckii*). Because it is not caused by a dermatophyte fungus, *tinea* (as with tinea versicolor) is a misnomer. This infection occurs most often in warm humid areas of Central or South America, Africa, Asia, and occasionally the coastal southern United States. It presents as an asymptomatic, light to dark brown or black, sharply marginated macule or patch, usually involving the palm and less likely the dorsal surface of the hand or plantar foot. Visible scaling is rare. The most important aspect of tinea nigra is the potential misdiagnosis as malignant melanoma. Other misdiagnoses may include postinflammatory hyperpigmentation, fixed drug eruption, or chemical stain.<sup>74</sup> Direct microscopic examination of a KOH wet-mount preparation of skin scrapings reveals gray-brown to green hyphae and budding yeast cells, and fungal culture is confirmatory. Tinea nigra is treated with a topical antifungal preparation such as miconazole, clotrimazole, or terbinafine cream. The application of keratolytic agents such as salicylic acid or Whitfield ointment (6% benzoic acid and 3% salicylic acid) or 10% thiabendazole solution is another therapeutic option.

### PIEDRA

Piedra is an asymptomatic fungal infection of the hair shaft caused by *Piedraia hortae* (black piedra) or various *Trichosporon* species (formerly known as *Trichosporon beigelii*; white piedra). The species that most commonly cause white piedra are *Trichosporon inkin*, *Trichosporon cutaneum* and *Trichosporon ovoides*.<sup>75,76</sup>

Black piedra is seen most commonly in tropical areas of South America, the Far East, and the Pacific Islands. It is characterized by small, hard, and adherent brown-black nodules on the hair shafts of the scalp, which on hair microscopy are composed of honeycomb-like masses of fungal ascospores. These nodules contain phosphorus, sulfur, and calcium, which are all part of the extracellular material involved in the organization of the fungus.<sup>77</sup> Fungal culture usually confirms the diagnosis. Traditional therapy consists of hair removal by clipping or shaving, and oral terbinafine may be useful.<sup>78</sup>

White piedra is seen in temperate climates of South America, Europe, Asia, Australia, and the southern United States. It may affect the scalp as well as eyelash, eyebrow, beard, axillary, or pubic hair. Traditional burkha-clad Muslim women may be predisposed to this condition.<sup>79</sup> White piedra may be underreported in the United States, with recent reports in children from the northeastern states, several of whom were immigrants. This observation suggests that cases in the United States may be primarily imported and hence influenced by immigration trends.<sup>80</sup> It is characterized by asymptomatic, soft, white-tan elongated nodules on the hair shaft that may be mistaken for the nits of head louse infestation or hair casts. Additionally, the differential diagnosis may include monilethrix and trichorrhexis nodosa. Microscopic examination of a hair mount reveals yeast-like

cells completely encircling the hair shaft and occasional hyphae perpendicular to the hair shaft. The organism can be recovered from a fungal culture. Again, clipping or shaving the hair is usually curative. Oral itraconazole and fluconazole have been demonstrated effective in open-label studies, but recurrence may be noted.<sup>79,80</sup> Concomitant use of an azole (i.e., ketoconazole) shampoo has been advocated as adjunctive therapy, and topical antifungal creams have also been used.

Although the etiologic agent of white piedra usually results in this benign hair condition, disseminated infection may occur in immunocompromised hosts, especially those with neutropenia and HIV infection.<sup>81,82</sup> Low-birthweight neonates are another population at risk for fungal septicemia with this organism.<sup>83</sup> Cutaneous lesions may occur with disseminated disease and consist of purpuric papules, nodules, and necrosis. Therapy of *Trichosporon* sepsis/multiorgan dissemination is difficult, because many isolates are resistant to amphotericin B, and the mortality rate is high.

## Candidiasis

Candidiasis (moniliasis) is an acute or chronic infection of the skin, mucous membranes, and occasionally internal organs caused by yeast-like fungi of the *Candida* genus. Although several candidal species may be associated with human infection, *C. albicans* is by far the most common cause. *C. albicans* is not a normal cutaneous saprophyte but usually exists in the microflora of the oral cavity, gastrointestinal tract, and vagina. It becomes a cutaneous pathogen when there is an alteration in host defenses, either localized or generalized, that allows the organism to become invasive.

Factors that predispose to candidiasis include endocrinologic disorders (i.e., diabetes mellitus, hypoparathyroidism, and Addison disease), genetic disorders (i.e., Down syndrome, acrodermatitis enteropathica, and chronic mucocutaneous candidiasis [CMC]), malignancy (especially leukemia or lymphoma), and certain systemic medications (i.e., antibiotics, corticosteroids, and immunosuppressive agents).

Newborns and infants are physiologically susceptible to candidal infection, which may be commonly manifested as oral candidiasis (thrush), diaper candidiasis, or intertrigo. Other presentations of candidal infection in childhood include vulvovaginitis, angular cheilitis (perlèche), and nail involvement (paronychia). Neonatal, congenital, systemic, and CMC are additional patterns of infection with *Candida*. Candidiasis in the infant is often traceable to an infected mother who may be a vaginal or intestinal carrier of the organism. These infants may harbor *C. albicans* in the mouth or intestinal canal, and the infected saliva or stools constitute a focus for cutaneous infection. The presence of *Candida* species in the mouths of children has been proposed as a possible factor contributing to dental caries.<sup>84</sup> There follows a review of several types of mucocutaneous candidiasis in children, including a discussion of congenital and neonatal candidiasis and risk factors for severe disease. (Diaper candidiasis is discussed in detail in Chapter 2.)

### ORAL CANDIDIASIS (THRUSH)

Oral candidiasis (thrush) is a painless or painful *Candida* infection of the tongue, soft and hard palates, and buccal and gingival mucosae. It is characterized by white to gray, friable, pseudomembranous patches or plaques overlying a reddened mucosa (Fig. 17-37) (see Chapter 2, Fig. 2-26) and is most commonly seen in infants. Thrush may be acquired at the time of delivery during passage through an infected birth canal, during nursing from the skin of the mother's breast or hands, or from imperfect sterilization of feeding bottles.<sup>85</sup> Oral candidiasis also occurs at a greater rate in children with cystic fibrosis, diabetes, or immunodeficiency and in those who have undergone organ transplantation.<sup>86,87</sup> In some of these instances, the predisposition toward this infection may be related to therapies for the condition (i.e., inhaled or oral corticosteroids in patients with asthma). It has also been shown to be positively correlated with dental caries in children.<sup>88</sup>

The diagnosis of oral candidiasis is often clinical, and it can be confirmed by gentle attempts to remove the curd-like plaques that, in distinction to milk or formula residue, adhere to the underlying oral



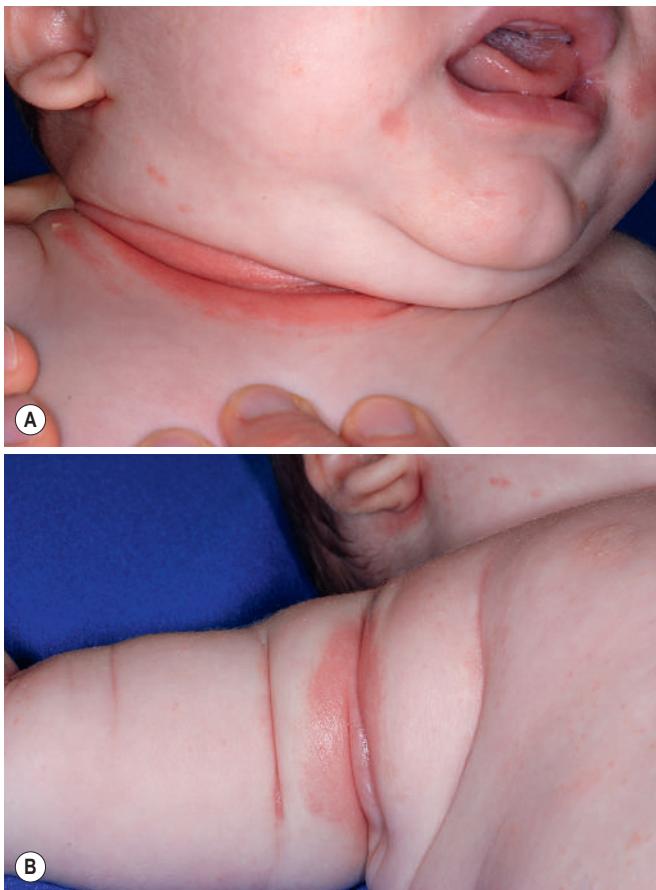
**Figure 17-37** Oral candidiasis. White, friable plaques on the dorsal tongue of an otherwise healthy infant girl.

mucosa. Removal is accomplished by gently rubbing the area with a cotton applicator or tongue blade, which results in an underlying inflammatory mucosal erosion. The organism may be identified by microscopic evaluation of a KOH wet-mount preparation of these materials or by fungal culture. Although most infants with oral thrush do not experience impairment of appetite or feeding, severe disease may be associated with such complications as well as significant pain. Immunocompromised infants often have a severe expression of oral candidiasis.

The usual approach to therapy, and one that is usually effective, is the administration of nystatin oral suspension, one dropperful in each cheek given four times daily. Massage of the suspension on the mucosa by the parent is useful after administration, and the medication is used for 7 to 14 days. Nystatin is unabsorbed from the gastrointestinal tract, as are some other topical therapies that have been used, including gentian violet, amphotericin B, miconazole, and clotrimazole. Options for older children include nystatin and clotrimazole tablets or troches. Although it has been suggested that clotrimazole or nystatin troches or suppositories may be inserted into the tip of a slit pacifier or nipple for the treatment of infants with oral candidiasis, these approaches have not been evaluated in controlled studies and the possibility of aspiration must be considered.<sup>85,89</sup> When treating infants with persistent or recurrent oral candidiasis, asymptomatic maternal vaginal candidiasis and candidal contamination of nipples or pacifiers should be considered as possible reservoirs for reinfection.<sup>90</sup> Oral antifungal agents, most notably fluconazole, have been demonstrated quite effective in the treatment of oral candidiasis in immunocompromised children.<sup>91,92</sup> In general, absorbable antifungal therapy should be used primarily if there is risk of dissemination or widespread disease is present.<sup>93</sup>

### INTERTRIGO

The moist warm conditions found in intertriginous areas favor the development of candidal infection. Intertrigo (see Chapter 3) refers to a condition marked by intense erythema in skin folds, including the axillary regions, the anterior neck fold (Fig. 17-38), posterior auricular regions, and inguinal creases. Although it does not always represent a fungal process, *C. albicans* infection is common, and secondary bacterial (i.e., *Staphylococcus aureus*) infection may occasionally be present. *Streptococcal intertrigo* refers to intertrigo in association with group A β-hemolytic streptococcus (GABHS; *Streptococcus pyogenes*) infection.<sup>94</sup> It presents with intertriginous inflammation that is well demarcated, weeping, and superficially eroded (Fig. 17-39). It is often associated with a foul odor and lacks the satellite papules and papulopustules that are characteristic of candidal intertrigo. Surface swabs



**Figure 17-38** Intertrigo. **(A)** Erythema and maceration of the anterior neck fold. Note the peripheral satellite papules and involvement of the auricular crease. **(B)** This infant also had involvement of the axillae. Skin swabs were positive for *Candida albicans*.



**Figure 17-39** Streptococcal intertrigo. This infant had well-demarcated erythema with erosive changes, weeping, and a foul odor. *Streptococcus pyogenes* was isolated on bacterial culture. Note the absence of satellite papules or pustules that are characteristic of candidal intertrigo.

are helpful for confirming the diagnosis via streptococcal rapid antigen test and/or bacterial culture.<sup>95</sup>

Treatment of intertrigo with a topical antifungal agent (i.e., clotrimazole, econazole, or ketoconazole cream) applied two to three times daily is usually sufficient. More severe cases may require the addition of a low-strength topical corticosteroid or when bacterial infection is



**Figure 17-40** Perlèche (angular cheilitis). Erythema, fissuring, and exudate of the mouth angle.

suspected, an appropriate oral antibiotic with activity against both *S. aureus* and GABHS.

### CANDIDAL VULVOVAGINITIS

*C. albicans* is a common inhabitant of the vaginal tract, and its incidence increases in diabetes and pregnancy and in females taking antibiotics or oral anovulatory preparations. When vulvovaginitis occurs, the labia become edematous and red, white patches appear on an erythematous mucosal surface, and leukorrhea develops. The resultant symptoms include painful itching, burning, and dysuria. The infection may spread to the perineum, perianal region, gluteal folds, and upper inner aspects of the thighs as well. Although vulvovaginitis is more common in adults, it occurs in premenarchal as well as adolescent females, and in the latter, it may be a marker for type 2 diabetes.<sup>96</sup> It accounted for nearly 62% of all gynecological problems seen during childhood and adolescence in one large study.<sup>97</sup> In premenarchal girls, psoriasis or atopic dermatitis may present with similar features and may be more common than candidiasis.<sup>98</sup> The differential considerations of candidal vulvovaginitis include bacterial infection, foreign body, contact dermatitis, poor hygiene, lichen sclerosus et atrophicus (typically quite distinguishable clinically) and sexual abuse.<sup>98,99</sup> The most common bacterial causes appear to be groups A and B β-hemolytic streptococci, *S. aureus*, *Proteus mirabilis*, *Escherichia coli*, and enterococci.<sup>97,100–102</sup>

The diagnosis of candidal vulvovaginitis is established by the clinical signs and symptoms and by demonstration of the fungus by KOH wet-mount examination and/or fungal culture. Treatment options include antifungal vaginal tablets, cream, or suppositories (i.e., clotrimazole, miconazole, nystatin, terconazole) used daily for 3 to 7 days (up to 14 days for nystatin). A single-dose regimen using a 500-mg vaginal tablet of clotrimazole was also found to be clinically efficacious.<sup>103</sup> A single-dose regimen of fluconazole (150 mg) is quite effective in adolescents and adults.

### PERLÈCHE

Perlèche (angular cheilitis) is a common disorder characterized by fissuring and inflammation of the corners of the mouth (Fig. 17-40) with associated maceration and exudate. This condition appears to be related to moisture collecting at the mouth angles and does not usually have any association with nutritional or vitamin deficiency. Whereas in adults it is often related to ill-fitting dentures, perlèche in children may be seen in conjunction with dental malocclusion, the presence of orthodontic appliances, and lip licking. Therapy is best accomplished by correction of the underlying predisposing factor; that is, the condition often improves after the completion of orthodontia or after modification of lip-licking behavior. Treatment consists of the application of a low-strength (i.e., class 6 or 7) topical corticosteroid ointment 2 to 3 times daily. A topical antifungal preparation (i.e., econazole or



**Figure 17-41** Chronic paronychia. Nail-plate ridging, periungual erythema, and cuticle loss are seen in this patient with chronic *Candida* infection.

clotrimazole) should be added for more severe presentations, because *C. albicans* is often present, and if secondary bacterial infection is present, topical or oral antibiotic therapy is indicated.

### CHRONIC PARONYCHIA

Chronic paronychia (see Chapter 7) is usually associated with *C. albicans* infection and presents with transverse ridging of the nail plate, loss of the cuticle, and mild proximal/lateral periungual erythema (Fig. 17-41). It is distinguished from acute paronychia not only by the natural history (acute paronychia is more sudden in onset) but by lack of the marked edema, pain, and pustule formation, which are classically seen in the acute (bacterial) type. Chronic paronychia in children may be related to repeated finger or thumb sucking. Therapy with a topical antifungal cream applied twice daily is usually effective, although the nail plate may take several months to grow out normally. Oral fluconazole may also be effective for severe or resistant involvement. Attempts to decrease moisture of the affected digits will accentuate the response to therapy and help to minimize recurrences.

### EROSIO INTERDIGITALIS BLASTOMYCETICA

Erosio interdigitalis blastomycetica (derived from Latin, meaning “an erosion between digits caused by a budding fungus”) is a red, itchy, and occasionally slightly painful eruption of the web spaces between the fingers or toes. It is most common in individuals whose hands or feet are exposed to moisture often and most commonly involves the lateral two web spaces (i.e., between the third and fourth and between the fourth and fifth digits). Erosio interdigitalis blastomycetica presents with erythema, maceration, and peeling of the affected region (Fig. 17-42) with a scaly and occasionally vesicular border. More severe presentations with marked inflammation and frank ulceration have been reported in adults and termed *interdigital ulcer*.<sup>104</sup> Erosio interdigitalis blastomycetica seems to be caused by infection with *C. albicans*, and occasionally there may be an associated Gram-negative infection (see Chapter 14). Treatment consists of keeping the hands and feet as dry as possible and the use of a topical antifungal and (when needed) antibacterial preparation.

### BLACK HAIRY TONGUE

*Black hairy tongue* is a term used to describe a disorder primarily affecting adults and occasionally adolescents that is characterized by hypertrophic, elongated filiform papillae that form a dense black to blue-black surface on the midportion of the dorsal tongue. It occurs less often in young children but has been observed in an infant as young as 2 months of age.<sup>105,106</sup> The etiology is unknown, but it is frequently attributed to *C. albicans* or bacterial infection and is often associated with the prolonged use of antibiotics, including erythromycin and



**Figure 17-42** Erosio interdigitalis blastomycetica. Erythema, maceration, and peeling of the fourth toe-web space. This eruption cleared rapidly with topical azole antifungal therapy.

linezolid. Treatment consists primarily of improved oral hygiene, and gentle brushing of the dorsal tongue with a soft toothbrush and a small amount of toothpaste two to three times daily is usually effective.

### NEONATAL AND SYSTEMIC CANDIDIASIS

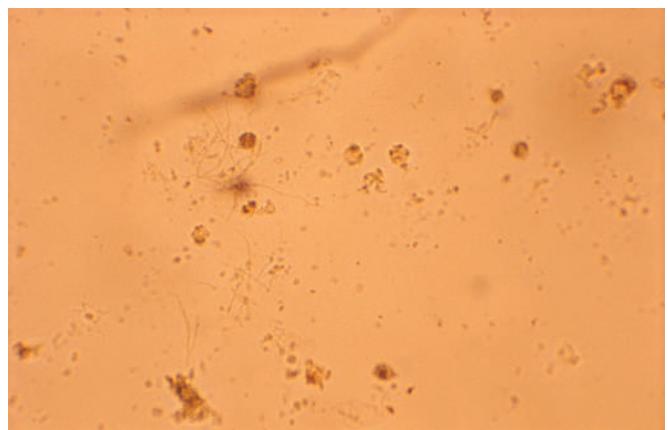
Two types of candidiasis in the newborn period have been reported: a congenital form in which the skin lesions are present at birth or within the first 6 days of life and a neonatal form commonly seen after the first week of life. Neonatal candidiasis develops as a result of infection acquired by passage through an infected maternal birth canal. This perinatal or postnatal acquisition of *Candida* encompasses several clinical presentations including localized disease (i.e., oral thrush and diaper dermatitis), systemic infection related to invasive procedures and infected indwelling devices, and invasive fungal dermatitis seen in extremely low-birthweight neonates. Although *C. albicans* is the primary pathogen, *Candida parapsilosis* is becoming a more significant pathogen in the neonatal setting (and in some reports has become the most commonly isolated species), and *Candida glabrata* has been reported after *in vitro* fertilization and embryo transfer.<sup>107–112</sup>

Congenital candidiasis is acquired *in utero* and may be associated with premature labor, especially in instances where a foreign body (i.e., intrauterine device [IUD] or cervical sutures) is present. It may also be associated with *Candida* chorioamnionitis.<sup>113</sup> A history of maternal candidal vulvovaginitis is common in infants with congenital candidiasis, although the former is present in a high percentage (up to 25%) of pregnant women and in most instances is not associated with this neonatal infection.<sup>114</sup> Congenital candidiasis tends to run a more benign course in full-term infants without risk factors but may result in serious systemic infection in premature neonates, especially those of extremely low birthweight. Other risk factors for invasive candidal infection include extensive instrumentation in the delivery room and invasive procedures utilized during the neonatal period. In patients with risk factors for dissemination, systemic antifungal therapy should be initiated.

Congenital cutaneous candidiasis (CCC) presents with multiple, widespread erythematous macules, papules, and pustules (Fig. 17-43) and occasionally bullae. In full-term infants, this form of candidiasis is often limited to the skin and resolves over 1 to 2 weeks.<sup>108</sup> The most common locations of involvement are the back, extensor surfaces of the extremities, and skin folds, with relative sparing of the diaper area.<sup>115</sup> Pustules on the palms and soles (Fig. 17-44) are a common and useful diagnostic finding. Oral thrush is uncommon in this setting, but nail changes (yellow discoloration, thickening, paronychia) (Fig. 17-45) are occasionally present. Such nail changes may be the sole manifestation of congenital candidiasis, and onychomadesis (separation of the nail plate from the nailbed) with nail shedding may occur.<sup>116</sup> The clinical findings in CCC may resemble erythema toxicum



**Figure 17-43** Congenital cutaneous candidiasis. Widespread erythematous papules and pustules in a 10-day-old male. This otherwise healthy child had involvement limited to the skin and no risk factors for dissemination. His mother reported a history of vulvovaginal candidiasis during the last trimester of pregnancy.



**Figure 17-46** KOH examination of candidiasis. Spores and pseudohyphae as noted on microscopic examination of skin scrapings from a patient with candidiasis.



**Figure 17-44** Congenital cutaneous candidiasis. Erythematous papules, papulovesicles, and pustules were present at birth in this full-term infant male. No extracutaneous involvement was noted.



**Figure 17-45** Congenital candidiasis. Yellow discoloration with ridging and nail-plate separation in a newborn male with no other manifestations of *Candida* infection.

neonatorum, bacterial folliculitis or pustulosis, bullous impetigo, and congenital herpes, varicella, enterovirus, or syphilis. The definitive diagnosis of CCC is made by the microscopic finding of spores and pseudohyphae on skin scrapings (Fig. 17-46) or culture of the organism. Another useful diagnostic modality is examination of the placenta, which may reveal typical changes of candidiasis (including funisitis, abscesses, or chorioamnionitis).<sup>115,117</sup> In patients with CCC limited to the skin and without risk factors for disseminated disease, topical antifungal therapy often suffices.

Systemic candidiasis occurs primarily in very low-birthweight (<1500 g) infants and is typically seen between the second and sixth weeks of life. The immature immune defenses of this population contribute to this propensity toward systemic disease.<sup>115</sup> Predisposing factors, in addition to prematurity, include presence of a central catheter or endotracheal tube, receipt of intravenous lipid emulsion, administration of broad-spectrum antibiotics, and use of intrapartum antibiotics.<sup>118</sup> Systemic candidiasis is uncommon in infants of birth weight greater than 1500 g, but when it occurs the greatest risk factors appear to be exposure to broad-spectrum antibiotics and thrombocytopenia (<50,000/mm<sup>3</sup>).<sup>119</sup>

Common features of systemic candidiasis include apnea, hyperglycemia, temperature instability, lethargy, hypotension, and increasing respiratory requirements.<sup>111</sup> The skin surface may or may not be involved. These patients may have candidal septicemia, meningitis, urinary tract infection, or disseminated disease. Since the kidneys act as a filter for *Candida*, spores may be present on microscopic examination of urine samples.<sup>117</sup> Renal pelvis fungus balls may be seen in up to 42% of these infants, and endocarditis, septic arthritis, endophthalmitis, and osteomyelitis may also occur. The diagnosis is confirmed by isolation of *Candida* from blood, urine, cerebrospinal fluid, or other normally sterile sites. Systemic candidiasis requires parenteral antifungal therapy and may result in permanent neurodevelopmental deficits in long-term survivors. The mortality rate in extremely low-birthweight (<1000 g) infants is 20% to 34% and even higher when *Candida* is isolated from more than one sterile body fluid.<sup>118,120</sup>

*Invasive fungal dermatitis* refers to a clinical entity seen in extremely low-birthweight infants and consists of a distinct cutaneous presentation of *Candida* infection in combination with a high risk for internal dissemination.<sup>114</sup> The affected infants develop lesions after several days of life. Skin involvement is characterized by erosive and ulcerative lesions (Fig. 17-47) with extensive crusting. Vesicles, bullae, and “burn-like” erythema may also be present, and desquamation and widespread denudation are common. A high index of suspicion should be maintained in extremely low-birthweight infants with any of these findings, because disseminated infection is common, including fungemia, meningitis, urinary tract infection, and other organ involvement. Potential risk factors for this form of candidiasis include vaginal birth, postnatal steroids, and prolonged hyperglycemia.<sup>114</sup> The immature skin barrier function seen in extremely premature infants is believed



**Figure 17-47** Invasive fungal dermatitis. Erythema with maceration, crusting, and peeling in an extremely low-birthweight newborn with candidiasis. (Courtesy of Moise Levy, MD.)

to be pathogenic, with skin serving as the portal of entry for this infection.<sup>114,121</sup>

### CHRONIC MUCOCUTANEOUS CANDIDIASIS

Chronic mucocutaneous candidiasis (CMC) is characterized by recurrent infections of the skin, nails, and oral, esophageal, or genital mucosae with *Candida* species, usually *C. albicans*. This disorder appears to be a common phenotype for a variety of defects in the immune response, most notably in the cellular branch of the immune system and mainly the specific responses to antigens of *Candida* species.<sup>122</sup> CMC may be seen in the setting of primary immunodeficiencies including severe combined immunodeficiency, dedicator of cytokinesis 8 (DOCK8) deficiency, signal transducer and activator of transcription (STAT) 3 deficiency causing autosomal dominant hyperimmunoglobulin (Ig) E syndrome, and autosomal recessive autoimmune polyendocrinopathy candidiasis with ectodermal dystrophy (APECED) associated with mutation in AIRE. More recently, CMC has been associated with various inborn errors of interleukin (IL)-17-mediated immunity, shown in some autosomal dominant kindreds to be associated with gain-of-function STAT1 mutations.<sup>123–125</sup> In patients with the STAT1 mutation, reduced production of interferon- $\gamma$  and IL-22 have also been demonstrated.<sup>125</sup> Pure CMC (without another syndrome association) has been reported in some families with mutations in the genes for the IL-17 receptor (*IL17RA*) and IL-17 ligand (*IL17F*).<sup>126</sup>

The clinical features of CMC are marked by the mucocutaneous findings. Oral candidiasis (thrush), esophageal candidiasis, candidal diaper dermatitis, candidal intertrigo, and paronychia that are persistent and recalcitrant to therapy are all common. Angular cheilitis (perlèche) is also seen. Generalized, scaly, erythematous, and crusted papules and plaques may be present, especially on the scalp, where they may lead to scarring alopecia. Nail involvement is notable for nail-plate thickening and discoloration, and chronic paronychia may be present. Systemic candidiasis does not usually occur in patients with CMC. Dental-enamel dysplasia occurs in some patients with APECED syndrome (see below), and at times may be so severe that it leads to early loss of dentition. Other infections may occur with increased incidence in these patients as well, most commonly tinea, pyogenic skin infection, sinusitis, pneumonitis, and urinary tract infection. Severe complications that may occur in patients with CMC include squamous cell carcinoma, functional debilitation of the hands, esophageal strictures, and cerebral aneurysms.<sup>127</sup>

The most common endocrinopathies noted in association with CMC are hypoparathyroidism, hypoadrenalinism (Addison disease), and gonadal failure. These endocrine abnormalities commonly do not appear until adolescence or adulthood, and therefore serial evaluations for endocrine function are indicated in patients with CMC, especially those with one endocrinopathy or with family members affected

with APECED.<sup>128</sup> APECED, which is also known as *autoimmune polyendocrinopathy syndrome type I (APS1)*, is an autosomal recessive disorder caused by mutations in the autoimmune regulator (AIRE) gene.<sup>129,130</sup> The classic triad of this disorder is CMC, hypoparathyroidism, and adrenocortical failure, and the diagnosis of APECED requires the presence of at least two of these components.<sup>131</sup> Besides the candidal infections and endocrine abnormalities, patients have ectodermal dystrophy manifested most commonly as alopecia areata, as well as nail dystrophy and dental-enamel defects. Other observed defects may include vitiligo, chronic active hepatitis, growth-hormone deficiency, thyroid disease, diabetes mellitus, pernicious anemia, keratopathy, ovarian failure, testicular failure, celiac disease, and iridocyclitis.<sup>127,129,132</sup> The autoimmune diathesis also is responsible for the candidal infections. Patients have been shown to have neutralizing autoantibodies directed against interferons, IL-17, and IL-22, cytokines that are important in immune responses to the candidal organism.<sup>126,133,134</sup>

Treatment of CMC includes addressing the immunodeficiency status (and augmenting or correcting it when feasible) and administration of topical and/or oral antifungal medications. Topical antifungal creams are useful for treatment of localized cutaneous lesions. Oral or vaginal candidiasis may benefit from oral troches or suspensions and vaginal creams or suppositories, respectively. The mainstays of therapy for CMC, however, are the oral antifungal agents, including ketoconazole, fluconazole, and itraconazole. When these agents are used as ongoing therapy for this indication, the possible side effects, potential for drug interactions, and risk-to-benefit ratio must all be taken into consideration. Biologic therapies directed at the observed cytokine aberrations in these disorders are being studied.

## Deep Fungal Disorders

In contrast to the superficial dermatophytes, which are confined to dead keratinous tissue, certain mycotic infections have the capacity for deep invasion of the skin or subcutaneous tissues as well as the potential for systemic infection, especially of the lungs and reticuloendothelial system. There follows a review of several deep fungal infections, which have been divided into the subcutaneous, systemic, and opportunistic mycoses.

### SUBCUTANEOUS MYCOSES

The subcutaneous mycoses are a group of disorders caused mainly by fungi that exist as soil saprophytes and are normally of low virulence but may result in infection involving the skin and subcutaneous tissues. Although these infections are found most often in adults with occupational exposure to soil and plants, all age groups are potentially susceptible. Rhinosporidiosis, which has been classified variably as a fungus or a protozoan parasite, has been included in this category and usually affects the nasal, nasopharyngeal, and ocular mucosae.

### Sporotrichosis

Sporotrichosis is a granulomatous fungal infection of the skin and subcutaneous tissues caused by *Sporothrix schenckii*, a dimorphic fungus of worldwide distribution commonly isolated from soil and plants. It occurs in patients of all ages but is observed most commonly in adult males who, because of their occupation or leisure-time activities, are likely to be exposed to contaminated soil or vegetation (farmers, florists, gardeners, forestry workers, miners, and individuals who work with contaminated packing material). Childhood infection, although significantly less common, does occur and may go undiagnosed without a high index of suspicion.<sup>135</sup> Although human transmission can occur after close contact with suppurative wounds of sporotrichosis, the majority of clustered cases are most likely related to simultaneous inoculation from the same source.<sup>136,137</sup> Although disease is usually limited to the skin and subcutaneous tissues, disseminated sporotrichosis with fungemia may occur, especially in the setting of HIV infection.<sup>138</sup>

The clinical presentation of sporotrichosis is variable, and several factors such as inoculum load, host immune status, virulence of the involved strain, and depth of the inciting trauma may influence the



**Figure 17-48** Sporotrichosis. Erythematous papules and nodules on the plantar surface with early lymphangitic (sporotrichoid) spread.

clinical presentation.<sup>139</sup> The lymphocutaneous form is most common in adults, and presents with a painless, erythematous papule or nodule that begins on exposed areas of skin, most commonly the upper extremity. The initial lesion often follows a penetrating injury such as that inflicted by a splinter, thorn, grain, rock, piece of glass, or cat scratch (cats are perhaps the only animals capable of transmitting this disorder<sup>140</sup>) contaminated with the organism. The lesions are often solitary and enlarge over several weeks. Secondary discrete lesions may develop and often progress toward more proximal sites, a pattern that has been referred to as "sporotrichoid"<sup>141</sup> (Fig. 17-48). Regional lymphadenopathy and lymphadenitis are common. The skin lesions may ulcerate centrally and heal with scarring, although spontaneous clearing is unusual. In a series of 25 children with sporotrichosis, 60% had lesions on an extremity (followed by the face as the next most common site), and the majority had the lymphocutaneous form of the infection.<sup>142</sup> Epidemic sporotrichosis related to transmission from infected cats was reported in 1998 through 2004 in Brazil and affected humans, cats, and dogs.<sup>143</sup>

The fixed cutaneous form of sporotrichosis is characterized by localized skin lesions without lymphatic involvement. The skin findings range from scaly papules to verrucous, ulcerated plaques or nodules with or without satellite lesions. This form seems more common in children, and there may be a delay in diagnosis given the lack of a typical sporotrichoid distribution pattern.<sup>135</sup> It has been hypothesized that children manifesting fixed cutaneous forms may possess host factors that limit the infection to the inoculation site, even if the strain is capable of producing the more classic lymphocutaneous form commonly seen in adults.<sup>144</sup> This form of sporotrichosis was reported in a 3-week-old neonate in whom the source of infection was unknown.<sup>145</sup>

Disseminated cutaneous sporotrichosis is rare and usually occurs in individuals with immunologic defects or chronic disease. In these patients the cutaneous lesions may be widespread and develop after hematogenous spread of the infection from a primary focus in the skin or an occult pulmonary focus. Multiple additional organs may be involved, including the bones, joints, and central nervous system (CNS). This form of sporotrichosis may mimic tuberculosis (especially with upper-lung radiographic lesions) and is associated with significant morbidity and mortality. Multifocal cutaneous ulcers have also been reported in sporotrichosis in association with misuse of topical corticosteroids and self-inoculation.<sup>146</sup> Osteoarticular sporotrichosis has been used to describe involvement presenting as tenosynovitis, periostitis, or monoarticular arthritis, often in immunosuppressed individuals.<sup>147</sup>

The differential diagnosis of cutaneous sporotrichosis includes atypical mycobacterial infection; bacterial abscess or ecthyma; *Nocardia*; foreign-body granuloma; chromoblastomycosis; cutaneous manifestations of systemic mycoses; leishmaniasis; anthrax; and tularemia. The gold standard for diagnosis is fungal culture of a skin-biopsy specimen. Direct examination of smears or biopsy material may be nonspecific. Histopathologic examination of skin-biopsy specimens may

reveal the organisms when enhanced via the application of special stains such as Gomori methenamine silver (GMS) or periodic acid-Schiff (PAS) stains. Molecular detection methods and serologic studies have also been utilized.<sup>139</sup>

The traditional treatment of choice for cutaneous sporotrichosis in adults has been orally administered saturated solution of potassium iodide (SSKI), 3 to 6 g per day for adults and half the dose for children. SSKI therapy may be associated with increased lacrimation or salivation, metallic taste, gastrointestinal discomfort, diarrhea, and headache. Treatment is continued until 4 to 6 weeks after clinical resolution of lesions. This therapy is still the most commonly used treatment in resource-limited settings.<sup>148</sup>

The treatment of choice for sporotrichosis in developed countries is usually oral itraconazole for 3 to 6 months with a reported success rate of 90% to 100% for cutaneous or lymphocutaneous disease.<sup>149</sup> In children the recommended dose is 5 mg/kg daily, and in adults a range of 100 to 400 mg daily has been recommended. Fluconazole is another option, although it may be less effective. Terbinafine and local hyperthermia are other potential therapies for nondisseminated disease, and amphotericin B is indicated for patients with life-threatening, disseminated, or extensive infection.

### Chromoblastomycosis

Chromoblastomycosis (chromomycosis) is an uncommon chronic fungal infection of the skin and subcutaneous tissue caused by a variety of dematiaceous fungi (filamentous fungi with melanin-type pigment in the fungal wall). At least five organisms are implicated in the disease, including species of *Phialophora*, *Fonsecaea*, or *Cladophialophora*, all of which are common inhabitants of decaying wood and soil. Several cases have been reported after penetrating wounds of the skin, especially from splinters and thorns.<sup>150</sup> The disease is rare during childhood and is seen most commonly in tropical and subtropical climates.<sup>151</sup> The highest number of cases are diagnosed in Madagascar.<sup>152</sup>

Chromoblastomycosis is characterized initially by the formation of small scaly papules that may expand into nodules. The lesions, which are most often confined to the lower leg or foot, coalesce into larger nodules and plaques and characteristically develop a very verrucous (warty) surface. There may be purulent drainage, and the lesions may be painless or tender. The surface may be studded with multiple "black dots." Longstanding lesions may result in edema of the extremity and scarring.

The differential diagnosis of chromoblastomycosis includes other deep fungal, mycobacterial, and bacterial infections, as well as cutaneous tuberculosis, leishmaniasis, leprosy, squamous cell carcinoma, and tertiary syphilis. The diagnosis is confirmed by microscopic recognition of the organism in KOH wet-mount preparations or tissue biopsy specimens and by fungal culture. When the disease is localized, the treatment of choice is surgical excision of the affected tissue. Several destructive modalities including cryotherapy, heat therapy, electrodesiccation, and radiation therapy have been used. In more advanced cases, surgical or destructive approaches are not feasible and medical therapy is necessary. Systemic agents utilized for chromoblastomycosis include itraconazole (which appears to be the most effective<sup>153</sup>), terbinafine, thiabendazole, ketoconazole, and 5-flucytosine.<sup>151</sup> Amphotericin B tends to be less effective. Amputation of the affected limb is usually a last resort.<sup>154</sup>

### Mycetoma

Mycetoma, also called *Madura foot*, is a chronic granulomatous infection of the subcutaneous tissues along with invasion of the fascia, muscles, and bone, and when an extremity is involved, enlargement of the affected area. Although the majority of lesions are seen on a lower extremity, they may also occur on the hand, shoulder, buttocks, knees, or other regions of the body. The organisms that cause mycetoma are usually introduced by skin trauma. Mycetoma is endemic in Latin America, the Indian subcontinent, Africa, and between the latitudes of 15° South and 30° North around the Tropic of Cancer (the so-called "mycetoma belt").<sup>155</sup> This belt includes Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Colombia, and Argentina.<sup>156</sup>

Mycetoma may be caused by various species of true fungi (eumycotic mycetoma), including *Pseudallescheria boydii*, *Madurella*

*mycetomatis*, *Madurella grisea*, and *Phialophora verrucosa*. It may also be caused by anaerobic fungus-like bacteria, the actinomycetes (actinomycotic mycetoma or actinomycetoma), usually by species of *Nocardia*, *Actinomadura*, or *Streptomyces*, including *Actinomadura madurae*, *Actinomadura pelletieri*, *Nocardia brasiliensis*, and *Streptomyces somaliensis*. These organisms exist as saprophytes in soil or on vegetable matter. The most common agent worldwide is *N. brasiliensis*. Mycetoma is uncommon in childhood and relatively rare in the United States, occurring most commonly in young adults and workers in rural tropical and subtropical areas who walk barefoot and are thus more readily exposed to the organisms.

The infection begins as one or more small, firm papules that gradually evolve into subcutaneous nodules with sinus tracts, draining abscesses, edema, and enlargement of the affected extremity. Purulent drainage is common and “grains” of various colors may be visible in the exudate, the color depending on the infecting organism. Eventually, crusting and granulation tissue may develop, and the infection may extend to the deeper tissue levels and bone. A preliminary diagnosis can be made by microscopic examination of the granules to identify their actinomycete or fungal nature, but tissue culture is generally necessary for confirmation. Treatment of mycetoma depends on the causative agent. Therapeutic options for actinomycotic mycetoma include sulfonamides, streptomycin, tetracyclines, rifampicin, ciprofloxacin, amikacin, penicillin, imipenem, and dapsone. Treatment of eumycotic mycetoma is more difficult and usually a combined approach of medical and surgical therapy. Small lesions may be best treated with complete excision. Medical therapies include the azole antifungals (especially ketoconazole and itraconazole) and amphotericin B.<sup>157</sup> Unfortunately there is no single drug that gives consistently good results, and longstanding cases with extensive tissue destruction and fibrosis are often resistant to all forms of therapy.

### Rhinosporidiosis

Rhinosporidiosis is a rare disorder caused by the organism *Rhinosporidium seeberi*. It occurs throughout the world but is most common in the tropics, especially in India and Sri Lanka. It has been occasionally reported in the United States, especially the southern portion. Although rare in children, a cluster of pediatric cases was reported in rural northeast Georgia between 1981 and 1994.<sup>158</sup> Studies have suggested a possible link to swimming or bathing in freshwater ponds, lakes, or rivers.<sup>159</sup> Although *R. seeberi* was originally thought to be a protozoan parasite, it has most consistently been classified as a fungus given its microscopic appearance and identification with fungal stains. Recent information supports its classification as a novel group of aquatic protistan parasites.<sup>159</sup>

Rhinosporidiosis is characterized by papules, nodules, and pedunculated vascular polypoid growths on the mucous membranes of the nose, nasopharynx, soft palate, and conjunctivae. Other potential sites of involvement include the upper respiratory passages, lacrimal sacs, skin, larynx, genitalia, or rectum. Tracheal involvement has been rarely reported.<sup>160</sup> The surface often has a raspberry-like appearance and is studded with tiny white or yellow nodules. The lesions may become hyperplastic and may reach enormous size, and symptoms are often associated with physical obstruction. Diagnosis is confirmed by microscopic examination, and the organism is notoriously difficult to isolate in culture. Fine-needle aspiration cytology may reveal the sporangia and spores of *R. seeberi*.<sup>161</sup> Treatment generally consists of electrosurgical destruction or surgical removal of lesions when feasible. Antimicrobial agents, most notably dapsone, have been reportedly effective in some patients.

### SYSTEMIC MYCOSES

The systemic mycoses comprise a group of fungal disorders that arise from internal foci, usually the lungs or upper respiratory tract. When the skin lesions result from dissemination of the infection, the prognosis is generally poor. Primary inoculation disease of the skin occasionally occurs with these infections. Disorders in this group include blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and histoplasmosis. Actinomycosis and nocardiosis, although often included under the group of disorders because of true fungi, are actually

caused by fungus-like Gram-positive bacteria and are discussed in the section on bacterial infections (see Chapter 14).

### Blastomycosis

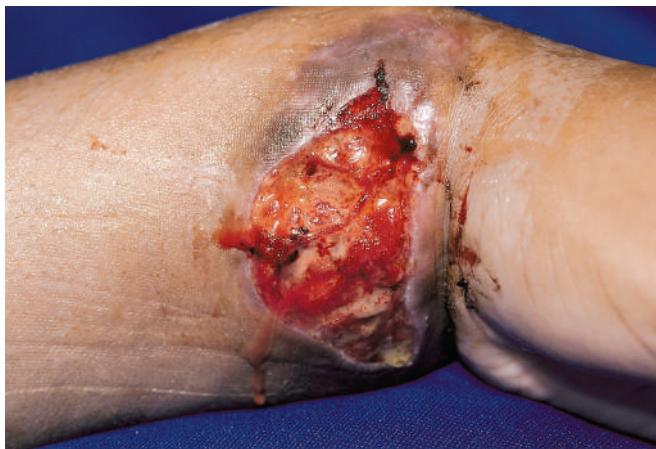
Blastomycosis (North American blastomycosis, Gilchrist disease, Chicago disease) is a systemic granulomatous infection caused by the dimorphic fungus, *Blastomyces dermatitidis*. It occurs most often in the southeastern and south central states that border the Mississippi and Ohio Rivers and the Great Lakes states. It is considered endemic in several focal areas of northern Wisconsin and Michigan. Blastomycosis occurs in three forms: pulmonary, disseminated (systemic), and primary cutaneous inoculation, which is quite rare. Primary inoculation blastomycosis has been reported primarily in laboratory technicians working with the organism and in pathologists who perform autopsies on animals or humans with the disease.<sup>162</sup> The organism has been cultured from soil, which is believed to be the reservoir for infection in humans.<sup>163</sup> Blastomycosis is rare in children, especially those under 1 year of age, and when it occurs, extrapulmonary disease (including CNS involvement) is fairly common.<sup>164,165</sup> South American blastomycosis is a chronic granulomatous disease caused by *Paracoccidioides brasiliensis* and is also known as paracoccidioidomycosis. It is discussed briefly later in this chapter.

Primary infection usually involves the lungs, and patients may exhibit nonspecific flu-like symptoms, cough, low-grade fever, night sweats, hemoptysis, or minimal symptomatology. Chest radiography is often nonspecific during acute infection. Many patients with acute pulmonary blastomycosis may go undiagnosed and thus untreated. The disorder may heal spontaneously, progress to chronic pulmonary disease with or without cavitation, or disseminate, primarily to skin, subcutaneous tissues, bones, and joints. Acute respiratory distress syndrome (ARDS) may occasionally occur.<sup>166</sup> Other potential sites of dissemination are the gastrointestinal tract, liver, spleen, genitourinary tract, and CNS.

Skin involvement in North American blastomycosis is most commonly associated with disseminated disease and only occasionally associated with primary inoculation. Primary cutaneous blastomycosis is extremely rare in children and often presents with a localized chancroid-like ulcer.<sup>167</sup> The primary types of skin changes noted in all forms of cutaneous blastomycosis are verrucous (warty) lesions and cutaneous ulcers.<sup>168</sup> Verrucous lesions present with heaped-up hyperkeratosis with a surrounding erythematous or violaceous color (Fig. 17-49). They may be confused with multiple other cutaneous



**Figure 17-49** Cutaneous blastomycosis. Verrucous, crusted, erythematous plaque on the chin in a 15-year-old male with respiratory symptoms and bone pain. (Reprinted with permission from Cummins RE, Romero RC, Mancini AJ. Disseminated North American blastomycosis in an adolescent male: a delay in diagnosis. Pediatrics 1998;102(4):977–9. © American Academy of Pediatrics. All rights reserved.)



**Figure 17-50** Cutaneous blastomycosis. Vegetative, ulcerated plaque of the volar wrist in the same patient shown in **Figure 17-49**. (Reprinted with permission from Cummins RE, Romero RC, Mancini AJ. Disseminated North American blastomycosis in an adolescent male: a delay in diagnosis. *Pediatrics* 1998;102(4):977–9. © American Academy of Pediatrics. All rights reserved.)



**Figure 17-51** Cutaneous coccidioidomycosis. Multiple verrucous papules and plaques in a patient with cutaneous coccidioidomycosis disseminated from a primary pulmonary infection.

infections or squamous cell carcinoma. The ulcerative lesions begin as papules or pustules and progress to superficial ulcers with granulation tissue (Fig. 17-50). Cutaneous lesions disseminated from a primary pulmonary focus are usually symmetrical and generally appear on the exposed areas of the body (the face, wrists, hands, and feet). Skin lesions may also occur over areas of osteomyelitis and present as draining sinus tracts. In patients with primary cutaneous inoculation blastomycosis, the skin lesions occur with focal lymphadenopathy or lymphangitis but without evidence for systemic involvement.<sup>169</sup> Sources for primary inoculation disease include clinical exposures as noted above (i.e., laboratory or morgue, primarily in adults), animal bite or scratch, and other forms of skin trauma. The skin lesions of blastomycosis heal eventually (even without therapy), often resulting in permanent scarring.

North American blastomycosis is diagnosed by identification of the thick-walled, broad-based budding yeast cells in tissue samples or growth in fungal culture. Serologic studies are not useful, and enzyme immunoassays are sensitive but not available on a widespread basis. Cytologic examination of specimens (i.e., sputum) may be useful.<sup>170</sup> Urine-antigen detection may be useful in children for both diagnosis and for monitoring response to therapy.<sup>171</sup> Deoxyribonucleic acid (DNA) probe and polymerase chain reaction (PCR) assays have also been reported.<sup>172</sup> A high index of suspicion must be maintained in the patient with cutaneous ulcers or verrucous skin lesions, especially if other symptoms of systemic disease are present, most notably those referable to the lungs or bones, and if the patient resides in (or has traveled to) an endemic area. A delay in diagnosis is common, especially in children.<sup>165,173,174</sup>

Treatment depends upon the extent of disease and immune status of the patient. Whereas observation alone may be an option for mild pulmonary or primary inoculation skin disease, most patients require therapy, especially those with severe disease or immunocompromised or disseminated involvement. Local excision has been utilized for small lesions limited to skin. Systemic therapeutic options for blastomycosis include itraconazole, ketoconazole, fluconazole, and amphotericin B. Azole antifungal therapy should be continued for at least 6 months and for at least 1 year in patients with blastomycotic osteomyelitis.<sup>175,176</sup> Life-threatening, CNS, or disseminated disease, as well as infection in the immunocompromised host, should be treated initially with amphotericin B, and therapy can be switched over to itraconazole after clinical stabilization.<sup>175,176</sup> Liposomal amphotericin B appears to have superior CNS penetration.

### Coccidioidomycosis

Coccidioidomycosis is a deep fungal infection caused by *Coccidioides immitis*, a soil saprophyte endemic in the hot, arid desert areas of the

southwestern United States (especially the San Joaquin Valley in California), Mexico, and parts of South America. Inhalation of air-borne arthroconidia results in infection, which in many cases is asymptomatic. Rare fomite transmission has been reported.<sup>177</sup> Occasional epidemics of coccidioidomycosis have been seen, often after severe dust storms and even in 1994 after a California earthquake.<sup>178</sup> The incidence of coccidioidomycosis has been increasing in the United States, and in some highly endemic regions nearly 100% of the population has serologic evidence of past exposure.<sup>162</sup>

*C. immitis* infection is often asymptomatic or may present with influenza-like symptoms of fever, cough, chest pain, headache, sore throat, and fatigue.<sup>179</sup> Erythema nodosum or erythema multiforme may develop. Generalized arthralgias may accompany these acute symptoms, and this syndrome is referred to as *desert rheumatism* or *Valley fever*. Acute pulmonary infection, which accounts for 98% of cases, usually resolves without therapy over several weeks.<sup>180</sup> Around 5% of patients will have asymptomatic residual lesions in the lungs, usually nodules or thin-walled cavities.<sup>180</sup>

Extrapulmonary disease occurs in a minority of patients, and in this case the organism disseminates hematogenously to any of several organs including the meninges, bones, joints, skin, and soft tissues. Disseminated disease is most common in African-Americans, Filipinos, and Native Americans, as well as in patients with immunosuppression.<sup>179</sup> More recently, *Coccidioides* species have become significant opportunistic pathogens in patients infected with HIV and in recipients of organ transplants.<sup>181</sup>

Skin involvement in coccidioidomycosis may be seen in the setting of acute disease or disseminated disease and, rarely, as a primary inoculation infection. During the acute phase of infection, a generalized erythematous macular exanthem may appear within the first 1 to 2 days of illness. As mentioned earlier, erythema multiforme or erythema nodosum lesions may also present during this phase of the illness, as may Sweet syndrome (see Chapter 20) or an entity referred to as *interstitial granulomatous dermatitis*. The latter refers to a granulomatous dermatitis that may occur in the setting of a variety of infectious, inflammatory, or autoimmune disorders.<sup>181</sup> In addition to these “parainfectious” cutaneous stigmata, infectious skin lesions may present (primarily with disseminated disease) as single or multiple verrucous, granulomatous papules and plaques (Fig. 17-51), subcutaneous abscess, acneiform papules, and pustules. Although lesions may occur anywhere on the skin surface, they are most common on the head (particularly the nasolabial fold), neck, and chest.<sup>182</sup> Cutaneous findings in coccidioidomycosis are not specific and as with many deep fungal disorders, may suggest a variety of potential diagnoses in the differential. Primary cutaneous inoculation is relatively rare and occurs through injury by contaminated splinters or thorns or by accidental inoculation in laboratory or autopsy rooms. This form of coccidioidomycosis is usually characterized by a painless

ulcerated plaque with lymphangitis and lymphadenopathy (similar to that seen in sporotrichosis or blastomycosis). Although healing usually takes place within a few months, there are rare reports of patients with primary cutaneous inoculation developing systemic dissemination.<sup>183</sup>

The diagnosis of coccidioidomycosis can be confirmed by demonstration of the characteristic large, thick-walled mature spherules with endospores in tissue-biopsy specimens. Fungal culture of materials such as pus, sputum, or aspirates will often grow *C. immitis*, but because the organism is highly infectious, special precautions are necessary to prevent laboratory accidents caused by air-borne spread of arthrospores. Serologic and skin testing are also useful in making the diagnosis of coccidioidomycosis. The coccidioidin skin test usually becomes positive soon after the development of symptoms in patients with primary infection, although anergy may be present in progressive disease.<sup>180</sup> IgM and IgG (complement fixation) antibodies may be present, the latter appearing between 4 and 12 weeks after infection and disappearing several months later if disease resolution occurs. Changes in the antibody titer may be useful for monitoring disease activity and response to therapy. A high titer of complement fixation antibody denotes severe extensive disease and a poorer prognosis; complement fixation antibodies in cerebrospinal fluid indicate the presence of CNS infection. *In situ* hybridization and PCR techniques may also be useful in confirming the diagnosis.<sup>181</sup>

The majority of infections with coccidioidomycosis are self-limiting, go undetected, and do not require specific therapy. Disseminated disease, however, may follow a fulminant course or persist for several years. The choice of the therapeutic agent and decisions regarding length of therapy depend on the immune status of the host, the seriousness of the infection, and the organs involved. Therapeutic options include amphotericin B, ketoconazole, itraconazole, and fluconazole. Amphotericin B is the recommended initial therapy for severe or progressive infection, and fluconazole is recommended for CNS infections.<sup>184</sup> Patients with CNS infection with *C. immitis* may require amphotericin B infusions into the cerebrospinal fluid. Pulmonary resection has a role in managing severe hemoptysis, sequestrations, or lung cavitations.

### Paracoccidioidomycosis

South American blastomycosis (paracoccidioidomycosis) occurs almost exclusively in South and Central America and is caused by infection with the dimorphic fungus, *P. brasiliensis*. The disorder is endemic in Brazil (where the majority of cases occur), Venezuela, Colombia, Ecuador, Argentina, and Peru. It may occur many years after relocation out of an endemic region.<sup>185</sup> Paracoccidioidomycosis has become an opportunistic infection in individuals with HIV infection. It is most common in adults and uncommon in childhood, when it is referred to as the *acute juvenile form*. It is thought that the organism lives as a saprophyte on vegetation or in soil and that the infection is acquired by direct implantation into the skin or mucous membranes, possibly through the practice of cleaning the teeth with small pieces of infected vegetation or in pulmonary lesions by direct inhalation of the organism.

Paracoccidioidomycosis may present with a wide spectrum of involvement, ranging from asymptomatic pulmonary infection to symptomatic infection involving one or several organs that may progress in a fulminant fashion. The most common organs of involvement are the lungs, skin, mucosae, lymph nodes, and bone. Mucocutaneous involvement presents with infiltrative, ulcerative lesions on the lips and in the mouth, pharynx, or nasal cavity. The ulcerative and verrucous plaques may extend and ultimately progress to destroy the nose, lips, and facies. Pain and dental loss may occur. Hematogenous or lymphatic spread results in subcutaneous abscesses, and the lymph nodes draining the affected areas are palpable, painful, and adherent to the overlying skin, occasionally progressing to form chronic sinuses and suppurative plaques. Primary cutaneous infection is rarely reported.<sup>186</sup> The juvenile form tends to be more aggressive and involve primarily the reticuloendothelial system.<sup>185</sup>

Paracoccidioidomycosis is diagnosed by recognition of the typical yeast forms in tissue specimens, fungal culture, serologic studies (mainly in immunocompetent hosts), or newer molecular methodologies such as PCR, which may be useful in observing response to

therapy.<sup>185</sup> Treatment usually consists of azole antifungals or amphotericin B.

### Histoplasmosis

Histoplasmosis is another deep fungal infection caused by a thermally dimorphic fungus, in this case, *Histoplasma capsulatum*. This organism (*H. capsulatum* var. *capsulatum*) is endemic in the Americas, especially in Ohio and the Mississippi river valleys and Latin America, and is more concentrated in places where the soil is enriched by bird excreta or bat guano.<sup>187</sup> The other variety, *H. capsulatum* var. *duboisii*, is endemic in some areas of Africa. Infection is usually acquired by inhalation of fungal microconidia and may result in various manifestations from asymptomatic infection to disseminated, progressive disease. Transmission from fomites, direct inoculation, organ transplantation, and sexual contact have also been reported.<sup>188</sup> Histoplasmosis affects infants and children as well as adults.

The manifestations of histoplasmosis are quite varied. The classically recognized forms of histoplasmosis are acute pulmonary, chronic cavitary, and disseminated. Primary infection is asymptomatic or produces very mild symptoms in up to 95% of patients. Many patients manifest pulmonary symptoms including cough and chest pain along with fever and malaise. A chronic pulmonary form may resemble tuberculosis both clinically and radiographically. Involvement of the reticuloendothelial system may occur, and accounts for most of the signs of progressive disseminated histoplasmosis (PDH). PDH tends to occur in patients with compromised cell-mediated immunity. Bone marrow involvement with pancytopenia is common, as are hepatosplenomegaly and lymphadenopathy.<sup>189</sup> Gastrointestinal bleeding, meningitis, adrenal gland involvement, and endocarditis may also occur with disseminated histoplasmosis. Disseminated disease occurs in fewer than 1% of those infected. Cardiac tamponade may develop in up to 25% of patients with pulmonary histoplasmosis.<sup>188</sup>

Skin involvement is uncommon in histoplasmosis but may be seen in the disseminated form and rarely in a primary inoculation form. The morphologic characteristics include papules, plaques, pustules, purpura, nodules, ulcers, abscesses, molluscum-like lesions, severe dermatitis, exfoliative erythroderma, and verrucous lesions. Erythema multiforme and erythema nodosum may both occur, usually in the setting of acute pulmonary infection. The characteristic ulcerative, mucocutaneous lesions of the nose, mouth, pharynx, larynx, genitals, and perianal region are seen in chronic disseminated disease and in patients with immunodeficiency. Lesions in these regions may present as superficial or deep ulcerations with heaped up borders, nodular masses, or verrucous plaques.<sup>190</sup> Oral manifestations are seen in 25% to 75% of patients with disseminated disease.<sup>191,192</sup>

Children with histoplasmosis tend to have more disseminated disease. In fact, 20% of apparently immunocompetent patients with disseminated infection are children.<sup>187</sup> A disseminated form of histoplasmosis in infants may be associated with transient hyperglobulinemia and T-cell deficiency and when occurring after exposure to a large inoculum of the pathogen, has a high mortality rate.<sup>193</sup> In children with histoplasmosis, the incidence of extensive ulcers along the gastrointestinal mucosa that give rise to diarrhea and other gastrointestinal disturbances suggests that organisms may be ingested rather than inhaled in these individuals.

The gold standards for diagnosing histoplasmosis are identification of the small intracellular yeast-like organisms in tissue specimens, sputum, or peripheral blood, and fungal culture. Tissue biopsies from skin or mucosal lesions reveal necrotizing granulomas along with the yeast forms. The usefulness of the histoplasmin skin test is quite low, given its nonspecificity especially in endemic areas.<sup>189</sup> *Histoplasma* serologies (including complement fixation and immunodiffusion precipitin bands) are available but hampered by high rates of false-positive and false-negative responses. Detection of *Histoplasma* antigen in urine may be useful but also has the disadvantage of many potential causes for false-positive results, especially other endemic mycoses.<sup>190</sup> An enzyme-linked immunosorbent assay (ELISA) against *H. capsulatum* circulating antigens has good sensitivity and excellent specificity,<sup>194</sup> although it may not be readily available. PCR assays are also being developed, although none is currently commercially available.

In mild cases of histoplasmosis, treatment may not be necessary, and the disorder runs a benign, self-limited course. For severe or widespread disease, systemic antifungal therapy with amphotericin B is usually indicated. For more localized or less severe disease (i.e., chronic pulmonary histoplasmosis), oral azole antifungal therapy is an option. Various regimens have been reported in pediatric patients. Disseminated childhood histoplasmosis has been treated successfully with itraconazole for 3 to 12 months, as well as with parenteral amphotericin B followed by oral ketoconazole, itraconazole, or voriconazole.<sup>187,193,195</sup> In patients with acquired immunodeficiency syndrome (AIDS) and severe histoplasmosis, amphotericin B is indicated, whereas itraconazole may be appropriate therapy for mild to moderate disseminated disease.<sup>196</sup> Fluconazole is less effective than the other azole antifungal agents, and clinical data on the newer azoles, voriconazole and posaconazole, are limited.<sup>190,192</sup>

## OPPORTUNISTIC MYCOSES

With the spread of AIDS and advancements in cancer chemotherapy, bone marrow and solid-organ transplantation, and both routine and intensive medical care, certain patient populations who are vulnerable to potentially fatal deep fungal infections have emerged. These organisms are generally nonpathogenic but in certain at-risk individuals who have an alteration or breakdown of host defenses may result in severe disseminated infection. The opportunistic mycoses to be discussed here include aspergillosis, cryptococcosis, fusarium, and mucormycosis. Risk factors for opportunistic mycoses are listed in Table 17-3.<sup>197</sup>

### Aspergillosis

Aspergillosis is an uncommon opportunistic fungal disease of the respiratory tract and other sites caused by a variety of *Aspergillus* species. Although *Aspergillus fumigatus* is the most commonly identified pathogen, *Aspergillus niger*, *Aspergillus flavus*, and an increasing number of other species have been reported in recent years. Invasive aspergillosis is most often seen in patients with prolonged neutropenia and in transplant recipients.<sup>198</sup>

**Table 17-3** Risk Factors for Opportunistic Mycoses/Invasive Fungal Disease

Factor	Comment
Neutropenia	Usually prolonged, severe
Hematologic malignancy	And associated chemotherapy
Transplant recipient	Primarily BMT/HSCT
HIV infection/AIDS	Especially cryptococcosis
High-dose corticosteroids	Often in setting of GVHD therapy
Broad-spectrum antibiotics	
Alterations of oropharyngeal and gastrointestinal mucosae	Via chemotherapy
Altered skin integrity	Catheter sites, skin breakdown or occlusion, burns, wounds
Presence of catheters	Vascular, urinary
Extremes of age	Premature infants, elderly persons
Prolonged hospitalization	ICU
Diabetes mellitus	Specific to mucormycosis
Total parenteral nutrition	

Modified from Gutierrez Paredes EM, Gamez Perez L, Gonzalez Rodriguez AJ, et al. Disseminated fusariosis in immunocompromised patients. Eur J Dermatol 2011;21(5):753–5, and Pfaller MA, Pappas PG, Wingard JR. Invasive fungal pathogens: current epidemiologic trends. Clin Infect Dis 2006;43:S3–14.

AIDS, Acquired immunodeficiency syndrome; BMT, bone marrow transplantation; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit.

*Aspergillus* species are ubiquitous and are normally nonpathogenic. When pathogenic, they primarily cause infection in the lung, although the skin, eyes, CNS, bones, gastrointestinal tract, liver, spleen, lymph nodes, nasopharynx, and genitourinary tract may also be affected. In children, the highest risk groups are those with AIDS, leukemia, corticosteroid or immunosuppressive therapy, chronic granulomatous disease, and severe combined immunodeficiency.<sup>199</sup> Neonates, especially premature ones, appear to be another population at risk for disseminated aspergillosis.<sup>200</sup> Other neonatal aspergillosis risk factors include corticosteroid use, prolonged hospitalization, and skin trauma from tape adhesive in relation to prolonged use of arm boards.<sup>201</sup> Despite aggressive therapy, invasive aspergillosis in children is associated with a mortality rate as high as 85%.<sup>202</sup> Cutaneous aspergillosis has also been reported in immunocompetent adults and children, typically after intravenous-catheter site occlusion or trauma.<sup>203–205</sup>

One of the most common characteristic manifestations of aspergillosis is the pulmonary intracavitary fungus ball. This is composed of colonies of *Aspergillus*, inflammatory exudate, cells, and fibrin in the form of a sphere that may measure from 1 to 5 cm in diameter. Although it occasionally causes hemoptysis, most patients with fungus balls are asymptomatic. Another form of pulmonary disease is invasive pulmonary aspergillosis, which may be necrotizing and is often associated with multiorgan dissemination.

Cutaneous aspergillosis may occur in two forms: primary or secondary. Primary cutaneous aspergillosis usually occurs at sites of skin injury such as intravenous-catheter insertion sites, burns, surgical wounds, or sites covered by various products including occlusive dressings and tape. Secondary cutaneous aspergillosis occurs with direct extension to the skin from underlying soft-tissue infection or hematogenous dissemination.<sup>206</sup> Less commonly, an opportunistic infection of the paranasal sinuses may result in mucopurulent or blood-tinged nasal discharge, headache, periorbital neuralgia, and rhinitis. With extension of this process, the face may become erythematous, swollen, warm, and tender, suggesting a diagnosis of cellulitis or erysipelas.

Cutaneous aspergillosis may initially present as nondescript erythematous macules, papules, or plaques. Common secondary findings include hemorrhagic bullae and necrosis (Fig. 17-52), which may extend rapidly. Eschar formation is often seen. In patients with hematogenous dissemination, embolic lesions present as widespread erythematous to purpuric macules and papules with ulceration and necrosis and may simulate the lesions of ecthyma gangrenosum (caused by *Pseudomonas aeruginosa*). Pustules overlying an erythematous patch are a common finding in the early cutaneous lesions of neonates and often progress to ulceration, necrosis, and eschar formation.<sup>207</sup>

The diagnosis of cutaneous aspergillus can be confirmed by tissue biopsy for histopathology and fungal culture. A deep-skin biopsy is



**Figure 17-52** Cutaneous aspergillosis. Erythematous plaque with necrosis and eschar formation in a young female with immunosuppression and disseminated *Aspergillus fumigatus* infection.

desirable in order to visualize the dermal and subcutaneous blood vessels given the angiotropic nature of *Aspergillus* species. Fungal stains applied to the biopsy material will reveal large fungal hyphae with "acute-angle" branching, and this method will enable a more rapid diagnosis than awaiting results of the fungal culture. Blood cultures are rarely positive. ELISA and PCR testing are available in some centers and may offer a more rapid and reliable means of diagnosing disseminated aspergillosis, especially in immunocompromised children.<sup>199</sup> The galactomannan antigen assay appears to be sensitive in diagnosing invasive aspergillosis in children, although the cutoff thresholds for this population continue to be studied.<sup>208–210</sup>

The treatment of aspergillosis depends on the underlying immune status of the patient and risk factors for disseminated infection. In most cases, systemic therapy is indicated. Occasionally, surgical approaches may suffice (i.e., primary cutaneous aspergillosis in a burn patient without underlying risk factors for disseminated disease). Although amphotericin B has been the mainstay of systemic therapy for years, in some patients this agent is associated with untoward side effects and in others it may result in a suboptimal response.<sup>198</sup> Azole antifungal agents such as itraconazole have also been used with mixed results. The newer broad-spectrum triazole, voriconazole, has been evaluated and demonstrated effective in adults and children with invasive aspergillosis, although the numerous drug interactions may limit its usefulness in some patients.<sup>198,211,212</sup> Caspofungin therapy has also been studied in salvage therapy for invasive aspergillosis, and a body-surface area dosing calculation is preferred over a weight-based regimen for treating children with this agent.<sup>213</sup>

### Cryptococcosis

*Cryptococcus neoformans* is a ubiquitous encapsulated fungus capable of causing severe disease in immunocompromised individuals, especially those with AIDS. Disseminated disease has been rarely observed in immunocompetent children.<sup>214</sup> Whereas it is well established as the most common cause of life-threatening fungal infection in adults with HIV infection, infection in children with HIV may occur in up to 1% of those with AIDS.<sup>215</sup> The organism has been found in various fruits, soil, pigeon excreta, and cow's milk. It is believed to be acquired via inhalation of aerosolized particles from the environment, and recent data suggest that *C. neoformans* may infect many immunocompetent children early in life, resulting in either asymptomatic infection or nonspecific "viral" symptoms.<sup>216</sup> The incidence of cryptococcosis has declined in the past decade, largely because of the improvements in HIV care and the use of highly active antiretroviral therapy (HAART).<sup>217</sup> *Cryptococcus laurentii* is a rare species that may also result in cutaneous lesions, although it is most often implicated in pulmonary, ocular, and disseminated infections.<sup>218</sup>

Cryptococcal infection most commonly presents as meningitis, meningoencephalitis, or sepsis. Infection may be localized to the lungs, producing focal pneumonia, patchy infiltrates, solitary nodules, abscesses, or pleural effusion. Pulmonary symptoms, however, may be absent or minimal, and although pulmonary involvement may be progressive, in most instances CNS manifestations predominate and infection is detected only after dissemination, which may include the skin. Cutaneous lesions may present months before other signs of systemic infection.<sup>219</sup> They may occasionally occur after trauma or extension from bony involvement but are usually the result of hematogenous spread from a pulmonary focus.

Skin lesions, which occur in 6% to 15% of patients with systemic infection, present most commonly on the head and neck, where they may often mimic the lesions of molluscum contagiosum. They begin as painless, firm, pink to red papules, pustules, or acneiform lesions. The molluscum-like lesions may be umbilicated or contain a tiny central hemorrhagic crust and may be multiple.<sup>219</sup> Surrounding inflammation is usually absent. As the lesions enlarge they may form infiltrated plaques, nodules, abscesses, or ulcers, often with raised papillomatous borders. In patients with primary inoculation cutaneous cryptococcosis, the clinical findings most often observed are ulcers, abscesses, or cellulitis.<sup>220</sup>

The diagnosis of cryptococcosis is confirmed by demonstration of the characteristic organism (surrounded by a polysaccharide capsule and with characteristic budding seen in India ink preparations) in cerebrospinal fluid, skin lesions, sputum, or tissue sections. Definitive

diagnosis relies on isolation of the organism from biopsy tissue or bodily fluids.<sup>221</sup> Serologic studies, immunoblotting, and ELISA or latex agglutination assays for the cryptococcal polysaccharide are other diagnostic modalities. The recommended therapy for cryptococcosis is amphotericin B with 5-flucytosine or fluconazole, because combination therapy appears to be superior to amphotericin monotherapy.<sup>222</sup> Fluconazole suppression is recommended after completion of the primary therapy.<sup>221</sup>

### Fusarium Infection

*Fusarium* species are molds that are normally found in soil and the air and may result in localized infections in the nail (fusarium onychomycosis or paronychia) or in burn sites or surgical wounds. However, invasive *Fusarium* infection (or fusariosis) is an increasingly prevalent, serious opportunistic fungal infection that occurs especially in patients with hematologic malignancy undergoing cytotoxic chemotherapy or bone marrow transplantation. Prolonged neutropenia seems to be the main risk factor for this infection. Skin lesions are common in patients with disseminated *Fusarium* infection and may serve as the portal of entry for more widespread involvement. Cutaneous involvement may be mistaken for aspergillosis given the potential clinical overlap in presentation. Disseminated fusariosis is considered to be the second most common opportunistic infection in neutropenic patients after *Aspergillus* and appears to be the most common agent resulting in fungemia with cutaneous lesions.<sup>223,224</sup>

Immunocompromised patients with *Fusarium* infection may have refractory fever, skin lesions, sinusitis, myalgias, or pneumonia. Endophthalmitis may occur from hematogenous seeding as opposed to the fusarial endophthalmitis that occurs in immunocompetent hosts as a complication of advanced keratitis or after ophthalmologic surgery.<sup>225</sup> Fungemia with multiorgan involvement is possible, and the organism is more often cultured from the blood than is *Aspergillus*. Disseminated infection is often notable for skin lesions, which occur in up to 80% of these patients.<sup>226</sup> Skin lesions of fusariosis may include paronychia, tinea pedis, onychomycosis, digital ulcers, or widespread lesions most often involving the extremities. The disseminated lesions present most often as painful, red to gray macules or papules, with purpura, necrosis, and eschar formation.<sup>227</sup> They may mimic the lesions of ecthyma gangrenosum.<sup>228,229</sup> Pustules, cellulitis, abscesses, bullae, and subcutaneous nodules may also occur, and "target lesions" have been described.<sup>229,230</sup> Less common manifestations may include panniculitis, sporotrichoid lesions, and intertrigo.<sup>224</sup>

Fusariosis is usually diagnosed via microscopic examination of skin biopsy specimens with confirmation by fungal culture of tissues and/or blood. Treatment is difficult and includes regular or lipid formulations of amphotericin B, itraconazole, and correction of the neutropenia with granulocyte colony-stimulating factor (G-CSF)– or granulocyte-macrophage colony-stimulating factor (GM-CSF)–stimulated granulocyte transfusions.<sup>229</sup> Newer antifungal agents such as voriconazole or posaconazole may also have a role in the treatment of this serious infection.<sup>230,231</sup>

### Mucormycosis

Mucormycosis (also known as *zygomycosis* or *phycomycosis*) is an opportunistic fungal infection caused by a group of organisms in the order Mucorales (of the class Zygomycetes). Infection of the immunocompetent host is extremely rare despite continual exposure to these organisms. Mucormycosis occurs mainly in immunocompromised individuals and in patients with debilitating diseases (i.e., diabetes mellitus, anemia, heart or liver disease, burns, leukemia, or lymphoma) and is among the most acute, fulminant, and fatal of all fungal infections.<sup>232</sup> It may also occur with increased incidence in patients exposed to hospital construction activity. It may involve any organ of the body but most commonly affects the skin, lungs, meninges, gastrointestinal tract, and structures of the head and neck. Up to 10% of cases of mucormycosis may occur in immunocompetent individuals without identifiable predisposing factors.<sup>233</sup> In children, mucormycosis is associated with many of the risk factors outlined in Table 17-3; in addition, prematurity, low birthweight, malnutrition, and use of wooden tongue depressors and cotton stockinettes have also been reported in association with this infection.<sup>234</sup> Whereas the incidence of mucormycosis may be increasing in adults, a

retrospective 7-year study at a large tertiary children's hospital suggested no such trend in pediatric patients.<sup>235</sup>

The causative fungi of mucormycosis include species of *Mucor*, *Rhizopus*, *Absidia*, *Cunninghamella*, and *Rhizomucor*. The most common cause of zygomycosis is *Rhizopus oryzae* (*arrhizus*). These organisms are saprophytic and grow in soil and on decaying organic materials such as vegetation, fruit, and bread.<sup>236</sup> The portal of entry for these infections varies with the site of the disease. Rhinocerebral mucormycosis is the most common form and affects primarily patients with diabetes as well as patients with immunocompromise.

Cutaneous or subcutaneous infections occur most often in diabetics with recurrent acidosis or in patients with a history of skin trauma or severe burns. This form of infection is characterized by hemorrhagic or necrotic papules and plaques, chronic indolent ulcers, and slowly enlarging dusky nodules. The initial lesion is often a small area of macular discoloration or dusky erythema that gradually enlarges and ulcerates. Necrosis may be marked, and there may be a foul-smelling purulent exudate. A gangrenous form results in rapid ulceration and necrotizing fasciitis-like tissue destruction. The skin lesions of cutaneous mucormycosis are not pathognomonic and may be confused with lesions of ecthyma gangrenosum, aspergillosis, deep fungal infections, other soft-tissue infections, pyoderma gangrenosum, or vasculitis.<sup>232,237</sup> The skin lesions may be primary or secondary, in which case they are related to hematogenous dissemination of the organism from a primary infection in another organ.

The rhinocerebral form is usually characterized by a suppurative necrotizing infection of the paranasal sinuses with periorbital pain, swelling, edema, proptosis, extraocular muscle paresis, and decreased visual acuity. This form is uniformly fatal within weeks when there is extensive involvement, and combined treatment with surgical debridement/resection and systemic antifungals is warranted.<sup>238</sup> Other reported forms of mucormycosis include gastrointestinal, pulmonary, and disseminated. An angioinvasive form of mucormycosis

has been described in neonates, usually those with the risk factors of prematurity, low birthweight, broad-spectrum antibiotic or corticosteroid therapy, and history of local skin trauma.<sup>239</sup> However, the most common types to occur in premature neonates appear to be the gastrointestinal and cutaneous forms.<sup>240</sup>

The diagnosis of mucormycosis relies on tissue biopsy and histologic examination. Broad, nonseptated, thick-walled hyphae are seen and may be noted to be invading cutaneous blood vessels. Fungal culture is confirmatory. Therapy is difficult and often requires a combination of surgical debridement, treatment of the underlying disease process, removal of the source of infection (when possible), and intravenous amphotericin B. Lipid formulations of amphotericin B appear to be more efficacious in treating CNS mucormycosis.<sup>241</sup> Posaconazole may be a reasonable option for those who are resistant to or intolerant of amphotericin.<sup>241</sup>

The complete list of 241 references for this chapter is available online at <http://expertconsult.inkling.com>.

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# 18 Infestations, Bites, and Stings

Parasites are a fascinating and important cause of skin disease in children. They produce their effects in various ways: mechanical trauma from bites or stings, injection of pharmacologically active substances that induce local or systemic effects, allergic reactions in a previously sensitized host, persistent granulomatous reactions to retained mouth parts, direct invasion of the epidermis, or transmission of infectious disease by blood-sucking insects.

## Arthropods

Arthropods are elongated invertebrate animals with segmented bodies, true appendages, and a chitinous exoskeleton. Those of dermatologic significance are the eight-legged arachnids (mites, ticks, spiders, and scorpions) and the six-legged insects (lice, flies, mosquitoes, fleas, bugs, bees, wasps, ants, caterpillars/moths, and beetles).

### ARACHNIDS

The term *mite* refers to a large number of tiny arachnids, many of which live at least part of their lives as parasites upon animals or plants or in prepared foods. Of greatest clinical significance are itch mites (*Sarcoptes scabiei*), grain mites, and harvest mites (chiggers). Avian mite dermatitis has also been recognized with increased incidence in recent years. Mites attack humans by burrowing under or attaching themselves to the skin, where they inflict trivial bites and cause associated dermatitides.

### Scabies

Scabies is a common skin infestation caused by the mite *S. scabiei*. This mite is an obligate human parasite residing in burrowed tunnels within the human epidermis. Mites of all developmental stages may burrow into skin, depositing feces in their tracks. The female mite also lays eggs in these burrows, which serves to further propagate the infestation. The adult female mite has a lifespan of around 15 to 30 days, measures around 400 µm, and lays 1 to 4 eggs per day, which hatch in 3 to 4 days.<sup>1,2</sup> After hatching, the larvae mature into adult mites in 10 to 14 days, and the duration of the whole life cycle is 30 to 60 days.

Scabies is transmitted most often by direct contact with an infested individual, although acquisition from fomites such as bedding and clothing is also possible. The survival time for a mite separated from the human host is estimated at several days. It is estimated that 15 to 20 minutes of close contact time is required for the transmission of scabies from one person to another. Scabies disproportionately affects women and children, as well as individuals with certain predisposing conditions, including immunocompromise, severe mental or physical handicap, and human immunodeficiency virus (HIV) infection. Scabies is seen worldwide in infants and children, and in the United States there seems to be a fairly high incidence in foreign-born adoptees, especially those from Asia or Latin America.<sup>3,4</sup> This latter observation is likely related to the high incidence of infestation seen in orphanages. Scabies continues to be a significant public health issue in the developing world, with a disproportionate burden of disease noted in children who live in overcrowded, lower socioeconomic tropical regions. High endemic rates of scabies are noted in closed communities and institutional environments.<sup>5</sup> In institutions, risk factors for scabies include institution type (with long-term care facilities and larger-sized institutions having higher incidence), extensive physical contact between patients and care workers, movement of patients, delay in diagnosis, and poor implementation of infection control or treatment.<sup>6</sup>

The incubation period for classic scabies is around 3 weeks, with reinfection resulting in more immediate symptoms.<sup>7</sup> The initial symptom of scabies is usually pruritus, which is often evident well before the clinical signs become apparent. Patients with scabies usually complain of worsening pruritus during nighttime hours. Infants and young children may also experience irritability and poor feeding. The skin findings include papules, nodules, burrows, and vesiculopustules (Figs. 18-1 through 18-5). The most common locations for scabies lesions are the interdigital spaces, wrists, ankles, axillae, waist, groin, palms, and soles. Burrows on the palms may reveal a pattern of scale reminiscent of the wake left on a water surface by a moving boat and has been termed the *wake sign*.<sup>8</sup> In infants, lesions may also be seen on the head (Fig. 18-6), which is rarely involved in older patients. Infants commonly have involvement of the palms, soles, and axillae. In older children and adolescents, the most common sites of involvement are the wrists, interdigital spaces, and waist. Although bullous lesions are uncommon in scabies, vesicles are often found in infants and young children, owing to the predisposition for blister formation seen in this age group. Occasionally the Darier sign may be positive, and hence the diagnosis of urticaria pigmentosa may be considered.<sup>9</sup> Genital involvement presenting as papules, crusted papules, or nodules (Figs. 18-7 and 18-8) and areolar lesions are other classic presentation patterns. Excoriations are commonly noted.

Scabies nodules are red-brown nodules (Figs. 18-9 and 18-10) that represent a vigorous hypersensitivity response of the host. They occur most commonly on the trunk, axillary regions, and genitalia and are seen primarily in infants. Although they eventually resolve, scabies nodules may be present for several months. They are occasionally misdiagnosed (both clinically and histologically) as signs of a neoplastic disorder (i.e., leukemia or lymphoma cutis).

Crusted, or Norwegian, scabies is a form of the disorder that presents as scaly, dermatitic papules or plaques. Crusted scabies may be localized or generalized and occurs primarily in immunocompromised patients (especially those with HIV infection) and in those who are mentally retarded or physically incapacitated.<sup>7</sup> The lesions of this disorder may mimic eczema (Fig. 18-11), psoriasis, warts, or a drug reaction, and nail dystrophy may be present. Crusted scabies is commonly misdiagnosed and mismanaged.<sup>10</sup> A delay in the diagnosis of crusted scabies may lead to the inadvertent exposure of multiple physical contacts. The lesions may become heavily crusted and hyperkeratotic and often are minimally pruritic. Crusted scabies is extremely contagious, given the large numbers of mites (thousands) that may be present. In classic scabies, only around 12 mites on average are present. Patients with crusted scabies are often the source for large epidemics within hospitals, given the lack of recognition and subsequent diagnostic delay.

Complications of scabies are generally mild. They include secondary bacterial infection, impaired skin integrity, pain, and rarely debilitation related to limitations in movement secondary to pain. Secondary infection is most commonly the result of *Staphylococcus aureus* or group A β-hemolytic streptococci and presents as crusting, oozing pustules or vesiculopustules. Bullous lesions have been described primarily in older adults, which on occasion may simulate (or possibly evolve into) the autoimmune blistering disorder, bullous pemphigoid.<sup>11,12</sup> Necrotizing vasculitis in the presence of lupus anticoagulant has also been reported.<sup>13</sup>

Animal-transmitted scabies, which is *Sarcoptes* infestation transmitted from domestic animals, usually results in a short-lived infestation with spontaneous resolution in the human host. The close relationship of humans with dogs makes the canine form of animal scabies



**Figure 18-1** Scabies. Erythematous papules with crusting in an infested male infant.



**Figure 18-2** Scabies. Erythematous papules and burrows involving the palm and wrist. Scrapings of lesions from the palmar creases have a high yield on microscopic examination.



**Figure 18-3** Scabies. Curvilinear burrow of the lateral hand.

(*S. scabiei* var. *canis*) the most common type transmitted to humans.<sup>14,15</sup> Canine scabies, or sarcoptic mange, causes patchy loss of hair with scaling in the dog. It is seen most commonly in undernourished, heavily parasitized puppies, and a presumptive diagnosis can be made on the basis of exposure to a pet with a pruritic eruption, alopecia, and the characteristic mouse-like odor of animals with extensive sarcoptic infestation. In children with canine scabies the papular



**Figure 18-4** Scabies. Crusted papule of the abdomen in an infant with scabies.



**Figure 18-5** Scabies. Erythematous papules and linear burrows of the plantar surface of the foot.

eruption most commonly involves the forearms, lower region of the chest, abdomen, and thighs. The distribution differs from that of human scabies in that it tends to spare the interdigital webs and the genitalia, and burrows are absent. The mite of canine scabies does not reproduce on human skin, and therefore the infestation is usually self-limited, clearing spontaneously over several weeks.

The diagnosis of scabies is suggested in the child with pruritus, a papular or papulovesicular eruption with burrows, and the characteristic distribution pattern. However, the differential diagnosis may be broad and includes atopic dermatitis, contact dermatitis, seborrheic



**Figure 18-6** Scabies. Erythematous papules and crusted papules of the scalp in an infant.



**Figure 18-7** Scabies. Erythematous papules of the penis with crusting of the glans penis. These findings are highly suggestive of scabies infestation.

dermatitis, Langerhans cell histiocytosis, impetigo, pyoderma, viral exanthem, papular urticaria, arthropod bites, and acropustulosis of infancy. The latter, which may represent a postscabetic hypersensitivity response, is discussed in detail in Chapter 2. A definitive diagnosis of scabies is made via mineral-oil examination (Box 18-1) with the microscopic identification of mites (Fig. 18-12) or their eggs or feces (scybala) (Fig. 18-13). Ideal skin lesions for sampling include burrows and fresh papules. In young patients in whom skin scrapings might be difficult, obtaining samples from adult contacts (i.e., parents) with lesions is a consideration. Skin biopsy is rarely necessary. A disposable skin curette (an instrument used for the destructive skin procedure, curettage) may be substituted for the scalpel blade if available and may be less frightening for young children and thereby minimize the risk of injury when performing the procedure in a very young or uncooperative child.<sup>16</sup> High-magnification video dermatoscopy is a noninvasive technique that has been reported for diagnosing scabies.<sup>17</sup>

Therapeutic options for scabies are listed in Table 18-1, and a few are discussed here in more detail. The treatment of choice for scabies



**Figure 18-8** Scabies. Nodules of the penis and inguinal regions in a young male recently treated for scabies.



**Figure 18-9** Scabies nodules. These infiltrative nodules persisted for 6 months after effective treatment for scabies.



**Figure 18-10** Scabies nodules. Early scabies nodules developing at sites of crusting; these lesions persisted long after adequate therapy for the infestation.

is 5% permethrin cream, which is applied from the neck down and left on for 8 to 14 hours and followed by thorough rinsing. Permethrin, a synthetic pyrethroid, is a neurotoxin and an excellent scabicide with low potential for toxicity. There appears to be little, if any, resistance of scabies to permethrin, and overall the response rate to treatment is

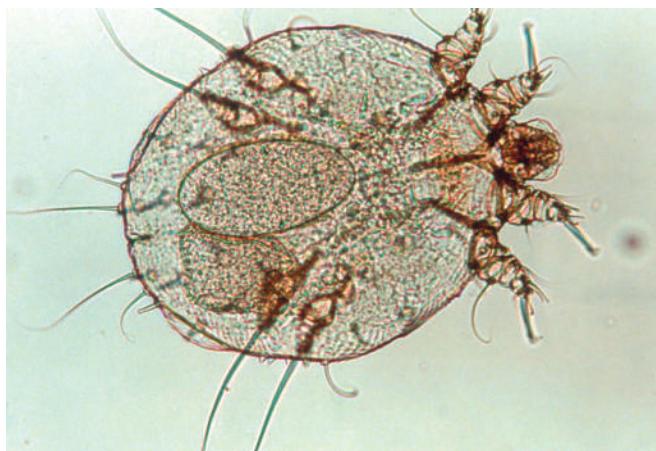
**Table 18-1** Treatment Options for Scabies

Name	Instructions for Use	Comment
Permethrin 5% cream (Elimite, Acticin)	Apply from neck down; rinse in 8–14 hours	Not for use under 2 months of age; may repeat in 1 week if necessary; treat scalp in infants
Lindane 1% lotion	Apply from neck down; rinse in 8–12 hours	Not recommended for infants; not first-line therapy; potential CNS toxicity
Sulfur 6% ointment	Apply from neck down for 3 consecutive nights; rinse 24 hours after last application	Older therapy; malodorous; compounded in petrolatum; safe in infants, pregnant females
Crotamiton cream (Eurax)	Apply from neck down for 2 consecutive nights; rinse 48 hours after last application	High failure rate; may require up to 5 applications
Benzyl benzoate	Apply nightly or every other night for 3 applications	Not available in the United States
Ivermectin (Stromectol)	200 µg/kg per dose given orally for 2 doses, 2 weeks apart	Off-label use; consider for severe infestations, crusted scabies, IC patients, scabies epidemics; should not be used under 5 years of age

CNS, Central nervous system; IC, immunocompromised.



**Figure 18-11** Crusted scabies. This heart-transplant recipient had eczematous, crusted plaques in a widespread distribution that was resistant to topical corticosteroid therapy. Mineral-oil preparation revealed many live scabies mites.

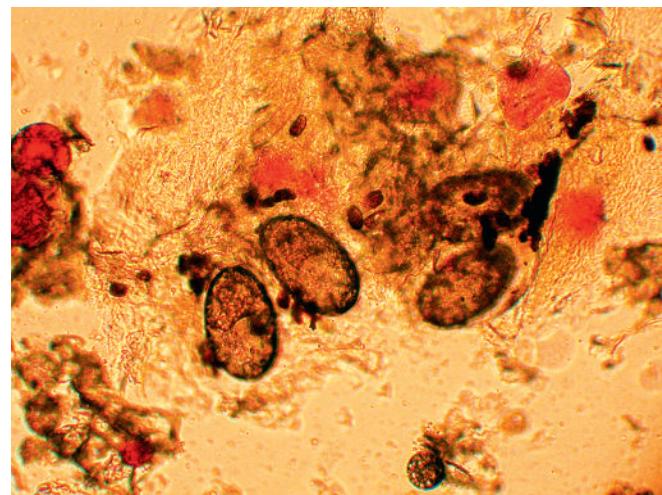


**Figure 18-12** Scabies mite. Note the eggs within the body of the mite. (Live scabies mite,  $\times 40$  magnification.)

excellent. A second treatment with permethrin 1 week after the first is often recommended, although studies suggest a relatively high cure rate after a single application.<sup>1,18</sup> Treatment of all close contacts is also recommended in an effort to minimize ongoing propagation of the infestation. In a systematic review and meta-analysis of scabies therapies, permethrin was demonstrated to be the most effective treatment.<sup>19</sup>

#### Box 18-1 Performing a Mineral-Oil Examination for Scabies

1. Apply a drop of mineral oil to the lesion(s) to be scraped.
  2. Scrape through the lesion with a number 15 scalpel blade (a small amount of bleeding is expected with appropriately deep scrapings).
  3. Smear contents of scraping on a clean glass slide.
  4. Add a few more drops of mineral oil.
  5. Place cover slip over oil and examine under microscope at low power.
- Criteria for a positive mineral oil examination:
- Scabies mite
  - or
  - Ova (eggs)
  - or
  - Scybala (feces)



**Figure 18-13** Scabies preparation. This mineral-oil preparation (performed on scrapings from the patient in Fig. 18-5) reveals multiple eggs (larger, oval bodies) and smaller fecal pellets ("scybala," the dark brown circular concretions).

Permethrin should be applied in a thin, even coat and rubbed in well to all skin surfaces. In infants, application should include the scalp and face, with care to avoid the regions around the eyes and mouth. Special attention should be paid to applying the medication to web spaces, the umbilicus, the genitals, and the gluteal cleft. Fingernails and toenails should be trimmed short and the medication applied as well as possible to the region under the nail edge. Permethrin is not recommended for infants younger than 2 months of age or for pregnant (pregnancy class B) or nursing women. It is vital for patients and

parents to understand that after appropriate therapy, signs and symptoms of scabies may not clear for 2 to 6 weeks after successful treatment, because the hypersensitivity state does not cease immediately after eradication of the infection.<sup>20</sup> The family should have this information before starting therapy, and it may be useful to provide a topical corticosteroid and oral antihistamine for symptomatic relief during this period.

Lindane 1% lotion was, for years, the primary therapy for scabies before the development of permethrin and escalating reports of lindane-related toxicities. Lindane is applied to the skin for 8 to 12 hours with reapplication in 1 week. Although the majority of untoward effects attributed to the use of lindane have been associated with inappropriate, prolonged, or repetitive use, true toxicity potential does exist and becomes more relevant in infants and small children, owing to a relatively greater skin surface and possibly higher blood level accumulations in this age group. When *in vitro* percutaneous absorption of 5% permethrin was compared to 1% lindane, it was shown that human skin was 20-fold more permeable to lindane. In addition, *in vivo* guinea pig blood and brain levels of lindane were fourfold greater than permethrin levels after a single application.<sup>21</sup> Reactions attributed to the use of lindane have included eczema, urticaria, aplastic anemia, alopecia, muscular spasms, and central nervous system toxicity manifested by irritability, nausea, vomiting, amblyopia, headache, dizziness, and convulsions.<sup>22–29</sup> Lindane-resistant scabies has also been an increasing problem in the United States and Central America. This agent, which is recommended as a second-line therapy, is banned in California. Other topical agents utilized in some areas for the treatment of scabies include 10% to 25% benzyl benzoate, 10% crotamiton, 0.5% malathion, and 2% to 10% sulfur ointment.

Ivermectin has been reported with increasing incidence as an off-label treatment option for scabies (it is not approved for this indication in the United States). This agent has been used extensively in veterinary medicine since 1981 for a wide variety of parasitic infestations in farm and domestic animals.<sup>30</sup> Oral ivermectin (Stromectol) is approved for the treatment of *Strongyloides* and onchocerciasis in adult humans. It is also effective for the treatment of loiasis and bancroftian filariasis.<sup>31</sup> Ivermectin acts by blocking chemical transmission across invertebrate nerve synapses that utilize glutamate or  $\gamma$ -aminobutyric acid (GABA), resulting in paralysis and death. It has selective activity against human parasites because of its high affinity for the channels found in the peripheral nervous system of invertebrates.<sup>32</sup> Several studies have evaluated the role of ivermectin in the treatment of scabies and found it very effective in either a single- or two-dose regimen of 200  $\mu\text{g}/\text{kg}$  per dose. Many recommend that this agent be given in two doses when used for classic scabies, separated by 1 to 2 weeks, because it is not ovicidal. Ivermectin is especially useful in immunocompromised patients with scabies and patients with crusted scabies, where it may be used alone or in combination with topical scabicides or keratolytic agents. When it is used in crusted scabies, ivermectin may need to be administered in three to seven doses, depending on the severity of the infection.<sup>33</sup> Topical 1% ivermectin, which is not readily available, has reportedly been effective as well.<sup>34,35</sup>

Regardless of the treatment used for scabies, environmental decontamination is important given the possibility of spread of scabies from fomites. Clothing, bed linens, and towels should be machine washed in hot water and dried using a high-heat setting. Clothing or other items (i.e., stuffed animals) that cannot be washed may be dry cleaned or stored in bags for 3 days to 1 week, because the mite will die when separated from the human host. In addition, systemic antibiotic therapy should be given if secondary bacterial superinfection is present. Scabies nodules can be treated symptomatically with topical or intralesional corticosteroids.

### Other Mites

Mites are small arachnids with mouthparts capable of puncturing and feeding on host tissue fluids. A variety of food and animal mites may result in pruritic dermatoses in exposed humans, and may also be vectors of infectious diseases. Mite bites should be considered in the patient with an unexplained, itchy papular skin eruption.

Harvest mites (chiggers, jiggers, "red bugs") are a member of the American harvest mite family and are commonly found in the



**Figure 18-14** Chigger bites. Multiple itchy, edematous, urticarial papules. Some revealed a small hemorrhagic punctum.

southern United States. Also known as *Trombicula alfreddugesi*, the chigger is distinct from other mites in that only the larva is parasitic to humans and animals. The eight-legged adult and nymphal stages are spent in a nonparasitic existence. Chiggers live in grain stems, in grasses, or in areas overgrown with briars or blackberry bushes, where they exist and feed on vegetable matter, minute arthropods, and insect eggs. The six-legged larva clings to vegetation awaiting the passage of an unsuspecting host and then attaches to the skin when the host brushes against the foliage.<sup>36</sup> The mite then injects an irritating secretion that causes itching and then drops to the ground to molt (or is scratched off) within a few days. The lesions of chigger bites present as urticarial, erythematous papules (Fig. 18-14). They occasionally reveal a hemorrhagic punctum, and in some patients there may be more diffuse erythema, vesicles, or bullae. Pruritus tends to be intense. The "summer penile syndrome" refers to a seasonal acute hypersensitivity reaction to chigger bites and presents with penile swelling, pruritus, and occasional dysuria.<sup>37</sup> Most patients have a history of recent exposure to woods, parks, or lawns.

Treatment of chigger bites consists of antihistamines, cool baths or compresses, and topical corticosteroids. Secondary infection should be treated with systemic antibiotics. Household vinegar (5% acetic acid) has been suggested as a useful measure for postexposure prophylaxis and treatment of pruritus.<sup>36</sup> Chiggers may be disease vectors for scrub typhus, hemorrhagic fever with renal syndrome, hantavirus pulmonary syndrome, and ehrlichiosis.<sup>38</sup>

Grain mites (straw itch mite, *Pyemotes ventricosus*) feed on the larvae of insects, seeds, grains, and plant stems. Persons coming into contact with infested straw and grain are particularly susceptible to this form of dermatitis.<sup>39</sup> This seasonal eruption presents as severely pruritic, pale pink to bright red macules, papulovesicles, or pustules followed by urticarial wheals. Occasionally, a purpuric eruption develops. In severe cases, constitutional symptoms and fever may be present, and the presentation may be mistaken for acute varicella. The eruption is self-limited and treatment, as with chigger bite reactions, is supportive.

Avian mites (fowl mites, bird mites) are divided into two genera, *Dermanyssus* and *Ornithonyssus*. They are known to infest humans accidentally, resulting in a pruritic, widespread papular dermatitis. *Gamasoidosis* is the term used to describe the human skin disorder resulting from nonburrowing, blood-sucking mites from birds and other animals.<sup>40</sup> The diagnosis of avian mite dermatitis is often overlooked because of lack of awareness and the small size of the mites.<sup>41</sup> Common causes include *Dermanyssus gallinae* (chicken mite), *Dermanyssus americanus* (American bird mite), *Ornithonyssus sylviarum* (northern fowl mite), and *Ornithonyssus bursa* (tropical fowl mite). *D. gallinae*, the most common cause, infects various birds including chickens, parakeets, pigeons, canaries, and starlings. Although the mite remains on the bird at night, during the day it may migrate to the nest and can survive without feeding for several months. When



**Figure 18-15** Avian mite dermatitis. Multiple papules and papulovesicles were very pruritic. Upon investigation, a bird's nest was noted near the window in this patient's bedroom and was believed to be the source of the infestation.

birds leave their nest in the spring or early summer, the mites search for other hosts, and human infestation may be the result. Clinical examination reveals papules (Fig. 18-15), vesicles, and urticarial lesions without burrows, because the mite does not burrow into the skin. The diagnosis of avian mite dermatitis is confirmed by identification of the mites found in pillows, bed sheets, clothing, nests, birds, and only rarely humans. Special attention should be given to potential sites for nesting, such as porches, attics, eaves, air conditioning systems, and ventilation ducts. Pet gerbils were the source for *O. sylviarum* and *D. gallinae* in one report.<sup>42</sup> Treatment for avian mite dermatitis, as with other mite bites, is symptomatic.

Other mites may result in similar, nonspecific, pruritic papular eruptions in the human host. The rat mite, *Ornithonyssus bacoti*, is found in rats, and extermination is often necessary for eradication.<sup>43</sup> It has also been reported in pet hamsters.<sup>44</sup> *Cheyletiella* mites are large, animal-specific nonburrowing mites that include *Cheyletiella blakei* (found on cats), *Cheyletiella yasguri* (found on dogs), and *Cheyletiella parasitovorax* (found on rabbits). When these mites are in close proximity to a human host, they bite quickly and run, returning to their animal host.<sup>45</sup> They are very difficult to visualize with the human eye. Skin lesions include grouped pruritic papules, urticarial wheals, and bullous lesions. Pets infested with *Cheyletiella* exhibit patches of fine, powdery scale ("walking dandruff"). Other mites of potential human concern include house-dust mites (*Dermatophagoides* species), the snake mite (*Ophionyssus natricis*), and the house-mouse mite (*Liponyssus sanguineus*).

*Demodex* mites are present normally in adult human hair follicles and sebaceous glands of the face, where they are considered to be "commensal ectoparasites."<sup>46</sup> They are less commonly present in childhood skin. The two species are *Demodex folliculorum* and *Demodex brevis*. "*Demodex folliculitis*" presents as a very itchy papular and pustular eruption on the face, usually in children with leukemia or HIV infection.<sup>46,47</sup> There may be an accentuation in the perioral regions. Reported topical therapies have included 5% permethrin, metronidazole, sulfur, and sodium sulfacetamide.

### Ticks

Ticks are large, globular arachnids with short legs, hard leathery skin, and mouthparts adaptable for sucking blood from mammals, birds, and reptiles. They are important vectors of diseases such as relapsing fever, rickettsial infections (Rocky Mountain spotted fever, Mediterranean spotted fever, Q fever, and ehrlichiosis; see Chapter 16), Lyme disease (see Chapter 14), babesiosis, Colorado tick fever, and tularemia. Although tick bites may be painful, the majority are painless and may go unnoticed.

Ticks are classified into three family groups: hard ticks (Ixodidae), soft ticks (Argasidae), and Nuttalliellidae.<sup>48</sup> They are found in grass,



**Figure 18-16** Tick bite. **(A)** This tick was found on clinical examination of the scalp of this 9-year-old male, who came to the office for an unrelated matter. He had been playing in a forested area in Michigan 3 days previously. **(B)** The tick, after gentle manual removal.

shrubs, vines, and bushes, from which they attach themselves to dogs, cattle, deer, and humans. Ticks penetrate the human epidermis with distal mouthparts called *chelicerae* (Fig. 18-16) and then insert another part called the *hypostome*, through which they feed on blood and deposit a variety of agents including anticoagulant and anti-inflammatory agents. Both acute and chronic dermatoses may result from tick bites. Acute changes include erythema, papules, nodules, bullae, ulceration, and necrosis. Multiple pruritic papules caused by infestation with tick larvae have also been reported.<sup>49</sup> Chronic changes include granulomas, alopecia, and secondary bacterial infection. Localized foreign-body-type reactions may result from retained mouthparts or improper tick removal and occasionally persist for months to years. T- or B-cell cutaneous lymphoid hyperplasia may also be noted, often with copious numbers of eosinophils when tissue biopsies are analyzed histologically. The B-cell type may be difficult to distinguish from true B-cell lymphoma.<sup>50</sup>

Nondermatologic findings that may result from tick bites include anaphylaxis, fever, headache, flu-like symptoms, abdominal pain, and vomiting. Tick paralysis is a reversible disorder characterized by ascending motor weakness and flaccid paralysis. It is believed to be caused by a salivary neurotoxin injected into the victim while the tick is engorging, and it appears that the tick must feed for several days before paralysis occurs. Tick paralysis occurs more commonly in young girls, possibly owing to their longer hair, which may augment tick attachment and hiding.<sup>51</sup> The classic clinical presentation includes an unsteady, ataxic gait followed by ascending symmetric paralysis, usually starting within 2 to 6 days of tick attachment. Upper extremity weakness and cranial nerve involvement (which may present as

dysphagia, drooling, facial weakness, and dysphonia) may occur. If intervention does not occur, involvement may extend to the respiratory musculature, resulting in respiratory failure and subsequent death. Most cases of tick paralysis occur in children, and the mainstay of treatment is tick removal, which usually results in rapid resolution of the signs and symptoms.<sup>51,52</sup>

Various methods of prevention for tick-borne diseases have been advocated. Avoidance of tick habitats may reduce risks, but this is not always feasible. Recommendations for clothing include wearing light-colored, long-sleeved clothes and footwear, tucking pants into socks and taping exposed edges.<sup>48</sup> Insect repellents containing N,N-diethyl-3-methylbenzamide (DEET) or picaridin applied to exposed areas of skin and permethrin applied to clothing are both effective parts of prevention (see below). Frequent examination of skin for ticks is also important in high-risk areas and during high-risk seasons.

Prompt tick removal is also important in reducing the transmission of disease. The entire tick must be removed completely, including the mouthpart and the cement the tick secretes to secure attachment.<sup>53</sup> A variety of commercial tick-removal devices are available and are quite successful. Manual extraction of a tick is performed with blunt, medium-tipped forceps. The tick is grasped as close to the skin as possible, and perpendicular traction is used to gradually extract the entire tick, taking care not to twist the forceps.<sup>53</sup> Should a portion of the tick be retained, a cutaneous punch biopsy will effectively remove it.

### Spiders

Spiders, because of their menacing appearance, are often blamed for more damage than they actually create. Virtually all of the serious spider bites on the North American continent are caused by the black widow spider and the brown recluse spider. Bites of the former tend to have milder outcomes, whereas bites of the latter often result in more severe sequelae.<sup>54</sup> Children are more vulnerable to the effects of spider bites. Patients reporting spider bites are often diagnosed in emergency departments as having skin or soft-tissue infection.<sup>55</sup> The gold standard for diagnosing spider bites is collection and proper identification of the biting spider, although this rarely occurs.

The black widow spider, or *Latrodectus mactans*, is a potentially dangerous spider found mainly in southern Canada, the United States, Cuba, and Mexico. It is recognized by its coal-black color and globular body (1 cm in diameter) with a red or orange hourglass marking on the underside of its abdomen (Fig. 18-17). A web spinner (in contrast to burrowing spiders), it lives in cool, dark places in buildings and little-used structures, woodpiles, and garages, and often spins its web across outdoor furniture. Consequently, a significant number of bites in the southern United States occur around the genitalia and buttocks.

The black widow spider bites humans only in self-defense. The female spider is more dangerous than the male as a result of her larger size and more potent neurotoxin.<sup>56</sup>  $\alpha$ -Latrotoxin, the potent black



**Figure 18-17** Black widow spider. Note classic red hourglass marking on the underside of the abdomen. (Courtesy of Dirk M Elston, MD.)

widow neurotoxin, triggers synaptic vesicle release from presynaptic nerve terminals and results in its effects via exocytosis of neurotransmitters.<sup>57</sup> Two red, punctate marks and local swelling are often seen, and burning or stinging with intense pain develops at the site of the envenomation. This is followed, usually within 10 minutes to an hour, by severe cramping abdominal pain and spasmodic muscular contractions, which peak in around 3 hours. Irritability, sweating, anxiety, and agitation are also common. Priapism may occur. Hypertension within the initial hours after the bite occurs in 20% to 30% of patients,<sup>56</sup> and although it may be severe, it is often asymptomatic in children.<sup>58</sup> Although the bite may be fatal, most children recover spontaneously in 2 to 3 days.

Treatment options for black widow spider bites include analgesics, benzodiazepines, calcium gluconate, and specific antivenin. Diazepam is the most commonly utilized benzodiazepine. Intravenous opioids are also utilized and seem very effective in providing symptomatic relief.<sup>59</sup> Antivenin therapy has been demonstrated useful, even when given as late as 90 hours after the bite.<sup>60</sup> Although specific antivenin may not be available in some parts of the world, redbuck-spider (*Latrodectus hasselti*) antivenin has also been shown to be effective in neutralizing *L. mactans* venom in mouse models.<sup>61,62</sup> Indications for the administration of *Latrodectus* antivenin are shown in Table 18-2, although use of this agent remains controversial in the United States. Potential reactions to antivenin include anaphylaxis and serum sickness.

Spiders of the *Loxosceles* genus cause cutaneous and subcutaneous injury primarily via the enzyme sphingomyelinase D (SMD) (see below). There are roughly 100 species of *Loxosceles* spiders, with 80% of them being found in the Western hemisphere.<sup>63</sup> The brown recluse spider, or *Loxosceles reclusa*, is the one of the most dangerous spiders in the United States. This spider is indigenous to the area spanning eastward from southeastern Nebraska and the eastern half of Texas to the western part of Georgia.<sup>64</sup> The northern boundary includes southern Missouri, Illinois, Indiana, and Ohio, and the southern boundary is the Gulf of Mexico. In nonendemic areas, such as the western United States, physician overdiagnosis of brown recluse bites (also known as *loxoscelism*) is common.<sup>65</sup>

The brown recluse spider has an oval, tan to dark brown body, about 1 cm in length and 4 to 6 mm in width. A dark-brown violin-shaped marking extends dorsally from the eyes back to the distal cephalothorax (Fig. 18-18), and there are three pairs of eyes, rather than the four seen in other spiders. The brown recluse spider thrives in human-altered environments such as attics, basements, and boxes.<sup>64</sup> When in the house, the spider is often found in storage closets (among clothing); when outdoors, it generally resides in grasses, rocky bluffs, woodpiles, and barns. Because of its normal shyness and predilection for dark recesses, it bites only in self-defense when approached.

The venom of *L. reclusa* contains numerous enzymes, most notably SMD2, as well as alkaline phosphatase, esterase, adenosinetriphosphatase (ATPase), and hyaluronidase. SMD may result in many effects, including lysis of red blood cells, complement activation, platelet activation, and thrombosis.<sup>66</sup> Activation of neutrophils results in the classic cutaneous necrosis seen and is a result of neutrophil secretion with subsequent endothelial damage, thrombosis, and ischemia. The local effect on tissues seems to be directly related to the amount of venom injected.

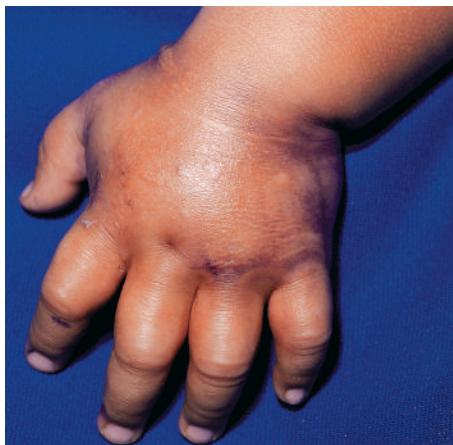
**Table 18-2** Indications for Administration of *Latrodectus* Antivenin

Indication	Comment
Hypertension	If uncontrolled
Pregnancy	
Comorbid conditions	Coronary artery disease, chronic obstructive pulmonary disease
Intractable pain	
Respiratory difficulty	

Modified from Quan D. North American poisonous bites and stings. Crit Care Clin 2012;28:633–59.



**Figure 18-18** Brown recluse spider. Note the brown, violin-shaped marking on the dorsal surface. The adjacent penny gives a size reference. (Courtesy of Dirk M Elson, MD.)



**Figure 18-19** Brown recluse spider bite reaction. Swelling and mild erythema are noted early in the course after a brown recluse spider bite.

The clinical presentation of loxoscelism begins within 6 hours of the bite, usually with pruritus, pain, and/or erythema at the site. These bites, however, may be relatively painless, and patients may be unaware of them occurring, which accounts for the rarity of spider identification in diagnosing these bites.<sup>67</sup> Within 24 hours, a red ring develops around the bite site and is followed by blue-purple discoloration (Fig. 18-19), occasional hemorrhagic blisters, and an increase in pain. Ultimately, gangrenous ulceration with necrosis and eschar formation occurs (Fig. 18-20), occasionally with bulla formation. Anesthesia is often present in the center of the affected area. A generalized petechial or morbilliform eruption may also be present.<sup>63</sup> Systemic findings may include chills, fever, nausea, and joint pain. Rare



**Figure 18-20** Brown recluse spider bite reaction. Massive deep ulceration with eschar formation. (Courtesy of Brooke Army Medical Center teaching file.)

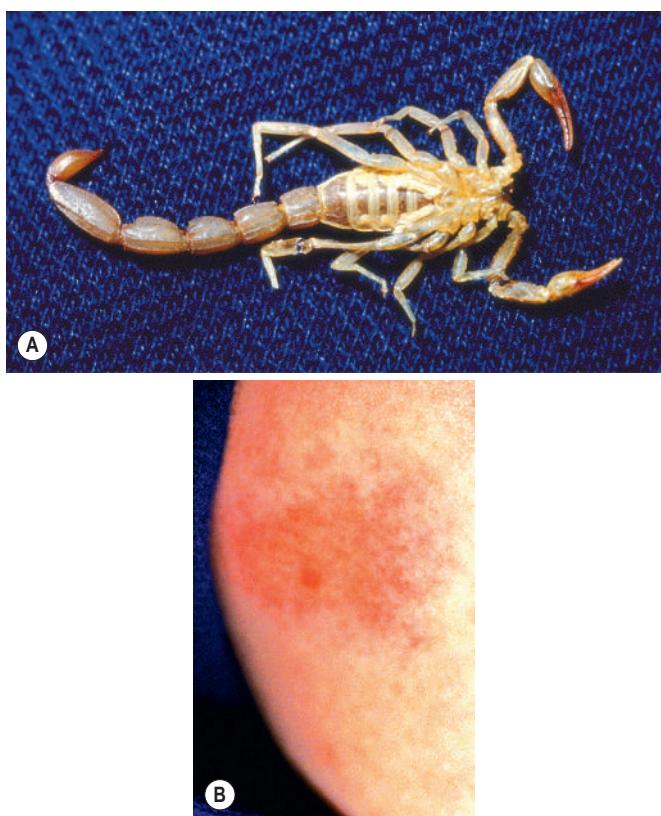
findings include severe hemolysis, renal failure, and pulmonary edema. Necrotizing fasciitis has also been reported.<sup>68</sup> Lymphangitis is not uncommon when the bite occurs on an extremity. In mild cases, *L. reclusa* bites may result only in a mild urticarial reaction. Systemic loxoscelism is uncommon overall (but when it occurs, it appears to be more common in children), and symptoms may include fever, malaise, vomiting, headache, and acute hemolytic anemia with jaundice. Renal failure rarely occurs.

Brown recluse spider bites heal very slowly, and scarring often results. Progression to pyoderma gangrenosum-like ulcers has been reported but is rare. For the majority of small, uncomplicated bite reactions, spontaneous healing is the rule. Conservative treatment measures for these patients include rest, ice compression, and elevation (RICE) of the affected area. Antibiotics should be considered if secondary bacterial infection is suspected. Aspirin, antihistamines (most notably cyproheptadine), and tetanus vaccination may be considered, and dapsone therapy has been utilized but must be closely monitored given the toxicity profile.<sup>64</sup> Dapsone is felt by some to be effective when administered early in the course of the bite reaction and may have its therapeutic effects via suppression of neutrophil chemotaxis. However, side effects including dose-related hemolysis, agranulocytosis, cholestasis, and methemoglobinemia limit its widespread use. When systemic signs and symptoms are present, fluid support should be given and systemic corticosteroids may be considered. Other reported therapies have included hyperbaric oxygen, vaso-dilators, heparin, nitroglycerin, electric shock, curettage, and surgical excision.<sup>63</sup> *Loxosceles* antivenin is available in some countries.

### Scorpions

Scorpions are tropical photophobic arachnids that hide by day and hunt by night. They differ from other arachnids in that they have an elongated abdomen ending in a stinger (Fig. 18-21, A). Scorpions are found worldwide, particularly in the tropics, and in North America they are generally seen in the southwestern United States and Mexico. The Buthidae family are the most toxic of scorpions and are found mainly in India, Spain, the Middle East, and northern Africa.<sup>56</sup> The major scorpion offender in the United States is *Centruroides exilicauda* (also known as *Centruroides sculpturatus* or the "bark scorpion").

Although the majority of scorpion stings in the United States are not severe and do not warrant significant medical therapy, children seem to be at greater risk of developing severe scorpion envenomation. Hence stings in children should be watched carefully, particularly during the first 4 hours, to assess for a more serious reaction. Most symptoms have their onset within 15 minutes after envenomation. The venom apparatus of the scorpion is carried in its curved stinger at the tip of the tail, which is swung over the scorpion's head to penetrate the victim's skin. During the day scorpions hide in shoes, closets, clothing, and crevices. Some species of ground scorpions, however,



**Figure 18-21** Scorpion (A) and scorpion sting, early reaction (B). Painful burning and erythema was present shortly after the sting.

may burrow and hide in gravel or children's sandboxes. They rarely attack humans but will do so when accidentally disturbed, brushed against, or stepped upon. The effect of the sting depends upon the amount of envenomation and the age and size of the individual. The majority of published reports of severe or fatal envenomation have been in children younger than 10 years of age.<sup>69,70</sup>

During a sting, the scorpion releases two noxious agents: a localized hemolytic toxin and a dangerous neurotoxic venom. The hemolytic toxin may cause a painful burning sensation with pronounced redness (Fig. 18-21, B), swelling, discoloration, severe necrosis, lymphangitis, and in some patients, disseminated intravascular coagulation or renal failure. The neurotoxic venom, which reaches the systemic circulation primarily via the lymphatics, may produce local numbness and a severe generalized reaction consisting of sweating, salivation, tightness in the throat, abdominal cramps, cyanosis, muscle jerking, tongue fasciculations, convulsions, and particularly in small children, respiratory paralysis and death. Tachycardia and hypertension are common and may persist for several hours. Pulmonary edema, with or without hemoptysis, and shock may develop. Local cutaneous reactions may vary and include erythema, petechiae, purpura, bullae, edema, induration, necrosis, and ulceration.<sup>71</sup> The diagnosis of scorpion sting is a clinical one, and experienced clinicians who practice in endemic regions can often recognize the clinical symptom pattern.<sup>72</sup>

Treatment for scorpion envenomation is difficult and without consensus on one gold standard of care. Immediate measures include application of a tourniquet above the area of the sting and the application of ice or cold water. *Serotherapy*, which refers to administration of scorpion antivenin, has been advocated by some but has been found ineffective by some investigators, and does not prevent the development of cardiac problems.<sup>56,73–75</sup> Antivenin *Centruroides* (scorpion) equine immune F(ab')<sub>2</sub> (Anascorp) has been approved by the United States Food and Drug Administration (FDA) as an orphan drug and has been shown to be associated with more rapid resolution of envenomation symptoms, decreased use of sedative-hypnotics, and lower levels of plasma venom levels.<sup>72,76</sup>



**Figure 18-22** Head louse. Note the elongated body, three pairs of legs, and nits (eggs) within the body of the louse.

Fluid resuscitation, sedation, and treatment of hypertension may be indicated after scorpion stings. Prazosin therapy has been shown to decrease the development of acute pulmonary edema.<sup>77</sup> A large series of severe scorpion envenomation in children suggested that the beneficial effects of antivenin and/or prazosin is questionable when hospital admission is delayed.<sup>70</sup> Continuous intravenous midazolam infusion has also been utilized to control agitation and involuntary motor activity.<sup>78</sup> Opioid analgesics may be required for pain relief. Although intravenous high-dose corticosteroid therapy was once recommended, it appears to offer no significant benefit in terms of mortality, duration of hospital stay, or cost.<sup>79</sup>

## INSECTS

Insects are the class of arthropods characterized by division into three parts (a head, thorax, and abdomen). Noxious insects are ubiquitous, affecting all humans in some manner at one time or another. The insects of medical significance include lice, mosquitoes, flies, fleas, bed bugs, bees, wasps, ants, caterpillars/moths, and beetles.

### Lice (*Pediculosis*)

Lice have plagued humans since ancient times. Infection is most common during times of stress, such as war, or in crowded environments such as schools, camps, or institutions. After widespread use of dichlorodiphenyltrichloroethane (DDT) after the end of the Second World War, there were relatively few reports of pediculosis in the United States. Subsequent restrictions on the use of DDT in the United States since 1973, however, resulted in an increase in the number of cases, particularly pediculosis capitis and pediculosis pubis. Lice occur wherever there are humans. They spend their entire life as ectoparasites depending on human blood for sustenance. Their existence independent of humans is generally not possible. All lice feed by pressing their mouth against the host's skin, piercing the surface, and injecting an anticoagulant to facilitate the blood flow during feeding.

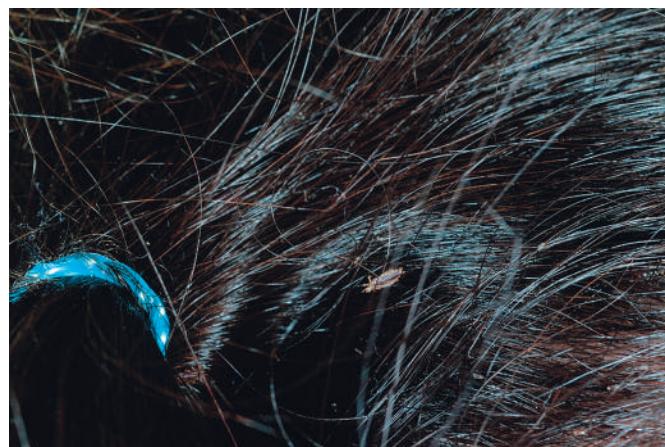
Lice are small, six-legged, wingless insects with translucent, gray-white bodies that become red when engorged with blood. They measure 1 to 4 mm in size, and are visible to the naked eye on close inspection. Three species of lice infest humans:

1. *Pediculus humanus corporis* (the body louse)
2. *Pediculus humanus capitis* (the head louse)
3. *Phthirus pubis* (the pubic or "crab" louse).

Body lice and head lice (Fig. 18-22) are very similar in appearance, with elongated bodies and three pairs of claw-like legs. Pubic lice, on the other hand, have short bodies and resemble crabs in appearance. The body louse is the only louse that can carry human disease, including louse-borne relapsing fever, trench fever, and epidemic typhus. Body and head lice are transmitted by close contact or occasionally via fomites including clothing (body louse) and combs, brushes, and hats or other headgear (head louse). Pubic lice are transmitted by intimate physical contact and are considered in most cases to be a sexually transmitted disease. Nonsexual transmission of pubic lice may occur, though, and probably accounts for most cases of



**Figure 18-23** Nits. These eggs are seen as tiny, gray-white specks attached firmly to hair shafts.



**Figure 18-24** Pediculosis capitis. Note the live head louse, easily seen with the naked eye.

itself is rarely observed on the skin. It obtains its nourishment by clinging to the patient's clothing and intermittently piercing the skin. The primary lesion is a small, red macule, papule, or urticarial wheal with a hemorrhagic central punctum. Primary lesions may be difficult to visualize owing to excoriations related to scratching, and secondary impetiginization may be present. The diagnosis of body lice is confirmed by finding lice or nits in clothing, often in seams. Treatment consists primarily of thorough deinfestation of all clothing and bedding. Treatment of the patient with 5% permethrin cream or lindane 1% lotion may also be useful, because an occasional louse may remain and return to feed.

Pediculosis pubis (pubic lice, crab lice) involves primarily the pubic area but may also involve the scalp, eyebrows and eyelashes, beard, and other hairy areas. Blepharoconjunctivitis may be the presenting signs when eyelashes are involved, and this pattern has been reported in infants and children.<sup>82</sup> Live lice and nits are usually seen. Itching may be the initial symptom, but in persistent cases eczematization or secondary infection may occur. A characteristic skin finding is maculae ceruleae, which are gray-blue macules on the abdomen and thighs. They are felt to represent hemosiderin deposition in the deep dermis as a result of the bites. Treatment of pubic lice is generally similar to that used for head lice (see below), as well as laundering of all clothing and bed linens. Eyelash involvement is usually treated with an occlusive agent such as petroleum jelly.

P. capitis (head lice) is by far the most common form of lice to affect children and usually affects those between 3 and 12 years of age. As mentioned, it is spread primarily through head-to-head contact and less commonly via fomites including headgear, combs, brushes, towels, and upholstery. The transmission from fomites may contribute to the increasingly challenging cycle of head-louse infestation. However, because most transmission occurs from direct contact with the head of an infested individual, the focus of control activities should be primarily on reducing the number of lice on the head and decreasing head-to-head contact.<sup>83</sup> All socioeconomic groups are affected, although African-Americans are less often infested with head lice, possibly related to the diameter, shape, or twisted nature of their hair shafts (which makes grasping of the shaft more difficult for the louse).<sup>80,84–86</sup> The clinical findings consist primarily of pruritus, with secondary excoriation and occasional secondary bacterial infection. Cervical and suboccipital lymphadenopathy may be present. Head lice do not transmit other infectious disease agents. The diagnosis is confirmed by finding live lice (Fig. 18-24) or viable nits on the scalp. In patients in whom the diagnosis is based only on nits, their viability can be confirmed by mounting them on a glass slide and performing microscopic evaluation at low power. Viable nits have an intact operculum (cap) on the nonattached end and a developing louse within the egg (Fig. 18-25).

Although the clinical syndrome of head lice infestation is not serious, it is a cause of significant psychosocial distress, embarrassment, and lost school and work days. The annual cost to society for

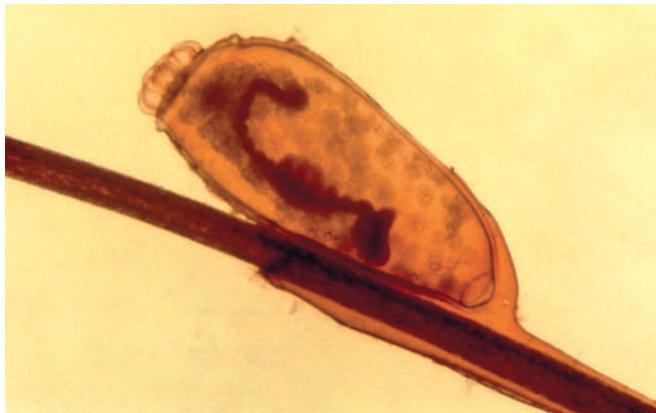
**Table 18-3** Differential Diagnosis of Nits

Diagnosis	Comment
Nits	Firmly adherent to hair shaft; not easily removed with fingers
Seborrheic dermatitis (dandruff)	Diffuse scalp scaling; scales occasionally adhere to hair but easy to remove; scalp erythema may be present
Hair casts	Keratin protein that encircles hair shaft; easily removed
Piedra	Fungal infection of hair; firm nodules attached to hair shafts, white or black in color
Psoriasis	Thick silvery scales, often present overlying red plaques on the scalp
Hair products	i.e., hairspray, mousse, gel

infestation involving the eyebrows and/or eyelashes in children, although the possibility of sexual abuse should always be considered in this setting.

Lice egg cases are called *nits* and are firmly attached to the hair shaft with a cement that makes them difficult to remove. They are gray to yellow-white in color and are seen as tiny pinhead specks measuring 0.3 to 0.8 mm (Fig. 18-23). The nits of head lice are attached to the hair shaft at a more acute angle than those of pubic lice.<sup>80</sup> Head-louse nits are usually laid within 1 to 2 mm of the scalp and, in general, attached nits further from the scalp are more likely to be nonviable. Nits are usually easily distinguished from hair casts or dandruff by the inability to remove them from the hair shaft and, if necessary, microscopic evaluation. The differential diagnosis of nits is shown in Table 18-3. Nits incubate for about 1 week, and then young lice hatch, passing through several nymph stages and growing into adult lice over 1 to 2 weeks. *P. corporis* (body lice) most commonly occurs in homeless individuals, refugees, victims of wars and natural disasters, and those living in crowded conditions.<sup>81</sup> The nits of the body louse attach firmly to clothing fibers, where they may remain viable for weeks. The louse

head lice in the United States is extremely high and includes costs for prescription and over-the-counter therapies, clinical appointments, school nursing time, and time lost from work for caregivers.<sup>87</sup> Since nonviable nits may persist on hair shafts for several months, the potential exists for misdiagnosing active infestation when in fact there is none. It has been tradition in some communities for “no nit” policies to be enforced, in which children with nits are excluded from school until they are adequately treated and all visible nits have been removed.



**Figure 18-25 Nit.** This  $\times 40$ -magnification light microscopy image shows a nit firmly attached to the hair shaft by a cement-like substance. Note the intact cap (operculum) and the developing louse within the egg.

Such policies may lead to unnecessary exposure to pediculicidal agents, missed school, and loss of parental work time.<sup>88</sup> The American Academy of Pediatrics recommends against no-nit policies, because they have not been effective in controlling head-lice transmission.<sup>89</sup> Misidentification of nonlice, non-nit debris (such as dandruff, fibers, dirt, scabs, hair casts) may also result in the overdiagnosis and consequent mismanagement of head lice.<sup>90</sup> Pediculicidal agents should be used only when viable nits or live lice are observed. In general, nits located close to the scalp are viable and unhatched, although in warmer climates, viable ones may be found several inches away from the scalp.

Treatment options for head lice are summarized in **Table 18-4**. Head-lice therapy is recommended for individuals diagnosed with an active infestation, and prophylactic therapy is recommended for bedmates and immediate members of the household of the infested index patient. The standard of care is application of 1% permethrin cream rinse to mildly damp hair, followed by rinsing 10 minutes later. Although permethrin is both pediculicidal and ovicidal, many physicians recommend a second treatment 7 to 10 days after the initial therapy. This agent is FDA approved for children as young as 2 months of age and is recommended as first-line therapy by the American Academy of Pediatrics.<sup>89</sup> Increasing resistance concerns have been reported with permethrin (see below).

Lindane (or  $\gamma$ -benzene hexachloride) is a slow-acting pesticide that has been used often in the past. This agent is stored in fat and nerve tissues, and concerns regarding absorption and neurotoxicity have resulted in many recommending against its use, although most reported toxicities occurred with incorrect usage. Lindane use has been banned in the state of California since 2002.<sup>91</sup> The synergized pyrethrins (i.e., pyrethrin + piperonyl butoxide) include extracts from the *Chrysanthemum* family. These agents are pediculicidal only, and

**Table 18-4** Treatments for Pediculosis Capitis (Head Lice)

Name	Instructions for Use	Comment
Permethrin 1% cream rinse (Nix)	Apply to damp hair after shampooing; leave on for 10 minutes, then rinse	Pediculicidal and ovicidal; repeat treatment in 7–10 days; OTC
Pyrethrin + piperonyl butoxide (RID, Pronto, A-200)	Apply to dry hair; leave on for 10 minutes, then rinse	Pediculicidal only; repeat treatment in 7–10 days; derived from chrysanthemum (do not use in patients with chrysanthemum or ragweed sensitivity); OTC
Lindane 1% shampoo (Kwell)	Shampoo into hair; leave on for 4 minutes and then rinse	Stored in nerve/fat tissue; possible CNS toxicity (although usually observed with incorrect usage) and resistance concerns; low ovicidal activity; not recommended as first choice therapy; repeat therapy in 9 days; Rx
Benzyl alcohol 5% lotion (Ulesfia)	Apply to dry hair; leave on for 10 minutes, rinse	Approved for children 6 months and older; pediculicidal only; kills lice by asphyxiation; contains no neurotoxic pesticide; repeat treatment in 7 days; Rx
Malathion 0.5% lotion (Ovide)	Apply to dry hair; rinse after 8–12 hours	Approved for children 6 years and older; ovicidal and pediculicidal; not first-line therapy; flammable; repeat therapy in 7–10 days, if needed; Rx
Spinosad 0.9% suspension (Natroba)	Apply to dry hair; rinse after 10 minutes	Approved for children 4 years and older; pediculicidal and ovicidal; repeat therapy in 7 days, if needed; Rx
Ivermectin 0.5% lotion (Sklice)	Apply to dry hair; rinse after 10 minutes	Approved for children 6 months and older; pediculicidal only; Rx
Trimethoprim-sulfamethoxazole (Bactrim)	8–10 mg/kg per day, divided, twice daily for 10 days	Occasionally used off-label (not FDA-approved for lice); purportedly kills symbiotic bacteria in louse gut; risk of severe allergic reactions; Rx
Ivermectin, oral (Stromectol, 3 or 6 mg tablets)	200 $\mu$ g/kg single dose; repeat in 1–2 weeks	Occasionally used off-label for resistant cases or crusted scabies; FDA-approved for strongyloidiasis, onchocerciasis; side effects include headache, dizziness, nausea, vomiting; not recommended in children weighing <15 kg; Rx
Manual nit removal	Comb with fine-toothed nit-removal comb	Difficult, tedious (see text); recommended by some in conjunction with pediculicides
Permethrin 0.5% spray (RID)	Spray on inanimate objects	For furniture and bedding; not for use on skin; OTC
Occlusive agents (petrolatum, olive oil, mayonnaise, liquid cleanser, others)	Applied and typically left on overnight, then rinsed out; blow-drying with hand-held dryer reported as useful in conjunction with liquid cleanser	Therapeutic goal is suffocation of lice; potentially limited by ability of lice to temporarily close breathing spiracles; no evidence-based data to support efficacy; none are FDA-approved for this indication

treatment failures are more common. Lindane is available as a 1% shampoo that is left in the hair for 4 minutes and then rinsed out.

Malathion is a weak organophosphate cholinesterase inhibitor that had been unavailable in the United States for several years. This agent was reintroduced in 1999 as a 0.5% lotion and approved for use in children 6 years of age and older. It is not considered a first-line therapy. Malathion is both pediculicidal and ovicidal, and resistance is quite rare, although it is occurring in some parts of the world.<sup>92</sup> The isopropanol-containing vehicle contributes to its effectiveness but also its flammability.<sup>80</sup> Malathion 0.5% lotion is applied to dry hair and rinsed after 8 to 12 hours. A single application is sufficient for most patients, but repeat treatment in 7 to 10 days is recommended if live lice are again noted.

Benzyl alcohol 5% lotion is FDA approved in children 6 months of age and older. This agent is a nonneurotoxic product that kills lice via blockage of their respiratory mechanism. Although head lice have evolved the ability to temporarily close their breathing spiracles (holes), benzyl alcohol 5% lotion stuns the spiracles open while the mineral-oil vehicle obstructs them, killing the lice via asphyxiation.<sup>93</sup> This product provides an alternative for parents who are concerned about the use of neurotoxic pediculicidal agents. Repeat therapy is necessary, and benzyl alcohol 5% lotion is not ovicidal.

Spinosad 0.9% suspension is a pediculicide approved in children 4 years of age and older. It originates from the fermentation of the *Saccharopolyspora spinosa* bacteria, which is normally found in soil, and it results in paralysis and death of the louse. It was found to have better efficacy than permethrin in one report.<sup>94</sup> Spinosad has pediculicidal and ovicidal activity and is applied to dry hair and rinsed off after 10 minutes. Therapy is repeated in 7 days if live lice are again noted. In a meta-analysis, Spinosad therapy was associated with superior efficacy (defined as being free of lice 14 days after the last treatment) compared with permethrin.<sup>95</sup>

Ivermectin 0.5% lotion is approved in children 6 months of age and older and is derived from the fermentation of the bacteria *Streptomyces avermitilis*. The oral form (see below) is used to treat disorders such as onchocerciasis and strongyloidiasis (and off-label occasionally for head lice and scabies). It is applied to dry hair and rinsed after 10 minutes. The manufacturer recommends against repeat therapy without discussing first with the healthcare provider. In a clinical trial of 78 patients with head lice, a single application of 0.5% ivermectin lotion was effective at eradicating lice in three fourths of patients through to day 15 after therapy.<sup>96</sup>

Other less conventional therapies have been used with variable success. These include 5% permethrin, oral trimethoprim-sulfamethoxazole, oral ivermectin, greasy preparations (i.e., olive oil, mayonnaise, and petroleum jelly, which are believed to work via occlusion of the respiratory spiracles of the adult louse), and styling gels.<sup>80,86,97</sup> None of these agents have been studied scientifically, and their true effectiveness remains unclear. Trimethoprim-sulfamethoxazole is believed to kill symbiotic bacteria present in the louse gut and was shown in one study to work synergistically with 1% permethrin cream rinse when the two were used in combination.<sup>98</sup> The potential for severe allergic reaction to this agent makes it less desirable as a lice therapy. Ivermectin has been used as an off-label oral therapy and has typically been dosed at 200 µg/kg (single dose, followed by a second dose in 7 days if persistent infestation is present), similar to when it is used for scabies.<sup>99</sup> In a prospective randomized trial, oral ivermectin (at a higher dose of 400 µg/kg) was found to be superior to 0.5% malathion lotion in children with difficult-to-treat infestations.<sup>100</sup> Thirty-minute applications of hot air have been studied as a potential therapy for head lice.<sup>101</sup>

Manual lice, and especially nit, removal is a tedious task that is unlikely to prevent spread of the infestation unless performed by professional nit-removing salons. Nits, given their firm adherence to the hair shaft, remain in place long after the viable louse has left the casing. It should be recalled that viable nits are deposited on hair close to the scalp (usually within 1 to 2 mm), and most nits that are further out than 5 to 7 mm are no longer viable. However, in some instances nit removal is desirable, such as for esthetic purposes or in response to societal pressures. This is accomplished with manual removal and with fine-toothed nit combs, which are widely available and occasionally packaged with pediculicidal agents. Wet combing refers to use of

the nit comb on damp hair, which is believed to slow down live lice and facilitate removal of nits. A variety of agents have been used in an effort to loosen the cement that attaches the nit to the hair shaft. These include vinegar, 8% formic acid (Step 2<sup>TM</sup>), and a variety of vinegar-based products.

The issue of drug resistance has emerged over the years and clearly appears to be a significant consideration in certain communities. Before assuming true drug resistance, however, other reasons for therapeutic failure should be considered. These include incorrect diagnosis, repeat infestation, and noncompliance with therapy. True resistance has been documented to permethrin, lindane, synergized natural pyrethrins, and malathion.<sup>102–106</sup> Malathion appears to be the agent with the least documented resistance, especially in the United States.<sup>102,103</sup> Lack of susceptibility to pyrethroid insecticides (permethrin, pyrethrins) is usually attributed to an amino acid substitution in a protein that confers "knockdown resistance" (termed the *kdr-like gene*), which subsequently desensitizes cholinergic nerves to the activity of these toxins.<sup>107,108</sup> However, the presence of this mutation has not correlated with clinical treatment failures with permethrin or pyrethrin in some series, suggesting the need for further study in identifying the exact mechanism(s) of resistance in these populations.<sup>92,109</sup>

Regardless of the method of therapy, other family members and close contacts should be examined, and those with evidence of infestation should also be treated. Play areas and furniture can be vacuumed, and bedding, clothing, and headgear should be machine washed in hot water and dried on a high-heat setting. Items that cannot be washed may be dry-cleaned or placed in sealed plastic bags for 2 weeks. Hats, combs, brushes, grooming aids, towels, school lockers and hooks, and other items that come into contact with the head or head coverings should not be shared. Combs and brushes may be coated with the pediculicide for 15 minutes or soaked in rubbing alcohol for 1 hour followed by washing in hot soapy water. Alternatively, these items can be discarded and replaced with new ones.

Information for patients regarding management and control of head lice is available from the National Pediculosis Association at [www.headlice.org](http://www.headlice.org).

## Mosquitoes and Flies

Flies and mosquitoes belong to the order Diptera. One of the largest orders of insects, it includes the two-winged biting flies, gnats, and mosquitoes. Of these, mosquitoes are the most important from the standpoint of human health. They are seen worldwide and may be vectors of many important diseases such as encephalitis (including West Nile encephalitis), malaria, yellow fever, and filariasis. In the United States, the most common insect bites of infants and children are those of mosquitoes.

Mosquitoes are attracted to bright clothing, heat, humidity, and human odors, particularly those of young children. Carbon dioxide, released mainly in the breath but also from the skin, is a long-range attractant for mosquitoes and can be detected from up to 36 meters away.<sup>110</sup> In unsensitized individuals, the ordinary mosquito bite produces only mild, local irritation. This manifests as a slight stinging sensation and a small, pruritic erythematous papule. In sensitized individuals, however, mosquito bites produce itching, urticarial wheals that may last for several hours to several days, or firm papules or nodules (Fig. 18-26) that may persist for longer periods. Occasionally, and particularly in the young, mosquito bites may produce blisters or hemorrhagic lesions. Excoriation of these lesions may result in secondary eczematization and impetiginization. Systemic Arthus-type reactions and anaphylaxis are rare but do occur. Hypersensitivity to mosquito bites has also been associated with Epstein-Barr virus-associated lymphoproliferative disorders.<sup>111,112</sup>

Although the diagnosis of insect bites is often obvious, differentiation from other papular, vesicular, and pruritic eruptions may also be suggested by the characteristic grouping of lesions, a central punctum when present, the acute nature of most reactions, and their seasonal incidence. Treatment of mosquito bites includes oral antihistamines, cool compresses, and topical antipruritic agents such as calamine lotion and topical corticosteroids. When topical corticosteroids are used, stronger preparations (i.e., class II through V) are most effective, with caution exercised not to apply these agents to the face, groin, or



**Figure 18-26** Severe mosquito bite reaction. An indurated, firm, edematous plaque with secondary petechiae from rubbing.

fold areas. Topical diphenhydramine should be avoided given risks of allergic contact sensitization. Cetirizine or loratadine taken prophylactically have both been shown to decrease immediate whealing and pruritus as well as delayed pruritus.<sup>113,114</sup>

Prevention is most effectively accomplished by the use of insect repellents (see below). Another important measure, especially during high-risk activities or exposure times, is the use of protective clothing (hats, socks and shoes, and long-sleeved shirts tucked into pants). Scented hairsprays, pomades, soaps, lotions, powders, colognes, and perfumes may attract all forms of stinging insects and should be avoided unless necessary. Although some have suggested that thiamine hydrochloride taken orally may help to repel insects, this measure remains unproven. Efforts at reducing mosquito populations include ultrasonic electronic devices for use by the consumer and insecticide spraying programs, which have been adopted by several communities.

Various species of biting flies (sandflies, gnats, black flies, deerflies, horseflies) are known to attack the exposed areas of the face, neck, arms, and legs, with the production of painful or pruritic papules or nodules, often with vesiculation. Although lesions often disappear in a few hours, they may persist for several days and can be quite annoying, particularly in small children. Treatment consists of the prophylactic use of insect repellents and treatment of symptoms with acetaminophen, antihistamines, calamine lotion, or topical corticosteroids.

Nonbiting flies, including common houseflies, tend to feed at open wounds, exudates, and cutaneous ulcers and may produce myiasis, a far less common but significant skin disorder. Myiasis is usually a travel-associated dermatosis and is caused most often by infestation with *Dermatobia hominis* (human botfly). It is most common after travel to Central and South America.<sup>115</sup> In this disorder, the adult female lays eggs on other arthropods (flies, mosquitoes, ticks), and this vector then transmits the larvae to the skin of the human host. The larvae penetrate skin, mature in the dermis and subcutaneous tissues, and eventually reach such a size (Fig. 18-27) that they are unable to spontaneously emerge. Clinically, patients present with furuncular nodules (Fig. 18-28) that may drain and often have a central opening (sinus tract), which serves as a site for respiration and excretion. The patient may report a sensation of "crawling in the skin." The lesions occur most commonly on the head and other exposed areas of the body, and small black spiracles may be seen through the overlying skin punctum.<sup>116</sup> Oral myiasis resulting in oral and maxillofacial mutilation have been reported in children living in tropical regions.<sup>117</sup> Treatments include extraction of the larvae through suffocation (petroleum jelly, butter, pork fat, paraffin, oil) or surgical extraction.<sup>115,116,118</sup>

Myiasis caused by *Cochliomyia hominivorax* (New World screw-worm) may occur in persons living in Central and South America or travelers to those regions and result in more tissue destruction. The third larval stage of these maggots contain powerful oral hooks at the



**Figure 18-27** Botfly larva. Note the posterior spines and odd shape of the second stage larva, which makes it difficult to dislodge through the overlying tiny skin orifice.



**Figure 18-28** Myiasis. A furuncular nodule with a small, central opening. Note the visible tip of the larva within the opening.

forepart, which enable burrowing into deeper tissues and significant destruction (Fig. 18-29).<sup>119,120</sup> These screwworms have a predilection for the eyes and nasal and oral mucosae. Mechanical removal of maggots, tissue debridement, and treatment for secondary sequelae (i.e., bacterial infection) are the mainstays of treatment, and topical and oral ivermectin have been utilized as adjunctive therapy.<sup>121,122</sup>

### Fleas

Fleas (Siphonaptera) exist universally among animals and humans. Those that most commonly attack humans in the United States are the human flea (*Pulex irritans*), the cat flea (*Ctenocephalides felis*), and the dog flea (*Ctenocephalides canis*). The eruption produced by a flea bite in a sensitized individual is an urticarial wheal or papule (Fig. 18-30) often with a centrally located hemorrhagic punctum. In highly susceptible individuals, particularly young children, wheals may progress and develop into tense bullae (Figs. 18-31 and 18-32). Flea bites are often multiple and grouped together in linear or irregular clusters on the arms, forearms, or legs or on areas where clothing fits snugly (thighs, buttocks, waist, and lower abdomen). Bites in a linear configuration (the "breakfast, lunch, and dinner" sign; Fig. 18-33) are common and relate to their tendency to jump and crawl but not fly. Treatment is similar to that described for mosquito bites.

Elimination of fleas by treatment of suspected animal carriers and cleaning/spraying of carpets, floors, crevices, and other potentially infested areas should be considered. It should be noted that for every flea seen on the pet there are many more in the environment, that flea collars are not completely effective, and that animal flea sprays and



**Figure 18-29** Myiasis caused by *Cochliomyia hominivorax*. Almost 50 of these larvae were extracted from the small, well-demarcated scalp ulcer of a 13-year-old girl with Darier disease, who contracted the infestation while hiking in Peru.



**Figure 18-30** Flea bites. Multiple excoriated, clustered red papules.

powders, if used, must be repeated every 2 weeks during the summer months to be effective.<sup>123</sup>

Tungiasis is a skin infestation caused by the gravid sand flea, *Tunga penetrans* (chigoe flea, jigger flea). It is endemic in South and Central America, parts of Africa, India, and Pakistan. Tungiasis is rare in the United States and usually seen in those who have traveled to an endemic region.<sup>124</sup> In tungiasis, the female flea attaches herself to the warm-blooded host, burrows through the epidermis into the dermis, and gradually enlarges. Clinical lesions are red nodules with a central punctum or ulceration, occasionally resembling an abscess. Treatment consists of flea removal, wound care, tetanus prophylaxis, and when necessary, treatment of secondary bacterial infection.<sup>124</sup>



**Figure 18-31** Bullous flea-bite reaction. Tense bulla and surrounding crusted papules in a patient with a hypersensitivity to flea bites.



**Figure 18-32** Bullous flea-bite reaction. Multiple tense bullae and secondary bacterial impetiginization in a patient with flea-bite hypersensitivity.

### Bed Bugs

Bed bugs are a member of the order Hemiptera, which also includes reduviid bugs. The most common species to parasitize humans is *Cimex lectularius*. Bed bugs are red-brown, blood-sucking, nocturnal insects that are 3 to 5 mm in size. They are wingless, with flattened oval bodies and three pairs of legs (Fig. 18-34). The female bug deposits eggs on rough surfaces, cracks, and crevices. They avoid light, hiding out during the day in cracks in walls and floors and in furniture and responding to warmth and carbon dioxide (which are both present in sleeping humans) at night. Bites present as erythematous papules, and the breakfast, lunch, and dinner sign may again be present. Bullous lesions may also occur.<sup>125</sup> Bed-bug bites most commonly occur on exposed areas of the face, neck, arms, or hands.

Systemic reactions which may possibly be attributable to bed-bug bites include urticaria, angioedema, asthma, and anaphylaxis. The bed bug is capable of traveling long distances in search of food, often from one house to another, and has been known to survive without food for up to 6 months to a year. It has been suggested that bed bugs may be vectors for hepatitis B, HIV, plague, yellow fever, tuberculosis, relapsing fever, leprosy, leishmania, filariasis, or trypanosomiasis, although there is little evidence to support that they are vectors for any communicable diseases.<sup>126–128</sup> Importantly, methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus faecium* were recovered from bed bugs collected from an impoverished community in Vancouver, British Columbia, suggesting that more studies are required to determine their potential to serve as vectors for transmission.<sup>129</sup> Since



**Figure 18-33** Flea bites. The classic linear configuration of flea bites (the breakfast, lunch, and dinner sign) caused by the tendency of fleas to jump and crawl rather than fly.



**Figure 18-34** Bed bug (*Cimex lectularius*). Note the flattened, oval body and three pairs of legs. The family that brought it in had been complaining of itchy, red bite reactions for several months.

In the late twentieth century, bed-bug infestations have been observed increasingly in homes, apartments, hotel rooms, bed and breakfasts, dormitories, hostels, trains, aircrafts, cruise ships, nursing homes, and hospitals.<sup>128,130,131</sup> Although the exact basis for the increased bed-bug resurgence is unclear, some have attributed it to increased worldwide travel, altered insecticide management, or increasing pesticide resistance.<sup>129</sup>

Treatment is directed at elimination of the bug from the environment with insecticides and eliminating potential hiding sites. Although individual lesions require no direct therapy, oral antihistamines, topical corticosteroids, or calamine lotion may be used for symptomatic relief. Systemic corticosteroids have occasionally been utilized. Preventive measures that have been advocated for bed-bug bites include wearing pajamas that cover the majority of skin, covering bedposts with petroleumatum, and manual inspection of hotel headboards and mattresses.<sup>132</sup> Once infestation has occurred, useful measures for

eradication may include vacuuming of exposed hiding locations, washing all linens in hot water and drying on low heat, steam cleaning, use of mattress and box spring encasements, discarding of furniture, placement of insect-growth regulators, and pesticide spraying.<sup>128,132</sup> Carbon-dioxide fumigation has also been demonstrated effective against bedbugs.<sup>133</sup>

### Bees, Wasps, and Ants

Bees, wasps, and ants belong to the order Hymenoptera, a large order of insects that contains about 100 000 species. Like most other insects, they have three pairs of legs and four wings and are recognized by the narrow isthmus separating the abdomen from the thorax. These insects have stingers that can result in local or systemic reactions in susceptible individuals. Hymenoptera venom allergy can result in life-threatening anaphylactic reactions and is responsible for at least 40 deaths per year in the United States.<sup>134,135</sup> The three families of stinging insects in the order Hymenoptera include Vespidae (yellow jackets, wasps, and hornets), Apidae (honey bees and bumble bees), and Formicidae (stinging ants).

Bees, the only insects that produce food eaten by humans, live in almost every part of the world except the North and South Poles. Honey bees live and work together in large groups and do not sting unless frightened or injured. Africanized ("killer") honeybees are hybridized honeybees (from interbreeding of African and domestic honey bees in South America) that tend to attack in swarms and have gradually been migrating into the United States. Wasps, among the most interesting and intelligent of insects, may live together in cooperative fashion, as seen with the so-called "social wasps" (hornets and yellow jackets), or may live as solitary insects. Most wasps are beneficial to humans, because they destroy large numbers of flies, caterpillars, and other insects that may be harmful. As with bees, wasps ordinarily do not sting humans unless they are bothered or frightened. However, yellow jackets and hornets tend to be quite aggressive, especially when near their nest or if disturbed.<sup>135</sup> Wasps are capable of multiple stings, because their stingers are smooth and retractable; bees, on the other hand, usually eviscerate themselves after a single sting, given the barbed nature of their stingers.<sup>136</sup>

Symptoms of bee or wasp stings vary from mild local pruritus, pain, and edema to general anaphylactic reactions with associated difficulty in breathing and swallowing, hoarseness, slurred speech, gastrointestinal disturbances, abdominal pain, dizziness, weakness, confusion, generalized edema, cardiovascular collapse, and occasionally sudden death.

Ants, like bees and wasps, have large glands at the tip of the abdomen from which they introduce venom into wounds produced by their bites. The majority of ants are not aggressive and rarely sting large organisms.<sup>137</sup> However, there are two groups that are considered medically important in the United States. The fire ant (*Solenopsis richteri* and *S. invicta*) is originally from South America and has spread rapidly in the southern United States, where it has become an agricultural pest and a health hazard.<sup>138</sup> It produces a venom more potent than that of other members of the order Hymenoptera. The fire ant was named for the extreme burning pain inflicted by its sting and tends to attack without warning.<sup>139</sup> During one bite cycle, the fire ant may inflict seven to eight stings in a circular pattern. The immediate reaction is characterized by a painful wheal and flare response, with vesicles developing over several hours. Pustular changes eventually occur, and some patients develop large, local erythematous reactions. Anaphylaxis is a common cause of significant morbidity and may be fatal. The harvester ant (*Pogonomyrmex* species), which also has a significant presence in the United States and is considered a stinging ant, is found primarily in the Southwestern states.

The treatment of ordinary bee, wasp, or ant stings consists of local application of antipruritic shake lotions (i.e., calamine lotion), cool compresses or cool baths, and oral antihistamines. A papain solution made of one part meat tenderizer to four parts water may help to relieve local symptoms of pain or discomfort. Severe allergic reactions are treated with epinephrine, antihistamines, oxygen, and systemic corticosteroids. Patients known to be at risk for severe systemic reactions to bee, wasp, hornet, yellow-jacket, or fire-ant stings should be given an epinephrine pen kit and be educated in its proper use in an emergency. Preventative techniques include education on practical

avoidance measures and referral to an allergist for consideration of allergen testing and immunotherapy.

Allergen immunotherapy is an effective form of prevention for certain individuals at risk for severe insect-sting reactions. Commercial venoms for both skin testing and immunotherapy are available for yellow jackets, white-faced hornets, yellow hornets, wasps, and honey bees, and the complementary deoxyribonucleic acid (cDNA) of most major allergens of bee and vespid venoms has been cloned and is available in a recombinant form.<sup>134,135</sup> Sequential bee-sting challenge tests can be used as a diagnostic tool to assess the need for venom immunotherapy in children who are allergic to bee venom.<sup>140</sup> Because the stinging insect cannot always be reliably identified, it is suggested that the testing physician include all geographically relevant insects when choosing the test panel.<sup>141</sup> Venom immunotherapy should be considered for any patient with a history of a systemic allergic reaction to a Hymenoptera sting. For fire-ant immunotherapy, imported fire-ant whole-body extract is the main reagent used.<sup>139</sup> The therapeutic goals of immunotherapy are to prevent life-threatening reactions, reduce morbidity from such stings, and decrease insect-sting anxiety.

### Blister Beetles

Blister beetles (*Cantharis vesicatoria*, order Coleoptera) contain cantharidin, a vesicant most concentrated in the beetles' genitalia, and the active principle of the purported aphrodisiac Spanish fly.<sup>142</sup> The lesions produced accidentally by crushing blister beetles, by discharge of their body fluid on the skin, or by external therapeutic use of cantharidin (as in the treatment of molluscum contagiosum; see Chapter 15) consist of slowly forming blisters that involve the outer layers of the skin. Treatment depends on the extent and location of lesions. Simple aseptic drainage of large bullae and cool compresses generally give adequate relief of symptoms. If vesicles are not traumatized, they usually resolve in 3 to 4 days with subsequent desquamation and healing. Blister-beetle ingestion, when reported, may result in oral mucosal blistering, abdominal pain, vomiting, hematuria, oliguria, and renal failure.<sup>143</sup> "Blister-beetle dermatitis" may also occur after exposure to cantharidin (or another vesicant, pederin, found in the genus *Paederus*) and may mimic shingles, herpes infection, allergic contact dermatitis or impetigo.<sup>144</sup>

### Papular Urticaria

Papular urticaria is a common condition of childhood characterized by a chronic or recurrent papular eruption caused by hypersensitivity to a variety of bites, including those of mosquitoes, fleas, bed bugs, and mites. It is often pruritic and uncomfortable, and the resultant scratching may result in open erosions and secondary bacterial superinfection. One of the most challenging aspects of papular urticaria is convincing parents that the lesions are related to a bite reaction and identifying and eradicating the source of the offending insect.<sup>145</sup>

Papular urticaria presents with multiple urticarial, 3- to 10-mm papules (Figs. 18-35 and 18-36). Lesions are commonly grouped or



**Figure 18-35** Papular urticaria. These edematous, red papules would intermittently swell and become itchier.

clustered in a fashion similar to acute bite reactions. They may be excoriated or crusted, and a central punctum may be visible overlying each papule. Papular urticaria is most common in the summer and late spring, and flea bites are the most common cause. Individual lesions tend to resolve over 1 to 2 weeks and may heal with postinflammatory erythema or hyperpigmentation (Fig. 18-37). Recurrent episodes are common, especially if there is ongoing exposure to the offending insects.

The differential diagnosis of papular urticaria includes ordinary urticaria, pityriasis lichenoides et varioliformis acuta (PLEVA), papular acrodermatitis of childhood (Gianotti-Crosti syndrome), and lymphomatoid papulosis. Histopathologic examination of skin-biopsy specimens reveals spongiosis (epidermal edema), subepidermal edema, and a mixed inflammatory infiltrate that often includes eosinophils.<sup>146</sup> Skin biopsy is useful both in confirming the diagnosis and in persuading the parents regarding the nature of the condition. Symptomatic treatment includes oral antihistamines and topical corticosteroids, as well as topical antipruritic preparations containing menthol, camphor, or pramoxine. Environmental control measures are also desirable when feasible.

### Insect Repellents

Protection from insect bites includes several measures such as avoiding infested areas, wearing protective clothing, and controlling insect populations when possible. However, the most effective avoidance measure in most situations is the application of insect repellent to the



**Figure 18-36** Papular urticaria. These edematous, pruritic red papules continued to intermittently enlarge for many months.



**Figure 18-37** Papular urticaria. These recurrent papules would heal with postinflammatory hyperpigmentation, only to recur with erythema, edema, and pruritus in the same locations.

### Box 18-2 Guidelines for the Safe Use of Insect Repellents in Children

Do not apply to infants under 2 months of age.  
 Read and follow all package directions and precautions.  
 Use just enough repellent to lightly cover the skin; do not saturate the skin.  
 Apply only to exposed skin; do not use on clothing or apply under clothing.  
 Apply sparingly to the face, and avoid contact with the eyes and mouth.  
 Do not apply to the hands of small children.  
 Do not allow young children to apply products themselves.  
 Do not use sprays in enclosed areas or near food.  
 If self-applied, rinse palms to avoid inadvertent contact with eyes and mouth.  
 Do not use on open skin, cuts, wounds, or inflamed areas.  
 Once inside, wash all treated areas with soap and water.  
 Keep repellents out of the reach of children.  
 Use a separate sunscreen; avoid using combined insect repellent-sunscreen products, because clinical data are limited.

skin. Several types of repellents are commercially available and include both synthetic chemicals and plant-derived essential oils.

DEET (formerly N,N-diethyl-m-toluamide) has traditionally been the most effective and most widely used repellent.<sup>147</sup> DEET is a broad-spectrum insect repellent that is effective against mosquitoes, biting flies, chiggers, fleas, and ticks.<sup>148</sup> Higher concentrations of DEET result in longer-lasting protection, although these effects seem to plateau at concentrations higher than 50%. In the United States, DEET is available in variable concentrations in multiple vehicles, including solutions, lotions, creams, gels, pump sprays, sticks, roll-ons, wristbands, and impregnated towelettes.<sup>110,147</sup> The mechanism of action of DEET is to provide a vapor barrier that deters the biting insect from coming into contact with human skin.<sup>149</sup> Firm guidelines or recommendations for choosing an appropriate DEET concentration are not available. However, it is generally accepted that products with 10% to 35% DEET will provide adequate protection in most circumstances.<sup>110</sup> Some general recommendations for the use of DEET-containing products are listed in Box 18-2.

The use of DEET in young children has been a source of some concern, given rare reports of potential neurologic toxicity. Small amounts of DEET may be absorbed through the skin yet seem to be completely eliminated (along with its metabolites) within 4 hours of application in adults.<sup>150</sup> Although the pharmacokinetics are not as well understood in children, reports of neurologic toxicity are rare, and, in fact, in one study of data collected by the American Association of Poison Control Centers, infants and children had lower rates of severe adverse events than did adults.<sup>151</sup> Many of the reports of DEET-related toxicity involved long-term, heavy, frequent, or whole-body application of DEET, and in some, the product was orally ingested.<sup>148,152</sup> In 1998 the Environmental Protection Agency (EPA) completed a reregistration eligibility decision for DEET, and in this process included a review of acute, subacute, and chronic toxicity data. The agency concluded that normal use of insect repellents containing DEET poses no significant risks to children or adults, that product labeling would be modified to include recommendations for safe use, and that child safety claims on labels were prohibited, given the lack of appropriate scientific data to support such claims.<sup>148,152,153</sup> Human-health risk assessments were conducted for DEET and picaridin (see below), and found no significant toxicological risks from typical use of these repellents.<sup>154</sup> Over a 6-year period of data collection as part of the DEET Registry, seizures were the most common neurologic symptom reported with a possible temporal relationship to DEET exposure. However, children were not disproportionately represented; there was no apparent relationship between DEET concentration and the severity of outcome; and the reports of neurologic events (when considered relative to the number of annual DEET applications in the United States) were quite low overall.<sup>155</sup> The American Academy of Pediatrics, in the Red Book discussion of mosquito bite prevention, recommends repellents with DEET concentrations not exceeding 30% and following such practical application guidelines as those outlined in Box 18-2.<sup>156</sup> The Centers for Disease Control and Prevention

recommends DEET at concentrations up to 50% for both adults and children over 2 months of age.

DEET-containing insect repellents should be carefully applied, because they may damage plastics, rayon, leather, spandex, and other synthetic fabrics. They are not damaging, however, to cotton or wool. In addition, it should be remembered that DEET-containing products are flammable. Combination products containing DEET and sunscreen are not recommended, given the potentially decreased effectiveness of the sunscreen and the different recommended application frequencies of these two products. Questions about the safety of DEET can be addressed by the EPA-sponsored National Pesticide Telecommunications Network at [www.ace.orst.edu/info/nptn](http://www.ace.orst.edu/info/nptn).

Picaridin is an insect repellent that is effective against mosquitoes, biting flies, and ticks. It is usually used in a concentration of up to 20%. Picaridin is reportedly of similar efficacy to DEET, is odorless, and will not damage plastics or fabrics.<sup>149</sup> Before its launch in the United States, picaridin was used fairly extensively in Europe and Australia. No serious adverse events have been reported to date. Another synthetic insect repellent available in the United States and Europe is IR3535, which fared poorly in an “arm-in-cage” study when compared to DEET.<sup>148</sup>

Plant-derived repellents may have repellent activity, but none compare to the effectiveness and duration of action of DEET.<sup>110</sup> These products usually contain essential oils from any of several plants, including citronella, cedar, eucalyptus, lemongrass, and soybean. Citronella is the active ingredient in most “natural” repellents marketed in the United States. It has a lemony scent and is available in an oil and in candles. However, in areas with epidemics of mosquito-borne diseases (such as West Nile virus) or in high-risk settings, these products should not be relied upon as the sole protection from bites. When compared to DEET, a blend of the top three performing essential oils was found to offer some protection against various species of mosquitoes but significantly less so than the chemical repellent.<sup>157</sup>

Other approaches to mosquito repellency include ingested garlic or vitamin B<sub>1</sub> and treated wristbands, each of which has less consistently demonstrated effectiveness. Permethrin, marketed in a 0.5% concentration (Permanone, Duranon, Cutter Outdoorsmen Gear Guard, Sawyer Clothing Tick Repellent, 3M Clothing and Gear) as a tick repellent, is also available and is sprayed on tents, clothing, and sleeping bags. This product is also effective against mosquitoes, flies, and chiggers and works as a contact insecticide, resulting in central nervous system toxicity to the insect.

### Caterpillars and Moths

Caterpillars represent the larval stage of butterflies and moths of the order Lepidoptera. The hairs of certain moths and caterpillars are known to produce dermatitis that can be severe and incapacitating to both children and adults. Dermatitis related to these insects has been known as *caterpillar dermatitis* and *lepidopterism*. In the United States, the most commonly seen and most irritating of these are those caused by the hairs of the brown-tail moth (usually seen in the northeastern part of this country) and the puss caterpillar (the larvae of the “flannel” moth, *Megalopyge opercularis*), seen from Virginia southward to the states bordering the Gulf of Mexico.<sup>158–160</sup> Contact with the oak processionary caterpillar (*Thaumetopoea processionea*), found especially in oak forests in European countries, may result in multiple symptoms including pruritus, dermatitis, conjunctivitis, pharyngitis, and respiratory distress.<sup>161</sup> In some instances, affected individuals did not have direct contact with the caterpillar but only with another individual who had experienced contact, suggesting the possibility of human-to-human transmission of the relevant substance(s).<sup>162</sup>

Reactions produced by contact with the hairs and spines of these moths and caterpillars may be associated with the release of histamine and other vasoactive substances or from mechanical irritation by caterpillar hairs that become imbedded in the pores of affected individuals. The precise mechanisms for these reactions are unclear, however, and may be related to irritant reactions, hypersensitivity reactions, or toxic envenomation.<sup>163</sup> They may be focal or more widespread. Examination typically reveals erythematous macules and papules, eczematous dermatitis, vesicles, urticaria, or even necrosis. Other reactions may include severe local pain, nausea, fever, swelling, numbness, muscle cramps, headache, seizures, and shock. The

diagnosis of moth or caterpillar dermatitis can be confirmed by microscopic examination of tape strippings or scrapings of involved areas with demonstration of offending hairs. Although the disorder is self-limiting, relief can be obtained with the use of oral antihistamines, topical corticosteroids, ice packs, and topical antipruritic agents. In patients with severe reactions, fluid support, narcotics, and systemic corticosteroids may be necessary.

## Other Cutaneous Parasites

### CUTANEOUS LARVA MIGRANS (CREEPING ERUPTION)

Cutaneous larva migrans (CLM; creeping eruption) is a self-limited skin eruption caused by the larval stages of the dog and cat hookworms, *Ancylostoma caninum* and *Ancylostoma braziliensis*, respectively. *Uncinaria stenocephala* has also been implicated. CLM is one of the most common skin diseases among travelers returning from tropical countries.<sup>164</sup> In the United States, most cases of CLM are contracted in the southeastern states, most notably Florida and Georgia.<sup>165</sup> Worldwide the disorder is most common in Mexico, Central and South America, Africa, Southeast Asia, and the Caribbean.<sup>165,166</sup> The adult hookworms release eggs while in the intestines of their definitive hosts (dogs or cats), and these eggs are passed along with stool onto sandy, warm soil. Humans become incidental hosts when larvae burrow through intact skin that comes into contact with the infested soil. The disorder is quite common in children because of high-risk behaviors (i.e., playing in the sand) seen in this age group. It occurs sporadically or in small epidemics in high-income countries and in tourists who have visited the tropics.<sup>167</sup> The most commonly involved areas are the extremities (especially feet), buttocks, and genitalia. The incubation period for CLM may be prolonged for weeks to months.<sup>168</sup> Preventative measures may include wearing shoes or sandals and sitting on a towel or chair while on sandy beaches.<sup>169</sup>

In the human host, the hookworm larvae are unable to complete their natural life cycle and remain confined to the upper levels of skin, wandering aimlessly and producing the characteristic cutaneous findings. Initially, skin findings may be limited to one or a few erythematous papules. Ultimately, serpiginous, raised, sharply demarcated plaques develop (Figs. 18-38 and 18-39) and may advance up to 1 to 2 mm per day. Follicular involvement with folliculitis (hookworm folliculitis) may also occur.<sup>164,170</sup> Vesicular or bullous lesions are rare. Without treatment, the larvae eventually die, but this may take several months. The lesions of CLM are extremely pruritic and may be complicated by pain and secondary bacterial infection. Although systemic dissemination of the parasite does not generally occur, eosinophilia is common and pneumonitis (Löffler syndrome) may occasionally be present.

The differential diagnosis of CLM may include other larval infestations such as *Strongyloides stercoralis* and *Gnathostoma spinigerum*. Scabies, jellyfish stings, and phytophotodermatitis may also mimic CLM.<sup>166</sup> Treatment options for creeping eruption include liquid nitrogen cryotherapy (which was a traditional mainstay of treatment) and oral anthelmintic agents. Cryotherapy is rarely effective and is traumatic for most young children; hence it should be avoided for this indication. Oral agents demonstrated to be effective include thiabendazole, albendazole, and ivermectin. Thiabendazole is given at a dose of 25 mg/kg per day divided into two doses for 2 to 5 days. Potential side effects include headache, dizziness, and gastrointestinal upset. Alternatively, topical thiabendazole (500 mg/5 mL) can be applied four times daily and is often effective. Oral albendazole seems to be one of the most effective and well-tolerated therapies. It is given at a dose of 200 to 400 mg twice daily for 5 to 7 days.<sup>171-173</sup> Side effects are rare with this agent, which has been used in nematode and cestode infestations. Use of these agents in young children has not been well studied. Ivermectin, an agent used primarily for onchocerciasis and other nematodes, has also been anecdotally reported as effective in open-label studies.<sup>164</sup> It is given as a single dose (200 µg/kg) and repeated in 1 to 2 weeks if necessary. In one series of 56 patients with CLM treated with single-dose ivermectin, the response rate was 98%.<sup>174</sup>



**Figure 18-38** Cutaneous larva migrans. A serpiginous, migratory plaque on the dorsal foot.



**Figure 18-39** Cutaneous larva migrans. The plantar surface of this young boy revealed a very itchy, linear plaque that was noted to continuously extend over the several days before diagnosis.

### CERCARIAL DERMATITIS (SWIMMER'S ITCH)

Cercarial dermatitis (swimmer's itch) is an itchy, inflammatory dermatosis that results from penetration of human skin by nonhuman schistosome parasites. It occurs after swimming or wading in freshwater lakes, especially in the midwestern United States and has also been demonstrated in the southwestern United States.<sup>175</sup> Cercarial dermatitis can also be acquired in the sea or brackish waters.<sup>176</sup> The most clinically relevant organisms are the *Trichobilharzia* species. The adult schistosomes reside in the mesenteric blood vessels of birds and mammals, and after passage from the blood to the intestine, eggs are deposited in water along with the host feces. Subsequently, miracidiae hatch and penetrate the intermediate host, usually snails.<sup>177</sup> Within the snail they develop into cercariae, which leave the snails and reside in the upper levels of lakes until they can again infect the definitive host. However, they may also infect accidental hosts such as humans.

Swimmer's itch occurs on exposed areas of skin, which are the sites most readily available to the cercariae. Because humans are not the

definitive host, the cercariae die within hours after skin penetration, and the host immune response results in the clinical eruption.<sup>178</sup> Often the initial infestation does not result in a reaction but causes sensitization, which results in the clinical eruption after subsequent exposures.<sup>177</sup> Examination of the skin usually reveals nonspecific, erythematous papules and papulovesicles (Figs. 18-40 and 18-41). Excoriation may be present, and secondary bacterial superinfection is an occasional complication. Postinflammatory hyperpigmentation is common.

The distribution of the lesions combined with the history of exposure to a freshwater lake will combine to suggest the diagnosis of swimmer's itch. Activities that involve more extensive contact with lake water (i.e., wading, working on the dock, and swimming) are more likely to be associated with the disorder than other activities like boating, skiing, and tubing.<sup>178</sup> Aquariums containing snails may also be a source of swimmer's itch.<sup>177,179</sup> Water analysis via filtration and polymerase chain reaction (PCR) detection may be useful if



**Figure 18-40** Cercarial dermatitis. Multiple pruritic, excoriated papules and papulovesicles on exposed surfaces of the skin. The patient had been swimming in a freshwater lake along with family members, several of whom developed similar lesions.



**Figure 18-41** Cercarial dermatitis. Itchy, excoriated papules and papulovesicles, occurring on exposed areas of skin.

confirmation is required and snails cannot be found.<sup>180</sup> Treatment is supportive and consists of topical corticosteroids, topical antipruritic agents, oral antihistamines, and rarely systemic corticosteroids for severe cases.

## Seabather's Eruption

Seabather's eruption, also known as *sea lice*, is not a true parasitic infestation but is commonly confused with cercarial dermatitis and is therefore included in this chapter. It results from a hypersensitivity reaction to the stinging nematocyst of a cnidarian (planula) larva, which includes jellyfish, Portuguese man-of-war, sea anemone, or fire coral (see below).<sup>181</sup> Most often it has been associated with exposure to the larval form of the thimble-sized jellyfish, *Linuche unguiculata*.<sup>181,182</sup> Seabather's eruption occurs most commonly in marine saltwaters off of Florida, in the Gulf of Mexico, and in the Caribbean. (A discussion of traditional jellyfish stings can be found in the following section.)

The skin lesions of seabather's eruption tend to be limited to areas covered by the swimming garment; the swimwear tends to act as a filter, draining water and maintaining contact of the planulae against the skin.<sup>183</sup> Skin findings may include erythematous papules, pustules, and papulovesicles (Figs. 18-42 and 18-43). Urticarial plaques may also be present, and pruritus is usually severe. Other symptoms may include fatigue, fever, chills, headache, abdominal pain, diarrhea, and nausea; these symptoms appear to be more common in children or in those who have severe envenomation.<sup>184</sup> Many patients recall having seen "thimble-sized" jellyfish in the waters, or tiny "black dots" along the water surface.<sup>181</sup> Symptoms may begin while in the water or when exiting, although in the majority of patients they begin several hours later. Longer swim times appear to increase the risk of seabather's eruption; in one report of 38 patients, the median duration of water exposure was 2.5 hours (range 1 to 8 hours).<sup>184</sup> Because freshwater is known to stimulate nematocyst discharge of toxins (via osmotic pressure change), removal of the bathing garment is recommended before rinsing, especially in areas where seabather's eruption warnings are posted.

The diagnosis of seabather's eruption is primarily a clinical one. It should be suspected in the patient with an itchy, papulovesicular eruption limited to covered areas of skin and occurring after exposure to saltwater. Skin biopsy<sup>181</sup> and serologic assays<sup>181,185</sup> have been used but are generally unnecessary. Treatment is symptomatic, as discussed earlier for swimmer's itch.

## Jellyfish Stings

Cnidarians (phylum Cnidaria) are a group of aquatic animals that includes jellyfish, corals, sea anemones, and hydras. The cnidarian



**Figure 18-42** Seabather's eruption. These edematous, erythematous papules were limited to sites covered by the swimming garment.



**Figure 18-43** Seabather's eruption. Erythematous papules and papulovesicles limited to sites covered by the swimming garment, following a vacation in the Caribbean.

body consists of a gastrovascular cavity with a single opening through which food is ingested and waste is released. Cnidarians have tentacles encircling their mouth and bodies that are radially symmetrical. The phylum Cnidaria consists of four classes: Hydrozoa (Portuguese man-of-war), Scyphozoa (true jellyfish), Cubozoa (box jellyfish or sea wasps), and Anthozoa (sea anemones and corals).

Jellyfish are marine invertebrates that are found both in the ocean and in fresh water. They are responsible for the most common ocean-related envenomations acquired by humans, which may result in three types of responses, including immediate allergic, immediate toxic, and delayed allergic reactions.<sup>186</sup> The surface of jellyfish bodies and tentacles is covered in specialized cells called *cnidoblasts* that contain in their cytoplasm a nematocyst, or a capsule filled with a toxic fluid that is injected into human skin at the time of contact.<sup>187</sup> Cutaneous reactions to jellyfish stings may include urticarial wheals, burning, pruritus, and tenderness. Papules and papulovesicles often occur in linear and wispy patterns, and more chronic postinflammatory pigmentary changes, scarring (including keloids), and

lichenification may occur. Occasionally observed findings include thrombophlebitis, tender regional lymphadenopathy, angioedema, papular urticaria, and distant hypersensitivity-type skin reactions (i.e., an id reaction). Fatal anaphylactic reactions are rare but when they occur are more common in children.<sup>188</sup> Other reported sequelae include a persistent lichen planus-like eruption and Guillain–Barré syndrome.<sup>186,189</sup> *Seabather's eruption* refers to a papulovesicular eruption occurring in covered areas of skin in response to contact with nematocysts from thimble-sized jellyfish larvae (see previous section).

Treatment for jellyfish stings is supportive, and traditional considerations include pain control, compression, application of vinegar (thought to help in deactivation of the nematocysts), avoidance of fresh water exposure (which may trigger firing of nematocysts), oral antihistamines, and manual removal of tentacles when visible. One systematic review of jellyfish-sting therapy suggested that vinegar may cause pain exacerbation or further nematocyst discharge unless the envenomation is believed to be from the bluebottle (*Physalia*), in which case it may be helpful; other authors, however, firmly believe in the benefit of topical vinegar in this setting.<sup>190,191</sup> Medical attention should be sought after a jellyfish sting, despite there being a lack of consensus on the most appropriate treatment regimen among emergency medicine physicians.<sup>192</sup> Cardiopulmonary resuscitation and use of an epinephrine pen (when available) may be necessary if anaphylaxis occurs. Useful preventive measures include wearing protective swim- or diving-wear and avoidance of areas known to be infested with jellyfish.

The complete list of 192 references for this chapter is available online at <http://expertconsult.inkling.com>.

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Sunlight emits a wide spectrum of radiation energy, extending from radio waves through infrared, visible, and ultraviolet (UV) light, to X-rays.<sup>1</sup> The wavelength range of visible light is 400 to 800 nm and is relatively harmless, except for individuals with photosensitivity disorders, such as porphyria, solar urticaria, and polymorphous light eruption (PMLE). The infrared range is 800 to 1800 nm. It is the UVA and UVB wavelengths (290 to 400 nm) that cause most cutaneous reactions, including in normal individuals who are exposed to sunlight, tanning booths, and an ever-expanding number of photosensitizers in the environment. Wavelengths less than 220 nm are absorbed by atmospheric gases, including oxygen and nitrogen, and those less than 290 nm are absorbed by the atmospheric ozone layer. The remaining middle wavelength (UVB, 290 to 320 nm) and long wavelength (UVA1, 340 to 400 nm; UVA2, 320 to 340 nm) UV radiation can reach the earth and be absorbed by biologic molecules. The skin is quite effective at protection from UV penetration, but the depth of penetration depends upon the wavelength. UVA easily reaches the deeper dermis, whereas UVB is absorbed in the epidermis and little reaches the upper dermis.

UV light also reaches the skin through reflection from snow (80% to 85%); sand (17% to 25%); water (5%, but up to 100% when the sun is directly overhead); sidewalks, and turf. UV light exposure also increases by 4% for every 1000-foot elevation above sea level. On a bright, cloudy day with thin cloud cover, it is possible to receive 60% to 85% of the amount of UV radiation present on a bright clear day. Hats and parasols provide only a moderate degree of protection, and surfaces with reflectivity greatly increase sunlight exposure.

## Tanning and Sunburn Reactions

The visible short-term effects of UV light exposure are sunburn (Fig. 19-1; see Fig. 26-15) and tanning. The ability to cause sunburn markedly declines with increasing wavelength. UVA light at 360 nm is 1000-fold less effective in causing skin erythema (sunburn) than UVA light at 300 nm. Thus UVB light is largely responsible for sunburn, with peak induction 6 to 24 hours after exposure. Sunburns gradually fade during the next 3 to 5 days, as the skin starts to desquamate. Reactivity to UVB light may range in severity from a mild asymptomatic erythema to a more intense reaction, with redness accompanied by tenderness, pain, edema, and, at times, vesiculation and bulla formation, particularly the day after the sunburn first appears. If the sunburned area is extensive, constitutional symptoms may include nausea, malaise, headache, fever, chills, and even delirium. Sunburn during childhood correlates with a higher risk of developing melanocytic nevi,<sup>2</sup> as well as UV light-induced skin cancers.

Tanning is also wavelength-dependent and is biphasic. Immediate pigment darkening results primarily from exposure to UVA light, is caused by alteration and redistribution of melanin, and fades in 6 to 8 hours. Delayed tanning usually results from exposure to UVB and peaks at about 3 days after exposure. Fair skin is only able to tan with UVB dosages about the erythema threshold (i.e., a sunburn is required on type II skin; type I skin cannot tan; Table 19-1). In contrast, darker skin types (i.e., type III and higher) can tan significantly without burning (at suberythemogenic doses). Sunburn causes apoptosis (cell death) of keratinocytes ("sunburn cells") or, if the dosage is high enough, induces cell cycle arrest, allowing the cell to undergo repair of their deoxyribonucleic acid (DNA) template before proliferating. Sunburn also depletes the protective Langerhans cells, causes epidermal thickening (which reduces exposure of the basal keratinocytes to UV radiation) as a protective mechanism, stimulates

release of inflammatory cytokines, and induces the formation of anti-oxidative enzymes (which reduce oxidative DNA damage). The tan induced by UVB involves increased melanin synthesis, increased numbers of melanocytes, and increased transfer of melanosomes to keratinocytes.

The long-term effects of chronic sun exposure include photoaging, photocarcinogenesis, and immunosuppression. Given its potential to penetrate more deeply into the dermis, UVA light is thought to play a particularly important role in photoaging. UVA light, but not UVB light, is able to penetrate through window glass, even if tinted.<sup>3</sup> Thus individuals who sit in offices exposed to UVA light through windows or drive cars extensively can show significant asymmetry in UVA damage on the face.<sup>4</sup> An exception is the laminated glass of windshields (as opposed to the nonlaminated glass on the sides of cars), which blocks most UVA light (up to 380 nm). Window films can be applied to block UVA radiation but allow vision.

UVA light is also the light used in indoor tanning, a practice prevalent particularly among older female adolescents.<sup>5,6</sup> This practice promotes skin damage, leading to an increased risk of both melanoma and nonmelanoma skin cancer and photodamage, but no increased protection against sun exposure.<sup>7,8</sup> The danger of using tanning facilities has led to legislation to control use by minors and limitations of exposure in several states. Nevertheless, the prevalence of use of a tanning salon by college-aged students was 60.4% in 2009, with 33.1% using tanning salons more than five times a year.<sup>9</sup> Many facilities now offer "safe" tanning, and these self-tanners are also available commercially. With all of these self-tanners, an artificial tan is produced by dihydroxyacetone (DHA), a sugar that interacts with the stratum corneum proteins to produce a brown pigment made of polymers called *melanoidins*, which resist washing.<sup>10</sup> Approximately 10.8% of adolescents have used a self-tanner, especially older Caucasian adolescents with a high to moderate level of sun sensitivity.<sup>11</sup> Self-tanners, unfortunately, provide minimal and transient sun protection, and their use is often in conjunction with tanning salon use rather than as a substitute.<sup>12</sup>

Prevention of sunburn depends primarily on the utilization of measures that reduce exposure to strong sunlight. This is especially important for fair-skinned individuals, particularly blue-eyed persons, redheads, blonds, and those with freckles who withstand actinic exposure poorly, burn easily, and, over the years, tend to suffer chronic effects of light exposure. Prophylactic measures to reduce the impact of harmful UV rays include timing of outdoor activities to avoid peak UV light exposure between 10:00 AM and 3:00 PM in the warmer seasons of the year; wearing broad-rimmed hats, sun protective clothing, and sunglasses; and staying in the shade. Light-textured materials such as T-shirts (especially when wet) give only partial protection.<sup>3</sup> Clothes with a tighter weave are commercially available (e.g., [www.coolibar.com](http://www.coolibar.com); [www.solumbra.com](http://www.solumbra.com)), or clothes can be laundered with a chemical (Tinosorb FD), which provides sun protection (e.g., Sun Guard).

Sunscreens occupy an important position in the management of UV light exposure.<sup>13-15</sup> The lifetime use of sunscreen and sun avoidance has been calculated to reduce the lifetime risk of developing UV light-induced skin cancer by 78%,<sup>16</sup> although whether use of sunscreens reduce the development of nevi remains controversial.<sup>17</sup> Promoting routine sunscreen use in the pediatric population is important, including among adolescents whose behaviors escape parental influence.<sup>18,19</sup> In order to be effective, adequate amounts of sunscreen must be applied to all areas exposed to UV light, and the sunscreen must be reapplied every few hours. It is critical that individuals continue sensible sun protection by means other than sunscreens and not increase their exposure because of sunscreen availability.



**Figure 19-1** Sunburn. This adolescent became more sensitive to ultraviolet light exposure while taking isotretinoin.

**Table 19-1** Skin Types and Photosensitivity

Skin Type	Reactivity to Sun	Examples
I	Very sensitive: always burns easily and severely, tans little or not at all	Individuals with fair skin, blond or red hair, blue or brown eyes, and freckles
II	Very sensitive: usually burns easily, tans minimally or lightly	Individuals with fair skin; red, blond, or brown hair; and blue, hazel, or brown eyes
III	Moderately sensitive: burns moderately, tans gradually and uniformly	Average white individuals
IV	Moderately sensitive: burns minimally, tans easily	Individuals with dark brown hair, dark eyes, and white or light brown skin
V	Minimally sensitive: rarely burns, tans well and easily	Brown-skinned (Middle Eastern and Hispanic) individuals
VI	Deeply pigmented: almost never burns, tans profusely	Blacks and others with heavy pigmentation

The most common sunscreen components and their absorbance capacity are listed in **Table 19-2**. Inorganic sunscreens (titanium dioxide and zinc oxide) protect skin by reflecting and scattering UV and visible light (290 to 700 nm); often, both of these agents are usually included in an inorganic sunscreen. Organic sunscreens absorb light at particular wavelengths into specific chemical UV filters and reemit the energy as insignificant quantities of heat. Newer organic sunscreen components now absorb in both the UVA and UVB spectrum, thus providing protection against the damaging effects of the broad spectrum of UV light. These newer sunscreens are photostable (in contrast to avobenzene, an earlier generation component), and include bis-ethylhexyloxyphenol methoxyphenol triazine (anisotriazine [Tinosorb S]), drometrizole trisiloxane (silatriazole [Mexoryl XL]), methylene-bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M), and terephthalylidene dicamphor sulfonic acid (Mexoryl SX). Unfortunately only avobenzene and Mexoryl SX are FDA-approved, so other newer sunscreen ingredients are not available in the US. Ideally, organic sunscreens should be applied 20 to 30 minutes before the onset of sun exposure, so that there is adequate time to bind to the stratum corneum and show effectiveness. The inorganic sunscreens can be applied immediately before sun exposure.<sup>20</sup> Sunscreens should be reapplied after swimming, periods of excessive perspiration, and washing or showering; water resistance for 40 minutes is specified on labeling. Oral sunscreens containing antioxidants (e.g., lycopene, vitamins C and E) and botanicals (e.g., polyphenols, such as green tea and flavonoids such as genistein) are now commercially available. They provide some protection against acute sun damage, but they are not as effective as topical sunscreens in preventing sunburns, their long-term protective effects are not clear, and they should not replace other forms of photoprotection for children.

Sunscreen labels in the United States are now required to reveal both the sun protection factor (SPF) and the capability of broad spectrum UVA protection.<sup>21</sup> The SPF rating can be determined by dividing the least amount of time it takes to produce erythema on sunscreen-protected skin by the time it takes to produce the same erythema without sunscreen protection. Thus individuals using a sunscreen with an SPF of 15 who normally burn after unprotected sun exposure, can theoretically stay out 15 times longer before getting the same degree of erythema, and thus only informs about protection against sunburn from UVB light. The additional benefit from use of a sunscreen with an SPF above 30 is small compared with the incremental benefit at lower SPF numbers, but higher SPF may be important for individuals with high photosensitivity or in intense sunlight. Furthermore, it should be recognized that the SPF is tested with a concentration of 2 mg/cm<sup>2</sup>, which is more than the majority of individuals apply. The designation "broad spectrum" provides information about the ability of the sunscreen to protect again nonerythema effects, especially from UVA light, including immune suppression, photoaging, and skin cancer.

The degree to which a person sunburns or tans depends on genetic factors and the natural protection of the skin. Skin types, accordingly, are ranked from skin type I, the most sensitive, to skin type VI, the least sensitive to sun damage (see **Table 19-1**). Because sun damage begins in children and is cumulative, it is strongly recommended that everyone adopt a program of sun protection and daily sunscreen use, preferably with an SPF of 15 or greater, from infancy on. Because increased melanin is not totally protective, even darker skinned individuals can burn and should use sunscreen.

Considerable media attention has focused on the need for UV light-induced vitamin D synthesis in the skin as a rationale for sun exposure. Indeed, UVB light induces the synthesis of vitamin D<sub>3</sub> in epidermal cells, and this vitamin D<sub>3</sub> is then hydroxylated in the liver (to 25-OH-vitamin D<sub>3</sub>) and kidney (to 1,25-OH-vitamin D<sub>3</sub>). However, the UV light exposure that stimulates vitamin D<sub>3</sub> production in the skin is inseparable from UV light exposure that is carcinogenic. Although vigorous sunscreen use may reduce the capacity of skin to produce vitamin D (and greater vitamin D deficiency has been linked to darker skin color), sunscreen use has not been linked with deficiency and oral administration of vitamin D likely suffices. The American Academy of Pediatrics recommends a minimum daily intake of vitamin D for infants, children, and adolescents to 400 IU/day, beginning shortly after birth.<sup>22</sup> Patients who require strict photoprotection as treatment should be monitored for possible vitamin D deficiency and provided dietary supplementation.<sup>23</sup>

Treatment of sunburn consists of cool compresses or cool tub baths in colloidal oatmeal (such as Aveeno), baking soda, or cornstarch; topical formulations with pramoxine or menthol; mild topical corticosteroid formulations; an emollient cream; and systemic preparations with analgesic and anti-inflammatory properties, such as nonsteroidal anti-inflammatory drugs (NSAIDs). When symptoms are severe, a short course of systemic corticosteroids (oral prednisone, or its equivalent, in dosages of 1 mg/kg per day, with tapering after a period of 4 to 8 days) will abort severe reactions and afford added relief.

Certain disorders predispose individuals to the adverse effects of UV light. For example, children with alopecia totalis (see Chapter 7),

**Table 19-2** Common Sunscreen Filters and Ultraviolet Protection

Sunscreen Filter	Wavelength Protection*
<b>ORGANIC SUNSCREENS</b>	
PABA derivatives	UVB
PABA and padimate O (octyl dimethyl PABA)	
Salicylates	UVB
Homosalate (homomethyl salicylate), octisalate (octyl salicylate), trolamine salicylate	
Cinnamates	UVB
Cinoxate (2-ethoxyethyl p-methoxycinnamate), octinoxate (octyl methoxycinnamate, Parsol MCX)	
Benzophenones	
Dioxybenzone (benzophenone-8)	UVB, some UVA2
Oxybenzone (benzophenone-3)	UVB, UVA2
Sulisobenzene (benzophenone-4)	UVA2, some UVA1
Others	
Avobenzone (butyl methoxydibenzoylmethane, Parsol 1789) <sup>†</sup>	UVA2 and UVA1
Ensulizole (phenylbenzimidazole sulfonic acid)	UVB
Meradimate (menthyl anthranilate)	UVA2
Drometrizole trisiloxane (Mexoryl XL)	UVB, UVA2, UVA1
Ecamsule (terephthalylidene dicamphor sulfonic acid, Mexoryl SX) <sup>†</sup>	UVA2, UVA1
Octocrylene	UVB
Bisotriazole (methylene bis-benzotriazolyl tetramethylbutylphenol, Tinosorb M)	UVB, UVA2, UVA1
Bemotrizinol (bis-ethylhexyloxyphenol methoxyphenyl triazine, Tinosorb S)	UVA2, UVA1
<b>INORGANIC SUNSCREENS</b>	
Titanium dioxide	UVA and UVB; if large enough particle, visible light
Zinc oxide	UVA and UVB; if large enough particle, visible light

PABA, Paraaminobenzoic acid; UVA, ultraviolet A light; UVB, ultraviolet B light.

\*UVB = 290 to 320 nm, UVA2 = 320 to 340 nm, UVA1 = 340 to 400 nm, visible light = 400 to 800 nm.

<sup>†</sup>Only organic UVA blockers in US.

just as adults with androgenetic alopecia and balding at the vertex, have a higher risk of developing skin cancer at the exposed site if not protected. Patients with diminished or absent melanin, as in oculocutaneous albinism (see Chapter 11), or with defective DNA-repair mechanisms, as in xeroderma pigmentosum (XP), have an increased tendency to develop UV light-induced DNA damage and cutaneous malignancy. Individuals with nevoid basal cell carcinoma syndrome (see Chapter 9), which predisposes to the early onset of numerous basal cell carcinomas, have mutations in the *PTCH* gene, a gene that can also be mutated by UV light exposure in sporadic basal cell carcinomas. Sunlight can also exacerbate or trigger certain dermatoses, among them acne (see Chapter 8); herpes simplex infection (see Chapter 15); lupus systematus, neonatal lupus, and dermatomyositis (see Chapter 22); Darier disease (see Chapter 5); pemphigus and bullous pemphigoid (see Chapter 13); and lichen planus and psoriasis (see Chapter 4).

## Photodermatoses

**Photosensitivity** is a broad term used to describe abnormal or adverse reactions to sunlight energy in the skin.<sup>24</sup> Photodermatoses must be distinguished from reactions to sunlight from exaggerated exposure, which is a normal response. Photodermatoses have been classified into four groups: 1) immunologically mediated; 2) drug- or chemical-induced; 3) with defective DNA repair; and 4) photoaggravation of existing conditions.<sup>25</sup>

Photosensitivity in a child should be suspected if the child develops a sunburn reaction, swelling, or intense pruritus after limited exposure to sunlight or shows a rash or scarring predominantly in sun-exposed areas (face, V of the neck, and dorsal surface of the arms and hands).<sup>26,27</sup> The history in a patient with a photosensitivity disorder is of great importance in determining the cause (Table 19-3). Examina-

**Table 19-3** Evaluation for Potential Photosensitivity Disorders

History	Age of onset; exposure to potential photosensitizers; season of the eruption; time of onset after exposure to the sun; duration of eruption; effect of window glass and exposure to other light sources, including tanning booths; history of atopy and other medical problems; response to medications and use of sunscreens; family history
Examination	Distribution and morphology
Phototesting	Action spectrum, time to onset, minimal urticarial dose, inhibition and augmentation spectra
Photopatch testing	If photoallergy is suspected
Laboratory	Complete blood count, metabolic panel, erythrocyte sedimentation rate, autoantibodies, esp. antinuclear antibody, porphyrins
Biopsy	Useful for lupus and possibly porphyrias, but not for other photodermatoses Fibroblast cultures for XP testing

XP, Xeroderma pigmentosum.

tion should focus on the distribution of lesions, including the areas of sparing.<sup>28</sup> In a photosensitivity disorder, the upper eyelids, postauricular and submental areas, nasolabial and neck folds, volar aspect of the wrist, and the antecubital fossae generally tend to be spared. The morphology of the lesions may be helpful as well (urticarial versus papular

versus vesicular, and the presence of lichenification, which suggests chronicity.

Phototesting can be helpful in determining the cause of an acquired photodermatoses. Exposure to UV light of different wavelengths may replicate the lesions, offering the opportunity to see morphology that may not be present at the time of the examination, confirming the suspicion of photosensitivity, and determining the UV range that triggers the disorder.<sup>29</sup> Further laboratory investigations, such as antibody testing for suspected collagen vascular disease (such as antinuclear antibodies [ANAs], anti-ds DNA, anti-Ro, and anti-La antibodies), blood and 24-hour urine porphyrin levels, and photopatch testing in patients with suspected photoallergy, may be necessary. Performing a biopsy is rarely useful, except for suspected lupus erythematosus.

## IMMUNOLOGICALLY MEDIATED PHOTODERMATOSES

### Solar Urticaria

Solar urticaria accounts for less than 1% of type I immunoglobulin (Ig) E-mediated type of sensitivity reactions and is characterized by a sensation of pruritus or burning and erythema.<sup>30-34</sup> Typically affected areas are the arms, legs, and upper chest; areas with regular sun exposure, such as the hands and face, are less commonly involved. It usually appears within 5 to 10 minutes of sunlight exposure and is followed almost immediately by a localized urticarial reaction confined to the exposed areas and an irregular flare reaction that may extend onto unexposed skin. Within 24 hours, lesions tend to resolve (usually in 1 to 3 hours); new lesions will not develop for 12 to 24 hours, even if subsequent exposure to sunlight occurs. Fixed solar urticaria, characterized by recurrent eruptions on the same body parts, is rare and less severe than typical solar urticaria.<sup>35</sup> Delayed fixed solar urticaria, occurring 6 hours after exposure, has been described.<sup>36</sup> Although the reaction is generally transient, scratching and rubbing may lead to secondary eczematization with persistent cutaneous changes. The disorder usually does not manifest until the third or fourth decade of life, and females are affected three times more often than males. It has been reported, however, as early as 1 week of age.<sup>37,38</sup> The condition persists for more than a decade in the majority of affected individuals and often for a lifetime. Systemic signs have occasionally been reported in association, including headache, nausea, wheezing, dizziness, syncope and rarely shock.

The cause of solar urticaria is unclear, but the pathogenesis involves interaction of a cutaneous photoallergen with IgE-specific mast cells, leading to mast cell degranulation. Often phototesting can confirm the diagnosis and determine the wavelength range that causes the photosensitivity. If positive, whealing generally occurs within minutes. In some patients, the sensitivity involves the UVB range through the visible light range; the majority of patients react within the range of 290 to 480 nm. A negative phototest occurs in many patients and does not exclude the diagnosis. In patients with mild forms of solar urticaria (those in whom the threshold is high), the disorder may be controlled simply by appropriate sunscreens and avoidance of prolonged unprotected sun exposure. Those individuals highly sensitive to sunlight, however, must completely avoid daytime exposure.

Nonsedating antihistamines,<sup>39</sup> antimalarials, corticosteroids, intravenous Ig (IVIG), and plasmapheresis have been beneficial. Omalizumab may be an option for patients with high levels of IgE who fail antihistamine therapy and has been successful in several (but not all) adult patients.<sup>40,41</sup> In some individuals, sun tolerance may be established by carefully metered, increasing exposures ("hardening") to natural or artificial light or the oral administration of a psoralen followed by UVA (PUVA) light.

### Polymorphous Light Eruption

Polymorphous light eruption (PMLE) is the most common of the immune-mediated disorders associated with photosensitivity.<sup>42,43</sup> It is predominantly a disorder of females in the second and third decades of life, and is estimated to occur in 10% to 15% of the US population. It occurs more often in individuals with lighter skin types. Although its etiology remains only partially understood, PMLE has been hypothesized to involve resistance to UV light-induced immune suppression and subsequently cell-mediated immune reactivity to a cutaneous

photoantigen. An autosomal dominant inherited form of PMLE has been described in Native Americans of both North and South America.<sup>44</sup> Onset of this hereditary form is in childhood, and female patients outnumber male patients 2:1.

Often referred to as *sun allergy* or *sun poisoning*, the clinical eruption consists of a group of polymorphic lesions that usually occur 1 to 2 days after intense sunlight exposure, often while on vacation. In some individuals, the eruption is first seen in the spring and persists with continued sun exposure, but may improve later in the summer as the skin "hardens" from UV light exposure. The lesions may range from small papular (Fig. 19-2), urticarial (Fig. 19-3), vesicular, or eczematous reactions to large papules, plaques,<sup>45</sup> or patterns resembling erythema multiforme. A "pinpoint" variant that resembles lichen nitidus clinically and histologically occurs more often in individuals with darker skin colors.<sup>46,47</sup> The areas of the body most commonly involved include the face, the sides of the neck, and sun-exposed areas of the arms and hands. In children, it most commonly begins on the face as an acute, erythematous, eczematous eruption with small papules. Pruritis may be severe. Lesions usually involute spontaneously in 1 to 2 weeks, provided no additional exposure to sunlight occurs.

Juvenile spring eruption is considered a subset of PMLE, and is characterized by photo-induced, dull-red edematous papules that are largely confined to the helix of the ears (Fig. 19-4).<sup>48</sup> Lesions may become vesicular and crusted, and occasionally appear on the dorsal aspects of the hands and on the trunk. Juvenile spring eruption occurs more commonly in boys than in girls, and particularly between the ages of 5 and 12 years. Protuberant ears and lack of hair cover have been strongly associated,<sup>49</sup> but skin color and use of sunscreen have not. Lesions heal within a week, without scarring, unless secondary



**Figure 19-2** Polymorphous light eruption. Papular lesions occurred 2 days after intense sun exposure.



**Figure 19-3** Polymorphous light eruption. Urticarial form.



**Figure 19-4** Juvenile spring eruption. Tiny papules and vesicles on the helix of the ears after sun exposure. Note that sun-shielded area behind the ear is uninvolved.

infection develops. Lesions are more difficult than PMLE to reproduce by exposure to UV light.<sup>50</sup>

The diagnosis of PMLE is suggested by the character of the lesions, their distribution, and their relationship to sun exposure. Although often unnecessary, PMLE can be confirmed by provocative light testing, which involves exposing the same site for about 4 consecutive days; it is important to use a site that has previously reacted but to perform the test early in the spring before hardening has occurred. The reaction, in contrast to that of solar urticaria, occurs within hours rather than minutes, lasts for days rather than hours, and is not urticarial. Some patients with systemic lupus erythematosus (SLE) acquire sun-induced lesions indistinguishable from those of PMLE, and serologic testing should be performed (see Chapter 22). In addition, erythema multiforme may be photodistributed and thus confused with PMLE;<sup>51</sup> in contrast with erythema multiforme, PMLE skin samples have shown no evidence of herpes simplex virus.

Prevention of PMLE consists of sunscreens with good coverage of the UVA spectrum (when applied adequately with 2 mg/cm<sup>2</sup>), sun-protective clothing, and the avoidance of midday sun exposure. Hardening or desensitization of skin by gradually increasing exposure 2 to 3 times weekly to narrowband UVB or PUVA light for 4 to 6 weeks before exposure helps the majority of treated patients. The addition of oral flavonoids (especially polypodium leucotomos given for 12 weeks) or antioxidants in sunscreens has shown benefit in preventing PMLE.<sup>52,53</sup> If patients severely affected by this disorder anticipate temporary intense or prolonged sun exposure, a short course of systemic corticosteroids can be administered. Topical steroids may provide relief in mild cases. Recent evidence suggests that topical vitamin D<sub>3</sub><sup>54</sup> or topical liposomal DNA-repair enzymes<sup>55</sup> may be of value. Antimalarials, β-carotene, and nicotinamide are of limited effectiveness.

### Actinic Prurigo

This photosensitivity disorder, also called *hydrea aestivale* and *Hutchinson summer prurigo*, is most commonly seen in the Indian and mestizo (mixed ancestry) populations of Mexico and other regions of Central and South America, although it has been described in the Caucasian and Asian populations.<sup>56-59</sup> It has been seen in many children in the United States and Canada but is rare in Europe. Most cases begin in childhood before puberty.<sup>60</sup> The condition is characterized by intensely itchy papules, plaques, and nodules, along with excoriations and scars (Figs. 19-5 and 19-6). Some patients can be very uncomfortable and show secondary eczematization and lichenification. Actinic prurigo predominantly affects exposed sites on the face and distal extremities, but may involve covered areas as well, particularly the sacrum and buttocks. Healed facial lesions leave minute linear or pitted scars. Seasonal exacerbation at the beginning of spring with improvement in the fall is common, although the lesions commonly do not clear during the winter; greater seasonal change occurs with higher latitudes. The oral or ocular mucosae are involved in 30% to 50% of cases. Cheilitis alone is seen in 28% of patients, but 83% of patients



**Figure 19-5** Actinic prurigo. Intensely itchy papules with excoriations in this mild case with secondary eczematization.



**Figure 19-6** Actinic prurigo. Note the excoriations and residual scars.

experience pruritus, tingling, and pain of the vermillion.<sup>61</sup> Ocular findings most commonly include photophobia and conjunctivitis.<sup>62</sup>

The diagnosis is generally based on the clinical appearance. Biopsy of skin is generally not useful, although histologic evaluation of lip and conjunctival biopsies shows the characteristic well-formed lymphoid follicles.<sup>63</sup> The presence of the eruption on both exposed and covered sites, its occurrence in winter, mucosal and conjunctival involvement, persistence beyond 4 weeks, and residual scarring of skin distinguish actinic prurigo from PMLE. Photosensitivity testing for minimal erythema dose is abnormal in up to two-thirds of patients. Human leukocyte antigen (HLA) DRB1\*0407 is found in 60% to 70% of patients with actinic prurigo, but only in 4% to 8% of DR4+ controls<sup>64-66</sup>; HLA DRB1\*0401 is present in up to 20% of affected individuals with actinic prurigo. Although individuals with PMLE do not show these associations, 35% of patients with typical actinic prurigo

have a history that suggests coexistence of actinic prurigo and PMLE or transition from one to the other.<sup>67</sup> Although the etiology of actinic prurigo is unknown, the strong association with HLA markers suggests a role for major histocompatibility complex (MHC)-restricted antigen presentation in the pathomechanism of the condition.

The disorder often has a chronic course that persists into adulthood; however, spontaneous resolution may occur during late adolescence. Vigorous sun protection and use of topical anti-inflammatory agents for the pruritus lead to improvement in the majority of patients. Short courses of systemic steroids can be helpful, but antimalarials and other immunosuppressive medications have not had much effect. Complete resolution may require the addition of thalidomide (usually 50 to 100 mg/day),<sup>68</sup> which results in rapid clearing.<sup>69</sup> The gradual introduction of exposure to narrow band UVB light has also helped some patients. Oral cyclosporine and azathioprine have had some success in a few refractory cases.

### Hydroa Vacciniforme

Hydroa vacciniforme (HV) is a rare disorder that is now known to result from chronic Epstein–Barr virus infection.<sup>70</sup> The classic lesions tend to appear each summer in children on uncovered parts of the body after exposure to sunlight. Boys are more often affected than girls. Rare familial cases have been described. The mean age of onset is 8 years.<sup>71</sup> Most patients show sensitivity to UVA light in monochromator phototesting, which may induce papulovesicular lesions.<sup>71</sup>

The primary lesion is a pruritic edematous papule, vesicle, or bulla that occurs within hours or days on uncovered surfaces exposed to sunlight.<sup>33</sup> Itching and burning, as well as mild constitutional symptoms may occur a few hours before the outbreak of the cutaneous lesions. Lesions tend to appear on the face, the sides of the neck, and extensor surfaces of the extremities, and are arranged symmetrically over the nose, cheeks, ears, and dorsal surfaces of the hands. The vesicles or bullae usually develop on an erythematous base and initially are rather tense. These are followed by central necrosis and umbilication that leads to healing with individual or confluent varioliform scarring within 1 to 2 weeks (Fig. 19-7). Mild conjunctivitis or keratitis may be associated. The disease usually flares after sun exposure, and, in most instances, involves spontaneously by the late teenage years with a mean duration of 9 years.<sup>71</sup>

A more severe and persistent vesiculonecrotic HV-like skin eruption is likely to be lymphoma (HV-like), which is associated with higher titer latent Epstein–Barr virus infection and monoclonal T-cell receptor gene rearrangements<sup>72–75</sup> (see Chapter 10). Patients have marked facial edema, hemorrhagic bullae, atrophic scarring, and severe disfigurement in both sun-exposed and sun-protected sites. Fever, hepatosplenomegaly, abnormal liver function testing, lymphadenopathy, hemophagocytosis, and hypersensitivity to mosquito bites may be associated.<sup>76</sup> HV-like T-cell lymphoma occurs primarily in pediatric patients from Central and South America and Asia.



**Figure 19-7** Hydroa vacciniforme. Varioliform scarring on the nose in an adolescent who had severe episodes when younger.

The diagnosis can be confirmed histologically. Treatment of HV consists of strict sun protection, including broad-spectrum sunscreens (SPF at least 30), protective clothing, and avoidance of midday sun exposure. No intervention has been uniformly successful. Antimalarial drugs, β-carotene, oral fish oils,<sup>77</sup> and “hardening” by treatment with narrowband UVB light have been used with some therapeutic success.<sup>78</sup> Low-dose prophylactic narrowband UVB light during spring months may also reduce disease severity. The psychosocial and emotional impairment of HV on quality of life is significant, given the extensive disfigurement from scarring and the effect on daily life of strict sun avoidance.<sup>79</sup> Because of the potential risk of HV progression to HV-like lymphoma, patients should be closely monitored for at least 10 years after diagnosis.

## Photosensitivity Induced by Exogenous Sources

Photosensitivity reactions may be phototoxic (photoirritant) or photoallergic (Table 19-4).<sup>80–83</sup> Exogenous photosensitizers may reach the skin by topical or systemic routes. The clinical course is brief, and elimination of the offending drug or sunlight exposure usually results in improvement. In rare cases, however, the photosensitivity may persist for months after the last known exposure to the offending chemical. Such individuals are known as persistent light reactors and the eruption (chronic actinic dermatitis) ranges from a chronic dermatitis initially restricted to sun-exposed surfaces to thickened hyperpigmented plaques. This rare disorder generally affects men and not pediatric patients.

### PHOTOTOXICITY

Phototoxic reactions are common and can be likened to a primary irritant reaction. A phototoxic reaction refers to a nonimmunologic exaggerated sunburn or sunburn-like reaction characterized by erythema (and at times swelling and blistering), occurring within a few minutes to several hours (usually within a period of 2 to 6 hours) after exposure to UVA light and followed by hyperpigmentation and desquamation confined to the exposed areas. This type of sensitivity usually occurs with the first exposure to the photosensitizing substance, when the systemic or percutaneous absorption of the sensitizing substances is in high enough concentration to result in a photo-induced cutaneous reaction.

Plant-induced photosensitivity (phytophotodermatitis) is the most common phototoxic reaction of children.<sup>84–87</sup> The large majority are phototoxic reactions caused by the presence of furocoumarin compounds (psoralens) found widely in such plants as Rutaceae (e.g., limes and lemons); Umbelliferae (e.g., parsnips, carrots, dill, parsley, meadow grass, common rue, giant hogweed, and celery, most often celery infected with a fungus that causes pink rot disease); and Moraceae (e.g., fig). Psoralens can also reach the skin after ingestion, as has been noted after ingestion of contaminated celery and subsequent outdoor and tanning salon UV light exposure. With systemic ingestion, all sun-exposed areas are susceptible to reaction. Psoralens have also been used therapeutically in topical or oral formulations in combination with UVA light (PUVA therapy) as treatment of psoriasis and vitiligo; given the safety issues with PUVA, this intervention is rarely used in children. Furocoumarins can also be components in Chinese herbal medications.<sup>88</sup> Inhalation of traces of giant hogweed have been reported to cause obstructive pulmonary symptoms, and contact with the eye can lead to blindness.<sup>89</sup>

Phytophotodermatitis usually begins within a day after exposure to the furocoumarin and sunlight, ranges in severity from mild erythema with or without erosion to severe blistering (Fig. 19-8), and eventuates in a characteristic dense inflammatory hyperpigmentation. A bizarre linear streaking configuration of the dermatitis (Fig. 19-9), with subsequent hyperpigmentation, especially on the face, chest, hands, and lower legs of children, is characteristic. At times, only the hyperpigmented streak appears without prior erythema (Fig. 19-10). The purple coloration of skin and bizarre patterning can be mistaken for child abuse and the blistering for herpes simplex infection.<sup>90–92</sup> Streaks on the trunk have been noted after dripping of lime juice (sometimes

**Table 19-4** Medications Most Commonly Associated with Phototoxic and Photoallergic Reactions

Phototoxic Medications	Photoallergic Medications
<b>Antibiotics</b>	<b>Antimicrobials (topical)</b>
Tetracyclines	Chlorhexidine
Sulfonamides	Hexachlorophene
Ciprofloxacin	Salicylanilides
Nalidixic acid	Sulfonamides
Isoniazid	
<b>Antifungals</b>	<b>Other topicals</b>
Griseofulvin	Sunscreens (especially benzophenones; see Table 19-2)
Voriconazole	Fragrances (sandalwood oil, musk ambrette, 6-methylcoumarin, oil of bergamot)
	Topical NSAIDs
	Promethazine hydrochloride
<b>Antipsychotics</b>	<b>Systemic agents</b>
Phenothiazines	Sulfonamides
Protriptyline	Griseofulvin
	Quinolones
	NSAIDs (diclofenac, piroxicam, ketoprofen)
	Quinidine, quinine
<b>Cardiac medications and diuretics</b>	
Amiodarone	
Quinidine	
Eurosemide	
Thiazides	
<b>NSAIDs</b>	
Naproxen, nabumetone, piroxicam, tiaprofenic acid, azapropazone	
<b>Calcium channel blockers</b>	
Amlodipine, diltiazem, nifedipine	
<b>Others</b>	
Retinoids	
Psoralens	
Furocoumarins	
Imatinib	
Sulfonylurea hypoglycemics	
Oral contraceptives	
Lamotrigine	
St. John's wort	
Tar (topical)	
Photodynamic therapy	
Dyes (acridine, methylviolet, eosin)	

NSAIDs, Nonsteroidal anti-inflammatory drugs.

used as a hair rinse or in drinks), and thumbprint-shaped macules on the lateral aspects of the trunk may be described after a parent with furocoumarins on the fingers picks up a child. Usually no treatment is necessary once the diagnosis is made, and the often-intense hyperpigmentation fades spontaneously over several weeks to months. However, severe burns have been induced in children by contact with phototoxins, especially giant hogweed and prolonged sunlight exposure, and have required debridement and surgical wound closure.<sup>89,93,94</sup>

Phototoxicity may present with a variety of manifestations. For example, sunburn reactions can occur with thiazide diuretics, tetracyclines (Fig. 19-11), retinoids, voriconazole, ciprofloxacin, and others, whereas skin fragility and blisters (pseudoporphyria) are the typical manifestation of exposure to NSAIDs, and telangiectasia results from calcium channel antagonists. Photoonycholysis most commonly occurs after administration of doxycycline<sup>95</sup> (see Chapter 8, Fig. 8-16). The phototoxicity from voriconazole, used to prevent fungal infections in transplant patients, occurs in 20% of treated children overall and in 47% of children treated for more at



**Figure 19-8** Phytophotodermatitis. Severe blistering associated with linear patterns of erythema and hyperpigmentation in a girl who had rinsed her hair with lime juice and then had intense sun exposure.



**Figure 19-9** Phytophotodermatitis. This child had been playing outside and was exposed to photosensitizing plants.



**Figure 19-10** Phytophotodermatitis. Intense hyperpigmentation in geometric patterns on the back of young girl whose mother had been squeezing citrus fruit before picking her up while on a vacation in the Caribbean.



**Figure 19-11** Photosensitivity from medication. Severe sunburn reaction despite sunscreen application in a teenager taking doxycycline for acne.



**Figure 19-13** Pseudoporphyria. Large bulla in a child receiving peritoneal hemodialysis.



**Figure 19-12** Pseudoporphyria. Blisters and erosions on the face of a child with juvenile idiopathic arthritis taking celecoxib.

least 6 months<sup>96</sup>; a dosage of at least 6 mg/kg twice daily has also been associated with a higher risk of developing voriconazole-induced phototoxicity.<sup>97</sup> The eruption can be confused with graft-versus-host disease in these immunocompromised patients<sup>98</sup> and has been associated with a 4.6% risk of developing nonmelanoma skin cancer in areas that had a phototoxic reaction at a mean age of 15.5 years.<sup>96</sup>

Pseudoporphyria is a non-immunologically mediated phototoxicity reaction characterized clinically by increased cutaneous fragility, vesiculobullae, and histopathologic features similar to those of patients with porphyria, but levels of porphyrins are normal.<sup>99</sup> It has been described in approximately 11% of children taking NSAIDs, especially naproxen sodium (Fig. 19-12, for juvenile idiopathic arthritis<sup>100</sup>) and is especially common in patients with blue/gray eye color and fair skin.<sup>101</sup> The disorder has also been described in individuals receiving other NSAIDs,<sup>102</sup> dapsone, ciprofloxacin,<sup>103</sup> furosemide, imatinib,<sup>104</sup> metformin, nalidixic acid, tetracyclines, retinoids, amiodarone, and voriconazole.<sup>105</sup> A similar, if not identical, disorder has also been described in patients receiving hemodialysis (Fig. 19-13).<sup>106</sup>

A careful history and the presence of normal porphyrin levels in serum, erythrocytes, urine, and feces will generally establish the diagnosis. The cutaneous fragility tends to reverse rapidly upon withdrawal of the causative medication, but may only gradually reverse or even persist with new lesions for up to 1 month after discontinuation of the medication.<sup>107</sup> Pseudoporphyria associated with hemodialysis has responded to treatment with N-acetylcysteine or glutathione. Disfiguring facial scarring is a residua in some affected children.

#### PHOTOALLERGY

Photoallergy is relatively uncommon and presumably is a form of cell-mediated delayed hypersensitivity.<sup>108,109</sup> The individual must first be

sensitized to the allergen, which can require 7 to 10 days. When exposed to UV light, the light is absorbed by the photoantigen, which is thought to cause a change in the molecule. Instead of sunburn-type reactions, photoallergic responses are generally characterized by immediate urticarial or delayed papular or eczematous lesions that are not followed by hyperpigmentation. After the first sensitization, subsequent photoallergic reactions generally appear within 24 hours, even after very brief periods of exposure. Sunscreens with chemical components (especially benzophenones) are the leading cause because of their extensive use, although the risk of reaction with sunscreens containing these agents is less than 1% of that for allergic contact dermatitis.<sup>110,111</sup> In the past, children showed photoallergic reactions to salicylanilides (antimicrobial agents formerly in soaps but now only in industrial cleaners) and fragrances (musk ambrette, oil of bergamot). These chemicals are no longer used in personal products, but children or adolescents have been known to find a cologne with oil of bergamot, apply it to the skin, and develop berloque (berlock) dermatitis after UV exposure.<sup>112</sup> Promethazine hydrochloride cream and topical nonsteroidal anti-inflammatory agents have caused photoreactions.

Suspected photoallergic contact dermatitis may be confirmed by photopatch testing. Photopatch testing is similar to traditional testing for contact dermatitis (see Chapter 3), except that two sets of patch tests are placed on the back. Twenty-four hours later, one set is uncovered and irradiated with UVA light. The following day a comparison is made of the covered and irradiated sites. A positive test reproduces the clinical eczematous lesion at the phototest site. Therapy is treatment with topical anti-inflammatory agents and avoidance of exposure to the offending antigen.

#### Genetic Disorders Associated with Photosensitivity

Photosensitivity is a prominent feature of several genetic disorders, many of which are associated with defective DNA repair. Some of these are described elsewhere in this text, such as Kindler syndrome (see Chapter 13), trichothiodystrophy (see Chapter 7), and ataxiatelangiectasia (see Chapter 12).

#### XERODERMA PIGMENTOSUM

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by cutaneous photosensitivity, a decreased ability to repair DNA damaged by UV radiation, and the early development of cutaneous and ocular malignancies.<sup>113,114</sup> The disorder is estimated to occur in one in a million individuals in the United States and Europe, and with an incidence in Japan as high as one in 40,000 persons. The risk of developing cutaneous malignancy does not diminish in patients

**Table 19-5** Subtypes of Xeroderma Pigmentosum

Gene/Protein	Protein Function	Incidence	Skin Disease	Neoplasia	Neurologic Change	Comments
XPA	Confirms damage	Especially in Japan	+++	+++	+ to +++	Lowest repair activity
XPB/ERCC3	Helicase	Very rare	++ to +++	+++	+++	CS (two kindreds) One case of TTD
XPC	Detects damage	Most common	++ to +++	++; melanoma	Rare	
XPD/ERCC2	Helicase	20% of cases	++	+	Late onset or none	Tremendous variability in phenotype; TTD; XP/CS
XPE/DDB2	Detects damage	Rare	+	Rare	None or mild	Mild phenotype
XPF/ERCC4	Nuclease	Fairly rare	++	Few to none	Usually none	
XPG/ERCC5	Nuclease	Very rare	+++	Few or none	Cockayne type	CS has been associated
XPV/POLH	Polymerase	30% of cases	++ to +++	Later onset	++ in a few	

CS, Cockayne syndrome; DDB, DNA damage-binding protein; ERCC, excision repair cross-complementing genes; TTD, trichothiodystrophy; XP, xeroderma pigmentosum; XP/CS, xeroderma pigmentosum/Cockayne complex; XPV, xeroderma pigmentosum variant; +, mild; ++, moderate; +++, severe.

with darker skin types.<sup>115</sup> Historically, seven complementation groups (XPA through XPG) have been described based on *in vitro* cell fusion studies (Table 19-5), which are now recognized to correlate with mutations in specific genes whose products affect DNA repair.

The basic abnormality is an absence of a component of the nucleotide excision repair complex, a multistep mechanism that includes recognition of the UV light-induced DNA lesion, unwinding of DNA, and then resynthesis and ligation of the DNA. Complementation groups XPC and XPE recognize and bind to damaged DNA.<sup>116-118</sup> XPA may help to assemble the DNA machinery around the damaged DNA site. This binding signals the XPB and XPD proteins to unwind the DNA in the damaged region and to allow DNA transcription. The XPF and XPG nucleases cut the DNA and allow excision of the UV light-induced pyrimidine dimers. DNA repair rates may range from 0% to 50% of normal levels. A variant form has been described (XPV). In the variant group, postreplication repair is defective, but excision repair is normal. More than half of all cases in the United States are caused by mutations in the genes encoding XPC (XPC), XPD (ERCC2), or XPV (POLH), although mutations in the genes encoding XPA and XPF are more common in Japan than in the United States and Europe.

In 75% of cases the first signs appear between 6 months and 3 years of age. The presenting feature of this disorder is photosensitivity to UV light, primarily at wavelengths 290 to 340 nm, but this sunburn after minimal UV light exposure only occurs in 50% to 64% of patients and is not a feature of XP patients with mutations in XPC, XPE, or XPV.<sup>119,120</sup> The sunburn may be severe with vesicles and bullae (Fig. 19-14) and is often accompanied by photophobia with chronic conjunctivitis during the first months of life. The other 40% of cases do not show this sunburn reaction and instead tend to manifest initially with the lentigines (freckle-like pigmentation) that otherwise follow the early sunburns (Figs. 19-15 and 19-16). The skin ages prematurely with atrophy, telangiectasia, mottled hyper- and hypopigmentation, keratoses, and ulcerations, but not wrinkling; these observations likely reflect the sensitivity primarily to UVB rather than to UVA light, which is the primary cause of solar elastosis.<sup>113</sup> With continued exposure, the skin becomes xerotic, leading to the name XP. Areas of skin ordinarily protected by clothing remain relatively normal or may eventually show similar features, but to a lesser degree. Affected children resemble adults with severe actinic damage by early childhood.

Other issues are epithelial neoplasms, severe eye involvement, progressive neurologic degeneration in some patients, and malignancy.<sup>121</sup> Several tumors occur with increased incidence in XP (basal cell and squamous cell carcinomas, angiosarcoma, fibrosarcoma, atypical fibroxanthoma, keratoacanthoma, and melanoma) (Fig. 19-17).<sup>122,123</sup> In patients younger than 20 years of age with XP, the overall risk of developing basal cell and squamous cell carcinomas is 10,000 times that of the normal population (median age 9 years), and of melanoma 2000-fold greater (median age 22 years).<sup>119,124</sup> Interestingly, the melanomas in XP show a high rate of PTEN mutations (mammalian target of rapamycin [mTOR] pathway activation) rather than the typical RAS pathway activation, which may be important in considering choice of small molecule inhibitors.<sup>125</sup> The tendency to develop these



**Figure 19-14** Xeroderma pigmentosum. Sunburn after minimal sun exposure was the clue to diagnosis of xeroderma pigmentosum in a 9-month-old boy. Note the early freckling on the upper cheeks. This boy with XPA developed severe neurologic degeneration (DeSanctis-Cacchione syndrome) despite vigorous sun protection and no evidence of even a premalignant skin lesion by his mid-20s.

neoplasms is a function of exposure to UV light and the subtype of XP (see Table 19-5). The lower risk of developing skin cancer in patients who show early sunburns<sup>119</sup> may reflect the earlier recognition of XP and intense early photoprotection. These tumors and their therapy cause considerable facial distortion. Patients with XP also have an approximately 10- to 20-fold increase in internal malignancies, including of the brain, lungs, hematopoietic system, kidney, and gastrointestinal tract, which may reflect concomitant sensitivity to physical and chemical carcinogens, such as cigarette smoke.<sup>119,126</sup> Although skin cancer is the most common cause of death (34%), internal cancer leads to death of 17% of patients.<sup>119</sup>

Patients also have an increased risk of developing carcinomas of the anterior portion of the tongue<sup>127</sup> and may show leukoplakia.<sup>126,128</sup> The ocular manifestations largely involve the anterior part of the eye that is exposed to UV light.<sup>129</sup> By 3 years of age, most patients show blepharitis, symblepharon, and crusts of the palpebral margins. With



**Figure 19-15** Xeroderma pigmentosum. Note the many black-colored facial lentigines, which should raise concern about the possibility of xeroderma pigmentosum.



**Figure 19-16** Xeroderma pigmentosum. Despite total avoidance of ultraviolet light after diagnosis at 2 years of age, this adolescent boy showed extensive pigmentary changes.

continuing UV light exposure, affected individuals show conjunctival melanosis, scarring, atrophy, entropion or ectropion, trichiasis (irritation caused by the eyelashes), and at times loss of the lower lid. Ocular surface cancer develops in 10% of patients. Corneal opacities and ulcerations, and choroidal melanomas have been described.<sup>130</sup>

Neurologic complications develop in approximately 30% of patients (termed the *DeSanctis–Cacchione syndrome*), most commonly in the XPA group,<sup>131</sup> but also with XPB, XPD, and XPG. These may include microcephaly with developmental delay, poor growth and sexual development, choreoathetosis, hyporeflexia, cerebellar ataxia, and sensorineural deafness. These neurologic changes may have their onset in infancy but may not occur in some patients until the second decade of life. Testing of deep tendon reflexes and routine audiometry are good screening studies.<sup>132</sup> In this subset, it is the neurologic degeneration that leads to death of patients (cause of death in 31% of all patients with XP), and at an earlier age (median age of death with neurodegeneration is 37 years vs. 29 years without neurodegeneration).<sup>119</sup>



**Figure 19-17** Xeroderma pigmentosum. Severe actinic damage in an 18-year-old girl with inadequate sun protection. Note the scarring from removal of several basal cell carcinomas, beginning at 10 years of age.

The neurologic abnormalities and photosensitivity may be seen in individuals with the XP/Cockayne syndrome (CS) overlap (see [Cockayne Syndrome](#) section).<sup>133,134</sup> DNA excision repair defects and UV light hypersensitivity are also seen in a subset of patients with trichothiodystrophy (photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature [PIBIDS]; see Chapter 7).<sup>113</sup> Patients with trichothiodystrophy do not show an increased risk of developing skin cancer, although the reason for this distinguishing feature is unclear. XP and trichothiodystrophy may also coexist.<sup>135</sup>

Suspicion of the diagnosis of XP is made through clinical observation. In the past, confirmation involved UV light sensitivity and DNA repair assays, but genetic analysis is now the preferred testing for confirmation and subtyping, which cannot be determined by clinical features alone. Whole exome sequencing has recently been performed<sup>136</sup> and has the advantage of analyzing the presence of mutation in all possible genes simultaneously. Immunohistochemistry of paraffin-embedded skin sections is a simple way to show absence of XPC.<sup>137</sup> Given the founder mutation in XPA in Japan, rapid genetic analysis for this mutation can easily be performed in individuals of Japanese descent.

All patients with XP require strict lifelong sun protection, including total sun avoidance, application of sunscreens that protect throughout the UVB and UVA spectrum, UV-light shields over windows, sun-protective clothing (a sun suit designed by the National Aeronautics and Space Administration [NASA] is also available), broad-rimmed hats, and sunglasses.<sup>138</sup> Methylcellulose eye drops should be applied to keep the corneas moist, and soft contact lenses should be worn to protect against mechanical trauma in individuals whose eyelids are severely deformed. Corneal transplantation may be required for patients with severe keratitis and corneal opacity. All patients should be given vitamin D supplementation, given the sun avoidance.<sup>139</sup> Patients should avoid cigarette smoke and other environmental carcinogens. Surveillance for skin cancer by dermatologists and ocular complications by ophthalmologists is imperative.

Individual premalignant and malignant tumors should be treated by cryosurgery, application of topical 5-fluorouracil or imiquimod cream,<sup>140,141</sup> and use of these treatments for 3 weeks every 3 to 6 months starting during childhood has been advocated as

prophylaxis.<sup>138</sup> Other interventions are intralesional interferon- $\alpha$ , or surgical removal as appropriate for the neoplasm.<sup>142</sup> Dermabrasion, laser resurfacing, and phenol-based peeling of skin with actinic damage have been helpful in reversing the pigmentary changes.<sup>143,144</sup> High-dose oral isotretinoin decreases the incidence of new skin cancers, but withdrawal of therapy results in reversal of its chemoprophylactic effect.<sup>145</sup> "Readthrough" of premature termination codons by aminoglycosides to restore DNA repair<sup>146</sup> and targeted repair of XPC mutations using transcription activator-like effector (TALE) nucleases<sup>139</sup> have been recently been shown as potential future interventions. XP has been diagnosed prenatally by showing DNA-repair defects in cultured amniotic fluid cells and by DNA analysis. Support groups for families with XP include the XP Society ([www.xps.org](http://www.xps.org)); XP Family Support Group ([www.xpfamilysupport.org](http://www.xpfamilysupport.org)), and the XP Support Group ([www.xpsupportgroup.org.uk](http://www.xpsupportgroup.org.uk)). A camp for families with XP (Camp Sundown) engages affected individuals and their families in daytime indoor activities and outdoor activities at night.

## COCKAYNE SYNDROME

Cockayne syndrome (CS) is a recessively inherited disorder caused by defects in repair of actively transcribed DNA, either ERCC8 (excision-repair cross complementing group 8; CSA) or more commonly ERCC6 (CSB).<sup>147-150</sup> A spectrum of severity for individuals with CS (classified as CS I, II, and III) or its variants (cerebrooculofacioskeletal syndrome [COFS] and UV-sensitive syndrome [UVSS]) has been described and modified criteria have been proposed (Box 19-1).<sup>150</sup> Arthrogryposis and congenital kyphosis are specific features of COFS. Whereas affected individuals with COFS and CS II show features from birth (e.g.,

### Box 19-1 Diagnostic Features and Subclassification in Order of Severity of Cockayne Syndrome and Its Variants

#### Major

Developmental delay  
Progressive microcephaly  
Progressive growth failure

#### Minor

Cutaneous photosensitivity  
Progressive sensorineural hearing loss  
Pigmentary retinopathy/cataracts  
Enophthalmia  
Enamel hypoplasia

Major criteria are required for diagnosis of CS I, CS II, and CS III in addition to at least 3 minor criteria.

#### COFS

Most severely affected:  
Death by infancy

#### CS II

Signs present at birth  
Fulfils diagnostic criteria by infancy  
Death usually 5 to 6 years of age

#### CS I

Signs first present by 2 years of age  
Fulfils diagnostic criteria during childhood  
Death usually in late teenage years

#### CS III

Signs first present at 3 to 4 years of age  
Fulfils diagnostic criteria by early teens  
Death usually at about 30 years of age

#### UVSS

Only presents with photosensitivity  
Survival is likely normal

COFS, Cerebrooculofacioskeletal syndrome; CS, Cockayne syndrome; UVSS, UV-sensitive syndrome.

weak cry, axial hypotonia, and peripheral hypertonia), other children with CS have no signs until infancy or even childhood, but retardation, microcephaly, deafness, and loss of developmental progress are progressive. COFS and CS II most commonly result from mutations in CSB, while most individuals with CSA mutations have a later onset and less severity.

The most common cutaneous change is photosensitivity, a feature in at least 75% of patients. Photosensitivity manifests as sunburn after brief exposure and may occur even after exposure through a windshield.<sup>151</sup> Within the spectrum, however, are patients without photosensitivity<sup>152</sup> or with photosensitivity but no other features (UVSS). Despite the photosensitivity, CS is not associated with sun-induced pigmentation or malignancy. Although this light sensitivity eventually disappears, erythema with telangiectasias characteristic of photosensitivity, mottled pigmentation, scarring, and atrophy of these sites remain as prominent features. Acral cyanosis and edema are another feature seen in about 75% of patients, and nail dystrophy (often subtle), hair abnormalities (sparse, thin, dry and/or pseudo "tiger-tail" appearance), and hypohidrosis have also been described. Associated pruritus without skin inflammation is not uncommon and may be the presenting feature to a dermatologist. Loss of subcutaneous fat and cachectic wasting produces a "bird-like" facies with sunken eyes (Fig. 19-18, A). Patients show a tendency toward progressive ataxia, long limbs in proportion to body length, quick bird-like movements, disproportionately large hands and feet, progressive contractures of the joints, and large protruding ears. A characteristic "salt and pepper" pigmentary retinopathy has been described; optic atrophy and cataracts are not uncommon. Mental retardation can be severe. Affected individuals are generally below the third percentile for height and weight. Other abnormalities may include thickened skull bones and intracranial calcification, especially of the basal ganglia, elevated transglutaminases, and renal disease.

There is no effective treatment for patients with this disorder, and most patients die by the third decade of life as a result of arteriosclerotic vascular disease, profound neurologic deterioration, or both. Patients with CS show defective DNA repair and hypersensitivity to UV light, which accounts for their photosensitivity.<sup>134,153</sup> Patients with CS show spasticity, ataxia, and peripheral neuropathy from demyelination, in contrast to neuronal degeneration in patients with XP. However, patients have been described with features of both XP and CS.<sup>133,154</sup> These patients usually have mutations in a different gene, ERCC5 (XPG), but occasionally in XPB or XPD. They show the short stature, sexual immaturity, and retinal pigmentation of CS, are sensitive to UV light, and develop the pigmentary abnormalities of XP, but not the cutaneous malignancy (Fig. 19-18, B). Administration of daily niacin in a patient with XP/CS led to a dramatic photoprotective effect both clinically and in cultured fibroblasts, reminiscent of improvement in patients with pellagra.<sup>155</sup>

## ROTHMUND–THOMSON SYNDROME

Rothmund–Thomson syndrome is an autosomal recessive disorder that occurs twice as often in boys than in girls.<sup>156</sup> Cutaneous features are seen in the first 2 years and often by 3 to 6 months of age. Most common are diffuse erythema and, at times, edema and vesication of the cheeks, forehead, chin, ears, buttocks, and extensor surfaces of the arms and legs, but sparing of the trunk. As the erythema resolves, the skin begins to show a reticulated pattern of telangiectasia, alterations in pigmentation (both hypopigmentation and hyperpigmentation), and areas of atrophy (poikiloderma) that progress until approximately 3 to 5 years of age (Fig. 19-19). Occasionally affected individuals are born with poikiloderma or develop poikiloderma after the first year of life. Children may develop bullae after sun exposure or spontaneously; this tendency appears to subside as patients grow older. Approximately 30% of patients develop verrucous hyperkeratoses on the hands, feet, knees, and elbows later in childhood or during adolescence. Although photosensitivity is a feature of many cases and exposure to sunlight may extend the distribution of the eruption, UV light is unlikely to be the sole cause of the poikiloderma, since it may be found before UV light exposure and also appears on unexposed areas. Adults with the disorder show an increased risk of development of squamous cell carcinomas at sites of the keratotic



(A)



(B)

**Figure 19-18** (A) Cockayne syndrome II. Note the typical facial features with enophthalmia, microcephaly, and protruding ears as well as growth failure in this 7-year-old girl with mutations in *ERCC6* (CSB). (B) Xeroderma pigmentosum/Cockayne syndrome caused by mutations in *ERCC5* (XPG). Note the facial features of CS but the sun-induced lentigines and photophobia of XP.

and atrophic lesions; melanoma and porokeratosis have also been associated.<sup>157,158</sup>

Patients are commonly short, and most show a history of low birth-weight and length as well as severe growth failure. Some have a characteristic facies with saddle nose, frontal bossing, wide forehead, and narrow chin, giving a triangular configuration to the face. Hypotrichosis with sparse or absent eyebrows or eyelashes (and sometimes involvement of the scalp, face, and body hair) occurs in 50% of patients, and premature graying has been reported. Nail dystrophy has been described in about 30% of patients, and dental abnormalities, caries, and periodontitis in almost 40%.<sup>159</sup>

Cataracts occur in about 6% to 40% of reported cases,<sup>156</sup> generally as bilateral anterior or posterior subcapsular opacities that evolve



**Figure 19-19** Rothmund–Thomson syndrome. Reticulated pattern of telangiectasia and both hypopigmentation and hyperpigmentation on the cheek and ear. (Courtesy of Sarah Chamlin, MD.)

rapidly. Although they are first noted between 3 and 7 years of age in most patients, they have been described in an infant at 4 months of age and may appear as late as 40 years of age. Hypogonadism occurs in one-quarter of patients (female patients may be amenorrheic; male patients may have undescended testes).

Defective bone development is a common characteristic that occurs in up to two-thirds of affected individuals. Most common are absence or hypoplasia of the thumbs, radius, and occasionally the ulna; brachymetacarpophalangy; syndactyly; clinodactyly; and fusion or agenesis of carpal and tarsal bones.<sup>160</sup> Both hyperostosis and osteoporosis with fractures have been described. Osteosarcoma has been described in 32% of patients, approximately half before 15 years of age, and most commonly affects the tibia or femur.<sup>156,161,162</sup> Surveillance for bone pain, swelling, or an enlarging lesion on a limb suggesting a tumor is important. Because of the risk of osteosarcoma, baseline radiologic evaluations of long bones are recommended by 3 years of age. Several other malignancies, aplastic anemia, and myelodysplasia have been described less commonly.<sup>163</sup>

Laboratory tests are usually normal, including assays of unscheduled DNA repair, increased sensitivity to alkylating agents such as mitomycin C, and chromosomes. Mutations in *RECQL4* have been found in 40% to 66% of affected patients<sup>164</sup> and have been associated with an increased risk of developing osteosarcoma.<sup>165</sup> *RECQL4* encodes a DNA helicase that is important for DNA replication, repair of UV light-induced DNA damage, and telomere maintenance.<sup>166,167</sup> Mutations in *RECQL4* also cause RAPADILINO and Baller–Gerold syndromes. RAPADILINO (radial hypoplasia, patellar hypoplasia/aplasia, cleft or high arched palate, diarrhea, dislocated joints, little size and limb malformations, slender nose, and normal intelligence) syndrome is associated with the osteosarcoma risk but not the poikilodermatous changes.<sup>168</sup> Baller–Gerold syndrome prominently features numerous bony defects and the risk of osteosarcoma, but the onset of poikiloderma is later and cataracts have not been described.

The early onset and noncutaneous features allow Rothmund–Thomson syndrome to be distinguished from other disorders with poikiloderma that are not related to *RECQL4* mutations (dyskeratosis congenita, Kindler syndrome, poikiloderma with neutropenia, hereditary sclerosing telangiectasia, Bloom syndrome, Fanconi anemia, XP, and nonhereditary disorders—chronic juvenile dermatomyositis and cutaneous T-cell lymphoma).<sup>169</sup> Any patient with poikiloderma deserves initial evaluation for neutropenia, which can distinguish patients with poikiloderma with neutropenia (Clericuzio type), another autosomal recessive genodermatosis resulting from mutations in the *C16orf57* gene.<sup>170–172</sup>

Individuals with the Rothmund–Thomson syndrome have a normal life span, although the development of cancer may lead to premature death in some patients. The poikiloderma and facial telangiectasia have been treated successfully with laser. Cataract extraction may be necessary.

### BLOOM SYNDROME

Bloom syndrome (congenital telangiectatic erythema) is a rare autosomal recessive disorder characterized by a triad of telangiectatic erythema, photosensitivity, and severe intrauterine and postnatal growth retardation.<sup>173</sup> Some 80% of affected children are male, and 50% are of Ashkenazi Jewish ancestry; the carrier rate among Ashkenazi Jews is 1 in 110 individuals. The disorder results from mutations in *BLM* (or *RECQL2*), a helicase of the RecQ family that participates in normal DNA replication.<sup>174</sup>

Affected patients are born at term with reduced body weight and size.<sup>175</sup> They have small, narrow faces with a prominent nose and ears, and the voice is high-pitched. Although physical growth is stunted, intellectual and sexual development is normal. Erythema of the cheeks in a butterfly distribution, often resembling lesions of lupus erythematosus, appears between the second and third week of life, and typically spreads with exposure to sunlight to involve the nose, eyelids, forehead, ears, and lips. The trunk, buttocks, and lower limbs tend to be spared. Although this light sensitivity eventually disappears, erythema, telangiectasia, mottled pigmentation, scarring, and atrophy of these sites remain as prominent features. Café-au-lait spots and areas of hypopigmentation have been described, especially on the trunk. Patients may show dolichocephaly, polydactyly, clinodactyly, syndactyly, cryptorchidism, shortened lower extremities, and clubbed feet.

Patients often have vomiting and diarrhea during infancy, which may be associated with gastrointestinal infections. The tendency toward recurrent respiratory infections increases the risk of chronic lung disease, the second most common cause of death in patients with Bloom syndrome. With increasing age, however, resistance to infection increases. Diabetes has been noted in 12% of patients<sup>176</sup>; men with Bloom syndrome are usually sterile, and women have reduced fertility.

Of the affected individuals, 20% develop malignancy, most commonly leukemia, at a mean age of 16 years. Lymphomas and leukemias occur 150 to 300 times more often than in normal individuals.<sup>177</sup> Solid tissue tumors of a wide variety of tissues, most commonly Wilms tumor, lymphosarcoma, and carcinomas of the oral mucosa and gastrointestinal tract, are seen at a mean age of 30 years in older, surviving individuals. Wilms tumor and osteosarcoma, however, have been described in the first decade of life. Decreased levels of IgG, IgM, and IgA, dysfunctional helper T cells, and abnormal delayed hypersensitivity have been described and may be related to defective lymphocyte maturation.

The diagnosis of Bloom syndrome can be confirmed by cytogenetic analysis. Patients have a high incidence of chromosomal breakage, sister chromatid exchanges, and quadriradial configurations.

Although there is no specific treatment, avoidance of sun exposure and protection by sunscreens can help prevent some of the cutaneous eruptions associated with photosensitivity. Appropriate antibiotics for gastrointestinal and respiratory tract bacterial infections are commonly helpful in the management of patients with this disorder. Because life expectancy is shortened by malignancy, periodic evaluation for possible neoplastic disease is advisable; however, exposure to ionizing radiation in screening tests should be minimized.<sup>178,179</sup>

### SMITH–LEMLI–OPITZ SYNDROME

Photosensitivity is a feature of Smith–Lemli–Opitz syndrome, an autosomal recessive disorder that results from mutations in the sterol Δ-7-reductase gene, part of the pathway of cholesterol biosynthesis.<sup>180</sup> This syndrome occurs in 1:20,000 births in populations of northern and central European origin. Hypospadias is a prominent feature, so Smith–Lemli–Opitz syndrome is more easily recognized in males. Other features are mental retardation, abnormal sleep

patterns, microcephaly, short or proximally placed thumbs, and congenital cardiac abnormalities, most commonly atrioventricular septal defect. Patients show a typical facies, and 80% show syndactyly of the second and third toes. Severe photosensitivity has been described in 57% of affected individuals<sup>181</sup> and typically occurs within minutes after exposure to UVA light.<sup>182,183</sup> Objective improvement in the photosensitivity has been demonstrated after supplementation with cholesterol.<sup>184</sup>

### HARTNUP DISEASE

Hartnup disease is a rare autosomal recessive, light-sensitive disorder characterized by a pellagra-like cutaneous eruption, neurologic abnormalities, and a specific aminoaciduria (caused by a defect in the cellular transport of a group of monoamino-monocarboxylic acids). The basic defects appear to be a failure in the absorption of tryptophan from the gastrointestinal tract and a renal tubular defect causing inadequate reabsorption of amino acids, including tryptophan. These result in reduced levels of available tryptophan and, accordingly, nicotinic acid, which in turn may be responsible for the pellagra-like photosensitivity. The condition results from mutations in *SLC6A19*,<sup>185</sup> which encodes the neutral amino acid transporter BOAT1.<sup>186</sup>

The biochemical defect (aminoaciduria) is a constant feature of Hartnup disease. Clinical manifestations, however, are intermittent, recurrent, and quite variable. The cutaneous eruption usually appears in the spring and summer. It may be present in early childhood, occasionally during early infancy and, when present, is usually seen in children between 3 and 9 years of age. The cutaneous manifestations consist of a symmetric distribution of erythematous macules that tend to coalesce and eventuate in well-margined red scaling lesions over light-exposed parts of the face, neck, uncovered areas of the arms, inframammary and perineal folds, elbows, knees, dorsal aspects of the hands, wrists, and lower legs. Once these lesions appear, they usually persist for weeks or months.

Acute dermatitis and blistering with secondary crusting and scarring frequently occur following sun exposure. These changes, together with marked postinflammatory hyperpigmentation, are similar to the findings seen in pellagra. Malnutrition and intercurrent infections frequently aggravate the dermatitis. Glossitis, angular stomatitis, vulvovaginitis, diffuse hair loss and fragility, and nail abnormalities (longitudinal streaking) may also be seen. In many patients, the cutaneous manifestations become milder with advancing age and subsequent sun exposure. Hartnup disease with cutaneous manifestations resembling acrodermatitis enteropathica has also been described.<sup>187</sup>

Cerebellar ataxia is the predominant neurologic feature of Hartnup disease. Seen in more than two-thirds of those affected by this disorder, the ataxia seems to occur during periods when the rash is most prominent or after acute episodes of febrile illness. The gait is broad-based and unsteady, and patients have both nystagmus and an intention tremor. Ocular abnormalities include diplopia and ptosis, and some patients have mental retardation, emotional lability, or frank psychosis.

The diagnosis of Hartnup disease is based on the clinical picture and demonstration of specific amino acid and indole excretion patterns (not the total amino acid excretion). Treatment consists of avoidance of sunlight exposure and prolonged oral administration of high doses (40 to 200 mg) of nicotinic acid or nicotinamide. Because nicotinamide does not cause the flushing generally associated with administration of nicotinic acid, the former is generally the drug of choice. Although the eruption and ataxia seem to improve when patients are adhering to this regimen, assessment of therapy is difficult because the natural history of the disorder is one of spontaneous remission and exacerbation.

### Pellagra

Pellagra is a systemic disturbance caused by a cellular deficiency of niacin resulting from inadequate dietary intake of niacinic acid or its precursor (tryptophan) or the ingestion of certain antinicotinic substances, such as phenytoin and isoniazid.<sup>188,189</sup> Niacin is required for the biosynthesis of ceramides and other stratum corneum lipids.

Given the supplementation in foods and vitamins, pellagra rarely occurs except in countries where nutritional deficiency is common.<sup>190</sup> However, it has been described in adolescents with anorexia nervosa, children with malabsorption syndromes, and individuals maintained on diets high in corn<sup>191</sup>; it is more commonly seen in people with chronic alcoholism and malnourished homeless persons.

The disorder is characterized by seasonal recurrences and a classic triad of dermatitis, diarrhea, and dementia.<sup>192</sup> The onset of the disorder, however, may be heralded by weakness, loss of appetite, abdominal pain, mental depression, and photosensitivity. In later stages, nervous symptoms may predominate to such a degree that the cutaneous lesions may be overlooked. These include delirium, dementia, posterolateral spinal cord degeneration, and pyramidal and peripheral nerve involvement.

The most prominent cutaneous lesions of pellagra are precipitated by the sun and, although not always present, begin as asymptomatic or pruritic symmetric erythematous scaling macules on areas exposed to sunlight, heat, friction, or pressure. The usual sites of involvement include the face, neck, dorsal surface of the hands, arms, feet, inguinal region, and, particularly in infants and small children, the diaper area. The eruptions begin as well-margined erythema and superficial scaling on sun-exposed areas resembling sunburn (with or without vesiculation or blister formation) that gradually subside, leaving a dusky brown-red discoloration. In acute cases the lesions may progress to vesiculation, ulceration, exudation, cracking, and, at times, secondary infection. With chronicity, lesions become more livid, thickened, scaly, and ultimately fissured, atrophic, and deeply pigmented. On the lower neck the eruption may appear as a broad collarette of dermatitis known as *Casal's necklace*. In cases in which the "necklace" is incomplete, the lesions maintain their symmetric and otherwise characteristic appearance. The nose has a fairly distinctive appearance with a dull erythema of the nasal bridge, slight scaling, and a powdery appearance. Mucous membrane involvement, when present, consists of painful fissures and ulceration. The lips and cheeks are thin and pale, the mouth is dry, and the tongue is red, swollen, and, at times, darkened (the so-called *black tongue*). Aphthous ulcers, fissuring, and angular cheilitis are also common.

When the diagnosis is suspected, measurement of the urinary excretion of N<sub>1</sub>-methylnicotinamide and/or pyridone (metabolites of

niacin) is helpful. Treatment of pellagra consists of a high-protein diet and nicotinic acid or nicotinamide in dosages of 100 to 400 mg/day supplemented by vitamin B complex. If a good diet can be maintained, complete recovery is the rule. The disease tends to be progressive and if untreated, may eventuate in death within several years.

## The Porphyrias

The porphyrias comprise a group of disorders of porphyrin, the chemical precursor for hemoglobin synthesis<sup>26,193-196</sup> (Table 19-6). Porphyrins, the only well-established photosensitizers made by the human body, are excited by visible light at the wavelengths 400 to 410 nm (Soret band) and emit a red fluorescence. When exposed to this wavelength in the presence of oxygen, porphyrins release energy that reacts with the oxygen to generate free radicals and singlet oxygen that causes damage to cells and tissues. β-Carotene quenches free radicals and singlet oxygen and thus may lessen the damage.

Two phenotypic patterns of phototoxicity are seen in patients with porphyria: the immediate effects characterized by pain, edema, erythema, and purpura; and the delayed effects, consisting of blistering and scarring. There are three main categories of porphyric disease in humans: erythropoietic, hepatic, and mixed, with mutations recognized in genes encoding ten enzymes of the heme biosynthetic pathway (Table 19-7). The erythropoietic porphyrias are divided into erythropoietic porphyria (autosomal recessive) and erythropoietic protoporphyrinia (EPP; autosomal dominant and less often autosomal recessive or X-linked dominant); the hepatic porphyrias include acute intermittent porphyria (AIP), porphyria cutanea tarda (PCT), hereditary coproporphyria, and variegate porphyria. Hepatoerythropoietic porphyria is a mixed form. Cutaneous findings are not a feature of δ-aminolevulinate dehydratase deficiency porphyria or AIP.<sup>26</sup> A distinctive, transient purpuric eruption, limited to areas exposed to blue light, has been described in transfused neonates with hyperbilirubinemia;<sup>197</sup> elevated levels of protoporphyrins and coproporphyrins were detected in plasma (Fig. 19-20). The American Porphyria Foundation offers patients information and support ([www.porphyriafoundation.com](http://www.porphyriafoundation.com)).

**Table 19-6** Pathway of Porphyrin Heme Biosynthesis, Enzyme Defects, and Disease

Metabolites	Enzyme	Type of Porphyria
Glycine + succinyl-CoA ↓	δ-Aminolevulinic acid synthase (ALA synthase) 1 and 2	X-linked (ALAS2, erythroid-specific)
δ-Aminolevulinic acid ↓	ALA dehydratase	ALA dehydratase
Porphobilinogen (PBG) ↓	PBG deaminase	Acute intermittent
Hydroxymethylbilane ↓	Uroporphyrinogen III synthase	Congenital erythropoietic
Uroporphyrinogen III ↓	Uroporphyrinogen decarboxylase	Porphyria cutanea tarda/ hepatocerebral
Coproporphyrinogen III ↓	Coproporphyrinogen oxidase	Hereditary coproporphyria
Protoporphyrinogen IX ↓	Protoporphyrinogen oxidase	Variegate
Protoporphyrin IX ↓	Ferrochelatase	Erythropoietic protoporphyrinia
Heme ↓		
Cytochromes, hemoglobin, and myoglobin		

**Table 19-7** Types of Porphyria

Type of Porphyria	Inheritance	Enzyme Deficiency	Photosensitivity	Scarring	Hypertrichosis	Other
<b>ERYTHROPOIETIC</b>						
Erythropoietic porphyria (EP)	AR XLR	Uroporphyrinogen III synthase (UROS); GATA binding factor 1 (GATA1)	+++	+++	+	Erythrodontia, splenomegaly, hemolysis, bone fragility
Erythropoietic protoporphyrinia (EPP)	AD/AR XLD	Ferrochelatase; δ-Aminolevulinic acid synthase, erythroid-specific (ALAS2)	++	+	±	Cholelithiasis, anemia, liver failure, marked skin burning or stinging
<b>HEPATIC OR COMBINED</b>						
Acute intermittent porphyria (AIP)	AD	Porphyrinogen deaminase	-	-	-	Acute abdomen and neuropsychiatric
Porphyria cutanea tarda (PCT)	AD	Uroporphyrinogen decarboxylase	++	++	+++	Milia
Hereditary coproporphyria (HCP)	AD	Coproporphyrinogen oxidase	+	+	+	Jaundice and anemia in the newborn (harderoporphyria); Acute abdomen and neuropathy
Variegate porphyria (VP)	AD	Protoporphyrinogen oxidase	+++	++	+	Acute abdomen
δ-Aminolevulinic acid dehydratase porphyria (ALAD porphyria)	AR	δ-Aminolevulinic acid dehydratase	-	-	-	Acute abdomen and neuropsychiatric
Hepatoerythropoietic porphyria (HEP)	AR	Uroporphyrinogen decarboxylase	+++	++	+	Erythrodontia, splenomegaly, anemia

AD, Autosomal dominant; AR, autosomal recessive; XLD, X-linked dominant; XLR, X-linked recessive.



**Figure 19-20** Purpuric phototherapy-induced eruption. Dramatic purpuric eruption at the areas of maximal blue light exposure in a baby with elevated plasma levels of protoporphyrins and coproporphyrins. The baby had been transfused for Rh incompatibility and treated for hyperbilirubinemia. Note the sparing at the site of lead placement.

### Congenital Erythropoietic Porphyria

Erythropoietic porphyria (congenital erythropoietic porphyria [CEP], Günther disease) is very rare.<sup>198</sup> It is characterized by the appearance of red urine during infancy (Fig. 19-21), severe photosensitivity that occurs in the first 2 or 3 years of life, splenomegaly, and hemolytic



**Figure 19-21** Congenital erythropoietic porphyria. The diaper of an affected baby demonstrates the red color of urine.

anemia.<sup>199</sup> Hemolysis *in utero* may present as hydrops fetalis, but 76% show manifestations by 5 years of age and 41% have at least one manifestation at birth.<sup>198</sup>

Photosensitivity is commonly absent in the neonatal period but generally becomes apparent during the first years of life as exposure to the sun increases. Phototherapy during the neonatal period for hyperbilirubinemia may lead to generalized blistering.<sup>200</sup> Rarely, the disorder is first manifested later in childhood or even adulthood.<sup>201</sup> Recurrent



**Figure 19-22** Congenital erythropoietic porphyria. Vesicles, bullae, and crusts on sun-exposed areas.



**Figure 19-23** Congenital erythropoietic porphyria. Brownish teeth that fluoresce under Wood lamp examination.

eruption of vesicles and bullae on sun-exposed areas of the skin (Fig. 19-22), filled with fluid that fluoresces pink, eventually results in mutilating ulceration, scarring, and loss of acral tissues, such as the ears, tip of the nose, eyelids, distal phalanges, and nails. Other common clinical features include hypertrichosis of the face and extremities and hyperpigmentation. The legendary werewolves of the Middle Ages, with fluorescent teeth and nails, mutilated and deformed ears, nose, and eyelids, and nocturnal habits due to their sensitivity to light, may have been persons afflicted with CEP. Asymptomatic pink hamartomatous papules of the perioral and perinasal area have been noted in several patients.<sup>198</sup>

The teeth are a pink to brown color (Fig. 19-23) and fluoresce under Wood lamp examination, because porphyrins bind to dental calcium phosphate. True erythrodontia of porphyria should not be confused with the pseudoerythrodontia of children with poor dental hygiene, which relates to overgrowth of fluorescent bacteria and can be removed. Microstomia, gingival recession, caries, and overcrowding of teeth are other features. Patients show a variety of ocular abnormalities that may lead to blindness, including photophobia, corneal scarring, ulceration, keratoconjunctivitis, and cataracts. The majority of patients have hemolytic anemia with associated splenomegaly. Neonatal jaundice, abnormal hepatic transaminases and hepatomegaly are sometimes reported, and pancytopenia has been described. Bone fragility results from the expansion of the bone marrow, although porphyrins may also be directly toxic to bone. The color of the urine of patients may vary from faint pink to burgundy or port wine, depending on the concentration of uroporphyrin.

The biochemical disturbance is a deficiency of the enzyme uroporphyrinogen III synthetase (UROS), resulting in marked overproduction of uroporphyrin I and coproporphyrin I in circulating erythrocytes, bone marrow cells, plasma, urine, and feces. The severity of the CEP is greater in patients who have heterozygous mutations

in ALAS2 (erythroid-specific mitochondrial 5-aminolevulinate synthase; see *Erythropoietic Protoporphyria* section).<sup>202</sup> Although most patients have biallelic mutations in UROS, mutation in the gene encoding GATA binding factor 1 (GATA1) can also cause CEP as an X-linked recessive disorder.<sup>203</sup> GATA1 is transcription factor that regulates the expression of UROS in developing erythrocytes but also is critical for normal erythropoiesis, globin gene expression, and megakaryocyte development. Affected children show thrombocytopenia, anemia that more closely resembles thalassemia, and dramatic increases in fetal hemoglobin (HbF). Wood light examination in patients with CEP may reveal reddish-orange porphyrin fluorescence in urine or aqueous suspensions of feces and thin smears of peripheral erythrocytes glow red under a fluorescent microscope. Patients (with UROS mutations) have normochromic anemia with elevated reticulocyte levels, circulating normoblasts, and normoblastic hyperplasia of the bone marrow.

The prognosis of CEP is poor in severe cases unless treated successfully by transplantation, with few patients surviving into the fourth or fifth decade of life.<sup>204,205</sup> Death, when it occurs, is often associated with hemolytic anemia. Bone marrow and allogeneic stem-cell transplantation may correct all disease manifestations except the erythrodontia.<sup>206</sup> Avoidance of light at wavelengths less than 510 nm markedly diminishes the cutaneous manifestations, anemia, and splenomegaly. This includes protection from light through window glass (including blinds and window filters that decrease the relevant visible spectrum), wearing protective clothing, and use of opaque sunscreens that block a broader spectrum. DHA, a component of sunless tanning agents, can block the visible light.<sup>207</sup> Ophthalmologic intervention with eye lubricants and topical antibiotics, dental management, and administration of supplemental vitamin D and bisphosphonates as needed for osteoporosis is important. Splenectomy for the hemolysis and chronic transfusion regimens to suppress bone marrow activity are variably successful. Surgical reconstruction has decreased the progressive disfigurement from ectropion, microstomia, and nasal deformity.<sup>205,208</sup> Prenatal diagnosis is possible by analysis of amniotic fluid and cells, and *in vitro* gene therapy for patients without a suitable transplant donor has been performed. Mild cases can be managed by avoiding sun exposure and trauma, as well as transfusions to suppress porphyrin overproduction.

### Erythropoietic Protoporphyria

Erythropoietic protoporphyrin (EPP), the most common form of porphyria in children, results from the combination of loss-of-function mutations of *FECH*, the gene encoding mitochondrial ferrochelatase, and on the other allele a polymorphism carried by 10% of Western Europeans in the noncoding region (IVS3-48T>C) of *FECH*.<sup>209–211</sup> Levels of ferrochelatase, which accelerates the incorporation of iron into protoporphyrin, are only 15% to 25% of normal levels in EPP. Although the disorder is autosomal dominant, parent-to-child transmission of overt disease is uncommon. Having polymorphisms on both alleles does not cause disease; however, true autosomal recessive disease with loss-of-function mutations on both alleles of *FECH* occurs in about 3% to 5% of affected individuals and may be associated with EPP.

X-linked (dominant) protoporphyrin (XLP) is a phenocopy of EPP and results from gain-of-function mutations in the X-linked erythroid-specific 5-aminolevulinate synthase (ALAS2) gene, which is essential for hemoglobin formation.<sup>212</sup> The incidence of XLP is 10% of that of EPP from *FECH* mutations in North America and even less in Western Europe.<sup>213</sup> Males with XLP have twofold higher erythrocyte protoporphyrin levels than patients with EPP, increasing their risk of photosensitivity and liver disease.

The common subtlety of clinical signs and symptoms and the absence of increased levels of protoporphyrin in urine (because of the relative insolubility of this porphyrin in water) may lead to failure of recognition of EPP. Nevertheless, the disease usually becomes symptomatic between 1 and 6 years of age because of photosensitivity.<sup>214</sup> The condition may be detected during infancy because the baby cries after brief exposure to sunlight. It manifests acutely from early spring to late summer as burning, stinging, or itching of the exposed skin after 5 to 30 minutes of sunlight exposure.<sup>215</sup> This burning sensation may be followed by pruritic reddened edematous plaques that



**Figure 19-24** Erythropoietic protoporphyrin (EPP). Vesicular lesions are only occasionally seen in patients with EPP.



**Figure 19-25** Erythropoietic protoporphyrin. Papular thickening of the skin after blistering is particularly common on the nose and overlying the knuckles.

return to normal within 1 to 2 days. Occasionally, papulovesicular (Fig. 19-24) and petechial eruptions occur and may persist for longer periods. Chronic changes include hypopigmentation, hyperpigmentation, and a papular thickening that gives a cobblestone appearance to the skin (Fig. 19-25). Despite the severely painful acute symptoms, chronic skin manifestations are often mild, ranging from grossly undetectable lesions to shallow linear or elliptical pits on the face, linear furrows around the lips, thickened hyperkeratotic skin, and a weather-beaten, leathery, or pebbly appearance, particularly over the nose or knuckles. Nails may be shed (photoonycholysis). Seasonal palmar keratoderma has been described as a sign of autosomal recessive EPP.<sup>216</sup>

Anemia has been reported in up to one-third of patients. Rarely, hypersplenism (which responds favorably to splenectomy) is associated with the anemia. Cholecystitis and cholelithiasis have been reported in up to 12% of patients, with gallstones consisting of almost pure protoporphyrin IX. Overall 20% to 30% of patients have manifestations of hepatic abnormalities, most commonly a mild increase in hepatic aminotransferases. Progressive hepatic failure occurs in 2% to 4% of patients, usually after 30 years of age, from retention of protoporphyrins, cholestasis, and eventual cirrhosis. However, cholestatic liver disease has even been described in affected infants.<sup>217</sup> The severity of the disease correlates with the amount of circulating protoporphyrins. Liver function testing should be performed annually, and alcohol and drugs with potential hepatotoxicity or cholestatic effects should be avoided. Carriage of null allele mutations, autosomal recessive EPP, and XLP have a higher risk of hepatic complications.<sup>212,218</sup>

Free protoporphyrin levels are high in circulating erythrocytes, plasma, bone marrow, liver, feces, and skin, but not in urine, so the best test is the free erythrocyte protoporphyrin level. Zinc-bound

erythrocyte protoporphyrins are high in XLP but not in EPP, because ferrochelatase is needed to synthesize both iron protoporphyrin (heme) and zinc protoporphyrin. Although total protoporphyrins (which are primarily free erythrocyte protoporphyrin) are usually measured if the more easily obtained “zinc-protoporphyrin level” is ordered, ensuring that the test measures the free erythrocyte protoporphyrins is important. Fluorescence of the erythrocytes can be demonstrated by Wood light or fluorescence microscopy.<sup>219</sup> In contrast to erythropoietic porphyria, fluorescence of teeth and nails is not present and there is no increase in fecal or urinary levels of uroporphyrins, although fecal protoporphyrins and coproporphyrins are increased. Ferrochelatase levels are 10% to 50% of normal in patient erythrocytes.

The management of EPP depends on limiting exposure to sunlight and use of sun-protective clothing and opaque sunscreens that block the wavelength range 400 to 410 nm. Some patients have had decreased photosensitivity after administration of β-carotene (Lumitene), which maximally absorbs in the visible spectrum at 450 to 475 nm and quenches free radicals in the skin. The usual dosage for children younger than 14 years of age is 30 to 150 mg and for adolescents is 120 to 180 mg (4 to 6 capsules a day). Skin yellowing, orange-colored stools, and occasional gastrointestinal upset may occur. Nevertheless, a recent systematic review did not confirm efficacy of β-carotene, vitamin C or N-acetylcysteine.<sup>220</sup> Narrowband UVB light using a PMLE protocol to harden skin (starting with 50% to 70% MED and increasing gradually) led to improvement in the majority of treated patients.<sup>221</sup> Subcutaneous implantation of 16 mg afamelanotide, an α-melanocyte-stimulating hormone analog to induce tanning, has markedly improved the quality of life in patients with EPP who have been treated chronically for up to 8 years.<sup>222</sup>

Transfusion may be required in patients with significant hemolytic anemia. Other therapeutic approaches that may be useful are oral administration of cimetidine, which reduces erythrocyte levels of protoporphyrin and photosensitivity; cholestyramine, which helps prevent reabsorption of protoporphyrin excreted into the intestinal lumen; and chenodeoxycholic or ursodeoxycholic acid. For patients with progressively deteriorating liver function, liver transplantation can be life saving,<sup>223,224</sup> but the risk of biliary complications is high; disease recurrence may be delayed by administration intravenously of hemin (an iron-containing porphyrin) and plasmapheresis.

### Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT) is the most common form of porphyria in adults and the second most common form of porphyria in children. Estimated to have an incidence of 1 in 25,000, it usually presents during the third and fourth decades of life. Autosomal dominant cases result from a mutation in uroporphyrinogen decarboxylase (*UROD*; decreases enzyme activity by 50%) and still need other genetic and environmental factors to manifest; to manifest clinical signs, *UROD* activity must be less than or equal to 20% of normal. In the familial form, the decreased *UROD* activity affects the liver, erythrocytes, and other tissues. Mutations in both *UROD* alleles usually lead to hepatocutaneous porphyria but may cause mild cutaneous disease.<sup>225</sup> About 80% of patients have the sporadic (type I) form in which the activity of *UROD* deficiency is inhibited specifically in the liver.

Skin lesions in PCT are vesicles or bullae on light-exposed cutaneous surfaces, especially the dorsal aspect of the hands, forearms, and face.<sup>226</sup> The blisters vary markedly in size from 1 mm to 3 cm across, with small blisters often being overlooked. They are most commonly filled by clear or slightly turbid liquid, but soon rupture, turn into erosions, and often become infected. On healing, the blister sites may scar or evolve into milia. These features may require differentiation from immunobullous disorders, especially epidermolysis bullosa acquisita (see Chapter 13). Other features include increased fragility of the skin, with erosions and ulcerations as a result of relatively minor trauma, hypertrichosis, and mottled hypopigmentation and hyperpigmentation of the face at sites of sun exposure. Sclerodermoid plaques (especially on the chest or temples) and dystrophic calcifications are rare in affected children.

PCT can be precipitated by iron overload, hepatitis C, human immunodeficiency virus (HIV), alcoholic cirrhosis, hemodialysis, or

administration of estrogens, hydantoins, griseofulvin, or chemotherapy drugs.<sup>227</sup> Accidental ingestion of the fungicide hexachlorobenzene was responsible for an epidemic of PCT in Turkey.<sup>228</sup> Mutations in *HFE*, associated with hemochromatosis; certain polymorphisms in cytochromes<sup>229</sup>; and the transferrin receptor gene (*TFRC*) also increase the risk.<sup>194</sup> Diabetes mellitus is present in 25% of patients with PCT, and patients not uncommonly show hepatomegaly and abnormal hepatic transaminase levels. The development of cirrhosis is a precursor of the hepatocellular carcinoma, which eventually develops in about 3% of patients.

Confirmation of the clinical diagnosis of PCT can be made by increased levels of urinary and fecal uroporphyrins, slightly elevated fecal coproporphyrin and protoporphyrin levels, and positive fluorescence of the urine with a Wood light. As with other forms of porphyria, skin biopsy specimens of vesicular lesions show subepidermal bullae with dermal papillae arising irregularly from the floor of the bulla into its cavity ("festooning"). Periodic acid-Schiff (PAS)-positive material is deposited around blood vessels and sometimes at the dermal-epidermal junction, sites where immunofluorescent studies show deposition of IgG and complement. Familial and sporadic cases can be distinguished by erythrocyte uroporphyrinogen-decarboxylase activity and uroporphyrinogen-decarboxylase genotyping.

Treatment is dependent on the elimination of triggering factors (e.g., alcohol, estrogen, iron ingestion). Treatment with low doses of hydroxychloroquine (3 mg/kg twice weekly) leads to drug-uroporphyrin complexes that are excreted. Clinical remission ensues in about 3 months, and biochemical remission is achieved in about a year. If antimalarial treatment is ineffective, phlebotomy is used to remove iron stores and porphyrins. Once biochemical remission is achieved, treatment is stopped and the patient is monitored for relapse, which generally occurs within 3 years until spontaneous remission. Spontaneous remission has been reported, but 5% to 16% of adults with long-standing untreated disease and chronic hepatitis develop hepatocellular carcinoma.

### Hepatoerythropoietic Porphyria

Hepatoerythropoietic porphyria, an extremely rare disorder, is considered to be a homozygous or heterozygous form of PCT. The disease is usually manifest before 2 years of age.<sup>230,231</sup> Dark urine is the most commonly observed sign. Skin lesions appear in childhood, and the activity of UROD in all organs is usually decreased to less than 10% of normal. The disorder is characterized by excessive porphyrin production in the liver and bone marrow, increased erythrocyte porphyrin levels, and severe photosensitivity with vesicles, bullae, crusts, and erosions. Skin fragility, hypertrichosis (that begins in infancy and early childhood), mutilating scarring deformities similar to those of CEP, and scleroderma-like changes of sun-exposed skin also occur. The face and dorsal aspect of the hands are the most severely affected areas. Malar hypertrichosis may be striking, and patients have erythrodontia (reddish brown teeth) that fluoresces when exposed to a Wood lamp. In addition to clinical features similar to those of erythropoietic porphyria, hepatoerythropoietic porphyria has biochemical abnormalities suggestive of PCT and EPP. The diagnosis is confirmed by finding huge elevations of erythrocyte protoporphyrin, urinary uroporphyrin, and fecal coproporphyrin. Sun avoidance is critical; plasma iron concentrations are normal, and phlebotomy is ineffective.

### Hereditary Coproporphyria

Hereditary coproporphyria has almost always been described in adults. The few cases that have been documented in children were initially mistaken for HV.<sup>232</sup> Rare homozygous cases have been reported in neonates with hepatosplenomegaly, hemolytic anemia, jaundice, and photosensitivity (harderoporphyria)<sup>233</sup>; feces show marked elevations of coproporphyrins. Some 20% to 30% of patients are photosensitive, and the skin lesions resemble those of PCT, chronic and usually appearing many days after sun exposure. Most patients have acute attacks of abdominal pain identical to those seen in AIP and variegate porphyria. Acute peripheral neuropathy has also been described. This condition, inherited as an autosomal dominant trait, is associated with a defect of coproporphyrinogen oxidase, resulting in accumulation of coproporphyrinogen III and its oxidized form, coproporphyrin III. Cutaneous eruptions occur concurrently with attacks of abdomi-

nal pain and psychiatric symptoms. The diagnosis is made by demonstration of elevated levels of coproporphyrin III in both urine and feces, and treatment is similar to that of patients with variegate porphyria, in addition to pain therapy for the acute abdominal attacks.

### Variegate Porphyria

Variegate porphyria (congenital cutaneous hepatic porphyria, South African porphyria) is an autosomal dominant disorder that results from heterozygous mutations in *PPOX* and decreased activity of protoporphyrinogen oxidase. This disease has its onset after puberty and generally appears in the fourth to fifth decades of life; only a few cases in childhood have been described.<sup>234</sup> It has a high incidence in the Afrikaners of South Africa.<sup>235</sup> Individuals with homozygous or compound heterozygous mutations can show severe photosensitivity with blistering and scarring beginning in infancy.<sup>236</sup> Other features are developmental delay, mental retardation, nystagmus, seizures, and short stature.<sup>237</sup>

The features of variegate porphyria resemble those of PCT but tend to be milder and less easily provoked. Clinical manifestations include sun sensitivity with vesicles or blisters on light-exposed surfaces, hyperpigmentation, a weather-beaten or waxy complexion with excessive furrowing of the forehead, cutis rhomboidalis frontalis, scars on the back of the neck and frontal hair margin, milia, and scleroderma-like plaques. The urinary findings overlap with those of both AIP and PCT, so that diagnosis is based on the plasma porphyrin fluorescence (6.26 nM) and a more than two-fold increase in excretion of fecal protoporphyrin. Treatment consists of avoidance of hepatotoxic agents and sun exposure, repeated phlebotomies, low-dose hydroxychloroquine therapy, and, in some patients, the administration of β-carotene.

### Acute Intermittent Porphyria and δ-Aminolevulinic Acid Dehydratase Porphyria

Acute intermittent porphyria (AIP) and δ-aminolevulinic acid dehydratase (ALAD) porphyria are rare disorders that share clinical features of episodes of acute abdominal pain associated with vomiting; constipation; peripheral paresis or paralysis; and psychological manifestations or psychoneuroses provoked by drugs that affect the liver, including barbiturates, sulfonamides, dapsone, griseofulvin, anticonvulsive agents, sulfonylurea compounds, and estrogens. Neither disorder tends to manifest before puberty or shows cutaneous features. AIP is an autosomal dominant disorder characterized by overproduction of porphyrin precursors (δ-aminolevulinic acid and porphobilinogen), which are excreted into the urine. ALAD porphyria, in contrast, is an even rarer autosomal recessive disorder with markedly deficient ALAD activity that results in overproduction of δ-aminolevulinic acid, but not porphobilinogen, in the urine.<sup>238</sup> False-positive urine porphyrin tests can be seen in children with heavy metal poisoning, including lead and mercury.<sup>239</sup>

The complete list of 239 references for this chapter is available online at <http://expertconsult.inkling.com>.

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The hypersensitivity syndromes are a group of disorders mediated by immunologic or hypersensitivity reactions to foreign proteins such as food or drugs, or to infectious agents, immunizations, and malignancies. Although diagnosis of these disorders is often relatively easy, difficulties commonly arise in determining the underlying cause. The most common hypersensitivity reactions are drug reactions,<sup>1</sup> and the skin is a common target. The overall incidence of drug reactions in hospitalized children is 9.5%,<sup>2</sup> and in outpatient children it is 2.5%, with reactivity to antibiotics occurring most often.<sup>3</sup> Urticarial and exanthematous reactions are seen most often.<sup>4</sup> If fever, lymphadenopathy, or facial edema accompanies an exanthematous drug reaction, the possible diagnosis of a systemic hypersensitivity disorder (drug reaction with eosinophilia and systemic symptoms [DRESS]) must be considered. The various types of drug reactions are summarized in **Table 20-1**. These include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), lichenoid drug eruptions (**Fig. 20-1**) (see Chapter 4), fixed drug eruptions, pustular eruptions (acute generalized exanthematous pustulosis [AGEP]), acneiform eruptions (see Chapter 8), pseudoporphyrria (see Chapter 19), drug-induced vasculitis (see Chapter 21), and drug-induced lupus (Chapter 22). Some children experience multiple antibiotic sensitivity, most commonly to penicillins, sulfonamides, cephalosporins, and macrolides.<sup>5</sup> In these children, the manifestations of drug sensitivity can be different; for example a child may show an exanthematous response to amoxicillin, DRESS after phenytoin, and erythroderma after ingestion of sulfamethoxazole within a period of a few months.<sup>6</sup> The general approach to a child with suspected drug reaction is outlined in **Box 20-1**.

## Allergic Reactions

Allergy may be defined as a specific acquired alteration in the capacity of an individual to react to an antigen. Mediated by circulating or cellular antibodies, allergic reactions may be classified as immunoglobulin (Ig) E-mediated hypersensitivity (type I), cytotoxic (type II), Arthus-type toxic immune complex reactions (type III), and delayed-type hypersensitivity (type IV). Type II/anaphylactic reactions include local and systemic manifestations of the interaction between antigen and tissue cells previously sensitized with skin-sensitizing reaginic antibody, usually IgE. This interaction of antigen and antibody results in the release of pharmacologically active substances that produce urticaria, angioedema, anaphylaxis, hay fever, and asthma. Type II/cytotoxic reactions include those reactions initiated by antibody interacting with an antigenic component of the cell surface. The antigen may be a natural component of the cell or an unrelated antigen that has become associated with the cell. Examples include pemphigus (see Chapter 13), hemolytic disease of the newborn, transfusion reactions, hemolytic anemia, leukopenia, or thrombocytopenia caused by the reaction of antibody with drugs attached to blood-cell surfaces. Type III/toxic immune complex reactions (Arthus-type reactions) are associated with the deposition of immune microprecipitates in or around blood vessels, which results in tissue damage through activation of complement or toxic products from leukocytes attracted to the areas. Examples include serum sickness, vasculitis, glomerulonephritis, and local Arthus reactions after injection of antigens into the skin, subcutaneous tissue, or muscle. Type IV/delayed-type hypersensitivity is the result of the interaction between antigen and specifically sensitized lymphocytic cells, which results in a mononuclear cell infiltration and the elaboration of toxic lymphoid cell products. Examples include tuberculin and other skin test reactions, allergic contact dermatitis (see Chapter 3), lichenoid drug eruptions (see **Fig. 20-1** and Chapter 4), fixed drug eruptions, TEN, and graft-versus-host-type

reactions (see Chapter 25). Patch testing may be useful in determining the cause of allergic contact dermatitis (see Chapter 3).

## Urticaria

Urticaria, a systemic disease with cutaneous manifestations, occurs at some time in the life of about 15% to 20% of all persons. It is characterized by the appearance of transient well-circumscribed skin lesions that present as erythematous, intensely pruritic elevated swellings (wheals) of the skin or mucous membranes. More than 80% of cases of new-onset urticaria resolve in 2 weeks and more than 95% of new-onset cases within 3 months.<sup>7</sup>

Urticaria usually represents a type I (or immediate) hypersensitivity reaction in which the protein or its metabolite binds to IgE on the surface of cutaneous mast cells, leading to activation, degranulation, and release of vasoactive mediators such as histamine, leukotrienes, and prostaglandins. Examples of immunologically mediated urticaria are reactions to latex and reactions to peanuts (see below). Urticaria may also result from nonimmunologic triggering of mast cell release, such as from radiocontrast media, aspirin, many types of nonsteroidal anti-inflammatory drugs (NSAIDs), or opiates.

Typical lesions of urticaria have an edematous center with a halo of erythema (**Fig. 20-2**). They vary from pinpoint-sized papules to large lesions several centimeters in diameter. Central clearing, peripheral extension, and coalescence of individual lesions result in a clinical picture of oval, annular, or sometimes bizarre serpiginous configurations (**Figs. 20-3** and **20-4**). When annular or serpiginous patterns of urticaria occur, they can be confused with erythema multiforme (EM) or serum sickness reactions (**Fig. 20-5**), and the designation *urticaria multiforme* has been proposed.<sup>8-10</sup> Other mimics of urticaria include urticarial vasculitis, Henoch-Schönlein purpura, acute hemorrhagic edema of infancy (see Chapter 21), systemic onset juvenile idiopathic arthritis (see Chapter 22), and cryopyrin-associated periodic syndromes (see Chapter 25).<sup>11</sup>

Urticaria may be localized to one small area or may become generalized (**Fig. 20-6**). Subcutaneous extension may result in giant wheals. In infants and young children, swelling of the distal extremities with acrocyanosis may be a prominent feature of the urticarial reaction. Occasionally, particularly in infants and young children, bullae may form in the center of the wheal, usually on the legs and buttocks. Individual wheals rarely persist longer than 12 to 24 hours. Parents can draw a circle around a few lesions to verify clearance of each individual lesion by approximately 24 hours or less. Those lasting longer than 24 to 36 hours are probably not true urticaria and may represent another vascular pattern such as urticarial vasculitis (see Chapter 21) or EM.

Urticaria of less than 6 weeks' duration is considered acute. In 80% of children, acute urticaria is the result of infection, often viral, whereas in adolescents food and drugs play a more significant role. Among foods, dairy products play a more common role in younger children, in contrast to nuts, seafood, berries, and grains in older children. Streptococcal infection, mycoplasma, histoplasmosis, and coccidiomycosis in endemic areas are also well-known triggers, although almost every infectious agent has been associated with urticaria. Overall, up to 10% of episodes of urticaria are related to drugs, and these are usually acute in nature. The penicillins are the most common drugs to trigger urticaria, but only 10% to 20% of individuals who report allergy to penicillin are really allergic when skin prick testing to penicilloyl-poly-lysine and then oral drug challenge (if negative) is performed.<sup>12</sup> Other drugs most likely to induce an urticarial drug reaction are cephalosporins, sulfonamides, tetracyclines

**Table 20-1** Drug Eruptions in Pediatric Patients

Eruption	Key Drugs	Lesional Pattern	Mucosal Changes
Urticaria	Penicillins, cephalosporins, sulfonamides, tetracyclines, aspirin/NSAIDs, radiocontrast media	Pruritic erythematous wheals	None
Angioedema	Aspirin/NSAIDs, ACE inhibitors	Swelling of subcutaneous and deep dermal tissues	May be present
Serum sickness-like reaction	Cephalosporins, penicillins, minocycline, sulfonamides, macrolides, rifampin, ciprofloxacin, griseofulvin, itraconazole, bupropion, fluoxetine, rituximab, H1N1 vaccine	Urticular or erythema multiforme-like	None
Exanthematous	Penicillins, sulfonamides, cephalosporins, antiepileptics	Erythematous macules and/or papules	None
Drug hypersensitivity syndrome	Phenytoin, phenobarbital, carbamazepine, lamotrigine, allopurinol, sulfonamides, dapsone, minocycline, aspirin, vancomycin, azithromycin, abacavir, nevirapine, Chinese medicine	Edema (especially periorbital); erythematous macules and/or papules; sometimes vesicles or bullae	May be present
Lichenoid*	Captopril, enalapril, labetalol, nifedipine, propranolol, gold salts, hydrochlorothiazide, furosemide, spironolactone, hydroxychloroquine, ketoconazole, penicillamine, griseofulvin, tetracycline, carbamazepine, phenytoin, NSAIDs, hydroxyurea, imatinib, dapsone, sulfasalazine, allopurinol, iodides and radiocontrast media, IFN- $\gamma$ , omeprazole, penicillamine, TNF inhibitors, sildenafil	Discrete flat-topped reddish-purple papules and plaques	May be present
Fixed drug	Sulfonamides, ibuprofen, acetaminophen, salicylates, tetracyclines, pseudoephedrine, loratadine, teicoplanin, metronidazole, macrolides, barbiturates, lamotrigine, potassium iodide, quinine, phenolphthalein, foods and food flavorings (especially tartrazine)	Solitary to few erythematous, hyperpigmented plaques	Unusual
Pustular (AGEP)	$\beta$ -Lactam antibiotics, macrolides, clindamycin, terbinafine	Generalized small pustules and papules	None
Acneiform <sup>†</sup>	Corticosteroids, androgens, lithium, iodides, phenytoin, isoniazid	Follicular-based inflammatory papules and pustules predominate	None
Pseudoporphyria <sup>‡</sup>	NSAIDs, COX-2 inhibitors, tetracyclines, furosemide	Photodistributed blistering and skin fragility	None
Vasculitis <sup>§</sup>	Penicillins, NSAIDs, sulfonamides, cephalosporins	Purpuric papules, especially on the lower extremities; urticaria, hemorrhagic bullae, digital necrosis, pustules, ulcers	Rarely
Stevens–Johnson syndrome/toxic epidermal necrolysis	Sulfonamides, antiepileptics, NSAIDs, acetaminophen, allopurinol, dapsone	Target lesions, bullae, epidermal necrosis with detachment	Present
Drug-induced lupus <sup>  </sup>	Minocycline, procainamide, hydralazine, isoniazid, penicillamine	Urticular, vasculitic, erythematous	Rare

ACE, Angiotensin-converting enzyme; AGEP, acute generalized exanthematous pustulosis; COX-2, cyclooxygenase-2; IFN, interferon; NSAID, nonsteroidal anti-inflammatory drug; TNF, tumor necrosis factor.

\*See Chapter 4.

<sup>†</sup>See Chapter 8.

<sup>‡</sup>See Chapter 19.

<sup>§</sup>See Chapter 21.

<sup>||</sup>See Chapter 22.

(especially minocycline), antiepileptics, and monoclonal antibodies, including omalizumab. Although cross-intolerant reactions are more common than IgE-mediated reactions with NSAIDs,<sup>13</sup> selective immediate reactions to NSAIDs are becoming increasingly recognized with the widespread use of these medications in children (especially ibuprofen).<sup>14</sup> *In vitro* testing (immunoassays and basophil activation testing) can detect specific IgE antibodies for a limited number of drugs and complement prick testing but should be performed within 1 year after the occurrence of a reaction.<sup>15</sup> Anaphylactoid reactions (anaphylaxis without identifiable specific IgE antibodies) most commonly result from ingestion of acetylsalicylic acid. Non-immunologically mediated urticaria may result from radiocontrast media and NSAIDs. Psychologic stress may exacerbate (but not cause) urticaria.

Urticaria that recurs often and lasts longer than 6 weeks is termed *chronic*. Chronic urticaria is much more common in adults than in

children<sup>16</sup>; it may be present continuously or nearly every day (“chronic continuous urticaria”) or as attacks separated by symptom-free periods of up to several weeks (“chronic recurrent or intermittent urticaria”).<sup>17</sup> Diagnosis and treatment of a patient with chronic urticaria demands a complete history and physical examination, appropriate laboratory evaluation, and an awareness of possible underlying disease.

If the trigger is not clear, a child may have idiopathic urticaria. However, 30% to 47% of children with chronic urticaria are now recognized to have autoimmune (also called *auto-reactive*) urticaria.<sup>18–22</sup> Autoimmune urticaria is caused by IgG antibodies recognizing the high-affinity IgE receptor (Fc $\epsilon$ RI $\alpha$ ) or less commonly, IgE itself.<sup>23</sup> Patients may have autoimmune thyroid disease and less commonly, celiac disease, type 1 diabetes, juvenile idiopathic arthritis, and systemic lupus erythematosus (Fig. 20-7).<sup>24</sup> Reactions from food or food



**Figure 20-1** Lichenoid drug eruption. Note the flat-topped character of these small papules. This girl reacted to carbamazepine.



**Figure 20-2** Urticaria. Transient well-circumscribed erythematous wheals occurred in this girl as a reaction to administration of cefixime. Note the edematous center and halo of erythema. Circling a lesion and noting whether it is clear 24 hours later facilitates diagnosis.



**Figure 20-3** Urticaria. Transient round and annular erythematous macules and slightly edematous plaques represent a reaction to cefdinir in this infant.

### Box 20-1 Approach to the Patient with Suspected Drug Reaction

#### Historical features

- Drugs taken, date of initiation, and duration
- Date of onset of eruption
- Response to removal and rechallenge

#### Clinical features

- Lesional morphology
- Number of lesions and distribution
- Involvement of mucous membranes
- Associated features: pruritus, fever, lymphadenopathy, visceral involvement

#### Laboratory testing

- Eosinophilia
- Specific IgE levels

#### Prick and intradermal tests for late phase reactions ( $\beta$ -lactam allergy)

#### Provocation testing

IgE, Immunoglobulin E.

additives have been described in 9%. However, the urticaria from food additives, artificial flavoring, or preservatives is not IgE-mediated but rather is a pseudoallergic reaction that is often delayed (4 to 12 hours after ingestion).<sup>25</sup> Among less common possible triggers of chronic urticaria are physical causes, foods and food additives, drugs (especially aspirin and NSAIDs), immunizations, insect bites, inhalant or contact allergens, and infections (parasites, *Helicobacter pylori*, *Chlamydia*, dental abscesses, sinus infections, low-grade urinary tract infection, and otitis). Chronic urticarial lesions with high fevers may also suggest cryopyrin-mediated auto-inflammatory disease (see Chapter 25). Urticarial vasculitis may be confused with chronic urticaria, but lesions persist beyond 24 hours (see Chapter 21).

In pediatric studies, remission rates at 1, 3, and 5 years after the onset of chronic urticaria range from 16% to 18%, 39% to 54%, and 50% to 68%, respectively, regardless of whether the chronic urticaria is autoimmune,<sup>20,22</sup> although being female and older than 10 years of age are poorer prognostic signs.

Further investigation should be based on the known underlying causes, history, and examination and could include complete blood count, erythrocyte sedimentation rate, antinuclear antibody, CH50,

free-T4, thyroid stimulating hormone, antithyroglobulin and antimicrosomal antibodies, skin prick tests for foods, food challenges, and stool examination for parasites. Food avoidance correlates better with a positive history of food reactivity than with positive prick testing.<sup>21</sup> The autologous serum skin test (ASST) through intradermal injection of the patient's own serum is used to confirm autoreactivity<sup>26</sup> and is more sensitive than the *in vitro* histamine-release urticaria test. However, new enzyme-linked immunosorbent assay (ELISA) and immunodot tests have recently been developed to measure anti-Fc $\epsilon$ RI $\alpha$  antibodies directly.<sup>27</sup>

Effective treatment of urticaria depends on identification of the etiologic factor and its elimination whenever possible.<sup>28</sup> First-line treatment in children is administration of a nonsedating histamine (H1) blocker such as cetirizine, loratadine, desloratadine, fexofenadine, or levocetirizine.<sup>29–32</sup> Dose escalation may then be required up to twofold to fourfold those used for management of allergic rhinitis.<sup>33,34</sup> Addition of hydroxyzine, diphenhydramine, or another sedating H1 blocker at night may be considered but should not replace nonsedating antihistamines. Sedating antihistamines are best administered about 1 hour before bedtime to minimize daytime drowsiness. Paradoxical hyperactivity and irritability, which requires discontinuation of the medication, has occasionally been described in some infants and children with the administration of H1 blockers, especially diphenhydramine. Doxepin, a tricyclic antidepressant with H1- and



**Figure 20-4** Urticaria. These annular and serpiginous wheals developed within minutes of eating shrimp.



**Figure 20-6** Urticaria. Wheals may coalesce and cover large areas of the body.



**Figure 20-5** Urticaria. Annular patterns of urticaria can be confused with erythema multiforme, and the term *urticaria multiforme* has been proposed.



**Figure 20-7** Urticaria. Chronic urticaria in this teenager in association with autoimmune diseases type 1 diabetes and hypothyroidism. He failed to respond to treatment with antihistamines and required systemic corticosteroids and methotrexate for control.

H<sub>2</sub>-antagonistic effects, has also been utilized for the treatment of chronic urticaria but may lead to intolerable sleepiness. Approximately 80% of patients respond to antihistamines. Concomitant administration of an H<sub>2</sub> blocker (such as ranitidine or cimetidine) tends to be of limited value, but a leukotriene receptor antagonist (e.g., montelukast) can be considered if antihistamines are insufficient. Antihistamine administration should be continued for a few weeks after clearance of the urticaria with gradual tapering of the dosage in order to determine whether they are still needed for control. Avoidance of aspirin and NSAIDs may be helpful, because these medications may exacerbate chronic urticaria. Monthly administration of subcutaneous omalizumab (150 to 300 mg for adolescents and adults) or cyclosporine may be required for chronic urticaria.<sup>32,35-38</sup> Dapsone, methotrexate, mycophenolate mofetil, cyclophosphamide, hydroxychloroquine, sulfasalazine, intravenous immunoglobulin (IVIG), and plasmapheresis have all been used for resistant chronic urticaria but have less evidence than omalizumab and cyclosporine.<sup>30,32,39-42</sup> The subcutaneous administration of 0.1 to 0.5 mL of epinephrine 1:1000 is often effective for patients with angioedema and severe urticaria. Although often effective in patients with severe or persistent urticaria,

administration of systemic corticosteroids should be reserved for acute reactivity in recalcitrant patients and should be limited to 10 days<sup>32</sup> because of the many potential side effects.

## Contact Urticaria

Urticaria may also occur from skin exposure to antigen<sup>43</sup> rather than through ingestion or inhalation (Fig. 20-8). In this case, the lesions tend to be localized to the site of contact, although rarely satellite lesions or even more generalized involvement has occurred. Exposure to certain jellyfish, corals, caterpillars,<sup>44</sup> moths, and chemicals can lead to contact urticaria through pharmacologic means. Immunologic reactions can also result in contact urticaria, as often occurs with exposure to fish or latex. Localized small wheals have also been described after contact with the spines of pet hedgehogs.<sup>45</sup> Aquagenic urticaria is a variant of contact urticaria in which small urticarial papules arise at follicles after exposure to water.



**Figure 20-8** Contact urticaria. Milk dripped on the thigh of this infant, leading to the rapid development of small wheals.



**Figure 20-10** Cholinergic urticaria. Discrete micropapular wheals are surrounded by a wide area of erythema and are induced by heat, exertion, or emotional stress.



**Figure 20-9** Dermographism. Sharply localized edematous reaction with a surrounding zone of erythema that occurs precisely at the site and within seconds of firm stroking of the skin.

Cholinergic urticaria (micropapular urticaria), which occurs in 5% to 7% of individuals with urticaria, is a very distinctive type.<sup>49</sup> It usually starts in adolescence and is associated with heat, exertion, or emotional stress. Cholinergic urticaria is characterized by a generalized eruption, especially on the trunk and arms, which consists of discrete, papular wheals, 1 to 3 mm in diameter, with or without a surrounding area of erythema (Fig. 20-10). The wheals first appear within minutes after sweating begins and occasionally are accompanied by exercise-induced bronchospasm, headache, gastrointestinal discomfort, and faintness. The duration of the eruption varies from 30 minutes to several hours; after an episode, a refractory period of about 24 hours ensues. A subset of patients with cholinergic urticaria have hypohidrosis or anhidrosis.<sup>50</sup>

Acetylcholine is thought to participate in the pathomechanism of wheal formation, but immediate type skin responses to one's own sweat, and less commonly, positive ASSTs have been described. Patients who react to their own sweat usually show nonfollicular wheals with satellites, whereas those individuals with cholinergic urticaria and positive ASST testing show a follicular-based process without satellite wheals. Once cholinergic urticaria occurs, the condition may recur for periods of months to years and then tends toward spontaneous improvement and resolution. Treatment consists of systemic antihistamines, particularly cyproheptadine, hydroxyzine, and nonsedating antihistamines such as cetirizine; awareness of potential precipitating factors; and avoidance of heat, excessive exertion, and excitement whenever possible. Another option is the use of oral anticholinergic medications to decrease sweating.<sup>51</sup>

Aquagenic urticaria, a disorder that resembles cholinergic urticaria, occurs most often in adolescence and is characterized by small, intensely pruritic, perifollicular papular wheals with surrounding erythema (Fig. 20-11). The palms and soles are spared. The disorder is precipitated by contact with water or perspiration (irrespective of temperature). Exercise and other cholinergic factors do not precipitate this disorder. Patients can drink water without adverse reaction. Antihistamines often improve reactivity, but do not totally suppress it.

Cold urticaria accounts for approximately 3% of chronic urticaria and has been documented in infants as young as 6 months. It is characterized by localized or generalized urticaria, sometimes with angioedema or anaphylaxis, that develops within a few minutes or hours after exposure to cold air or water, often upon rewarming. The urticaria may be confined to the area of skin in contact with cold (in milder cases) but may be generalized. In highly sensitive individuals, it may be associated with respiratory or cardiovascular compromise, especially with water immersion. The result is hypotension and on occasion, syncope, loss of consciousness, and drowning.<sup>52</sup> Respiratory signs such as nasal stuffiness, cough, and dyspnea, and oral or gastrointestinal symptoms such as swelling of the lips, swelling of the oral mucous membranes, dysphagia, and abdominal cramps may occur. Patients who experience oropharyngeal reactions to cool liquids or

## Physical Urticarias

The physical urticarias are a group of disorders in which wheals occur in response to various physical stimuli.<sup>46</sup> These include dermatographism and pressure, cholinergic, aquagenic, solar (see Chapter 19), and cold urticaria. Dermographism and cholinergic urticaria are quite common; cold urticaria is less common; and other patterns of physical urticaria are relatively rare.

Dermographism (dermatographism) is manifested by a sharply localized edematous or wheal reaction with a surrounding zone of erythema that occurs precisely at the site and within seconds of firm stroking of the skin (Fig. 20-9). The wheal tends to be maximal in size and intensity at about 6 minutes after onset and persists for approximately 15 minutes. This common phenomenon, known as the *triple response of Lewis*, is often seen in infants, occurs in about 50% of children, and is noted in only about 1% of adolescents or adults.

Pressure urticaria is a variant of dermatographism characterized by the development of hives or a deeper swelling simulating angioedema after local pressure such as from clothing or jewelry, or weight bearing.<sup>47</sup> The reaction is often painful rather than pruritic and may occur immediately after the pressure or more commonly, after a 4- to 6-hour delay ("delayed pressure urticaria").<sup>47</sup> Because of this delay in appearance, patients often fail to appreciate the cause of the disorder. The palms and soles are most commonly involved. Patients respond poorly to antihistamine therapy; some patients have responded to the leukotriene antagonist, montelukast.<sup>48</sup>



**Figure 20-11** Aquagenic urticaria. Small, intensely pruritic, perifollicular papular wheals with surrounding erythema that occur after contact with water or perspiration, regardless of temperature.

foods (especially lip swelling) are at increased risk for the development of systemic reactions.

Cold urticaria in children and adolescents is usually acquired, occurs more often in girls, and often appears suddenly. Anaphylaxis has been described in up to 30% at presentation.<sup>53</sup> Once symptoms develop, they are generally short-lived and recurrences usually disappear after a few months or years. Secondary forms of cold urticaria may also be associated with cold hemolysin and cold agglutinin syndromes. These forms, generally seen in adults, cause Raynaud phenomenon, acrocyanosis, and cutaneous ulcers. Some cases of cold urticaria manifested by itching, erythema, purpura, atypical Raynaud phenomenon, and ulceration are the result of cryoglobulins (see Chapter 21).

Cold urticaria can rarely be a manifestation of familial cold autoinflammatory syndrome (FCAS), an autosomal dominant disorder resulting from mutations in *CIAS1/NLRP3* (see Chapter 25). It is characterized by an urticarial or papular eruption, fever, chills, arthralgia, and sometimes headache, malaise, muscle tenderness, and significant leukocytosis. Patients more commonly complain of burning or stinging than of pruritus. Although the tendency to familial cold urticaria generally persists for life, the severity may decrease with advancing age. It generally develops after a latent period of several hours, and once it develops, it may persist for up to 48 hours. Familial atypical cold urticaria (FACU) is an autosomal dominant disorder with onset during childhood in which the urticaria and/or angioedema develop shortly after cold exposure (not delayed). Cold-stimulation testing is negative (no wheal), and in contrast with FCAS, patients do not have fever, chills or joint complaints.<sup>54</sup> Phospholipase C, gamma 2 (PLCG2)-associated antibody deficiency and immune dysregulation (PLAID) is a newly characterized autosomal dominant immunodeficiency syndrome associated with evaporative cold urticaria.<sup>55,56</sup> The cold urticaria presents within the first year in all patients and is characterized as pruritic blotchy macules but not true wheals; ice cube testing is negative. Patients may develop ulcerative lesions of the nasal tip, and occasionally fingers and toes, during the neonatal period that heals by infancy. They have a tendency to develop granulomatous dermatitis, which may be widespread.<sup>56</sup> Recurrent sinopulmonary infections, common variable immunodeficiency (CVID), and autoantibodies (especially antinuclear and anti-thyroid antibodies) are commonly associated.

The diagnosis of cold urticaria requires a careful history and investigation for other possible etiologic factors. The diagnosis may be confirmed by reproducing signs through local application of an ice cube for periods of 2 to 10 minutes with observation after removal for at least 10 minutes. The best areas for this testing are the face, neck, and particularly the arms (Fig. 20-12). Some patients fail to respond to ice but do respond to cold water or generalized cooling of the body. Critical temperature threshold testing shows an inverse relationship with disease severity and activity, which can be helpful for assessing both the severity and the impact of therapy.<sup>57</sup> Cold urticaria should be distinguished from cold-induced cholinergic urticaria, in which



**Figure 20-12** Cold urticaria. Application of an ice pack to an extremity for 2 to 10 minutes can induce a wheal.

cholinergic urticaria occurs while exercising in the cold and is not induced by ice cube testing. Immediate ice cube tests also tend to be negative with FCAS, FACU, and PLAID syndromes.

Underlying disorders are rare in children. Cryoglobulinemia, cryofibrinogenemia, and cold agglutinins have all been reported, particularly in adults, and can reflect an underlying diagnosis of essential mixed cryoglobulinemia, hepatitis, autoimmune disease, or lymphoma. Cold urticaria can also be associated with infectious disorders (toxoplasmosis, Epstein–Barr virus [EBV], *H. pylori*, hepatitis C, and human immunodeficiency virus [HIV]) and autoimmune disease (particularly lupus erythematosus or celiac disease).

Patients with cold urticaria, and particularly with severe or widespread urticarial reactions, should carry epinephrine and be forewarned of the risk of drowning after loss of consciousness when swimming or bathing in cold water. The treatment of cold urticaria is aided by oral administration of antihistamines, particularly nonsedating H1 blockers, although the sedating antihistamine cyproheptadine is also particularly helpful for cold urticaria, and leukotriene receptor antagonists have been used adjunctively. Increases in doses of nonsedating antihistamine to four times the standard dosages have shown additional benefit (vs. standard dosing) without increased adverse events.<sup>58</sup> For those patients who are unresponsive to systemic antihistamines and have increased levels of IgE, treatment with omalizumab may be helpful.<sup>59</sup> Desensitization to cold is an alternative that is now rarely performed; an extremity is gradually cooled in cold water for 5 to 10 minutes per day with a gradual increase in the time of exposure and decrease of the temperature over a period of weeks or months. This treatment is not regularly effective and must be done cautiously in an effort to minimize the risk of systemic reaction. Patients with cold urticaria as a manifestation of an autoinflammatory syndrome often require interleukin (IL)-1 blockers (e.g., anakinra) for response.<sup>60,61</sup>

## Anaphylaxis

Anaphylaxis is a life-threatening, immediate hypersensitivity reaction to the administration of an antigen that has previously produced a specific sensitization. It is characterized within minutes to 1 hour after injection or ingestion of antigen by pruritus of the palms, soles, and scalp, urticaria, and/or angioedema with systemic signs (weakness, dyspnea, hypotension, and circulatory collapse). Mucosal involvement of the airway leads to acute respiratory distress, and swelling of the gastrointestinal mucosa can result in abdominal pain, vomiting, or diarrhea. The incidence in children and adolescents is 10.5 episodes per 100,000 person-years, and most children have a personal history of atopy. Anaphylaxis can occur during infancy,<sup>62</sup> although the risk peaks during early childhood and decreases thereafter.<sup>63</sup> A biphasic reaction may occur, with recurrence usually within 8 hours of the initial episode. Anaphylactic reactions most often occur after ingestion of foods,<sup>64</sup> especially peanuts, cow's milk, and hen's eggs in children

(vs. wheat and shellfish in adults), or in response to drugs or insect venom.<sup>55,66</sup> Anaphylactic reactions to latex and peanuts are particularly troublesome, because they are so ubiquitous in the environment. Having asthma as well as IgE-mediated food allergy increases the risk of developing food-induced anaphylaxis. Exercise-induced anaphylaxis may also occur and is commonly food-dependent. Two subtypes have been described: nonspecific food-dependent exercise-induced anaphylaxis, in which filling the stomach before exercise is responsible, regardless of the kind of food ingested, and specific food-dependent exercise-induced anaphylaxis, an IgE-mediated food allergy in which anaphylaxis only occurs in combination with exercise. Several types of foods have been described to trigger exercise-induced anaphylaxis, but wheat appears to be most common.<sup>67</sup>

## LATEX ALLERGY

Latex allergy is a reaction to a peptide in natural rubber and occurs most commonly in children with spina bifida, presumably owing to the frequent exposure to catheters and latex gloves.<sup>68</sup> The use of latex-free or latex-safe equipment has markedly lowered the risk to children with spina bifida.<sup>69</sup> Atopic children also show an increased risk of latex allergy,<sup>70</sup> with up to 4% showing prick test reactivity.<sup>71</sup> Type I hypersensitivity reactions to latex may range from contact urticaria to life-threatening anaphylaxis. Severe anaphylactic shock without cutaneous erythema or urticaria has been described.<sup>72</sup> Type I reactions to latex differ from the type IV contact dermatitis reaction to antigens in rubber products (see Chapter 3). Children with type I hypersensitivity reactions often experience lip swelling after sucking on a pacifier or blowing up a balloon (Table 20-2). Aerosolized powder from latex gloves and inhalation may lead to runny nose, sneezing, itchy, swollen eyes, and wheezing in susceptible individuals. Approximately half of persons who react to latex show reactivity to certain foods, resulting in oral mucosal pruritus, urticaria, and wheezing; bananas, kiwis, avocados, and chestnuts contain proteins that cross-react with latex and are most commonly associated.<sup>73</sup>

Skin prick testing is most likely to yield positive responses to either latex or cross-reacting foods. Serum latex-specific IgE by Immuno CAP can also be used to detect type I reactivity to latex, but the high rate of false positives should be taken into account when making a diagnosis of latex allergy in patients with pollen allergy (30%), especially in those sensitized to more than one pollen species.<sup>74</sup> Avoidance of latex and related triggers is critical, and nonlatex substitutes such as Mylar balloons and vinyl or neoprene gloves are generally available. Desensitization is the only effective way to resolve latex allergy; percutaneous and sublingual approaches appear to be safer than subcutaneous administration.<sup>75</sup>

## NUT ALLERGY

Nut-induced anaphylaxis is a risk in the 1.1% of individuals who are allergic to peanuts and tree nuts<sup>76,77</sup> and has resulted in 50 to 100 deaths annually in the United States. Screening tests such as prick tests and radioallergosorbent tests (RASTs) are suggestive, but only food challenge confirms reactivity. Avoidance of peanuts is extremely difficult, and there has been no means to protect against accidental ingestion, which often occurs despite reassurance from servers.<sup>78</sup> Allergic reactions through kissing are well documented, particularly in adolescents.<sup>79</sup> In one study, 13% of subjects still had detectable levels of peanut 1 hour after ingestion of two tablespoons of peanut butter on a sandwich.<sup>80</sup> Although prenatal and postnatal avoidance of peanuts has been encouraged for at-risk individuals in the past, new data suggests that exposure to small amounts can lead to tolerance.<sup>81,82</sup> In a landmark trial of 500 infants at risk for peanut allergy, infants who avoided peanuts had a much higher risk of developing allergy than those who were given small numbers of peanuts regularly, regardless of whether they were sensitized to peanuts at baseline.<sup>82</sup> These data have led to the suggestion that 4- to 8-month-old infants at risk for peanut allergy with negative prick testing for peanuts or mildly positive prick testing and a nonreactive peanut challenge should be administered 2 g peanut protein three times weekly for at least 3 years.<sup>83</sup>

Omalizumab substantially increases the threshold of sensitivity to peanuts and may protect against unintended ingestion.<sup>84</sup> Oral immunotherapy with gradual increases in exposure to peanuts can decrease basophil activation, titrated skin prick tests, and peanut-specific IgE levels within 6 months.<sup>85</sup>

The treatment of anaphylaxis consists of the intravenous administration of antihistamines such as diphenhydramine (1.25 mg/kg), subcutaneous epinephrine (the adult dose AutoInjector contains 0.3 mg of epinephrine as 0.3 mL of epinephrine 1:1000, and the pediatric dose AutoInjector contains 0.15 mg of epinephrine as 0.3 mL of epinephrine 1:2000) for grade 2 anaphylaxis or higher,<sup>86</sup> and sometimes intravenous corticosteroid.<sup>87,88</sup> Epinephrine is the only medication shown to be life-saving when administered promptly, but it is underutilized.<sup>89</sup> Patients should have easy access to at least 2 doses of an epinephrine AutoInjector, with thorough training regarding correct use of a given device and an emergency action plan. In addition to EpiPen, Auvi-Q is a new AutoInjector available for children (and adults) that provides audio and visual cues regarding patient use and was found favorable to the traditional AutoInjector for method of instruction, preference to carry, and device size.<sup>90</sup>

Because of the delay before onset of effectiveness, oral medications are not indicated. If hypotension is present, intravenous fluids should be initiated to permit the rapid administration of plasma volume expanders, fluids, and electrolytes. Once shock is overcome and oral fluids are well tolerated, oral corticosteroids may be initiated. Anyone at risk for anaphylaxis should wear a medic alert bracelet and carry epinephrine in case of emergency. Management of anaphylaxis in schools has recently received attention, especially because of its distinct challenges and the need to be able to urgently administer epinephrine.

## Angioedema

The term *angioedema* (also called *giant urticaria* or *Quincke edema*) describes swelling of the eyelids, hands, feet, genitalia, the lips, tongue, airway, and gastrointestinal tract.<sup>91</sup> When it occurs in association with wheals, angioedema is a feature of urticaria. Fifty percent of patients with angioedema also show urticaria, and 10% of infants and children with urticaria show at least mild angioedema. Angioedema may be a component of anaphylactic reactions.

Angioedema without wheals has been recently classified by the European Academy of Allergy and Clinical Immunology into four acquired and three hereditary forms.<sup>92</sup> Angioedema is defined as hereditary when: (1) there is family history of angioedema in a first- or second-degree relative; (2) there is a mutation in *SERPING1* (encoding C1 inhibitor [C1-INH]) or *FXII* (encoding factor XII, a coagulation factor); and (3) there is a familial deficiency of C1-INH. Although

**Table 20-2 Examples of Latex Products in Household and Medical Use**

Household	Medical
Balloons	Adhesive tape
Balls (basketball, Koosh, squash, tennis)	Bandages
Cell phone cases	Blood pressure cuffs
Computer mouse pads	Bulb syringes
Condoms	Catheters
Disposable diapers/rubber pants	Dental devices
Erasers	Electrode pads
Gloves for dishwashing	Face masks and their straps
Pacifiers, nipples	Gloves
Rubber bands	Injection ports
Rubber cement	Rubber syringe stoppers
Rubber raincoats and rubber boots	Stethoscope tubing
Shoe soles	Tourniquets
Socks with elastic	Vial stoppers
Sports equipment	Wound drains
Swimming masks and goggles	
Toys	
Underwear	

factor XII deficiency is more uncommon than C1-INH-hereditary angioneurotic edema (HAE), the clinical features of deficiency of C1-INH and deficiency of factor XII are similar,<sup>93</sup> and laboratory testing is required to distinguish these autosomal dominant disorders. Two of the three acquired forms (induced by angiotensin-converting enzyme inhibitors and a nongenetic form of C1-INH deficiency) usually occur in adults. Most cases of idiopathic acquired angioedema are histamine-responsive (histaminergic; termed *idiopathic histaminergic acquired angioedema [IHA-AAE]*), and medications (especially aspirin and NSAIDs), allergens, and physical agents have been implicated.

## C1 Inhibitor-Hereditary Angioneurotic Edema

Hereditary angioneurotic edema (HAE; hereditary angioedema) is characterized by recurrent episodes of edema of the subcutaneous tissue, particularly the hands, feet, and face, and of the gastrointestinal and/or upper respiratory tracts. Occurring in approximately 1 in 50,000 to 1 in 10,000 persons,<sup>94</sup> the defect results from a deficiency (85% of patients; type I) or dysfunction (15% of patients, type II) of the inhibitor of the first component of complement [C1-INH]. Deficiency or dysfunction of C1-INH leads to transient episodes of increased vascular permeability with increased cleavage of C4 by C1, depleting C4 levels. The major factor responsible for edema formation is now known to be bradykinin, which can induce leakage of postcapillary venules. Bradykinin is produced when high molecular-weight kininogen is cleaved by plasma kallikrein, the activity of which is controlled by C1-INH. HAE without urticaria and with no dysfunction or deficiency of C1-INH has been described.<sup>95</sup>

The earliest symptoms of HAE often begin in infancy or early childhood, with 50% of cases manifesting before the age of 10 years. The frequency and severity of attacks are typically exacerbated during adolescence and subside in the fifth decade. Onset during the first decade is associated with greater severity.<sup>96</sup> Based on survey data, prodromes have been described in 82.5% to 95.7% of patients surveyed, most commonly involving the skin or gastrointestinal tract and hours to days before the onset of angioedema; fewer than 10% reported were rarely or never able to predict an attack.<sup>97</sup> Affected individuals are prone to sudden attacks of circumscribed subcutaneous edema (angioedema) without associated urticaria. It usually affects the face or an extremity and may be severe enough to cause remarkable disfigurement of the affected parts. Areas of swelling may migrate, but the condition generally subsides within 24 to 72 hours. Several weeks of remission generally follow attacks. The skin and mucosal lesions may appear spontaneously or may be precipitated by minor trauma, especially dental work or surgery,<sup>98</sup> strenuous exercise, infection (especially of the airway), menses, pregnancy, administration of oral contraceptives or angiotensin-converting enzyme inhibitors, extremes of temperature, or emotional disturbances. There is no pitting, discoloration, redness, pain, or itching associated with the edema. However, many affected children show a nonpruritic serpiginous rash that resembles erythema marginatum.<sup>99</sup>

Gastrointestinal involvement is the presenting sign in 40% to 80% of affected children.<sup>100</sup> The recurrent colic and severe abdominal pain can simulate the acute abdominal pain of appendicitis. Nausea, vomiting, and diarrhea are additional complaints. Abdominal ultrasound may demonstrate edematous swelling of the intestinal wall and free peritoneal fluid. Involvement of the mucous membranes of the hypopharynx and larynx, although seen less often, may be particularly devastating; up to 25% of patients experience asphyxia, which is the leading cause of death and usually occurs during the third decade of life.

Diagnosis of HAE can be confirmed by the finding (at least twice and separated by 1 to 3 months) of reduced levels of C4 or C1-INH (quantitative and/or functional), or both. For those with C1-INH deficiency, levels tend to be 10% to 40% of normal, reflecting the haploinsufficiency. Of note, C4 and C1-INH levels do not tend to reach adult levels until about 3 years of age, necessitating genetic testing in infants. If levels of C4 are reduced in the presence of normal levels of C1-INH

protein, confirmation must rely on demonstration of a functional lack of C1-INH by chromogenic or immunoenzymatic assay.

Antihistamines and corticosteroids have not been effective in the management of patients. Epinephrine is beneficial in the control of swelling in only a very few patients. Tracheostomy commonly is life-saving in patients with laryngeal obstruction, but plasma-derived human C1-INH concentrate is available for treatment of acute episodes.<sup>101–103</sup> The median time to onset of relief in one pediatric study was 25 minutes and to complete resolution was 8 hours.<sup>103</sup> The US Hereditary Angioedema Association and others have proposed recommendations for comprehensive care of patients with HAE.<sup>104,105</sup> Recombinant C1-INH from transgenic rabbits has recently been approved for use in acute attacks.<sup>106</sup> Ecallantide,<sup>107</sup> a specific inhibitor of plasma kallikrein, and icatibant,<sup>108</sup> an inhibitor of the bradykinin receptor B2, are both used for acute attacks, but they have short half-lives and are not appropriate for prophylaxis.

In general, attacks tend to be less frequent and less severe in children, and most will not require long-term prophylaxis. However, prophylactic C1-INH administration with dosage escalation may be considered for children with more than two attacks per month, the need for acute treatment more than once annually, or more than one episode of severe abdominal pain in a year.<sup>109,110</sup> When used prophylactically, the concentrate reduced the median monthly attack rate by almost eightfold.<sup>101</sup> Antifibrinolytics (ε-aminocaproic acid and tranexamic acid) are less efficacious than other approaches and are now rarely used for prophylaxis. Attenuated androgens such as danazol are only appropriate for short-term prophylactic therapy, such as before dental procedures, because of their potential side effects.

As prevention, children and adolescents with HAE should not participate in contact sports, and toddlers should not attend daycare before kindergarten to minimize the risk of infection that could trigger attacks. Even the eruption of teeth and minor mechanical trauma can induce edema formation. If menstruation worsens HAE symptoms, long-term prophylactic doses can be increased, but oral contraceptives are triggers of the angioedema and should be avoided. Although use of angiotensin-converting enzyme inhibitor is unusual in children, these medications can exacerbate the signs of angioedema in affected individuals and should be avoided.<sup>111</sup>

## Scombroid and Ciguatera Fish Poisoning

Scombroid fish poisoning (scombrotoxicism) is a clinical syndrome that results from the ingestion of spoiled fish of the Scombroidea family (tuna, mackerel, and bonito) and fish such as bluefish, mahi-mahi, amberjack, herring, sardines, and anchovies.<sup>112,113</sup> The disorder, thought to be related to high levels of histamine and sarcine produced when these fish are improperly refrigerated, is characterized by pruritus, a diffuse erythema of the face and upper body,<sup>114</sup> somewhat resembling a sunburn and at times, giant hive-like lesions that develop within minutes to hours after ingestion of the toxic fish. Bacteria in the fish express a decarboxylase that converts histidine to histamine, which resists cooking and freezing. Symptoms resemble a histamine reaction and commonly include a hot, burning sensation rather than pruritus. The conjunctivae are often markedly injected, and many patients have a severe throbbing headache, tachycardia, palpitations, nausea, vomiting, abdominal cramps, diarrhea, dryness and a burning sensation or peppery taste in the mouth, urticaria, angioneurotic edema, oral blistering, hypotension, blurred vision, and asthma-like symptoms. Although superficially resembling an allergic reaction, patients with scombroid fish poisoning can be reassured that they do not have fish allergy and that scombroidosis will not occur when fish are handled properly. Symptoms are generally self-limiting and even if untreated tend to resolve within 8 to 10 hours. Treatment is supportive, and most patients treated with oral antihistamines become asymptomatic within 2 or 3 hours.

In contrast to scombroid fish poisoning, ciguatera fish poisoning is a common disorder endemic throughout the Caribbean and Indo-Pacific islands but has been reported in the United States. It is caused by the ingestion of ciguatoxin,<sup>115</sup> which originates from a dinoflagellate (*Gambierdiscus toxicus*). Present in certain fish such as the red snapper, amberjack, and sturgeon, ingestion of affected fish (whether

cooked, raw, or frozen) may result in this disorder. Clinical symptoms, which usually appear within 12 hours but sometimes within minutes after ingestion of ciguatoxin, include abdominal pain, cramping, diarrhea, nausea, vomiting, paresthesias, pain or burning when cold water is touched, arthralgia, myalgia, and in severe cases, hypotension, shock, respiratory depression, paralysis, coma, and death. The duration of illness averages 8.5 days but may be prolonged. Treatment consists of supportive measures, and intravenous mannitol has been found to be extremely effective, lessening the neurologic and muscular dysfunction of affected patients within minutes of administration.<sup>115</sup>

## Serum Sickness and Serum Sickness-Like Reactions

Serum sickness is an allergic reaction characterized by a cutaneous eruption (morbilliform, urticarial, or purpuric),<sup>116,117</sup> malaise, fever, lymphadenopathy, splenomegaly, proteinuria, and arthralgias.<sup>118</sup> The syndrome, originally noted and most commonly seen after the administration of antiserum of horse or rabbit origin, is now rarely encountered. However, serum sickness-like reactions (SSLRs) occasionally occur in children, especially 1 to 3 weeks after exposure to cefaclor, which has been described in approximately 0.2% of treated children.<sup>119,120</sup> Penicillins (especially amoxicillin),<sup>121</sup> tetracyclines,<sup>122</sup> cefprozil, sulfonamides, macrolides,<sup>123</sup> ciprofloxacin, rifampin,<sup>124</sup> griseofulvin,<sup>125</sup> itraconazole, fluoxetine, bupropion,<sup>126</sup> rituximab,<sup>127,128</sup> and the H1N1 influenza vaccine<sup>129</sup> have also been implicated as triggers of SSLR.<sup>3</sup> SSLR more closely resembles urticaria (or urticaria multiforme) than true serum sickness (Figs. 20-13 and 20-14), and lesions commonly show large areas of lilac or violaceous discoloration, especially centrally (Fig. 20-15). This classic observation has led to use of the term *purple urticaria* to describe the skin lesions seen in SSLR. Noncutaneous features most commonly include fever, malaise, lymphadenopathy, and arthralgias with periarticular swelling, particularly symmetrically involving the knees and metacarpophalangeal joints (Fig. 20-16). True arthritis is uncommon and seen significantly less often than in patients with true serum sickness. Affected children may also demonstrate facial edema, eosinophilia, headache, myalgia, and gastrointestinal symptoms, but renal and neurologic disease is rarely associated. Histologic evaluation of biopsy section may reveal vasculitis associated with cutaneous deposition of immune complexes, but hypocomplementemia and circulating immune complexes, as seen in true serum sickness, are absent.

SSLR generally is a self-limiting disease that subsides within 2 to 3 weeks after discontinuation of the causative agent. In the case of cefaclor, biotransformation of the parent drug, genetic defects in metabolism of reactive intermediates, and increased *in vitro* lymphocyte cytotoxicity have been thought to participate.<sup>130</sup> SSLR has been described as well in association with other drugs,<sup>118</sup> infection with



**Figure 20-13** Serum sickness-like reaction. Urticarial wheals occurred 2 weeks after exposure to cefaclor.



**Figure 20-14** Serum sickness-like reaction. Serpiginous and annular lesions that persisted more than 24 hours in a reaction to amoxicillin.



**Figure 20-15** Serum sickness-like reaction (SSLR). Note the central lilac discoloration, similar to that of erythema multiforme and typical of SSLR. This girl developed the reaction after 10 days of amoxicillin.



**Figure 20-16** Serum sickness-like reaction (SSLR). Note the swollen hand and large urticarial wheals in this girl with SSLR and arthralgias.

hepatitis B or C, and immunization against hepatitis B, rabies, and tetanus toxoid. Treatment with antihistamines, NSAIDs, and if severe, a short course of systemic corticosteroids helps to alleviate symptoms. In general, the risk of cross-reaction among  $\beta$ -lactam antibiotics is low, and patients who have reacted to cefaclor or cefprozil will usually tolerate other cephalosporins.

## Exanthematous Eruptions

The most common drug eruptions are morbilliform or exanthematous eruptions, characterized by erythematous macules and/or papules (Figs. 20-17 and 20-18). The risk of this type of eruption is increased by viral infection, such as the near 100% incidence of an exanthematous reaction in patients taking penicillin who have EBV infection, or the increased risk of drug reactions in patients taking sulfonamides who have human immunodeficiency virus (HIV) infection.

Most commonly, an exanthematous eruption begins 7 to 14 days after initiation of a new medication and sometimes after drug discontinuation. If an individual is rechallenged after an initial course of taking a medication, the reaction may develop within a few days. Most commonly, the eruption is symmetric and begins initially on the trunk before becoming generalized. Mucous membranes are usually spared, but palms and soles are often involved. Patients may experience varying degrees of associated pruritus and some have low-grade fever. Not uncommonly the eruption turns more of a brownish-red color in 7 to 14 days and may desquamate.

Penicillins, sulfonamides, cephalosporins, and antiepileptics are the most likely categories of drugs to cause exanthematous reactions. Viral exanthems tend to be indistinguishable from exanthematous drug eruptions and more commonly occur in pediatric patients. Eosinophilia favors a diagnosis of drug reaction; biopsy is generally not helpful. More severe drug reactions may be heralded by facial edema or marked eosinophilia, as in systemic hypersensitivity syndrome, or by mucous membrane lesions and dusky skin, as in SJS or toxic epidermal necrolysis.

Treatment is largely supportive. The decision to discontinue a drug must be made based on the need for continuing the medication. Many patients will show clearance of the eruption despite continuation of medication (for example, when an infant with otitis is treated with amoxicillin). However, patients may show progression to erythroderma. Desensitization has been used for reactions to sulfonamides in patients with HIV infection.

## Drug Reaction with Eosinophilia and Systemic Symptoms

This reaction, which is also called *drug hypersensitivity syndrome* (DHS), presents as an exanthematous drug reaction in association



**Figure 20-17** Exanthematous drug reaction. (A) and (B) Erythematous papules in an infant administered amoxicillin for otitis media. Given the distribution, a viral exanthema (Gianotti-Crosti) would also be considered.

with fever, facial swelling, conjunctivitis, and often internal organ involvement that leads to mortality in 10% of patients.<sup>131,132</sup> The clinical manifestations of DRESS syndrome typically begin 1 to 6 weeks after initiation of a responsible medication.

Fever and malaise often appear first and may be seen in association with cervical lymphadenopathy and pharyngitis. The cutaneous eruption occurs in approximately 75% of patients. It often starts on the face with edema, especially periorbital, then erythema and pruritus (Fig. 20-19). The erythema then spreads caudally. The exanthematous eruption raises concern about SJS or TEN; the lack of mucosal involvement in DRESS can be a useful distinguishing feature.

Of visceral sites of involvement, the liver is most common (about 50%), and the hepatitis may be fulminant, leading to death. Lymphadenopathy is often seen, and patients may complain of joint pain. Inflammation of the kidney, central nervous system, heart, and lungs has often been described. Thyroiditis occurs in a subset of patients and may not be noted until 2 to 3 months after onset. Atypical lymphocytosis and eosinophilia are seen in most affected individuals early in the course.

DRESS is most commonly caused by trimethoprim-sulfamethoxazole and the aromatic anticonvulsant agents, although viral infection has also been linked to DRESS. Sulfonamides are metabolized by acetylation to a nontoxic metabolite for renal excretion; slow acetylation has been associated with an increased risk of developing DRESS. Only aromatic amine forms of sulfonamides require this



**Figure 20-18** Exanthematous drug reaction. Confluence of erythematous macules from administration of cefdinir.



**Figure 20-19** Drug reaction with eosinophilia and systemic symptoms (DRESS). Three weeks after initiation of carbamazepine, this boy developed facial edema with dusky erythematous papules. The pruritic eruption subsequently spread caudally. Hepatic transaminase levels were noted to be significantly increased.

mechanism (e.g., these reactions do not occur with sulfonylureas and furosemide). Aromatic antiepileptics are metabolized by the cytochrome P450 system, and hereditary alterations in metabolism may lead to the accumulation of toxic arene oxide metabolites. Because these medications cross-react, affected individuals should avoid phenobarbital, phenytoin, carbamazepine, oxcarbazepine and lamotrigine.<sup>133</sup> Alternative antiepileptics include valproic acid, benzodiazepines, gabapentin, zonisamide, topiramate, levetiracetam, and vigabatrin. Other drugs that less commonly cause this syndrome are minocycline, amoxicillin, dapson, vancomycin,<sup>134</sup> abacavir, nevirapine,<sup>135</sup> aspirin,<sup>136</sup> allopurinol, azithromycin,<sup>137</sup> and traditional Chinese medicine.<sup>138</sup> Reactions to doxycycline have not been described in

patients who develop DRESS in response to minocycline. Clinical signs may vary dependent on causative drug. For example, lamotrigine rarely causes eosinophilia, abacavir leads to primarily respiratory and gastrointestinal manifestations without eosinophilia or hepatitis, and allopurinol reactions often involve the kidney.<sup>6,139</sup>

The eruption of DRESS syndrome persists for weeks to months after medication withdrawal. After an initial period of improvement, the cutaneous and visceral manifestations of DRESS may flare 3 to 4 weeks after onset. Lymphocyte transformation tests may be useful in confirming the triggering medication but should be performed 5 to 8 weeks after onset in patients with DRESS.<sup>140</sup> Challenge with the offending drug after initial reaction leads to reactivation of the fever and erythroderma within hours after initiation.

A role for concurrent herpes family viral infections has been emphasized in adult DRESS, particularly with reactivation of EBV and human herpesvirus (HHV) 6.<sup>141,142</sup> A recent pediatric study found concomitant evidence of HHV6 infection in 50% of the children, and in association with greater pulmonary involvement (50%) and longer duration of fever and hospital stay.<sup>132</sup>

Patients with suspected DRESS should have a variety of laboratory tests to consider visceral involvement. These include complete blood count, hepatic transaminases, serum creatinine level, urinalysis, and thyroid testing (which should be repeated after 2 to 3 months). Although topical corticosteroids and antihistamines may quell the pruritus in mild cases, patients with visceral involvement (especially for hepatitis, myocarditis, and interstitial pneumonitis) should be treated with systemic corticosteroids (1 to 2 mg/kg per day) for a few weeks, with gradual taper thereafter. Systemic corticosteroid treatment tends to shorten the hospital stay and reduce febrile days.<sup>132</sup> Anecdotal cases of successful treatment of DRESS with IVIG have been described.<sup>143</sup> Counseling of family members is important, because first-degree relatives of individuals with DRESS have a higher risk of developing these drug reactions.

## Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are now considered to be variants of the same hypersensitivity disorder.<sup>144,145</sup> The incidence of these conditions is 1 to 3 per million persons per year, although in patients with HIV infection the incidence is 1 per 1000 persons per year.<sup>146</sup> In a study of 708 patients, approximately 18% were children.<sup>147</sup> Classification has been based on the degree of epidermal detachment. Epidermal detachment of less than 10% of the total body surface area is considered SJS; more than 30%, TEN; and between 10% and 30%, a transitional SJS-TEN overlap condition. In children, SJS is seen more often than TEN or SJS-TEN overlap; in one study, 85% of pediatric cases had SJS, whereas 6% had SJS-TEN overlap and 9% had TEN.<sup>148</sup> Patients may appear to have SJS initially, but it evolves into typical TEN (Table 20-3). At one time, SJS was lumped with EM (see *Erythema Multiforme* section), which is now considered to be a distinct entity, primarily resulting from hypersensitivity to herpes simplex infection. Similarly, TEN was once confused with staphylococcal scalded skin syndrome (SSSS), a more superficial and crusted disorder in which the superficial blistering is caused by an exfoliatin produced by *Staphylococcus aureus* (see Chapter 14).

The underlying triggers of SJS and TEN are similar, although drugs cause the majority of cases overall and almost all cases of TEN (Box 20-2).<sup>149–154</sup> In children, SJS is much less commonly caused by medication than in an adult.<sup>155</sup> Most patients show evidence of SJS or TEN 7 to 21 days after the first drug exposure. Occurrence is almost always within the first 8 weeks of drug use and rarely within the first few days of drug administration. Children with an earlier onset (mean 2 to 3 days) have been previously exposed to the drug or a cross-reacting analogue. Although more than 200 medications have been implicated as potential triggers of SJS-TEN, sulfonamides, penicillins, phenobarbital, carbamazepine, and lamotrigine have been most strongly associated with SJS-TEN.<sup>154</sup> An algorithm for assessing drug causality in epidermal necrolysis (ALDEN) has been proposed and correlates well with case-control analysis results.<sup>156</sup> Patients carrying HLA-B\*15:02,

**Table 20-3** Classification of Stevens–Johnson Syndrome, Toxic Epidermal Necrolysis, and Stevens–Johnson Syndrome–Toxic Epidermal Necrolysis Overlap

	SJS	SJS-TEN	TEN
Lesional morphology	Targetoid lesions, dusky red macules, bullae	Targetoid lesions, dusky red macules, bullae	Targetoid lesions, dusky erythematous macules and plaques; detachment of epidermis
Localization of skin lesions	May be scattered and isolated; may be confluent, especially on the trunk and face	May be scattered and isolated; often confluent	Usually extensive involvement with widespread confluence
Involved skin	<10%	10% to 30%	>30%
Biopsy features	More interface dermatitis	Significant interface dermatitis + necrolysis	Predominantly necrolysis
Mucosal changes	Prominent	Prominent	May be less than in SJS
Systemic involvement	Often present	Always present	Always present

SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

**Box 20-2 Most Common Pharmacologic Triggers of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis**

- Allopurinol
- Barbiturates
- Carbamazepine
- Lamotrigine
- NSAIDs
- Penicillins
- Phenytoin
- Sulfonamides

NSAID, Nonsteroidal anti-inflammatory drug.

which is common in the Asian population, are at strongly increased risk for carbamazepine-induced SJS/TEN, and this population should have human leukocyte antigens (HLAs) screened before initiating antiepileptic drugs.<sup>157,158</sup> Other HLA antigens are being recognized in non-Asian populations.<sup>159</sup> Aromatic antiepileptics (phenobarbital, phenytoin, carbamazepine, lamotrigine) tend to cross-react and cannot be substituted for each other. Drugs with longer half-lives are associated with a higher incidence than those related but with shorter half-lives. NSAIDs, including ibuprofen, and acetaminophen<sup>154</sup> may also be triggers and possibly exacerbants with other drugs, and are best avoided during hospitalization for SJS-TEN.

Mycoplasma infection is the most likely infectious trigger of SJS in pediatric patients<sup>148,149,160</sup> and may be associated with less severe disease than drug-induced SJS.<sup>150</sup> Based on a recent literature review of more than 200 cases of mycoplasma-induced “SJS” and “EM” in children, an alternative diagnosis of “Mycoplasma pneumoniae-induced rash and mucositis” has been suggested for this disorder,<sup>161</sup> distinguished clinically by its prominent mucositis (oral, ocular, urogenital) and usually sparse cutaneous involvement. Other infections,<sup>151,152</sup> neoplasia, autoimmune disorders, and vaccination<sup>153</sup> have also been implicated, particularly herpes simplex virus, which is more typically linked to EM.

SJS and TEN are disorders of keratinocyte death (apoptosis), and granulysin is the main mediator.<sup>159</sup> Micro-ribonucleic acid (miR)-18a-5p, which targets an apoptosis gene (*BCL2L10*), has recently been identified as a serum biomarker that can distinguish early TEN from other drug eruptions.<sup>162</sup> Lymphocyte transformation tests have helped to identify the causative agents in some affected children, but in contrast to those for children with DRESS syndrome, need to be performed during the first week of the disorder.<sup>140</sup> The risk of developing SJS and TEN is significantly increased in patients with HIV infection and who have a decreased capacity to detoxify reactive intermediate drug metabolites (e.g., slow acetylators or individuals with defects in epoxide hydrolase-mediated detoxification).

Older children and adults are most likely to develop this spectrum of disorders, but the condition has been described in young infants



**Figure 20-20** Stevens–Johnson syndrome. Note the bullae on the sole in this girl who reacted to lamotrigine.

and neonates.<sup>163</sup> High fever, pronounced constitutional symptoms, and varying degrees of generalized targetoid lesions, bullae, epidermal detachment, and mucosal erosions (of at least two sites) are characteristic (see Table 20-3).<sup>164–166</sup> Patients not uncommonly show a 1- to 14-day prodromal period before the abrupt eruption of the typical features. During this prodromal period, affected children may show fever, malaise, headache, cough, coryza, sore throat, vomiting, diarrhea, chest pain, myalgia, and arthralgias.

Cutaneous involvement most often appears initially on the face and upper trunk. Palms and soles are commonly involved (Figs. 20-20 and 20-21). Erythematous and purpuric macules may develop flaccid gray discoloration or bullae (Figs. 20-22 and 20-23), become confluent, and sometimes detach, leaving a raw, denuded base (Figs. 20-24 and 20-25). Some of the macular lesions may show a dusky center, which gives a target-like (targetoid) appearance; however, the characteristic concentric rings of EM are absent. Some patients show limited targetoid lesions and little detachment (more typical of SJS), and others show extensive detachment (more typical of TEN). The early morbilliform eruption of TEN may be localized but more often is an extensive, painful erythroderma. After exerting light mechanical pressure with a finger to an area of erythema, the epidermis in patients with either SJS or TEN becomes wrinkled and peels off like wet tissue paper (see Fig. 20-25), the characteristic Nikolsky sign. The Nikolsky sign may be seen in patients without clinical evidence of epidermal detachment and can be a useful diagnostic tool. In addition to SJS and TEN, however, the Nikolsky sign may be seen in a variety of other bullous disorders (especially pemphigus, epidermolysis bullosa [see Chapter 13] and the SSSS [see Chapter 14]). Histopathologic examination of affected skin demonstrates necrosis of the lower epidermal cells with a sparse mononuclear cell infiltrate, and in the case of TEN, extensive



**Figure 20-21** Stevens–Johnson syndrome (SJS). Intensely erythematous macules are nearly confluent the palms of this boy with SJS from carbamazepine.



**Figure 20-22** Toxic epidermal necrolysis. Note the extensive small bullae that later coalesced and led to extensive denudation.



**Figure 20-23** Stevens–Johnson syndrome. Purpuric macules became bullous. Note the inflammation of the conjunctivae and lips.

necrosis with a subepidermal split. The epidermal necrosis correlates with the dusky blue coloration of lesions. The nails become dystrophic because of nailbed inflammation (Fig. 20-26).

Extensive mucosal involvement is more typical of SJS than TEN. The mucosal manifestations of SJS tend to occur 1 to 2 days before



**Figure 20-24** Toxic epidermal necrolysis. Note the discrete bullae on the scrotum sloughing of mucosae at the glans. The sloughed skin resembles wrinkled, wet, tissue paper.



**Figure 20-25** Toxic epidermal necrolysis (TEN). Note the sloughing of skin on the ear, which is exacerbated by gentle stroking of the area (positive Nikolsky sign). The mucosal involvement in this boy originally was typical of Stevens–Johnson syndrome, but he progressed to the extensive denudement of TEN.

cutaneous manifestations. The mucous membranes of the lips, tongue, buccal mucosae, eyes, nose, genitalia, and rectum may show extensive bullae with grayish white membranes, characteristic hemorrhagic crusts, and painful superficial erosions and ulcerations (Figs. 20-27 and 20-28). Uncommonly, the esophageal and respiratory epithelial mucosae are affected. By definition, two or more mucosal surfaces are involved. The oral mucosa is always affected, resulting in inability to drink or eat and leading to a risk of dehydration. Genital area lesions lead to painful micturition and defecation. Although lesions of the oral mucosae tend to heal without scarring, strictures or stenosis of esophageal, vaginal, urethral, and anal mucosae have been described as sequelae.

Severe purulent conjunctivitis with photophobia is the typical ocular manifestation (see Fig. 20-28).<sup>167</sup> Corneal ulcerations, keratitis, uveitis, and panophthalmitis may also occur. Sequelae occur in 40% of patients<sup>168</sup> and may be grave, with a possibility of keratoconjunctivitis sicca, corneal ulceration or neovascularization, trichiasis, symblepharon, and partial or even complete blindness.<sup>169</sup> The severity of



**Figure 20-26** Toxic epidermal necrolysis. Residual nail dystrophy in an adolescent girl who also had widespread postinflammatory hyperpigmentation.

### Box 20-3 Features of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

Constitutional	
Fever	
Dehydration	
Mucocutaneous	
Stomatitis with hemorrhagic crusts	
Oral and genital erosions	
Dysphagia	
Purulent conjunctivitis with photophobia	
Occasionally esophageal and pulmonary mucosal sloughing	
Dusky erythematous macules, targetoid lesions, bullae, and skin sloughing	
Visceral	
Lymphadenopathy	
Hepatosplenomegaly with hepatitis	
Uncommonly: pneumonitis, arthritis, myocarditis, and nephritis	
Laboratory abnormalities	
Increased erythrocyte sedimentation rate (100%)	
Leukocytosis (60%)	
Eosinophilia (20%)	
Anemia (15%)	
Elevated hepatic transaminase levels (15%)	
Leukopenia (10%)	
Proteinuria, microscopic hematuria (5%)	



**Figure 20-27** Stevens–Johnson syndrome. Mucous membrane involvement with severe swelling and hemorrhagic crusting of the lips.



**Figure 20-28** Stevens–Johnson syndrome. This boy shows early ophthalmic involvement with conjunctival injection, eyelid edema, erythema, and exudative crusting.

the acute ophthalmologic manifestations does not correlate with long-term complications. Pulmonary involvement may occur as an extension from the oropharynx and tracheobronchial tree or may be the result of pneumonitis associated with an initiating viral infection or secondary infection. In extreme cases, renal involvement with hematuria, nephritis, and in some cases, progressive renal failure may result. Esophageal or tracheal ulceration, pyoderma, lymphadenopathy, hepatosplenomegaly with elevated transaminase levels, myocarditis, arthritis and arthralgias, and/or septicemia may also complicate the disorder (Box 20-3).

SJS is most often confused with Kawasaki disease. However, the conjunctivitis of Kawasaki disease lacks exudation, and the mucosal erythema and dryness is not associated with hemorrhagic crust and mucosal denudation<sup>170</sup> (see Chapter 21). The targetoid cutaneous lesions of SJS may resemble the target lesions of EM (see **Erythema Multiforme** section), a disorder usually attributed to herpes simplex infection in children; EM may also show blistering of the lip and oral mucosae that resembles SJS, although the blisters of EM are usually fewer and less symptomatic.<sup>171,172</sup> The cutaneous lesions of EM are more often found on the extremities and/or face, whereas the atypical target or purpuric lesions of SJS are more commonly located on the trunk.<sup>172</sup> Children with the rare immunobullous disorder, paraneoplastic pemphigus, may exhibit the mucocutaneous manifestations of SJS or TEN; the presence of epidermal acantholysis in biopsy specimens and the demonstration of antibody deposition in indirect immunofluorescence testing or immunoblot evaluation of serum allows paraneoplastic pemphigus to be distinguished (see Chapter 13). Other immunobullous disorders may also be confused with TEN (see Chapter 13). TEN and SSSS are usually easily distinguished: the blisters of TEN lead to denudement with keratinocyte apoptosis, whereas the desquamation of SSSS is superficial. In SSSS, the staphylococcal exfoliatin targets desmoglein 1, a desmosome component; because desmoglein 3 in the lower epidermis is able to compensate for desmoglein 1, the blistering of SSSS is superficial rather than panepidermal. SSSS also shows a different distribution with periorificial predominance and not mucosal involvement. Features of TEN occur as a severe manifestation of acute graft-versus-host disease, which is otherwise distinguished by history, other clinical findings, and histologic findings (see Chapter 25).

Although mild cases of SJS may show significant improvement within 5 to 15 days, the course of SJS or TEN is often protracted and may last more than a month. Epidermal detachment may be extensive, leading to massive fluid loss similar to that of a patient with burns. Bacterial superinfection with sepsis, impairment of temperature regulation, severe dehydration, electrolyte imbalance, excessive energy expenditure, and alteration in immunologic function are the usual complications. End-organ failure can be severe despite adequate supportive therapy. In adults, the mortality rate of SJS is 5%, transitional SJS-TEN 10% to 15%, and TEN 30% to 35%. Rates in children have been lower. A composite score (SCORTEN) has been used in adults to predict mortality<sup>173</sup> and has recently been shown to be predictive in pediatric patients of mortality, length of hospital stay, and infectious complications, especially when scored on admission.<sup>174</sup>

SJS and TEN are life-threatening disorders, and patients should be hospitalized. If damage to the epidermis is extensive, patients should

be admitted to an intensive care unit or burn unit to allow special attention to fluid requirements, electrolyte balance, intravenous caloric replacement, and avoidance of secondary infection. If possible, all drugs administered within 2 months before onset of the eruption should be discontinued,<sup>175</sup> and infectious causes should be sought and treated. Severe oropharyngeal involvement often necessitates frequent mouthwashes and local application of a topical anesthetic. When ocular involvement is present, ophthalmologic consultation should be obtained. Most recently, short-term use of potent topical corticosteroids and application of amniotic membrane to the entire ocular surface has been advocated to preserve visual acuity and an intact ocular surface.<sup>176–178</sup> Patients should receive intravenous fluids and either a liquid diet, if tolerated, or parenteral nutrition; the measured resting energy requirement in pediatric SJS/TEN is increased by 30%.<sup>179</sup> A mouthwash containing Maalox, elixir of diphenhydramine, and viscous lidocaine (mixed 1:1:1) can be soothing and decrease pain. Oral histamines such as hydroxyzine or diphenhydramine can be beneficial, and more vigorous pain control is often necessary. Of note, TEN has also been associated rarely with acetaminophen ingestion in children.<sup>180</sup>

Manipulation should be avoided, but if necessary, should be performed in a sterile fashion. Intact areas of skin should be kept dry. Open wounds should be cleansed daily. Detached areas should be covered with nonadherent, moist dressings (such as petrolatum-impregnated gauze) until reepithelialization occurs. Periorificial areas can be treated with antibiotic ointment (such as bacitracin or mupirocin). Biologic dressings or skin equivalents may be considered for patients with extensive denudation.<sup>181</sup>

The response to supportive care alone has been excellent in the majority of children.<sup>182</sup> The administration of systemic medications as treatment is controversial, and there is little evidence-based data to support its use, especially in pediatric patients. Short-term administration of intravenous systemic corticosteroids (4 mg/kg per day) or pulsed intravenous steroids is sometimes advocated if started within the first 2 to 3 days of a drug-induced reaction.<sup>183,184</sup> However, several anecdotal reports and open-label, noncomparative trials have not demonstrated efficacy.<sup>185</sup> Continuing use of systemic steroids may increase morbidity and mortality from secondary infection, prolonging wound healing, masking early signs of sepsis, and triggering gastrointestinal bleeding. IVIG has been promoted as treatment of SJS and particularly TEN. Although some children with SJS or TEN have had shorter duration of fever and decreased development of new blisters with early administration (within 24 to 48 hours) of 2.5 to 3 g/kg per day IVIG for 3 days,<sup>186–189</sup> other studies have shown no benefit to the use of IVIG,<sup>190</sup> including for pediatric disease.<sup>191,192</sup> Double-blind, randomized, controlled trials have not been performed. Cyclosporine, cyclophosphamide, and plasmapheresis<sup>193</sup> have also been used anecdotally with good results. Thalidomide administration has been linked to increased mortality in a randomized placebo-controlled trial.<sup>194</sup>

Long-term sequelae occur in 45% of affected children, including cutaneous dyschromia in 42%, which may persist for years.<sup>148</sup> Sun exposure should be avoided and sunscreens used liberally for at least a few months because of the potential for ultraviolet light-induced worsening of the residual dyspigmentation. Persistent nail dystrophy or onychia is also commonly reported (see Fig. 20-26).<sup>169</sup> Late ocular complications include dry eye syndrome (59%), subconjunctival fibrous scarring (33%), corneal erosions (29%), and in fewer than 25%, trichiasis, symblepharon, and visual loss.<sup>195</sup> Artificial tears and lubricants may be required for several years after diagnosis, if not lifelong, because ocular disease tends to progress after hospital discharge. A high rate of recurrence of SJS in children has recently been disclosed, with approximately 20% of children readmitted at least once for recurrent episodes. These episodes occurred between 2 months to 7 years after the index episode and were more often related to drug ingestion than mycoplasma infection.<sup>148,196</sup>

## Fixed Drug Eruption

*Fixed drug eruption* is a term used to describe a sharply localized, circumscribed round or oval dermatitis that characteristically recurs in

the same site or sites each time the offending drug is administered.<sup>197,198</sup> The persistent residual hyperpigmentation leads to the name of the eruption, although occasionally lesions do not become pigmented.<sup>199</sup> In one series, fixed drug eruption was second in incidence to exanthematous reactions to drugs and occurred in 22% of children with cutaneous reactions to drug ingestion.<sup>200</sup> Lesions first occur 1 to 2 weeks after initial ingestion of the drug, but within 30 minutes to 8 hours after subsequent exposures. Fixed drug eruptions are type IV immune reactions and have recently been shown to result from CD8+ memory T cells that persist intraepidermally at site of involvement and, upon stimulation by drug, release interferon (IFN)- $\gamma$ , leading to inflammation. Fas–Fas ligand interactions lead to the demonstrated basal keratinocyte apoptosis.

Lesions are solitary at first, but with repeated attacks, new lesions usually appear and existing lesions may tend to increase in size to more than 10 cm in diameter. Not uncommonly, lesions recur at the same site(s). The lesions tend to be erythematous, edematous, and dusky at their onset with well-defined borders. At times they may become bullous (Fig. 20-29), with subsequent desquamation or crusting and a residual hyperpigmentation that may persist for months (Fig. 20-30). Lesions can occur anywhere on the body but have a predilection for the perioral area, lips, hands, trunk, and genital region.<sup>201,202</sup> In a series of affected boys with genital involvement, the clinical presentation usually consisted of swelling and erythema of the penis and/or scrotum associated with pruritus or burning, restlessness, urinary retention, and painful micturition.<sup>202</sup>

By far the most common trigger of fixed drug eruptions in children is cotrimoxazole and other sulfa drugs. Acetaminophen, ibuprofen,<sup>203</sup>



**Figure 20-29** Fixed drug eruption. Well-defined, dusky erythematous plaques that may be bullous.



**Figure 20-30** Fixed drug eruption. The residual hyperpigmentation at the site of a fixed drug eruption may persist for months.

and less commonly, loratadine<sup>204</sup> and pseudoephedrine have also been causative, and a careful history of administration of over-the-counter products is of key importance. Although phenolphthalein was a common cause in the past, its elimination from over-the-counter laxatives has markedly diminished its culpability. Other causative preparations include phenytoin, ciprofloxacin, metronidazole, penicillin, tetracyclines, erythromycin, teicoplanin,<sup>205</sup> quinine and its derivatives, salicylates, potassium iodide, and metronidazole. Fixed food eruptions have been described after ingestion of various food substitutes and flavorings (especially tartrazine, as in artificially colored cheese crisps),<sup>206</sup> as well as licorice, cashews, lentils, and asparagus.

The diagnosis of fixed drug eruption is often missed, leading to repeated ingestion of the medication and recurrence. Lesions may be mistaken commonly for insect bites, urticaria, and, if more extensive, EM or in their stage of hyperpigmentation for erythema dyschromicum perstans. Biopsy can aid in the diagnosis of fixed drug eruption, especially in the early stage in which a lichenoid infiltrate with necrotic keratinocytes may be seen. Avoidance of the offending agent is key, but the associated pruritus can be controlled by application of medium-strength to potent topical corticosteroids. If necessary, challenge with the drug usually confirms the causative agent within 30 minutes to 8 hours, but theoretically can trigger a more severe reaction. Patch testing at the site of a previous lesion can lead to a positive result in up to 30% of patients.<sup>207</sup>

## Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP) is characterized by the acute onset of a generalized erythroderma topped with small, nonfollicular, sterile, pinpoint pustules, usually in association with fever (Figs. 20-31 and 20-32). The pathogenesis is poorly understood, but some cases have had variants in the gene encoding the IL-36 receptor antagonist (see Deficiency of IL-36 Receptor Antagonist [DITRA] section, Chapter 4).<sup>208</sup> The condition usually resolves spontaneously after 4 to 10 days with a characteristic pattern of desquamation. AGEP has been described in several children,<sup>209,210</sup> although it is much more common in adults. Medication has been the usual trigger in adults and can cause AGEP in children.<sup>211–213</sup> Among triggering agents have been antibiotics (amoxicillin-clavulanate, cephalosporins, macrolides, clindamycin, and terbinafine), paroxetine, and contrast agents. The majority of affected children, however, are administered no medication, suggesting that the condition is often triggered in response to viral infection or possibly vaccine administration.<sup>210</sup> Pustular psoriasis is the key differential diagnosis.



**Figure 20-31** Acute generalized exanthematous pustulosis. Affected individuals show large areas with erythroderma topped with nonfollicular, tiny, sterile pustules, usually in association with fever. Although often triggered by a virus or vaccination in children, this boy was taking an antiepileptic medication.

## Erythema Multiforme

Erythema multiforme (EM) is a specific self-limited hypersensitivity syndrome with a distinctive clinical pattern, the hallmark of which is the erythematous ring (the so-called *iris* or *target* lesion). The condition can occur at any age but is most commonly seen in young adults; 20% of cases occur in children. The majority of cases of EM in children are precipitated by herpes simplex virus (HSV) type 1 infection,<sup>214</sup> although HSV type 2 infection has been described in affected adolescents.<sup>215,216</sup> Approximately 50% of cases follow herpes labialis infection, usually by 3 to 14 days, although concurrent infection and EM have been noted. HSV deoxyribonucleic acid (DNA) has been detected in the early erythematous papules or the peripheral area of target lesions in 80% of patients with EM<sup>215</sup> despite the low recovery of herpes simplex in cultures of lesions.<sup>217</sup> When associated with HSV, the disorder has been termed *herpes-associated EM (HAEM)*. Other viral disorders, including varicella,<sup>218</sup> orf, and EBV infection, have been implicated, and histoplasmosis has been associated in endemic areas. EM in association with high fever can be a sign of Kawasaki disease, especially in infants<sup>219</sup> (see Chapter 21, Fig. 21-31).

The diagnosis of EM can generally be made by the clinical features and distribution of lesions (Box 20-4). The eruption is symmetric and may be noted on any part of the body, with a predilection for the palms and soles (Fig. 20-33), backs of the hands and feet, and extensor surfaces of the arms and legs. Lesions may be grouped, especially at the elbows and knees. As the disorder progresses over 72 hours (and occasionally as long as a week), lesions may extend to the trunk, face, and neck. Once present, lesions are fixed for at least 7 days.

The primary lesion of EM develops abruptly without a prodromal period (Figs. 20-34 and 20-35). The classic lesion is a “target” or “iris” lesion, in which there are three concentric zones: a central dusky cyanotic or violaceous region, a paler edematous zone, and a peripheral red ring, thus creating the multiformity of lesions. The central dusky clearing represents epidermal cell necrosis. Atypical papular lesions may have only two zones or poorly defined borders. Lesions may also become bullous (bullous EM) (Fig. 20-36), but in contrast to epidermal necrolytic disorders, less than 2% of the body surface area is generally involved. Careful inspection of the eruption in EM may disclose fine petechiae. Most lesions are asymptomatic, but itching or burning has been described. The isomorphic response

### Box 20-4 Clinical Features of Erythema Multiforme

- Acute, self-limited, recurrent course
- Duration of 1 to 4 weeks
- Symmetrically distributed, fixed lesions
- Concentric color changes in at least some lesions (“iris” or “target” lesions)
- If present, mucosal involvement limited to the mouth
- In children, most likely cause for recurrent disease is herpes simplex virus



**Figure 20-32** Acute generalized exanthematous pustulosis. Pinpoint sterile papulopustules overlying erythroderma. No medication was associated, and the condition was attributed to a virus.



**Figure 20-33** Erythema multiforme (EM). Round erythematous swollen plaques and target lesions on the palms. This girl developed in EM in association with her systemic lupus erythematosus.



**Figure 20-36** Erythema multiforme, bullous. If central epidermal necrosis is extensive, the center of the lesion may become bullous.



**Figure 20-34** Erythema multiforme. Classic target lesions and marginated wheals with central vesicles are characteristic.



**Figure 20-37** Erythema multiforme (EM). The trigger for erythema multiforme in children is commonly herpes simplex infection, which often precedes EM but may be detectable at the time when the EM is present.



**Figure 20-35** Erythema multiforme. Extensive target lesions on the thighs of a 12-year-old girl. The recurrent reaction was suppressed by administration of oral acyclovir.

(koebnerization) appears to participate in the development of lesions, with trauma and ultraviolet light injury as triggers.

Oral lesions are seen in 25% to 50% of children, usually in conjunction with cutaneous lesions. They initially appear as bullae that break soon after formation, accompanied by swelling and crusting of the lips

and erosions of the buccal mucosa and tongue. Gingival involvement is rare, which helps to distinguish EM from primary herpes simplex infection of the mouth (Fig. 20-37). Most children with mucosal involvement have a few lesions and are mildly symptomatic; however, patients with extensively crusted lips and large bullous target lesions that may mimic SJS have been described.<sup>171,172</sup> Systemic manifestations, when present, are mild and consist of low-grade fever, malaise, and in rare cases, myalgia or arthralgia.

Biopsy of skin lesions is usually not needed to make a diagnosis of EM. It should be performed only to consider other conditions such as lupus erythematosus or vasculitis.<sup>220</sup> Focal liquefaction degeneration of epidermal keratinocytes and exocytosis of mononuclear cells in the epidermis are seen.

Most episodes of EM heal within 2 to 3 weeks without sequelae. Recurrences a few times yearly, however, are common. Symptomatic treatment with oral antihistamines usually suffices. Given the association with HSV, however, prophylactic therapy with oral acyclovir (5 to 10 mg/kg per day) for 6 to 12 months should be considered for patients with recurrent disease.<sup>215</sup> Episodic therapy with acyclovir is not useful. Administration of immunosuppressive agents, such as oral corticosteroids, leads to longer and more frequent episodes.

### Annular Erythemas

The annular erythemas (erythema marginatum, erythema annulare centrifugum [EAC], erythema migrans, and annular erythema of

infancy) represent a group of reactive vascular dermatoses that are distinguished primarily by their oval, annular, arcuate, circinate, polycyclic, reticular, or serpiginous configurations with individual characteristics that allow differentiation into distinctive clinical categories.<sup>221</sup> They must be distinguished from other annular lesions seen in children, especially tinea, urticaria multiforme, EM and SSLR, annular pityriasis rosea, neonatal and subacute lupus erythematosus, granuloma annulare, and the annular lesions of erythrokeratoderma variabilis (see Chapter 5).

### ERYTHEMA MARGINATUM AND RHEUMATIC FEVER

Erythema marginatum is a distinctive form of annular erythema that occurs on the trunk (especially on the abdomen) and the proximal extremities of patients with active rheumatic fever.<sup>222,223</sup> It is seen more commonly in children than in adults with rheumatic fever but still only occurs in 6% of affected children.<sup>224</sup> The occurrence of erythema marginatum often follows the onset of migratory arthritis by a few days, but at times may also occur many months after the carditis.

Often easily overlooked, lesions are evanescent pink macules or papules that fade centrally in a few hours to several days, leaving a pale or sometimes pigmented center. They spread rapidly to form non-pruritic rings or segments of rings with elevated reticular, polycyclic, or serpiginous borders and may recur in crops in different areas. Lesions are commonly seen more easily in the afternoon, and coalescence of polycyclic lesions often results in a characteristic chicken wire-like appearance. Gentle warming of the skin tends to enhance visualization of pale or barely perceptible lesions. Although the eruption seldom lasts more than several weeks, occasionally it may recur at sporadic intervals for several months to years.

Erythema marginatum presents a clinical picture that characteristically resembles a variety of dermatoses, including urticaria, EM, and other transient figurate erythemas.<sup>225</sup> Unlike the characteristic rash of juvenile idiopathic arthritis (see Chapter 22), lesions of erythema marginatum are larger, spread centrifugally with central clearing, and are limited to the trunk and sometimes the proximal limbs. Histologic features of a neutrophilic perivascular infiltrate in the papillary dermis aid in diagnosis.

The most common associated features are carditis (76% to 93% of patients), fever (62%), congestive heart failure (44%), and arthritis (39% to 53% of patients). Sydenham chorea is rarely seen. Approximately 2% of patients show urticarial lesions without annular rings,<sup>226</sup> and up to 2% have subcutaneous nodules, usually a late manifestation. The nodules of rheumatic fever are smaller than those seen in juvenile idiopathic arthritis and usually clear within a month. They tend to occur in crops, are symmetrically distributed, are nontender, and are more readily felt than seen, requiring a careful search. Differentiation of subcutaneous nodules of rheumatic fever from rheumatoid nodules and granuloma annulare is not possible on clinical or histologic grounds alone and requires the presence of other features.

Currently accepted criteria for the diagnosis of rheumatic fever include two major or one minor manifestation and evidence of recent group A streptococcal disease. The major manifestations include erythema marginatum, carditis, polyarthritis, chorea, and subcutaneous nodules. The minor manifestations include fever, arthralgias, previous rheumatic fever or rheumatic heart disease, leukocytosis, elevated erythrocyte sedimentation rate or positive C-reactive protein, and prolonged PR interval. Typical erythema marginatum has also been described in a patient with psittacosis.<sup>227</sup>

### ERYTHEMA ANNULARE CENTRIFUGUM

Erythema annulare centrifugum (EAC) is an eruption characterized by persistent erythematous annular lesions, each with a clear center and a raised, thin, wall-like border that slowly enlarges centrifugally. Synonyms for EAC include *gyrate erythema* and *erythema perstans*.

Primary lesions of EAC tend to be single or multiple erythematous, edematous papules with a predilection for the trunk, buttocks, thighs, and legs (Figs. 20-38 and 20-39). They are asymptomatic except for occasional mild pruritus. The rings extend peripherally, usually slowly,



**Figure 20-38** Erythema annulare centrifugum (EAC). Slowly expanding annular lesions have dusky centers and palpable scaly erythematous borders. Although the annular rings showed no evidence of fungus, the EAC was thought to result from the patient's underlying tinea pedis.



**Figure 20-39** Erythema annulare centrifugum. No cause was found for the recurrent annular lesions in this infant.

1 to 3 mm/day, sometimes up to 4 cm in a week. New lesions may form within the original circle. The resulting overall shape may be irregular, oval, circinate, semiannular, target-like, or polycyclic. The borders may eventually reach a size of 10 cm or more in diameter. The duration of the disease is extremely variable and may go on for weeks or months and, with new lesions appearing in successive crops, often for years.

At times the palpable border of the expanding ring may be topped by microvesicles or may show a fine collarette of scale on its trailing edge, suggesting a diagnosis of tinea corporis. Fungal infections can be distinguished by their more pronounced epidermal changes, with vesication or scaling or both at the edge of the lesions, by microscopic examination of skin scrapings, and by fungal culture. When the diagnosis is uncertain, histopathologic examination of cutaneous lesions showing focal infiltration of lymphocytes around the blood



**Figure 20-40** Erythema annulare centrifugum. This 10-year-old boy has had chronic, transitory annular plaques on the face, trunk, and extremities since the first weeks of life. They only clear transiently with febrile episodes.

vessels and dermal appendages in a “coat sleeve” arrangement may help to establish the diagnosis.

The etiology of EAC is unknown. Although it often occurs without apparent cause, most cases appear to be related to hypersensitivity to drugs, fungi, viruses (*molluscum poxvirus*<sup>228,229</sup> and *herpes zoster*,<sup>230</sup> certain foods, blood dyscrasias, autoimmune endocrinopathies or hepatitis,<sup>231</sup> or neoplastic disease (lymphomas). A neonate with EAC in association with *pseudomonas* sepsis infection has been described.<sup>232</sup>

Because EAC represents a hypersensitivity reaction, treatment depends on the determination and removal of the underlying cause. Antihistamines produce variable and usually incomplete relief; topical corticosteroids tend to be ineffective. Although systemic corticosteroids may aid the temporary resolution of lesions, unless the underlying cause is removed, the disorder commonly recurs as soon as medication is discontinued. Empiric treatment with oral fluconazole is often dramatically effective (personal communication, AJM), suggesting that fungal disorders are a common trigger. Cases with onset during the neonatal period or early infancy and persistence into adulthood have been described (Fig. 20-40).<sup>233,234</sup> The eruption in these cases clears with febrile episodes or subcutaneous administration of IFN- $\alpha$ .

### Annular Erythema of Infancy

Annular erythema of infancy may be a subset of EAC or a distinct entity in which infants have cyclic eruptions of urticarial annular erythema without a demonstrable underlying cause.<sup>235</sup> Lesions of classic annular erythema of infancy last for only a few days, in contrast to the more persistent lesions of EAC. This benign disorder is asymptomatic. It may resolve spontaneously after 3 to 11 months.<sup>235</sup> Neonatal lupus (see Chapter 22) must be considered. Neutrophilic figurate erythema of infancy is considered a neutrophilic variant of annular erythema of infancy, although the recurrences of the annular erythema may continue beyond infancy.<sup>236</sup>

### ERYTHEMA MIGRANS

Erythema migrans (erythema chronicum migrans), the earliest sign of Lyme disease, is a cutaneous eruption that occurs after a tick bite and is characterized by single or multiple erythematous expanding lesions with advancing indurated borders and central clearing (see Chapter 14). Erythema migrans is caused by the tick-borne spirochete *Borrelia burgdorferi* (see Figs. 14-40 and 14-41).

### Panniculitis

**Panniculitis** is a term to describe a group of disorders in which the major focus of inflammation is in the subcutaneous fat (Box

### Box 20-5 Classification of the Subtypes of Panniculitis

Erythema nodosum
Infection
Bacterial
Mycobacterial (erythema induratum of Bazin)
Fungal
Enzymatic disorders
$\alpha_1$ -Antitrypsin disease
Pancreatic disease
Poststeroid
Malignant panniculitis
Cytophagic histiocytic panniculitis
Subcutaneous panniculitis-like T-cell lymphoma
Edematous, scarring vasculitic panniculitis (hydroa-like lymphoma)
Lipoatrophic panniculitis
Associated with autoimmune disorders: systemic lupus erythematosus, deep morphea, juvenile dermatomyositis (usually subclinical), polyarteritis nodosa
Lipophagic panniculitis of childhood
Atrophic connective tissue panniculitis of the ankles
Recurrent lobular panniculitis
Physical agents
Cold panniculitis (popsicle, equestrian)
Injections, including factitial
Blunt trauma
Subcutaneous fat necrosis of the newborn
Sclerema neonatorum
Selected syndromes
H syndrome
CANDLE syndrome

CANDLE, Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature.

**20-5).**<sup>237-240</sup> The pathomechanism of most of these disorders is poorly understood. The most common subgroup is erythema nodosum, which is often associated with streptococcal infection in children but is considered a hypersensitivity disorder seen with several systemic disorders. Other forms of panniculitis are also commonly linked to systemic disorders, particularly collagen vascular disorders (see Chapter 22), Behcet syndrome (Chapter 25), lymphomas (see Chapter 10), diabetes (see Chapter 23), thyroid disease,  $\alpha_1$ -antitrypsin or pancreatic enzyme deficiency, and in association with generalized lipodystrophy. Disorders of the dermis, such as leukocytoclastic vasculitis and granuloma annulare, may show subcutaneous involvement but would not be considered primarily panniculitides. Infection may also lead to panniculitis, for example, especially with tuberculosis and erythema induratum of Bazin and less commonly with atypical mycobacterial infection<sup>241-244</sup> (see Chapter 14). Particularly in children who are immunocompromised, lobular panniculitis can be a feature of deep fungal infection (candidiasis, fusariosis,<sup>245</sup> aspergillosis, cryptococcosis, histoplasmosis, sporotrichosis, and chromomycosis) or bacterial infection (e.g., *Neisseria meningitidis*, *Streptococcus pyogenes*, *S. aureus*, *Klebsiella*, and *Pseudomonas* and *Nocardia* species).<sup>246</sup> Subcutaneous fat necrosis of the newborn and sclerema neonatorum are discussed in Chapter 2.

Classification of the panniculitides may be difficult, and several previous subtypes such as Weber–Christian disease and Rothman–Makai syndrome are no longer considered to be separate entities. Histopathologic evaluation of a biopsy large enough to include subcutaneous fat is often required to confirm the diagnosis of a specific form of panniculitis. Sections may show primarily septal involvement, as in erythema nodosum, or be lobular, as in the panniculitis associated with  $\alpha_1$ -antitrypsin disease. A largely lobular form with needle-shaped clefts within lipocytes is characteristic of subcutaneous fat necrosis of the newborn, sclerema neonatorum, and poststeroid panniculitis,<sup>247</sup> whereas necrosis is an early finding of the panniculitis induced by pancreatic enzymes.<sup>248,249</sup>

Cold panniculitis, which is most common in infants and children, is characterized by painful, poorly defined, erythematous plaques or subcutaneous nodules that develop in areas exposed to cold (Fig. 20-41).<sup>250</sup> Lesions appear several hours to 3 days after exposure and subside spontaneously, generally after a few weeks to a few months, leaving



**Figure 20-41** Popsicle panniculitis. This subtle erythematous macule resulted from cold panniculitis of the cheek after sucking on a popsicle. At times, the erythema is much more intense.

temporary residual pigmentation. The development of cold panniculitis in children appears to be related to the fact that subcutaneous fat solidifies more readily at lower temperatures in infants and young children than it does in adults. Cold panniculitis is often seen on the cheeks of toddlers and young children who suck popsicles ("popsicle panniculitis"),<sup>251</sup> at sites of contact with ice bags, cooling blankets before cardiac surgery or in treatment of arrhythmias,<sup>252</sup> and on the thighs and buttocks of young equestrians ("equestrian panniculitis"). Affected children are otherwise usually healthy, and no intervention is necessary.

The red or purple-red nodules of factitial panniculitis result from the injection of foreign substances into the subcutaneous tissue. Diagnosis requires a high index of suspicion but can be confirmed if foreign material is found in biopsy sections. For example, polarized light microscopic examination may show birefringent particles or, as in the case of injected silicone, oily substances with a characteristic Swiss cheese-like picture of oil cysts surrounded by fibrosis and inflammation. Milk, feces, mineral oil, and paraffin are among other substances that may be injected, leading to factitial panniculitis. In young children, these factitial lesions raise the possibility of Munchausen syndrome by proxy<sup>253</sup> (see Chapter 26).

Poststeroid panniculitis, a rare entity of childhood, is characterized by small, sometimes pruritic or painful subcutaneous nodules on the cheeks, arms, trunk, and buttocks of young children. These generally develop within 2 to 4 weeks after the sudden discontinuation of systemic corticosteroid therapy.<sup>254</sup> Lesions tend to regress spontaneously without scarring.

Panniculitis can be a feature of malignancy, particularly lymphoma. Subcutaneous panniculitis-like T-cell lymphoma more commonly occurs in adolescents but has been described in infants<sup>255–257</sup> (see Chapter 10).<sup>258,259</sup> Patients develop skin-colored to erythematous, often painful, subcutaneous nodules or hemorrhagic plaques. Fever, mucosal ulcerations, hepatosplenomegaly with hepatic failure, pancytopenia, and intravascular coagulopathy are associated features. Biopsy sections show often atypical lymphocytes surrounding adipocytes (lobular panniculitis). The minority of affected children have associated hemophagocytosis, which portends a poor prognosis. In children, in contrast with adults, the face is commonly affected and systemic involvement is more common. Molecular genetic analysis and immunophenotyping should be performed; most show clonal rearrangement. Suggested treatment includes initial administration of cyclosporine and prednisone for the inflammatory component, followed by combination chemotherapy for the lymphoma. Bexarotene has recently shown efficacy.<sup>260</sup>



**Figure 20-42** Traumatic fat necrosis. The panniculitis occurred after blunt trauma to the cheek and led to lipoatrophy.

Cytophagic histiocytic panniculitis is characterized by chronic panniculitis in association with fever, hepatosplenomegaly, and pancytopenia because of bone marrow hemocytophagocytosis. Histologically, the finding of cytophagic histiocytic panniculitis represents a reaction pattern that may be benign (in association with infection, especially EBV) or may prove to be associated with subcutaneous T-cell lymphoma. Panniculitis in association with vasculitis is a feature of hydroa-like lymphoma associated with EBV infection (see Chapter 19).

$\alpha$ 1-Antitrypsin is a protease inhibitor made by the liver. Most normal individuals carry the MM genotype (i.e., both alleles are M) and have normal levels of  $\alpha$ 1-antitrypsin. Heterozygotes with one S or Z allele have a moderate deficiency of the inhibitor; individuals who are homozygous for the Z allele have a severe  $\alpha$ 1-antitrypsin deficiency. The clinical manifestations of  $\alpha$ 1-antitrypsin deficiency in children or adults may be cirrhosis, emphysema, pulmonary effusions, pulmonary embolism, membranous proliferative glomerulonephritis, pancreatitis, arthritis, vasculitis, angioedema, and panniculitis.<sup>261</sup> The panniculitis is usually seen in homozygotes but has been described in heterozygotic pediatric patients, including the MS phenotype.<sup>262</sup> It is characterized by erythematous to purple tender nodules or plaques most commonly seen on the lower trunk, buttocks, and proximal extremities after trauma. Deep necrotic ulcerations may develop and discharge an oily material. Lesions are often persistent and resistant to therapy but eventually heal with scarring and atrophy. Replacement of  $\alpha$ 1-antitrypsin by intravenous infusion is the most effective therapy and can lead to rapid clearance of the panniculitis.

Patients with cutaneous polyarteritis nodosa (PAN), a form of deep dermal and subcutaneous vasculitis, typically show painful oval or linear nodules on the lower extremities surrounded by livedo reticularis and often stellate necrosis (see Chapter 21, Figs. 21-16 and 21-17).<sup>263</sup> Raynaud phenomenon is rarely described, but digital lesions may progress to gangrene.<sup>264</sup> Streptococcal pharyngitis may precede the eruption.<sup>265</sup> Although the cutaneous features may manifest as an isolated benign form, the multisystemic form of PAN should be considered in children with distal livedo reticularis and distal ischemic necrosis in association with weight loss, fever, abdominal pain, musculoskeletal signs, renal disease, and peripheral neuropathy.<sup>266–268</sup> Mutations in *CECR1*, encoding adenosine deaminase 2, have recently been described as causative in families with systemic PAN.<sup>269</sup>

Other forms of panniculitis include pancreatic panniculitis, a disorder that probably results from breakdown of subcutaneous fat caused by enzymes released into the circulation from a nodular or neoplastic pancreatic disease; erythema induratum, a deep-seated subcutaneous infiltration of the lower legs, especially the posterior calves, that often ulcerates before healing and results in atrophic scars (see Chapter 14); and traumatic panniculitis, a disorder consisting of hard, indurated, inflamed nodules that occur after injury (Fig. 20-42). Lobular panniculitis may also lead to lipoatrophy (Fig. 20-43).<sup>270–272</sup> Most often seen with systemic lupus erythematosus,<sup>273</sup> deep morphea and juvenile dermatomyositis<sup>274</sup> may also manifest with panniculitis that resolves with lipoatrophy (see Chapter 22). Residual lipoatrophy at the ankles in association with lobular panniculitis and lipophages has



**Figure 20-43** Panniculitis and lipodystrophy. This teenager had autoimmune hepatitis and acanthosis nigricans in association.



**Figure 20-45** Erythema nodosum. These inflamed nodules proved to be a hypersensitivity reaction to group A  $\beta$ -hemolytic streptococcal infection.



**Figure 20-44** Erythema nodosum. Tender, red, oval nodules on the extensor aspect of the legs. Note that several have darkened and resemble bruises.

been described with and without autoimmune disorders of other types, particularly thyroiditis and diabetes mellitus.<sup>275–277</sup> Panniculitis and lipoatrophy (particularly of the buttocks) are also features of *H syndrome*, an autosomal recessive disorder with panniculitis resulting from mutations in *SLC29A3*, a nucleoside transporter.<sup>278–281</sup> *H syndrome* is characterized by hyperpigmentation (often with induration) and hypertrichosis of the inner thigh that usually spreads to involve the middle and lower parts of the body with conspicuous sparing of the knees and buttocks. Patients also show hepatosplenomegaly, heart anomalies, and hypogonadism. Panniculitis with vasculitis and atypical cells is also a feature of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome (see Sweet Syndrome [Acute Febrile Neutrophilic Dermatosis] section).<sup>282</sup>

## Erythema Nodosum

Erythema nodosum is a hypersensitivity reaction characterized by red, tender, nodular lesions.<sup>283</sup> Occurrence peaks during adolescence and is rare in children younger than 2 years of age. During childhood, girls are affected slightly more than boys, in contrast to adults, in which women are affected three to four times more often than men. The disease has its greatest incidence in the spring and fall and is less common in summer.

Lesions are most often seen on the pretibial surfaces (Fig. 20-44) but occur more commonly in affected children on the thighs, arms, trunk, and face than in adults.<sup>284</sup> They are most often 1 to 5 cm in diameter and are symmetrically distributed. Lesions are occasionally located on the knees, ankles, thighs, extensor aspects of the arms, the face, and the neck. They are rarely found on the palms or soles (Fig. 20-45). Initially they appear as bright to deep red, warm, tender, oval, slightly elevated nodules. After a few days they develop a brownish red

### Box 20-6 Underlying Causes of Erythema Nodosum

Idiopathic (=50%)

Infections

$\beta$ -Hemolytic streptococcal infection, especially pharyngitis (most common detectable cause)

Mycoplasma, upper respiratory viruses (Epstein-Barr virus), mycobacteria (tuberculosis and atypical), coccidiomycosis in endemic areas

Uncommon: *Trichophyton mentagrophytes*, *Yersinia*, *Shigella*, hepatitis B, brucellosis, meningococcosis, Neisseria infection, cat-scratch disease, human immunodeficiency virus infection, *Chlamydia*, blastomycosis, histoplasmosis, sporotrichosis, syphilis, pertussis, *Escherichia coli*, leprosy

Inflammatory

Sarcoidosis

Inflammatory bowel disease

Behcet disease

Malignancy (especially leukemia)

Drugs

Oral contraceptives, sulfonamides, penicillins

Pregnancy

or purplish bruise-like appearance that is characteristic. Lesions do not ulcerate or leave scars.

Despite investigation, no underlying cause is found in most pediatric patients. Although possible etiologic causes are numerous (Box 20-6), the most common in the pediatric patient is  $\beta$ -hemolytic streptococcal infection. The list of other associated disorders is long, especially other infectious diseases (including tuberculosis, *Yersinia* infection, *Trichophyton mentagrophytes*<sup>285</sup> and infectious mononucleosis), administration of oral contraceptives, inflammatory bowel disease, celiac disease, and sarcoidosis.<sup>286–291</sup> In patients with coccidiomycosis, the presence of erythema nodosum suggests a positive prognostic sign and decreased risk of dissemination. Erythema nodosum leprosum shows panniculitis with leukocytoclastic vasculitis in biopsy sections.<sup>292</sup>

The eruption usually lasts 3 to 6 weeks but may recede earlier. Recrudescences may occur over a period of weeks to months, but attacks are seldom recurrent. Arthralgias may precede, coincide with, or follow the eruption in as many as 90% of cases. In the 10% of patients in whom the condition may present as a recurring disorder, recurrences are often associated with repeated streptococcal infection.

Erythema nodosum has a characteristic clinical picture, and diagnosis generally can be made on the basis of physical examination alone. Although diagnosis is usually not difficult, common bruises, cellulitis or erysipelas, deep fungal infections (such as Majocchi granuloma or sporotrichosis), insect bites, deep thrombophlebitis, angiitis, erythema induratum, and fat-destructive panniculitides can be confused with this disorder. Eccrine hidradenitis can resemble erythema nodosum on the palms or soles.<sup>293</sup> When the diagnosis is in doubt, bacterial and fungal cultures and histologic examination of skin biopsy specimens generally will help clarify the diagnosis.

The management of erythema nodosum is directed at identification and treatment of the underlying cause. Minimal evaluation usually involves obtaining a complete blood count (CBC), throat culture, an antistreptolysin O (ASO)/deoxyribonuclease (DNase) B titer, chest radiograph, and tuberculin testing. Bed rest with elevation of the patient's legs helps reduce pain and edema. When pain, inflammation, or arthralgia is prominent, NSAIDs can be prescribed. Salicylates, colchicine, potassium iodide and if severe, a short course of systemic corticosteroids are the most commonly used alternative therapies. In chronic or recurrent cases, detailed investigations must be performed to uncover the underlying cause. Intralesional corticosteroids commonly cause rapid involution of individual lesions, and in persistent or recurrent eruptions oral corticosteroids may be beneficial.

## Eccrine Hidradenitis

Idiopathic palmoplantar hidradenitis occurs suddenly in otherwise healthy children as erythematous painful nodules on the palms and soles.<sup>294</sup> The condition has been linked to vigorous physical activity, excessive sweating, and prolonged exposure to moisture. Some have suggested that this disorder may in some patients be synonymous with "Pseudomonas hot foot syndrome" (see Chapter 14). Lesional biopsies show neutrophilic perieccrine infiltrates, and the lesions are thought to result from mechanical rupture of the eccrine glands. Plantar surfaces are more commonly involved, leading to consideration of erythema nodosum, EM, bite reactions, chilblains, cellulitis, and embolic disease. In one affected infant, the eccrine hidradenitis delayed walking.<sup>295</sup> Although episodes recur in up to 50% of children, resolution typically occurs in 1 to 4 weeks, especially with rest. Therapy with topical and systemic corticosteroids is not clearly beneficial, although NSAIDs are often prescribed. Colchicine has also been used.<sup>296</sup>

Another form of eccrine hidradenitis is neutrophilic eccrine hidradenitis, a complication of cancer chemotherapy. Neutrophilic eccrine hidradenitis tends to develop 7 to 14 days after initiating chemotherapy, most commonly cytarabine. The disorder reflects the direct cytotoxicity of chemotherapy to the eccrine glands. Affected children are usually febrile, and the eruption is most commonly characterized by erythematous papules and plaques on the trunk, extremities, and face.<sup>297</sup>

## Cutaneous Reactions to Cold

A variety of conditions can occur when one is exposed to cold. Frostbite is caused by exposure to extreme cold. Trench foot and immersion foot are caused by a combination of cold and wetness. Perniosis (chilblains) represents an exaggerated response to cold and dampness in a predisposed individual. Individuals may also develop cutaneous changes after exposure to cold with dysproteinemia, such as with cryofibrinogenemia or cryoglobulinemia.

### FROSTBITE

Frostbite is a disorder caused by the actual freezing of tissue at temperatures of extreme cold ( $-19^{\circ}\text{C}$  to  $-23^{\circ}\text{C}$  [ $-2^{\circ}\text{F}$  to  $-10^{\circ}\text{F}$ ]).<sup>298,299</sup> The duration of exposure, wind velocity, dependency of an extremity, application of emollients, and factors such as fatigue, injury, immobility, and general health potentiate the effects of the cold.<sup>300</sup> Frostbite is caused by direct cold injury to the cell, vascular insufficiency (constriction and vasoocclusion), and damage from inflammatory mediators. The vasoconstriction that occurs is an effort to conserve core body temperature at the expense of the distal extremities. Frostbite generally affects exposed areas such as the toes, feet, fingers, nose, cheeks, and ears. Rarely, frostbite has resulted elsewhere from application of an ice pack<sup>301</sup> or from improper use of commercially available cryotherapy devices for wart removal.<sup>302</sup>

Four degrees of severity have been described. Frostnip, or first-degree frostbite, shows redness, edema, and transient discomfort. In mild cases, the affected area returns to normal within a period of a few hours with at most mild desquamation. Second-degree frostbite

presents with marked erythema and swelling; the numbness is replaced by burning pain, and within 24 to 48 hours, vesicles and bullae appear. Although healing occurs, patients may show continuing sensory neuropathy and cold sensitivity. In third-degree frostbite, hemorrhagic bullae or waxy, mummified skin is seen, consistent with extensive tissue loss. Full-thickness involvement of the skin, muscle, tendon, and bone occurs in fourth-degree frostbite; although recovery is possible, amputation (either surgical or autoamputation) results for most patients.<sup>303</sup>

The current goal of treatment is rapid rewarming to prevent further cold exposure and restore circulation.<sup>304</sup> The water bath temperature should be at least  $40^{\circ}\text{C}$  ( $104^{\circ}\text{F}$ ). Slow rewarming, use of dry heat, and rubbing with ice are all contraindicated. Pain during thawing and immediately after thawing should be treated with potent analgesics and sedatives. Core warming and fluid resuscitation are also important in patients with hypothermia. Other measures include wound care, administration of tetanus toxoid, avoidance of pressure and even light contact with the affected area, and vigorous treatment of infection when present. Thrombolytic therapy with intraarterial infusion of tissue plasminogen activator or iloprost (vasodilator) can improve perfusion.<sup>304–306</sup> If surgical measures are required, they should be delayed as long as possible. Because the prediction of tissue loss is difficult, amputation of necrotic tissue is best deferred for a period of at least 60 to 90 days to allow time for contracture, shrinkage, and the formation of a definitive line of demarcation between necrotic and viable tissue.

### TRENCH FOOT (IMMERSION FOOT)

Trench foot is a cold-induced nonfreezing injury of the extremities that occurs in individuals constantly exposed to a wet and cold environment. The disorder resembles a mild to moderate frostbite, has predominantly been noted in the homeless,<sup>307</sup> and is uncommon in children, although ice skaters and ice-hockey players are at risk.<sup>299</sup>

During exposure there is usually an initial uncomfortable feeling of coldness followed by virtually no discomfort and at times, a feeling of warmth as the nerves become sensitive. The limb becomes cold, numb, blue, swollen, and pulseless. The pain is aggravated by heat and relieved by cold. The ischemic tissue is prone to infection. In severe cases there is muscle weakness, joint stiffness, and gangrene that usually heals without tissue loss. A form of immersion foot has also been described in patients exposed to warm water for long periods of time. This disorder, characterized by a wrinkling, blanching, and maceration of the skin on the plantar and lateral aspects of the feet, has largely been reported in military personnel in tropical areas and in individuals who wear insulated boots for long periods of time. This form is generally reversible, leaving no residual disability.

Prevention is the best treatment. The skin should be rapidly dried should the condition occur. In the warm-water form of immersion foot, the application of silicone grease before water immersion may be helpful.

### PERNIOSIS

Perniosis (chilblains) is an exaggerated response to cold in predisposed individuals.<sup>308,309</sup> In pediatric patients, it largely is seen in teenagers but has been described in younger children.<sup>310</sup> It has been noted in several adolescents with anorexia nervosa<sup>311</sup> and may relate to impaired thermoregulation. Wet linings in shoe boots have also been blamed. Characterized by the occurrence of localized cyanosis, erythematous nodules, or ulcerations on exposed extremities in cold and damp weather, the disorder is most common in Northern Europe and the northern United States.

Perniotic lesions may also be seen in patients with lupus erythematosus (see Chapter 22), hemolytic anemia, and chronic myelomonocytic leukemia.<sup>312</sup> Painful chilblain-like lesions on the fingers, toes, and ears during early childhood is the pathognomonic features and usually the first manifestations of familial chilblain lupus, an autosomal dominant disorder that is caused by heterozygous mutations in *TREX1* (3' repair exonuclease 1) or in one family, *SAMHD1* (SAM domain and HD domain-containing protein 1).<sup>313,314</sup> Affected

individuals subsequently develop arthralgias, antinuclear antibodies (ANA), and sometimes cytopenias. These ulcerating chilblain-like lesions, often leading to digital ischemia, tend to occur during infancy in 40% of individuals with Aicardi–Goutières syndrome, an autosomal recessive disorder that results from biallelic mutations in *TREX1* and *SAMHD1*, as well as *RNASEH2A*, *RNASEH2B* (a later-onset form), and *RNASEH2C*.<sup>315–317</sup> The feet and hands are often cold, even without chilblain lesions. Affected children also have microcephaly, inflammatory encephalopathy and developmental delay, and arthritis. Biopsies may resemble lupus erythematosus,<sup>318</sup> and autoimmune antibodies may be present. Upregulation of IFN-stimulated genes has been demonstrated in patients with both familial chilblain lupus and Aicardi–Goutières syndrome.

Mild cases of perniosis are manifested by an initial blanching and then by ill-defined erythematous macules that become infiltrated and vary from a dark pink to a violaceous hue. In most cases the disorder is characterized by edematous patches of erythema or cyanosis that appear 12 to 24 hours after exposure to cold. Initially patients are usually unaware of the disorder. With time the areas become edematous and bluish red and eventually develop numbness, tingling, pruritus, burning, or pain.

Individual lesions tend to appear in a symmetrical distribution, principally on the dorsal aspect of the phalanges of the fingers (Fig. 20-46) and toes (Fig. 20-47) and on the heels, lower legs, thighs, nose, and

ears. The course is usually self-limiting and lasts 2 or 3 weeks. In young girls and adolescent women who wear skirts rather than slacks, the calves and shins are common sites of involvement. Chronic perniosis occurs repeatedly during cold weather and disappears during warm weather. Blistering and ulceration occasionally occur, and at times, lesions may heal with residual areas of pigmentation.

Children with more persistent or atypical lesions should have laboratory testing to eliminate possible underlying causes. These include CBC, ANA, and cryoglobulin, cryofibrinogen, and cold agglutinin levels. Serum protein electrophoresis levels are usually assessed in affected adults, but the incidence of patients with monoclonal gammopathy is much lower in children. Treatment consists of proper clothing to prevent undue exposure to cold, application of antipruritics, soothing lotions or ointments, and in severe cases, administration of nifedipine<sup>319,320</sup> or pentoxifylline.<sup>321</sup> Hydroxychloroquine has also been reported to improve pernio.<sup>322</sup>

### COLD-SENSITIVE DYSPROTEINEMIAS

The cold-insoluble proteins that precipitate at low temperatures include cryoglobulins, cryofibrinogens, and cold agglutinins. Cryoglobulins are composed of immunoglobulins (see Chapter 21), often in association with hepatitis C virus ribonucleic acid (RNA).<sup>323</sup> Cryofibrinogenemia involves increased circulating levels of fibrinogens (as well as fibrins and fibrin-split products) that gel in the cold.<sup>324,325</sup> In contrast to cryoglobulins, which may be found in serum samples, cryofibrinogens are consumed in clotting and thus are only present in plasma samples. Cold agglutinins are antibodies that promote aggregation of erythrocytes with cold exposure and are most commonly found in pediatric patients with mycoplasmal infection, although association with EBV has also been described.<sup>326</sup> Because cryoproteins may precipitate at a temperature as high as 35°C, the blood sample for testing must be maintained at 37°C until centrifugation. For testing, the sample is chilled to 4°C for 72 hours.

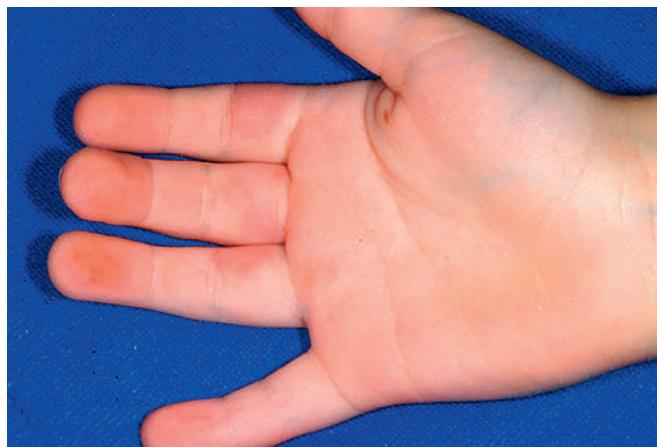
The most common manifestation of cold-induced dysproteinemia is palpable purpura that is often retiform (net-like) (see Chapter 21) and can progress to severe vasoocclusion (Fig. 20-48). Most individuals with cold-related occlusion syndromes have circulating cryoglobulins rather than cryofibrinogens or cold agglutinins. Other manifestations of increased levels of circulating cryoglobulins are urticaria, urticarial vasculitis, cold urticaria, livedo reticularis, pernio, Raynaud phenomenon, acral bullae, and digital ulcerations. In children, cryofibrinogenemia usually occurs as a secondary disorder related to infection,<sup>327</sup> but primary cryofibrinogenemia has been described and may respond to stanozolol.<sup>328</sup> The most common visceral manifestations of cryofibrinogenemia are arthralgias, weakness, neuropathy, and glomerulonephritis. A rare autosomal dominant form has been described in children and is characterized by painful purpura, slow healing of small ulcerations, and pedal edema during the winter season.<sup>329</sup> If cold agglutinins cause clinical problems, the typical manifestation is hemolysis; acrocyanosis, Raynaud phenomenon, livedo reticularis, and necrosis have rarely been described. Identification and treatment of the underlying disorder, as well as cold avoidance, are important.

### Cutaneous Reactions to Heat

Burns are the most common adverse reaction to heat (see Chapter 26). Erythema ab igne rarely occurs in the industrialized world with central heating.

### ERYTHEMA AB IGNE

Erythema ab igne is an acquired, persistent reticulated erythematous and pigmented condition of the skin produced by prolonged or repeated exposure to moderately intense, but not burning, heat. It most commonly occurs from use of heating pads but has been described after exposure to heat from fireplaces, hot water bottles, radiators, heating elements in cars,<sup>330</sup> heating blankets in the intensive care unit,<sup>331</sup> and exposure to laptop computers (on the thighs).<sup>332,333</sup>



**Figure 20-46** Perniosis (chilblains). Edematous red, painful nodules appeared on the fingers after exposure to cold.



**Figure 20-47** Perniosis (chilblains). Note the inflamed nodules on the toes of this adolescent girl. Although nodules resolved, painful nodules continued to develop on an annual basis beginning in January and lasting until April. She was otherwise healthy.

**A****B**

**Figure 20-48** Cryoglobulinemia. In this patient, palpable purpura and early vasoocclusion (**A**) progressed within 24 hours to severe vasoocclusion (**B**), requiring digital amputation.



**Figure 20-49** Erythema ab igne. Reticulated brown pigmentation on the lower back after prolonged exposure to a heating appliance.

The disorder is characterized by a mottled appearance of the skin exposed to the heat and eventually is manifested by a reticulated, annular, or gyrate erythema that progresses to a pale-pink to purplish dark-brown color with superficial venular telangiectasia and hyperpigmentation (Fig. 20-49). As in burn scars, squamous cell carcinomas have been reported in plaques of erythema ab igne. When present, these carcinomas tend to be aggressive, with metastases occurring in more than 30% of cases.

Treatment of erythema ab igne consists of protection from further exposure to the offending heat source. Once exposure to heat is

discontinued the erythema may fade, but the hyperpigmented changes are often permanent.

## Sweet Syndrome (Acute Febrile Neutrophilic Dermatosis)

Acute febrile neutrophilic dermatosis (Sweet syndrome) is characterized by raised painful papules, nodules, plaques, or bullae on the limbs, face, and neck, accompanied by fever and leukocytosis.<sup>334,335</sup> Many children have a history of upper respiratory tract illness 1 to 3 weeks before the onset of lesions. The disorder has been described in an infant as young as the first weeks of life,<sup>336</sup> but only 5% of cases are in children.<sup>337</sup> It is most common in women between 35 and 66 years of age.

Although commonly “idiopathic,” 58% of children with Sweet syndrome have an associated underlying disease, which is usually uncovered by complete history and physical examination, as well as a CBC with smear evaluation. Most of these are “parainflammatory” conditions with infection, although upper respiratory tract infection is most common, 1 to 3 weeks before the eruption, otitis media, viral meningitis, and human immunodeficiency virus.<sup>338</sup> Sweet syndrome has also been described with immunodeficiency<sup>339</sup> (T-cell deficiency,<sup>340</sup> CVID,<sup>341</sup> glycogen storage disease with neutropenia, and chronic granulomatous disease).<sup>342,343</sup> Other associated inflammatory disorders are inflammatory bowel disease,<sup>344</sup> systemic lupus erythematosus,<sup>345,346</sup> chronic multifocal osteomyelitis, vasculitis,<sup>334</sup> and Takayasu arteritis. Approximately 25% of children with Sweet syndrome have an underlying neoplastic or premalignant disorder (myelogenous leukemia, juvenile myelomonocytic leukemia,<sup>338</sup> myelodysplastic syndrome,<sup>347</sup> acute lymphoblastic leukemia, osteosarcoma, aplastic anemia, or Fanconi anemia<sup>348</sup>). Paraneoplastic Sweet syndrome more often presents on the face and oral mucosa. In such cases, the Sweet syndrome manifests simultaneously with the malignancy, suggesting that the possibility of malignancy must be investigated upon presentation but is unlikely to develop after the initial evaluation. Drugs have been linked to Sweet syndrome: granulocyte or granulocyte-macrophage colony-stimulating factor,<sup>349</sup> all-transretinoic acid,<sup>350</sup> trimethoprim-sulfamethoxazole, carbamazepine, imatinib, and minocycline, but in each case the patient had an underlying inflammatory or neoplastic disorder. A Sweet-like syndrome during the first 6 months of life has been associated with neonatal lupus and CANDLE syndrome, an auto-inflammatory disorder caused by mutations in the *PSMB8* gene.<sup>351,352</sup> The lesions of CANDLE syndrome tend to be annular and show a characteristic mixed infiltrate with atypical myeloid cells, which aids in the diagnosis.

Patients with acute febrile neutrophilic dermatosis usually have spiking fevers early in the course associated with raised, brightly erythematous, painful papules, plaques, or nodules asymmetrically distributed on the face, neck, and limbs (particularly the upper arms), with sparing of the areas between the upper chest and thighs. Lesions often occur in crops, and pathergy is common. Elevated plaques measure 1 cm or more in diameter, are distributed in an asymmetric pattern, and tend to develop partial clearing, resulting in an arcuate configuration as the border of the lesion advances (Fig. 20-50). They are indurated, red to plum-colored, and heal without scarring, often leaving a residual reddish brown color (Fig. 20-51). Larger plaques commonly have a mammillated surface from edema that simulates vesicles but is firm to palpation.

Leukocytosis ranging from 15,000 to 20,000 (with 80% to 90% polymorphonuclear leukocytes) is common, and myalgia, polyarthralgia, and polyarthritides of large joints have been reported in 15% to 25% of patients.<sup>353</sup> The fever precedes the cutaneous eruption by days to weeks in at least 50% of patients. Conjunctivitis and episcleritis may be present. Systemic inflammatory response syndrome with septic shock and multiorgan dysfunction has been associated in one child.<sup>354</sup> Rarely, postinflammatory slack skin with arterial laxity and aortic or mitral valve regurgitation has followed Sweet syndrome<sup>355,356</sup>; these children may develop potentially fatal coronary artery disease.<sup>357,358</sup>

Acute febrile neutrophilic dermatosis generally presents a fairly characteristic clinical picture that can be confirmed by cutaneous



**Figure 20-50** Sweet syndrome. Asymmetric indurated annular plaques.



**Figure 20-51** Sweet syndrome. Asymmetrically distributed indurated plum-colored plaques and nodules. (Courtesy of Dr Sarah Chamlin.)

biopsy. To establish the diagnosis, it has been suggested that patients must fulfill both major criteria and at least two of the minor criteria (Box 20-7). Biopsy specimens show a dense dermal perivascular infiltration of polymorphonuclear leukocytes, sometimes with nuclear dust, but without vasculitis. A similar histologic picture can be seen in patients with neutrophilic urticarial dermatosis, usually related to underlying systemic lupus erythematosus in pediatric patients<sup>359</sup> but distinguishable clinically from Sweet syndrome by urticarial macules or plaques without edema and lasting less than 24 hours.

If untreated, lesions of Sweet syndrome may extend and persist for up to a year, eventually resolving spontaneously without residual scarring. Patients generally respond to systemic corticosteroids (1 to 2 mg/kg per day) within a few days. Once the patient responds, the systemic corticosteroids should be tapered gradually over 2 to 3

#### Box 20-7 Major and Minor Criteria for Diagnosis of Sweet Syndrome

##### Major criteria

- Abrupt onset of tender or painful erythematous or violaceous plaques or nodules
- Predominantly neutrophilic infiltration of the dermis without leukocytoclastic vasculitis

##### Minor criteria

- Illness preceded by fever or infection
- Fever accompanied by arthralgia, conjunctivitis, or underlying malignancy
- Leukocytosis  $>10,000/\text{mm}^3$
- Good response to systemic corticosteroids and lack of response to antibiotics

months in an effort to prevent recurrences; some patients respond to corticosteroids but experience a flare with withdrawal. Potassium iodide, colchicine, dapsone, methotrexate, cyclosporine, and chlorambucil are treatment alternatives.

### Bowel-Associated Dermatosis-Arthritis Syndrome

Bowel-associated dermatosis-arthritis syndrome (intestinal bypass disease, bowel bypass syndrome) was originally described as a complication of jejunointestinal bypass surgery, which is only rarely performed in an adolescent for obesity.<sup>360</sup> However, the disorder has also been described in individuals with gastrointestinal disorders, including inflammatory bowel disease.<sup>361</sup> The disorder is characterized by a flu-like illness (chills, malaise, and myalgia), asymmetric polyarthritis, tenosynovitis, thrombophlebitis, retinal vasculitis, and crops of skin lesions. Lesions are most often seen on the arms and hands and less often on the shoulders and flanks. They are generally asymptomatic or mildly pruritic. Lesions begin as 3- to 10-mm erythematous macules, which develop into purpuric vesiculopustules that undergo central necrosis and resemble insect bites. Lesions over acral areas may be painful and often mimic the pustulovesicular lesions of gonococcemia; lesions on the shins or ankles, which are generally erythematous, tender nodules, may be mistaken for erythema nodosum.

The eruption usually lasts for 2 to 6 days and recurs at varying intervals for weeks to months. It is thought to result from bacterial overgrowth in blind intestinal loops and production of circulating immune complexes directed against the bacterial peptidoglycans. Biopsies of skin show a massive dermal infiltrate of neutrophils showing leukocytoclasia and occasionally a necrotizing vasculitis; some patients show lobular neutrophilic and septal panniculitis.

Short-term treatment of 1 mg/kg per day of prednisone markedly ameliorates the cutaneous and rheumatologic manifestations. Tetracycline, minocycline, metronidazole, clindamycin, sulfisoxazole, and dapsone have been suggested for both acute exacerbations and chronic prophylaxis. Surgical revision is curative.

### Hypereosinophilic Syndrome

Hypereosinophilic syndrome is a multisystemic disorder characterized by peripheral blood eosinophilia of at least 1500 eosinophils/ $\mu\text{l}$  without parasitic or allergic causes. Characteristically, the increase in eosinophils is present for 6 months or longer and is associated with infiltration of organs by eosinophils.<sup>362</sup> The condition is seen primarily in middle-aged men, but pediatric patients have been described.<sup>363,364</sup> The pathogenesis of the hypereosinophilic syndrome remains unknown, but many affected individuals have myeloproliferative disorders. The activated eosinophils are thought to cause the end-organ damage.

The manifestations can be variable, and almost any organ system can be involved. Approximately 50% of patients demonstrate cutaneous involvement. Pruritic erythematous or hyperpigmented macules,



**Figure 20-52** Hypereosinophilic syndrome. This patient shows purpuric areas on the palms, but a wide variety of cutaneous manifestations occur in 50% of patients, ranging from pruritic erythematous or hyperpigmented macules and papules to serpiginous lesions with vesicles to purpuric papules, petechiae, and livedo reticularis.

papules, serpiginous lesions with vesicles, purpuric papules (Fig. 20-52), splinter hemorrhages, nailfold infarcts, urticaria, Wells syndrome (see *Wells Syndrome*), erythema annulare, diffuse erythema, angioedema, livedo reticularis, and nodules, some of which are ulcerated, and mucosal ulcers have been described. These lesions may appear anywhere on the body but are generally present over the trunk and extremities.

Except for the blood and bone marrow involvement, cardiovascular disease is the major cause of morbidity and mortality. The heart often shows restrictive cardiomyopathy and subendocardial fibrosis; myocardial infarction may result.<sup>363</sup> Pulmonary complications (seen in 40% of patients) include interstitial infiltrates, a persistent nonproductive cough, and pleural effusion. Neurologic findings include hemiparesis, dysesthesias or paresthesias, slurred speech, confusion, and at times, coma. Affected individuals often show hepatosplenomegaly. Hepatic dysfunction, diarrhea with or without malabsorption, and renal involvement with persistent hematuria and hypouricemia have also been reported.

Hypereosinophilic syndrome is now classified based on underlying pathology as: (1) myeloproliferative, (2) lymphoproliferative, (3) idiopathic/undefined, (4) overlapping, (5) associated, and (6) familial.<sup>365</sup> Treatment is now specific to the underlying disease. However, systemic corticosteroids are the treatment of choice for most pediatric patients. Mepolizumab, which inhibits IL-5, is another option,<sup>366</sup> and imatinib has revolutionized the therapy for patients with the myeloproliferative form of the hypereosinophilic syndromes. Other treatment modalities are hydroxyurea, vincristine, IFN- $\alpha$ 2b, and fludarabine.<sup>367</sup>

## Wells Syndrome

Wells syndrome (eosinophilic cellulitis) occasionally occurs in pediatric patients, including in neonates and young children.<sup>368-371</sup> The condition starts with a prodromal burning sensation or itching and spreads rapidly for 2 or 3 days. Patients most commonly show sudden outbreaks of erythematous, often painful or pruritic, edematous urticarial or cellulitis-like plaques, often with sharp pink or violaceous borders. The morphology of lesions can vary. Although most children show plaque-type Wells lesions, annular granuloma-like lesions and papulovesicular, papulonodular, urticarial, bullous, and fixed drug-like lesions have been described. Lesions most commonly affect the lower limbs, followed in incidence by the upper limbs, trunk, face, scalp, and neck. The disorder gradually subsides over 2 to 8 weeks to be replaced by blue or slate-colored indurated patches that slowly fade. Recurrences are typical. The preceding history of insect bites,

### Box 20-8 Most Common Physiologic Changes of Pregnancy and the Postpartum Period

Skin	Striae Acrochordons
Vascular	Palmar erythema Hemorrhoids Varicosities Edema, nonpitting Spider angiomas Pyogenic granulomas
Pigment	Melasma Linea nigra Hyperpigmentation of the areolae
Hair	Hirsutism Postpartum alopecia Telogen effluvium Androgenetic alopecia Nail dystrophy

parvovirus B19 infection,<sup>372,373</sup> fungal infections, drug eruptions (particularly penicillin), reactions to vaccinations,<sup>374</sup> or underlying hematologic disease in some patients suggests that Wells syndrome represents a hypersensitivity reaction.

The clinical picture is striking, and the affected areas often resemble acute bacterial cellulitis, urticaria, insect bites, or a vesiculobullous contact dermatitis. Biopsy is usually necessary to confirm the diagnosis and shows diffuse infiltration of eosinophils throughout the dermis with "flame figures," which can be seen in a variety of disorders of eosinophil activation. Peripheral eosinophilia is common. Although the prognosis of Wells syndrome is generally excellent and most lesions tend to fade spontaneously, systemic corticosteroids hasten resolution. Dapsone, griseofulvin, minocycline, cyclosporine, and colchicine have sometimes been found to be effective.<sup>375</sup>

## Pregnancy and Pregnancy-Related Dermatoses

Pregnant adolescents may show a variety of physiologic changes during their pregnancy and postpartum periods (Box 20-8). In addition to these physiologic changes, a variety of pruritic dermatoses in association with pregnancy have been described. Although controversial, the specific dermatoses of pregnancy have recently been reclassified into pemphigoid gestationis (4.2%); pruritic urticarial papules and plaques of pregnancy (PUPPP) (21.6%); cholestasis of pregnancy (3%); a new category of atopic eruption of pregnancy, which includes eczema during pregnancy (49.7%), prurigo of pregnancy (0.8%), and pruritic folliculitis of pregnancy (0.2%); and miscellaneous dermatoses (20.6%) (Table 20-4).<sup>376-378</sup> Pustular psoriasis (see Chapter 4) may be triggered by pregnancy as well and presents during the third trimester with erythematous patches studded with subcorneal pustules. Pustular psoriasis of pregnancy (also called *impetigo herpetiformis*) may lead to stillbirth or neonatal death because of placental insufficiency. Apart from pemphigoid gestationis, an intensely pruritic immune-mediated blistering eruption (reviewed in Chapter 13), the cause of pregnancy-related dermatoses is unknown.

PUPPP, also called *polymorphic eruption of pregnancy (PEP)*, is the most common cutaneous disorder specifically related to pregnancy.<sup>379</sup> Intensely pruritic, the dermatitis occurs late in the third trimester or in the immediate postpartum period. It occurs in approximately 1 in 160 pregnancies and 75% of the time affects a primigravida.<sup>380</sup> The disorder has only once been described in the neonate of an affected mother (in contrast to pemphigoid gestationis).<sup>381</sup> This is a disorder of exclusion, and no diagnostic test is available.

**Table 20-4** Classification of Pruritic Dermatoses of Pregnancy

Name	Alternate Names	Risk to Fetus
Pemphigoid gestationis	Herpes gestationis, gestational pemphigoid	Increased risk of prematurity and small-for-gestational-age babies
Pruritic urticarial papules and plaques of pregnancy (PUPPP)	Toxic erythema of pregnancy, polymorphic eruption of pregnancy (PEP)	None
Atopic eruption of pregnancy, eczema in pregnancy, prurigo of pregnancy	Prurigo gestationis (of Besnier), papular dermatitis of pregnancy, early onset prurigo of pregnancy, pruritic folliculitis of pregnancy	None
Cholestasis of pregnancy	Obstetric cholestasis, intrahepatic cholestasis of pregnancy	Increased risk of premature labor, fetal distress, meconium staining, and fetal death



**Figure 20-53** Pruritic urticarial papules and plaques of pregnancy. Note the small erythematous papules and urticarial wheals on the distended abdomen of this pregnant adolescent.

The condition usually begins as 1- to 2-mm urticarial papules on the abdomen (Fig. 20-53), often within the abdominal striae. These papules soon coalesce to form large erythematous plaques and then spread to involve the abdomen, buttocks, thighs, and in some cases, the arms and legs. The upper chest, face, palms, soles, and mucous membranes tend to be spared. Although pruritus is commonly extreme, and patients are often unable to sleep, excoriations are rare. Topical application of corticosteroids usually provides symptomatic relief; if the condition is severe or unresponsive to topical medication, brief courses of systemic corticosteroids are often beneficial.

Intrahepatic cholestasis of pregnancy occurs in 1 in 1500 pregnancies (20% of cases of obstetrical jaundice) and is characterized by intense pruritus. The only skin lesions are excoriations. By definition, affected females have generalized pruritus without history of exposure to hepatitis or hepatotoxic drugs, with appearance usually during the last trimester of pregnancy and disappearance within 2 to 4 weeks after delivery. The condition tends to recur during subsequent pregnancies in 65% of affected women and has been associated with risks to the fetus (see Table 20-4). The risk with twin pregnancies is higher, and a positive family history is seen in 50% of affected individuals.

Pruritus tends to be worse at night and on the trunk, palms, and soles. No primary skin lesions are seen. Approximately half of affected patients show jaundice, dark urine, or stools light in color. More severely affected women may have malabsorption, including that of vitamin K. The diagnosis can be confirmed by finding increased serum bile acids without evidence of viral hepatitis or another explanation. Treatments include rest and a low-fat diet, cholestyramine, oral guar gum (a dietary fiber that lowers bile acid levels), and ursodeoxycholic acid (which can substitute for more toxic bile acids).

*Prurigo of pregnancy* is a term used to describe a heterogeneous group of disorders that occurs earlier than PUPPP, usually in mid-trimester, and is now included as part of atopic eruption of pregnancy

(see Table 20-4). Cholestasis as a cause of pruritus must be eliminated through finding normal liver function tests. Pruritic folliculitis of pregnancy, a subset of prurigo of pregnancy, presents between the fourth and ninth months of pregnancy as a pruritic follicular papular and pustular eruption and generally resolves within a few weeks after delivery. Eczema in pregnancy presents, most commonly during the second trimester, as eczematous patches and plaques that can be generalized. Topical application of corticosteroids or narrow-band ultraviolet B (UVB) light have been helpful in the management of this subset of patients.

## Autoimmune Progesterone Dermatitis

This rare disorder most commonly begins at menarche and is thought to represent an autoreactivity reaction to progesterone.<sup>382</sup> It thereafter occurs approximately 3 to 10 days before the onset of menstrual flow and ends approximately 2 days into menses. It may also be seen in individuals on anovulatory hormone therapy and in pregnant women during the first trimester of pregnancy. The condition is characterized by urticarial vesiculobullae, papules, pustules, EM, and dyshidrotic eczema-like eruptions on the extensor surfaces of the thighs, forearms, hands, and buttocks.<sup>383,384</sup> Rarely, the disorder may manifest with angioedema and laryngeal spasms requiring epinephrine administration.<sup>385</sup>

The diagnosis of autoimmune progesterone dermatitis can be confirmed by an urticarial wheal at the site of intradermal skin test to an aqueous progesterone suspension. Treatment consists of estrogens or tamoxifen. Oophorectomy can be considered for patients unresponsive to other modes of therapy.

The complete list of 385 references for this chapter is available online at <http://expertconsult.inkling.com>.

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The term *vasculitis* refers to inflammation of blood vessels, a finding that can be seen in association with a variety of clinical manifestations and as either a primary or secondary phenomenon. Along with vessel inflammation there is deposition of fibrinoid material in vessel walls and the presence of nuclear fragments (nuclear dust) resulting from disintegration of neutrophilic nuclei (karyorrhexis) within the vessel wall and surrounding tissues (hence the terminology *leukocytoclastic vasculitis*). The presence of vasculitis may result in tissue injury owing to vascular stenosis, occlusion, aneurysm, or rupture. The incidence of childhood vasculitis is approximately 50 cases per 100,000 children per year, with geographic differences noted throughout the world.<sup>1</sup>

The vasculitic disorders are a heterogeneous group of conditions, many of which present with (or eventually result in) cutaneous manifestations. Classification of the vasculitides is difficult and has most often been based on the gross and microscopic features of the disease process, primarily the vessel size involved (i.e., large, medium-sized, or small). Large-vessel vasculitides, which will not be discussed here, include giant-cell (temporal) arteritis and Takayasu arteritis. Medium-sized vasculitides involve predominantly visceral arteries and include two of the most common forms of pediatric vasculitis syndromes, polyarteritis nodosa (PAN) and Kawasaki disease (KD), both of which will be discussed. The other entities covered in this chapter all represent small-vessel disorders, which tend to involve primarily capillaries and venules. It should be remembered that this classification of vasculitis based on vessel size is imprecise, and overlap in the size of involved vessels is common. A summary classification of pediatric vasculitides is shown in Table 21-1. The original patient groups used to develop vasculitis classification criteria by the American College of Rheumatology (ACR) did not include children. Subsequently the vasculitis working group of the Pediatric Rheumatology European Society (PRES), in conjunction with the European League Against Rheumatism (EULAR) and the Pediatric Rheumatology International Trials Organization (PRINTO), more recently developed and validated criteria for some of the most common childhood vasculitides, a process that culminated at the 2008 Ankara Consensus Conference.<sup>2,3</sup> A summary of these criteria is shown in Table 21-2.

## Henoch–Schönlein (Anaphylactoid) Purpura

Henoch–Schönlein purpura (HSP), also known as *anaphylactoid purpura*, is a form of small-vessel vasculitis that occurs primarily in children (especially boys) between 2 and 11 years of age, most commonly occurring in children under the age of 5 years. It is the most common type of childhood systemic vasculitis. The classic presentation is a combination of nonthrombocytopenic palpable purpura in dependent areas, arthritis, abdominal pain, and glomerulonephritis. HSP is an inflammatory disorder that has been linked hypothetically to several potential etiologic agents including group A β-hemolytic streptococci (GABHS), other bacterial or viral organisms, immunizations, and drugs, although the exact etiology remains unclear.<sup>4</sup> There are reports of patients with coexisting HSP and acute rheumatic fever, highlighting the potential association between GABHS and HSP.<sup>5</sup> *Bartonella henselae* has also been suggested as a potential etiologic infectious agent.<sup>6</sup> Although the nature of the immunologic reaction in HSP is not completely clear, the common history of antecedent upper respiratory tract infection preceding the onset of symptoms suggests a hypersensitivity phenomenon resulting in localized or widespread

vascular damage. A fairly consistent immunologic observation is the deposition of immunoglobulin (Ig) A immune complexes in affected organs (i.e., skin, kidneys) when studied by immunofluorescence. IgA complexes, however, are not a necessary requirement for the development of HSP, and their absence should not exclude the diagnosis. Around one-third of patients have elevated serum IgA levels.<sup>7</sup> Several polymorphisms involving cytokines and cell-adhesion molecules that modulate inflammatory responses and endothelial cell activation have been observed and may correlate with disease susceptibility, extent of involvement, and/or severity of renal disease.<sup>8</sup> Mutations in the *MEFV* gene, which is classically associated with familial Mediterranean fever with homozygous or compound heterozygous mutation, have been described in some patients with HSP and may portend more common gastrointestinal and joint involvement and edema.<sup>9</sup>

The clinical picture of HSP is often, but not always, distinctive. Most patients with a rash present with an initial urticarial eruption of macules and papules (Fig. 21-1) that rapidly become purpuric and are distributed primarily on the lower extremities (Figs. 21-2 through 21-4) and buttocks (Fig. 21-5). Lesions may also occur on the upper extremities, trunk, and face, and in some instances skin lesions may develop in patterns at pressure sites. In some patients, petechiae (Fig. 21-6) or ecchymoses ("bruises") (Fig. 21-7) may predominate over palpable purpuric lesions. The cutaneous eruption is the presenting feature of HSP in 50% of cases.<sup>4</sup> Newer purpuric lesions develop and may result in a polymorphous appearance. Other skin lesion morphologies, including vesicular or bullous lesions, erosions or ulcers, necrosis, gangrene, and even erythema multiforme-like lesions, may occur.<sup>10,11</sup> Marked edema of the hands, feet, scalp, or face may also be seen, especially in younger patients.<sup>4,12</sup> The disease often consists of a single episode that may last for several days to weeks, but in some cases recurrent attacks may occur at intervals for weeks to months.

Individual lesions of HSP occur in crops, tend to fade after about 5 days, and eventually are replaced by areas of hyperpigmentation or ecchymoses. Although the differential diagnosis of the skin lesions may include drug reaction, erythema multiforme, or urticaria, the presence of palpable purpura (the hallmark of leukocytoclastic vasculitis) will usually clarify the true nature of the disorder. This characteristic finding, created by edema and extravasation of erythrocytes, gives individual lesions their diagnostic palpable and purpuric appearance as well as their nonblanching quality (i.e., individual lesions cannot be blanched when viewed through a glass slide exerting pressure over the surface, a technique called *diascopy*).

Occasionally the face, mucous membranes of the mouth and nose, and the anogenital regions may show petechiae. In males, vasculitis of the scrotal vessels may lead to acute scrotal swelling with or without erythema or purpura (Fig. 21-8). Pain may be severe, and this presentation may mimic that of testicular torsion or other causes of "acute scrotum," necessitating ultrasonography and/or radionuclide scans to help differentiate between these disorders.<sup>13</sup> In one study, roughly 20% of males with HSP had scrotal involvement, and these patients were noted to have an association with headache, edema, and elevated C3 levels.<sup>14</sup>

Systemic involvement in HSP, which is seen in up to 80% of cases, most commonly occurs in the kidneys, gastrointestinal tract, and joints. The degree of systemic involvement varies, with joint or gastrointestinal symptoms seen in as many as two-thirds of affected children. Renal disease occurs most often and is the most significant correlate of long-term prognosis.<sup>7</sup>

The clinical expression of HSP kidney involvement varies from transient microscopic hematuria to rapidly progressive glomerulonephritis. Glomerulonephritis is seen overall in 40% to 50% of children with

**Table 21-1** Classification of Pediatric Vasculitides

Predominant Vessel Size	Disorder
Large	Takayasu arteritis
Medium	Polyarteritis nodosa Kawasaki disease
Small	Hypersensitivity vasculitis (cutaneous leukocytoclastic vasculitis) Henoch-Schönlein purpura Acute hemorrhagic edema of infancy Hypocomplementemic urticarial vasculitis Cryoglobulinemic vasculitis Erythema elevatum diutinum (primarily adults) ANCA-associated: Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) Churg-Strauss syndrome Microscopic polyangiitis

ANCA, Antineutrophil cytoplasmic antibody.



**Figure 21-1** Henoch-Schönlein purpura. These early lesions are urticarial in nature. Note associated central erosion/crusting in some of the plaques.

**Table 21-2** Diagnostic Criteria for Some Childhood Vasculitides: Ankara Classification\*

Disorder	Diagnostic Criteria
Henoch-Schönlein purpura	Purpura or petechiae (mandatory) with lower limb predominance <sup>†</sup> and at least one of following 4 criteria: Abdominal pain Histopathology (LCV with IgA deposits or proliferative GN with IgA deposits) Arthritis or arthralgia Renal involvement
Childhood polyarteritis nodosa	Histopathology (necrotizing vasculitis in medium- or small-sized arteries) or angiographic abnormalities <sup>‡</sup> (mandatory) plus 1 of the following 5 criteria: Skin involvement <sup>§</sup> Myalgia/muscle tenderness Hypertension Peripheral neuropathy Renal involvement
Granulomatosis with polyangiitis <sup>  </sup>	At least 3 of the following 6 criteria: Histopathology (granulomatous inflammation within artery wall or perivascular area) Upper airway involvement <sup>¶</sup> Laryngotracheobronchial stenosis Pulmonary involvement** ANCA positivity Renal involvement

Modified from Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria. Ann Rheum Dis 2010;69:798–806.

ANCA, Antineutrophilic cytoplasmic antibody; GN, glomerulonephritis; Ig, immunoglobulin; LCV, leukocytoclastic vasculitis.

\*Also referred to as EULAR/PRINTO/PRES criteria.

<sup>†</sup>For purpura with atypical distribution, demonstration of IgA deposit in biopsy required.

<sup>‡</sup>Angiography: aneurysm, stenosis, or occlusion of medium- or small-sized artery.

<sup>§</sup>Livedo reticularis, nodules, infarctions.

<sup>||</sup>Formerly known as Wegener granulomatosis.

<sup>¶</sup>Purulent/bloody nasal discharge, recurrent epistaxis/crusts/granulomas, septal perforation or saddle nose deformity, sinusitis.

<sup>\*\*</sup>Nodules, cavities, or fixed infiltrates.



**Figure 21-2** Henoch-Schönlein purpura. Urticarial, purpuric papules and plaques on the lower extremity.

HSP and is usually transient and benign.<sup>15</sup> The renal lesion in HSP is indistinguishable histopathologically from that of IgA nephropathy (Berger disease), although the latter tends to occur more often in older patients.<sup>4</sup> The renal involvement may not become apparent for several weeks; hence the importance of long-term follow-up monitoring for development of this complication. Most often, however, if kidney involvement is going to be seen, it will be found within 3 months of disease onset.<sup>16</sup> Potential correlates of kidney disease in HSP include age over 4 years, persistent purpura, severe abdominal pain, and depressed coagulation factor XIII activity less than 80%.<sup>16</sup> Initial renal insufficiency appears to be the single best predictor of the further clinical course in children with HSP nephritis.<sup>17</sup>

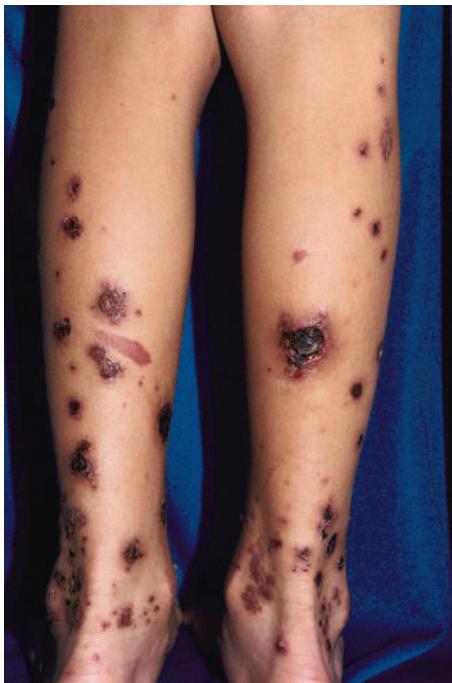
Gastrointestinal signs and symptoms result from edema and hemorrhage of the bowel wall as a result of vasculitis. They most often include colicky abdominal pain (that may be severe and associated with vomiting), hematochezia, and hematemesis. Visceral infarction or perforation, pancreatitis, cholecystitis, esophageal involvement, colitis, protein-losing enteropathy, intussusception, hemorrhage, or



**Figure 21-3** Henoch–Schönlein purpura. Palpable purpuric papules and plaques.



**Figure 21-5** Henoch–Schönlein purpura (HSP). Palpable purpura of the buttocks, a classic site of involvement in HSP.



**Figure 21-4** Henoch–Schönlein purpura. These purpuric plaques became bullous with subsequent necrosis.



**Figure 21-6** Henoch–Schönlein purpura. This patient had small petechial macules of the upper extremities with larger, more classic purpuric plaques of the buttocks and lower extremities.

shock may also be associated. Intussusception, seen in up to 2% of patients, is more common in boys. Because non-HSP-associated intussusception generally occurs in children younger than 2 years of age, when intussusception is diagnosed in older children HSP must be strongly considered. Chronic intestinal obstruction with ileal stricture has also been reported, occurring months after resolution of the acute illness.<sup>18</sup>

Joint involvement in HSP is characterized by tender and painful joints with primarily periarticular swelling. True arthritis is less common. Although the ankles and knees are most often affected, the elbows, hands, and feet may also be involved. HSP joint symptoms tend to be oligoarticular. Arthritic symptoms are usually transient and rarely result in permanent deformity.

In addition to the skin, genitourinary and gastrointestinal tracts, and joints, other organ involvement is occasionally seen in HSP. Central nervous system (CNS) involvement results most commonly in headache and occasionally behavioral alteration, hyperactivity, intracerebral bleeds, paresis, or seizures.<sup>4,19</sup> Status epilepticus has been

rarely reported.<sup>20</sup> Respiratory involvement may range from an asymptomatic pulmonary infiltrate to recurrent episodes of pulmonary hemorrhage. Bleeding diathesis may occasionally occur.

The diagnosis of HSP is seldom difficult when patients exhibit the classic “tetrad” of organ involvement (skin, kidneys, gastrointestinal tract, and joints). However, many patients show only some of these findings, and the differential diagnosis depends on which organ-specific symptoms predominate. The differential diagnosis of palpable purpura may include hypersensitivity vasculitis (HV) (usually caused by drug reaction; see Hypersensitivity Vasculitis section), hemorrhagic diathesis (i.e., factor deficiency), or sepsis. In addition, the more “ecchymotic” lesions of HSP may be mistaken for child abuse<sup>21</sup> and must be evaluated within the context of the overall clinical presentation. When the diagnosis remains in doubt, histopathologic examination of a skin biopsy specimen is useful in confirming the presence of vasculitis. Direct immunofluorescence revealing IgA immune complexes is highly suggestive of but not pathognomonic for HSP. Other laboratory investigations to be considered include serum chemistry profile, blood-cell counts, coagulation studies, abdominal radiographic studies, stool guaiac testing, urinalysis, and kidney biopsy.

The overall prognosis for most patients with HSP is excellent, and full recovery without permanent residua is the norm. The disease tends to run its course over 4 to 6 weeks. In younger children, the disease is generally milder and of shorter duration with fewer renal and gastrointestinal manifestations and few recurrences. Renal disease is the most important prognostic indicator, and end-stage renal disease may occur in up to 5% of patients with nephritis.



**Figure 21-7** Henoch-Schönlein purpura. Occasional patients have ecchymotic (bruise-like) lesions without classic purpura, as in this 9-year-old male.



**Figure 21-8** Henoch-Schönlein purpura (HSP). This patient with HSP developed an acute onset of scrotal pain with edema and purpuric changes.

Long-term follow-up care is indicated in patients with kidney involvement. Recurrent flares of HSP may occur in up to 3% of patients, and in one study had a lag period of 2 to 26 months after the initial presentation.<sup>22</sup>

Supportive care is sufficient for the majority of patients, and nonsteroidal anti-inflammatory agents are useful for significant joint pain. The goals of HSP therapy are to minimize symptoms, decrease short-term morbidities, and prevent chronic renal insufficiency.<sup>23</sup> Systemic corticosteroids have been advocated for patients with severe gastrointestinal, joint, or scrotal involvement, as well as for renal involvement. They are generally not recommended for rash, mild joint pain, or mild abdominal discomfort alone. Various regimens have been recommended for HSP nephritis, including oral methylprednisolone or prednisone, high-dose intravenous pulse methylprednisolone, urokinase, cyclophosphamide, mycophenolate mofetil, azathioprine, plasma exchange, dipyridamole, and heparin/warfarin.<sup>17,24–29</sup> The benefits of systemic steroid therapy for HSP remain somewhat controversial. A meta-analysis revealed that corticosteroids reduced the mean resolution time of abdominal pain, reduced the odds of



**Figure 21-9** Acute hemorrhagic edema of infancy. Medallion-like ("cockade") purpura in a newborn female with congenital onset of the disease.



**Figure 21-10** Acute hemorrhagic edema of infancy. Purpuric patches with scalloped borders in an infant male with the disorder.

developing persistent kidney disease, and reduced the odds of both surgical intervention and recurrence.<sup>23</sup> However, in a long-term study assessing outcomes 8 years after a randomized placebo-controlled prednisone study in a cohort of 171 HSP patients, there were no differences between prednisone and placebo groups with regard to hematuria, proteinuria, or hypertension.<sup>30</sup> A retrospective cohort study of hospitalized children with HSP revealed an association between decreased hazard ratios for abdominal surgery, endoscopy and abdominal imaging, and early corticosteroid exposure.<sup>31</sup> Taken together, these and other reports suggest the need for more controlled studies of the effect of corticosteroids on HSP outcomes.

## Acute Hemorrhagic Edema of Infancy

Acute hemorrhagic edema (AHE) of infancy (AHE of childhood, Finkelstein disease) is a form of leukocytoclastic vasculitis characterized by fever, large purpuric skin lesions, and tender edema and reported most often in infants and children between the ages of 4 months and 3 years. The cutaneous lesions often have a "cockade" (medallion-like) pattern, with scalloped borders and central clearing (Fig. 21-9). They begin as edematous papules with petechiae and expand centrifugally with coalescence to result in the characteristic clinical pattern (Figs. 21-10 and 21-11).<sup>32</sup> Facial edema is common. Although the cutaneous eruption may be impressive, patients are usually otherwise well, and involvement of the gastrointestinal tract, kidneys, and joints is uncommon. Intussusception has been rarely observed.<sup>33</sup> The etiology



**Figure 21-11** Acute hemorrhagic edema of infancy. Multiple purpuric papules and plaques in the same patient shown in [Figure 21-10](#).



**Figure 21-12** Hypersensitivity vasculitis (HV). Multiple purpuric papules in an adolescent female with a drug-induced HV.

is unclear, although an infectious trigger (i.e., upper respiratory infection, conjunctivitis, pharyngitis, otitis media, or pneumonia) is hypothesized. Prodromal symptoms most often are limited to those of respiratory tract illness or diarrhea.<sup>34</sup>

Skin biopsy in AHE reveals leukocytoclastic vasculitis similar to HSP. Direct immunofluorescence studies, however, do not consistently reveal IgA deposition and in up to three-quarters of patients are entirely negative.<sup>32–36</sup> Laboratory findings may include leukocytosis and an elevated erythrocyte sedimentation rate, but hematuria, proteinuria, and hematochezia are usually absent. The course of AHE is marked by a rapid onset with a short benign course followed by complete recovery, usually over 1 to 3 weeks.<sup>37</sup> No treatment is generally necessary, because AHE is typically a self-limited process. Although the disorder resembles HSP, controversy exists over whether it represents an infantile form of HSP or whether it is a distinct and unrelated clinical entity. Arguments in favor of the latter include the lack of internal organ involvement, the absence of IgA immune deposits in most patients, and the benign course without a propensity toward recurrences.



**Figure 21-13** Hypersensitivity vasculitis (HV). Petechial macules of the penile shaft, glans penis, and scrotum in a young male with HV.

## Hypersensitivity Vasculitis

*Hypersensitivity vasculitis (HV)* (cutaneous small-vessel vasculitis, cutaneous leukocytoclastic vasculitis, cutaneous leukocytoclastic angiitis) is a term used to denote a leukocytoclastic vasculitis involving primarily the skin and in most cases is secondary to a drug ingestion or infectious process. It is most common in adults and significantly less common in children, in whom HSP is the most common form of cutaneous vasculitis. Potential infectious etiologies of HV include Streptococci, hepatitis B and C, nontyphoidal *Salmonella*, and *Mycobacteria* (both tuberculous and nontuberculous).<sup>38,39</sup>

The diagnosis of HV is one of exclusion, and other causes of primary cutaneous vasculitis (i.e., HSP, cryoglobulinemic vasculitis [CV]) or secondary cutaneous vasculitis (i.e., urticarial vasculitis [UV], connective tissue disorders, malignancy, endocarditis, Behcet disease) must be ruled out. The lesions of HV tend to occur in “crops” (groups of lesions of similar age) because of simultaneous exposure to the inciting antigen.<sup>40</sup>

Patients with HV most often present with palpable purpura ([Fig. 21-12](#)) and less often with urticaria, vesicles, pustules, superficial ulcers, or necrotic lesions. The lesions may be smaller and petechial in appearance in some patients ([Fig. 21-13](#)). Skin involvement is most notable in dependent areas and in areas of trauma or tight-fitting clothing.<sup>41</sup> Symptoms are usually absent, although pain or burning may be present, and systemic involvement is uncommon.

The list of potential drug causes of HV is extensive and includes multiple classes of antibiotics, nonsteroidal anti-inflammatory agents, antiepileptic drugs, insulin, propylthiouracil, omeprazole, and oral contraceptives.<sup>41–46</sup> (For a more complete listing of potential drug

etiologies, see Chapter 20.) Identification and withdrawal of the offending agent is vital in patients with HV, and in those with skin-limited disease no other specific therapy is usually necessary. For patients with either severe cutaneous or systemic involvement, therapeutic options include corticosteroids, colchicine, dapsone, or other immunosuppressive agents. The lesions of HV usually resolve over weeks to months with resultant postinflammatory hyperpigmentation.

## Urticular Vasculitis

*Urticular vasculitis (UV)* refers to a type of cutaneous leukocytoclastic vasculitis that presents with urticarial features and is often associated with an underlying systemic disease. In contrast to common urticaria, the lesions of UV are distinct in that they last for longer than 24 to 48 hours, often have a dusky or purpuric appearance, are associated more often with burning than pruritus, and leave postinflammatory hyperpigmentation after resolution ([Fig. 21-14](#)).<sup>40,47</sup> Confirmation of the diagnosis of UV often requires skin biopsy given the potential overlap with other conditions, especially allergic urticaria.<sup>48</sup> Deposits of IgG, complement, or fibrin may be found around blood vessels in UV in up to 80% of patients.<sup>49</sup>

UV may be idiopathic or associated with other diseases including autoimmune disorders, infections, drug reactions, or paraneoplastic syndromes. Most patients can be characterized as having either normocomplementemic UV (in which case the majority represent



**Figure 21-14** Urticarial vasculitis. These urticarial plaques, which had been persistent and had a faint purpuric quality, revealed leukocytoclastic vasculitis on histologic evaluation. The patient was ultimately diagnosed with systemic lupus erythematosus.

idiopathic UV) or hypocomplementemic UV (see the following section). Patients with hypocomplementemic UV have a propensity toward more severe multiorgan involvement and systemic disease associations.<sup>40,47,48</sup> The most commonly associated autoimmune disorders are systemic lupus erythematosus (SLE) and Sjögren syndrome (see Chapter 22). Serum sickness-like reactions to drugs, cryoglobulinemia, and hepatitis C virus (HCV) infection are also associated in some patients with UV.

### HYPOCOMPLEMENTEMIC URTICARIAL VASCULITIS SYNDROME

*Hypocomplementemic urticarial vasculitis syndrome (HUVS)* is the terminology used to describe patients with UV in association with angioedema and systemic symptoms, most often obstructive pulmonary disease and ocular inflammation (conjunctivitis, iritis, episcleritis, uveitis). Glomerulonephritis and arthritis may also be present, and the condition is relatively rare in pediatric patients.<sup>50</sup> Decreased serum Clq levels are seen in most patients, and autoantibodies against this factor are detectable in the serum.<sup>47</sup> Although antibodies to Clq are also found in some patients with SLE, HUVS appears to be a unique entity.

The cutaneous lesions of UV are urticarial in nature, favor the trunk and proximal extremities, and often have a purpuric quality. The primary distinguishing features are the persistence of lesions longer than is typical for allergic urticaria (2 to 6 hours), pain or burning, and associated hyperpigmentation as the lesions resolve. If the diagnosis of UV is confirmed, a thorough physical examination and laboratory investigation to assess for associated conditions are indicated. If an underlying disease is identified, specific therapy for that disorder is indicated. There is otherwise no specific therapy for UV. Various therapeutic modalities including prednisone, hydroxychloroquine, indomethacin, azathioprine, colchicine, methotrexate, cyclophosphamide, cyclosporine, intravenous Ig and dapsone have been used but with an inconsistent response.<sup>41,47–49,51,52</sup>

### Cryoglobulinemic Vasculitis

Cryoglobulins are circulating IgGs that precipitate at temperatures below 37°C and may be associated with any of several infectious, autoimmune, or malignant disorders. When these immune complexes deposit in blood-vessel walls and activate complement, CV results. Cryoglobulins have been classified into three types based on the presence or absence of monoclonality and their association with rheumatoid factor. Type I (monoclonal cryoglobulinemia) is a monoclonal antibody and is usually associated with a hematologic malignancy, whereas types II and III are composed of a mixed antibody response and hence are termed *mixed cryoglobulinemia*. The terminology essen-

tial mixed cryoglobulinemia is used to describe mixed cryoglobulinemia in the absence of other identified infectious, immunoblastic, or neoplastic disorders.<sup>53</sup> The most common infectious disease to be associated with CV is HCV, which is associated with mixed cryoglobulins.<sup>54</sup> In one large series of adults with SLE, cryoglobulins were detected in the sera of 25% of the patients and were associated with an increased incidence of HCV infection.<sup>55</sup> Patients with CV may experience a variety of skin manifestations including purpura, papules, nodules, skin necrosis, urticaria, livedo reticularis, and bullous or ulcerated lesions.<sup>41</sup> The classic triad of CV is purpura, weakness, and arthralgias, along with possible multiorgan involvement.<sup>53</sup> Treatment for CV should be directed toward the underlying systemic disease when one is identified. The main goals of therapy for mixed cryoglobulinemia are to eradicate HCV infection, delete the underlying B-cell clonal expansions that occur, and deplete the cryoproteins. A variety of anti-inflammatory, antiviral, and immunosuppressive agents (including pegylated interferon- $\alpha$ , ribavirin, and rituximab) have been used to this end with variable success.<sup>56</sup>

### Necrotizing Vasculitis with Granulomas

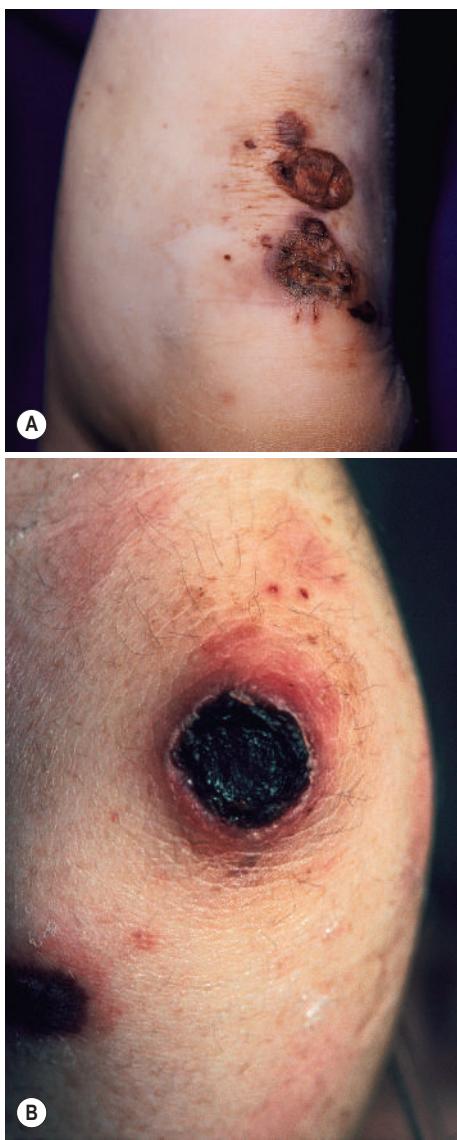
There are several systemic diseases in which necrotizing vasculitis is seen in association with granulomatous changes, including granulomatosis with polyangiitis (GPA), allergic granulomatosis (Churg-Strauss syndrome), and lymphomatoid granulomatosis. The first two will be discussed in this section. These disorders are primarily seen in adults but may occasionally occur in children. They are often associated with antineutrophil cytoplasmic antibodies (ANCA), which may play a pathogenic role and more importantly are useful in the diagnosis and management of (mainly small-vessel) vasculitides.<sup>7</sup> GPA and Churg-Strauss syndrome, along with the entity microscopic polyangiitis (MPA), have been collectively referred to as *ANCA-associated vasculitides*. MPA, which is not discussed in detail here, is characterized by a necrotizing small-vessel vasculitis without granuloma formation and with a similar presentation to GPA with less common involvement of the ear, nose, and throat, and occasional limitation to the kidneys.<sup>57</sup> Pulmonary capillaritis and necrotizing glomerulonephritis are seen, as are constitutional symptoms such as fever, malaise, arthralgias, myalgias, and weight loss.<sup>58</sup> Severe anemia may occasionally be the presenting symptom of MPA.<sup>59,60</sup>

### GRANULOMATOSIS WITH POLYANGIITIS

GPA (formerly known as *Wegener granulomatosis*) is a necrotizing granulomatous vasculitis of small- to medium-sized arteries involving the upper and lower respiratory tract in association with kidney involvement and variable degrees of vasculitis in other organ systems. Although it is quite rare, among the primary systemic vasculitides in children GPA is one of the most common and has an annual incidence of 0.03 to 3.2 per 100,000 children.<sup>61</sup> Classification criteria for GPA have been proposed by the ACR and the EULAR/PRES.<sup>61</sup> The latter diagnostic criteria have been demonstrated more sensitive in classifying pediatric GPA than the ACR criteria.<sup>62</sup>

GPA usually presents with constitutional symptoms (malaise, fatigue, fever, and weight loss), and symptoms referable to the upper and/or lower respiratory tracts include cough, rhinorrhea, nasal stuffiness, nasal mucosal erosions or ulcers, earache, or sinusitis. Hemoptysis or pleurisy may be present, and nodular cavitary lesions in the lungs are a characteristic finding on radiographic studies. The nose, nasal sinuses, nasopharynx, glottis, trachea, bronchi, and lungs may all be affected by the necrotizing vasculitis, and subglottic stenosis and nasal deformity may result, the former occurring more commonly in children.<sup>63</sup> Conjunctival injection may be present, as may arthralgias, myalgias, and glomerulonephritis, although pediatric disease may present without renal involvement. End-stage renal failure may occasionally result.

Skin involvement occurs in up to 53% of pediatric patients with GPA.<sup>63,64</sup> The manifestations are variable but most commonly consist of palpable purpura. Necrotic papules and plaques (Fig. 21-15), subcutaneous nodules, vesicles, pustules, and ulcers resembling pyoderma gangrenosum may occur. Papulonecrotic lesions may favor the



**Figure 21-15** Granulomatosis with polyangiitis (GPA; formerly known as Wegener granulomatosis). Painful, ulcerative, necrotic plaques on the ankle (**A**) and elbow (**B**) of a female with GPA.

extremities (especially the elbows) but may also occur on the face and scalp.<sup>41</sup> Purpura occurring on the lower extremities in conjunction with abdominal pain and hematuria may be the presenting feature of GPA, and this constellation may mimic HSP in the early stage.<sup>65</sup> Gingivitis can occur and presents as spongy, friable, and exuberant tissue with petechiae and preferential involvement of the interdental papillae. Ophthalmologic findings (which may occur in up to 50% of patients) include not only conjunctivitis, but also dacryocystitis, episcleritis, corneoscleral ulceration, retinal artery thrombosis, uveitis, proptosis, cavernous sinus thrombosis, and pseudotumor of the orbits. Pericarditis, endocarditis, and coronary vasculitis have been reported, and peripheral neuropathy and cerebral vasculitis, with or without subarachnoid or intracerebral hemorrhage, have been noted in up to 25% of patients.

The diagnosis of GPA is suggested by the clinical presentation and confirmed by tissue biopsy examination in conjunction with laboratory findings. Histologic evaluation of tissues (especially skin, lung, or kidney) reveals the characteristic necrotizing granulomatous vasculitis picture, which is highly suggestive of (but not pathognomonic for) GPA within the appropriate clinical context. Up to 80% of patients with GPA have positive cytoplasmic ANCAs (c-ANCA) and usually

negative perinuclear ANCAs (p-ANCA) on laboratory testing. In one series of pediatric patients with GPA, c-ANCA positivity correlated with kidney involvement.<sup>63</sup>

Before the advent of cytotoxic agents, GPA was nearly always a fatal disease with a mean survival of 5 months. The most commonly used treatment is a combination of immunosuppressive agents, most often glucocorticoids and cyclophosphamide and occasionally azathioprine.<sup>7,8,61</sup> Less commonly utilized therapies include plasmaapheresis, extracorporeal membrane oxygenation, intravenous immunoglobulin (IVIG), mycophenolate mofetil, and rituximab. Survival rates have improved with the addition of cytotoxic agents to the corticosteroids, but side effects and toxicities related to these drugs are a major source of morbidity. The use of methotrexate is advocated by some, and this agent has shown promise both in induction therapy in combination with glucocorticoids and in maintaining remission of the disease after induction with a cyclophosphamide and glucocorticoid regimen.<sup>66,67</sup> Cotrimoxazole is often used for treatment of GPA and may have benefit both in the prevention of opportunistic infection and in modifying disease activity.<sup>8,61</sup> Long-term morbidities related to GPA and its therapy may include infertility, skeletal complications (osteoporosis, avascular necrosis), renal failure, subglottic stenosis, hearing impairment, and nasal septal or upper airway deformities.<sup>68,69</sup>

### CHURG–STRAUSS SYNDROME

Churg–Strauss syndrome (CSS, allergic granulomatosis, eosinophilic GPA) is a rare condition characterized by atopic manifestations and a granulomatous vasculitis involving small- and medium-sized arteries. It occurs primarily in males between 30 and 40 years of age and only rarely in children. A distinguishing feature of CSS-associated asthma compared with typical allergic asthma is the late onset in the former, at a mean age of 35 years.

Patients with CSS often experience a prodromal phase during which time they have allergic rhinitis and asthma, and occasionally sinusitis and nasal polyps. After several years, they develop peripheral eosinophilia, eosinophilic tissue infiltration, worsening of their asthma, gastroenteritis, and diffuse pulmonary infiltrates (second phase). The third, or vasculitic, phase presents with fever, weight loss, and widespread vasculitis and inflammation. If left untreated, this phase may result in death. Clinical manifestations may include arthralgias, myositis, peripheral neuropathy, eosinophilic pneumonitis (Löffler syndrome), and occasional renal, cardiac, CNS, or ocular involvement. Cardiac involvement occurs in roughly half of the patients and may include pericarditis, myocarditis, and tamponade.<sup>70</sup> Skin involvement may occur in up to 70% of patients and includes palpable purpura, petechiae, subcutaneous nodules, urticaria, livedo reticularis, and papulonecrotic lesions similar to GPA.<sup>41,71</sup> Digital ischemic ulcers and Raynaud phenomenon have also been noted.<sup>72</sup>

The ACR criteria for the diagnosis of CSS support the diagnosis when four of the following six criteria are met: asthma, eosinophilia greater than 10%, mononeuropathy/polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormality, and biopsy containing a blood vessel with extravascular eosinophils.<sup>73</sup> Laboratory studies may be useful, because approximately 70% of adult patients with CSS have a positive ANCA, usually perinuclear with antimyeloperoxidase specificity (MPO-ANCA).<sup>72</sup> However, in contrast to adult patients, pediatric patients with CSS may be negative for ANCA.<sup>70,74,75</sup> In adults, ANCA positivity appears to portend more common ear-nose-throat manifestations (rhinitis, sinusitis, polyps), peripheral nerve involvement, and renal disease, whereas ANCA negativity may predict more common cardiomyopathy.<sup>76</sup>

CSS is treated with glucocorticoids with or without the addition of other immunosuppressive agents (i.e., cyclophosphamide, azathioprine), and the prognosis has traditionally been fairly favorable with a lower mortality rate in comparison to other systemic vasculitides. Combination therapy with other agents including cyclophosphamide, azathioprine, infliximab, or methotrexate may be useful in some patients. Steroid-dependent asthma, however, is common and may persist even after the vasculitis is in remission.<sup>77</sup> In a large series of children with CSS, more common cardiopulmonary manifestations, less common peripheral neuropathy, and higher mortality were noted when compared with the clinical experience in adults.<sup>74</sup> However, in

another smaller series, mononeuritis multiplex was present in 60% of children with CSS.<sup>75</sup>

## Erythema Elevatum Diutinum

Erythema elevatum diutinum (EED) is an uncommon dermatosis seen most often in middle-aged adults and characterized by violaceous papules, plaques, and nodules that have a predilection for acral and extensor surfaces. Common locations for the lesions of EED include the elbows, knees, dorsum of the hands and feet, pretibial surfaces, buttocks, and skin overlying the Achilles tendon.<sup>78</sup> The trunk and mucous membranes are usually spared. Histologically the lesions reveal a leukocytoclastic vasculitis.

EED presents with papules and plaques ranging in size from a few millimeters to several centimeters. They may be yellow and simulate xanthomas, but more often they are violaceous to brown, and less commonly erythema, vesicles, or bullae may be present. The differential diagnosis may include Kaposi sarcoma or bacillary angiomatosis. Although the lesions are typically asymptomatic, they may be tender or painful and may be accompanied by systemic abnormalities such as arthralgias, fever, and malaise. A burning sensation within lesions has been reported by some patients and may worsen in the evening or after exposure to cold temperatures.<sup>79</sup> Spontaneous involution may occur after a period of years without scarring, but residual hypopigmentation or hyperpigmentation is common.

The pathogenesis of EED is unknown, although it is believed to be an immune complex-mediated vasculitis. It has been described in association with various conditions, including hematologic malignancies, infections, autoimmune disease, and inflammatory bowel disease.<sup>78,80</sup> Rheumatoid arthritis-associated EED may present with the skin lesions in conjunction with peripheral ulcerative keratitis.<sup>81</sup> In recent years, EED has emerged as a dermatosis associated with human immunodeficiency virus (HIV).<sup>82</sup> It has been reported in a young woman with juvenile idiopathic arthritis,<sup>83</sup> as well as in a school-aged boy with a history of recurrent streptococcal pharyngotonsillitis, in whom it abated after dapsone therapy and tonsillectomy.<sup>84</sup>

EED tends to run a chronic course and may be persistent or may occasionally spontaneously resolve. Although topical or intralesional corticosteroids may sometimes be useful, the response to these agents is generally unsatisfactory. Dapsone may be effective and to many is considered the treatment of choice, although the lesions often recur upon discontinuation. Other reported therapies include colchicine, tetracycline, and cyclophosphamide. Surgical excision of large nodules is another therapeutic option.

## Polyarteritis Nodosa

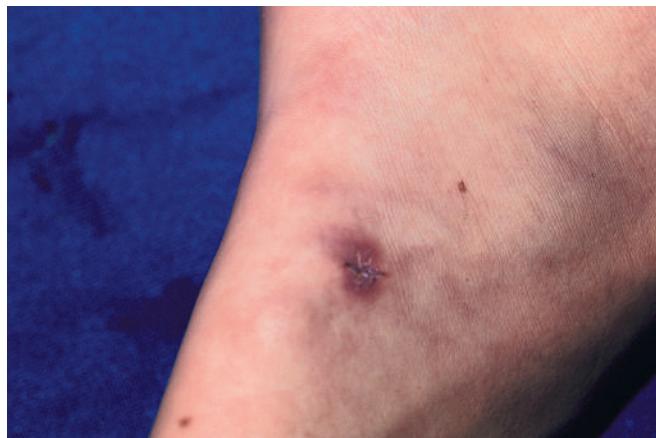
Polyarteritis nodosa (PAN), also known as *periarteritis nodosa*, is a relatively uncommon vasculitis in children that is characterized by inflammation of medium-sized (and in some cases, small-sized) arteries. Several subtypes of PAN have been identified, and the prognosis is variable and largely dependent upon the extent of associated (extra-cutaneous) organ involvement. The two variants discussed in this section are cutaneous PAN (cPAN) and systemic PAN. An infantile type of PAN may occur in children under 2 years of age but is now considered by most to represent a severe form of KD. The clinical features of pediatric PAN are briefly summarized in Table 21-3.

Patients with PAN often have constitutional symptoms including fever, malaise, and weight loss, as well as myalgias and arthralgias. Painful skin nodules, purpura, ulcerations, and livedo reticularis (Fig. 21-16) are the most common cutaneous findings. The nodules vary from 0.5 to 1 cm, are tender to palpation, and are usually red-purple (Fig. 21-17). They may follow the course of superficial arteries and are especially common around the knee, anterior lower leg, and dorsum of the foot.<sup>41</sup> Healing of the ulcerative skin lesions of PAN may result in atrophic, ivory-colored, stellate-shaped scars and hyperpigmentation.<sup>40</sup> Peripheral ischemia with infarction or gangrene may occur (Fig. 21-18). Other manifestations include abdominal pain, hematochezia, neuropathy, Raynaud phenomenon, and cardiac and

**Table 21-3** Clinical Features of Polyarteritis Nodosa in Childhood

	TYPE	
	Systemic PAN	cPAN
Presentation	Fever, CS	Fever, mild CS
Skin findings	Nodules, purpura, ulcers, livedo reticularis, infarction/gangrene, edema, Raynaud phenomenon	Nodules, purpura, ulcers, livedo reticularis, edema, gangrene
Extracutaneous involvement	Cardiac, renal, CNS/PNS, musculoskeletal, gastrointestinal, rarely pulmonary	Musculoskeletal, occasional PNS
Prognosis	Variable; relapse in around 35%	Good

Modified from Eleftheriou D, Dillon MJ, Tullus K, et al. Systemic polyarteritis nodosa in the young: a single-center experience over thirty-two years. *Arth Rheum* 2013;65(9):2476–85, and Bansal NK, Houghton KM. Cutaneous polyarteritis nodosa in childhood: a case report and review of the literature. *Arthritis* 2010;2010:687547. CNS, Central nervous system; cPAN, cutaneous polyarteritis nodosa; CS, constitutional symptoms (fever, fatigue, weight loss); PAN, polyarteritis nodosa; PNS, peripheral nervous system.



**Figure 21-16** Polyarteritis nodosa. Reticulate mottling (livedo reticularis) on the medial foot of a patient with polyarteritis nodosa.



**Figure 21-17** Polyarteritis nodosa. These dusky red nodules were firm and tender to palpation.



**Figure 21-18** Polyarteritis nodosa. This child with polyarteritis nodosa developed dusky red changes of the toes, followed by necrosis, as a manifestation of peripheral ischemia.

renal involvement, which may lead to renovascular hypertension. Pericarditis and valvular heart disease may occur. The lungs are usually spared in patients with PAN, although pleural effusions and pneumonitis have been reported.<sup>85</sup> Death, when it occurs, is usually attributable to renal failure, intracranial or intraabdominal hemorrhage, hypertensive heart failure, disseminated infection, or myocardial involvement.

Although the cause of PAN is unknown, it is presumed to represent a hypersensitivity-type immune-complex vasculitis with deposits of IgM, C<sub>3</sub>, or both in affected vessel walls.<sup>86</sup> Hepatitis B virus infection is associated in some cases, and group A streptococcal infection has been suggested as another potential infectious etiology. Laboratory findings may reveal anemia, leukocytosis, thrombocytosis, and an elevation of acute-phase reactants.<sup>87</sup> Serologic markers may be useful, as patients may have a positive ANCA (usually p-ANCA, although c-ANCA has also been observed). However, serologic studies alone are of limited use in the diagnosis of PAN given their lack of specificity or sensitivity. Skin biopsy is diagnostically valuable and reveals fibrinoid necrosis and inflammation of arteries in the deep dermis and subcutaneous layer and in some cases, septal panniculitis. Direct immunofluorescence studies are variable, occasionally revealing IgM or C<sub>3</sub> deposition. Mutations in the gene for familial Mediterranean fever, *MEFV*, are found in some pediatric patients with PAN and may represent a susceptibility factor, especially in countries where familial Mediterranean fever and its carriers are more common.<sup>88</sup>

cPAN (also known as *benign cPAN*) is the terminology used to describe a clinical variant of PAN in which cutaneous lesions predominate and there is no (or very limited) extracutaneous involvement. It is the most common form of PAN in children and tends to have a chronic course notable for remissions and relapses. The typical skin findings in cPAN are painful red nodules, especially on the lower extremities and malleoli with ulcers, purpura, and livedo reticularis. Peripheral gangrene and autoamputation occur with greater incidence in pediatric patients who have onset of cPAN in the first decade of life.<sup>89</sup> Constitutional symptoms including fever, arthralgias, myalgias, and peripheral nervous system involvement (mononeuritis mul-

tiplex, peripheral neuropathy, cranial nerve palsy) may occur, but visceral involvement is absent. The most notable laboratory aberrations are leukocytosis and elevation of the erythrocyte sedimentation rate.<sup>90</sup> The definitive diagnosis of cPAN is established by histopathologic features in tissue-biopsy specimens. The overall outcome of cPAN is favorable, although there are rare reports of cPAN evolving into systemic disease.

The mainstay of management for PAN is systemic corticosteroids. Cyclophosphamide, dipyridamole, azathioprine, intravenous γ-globulin, methotrexate, and plasma exchange have also been used.<sup>87,91,92</sup> Refractory disease has been treated with tumor necrosis factor (TNF)-α blockade (infliximab, etanercept, adalimumab), and rituximab has also been reported as effective.<sup>93,94</sup> In patients with skin-limited disease, therapy with aspirin or nonsteroidal anti-inflammatory agents has also been advocated.<sup>58,90,95</sup>

## Kawasaki Disease

Kawasaki disease (KD; also acute febrile mucocutaneous lymph node syndrome) is an acute febrile disease of childhood that is one of the leading causes of acquired heart disease in the world. It was described initially in 1967 by Tomisaku Kawasaki. KD is most prevalent in Japan, and its incidence is much higher in Asian-American populations, possibly suggesting a unique genetic susceptibility. Pathologically, KD is a vasculitis involving the small and medium-sized muscular arteries with a predilection for involvement of the main coronary vessels.<sup>96</sup> As mentioned earlier in this chapter, many believe that the entity referred to in the past as infantile PAN represents in fact a severe phenotype of KD.

The majority of cases of KD occur in children younger than 5 years of age, with a peak incidence in those 2 years and younger. The disease tends to be more common in boys than girls, and the attack rate in siblings (1%) is 10-fold higher than in the general population.<sup>97</sup> The mean age of patients with KD is younger in Japan than in the United States. Regional epidemics of KD have been observed, and the disease may occur year round, although larger numbers occur during the winter and early spring. The incidence of KD in the United States is estimated at 19 to 21 per 100,000 children younger than 5 years.<sup>98,99</sup>

The diagnosis of KD may be challenging, and misdiagnosis is common. In fact, missed diagnosis of KD is among the most common malpractice verdicts against child health practitioners.<sup>100</sup> Increasingly, atypical or “incomplete” presentations of KD are being diagnosed and tend to be more common in the youngest patients, in whom an extremely high level of suspicion must be maintained.<sup>100</sup> The diagnosis of KD should be considered in any infant with prolonged, unexplained fever. Delays in diagnosis and initiation of therapy may also occur more often in older children, who overall have a lower prevalence of disease.<sup>101</sup> In a large prospective study of patients with KD, common associated symptoms noted within 10 days before the diagnosis included irritability, vomiting, anorexia, cough, diarrhea, rhinorrhea, weakness, abdominal pain and joint pain.<sup>102</sup>

The diagnostic criteria for KD are listed in Box 21-1. KD should be considered in the differential diagnosis of any infant or child with fever, rash, and red eyes.<sup>97</sup> The fevers in KD are usually of abrupt onset and are quite high (>39°C), and the response to antipyretics is usually minimal. The fever usually lasts 1 to 2 weeks in the absence of treatment but may last as long as 3 to 4 weeks.<sup>103</sup> Although the Centers for Disease Control and Prevention (CDC) case definition of KD specifies fever persisting for 5 or more days, the diagnosis of KD is in some instances established before this time when other supporting features are present. The conjunctival injection (Fig. 21-19) is distinctive, with involvement of the bulbar conjunctivae more often than the palpebral conjunctivae and the absence of exudate (which may help in the differentiation from adenoviral infection). Perilimbal sparing (presenting as a white halo around the iris, Fig. 21-20) is characteristic and may be useful in differentiating KD eye involvement from other infectious or allergic processes.<sup>97</sup> Irritability is common in children with KD and may relate to cerebral vasculitis or aseptic meningitis.<sup>104</sup>

Oropharyngeal changes in KD are most notable for dry, red, fissured, and crusted lips (Figs. 21-21 and 21-22). Hyperemia of the oral mucosa and a red strawberry tongue (Fig. 21-23) (similar to that seen

### Box 21-1 Diagnostic Criteria for Kawasaki Disease

#### Classic Kawasaki Disease (KD)

Fever for 5 days or more,\* plus at least 4 of the following 5 clinical signs:

- Bilateral nonexudative bulbar conjunctivitis
- Oral mucous membrane changes: erythema of the oropharyngeal mucosa, injected or fissured lips, strawberry tongue
- Peripheral extremity changes: erythema or edema of hands/feet (acute), periungual desquamation (convalescent)
- Polymorphous rash
- Cervical lymphadenopathy (at least 1.5 cm, often unilateral)

#### Incomplete KD

Fever for  $\geq 5$  days with 2 or 3 of the above clinical criteria

#### Atypical KD

Patients who fulfill KD criteria but who have a clinical feature that is not typically seen with KD

\*In the presence of fever and the other diagnostic criteria for KD, experienced physicians may make the diagnosis before the fifth day of fever. Rowley AH, Shulman ST. Kawasaki syndrome. *Pediatr Clin N Am* 1999;46(2):313–29.

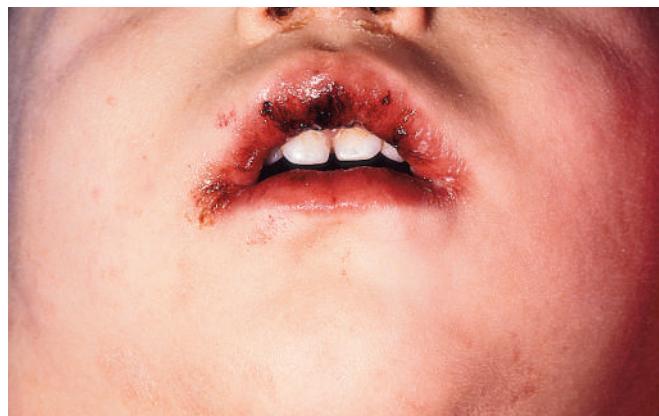


**Figure 21-19** Kawasaki disease. Nonexudative, bulbar conjunctival injection.



**Figure 21-20** Kawasaki disease. The conjunctivitis in this patient demonstrates the notable perlimbal sparing (halo of noninvolvement adjacent to the iris).

in streptococcal scarlet fever) are also seen. The peripheral extremity changes include nonpitting edema of the dorsal hands (Fig. 21-24) and feet (Fig. 21-25) and erythema of the palms and soles (Fig. 21-26). The edema is characterized by flesh-colored or red-violaceous brawny swelling, along with fusiform swelling of the digits and taut skin noted on the dorsal surfaces. Patients may complain of pain or



**Figure 21-21** Kawasaki disease. Lip hyperemia and crusting with fissures.



**Figure 21-22** Kawasaki disease. Lip hyperemia with mild crusting. Note the associated facial eruption.

refuse to walk. Periungual desquamation (Fig. 21-27) is a later finding, generally seen in the subacute or convalescent stages of KD. It begins at the tips of the digits and over a period of days to weeks, gradually progresses to involve the fingers, toes, palms, and soles. Recurrent episodes of skin peeling after upper respiratory tract infection may occur in up to 11% of KD patients for several years after their recovery.<sup>105</sup> Transverse linear grooves in the nail plates (Beau lines; Fig. 21-28) may also be appreciated months into the course of disease.

Cervical lymphadenopathy is the least common feature seen in KD, occurring in approximately 50% to 75% of patients.<sup>103</sup> When present it is usually quite obvious on physical examination given the size of the involved node(s). The diagnostic criterion specifies a size of at least 1.5 cm. Some patients with KD present with solely fever and unilateral enlargement of cervical lymph nodes. Generalized lymphadenopathy is not a feature of KD.

The cutaneous eruption of KD is polymorphous, and the majority of patients will have skin manifestations at some point during their illness. The most common presentations are that of a nonspecific, diffuse macular and papular erythematous eruption (Fig. 21-29) or a diffuse urticarial process (Fig. 21-30). A scarlet-fever-like rash with "sandpaper" papules on a background of erythema and erythema-multiforme-like lesions (Fig. 21-31) may also occur. Small pustules superimposed on urticarial erythema have also been observed.<sup>106</sup> An important finding on skin examination is accentuation of the eruption in fold areas, especially the groin (Figs. 21-32 and 21-33), which is quite common and should increase the practitioner's suspicion for KD in the presence of other suggestive clinical features. This erythematous, desquamating perineal eruption was found to occur in 67% of patients with KD in one series.<sup>107</sup> Erythema, induration, and



**Figure 21-23** Kawasaki disease. Hyperemia of the tongue with prominent lingual papillae ("red strawberry tongue").



**Figure 21-26** Kawasaki disease. Confluent, erythematous patches and plaques of the sole in a young boy with Kawasaki disease.



**Figure 21-24** Kawasaki disease. Nonpitting edema of the hand in a young male with Kawasaki disease.



**Figure 21-27** Kawasaki disease. Digital and periungual desquamation occurred late in the course of the disease in this boy who had coronary arterial aneurysms.



**Figure 21-25** Kawasaki disease. Mild edema of the feet accompanied by blanchable, erythematous macules and patches.



**Figure 21-28** Kawasaki disease. Transverse ridges (Beau lines) and nail-plate separation, which may occur several months after treatment for Kawasaki disease.

ulceration at the bacillus Calmette–Guérin (BCG) vaccination site have been described during the course of KD.<sup>108,109</sup> Rarely, severe peripheral ischemia with resultant gangrene may occur (Fig. 21-34).<sup>103</sup> Although the cutaneous eruption of KD is quite polymorphous, vesicles, bullae, and purpura are virtually never seen. The histopathologic features of skin biopsy material from patients with KD are nonspecific.

A psoriasis-like skin eruption, occasionally with a pustular psoriasis appearance, may also be seen in children during the acute or convalescent phases of KD.<sup>110,111</sup> In one series, two of nine patients had a family history of psoriasis, and in all of the patients, the psoriasis resolved with therapy for the KD and did not recur.<sup>110</sup> Whether this observation reflects activation of "latent" psoriasis in genetically



**Figure 21-29** Kawasaki disease. This young girl has hyperemic lips with crusting and a diffuse, confluent erythematous skin eruption.



**Figure 21-30** Kawasaki disease. Urticular patches are the prominent skin finding in this patient.



**Figure 21-31** Kawasaki disease. This child had a diffuse erythematous eruption with annular and targetoid (erythema multiforme-like) lesions.

predisposed individuals or a common etiologic agent for both KD and psoriasis is unclear.

The differential diagnosis of children with fever, rash, and red eyes is broad, and in addition to KD includes toxin-mediated bacterial infections (scarlet fever, toxic shock syndrome, staphylococcal scalded-skin syndrome), Rocky Mountain spotted fever, viral exanthematosus illnesses (i.e., adenovirus, measles, enterovirus), drug reactions (including Stevens–Johnson syndrome and toxic epidermal necroly-



**Figure 21-32** Kawasaki disease. The classic perineal eruption of Kawasaki disease is notable for accentuation in folds and desquamation.



**Figure 21-33** Kawasaki disease. This perineal and genital desquamation was preceded by pustules and occurred in a 5-year-old boy with high fevers, conjunctival injection, oropharyngeal changes, lymphadenopathy, and markedly elevated inflammatory markers.



**Figure 21-34** Kawasaki disease. Peripheral ischemia with gangrene of the distal digits.

sis), and a variety of other infectious, inflammatory, or connective tissue disorders. The differentiation of KD from acute adenoviral infection can be challenging. Although the presentations of these two processes can be very similar, two potentially distinguishing features of adenovirus infection are a purulent (vs. nonpurulent) conjunctivitis and the lack of a perineal accentuation of the rash.<sup>112</sup> A Kawasaki-like syndrome has also been observed in adults infected with HIV.<sup>113</sup> Because there exists no reliable diagnostic test to confirm KD, the

### Box 21-2 Clinical Clues to the Diagnosis of Kawasaki Disease

- Persistent fever for more than 5 days
- Fever unresponsive to antipyretics
- Extreme irritability, inconsolable nature of child
- Perilimbal sparing of conjunctival injection
- Perineal accentuation of erythematous/desquamating rash
- Erythema, induration or ulceration of BCG vaccination site
- Sterile pyuria
- Gall bladder hydrops
- Increasing ESR in light of clinical improvement/defervescence

BCG, Bacillus Calmette-Guérin; ESR, erythrocyte sedimentation rate.

**Table 21-4** Laboratory Findings in Kawasaki Disease

Finding	Comment
Leukocytosis	Often neutrophilic; toxic granulations may be present
Anemia	Normocytic, normochromic
Thrombocytopenia	Associated with severe coronary disease, myocardial infarction
Thrombocytosis	In subacute stage (usually ≥10–14 days after onset of illness)
Increased ESR	Normalizes over 6–10 weeks
Increased CRP	Normalizes in 2–5 days with treatment
Low albumin	
Abnormal lipids	Decreased HDL, total cholesterol; increased triglycerides, LDL
Increased transaminases, bilirubin	Secondary to gallbladder hydrops
Sterile pyuria	Mild proteinuria occasionally
CSF pleocytosis	Mononuclear
Increased NT-proBNP	Associated with cardiomyocyte stress; may be a marker for those developing coronary artery disease

CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N-terminal probrain natriuretic peptide.

diagnosis continues to rest on clinical vigilance, and the overall picture of the patient. Box 21-2 lists some useful clues to the diagnosis of KD.

Recurrent toxin-mediated perineal erythema (RTPE) is a benign, self-limited mucocutaneous disorder that may mimic some aspects of KD. The reported patients had perineal erythema, occasional involvement of the axillary and inguinal folds, and occasional desquamation of the fingers and feet.<sup>114</sup> Patients may report a recurrent history of such eruptions and are generally otherwise well. RTPE is believed to be caused by a unique clinical response to toxins elaborated by streptococci and staphylococci. Some patients have had positive pharyngeal or perianal cultures for GABHS.<sup>114,115</sup>

Other clinical features of KD include cardiac manifestations, CNS and gastrointestinal involvement, extreme irritability, lethargy, urethritis with sterile pyuria, anterior uveitis, musculoskeletal complaints (arthritis and arthralgia), and peripheral gangrene. CNS involvement may include meningeal signs with cerebrospinal fluid (CSF) pleocytosis, cerebral infarction, sensorineural hearing loss, and cranial nerve palsies. Gastrointestinal manifestations include hepatomegaly, hepatitis, gallbladder hydrops, diarrhea, and jaundice. Laboratory findings of KD are listed in Table 21-4.

Cardiac sequelae represent the most serious complications of KD. Cardiac involvement may occur during the acute or later stages of the disease. Early manifestations include pericardial effusions and myocarditis, which may present with tachycardia and gallop rhythm.<sup>96</sup> Congestive heart failure, arrhythmias, and valvular regurgitation (especially mitral) may also occur. The most significant cardiac

complication, though, is the development of dilatation or aneurysms of the coronary arteries, which occur in up to 5% to 10% of patients despite the use of appropriate therapy (and in up to 20% of untreated children).<sup>100,116,117</sup> Changes in the coronary arteries may continue to evolve beyond the acute phase of the illness, but the development of aneurysms more than 8 weeks after the acute illness is quite unusual. Although death owing to coronary occlusion has occasionally been noted after apparent recovery from the illness, most deaths occur suddenly between 3 and 8 weeks after the onset of the disease. "KD shock syndrome" is a rare association, presenting during the acute phase with hypotension and a shock-like state.<sup>117</sup>

The etiology of KD remains a mystery. Hypothetical causes have included infectious agents (via conventional antigen), a toxin-mediated superantigen process, genetic predisposition, and immune activation. In support of an infectious etiology are the fact that KD presents in a similar fashion to some other self-limited exanthematosus diseases, the seasonal predilection, the rare occurrence in infants under the age of 6 months (possibly suggesting protective maternal immunity), and the rarity of recurrences.<sup>97</sup> Many agents have been implicated, but none proven definitively, including *Staphylococcus*, *Streptococcus* species, *Candida* species, *Rickettsia* species, herpesviruses, *Mycoplasma pneumoniae*, human adenoviruses and Gram-negative bacteria.<sup>96,118–120</sup> Superantigen-secreting bacteria such as staphylococci and streptococci, specifically those that stimulate a Vβ2 T-lymphocyte response, have been postulated to be involved in the pathogenesis of KD.<sup>121</sup> IgA plasma cells have been identified in coronary vessel walls, pancreas, kidney, and respiratory tract in patients who succumbed to KD, suggesting entry of the KD etiologic agent through the upper respiratory tract with systemic spread to other organs.<sup>122</sup> The genetic predisposition hypothesis is appealing, given the disproportionately high attack rate among children of Japanese, Chinese, and Korean ethnicity, but the exact association remains unclear. Polymorphisms in the genes for C-reactive protein and TNF-α may be associated with a predisposition toward KD, with single-nucleotide polymorphisms occurring with greater frequencies in KD as compared with control subjects.<sup>123</sup> Candidate genes identified for KD include *ITPKC*, *FCGR2A*, *CAMK2D*, *CSMD1*, *LNX1*, *NAALADL2*, and *TCP1*, among many others.<sup>124–128</sup> A remarkable seasonality of KD has been observed, which is shared among extra-tropical areas (those north of the Tropic of Cancer) in the Northern Hemisphere.<sup>129</sup> A time series analysis of three geographically distinct regions with a high KD incidence (Japan, San Diego, and Hawaii) suggests that tropospheric wind currents may influence the development of disease via fluctuations in wind circulation (and possibly wind-borne transmission of the KD trigger).<sup>130,131</sup> Research into the pathogenesis of KD has been extensive, but the etiology remains elusive.

Treatment of KD is predicated on the ability to recognize the condition and rapidly render a diagnosis, which in some patients remains a challenge. The ultimate goals of therapy are to reduce inflammation and thus the potential for damage to the arterial wall.<sup>97</sup> The mainstays of therapy for KD are IVIG and aspirin, which should be initiated within the first 10 days of illness whenever possible.<sup>101</sup> In the United States, IVIG is generally given in one intravenous infusion of 2 g/kg infused over 12 hours, which was shown to be more effective than the more traditional 4-day course.<sup>132</sup> Issues surrounding IVIG therapy in KD include the expense of the preparation and the potential transmission of blood-borne pathogens, such as hepatitis C. Such transmission of infectious diseases is extremely rare since the institution of the current purification and processing practices in 1994.<sup>100</sup> A subgroup of patients with KD are resistant to IVIG therapy and seem to be at greatest risk for the development of coronary artery aneurysms and long-term sequelae.<sup>96</sup>

Aspirin is also started concurrently with IVIG, initially at a dosage of 80 to 100 mg/kg per day (in 4 divided doses) until the fever subsides (child is afebrile for 48 to 72 hours). This high-dose regimen is useful for its anti-inflammatory effect. Low-dose aspirin therapy (3 to 5 mg/kg per day) is then recommended, primarily for its antiplatelet effect. Unless the echocardiogram detects coronary artery abnormalities, aspirin therapy is discontinued once the laboratory studies normalize, which is usually within 2 months of the onset of disease. Risks of aspirin therapy include hepatitis, hearing loss, and Reye syndrome, the latter of which is mainly of significance in the setting of acute

varicella or influenza. Lower doses of aspirin (i.e., 30 to 50 mg/kg per day) are used in Japan given concerns in that population about potential hepatotoxicity. The exact role of aspirin therapy, as well as the risk-to-benefit ratio of high-dose versus low-dose regimens in patients with KD remains controversial.

Whereas the majority of patients with KD have an excellent response to the above therapies, approximately 5% to 15% have a suboptimal response. In these patients, a second dose of IVIG is often effective.<sup>125</sup> Other therapies that have been evaluated for KD (and for which there is no current consensus) include corticosteroids, pentoxifylline, and anti-TNF agents. A randomized prospective study failed to show any significant advantages of the addition of intravenous methylprednisolone to conventional primary KD therapy.<sup>133</sup> Other studies, however, have found that corticosteroids may in fact play a useful role as adjunctive initial therapy and that patients treated with steroids may have fewer coronary artery abnormalities.<sup>134,135</sup> Infliximab, a chimeric monoclonal antibody to TNF- $\alpha$ , has been used increasingly for IVIG-resistant disease in hospitalized patients in the United States<sup>136</sup> and has become the most commonly used third-line agent for KD.<sup>137</sup> It has been shown to be both efficacious and safe when compared to a second infusion of IVIG in patients who had received initial IVIG therapy.<sup>138,139</sup> Etanercept, another TNF- $\alpha$  inhibitor, has also been demonstrated effective in smaller-scale studies.<sup>140,141</sup> Rituximab may also be a useful therapeutic agent for resistant KD.<sup>142</sup>

Long-term cardiac follow-up monitoring of patients with KD should include an echocardiogram once or twice during the first 2 months after illness onset with further follow-up study depending on the individual patient's coronary artery status. Children whose coronary arteries are normal at 2 months after the diagnosis of KD are considered free of cardiac disease, although several experts consider a history of KD to be a risk factor for the later development of coronary artery disease.<sup>100</sup> Vascular lesions in adult survivors of KD may include coronary artery aneurysms, calcification, and stenosis, as well as valvular incompetence and myocardial fibrosis, either focal or diffuse.<sup>143</sup> The outcomes for patients with KD who are diagnosed at the extreme ends of the age spectrum (<6 months or >9 years) appear to be sub-

optimal, with a greater incidence of coronary artery abnormalities.<sup>144</sup> "Recurrent fever syndrome," characterized by the reappearance of inflammatory symptoms after successful therapy for KD, has been observed in some patients; it may resemble the clinical entity known as periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome and suggests a possible genetic predisposition to auto-inflammatory responses or environmental exposure susceptibility in these cohorts.<sup>145</sup>

The complete list of 145 references for this chapter is available online at <http://expertconsult.inkling.com>. 

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The connective tissue (collagen vascular, rheumatic) disorders represent a group of diseases characterized by inflammatory changes of the connective tissue in various parts of the body. Among these, juvenile idiopathic arthritis (JIA), lupus erythematosus, juvenile dermatomyositis (JDM), systemic and localized forms of scleroderma, eosinophilic fasciitis, Sjögren syndrome, mixed connective tissue disease (MCTD), and antiphospholipid antibody syndrome (APS) exhibit specific cutaneous findings.

## Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a group of seven arthritides of children under the age of 16 years that last longer than 6 weeks and are of unknown cause. JIA encompasses the former term *juvenile rheumatoid arthritis*, as well as other arthritides in children.<sup>1</sup> These include systemic arthritis (Still disease), oligoarthritis, rheumatoid factor (RF)-negative polyarthritis, RF-positive polyarticular arthritis, psoriatic arthritis, and enthesitis-related arthritis (Box 22-1).<sup>1,2</sup> Overall, juvenile arthritis has a prevalence of up to 1:1000 children under the age of 16 years.<sup>3</sup> Approximately 6% of these children have systemic-onset disease; 13%, RF-negative polyarticular arthritis; 2%, RF-positive polyarticular arthritis; 52%, oligoarthritis; 12%, enthesitis-related arthritis; 8%, psoriatic arthritis (see Chapter 4); and 8%, undifferentiated arthritis.<sup>4</sup> However, subtype distribution varies among countries; for example, although oligoarthritis is most common in Europe, polyarthritis is more common in New Zealand and India. RF, usually an immunoglobulin (Ig) M antibody against IgG, rarely occurs in children, especially children under 7 years of age, and is associated with greater synovial erosion with a poor prognosis. Antinuclear antibody (ANA) levels (which are positive in 10% of normal children, usually at a level of 1:40 to 1:80) are most commonly positive in children with oligoarticular disease (40% to 80%), especially in girls and with uveitis. The different subtypes of JIA are associated with human leukocyte antigen (HLA) types. Oligoarthritis is associated with HLABR8, HLABR6, and HLABR5, with chronic uveitis in oligoarthritis linked to HLABR5. RF-positive polyarticular JIA has been associated with HLABR4, whereas RF-negative polyarthritis has been linked to HLABR8, HLADPw3, and HLADQw4. Systemic-onset disease has been associated with HLABR4, HLABR5, and HLABR8, and the enthesitis-related arthritis (juvenile spondyloarthritis) with HLAB27 and a striking familial occurrence. Patients with JIA and coexisting atopy have been shown to have more active disease and worse outcomes, possibly because of ongoing immune dysregulation.<sup>5,6</sup>

Of the various forms of JIA other than psoriatic arthritis, systemic-onset disease is the only one with known cutaneous findings. Its underlying pathomechanism involving dysfunction in the innate immune system, its clinical features, and its poor response to therapies that ameliorate other forms of JIA have led several investigators to classify systemic JIA as an auto-inflammatory, rather than autoimmune, disease (see Chapter 25).<sup>7,8</sup> Systemic-onset disease affects boys and girls equally.<sup>9</sup> The eruption of systemic-onset JIA is usually intermittent, occurring most often when patients have their characteristic daily or twice daily spiking fevers. The fevers generally reach 39°C or higher, and the children appear acutely ill with exacerbation of joint pain when fevers occur. The characteristic flat to slightly elevated macules or occasionally papules may resemble urticaria but are not pruritic. They typically measure 2 mm to 6 mm in diameter. Lesions vary from salmon-pink to red and display a characteristic slightly irregular or serpiginous margin. The blanching macules are often evanescent and commonly subside during periods of remission and a few hours after defervescence. Individual lesions may coalesce to form

large plaques 8 to 9 cm in diameter. The eruption occurs predominantly on the trunk but often affects the extremities and occasionally the face (Fig. 22-1); it is accentuated by local heat or trauma. Seen in 25% to 50% of patients, it may precede fevers or visceral involvement by up to 3 years. In some patients the rash occurs during a period of only 1 week, in others for a year or more. Persistent pruritic papules and plaques can occur in children with systemic JIA (and more often in adults). Biopsy helps confirm the diagnosis and shows dyskeratosis of the upper epidermis and sparse inflammation.<sup>10</sup>

Many patients have extraarticular features, particularly hepatosplenomegaly, pleuritis, pericarditis, and lymphadenopathy, which may predate the joint manifestations by weeks to, rarely, years. Approximately 50% of affected individuals have a mild oligoarticular course with a good prognosis for remission; of the remaining 50%, approximately half will develop severe, recalcitrant, and destructive progressive polyarticular arthritis. Other complications of systemic-onset JIA include secondary amyloidosis, secondary infection, osteoporosis, and growth retardation.

Oligoarticular JIA occurs more often in girls than in boys and peaks between the ages of 2 and 4 years. Children with oligoarticular JIA often limp and show joints that are warm and effused, but not red and hot. In about 50% of cases, the onset is monoarticular with the knee, ankle, or elbow most commonly affected; small joints are usually spared. The acute onset of painful monoarthritis with refusal to bear weight is unlikely to be JIA, and infectious, traumatic, and malignant causes of joint pain should be considered. Approximately 20% to 30% of children with JIA have uveitis, which occurs most commonly in ANA-positive girls with early onset oligoarthritis.<sup>11,12</sup> The classic picture is a chronic bilateral anterior uveitis, which is usually asymptomatic until significant, and sometimes irreversible damage to intraocular structures occurs. Patients with oligoarticular JIA and uveitis have worse ocular outcomes relative to patients with other causes of uveitis, necessitating regular screening examinations.<sup>13</sup> Treatment of the uveitis includes topical corticosteroids, mydriatics, systemic immunosuppressive agents, and surgical management of complications.

Polyarthritis usually has an insidious onset, although it may be acute. It can involve both large and small joints (particularly of the hands and feet), and commonly involves the temporomandibular joints and cervical spine. Lymphadenopathy, hepatomegaly, and fevers may occur, although the fevers do not show the daily (quotidian) spikes seen in systemic JIA.

Children with enthesitis-related arthritis have inflamed tendons in addition to arthritis of one or more joints. Most affected individuals are boys over the age of 10 years. Although children rarely show typical ankylosing spondylitis at onset, spondyloarthropathy not uncommonly develops by adulthood.<sup>14</sup> Arthritis associated with inflammatory bowel disease is a subset of this type. Acute anterior uveitis can occur in up to 27% of children and tends to present as an acutely painful, red, photophobic eye in contrast to the asymptomatic uveitis seen in oligoarticular JIA.

Although more characteristic of SLE, scleroderma, and dermatomyositis, patients with JIA may also demonstrate cuticular telangiectasias. Subcutaneous nodules rarely are seen in children with JIA and occur most commonly in patients with RF-positive polyarthritis, particularly if the disease is recalcitrant to therapy. Barely palpable to several centimeters in size, they may be the first presenting sign of JIA. Their most common location is near the olecranon process on the ulnar border of the forearm. Less commonly they may occur on the dorsal aspect of the hands, on the knees and ears, and over pressure areas such as the scapulae, sacrum, buttocks, and heels. In the areas of fingers and toes, subcutaneous nodules are only a few millimeters

### Box 22-1 Subtypes of Juvenile Idiopathic Arthritis

#### Systemic-Onset Arthritis

Definition: Arthritis with or preceded by daily fever of at least 2 weeks' duration plus at least one of the following:

- Evanescent, nonfixed erythematous eruption
- Generalized lymphadenopathy
- Serositis
- Hepatosplenomegaly

#### Oligoarthritis

Definition: Arthritis that affects one to four joints during the first 6 months of disease. Two subtypes occur: 1) persistent oligoarthritis that never affects more than four joints; and 2) extended oligoarthritis that affects a total of five or more joints after the first 6 months of the disease

#### Exclusions:

- Family history of confirmed psoriasis in at least one first- or second-degree relative
- Family history of confirmed HLA B-27-associated disease in at least one first- or second-degree relative
- HLA-B27 positivity in a boy with the onset of arthritis after 8 years of age
- Positive RF testing
- Presence of systemic-onset arthritis as defined

#### Polyarthritis (RF-negative)

Definition: Arthritis that affects five or more joints during the first 6 months with RF-negative testing at least twice and at least 3 months apart. Systemic-onset JIA must be excluded

#### Polyarthritis (RF-positive)

Definition: Arthritis that affects five or more joints during the first 6 months of disease, associated with a positive RF test twice and at least 3 months apart. Systemic-onset JIA must be excluded

#### Psoriatic Arthritis

Definition: Must have arthritis and psoriasis, or arthritis and at least two of the following:

- Dactylitis
- Nail pitting or onycholysis
- Family history of confirmed psoriasis in at least one first-degree relative

#### Enthesitis-Related Arthritis

Definition: Arthritis and enthesitis, or arthritis or enthesitis and at least two of the following:

- Sacroiliac joint tenderness and/or inflammatory spinal pain
- HLA-27 positivity
- Family history of at least one first- or second-degree relative with confirmed HLA-27-associated disease
- Anterior uveitis that is usually symptomatic (pain, redness, photophobia)
- Onset of arthritis in a boy after the age of 8 years
- Systemic-onset JIA and confirmed psoriasis in at least one first- or second-degree relative must be excluded

HLA, Human leukocyte antigen; RF, rheumatoid factor; JIA, juvenile idiopathic arthritis.



**Figure 22-1** Juvenile idiopathic arthritis (JIA). Evanescent macular eruption occurred with fever in this boy with systemic-onset JIA.

in size. Subcutaneous nodules are firm and nontender and may be attached to the periarticular capsules of the fingers. They can be easily confused with the subcutaneous form of granuloma annulare (see Chapter 9). Rheumatoid nodules and JIA must also be distinguished from fibroblastic rheumatism, a rare disorder characterized by the sudden but sometimes progressive onset of cutaneous nodules (Fig. 22-2), flexion contractures, and polyarthritis.<sup>15,16</sup> Some affected individuals respond to methotrexate or interferon (IFN)- $\alpha$ . Methotrexate<sup>17</sup> and tumor necrosis factor (TNF) inhibitor<sup>18</sup> treatment have been linked to induction of subcutaneous nodules, most often in rheumatoid arthritis, but this nodulosis has only been described in adults.

Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) continue to be the first-line therapy in all but those with systemic JIA,<sup>19,20</sup> in addition to physical therapy and psychosocial support.<sup>21</sup> NSAIDs that preferentially inhibit the cyclooxygenase-2 (COX-2) enzymes have fewer gastrointestinal (GI) adverse effects and may be preferred in some patients. Pseudoporphyria, presenting with tense blisters in photodistributed sites, has most commonly been associated with the use of naproxen sodium but has been reported after administration of other NSAIDs as well, including COX-2 inhibitors (see Chapter 19).

Intraarticular injections of corticosteroids are used for children who do not respond to NSAID therapy or as initial therapy for oligoarthritis.<sup>22</sup> Methotrexate is usually the second line of treatment for persistent, active arthritis but is best initiated early in the disease course. Patients with oligoarticular arthritis tend to respond most favorably.<sup>23,24</sup> Blockade of TNF with biologics (etanercept, infliximab, adalimumab) in combination with methotrexate, is particularly effective for children with polyarticular arthritis.<sup>25</sup> Sulfasalazine has largely been used for enthesitis-related arthritis.

Systemic-onset JIA responds poorly to NSAIDs and TNF- $\alpha$  blockers (30% response) but will typically respond to corticosteroids and often to anakinra or canakinumab (anti-interleukin [IL]-1 receptor antagonists),<sup>26,27</sup> tocilizumab (humanized anti-IL-6 receptor monoclonal antibody),<sup>28–30</sup> abatacept (T cell-activating agent/IgG1 fusion protein),<sup>31</sup> or methotrexate.<sup>32,33</sup> Moderate or high dosages of systemic corticosteroids, including pulse intravenous steroids to avoid long-term high-dose treatment, are occasionally used for short periods while awaiting the effects of other medications. As a chronic



**Figure 22-2** Fibroblastic rheumatism. Firm skin-colored papules and nodules on the fingers and palm of this young boy with juvenile idiopathic arthritis.

inflammatory disorder and in relation to usage of systemic corticosteroids, JIA is associated with an increased risk of osteoporosis, which can be countered by treatment with calcium and vitamin D supplementation, bisphosphonates, and calcitonin.<sup>34</sup>

### MACROPHAGE ACTIVATION SYNDROME

Macrophage activation syndrome (MAS), a severe, life-threatening complication of systemic-onset JIA and other connective tissue diseases,<sup>35</sup> is associated with hemophagocytosis of activated macrophages/histiocytes and multiorgan dysfunction. When observed in the absence of underlying connective tissue disease, this diagnosis is termed *hemophagocytic lymphohistiocytosis (HLH)* and can be primary (when familial) or secondary (typically in the setting of infection or malignancy) (see Chapter 10). The pathophysiology of both MAS and HLH are speculated to involve inability of natural killer (NK) or CD8 T cells to lyse infected antigen-presenting cells, leading to ongoing infection and resultant “cytokine storm.” Patients show the sudden onset of fever, hemophagocytosis with hepatic dysfunction, disseminated intravascular coagulation, and sometimes encephalopathy, respiratory distress, and renal failure. The disease may present as pancytopenia with a falling erythrocyte sedimentation rate (ESR), in contrast to the increased ESR associated with flaring JIA. Formal diagnostic criteria for MAS are currently lacking, but a recent international consensus survey of pediatric rheumatologists revealed the 10 most useful diagnostic features: decreasing platelet count, hyperferritinemia, evidence of macrophage hemophagocytosis in the bone marrow, increased liver enzymes, decreasing leukocyte count, persistent continuous fever greater than 38°C, falling ESR, hypofibrinogenemia, and hypertriglyceridemia.<sup>36</sup> Patients with MAS and systemic JIA have been shown to harbor defects in NK-cell function and in genes that encode proteins crucial to lymphocytic cytolytic activity, including Munc 13-4 and perforin, which are also implicated in primary familial hemophagocytic lymphohistiocytosis.<sup>37</sup> Early recognition of MAS and treatment with high-dose corticosteroids with or without cyclosporine, etoposide, and/or etanercept may be life saving.<sup>38</sup>

## Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterized by autoantibody accumulation with immune complex deposition leading to end-organ damage. It often involves the skin but may affect almost any organ system. Autoantibodies are the hallmark of SLE, and activated B cells, T helper cells, and the cytokines that modulate inflammatory responses are thought to be the most appropriate targets for therapy. Both genetic and environmental factors are thought to play roles in its pathogenesis. Reports of familial cases and a high concordance for clinical disease in monozygotic, but not dizygotic, twins support a strong genetic contribution to the development of SLE. SLE has been linked to several genetic susceptibility loci that encode protein products involved in innate and adaptive immunity, particularly in pathways of apoptosis and immune complex clearance, activation of toll-like receptors (TLRs), and signaling of type I IFN and nuclear factor (NF)-κB.<sup>39–43</sup> The availability of whole exome sequencing has led to the discovery of pathogenic mutations in autosomal recessive juvenile-onset SLE (PRKCD, encoding protein kinase C $\delta$ ),<sup>44</sup> complement deficiency leading to SLE,<sup>45</sup> and autosomal recessive hypocomplementemic urticarial vasculitis (DNASE1L3).<sup>46</sup> Although most individuals with SLE do not have monogenic disease, these discoveries may increase understanding of the pathogenesis and lead to new ideas for therapy.

Environmental triggers, including ultraviolet (UV) light, medications, pesticides, heavy metals, tobacco, and infections, have all been linked to the development of SLE. In particular, exposure to UV light is a trigger, not only for cutaneous manifestations, but also for flares of systemic disease.<sup>47</sup>

Approximately 15% to 20% of all cases of SLE occur within the first 2 decades of life. Of these, 60% occur between the ages of 11 and 15 years, 35% between 5 and 10 years, and 5% in children younger than 5 years of age. Other than neonatal lupus erythematosus (NLE), the disorder is rarely seen before the age of 3 years. Disease onset in the

first decade of life is associated with a female to male ratio of 4:3, which increases to female predominance in the second decade (4:1), compared with a ratio of 9:1 in patients with adult-onset SLE. The overall prevalence is 5 to 10 out of 100,000 children, and both increased prevalence and severity are seen in African-American and Hispanic children, especially because of the increased prevalence of nephritis.<sup>48</sup> In comparison with SLE in adults, affected children have more severe disease in general, with an increased incidence of renal, neurologic and hematologic involvement at the time of diagnosis.<sup>49–51</sup> In one study, 77% of pediatric patients required moderate to high dosages of corticosteroids, compared with 16% of adult patients.<sup>52</sup>

About 80% of patients with SLE have cutaneous involvement at some time, often as the presenting sign. Diagnosis of SLE requires Systemic Lupus International Collaborating Clinics (SLICC) criteria that were established in 2012 (Table 22-1) and are more accurate at classification than the previous criteria established by the American College of Rheumatology (ACR) in 1982. The 1982 criteria included four mucocutaneous features: the malar eruption, discoid eruption, photosensitivity,<sup>53</sup> and oral ulcerations. In 2012, the dermatologic criteria for SLE were broadened to include the variety of subtypes of cutaneous lupus under either acute or chronic cutaneous lupus criteria. In addition, to prevent duplication of highly correlated terms related to cutaneous lupus, photosensitivity was replaced with diffuse, nonscarring alopecia.<sup>54</sup>

### Cutaneous Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) may occur as an isolated finding or in the setting of underlying SLE. Features of CLE may be classified as lupus-specific or nonspecific, based on clinical and histopathologic characteristics. Lupus-specific subsets of cutaneous disease characteristically demonstrate lupus-specific features on histopathology, including interface dermatitis and mucin deposition. These include acute CLE (ACLE), subacute CLE (SCLE), intermittent CLE (ICLE), and chronic cutaneous lupus erythematosus (CCLE). Lupus-nonspecific cutaneous disease includes a variety of reactive phenomena, which are not pathognomonic or specific for SLE but typically occur in active disease.

ACLE may present with a malar or butterfly rash or a more generalized morbilliform photodistributed eruption. In particular, the malar rash, while seen in approximately 60% of patients with SLE,<sup>53</sup> is not specific, but when present is often a sign of underlying systemic disease. This erythematous, mildly scaling eruption (Fig. 22-3) often appears over the cheeks and bridge of the nose, resembling the shape of a butterfly. It can be confused with the malar erythema of seborrheic dermatitis, erythematotelangiectatic acne rosacea, parvovirus infection, or cutaneous lichenoid graft-versus-host disease<sup>55</sup>; seborrheic dermatitis typically involves the nasolabial fold and shows



**Figure 22-3** Systemic lupus erythematosus. Mild scaling and erythema of the malar rash.

**Table 22-1** Criteria for Classification of Systemic Lupus Erythematosus (SLICC)

Criterion*	Comments
<b>CLINICAL CRITERIA</b>	
1 Acute cutaneous lupus	Lupus malar rash (fixed erythema, flat or raised, over malar eminences, usually sparing nasolabial folds), bullous lupus, photosensitive lupus rash (not dermatomyositis), maculopapular lupus rash, or toxic epidermal necrolysis variant Subacute cutaneous lupus (nonindurated annular polycyclic or psoriasisiform lesions that resolve without scarring)
2 Chronic cutaneous lupus	Classic discoid eruption (erythematous plaques with adherent keratotic scaling and follicular plugging, often atrophic scarring and dyspigmentation if older lesion; localized if only above the neck, otherwise generalized), lupus panniculitis (profundus), hypertrophic (verrucous) lupus, lupus tumidus, chilblains lupus, discoid lupus/lichen planus overlap, mucosal lupus
3 Oral ulcers	Palate, buccal, tongue, or nasal mucosa (no other cause identified)
4 Alopecia, nonscarring	Diffuse thinning or hair fragility in the absence of other causes (such as alopecia areata, iron deficiency, drugs, or androgenetic alopecia)
5 Synovitis	Must involve two or more joints with swelling or effusion or tenderness and at least 30 minutes of morning stiffness
6 Serositis	Pleuritis, pleural effusions or pleural rub; pericardial pain, effusion, rub or pericarditis without other cause
7 Renal	Persistent proteinuria $>0.5$ g/day or red blood cell casts
8 Neurologic	Seizures, psychosis, myelitis, mononeuritis multiplex, peripheral or cranial neuropathy, acute confusional state (all without other known cause)
9 Hemolytic anemia	
10 Leukopenia	$<4000/\text{mm}^3$ at least once or lymphopenia of $<1000/\text{mm}^3$ at least once without other cause
11 Thrombocytopenia	$<100,000/\text{mm}^3$ at least once without other cause
<b>IMMUNOLOGIC CRITERIA</b>	
1 Positive ANA	Above laboratory reference range
2 Anti-ds DNA antibody	Above laboratory reference range ( $>2$ -fold if by ELISA)
3 Anti-Sm antibody +	
4 Antiphospholipid antibody +	+ Lupus coagulant or anti-β2-glycoprotein I, medium- or high-titer anticardiolipin antibody, or false positive
5 Low complement	C3, C4, CH50
6 Direct Coombs test	In the absence of hemolytic anemia

ANA, Antinuclear antibody; DNA, deoxyribonucleic acid; ds, double-stranded; ELISA, enzyme-linked immunosorbent assay; SLICC, Systemic Lupus International Collaborating Clinics; Sm, Smith.

\*At least four criteria are required, including at least one clinical and one immunologic criterion. Biopsy-proven lupus nephritis plus a positive ANA or anti-ds DNA is also sufficient.



**Figure 22-4** Systemic lupus erythematosus. Note periungual telangiectasia, but also the relative sparing of the skin overlying the joints, in contrast to the distribution of Gottron lesions in juvenile dermatomyositis.

scaling as well. Brightly erythematous papules and plaques can also be seen on the photo-exposed extremities and V-shaped region of the neck. When this eruption presents on the dorsal aspect of the hands in SLE, the areas overlying joints are typically spared (Fig. 22-4), in contrast to JDM.

SCLE, which represents 10% to 15% of all cases of CLE, only occasionally occurs in pediatric patients.<sup>56,57</sup> The cutaneous lesions of SCLE arise quite suddenly, mainly on the upper trunk, extensor surfaces of the arms, and dorsal aspect of the hands and fingers. The lesions may be annular and may enlarge and merge into psoriasisiform or polycyclic lesions with thin and easily detached scales (Fig. 22-5). UV light is usually associated with exacerbations, but lesions tend to be nonscarring. Although arthritis and fatigue are common, patients usually only have mild systemic manifestations. The majority of patients with SCLE have anti-Ro (SS-A) antibodies and many have anti-La antibodies. Nonbullos annular lesions that clinically and histologically resemble Sweet syndrome (see Chapter 20) can also be seen as a manifestation of SLE; biopsy shows unique histologic features called the *histiocytoid form* of neutrophilic dermatosis.<sup>58</sup> Rowell syndrome was originally described as an erythema multiforme-like eruption in association with lupus (classically CLE), anti-La antibodies, and speckled ANAs; although controversy exists, most of these cases are probably SCLE or the concurrence of lupus and erythema multiforme.<sup>59</sup> SCLE is treated by strict sun protection, topical anti-inflammatory agents, antimalarials, and occasionally systemic corticosteroids.

Tumid lupus (lupus erythematosus tumidus) is a form of ICLE. Red to purplish urticarial plaques, which are relatively fixed in shape and do not undergo atrophy or scaling, usually occur on the face or other exposed areas of the body as a sign of photosensitivity. The progression rate of lupus erythematosus tumidus to SLE is unknown.

CCLE is an umbrella term used to describe lesions of discoid lupus erythematosus (DLE), lupus panniculitis, and chilblain lupus.



**Figure 22-5** Subacute cutaneous lupus erythematosus. The annular and polycyclic erythematous scaling lesions arose suddenly on this adolescent's anterior chest after sun exposure.



**Figure 22-6** Discoid lupus erythematosus (DLE). This young girl showed well-circumscribed, elevated, indurated, red to purplish annular plaques of DLE.

Individual lesions of DLE are well-circumscribed, elevated, indurated red to purplish plaques with adherent scale (Figs. 22-6 and 22-7) and fine telangiectasia. When untreated or as a sequela, discoid lesions may develop persistent areas of hyperpigmentation or hypopigmentation with atrophy. Discoid lesions can be asymmetric and are often exacerbated by exposure to UV light. DLE is most commonly found on the face, often with lesions on the ear helices and conchal bowls. Although the face is often the sole site of DLE without SLE, the scalp, arms, legs, hands, fingers, back, chest, abdomen, and even mucosal areas (Fig. 22-8) may also be involved. At times the openings of hair follicles are dilated and plugged by an overlying scale. If the scale is thick enough, it can be lifted off in one piece. The undersurface then reveals follicular projections that resemble carpet tacks, a characteristic sign of LE. Discoid lesions have been described in a linear orientation that follows the lines of Blaschko.<sup>60,61</sup>

In childhood, DLE is rare, and less than 3% of patients with DLE develop disease before the age of 10 years. DLE may present as an isolated finding or, more commonly, as a manifestation of underlying SLE. Some patients develop full criteria for SLE over time, mandating serial clinical and serologic evaluations for systemic disease. In adults, the rate of progression of DLE to SLE is reported to range from 0 to 28%, with an interval between onset of DLE and SLE ranging from months to decades.<sup>62–64</sup> Some studies in both adults and children have demonstrated that patients with generalized lesions (above/below the neck) are at higher risk for SLE.<sup>65–67</sup> In addition, adults with rising



**Figure 22-7** Discoid lupus erythematosus (DLE). The ear is often involved with DLE. Note the well-defined plaques of purplish erythema, focal overlying scaling, and postinflammatory hyperpigmentation and depigmentation.



**Figure 22-8** Discoid lupus erythematosus. Dyspigmentation and atrophy of the hard palate.

ANA titers, elevated ESR levels, anemia, leukopenia, arthralgias, nail changes, and evidence of nephropathy may predict progression to systemic disease.<sup>68–71</sup> Small studies in children have demonstrated an early rate of progression to SLE approaching 25% to 30% during a variable follow-up duration of months to years.<sup>65,72–75</sup> However, children with DLE who develop SLE appear to follow a benign course of systemic disease, with 89% of patients in one study meeting SLE classification criteria with mucocutaneous limited manifestations and no evidence of end-organ damage over 5 years of follow-up study.<sup>72</sup>

Intense inflammation of the fat (lupus panniculitis, lupus profundus) occurs in approximately 2% of patients with CLE, and may be associated with DLE, SLE, or, not uncommonly, as an isolated



**Figure 22-9** Lupus panniculitis. This boy with systemic lupus erythematosus and lupus panniculitis (lupus profundus) developed tender nodules on the thighs that ulcerated.

disorder.<sup>76</sup> Lesions are seen as firm, often asymptomatic, sharply defined, rubbery dermal and subcutaneous plaques or nodules with a predilection for the scalp, forehead, cheeks, upper arms, breasts, thighs, and buttocks. Although the skin overlying the lesions usually appears normal, it often ulcerates (Fig. 22-9) or becomes depressed. Biopsy shows a perivascular lymphocytic, plasma cell, and histiocytic infiltration in the deep dermis and subcutaneous fat without accompanying fat necrosis. The panniculitis may be lobular alone or involve both septae and lobules; most specimens show mucin deposition. Direct immunofluorescence often reveals Iggs or C3 deposits at the basement membrane. Approximately 70% of patients with lupus panniculitis also have typical lesions of DLE, and 50% eventually develop systemic involvement or symptoms of SLE such as fever, arthralgia, and lymphadenopathy. Lesions of lupus profundus may persist for years and leave significant disfigurement. Although erythema nodosum (see Chapter 20) may occur in a patient with SLE, lupus panniculitis can often be distinguished by its lack of tenderness, greater chronicity, and lack of predilection for the lower legs. Lupus panniculitis must also be distinguished from subcutaneous lymphoma by histologic features and T-cell rearrangement studies. Inflammatory panniculitis followed by lipoatrophy, likely autoimmune in mechanism but not associated with SLE or dermatomyositis, can involve localized areas, such as the ankles or abdomen.<sup>77</sup> Lipoatrophic panniculitis can also be seen in type 1 diabetes, Hashimoto thyroiditis, and JIA, which may manifest years after the onset of the panniculitis. The tender erythematous nodules demonstrate lobular panniculitis on histopathology. With clearance, these nodules leave lipoatrophy that may progress to partial or even generalized lipodystrophy. Administration of systemic corticosteroids and/or steroid-sparing agents such as methotrexate can stop the development of nodules. Lipodystrophy and tender erythematous nodules are also a feature of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE syndrome),<sup>78</sup> a proteasome auto-inflammatory disorder (see Chapters 20 and 25).



**Figure 22-10** Livedo reticularis. Bluish-red reticulated discoloration of the back in a teenager with systemic lupus erythematosus.

## Nonspecific Manifestations of SLE

Nonspecific manifestations of SLE are distinguished by the absence of lupus-specific changes on histopathology. These include a variety of reactive and inflammatory eruptions and are typically observed in active SLE. Livedo reticularis (Fig. 22-10, see also Fig. 12-81), blotchy bluish-red discoloration of the skin due to vasospasm, is seen in several collagen vascular disorders, among them SLE, drug-induced SLE, APS, and scleroderma. Aggravated by exposure to cold, the reticulated erythema tends to be persistent and is most commonly found on the lower extremities. Raynaud phenomenon, seen in 10% to 30% of patients with SLE, may precede the onset of SLE by months or years. This phenomenon is described in more detail in the section on systemic sclerosis (SSc). Pernio (chilblains) are tender cyanotic to reddish-blue nodular swellings on the fingers or toes (see Chapter 20). Chilblain lupus manifests as cold-induced, reddish-blue, inflammatory acral lesions that may ulcerate (see Chapter 20).<sup>79-82</sup> Although sporadic chilblain lupus has been described in adolescents, most of the affected younger children have a familial form of chilblains (see Chapter 20). Chilblains must be distinguished from stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI syndrome), a recently described auto-inflammatory disorder with acral vasculopathy that can be exacerbated by cold (see Chapter 25, Fig. 25-26).<sup>83,84</sup>

Chronic urticaria-like lesions (urticarial vasculitis) in children with SLE may be distinguished from classic urticaria by their tendency to persist longer than 24 hours and their lesser tendency to be pruritic (see Chapter 21, Fig. 21-14). A manifestation of immune complex deposition, urticarial vasculitis generally occurs in patients demonstrating clinical or serologic evidence of systemic disease activity, especially hypocomplementemia. Biopsy confirms the presence of leukocytoclastic vasculitis. Leukocytoclastic vasculitis can also be seen in biopsy specimens from purpuric lesions in patients with SLE. These purpuric lesions may ulcerate, leaving significant scarring. Erythema and papular telangiectasia of the palms and fingers (Fig. 22-11), linear telangiectasia of the cuticles and periungual skin (with or without thromboses), and periorbital or hand and feet edema,<sup>85</sup> are other nonspecific cutaneous features of SLE.

Although bullous or crusted lesions of SLE may simply reflect fragility of skin because of liquefaction degeneration of basal keratinocytes, a distinctive complication of SLE resembles bullous or epidermolysis bullosa acquisita (EBA) and has been called *bullosic (or vesiculobullous) SLE (BSLE)* (see Chapter 13, Fig. 13-32).<sup>86,87</sup> Indirect immunofluorescence on salt-split skin shows Ig and C3 deposits on the dermal side, and immunoblotting shows autoantibodies directed against type VII collagen, as in patients with EBA (see Chapter 13).<sup>88,89</sup> Subtle variations in IgG subtypes between EBA and BSLE have been shown by IgG subtyping. Other forms of immunobullous disorder, such as linear IgA disease, have also been described in association with SLE, emphasizing the need for immunofluorescence testing.<sup>90</sup>



**Figure 22-11** Systemic lupus erythematosus. Erythema and papular telangiectasia on the palm and fingers of a child with lupus erythematosus.



**Figure 22-13** Self-healing juvenile cutaneous mucinosis. The young girl developed numerous skin-colored to erythematous nodules and swelling on the fingers, and also on the periorbital areas and trunk. She was otherwise well, and the lesions cleared during the subsequent years without intervention.



**Figure 22-12** Papulonodular dermal mucinosis in systemic lupus erythematosus (SLE). This teenager with long-term SLE in good control developed firm pruritic induration of the upper back and proximal arms with some palpable nodularity (indicated by arrows). Deposition of mucin, resembling that of scleredema, was noted in biopsy sections.



**Figure 22-14** Systemic lupus erythematosus. The gingival and buccal mucosae are red, edematous, and eroded, with subtle whitening. Note the roughness and erythema of the lips with the subtle whitening of the vermillion border.

Mucin deposition is a typical characteristic seen on skin biopsy sections of individuals with SLE. However, skin-colored, sometimes pruritic papules and nodules involving primarily the trunk, upper extremities, and occasionally the face are a clinical feature of SLE that reflects large amounts of mucin in the mid-dermis between collagen bundles<sup>91,92</sup> (Fig. 22-12). Papulonodular (dermal) mucinosis of SLE may occur any time during the course, including before onset of other features, and has a course that is independent of the course of the SLE. Mucinosis in children is also a histologic feature of self-healing juvenile cutaneous mucinosis (SHJCM), an unusual disorder characterized by the acute onset of multiple skin-colored to dusky erythematous asymptomatic papules and nodules.<sup>93,94</sup> Lesions mainly occur on the head and periarticular areas, and can be a few centimeters in diameter (Fig. 22-13), in contrast to the more diffuse and, if discrete, papular lesions of the papulonodular mucinosis of SLE. Fever, muscle tenderness, arthralgias, and weakness may be associated.<sup>95</sup> Lesions spontaneously resolve during the subsequent months to a few years. Biopsy samples can be erroneously misdiagnosed as panniculitis or proliferative fasciitis,<sup>96</sup> but mucin stains allow the characteristic

deposition of large amounts of mucin to be identified so that the family can be reassured.

Mucosal membrane lesions (gingivitis, mucosal hemorrhage, erosions, and small ulcerations) are seen in 3% of patients with CLE and in up to 30% of pediatric patients with the systemic form of the disorder. A silvery whitening of the vermillion border of the lips is highly characteristic, and the lips may show slight thickening, roughness, and redness, with or without superficial ulceration and crusting (Fig. 22-14). The gingival, buccal, and nasal mucosae may also appear red, edematous, friable, and eroded, or may exhibit silvery white changes.

Several forms of alopecia may occur in patients with SLE (overall in about 30% of patients). First, discoid lupus may present with scarring alopecia associated with multiple well-demarcated patches (Fig. 22-15) that exhibit erythema, scaling, telangiectasia, atrophy, and plugging (the classic changes of DLE). Second, patients with SLE may develop hair fragility, especially with acute exacerbations, that leads to hair breakage several millimeters from the roots, resulting in a receding hairline with a short, unruly, broken hairs ("lupus hair"), especially at the temple and forehead. Telogen effluvium may also



**Figure 22-15** Systemic lupus erythematosus (SLE). Discoid plaque associated with scarring alopecia of the scalp in a patient with SLE.

occur in patients with SLE. Finally, there is an increased incidence of alopecia areata in patients with SLE, and these patients tend to have classic scalp dermoscopic findings including exclamation-mark hairs, black dots, broken hair, and yellow dots (see Chapter 7).<sup>97,98</sup>

The most common symptoms of SLE at presentation are constitutional (malaise, fever, and weight loss).<sup>53</sup> The arthritis, which occurs in up to 79% of pediatric patients,<sup>53,99</sup> is a symmetric polyarthritis involving both small and large joints. It is commonly quite painful (in contrast to the arthritis of JIA), often out of proportion to the clinical findings, and tends to be nondeforming. Approximately 55% of pediatric patients develop renal involvement, most often during the first year of the SLE. Four types of nephritis have been described based on renal biopsy pattern: mesangial lupus nephritis, focal proliferative, diffuse proliferative, and membranous glomerulonephritis. Diffuse proliferative glomerulonephritis occurs most commonly (40% to 50%) but carries the worst prognosis, leading to end-stage renal disease in approximately 10% to 15% of patients with lupus nephritis.<sup>100</sup> The presence of anti-double-stranded (anti-ds) deoxyribonucleic acid (DNA) antibodies and hypocomplementemia is commonly associated with severe renal damage. Pulmonary involvement, particularly pleuritis, occurs in up to 30% of patients. Cardiac manifestations, including pericarditis, myocarditis, vasculitis affecting coronary arteries, and Libman-Sachs endocarditis, occur in approximately 15% of patients. A recently recognized issue, however, is the long-term risk of accelerated atherosclerosis<sup>100</sup>; as a result, the overall survival for SLE has improved for all causes except cardiovascular disease. Individuals with childhood-onset SLE can develop myocardial ischemia as early as 20 to 30 years of age. Neuropsychiatric SLE (central nervous system [CNS] involvement) most commonly features headache, seizures, alterations in mental status, psychosis, and peripheral neuropathy, and is seen in 20% to 30% of affected children<sup>101</sup>; most show evidence of neuropsychiatric involvement during the first year of the disease, but cognitive dysfunction occurs in almost 25%. Neuroimaging studies may show structural abnormalities, such as infarction; the addition of single-photon emission computed tomography (SPECT) scans may show evidence of cerebral vasoconstriction and vasculitis as perfusion abnormalities and allow a diagnosis of lupus psychosis. Lymphadenopathy, although it occurs more commonly in adults, is seen in up to 40% of children with SLE. Ocular findings are seen in 25% of patients (cotton-wool patches, optic neuropathy, perivasculitis, and edema of the optic disk).

The diagnosis of SLE is chiefly clinical and is based on the presence of cutaneous lesions, systemic manifestations, and confirmatory laboratory tests (see Table 22-1). Biopsy of cutaneous lesions will confirm the diagnosis and shows: 1) hyperkeratosis with keratotic plugging; 2) epidermal atrophy; 3) liquefactive degeneration of basal cells; and 4) a patchy, chiefly lymphoid cell infiltrate, especially around appendages and vessels.<sup>102</sup> Biopsy of lesional skin in DLE or SLE usually shows the deposition of immunoreactants at the epidermal–dermal border (the lupus band test). Sun-exposed areas should be avoided for this biopsy

because of the risk of a false-positive lupus band test at sun-exposed sites.

Serologic examination is the most important evaluation for children thought to have SLE, and ANA is the most valuable screening test. The serologic profiles in children with SLE are similar to those of adults, although some authors have reported a slightly increased incidence of positive antibody tests. The ANA test is almost always positive when a human substrate is used (e.g., Hep-2 cells); in contrast, 5% to 10% of patients with SLE show a negative ANA test when nonhuman tissues are used for testing. Having a positive ANA test does not make a diagnosis of lupus. It can be seen in patients with several other collagen vascular disorders and is present in 5% to 10% of the normal population.<sup>103</sup> However, an ANA level of greater than 1:160 usually suggests an autoimmune disorder. Five patterns of ANA have been described: speckled (the most nonspecific); homogeneous; peripheral or shaggy (most patients with SLE and this pattern have anti-ds [also called native] DNA antibodies]; nucleolar pattern (often seen in patients with scleroderma); and centromere pattern (largely associated with calcinosis, Raynaud, esophageal dysmotility, sclerodactyly, and telangiectasia [CREST]; see discussion on SSc).<sup>104</sup>

Monitoring of serum complement is a critical test for determining lupus activity. The development of hypocomplementemia commonly signals the onset of renal disease. Total complement activity is monitored by functional hemolytic assay (CH50). Specific complement levels, particularly of C3 and C4, should be routinely checked by single radioimmunodiffusion assay. Not uncommonly, C4 levels may be depressed when C3 is normal, probably because patients with SLE are often missing one or more C4 alleles.<sup>104</sup>

One risk factor for the development of SLE, especially with onset during childhood, is hereditary deficiency of the early complement components, C1 (C1q and less often C1r/s), C4, C2, and C3.<sup>105</sup> Virtually all children with C1q deficiency develop SLE.<sup>106</sup> The SLE that occurs in complete C1- or C4-deficient individuals typically presents early during childhood. C2-deficient individuals tend to have a lower risk and less severe disease with lower titers of antinuclear antibodies, but increased anti-Ro antibodies. Lupus and other autoimmune disorders do not tend to occur in individuals with deficiency of the later components of complement, which instead are associated with an increased risk of developing infections, including neisserial infections. Lupus has also been associated with patients and carriers of chronic granulomatous disease, and in patients with IgA deficiency.

Children who may have lupus should be tested for the presence of anti-ds DNA antibodies, which are found in about 50% of patients with SLE and have been associated with an increased risk of renal disease, particularly if complement levels are low. In contrast, antiribosomal P antibodies are inversely associated with renal involvement in juvenile-onset SLE.<sup>49</sup> Anti-single-stranded (ss) DNA antibodies are found in about 70% of patients and are nonspecific. However, complement-fixing anti-ss DNA antibodies are associated with renal disease, even without anti-ds DNA antibodies. Some patients with SLE have antibodies directed against nuclear ribonuclear proteins (nRNPs). Patients with anti-nRNP antibodies (30% to 40%) have a lower risk of renal disease and a better prognosis. Anti-nRNP antibodies and a speckled ANA pattern have also been described in patients with an overlap syndrome of lupus in association with sclerodactyly, esophageal dysmotility, Raynaud phenomenon, and pulmonary disease (MCTD). The Raynaud phenomenon typically precedes the appearance of other signs and symptoms by several years in affected children. Fever, arthralgia, and myalgia are associated, and patients often have hypergammaglobulinemia, a positive RF, and normal complement levels.<sup>107</sup> The anti-Smith (Sm) antibody is specific for SLE, occurs in 20% to 35% of patients, and is associated with a higher risk of renal disease. Anti-Ro and anti-La antibodies are less common in children than in adults (except in NLE, see *Neonatal Lupus Erythematosus* section) and occur in about 20% (anti-Ro) and 10% (anti-La) of children with SLE; they are associated with the highest risk of photosensitivity. SCLE is rare in children, but anti-Ro and anti-La antibodies can also be seen in children with SLE and complement deficiencies or Sjögren syndrome (see *Sjögren Syndrome* section).<sup>108</sup> Antiphospholipid (aPL) antibodies can occur in up to 65% of children with SLE and should be monitored annually; they portend for the development of irreversible organ damage, not just a higher risk of thrombosis.<sup>109</sup>

**Table 22-2** Features of Drug-Induced Lupus Erythematosus

	<b>Skin Features</b>	<b>Noncutaneous Signs</b>	<b>Laboratory Findings</b>	<b>Most Common Pediatric Trigger(s)</b>
Drug-induced SLE	Photosensitivity, purpura, erythema nodosum, urticaria and urticarial vasculitis, necrotizing vasculitis Usually absent: malar or discoid rash (except TNF inhibitors), mucosal ulcers, alopecia, Raynaud phenomenon	Fever, arthralgias, myalgias, pericarditis, pleuritic, sometimes hepatitis Usually absent: CNS, renal, pulmonary involvement Hepatic changes from minocycline	ANA, antihistone antibodies, elevated ESR May be mild cytopenia	Minocycline, occasionally TNF- $\alpha$ inhibitors
Drug-induced SCLE	Annular polycyclic lesions and/or papulosquamous lesions, including on legs Less commonly, erythema multiforme-like or vesiculobullous lesions, necrotizing vasculitis	Usually no arthritis, serositis, or major organ involvement	ANA, anti-Ro, anti-La	Terbinafine, griseofulvin NSAIDs (piroxicam, naproxen)
Drug-induced CCLE	Discoid lesions in photosensitive distribution	Usually no other signs	ANA	TNF- $\alpha$ inhibitors

ANA, Antinuclear antibody; CCLE, chronic cutaneous lupus erythematosus/discoid lupus; CNS, central nervous system; ESR, erythrocyte sedimentation rate; NSAID, nonsteroidal anti-inflammatory drug; SLE, systemic lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus; TNF, tumor necrosis factor.

Other useful laboratory tests include the ESR as a measurement of inflammation; complete blood counts to detect leukopenia, thrombocytopenia, and a Coombs-positive hemolytic anemia; and routine urinalysis with blood urea nitrogen (BUN) and creatinine levels to detect renal abnormalities. Renal biopsy and serial blood pressure measurements are important tools for managing children with SLE and evidence of renal disease. If a patient with SLE has cytopenia and unexplained fever, the diagnosis of MAS, as described under JIA, must be considered. The disease is best recognized by hyperferritinemia and subsequently hypertriglyceridemia and hypofibrinogenemia.<sup>110</sup>

Lupus may be triggered in pediatric patients by drugs, although the features tend to be milder and occurrence is considerably less than in adults, likely reflecting the more limited use of medications in children that are associated with the highest risk. These high-risk drugs are procainamide (occurrence 15% to 20%) and hydralazine (occurrence 5% to 8%).<sup>111-113</sup> The cutaneous features of drug-induced lupus can be divided into those of SLE, SCLE, and CCLE or DLE (Table 22-2). More than 80 drugs can cause drug-induced lupus, especially with SLE-like manifestations.<sup>113,114</sup> In drug-induced SLE, the typical cutaneous features of classic SLE are often absent (e.g., malar rash, discoid lesions, Raynaud phenomenon, mucosal ulcers, alopecia). Rather, photosensitivity, lesions involving the skin vasculature (livedo reticularis, palpable purpura, ulcers, bullae, urticaria and urticaria vasculitis) and erythema nodosum are most often described. The exception is reactions caused by TNF- $\alpha$  antagonists, which rarely cause drug-induced lupus but may manifest as the malar rash or discoid lesions.<sup>115-118</sup>

The most common cause of drug-induced SLE in pediatric patients is minocycline, primarily used by adolescents with acne (see Chapter 8); overall the risk is low. This reactivity to minocycline is specific and has not been described in patients who are administered tetracycline or doxycycline. Patients usually experience malaise in association with myalgia, arthralgia, or arthritis. Livedo reticularis, antineutrophil antibodies, and elevation of hepatic transaminase levels have been described, but evidence of vasculitis, renal disease, and neurologic involvement are unexpected. Drug-induced lupus from minocycline occurs most commonly in female patients and at an average of 2 years after starting the medication. Affected individuals usually show a symmetric polyarthralgia or polyarthritis involving the small joints of the wrists and hands. Isoniazid, hydralazine, and procainamides may lead to the polyserositis of lupus but rarely cause cutaneous or renal disease. Drug-induced lupus is usually associated with increased titers of antihistone antibodies, a positive ANA level, and often anti-ss DNA antibodies. Anti-ds DNA antibodies are usually absent and complement levels tend to be normal.

Drug-induced SCLE shows the typical cutaneous features of SCLE, appearing at sun-exposed areas as annular polycyclic or papulosqua-

mous lesions, but the legs are often involved, in contrast to classic SCLE. Disease usually develops 4 to 20 weeks after initiation of treatment. The most common drugs to trigger SCLE in children are antifungals (terbinafine and griseofulvin),<sup>119</sup> but other groups are antihypertensives, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, statins, and IFNs.<sup>119,120</sup> Drug-induced CCLE is very rare, and usually results from use of TNF- $\alpha$  antagonists. Discontinuation of the offending agent is the most important intervention, with topical application of anti-inflammatory medications if needed and systemic corticosteroids if a vasculitis is present. Cutaneous changes may improve within weeks after drug discontinuation, but complete resolution may be prolonged over several months.

The prognosis for children with SLE has improved dramatically from nearly 100% mortality to a survival rate of greater than 90% because of earlier recognition and earlier and more aggressive therapy.<sup>121,122</sup> The main causes of death in children are renal failure, CNS lupus, myocardial infarction, cardiac failure, or infection. Although life expectancy is increased, the sequelae of disease activity and administration of systemic medications cause considerable morbidity in 88% of patients.<sup>123</sup> These include hypertension, growth retardation, chronic pulmonary impairment, premature atherosclerosis, ocular abnormalities, permanent renal damage, neuropsychiatric and neurocognitive impairment, osteoporosis, musculoskeletal damage, and gonadal impairment. Therapy for SLE currently depends on the extent of local and systemic involvement.<sup>124-126</sup> Discoid lesions without SLE usually respond to topical anti-inflammatory medications and sun protection, but antimarial and occasionally systemically administered corticosteroids may be needed for control.<sup>127</sup> Pulsed dye laser has reduced inflammation for facial lesions refractory to topical anti-inflammatory medications and hydroxychloroquine (see next paragraph).<sup>128</sup> Avoidance of exposure to sun and unshielded fluorescent light by wearing hats, sun-protective clothing, and appropriate broad-spectrum sunscreens with UVA as well as UVB protection is essential. These include sunscreens with a sun protection factor (SPF) of 30 or greater that contain good UVA blockers, such as titanium dioxide, zinc oxide, avobenzene, and/or the newer, more photostable UVA organic blockers (see Chapter 19). Cosmetic camouflage is an option for patients with residual dyspigmentation. Topical corticosteroids or calcineurin inhibitors (tacrolimus, pimecrolimus)<sup>129</sup> are effective for most inflamed cutaneous lesions, although relatively potent formulations may be required.

Antimalarial therapy is considered first-line systemic therapy for cutaneous lupus and is beneficial for long-term suppression of the disease.<sup>130,131</sup> In adults, hydroxychloroquine has been shown to delay disease onset, prevent flares, retard renal damage, and reduce autoantibody accumulation.<sup>132</sup> For patients who are not helped by hydroxychloroquine monotherapy, quinacrine can be added without increased

risk of retinal toxicity. In a study of adults with cutaneous lupus who were not successfully treated with hydroxychloroquine monotherapy, the addition of quinacrine 100 mg once daily to hydroxychloroquine produced significant clinical improvement in 67% of patients, as measured by reduction in the cutaneous lupus activity scale.<sup>133</sup> According to the recommendations of the American Academy of Ophthalmology, patients treated with an antimalarial should have a pretreatment ophthalmologic examination and annual screening after 5 years, or sooner if there is an unusual risk factor, to detect early retinopathy. In addition to standard testing of the parafoveal area (10-2 field evaluation), at least one form of the newer, more sensitive objective testing (multifocal electroretinogram, spectral domain optical coherence tomography, or fundus autofluorescence) should be performed.<sup>134</sup> The appropriate dosage of hydroxychloroquine for children is up to 6.5 mg/kg per day, with a maximum dosage of 400 mg/day. Several months of antimalarial therapy may be required before efficacy is seen.

For patients with severe refractory disease, thalidomide has proven efficacy in cutaneous lupus, although its side effect profile often limits routine use.<sup>135</sup> Lenalidomide, a thalidomide analog, may also be used for severe scarring disease. A small study of patients with refractory CLE found that 86% achieved clinical remission with no influence on systemic disease. The drug is associated with fetal embryopathy, cytopenias, and an increased risk of thrombosis but, in contrast to thalidomide, not peripheral neuropathy.<sup>136,137</sup>

Patients with mild disease and arthralgias without nephritis may respond to NSAIDs, although GI irritation is a risk. Although aspirin is generally not a treatment of choice for the arthralgias, 1 to 3 mg/kg per day or and 81 mg tablet is the recommended dosage for individuals with elevated levels of IgG aPL antibodies.

In patients with more than mild disease, corticosteroids are the mainstay of therapy. In general, children are treated more aggressively than adults, with 97% receiving systemic steroids and 66% receiving other immunosuppressive drugs.<sup>138</sup> High dosages of systemic corticosteroids are usually given until complement and anti-ds DNA antibody levels normalize with improvement noted in the clinical state. High-dosage pulsed intravenous methylprednisolone (30 mg/kg) is generally administered for significant acute flares. Corticosteroids can then be administered orally and tapered slowly to the lowest possible level that controls the disease. Both alternate-day and single-morning dose therapy may be effective for maintenance, although alternate-day dosing is preferable to lower the risk of growth retardation. Avascular necrosis occurs more commonly in children than in adults (10% to 15%) from steroid usage. Children with SLE and immunosuppressive medications are at increased risk of infection, including pneumococcal infection; unfortunately the response to administration of pneumococcal vaccination has been poor. Patients should not receive live vaccinations during corticosteroid administration, and placement of a tuberculin test before starting therapy is recommended.

Given the association of chronic use of systemic corticosteroids with adverse effects on major organs (renal, cardiac, neurologic) and the recalcitrance of many patients to steroids alone, other immunosuppressive medications have also been administered to achieve or maintain disease control. The addition of an immunosuppressive agent to the corticosteroid has been shown to be more beneficial for patients with nephritis than the corticosteroid alone and allows a reduction of steroid dosage.<sup>139</sup> Azathioprine, methotrexate, and, more recently, mycophenolate mofetil<sup>140</sup> may reduce disease activity or allow lowering of the steroid dosage.<sup>141</sup> The recommended pediatric dosage for azathioprine is 2.5 to 3.5 mg/kg per day. For methotrexate the dosage is 0.4 to 0.6 mg/kg per week with folate given daily or on days without methotrexate, and for mycophenolate mofetil, it is 0.5 to 3 g/day (600 to 1200 mg/m<sup>2</sup> per day). Cyclophosphamide use is most commonly reserved for patients with CNS disease or severe nephritis. The major potential side effects of these agents are hemorrhagic cystitis and sterility (cyclophosphamide); hepatitis (azathioprine); and aplastic anemia, infection, and malignancy (both cyclophosphamide and azathioprine). Mycophenolate mofetil has a better side-effect profile. Dapsone is of little value for SLE but can be quite effective for BSLE. Autoantibodies and polyclonal B-cell activation are thought to be important in the pathomechanism of SLE; targeting of specific B cells with rituximab (anti-CD20 chimeric mouse/human monoclonal antibody) has led to improvement, particularly for lupus nephritis and

autoimmune cytopenia. Use of higher dosages than used for lymphoma (e.g., 750 mg/m<sup>2</sup> rather than 350 mg/m<sup>2</sup>), repeated therapy, and combination therapy (e.g. with cyclophosphamide and corticosteroids) has led to improved disease activity and decreased steroid burden without an increased risk of infection requiring hospitalization.<sup>142</sup> For end-stage renal disease, dialysis and transplantation are therapeutic options. Autologous stem-cell transplantation has been associated with significant morbidity and mortality, as well as high relapse rates in pediatric cases.<sup>124</sup>

Levels of 1,25-dihydroxy vitamin D and intact parathyroid are significantly lower in children with SLE, especially if they are overweight.<sup>143</sup> Preventive therapy for osteopenia in pediatric patients with SLE should include high dietary calcium intake with supplemental calcium and vitamin D (osteocalcin) as needed.<sup>144</sup> Maintenance of a good exercise program and minimizing steroid weight gain are also helpful. Although bisphosphonates are not routinely given to pediatric patients, their use in patients with pathologic fractures secondary to steroid-induced osteoporosis should be considered.

## Neonatal Lupus Erythematosus

Neonatal lupus erythematosus (NLE) is a unique variant of lupus erythematosus found in infants born to mothers with, or who have a tendency for, SLE, Sjögren syndrome, or undifferentiated autoimmune syndrome (Box 22-2).<sup>145-147</sup> The occurrence of NLE is not related to titers and is not strictly genetic, based on its discordance in identical twins.<sup>148</sup> Nevertheless, developing the skin manifestations of NLE has been linked to carrying a polymorphism in the TNF- $\alpha$  receptor (308A; increases TNF- $\alpha$  expression in response to UV light) and the HLA genotypes DRB1\*03.<sup>149</sup> Cardiac block has been increased with DRB1\*04 and Cw\*05<sup>150</sup> and a polymorphism in TGF- $\beta$  (Leu10, associated with increased fibrosis)<sup>151</sup>; DRB1\*13, and Cw\*06 are protective.<sup>150</sup> The diagnosis of NLE is most important as a marker for the mother, who is at risk. Approximately half of mothers of affected infants are asymptomatic at the time of delivery, and about half of these originally asymptomatic mothers develop SLE, Sjögren syndrome, or, most often, undifferentiated autoimmune syndrome within a median of 3 years. In addition, mothers with undifferentiated disease may progress to reach a diagnosis of SLE, Sjögren syndrome, or overlap syndromes.<sup>152</sup> Thus mothers of affected infants with NLE must be monitored and evaluated regularly.

Approximately 50% to 78% of babies with NLE show cutaneous manifestations at some point, with onset usually by a few weeks of age.<sup>153</sup> However, up to 23% of affected babies show manifestations at birth, especially the cardiac manifestations and occasionally the cutaneous features.<sup>154</sup> Typically, new lesions do not occur after approximately 3 months of age. Lesions are most commonly localized to sun-exposed areas, particularly on the head and neck, and the extensor surfaces of the arms, but they may occur anywhere on the skin surface. Lesions have been described in the genital area and on the palms and soles in 5% of patients.<sup>155</sup>

A variety of cutaneous manifestations have been described. Annular lesions or periorbital erythema (termed *raccoon eyes*, *owl eyes*, or *eye mask*) (Figs. 22-16 through 22-18) should always trigger consideration of the diagnosis in an infant. The annular lesions (see Fig. 22-17; Fig. 22-19) may be confused with annular erythema of infancy, Sweet syndrome,<sup>156,157</sup> or neonatal dermatophyte infection.<sup>158</sup>

### Box 22-2 Neonatal Lupus Erythematosus

- Seen in infants born to mothers with a tendency for systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, or undifferentiated connective tissue disease
- May present as lupus-like rash, often in areas of sun exposure; facial erythema, especially periorbitally (*raccoon eyes*), annular lesions, discoid lesions, atrophic lesions, and/or telangiectasia
- Associated with anti-Ro (SS-A), anti-La (SS-B), and anti-U,RNP (nRNP) antibodies
- Congenital atrioventricular heart block in 15% to 30%



**Figure 22-16** Neonatal lupus erythematosus. Raccoon eyes and annular forehead plaques.



**Figure 22-19** Neonatal lupus erythematosus. (A) and (B) Annular plaques without detectable scale on the face, scalp, trunk and extremities.



**Figure 22-17** Neonatal lupus erythematosus. Annular scaling plaques on the cheeks of this 6-week-old boy.



**Figure 22-18** Neonatal lupus erythematosus. Purplish erythema with focal atrophy in a reticular pattern on the face and scalp.



**Figure 22-20** Neonatal lupus erythematosus. Discoid lesions with atrophy and dyspigmentation on the face of a 2-month-old infant. His mother first showed signs of systemic lupus erythematosus 1 year after this baby was born.

marmorata telangiectatica congenita<sup>160,161</sup> or an extensive capillary malformation.<sup>162</sup> An infant with congenital varicelliform lesions has also been described.<sup>163</sup> In addition to the cutaneous eruption, mucosal ulcerations have been noted in several affected babies.

NLE is the most common cause of congenital heart block. Congenital heart block occurs in 15% to 30% of affected patients, owing to *in utero* inflammation, fibrosis, and calcifications of the atrioventricular node and sometimes the sinoatrial node; 10% of patients with cardiac disease have cardiomyopathy.<sup>148,164</sup> Although the cardiomyopathy is

Discoid lesions (Fig. 22-20), scaly atrophic macules and patches, and telangiectasia<sup>159</sup> have also been described. Atrophic lesions may resemble round ice-pick scars, are often congenital, and commonly localize to the temporal areas of the forehead. The telangiectasia may be more petechial or may resemble the reticulated lesions of cutis

usually apparent early, rarely it first manifests several months after birth.<sup>165</sup> Unlike the cutaneous complications of NLE, congenital heart block is usually irreversible. Some infants with first-degree and, rarely, with second-degree heart block have shown spontaneous resolution during the first few months of life, but the majority of patients progress rapidly to third-degree block, including after birth. Two-thirds of infants with heart block require pacemakers.<sup>166</sup> Cardiac disease results in a 20% mortality<sup>167</sup> not only from the heart block, but also congestive heart failure or other associated complications such as transposition of the great vessels, patent ductus arteriosus, septal defects, and endocardial fibroelastosis.

Other systemic complications include liver involvement in 10% to 26% of patients (generally manifested by hepatomegaly and abnormalities of liver function tests, but occasionally cholestatic disease and liver failure),<sup>148,164</sup> splenomegaly, lymphadenopathy and hematologic abnormalities in 27% of affected infants, including leukopenia, thrombocytopenia,<sup>168</sup> and anemia (both Coombs positive and Coombs negative). Subclinical evidence of CNS disease has been seen on computerized tomographic scans and ultrasounds,<sup>169</sup> but clinical neurologic features are unusual.<sup>170,171</sup> Hydrocephalus has recently been described as an uncommon complication, suggesting that imaging studies are appropriate for NLE infants with a head circumference greater than the 95th percentile.<sup>172</sup> CNS vasculitis and stroke have also been described.<sup>173,174</sup>

NLE results from the transplacental passage of maternal antibodies.<sup>175</sup> In 95% of cases, these antibodies are anti-Ro (SS-A) antibodies, often in association with anti-La (SS-B) antibodies. These antibodies have been found at sites of pathology in the epidermis and heart.<sup>176</sup> A subset of infants with neonatal lupus and their mothers have anti-U<sub>1</sub>RNP (nRNP) antibodies, although cardiac disease is extremely rare in this subset.<sup>163,177</sup> Infants and mothers may also demonstrate a positive ANA titer and aPL antibodies.<sup>176</sup> Breastfeeding has not been shown to alter antibody levels or affect the development of cutaneous lesions.<sup>178</sup>

The anti-Ro antibodies have been shown to be causative for the cardiac block. Anti-Ro antibodies bind to fetal, but not to adult, cardiac myocytes and selectively injure the conducting system, a process that involves plasmin<sup>179</sup>; anti-U<sub>1</sub>RNP antibodies do not bind to cardiac myocytes. When pregnant mice are injected with anti-Ro/La antibodies intraperitoneally, the antibody binds to the heart, epidermis, and liver, sites of inflammation in NLE, and is associated with tissue apoptosis.<sup>180</sup> Overall, 10% to 20% of babies of women with anti-Ro with/without anti-La antibodies develop cutaneous NLE; 1% to 2% develop heart block, and 27% show laboratory abnormalities.<sup>181</sup>

The diagnosis of NLE is aided by the presence of typical cutaneous lesions, systemic manifestations, and confirmatory laboratory studies (positive anti-Ro, anti-La, or anti-U<sub>1</sub>RNP antibody tests of the infants and mothers). Because of the possibility of involvement of internal organs, a thorough physical examination, complete blood cell count with platelet count, and liver function tests are often recommended for infants suspected of having NLE. Infants with bradycardia or a murmur deserve an electrocardiogram and echocardiography. If any question regarding the diagnosis remains, cutaneous biopsy of a skin lesion can be performed and will show histopathologic features of lupus with injury to the basal epidermal cells as a prominent feature.<sup>182</sup>

Clearance of cutaneous lesions generally occurs by 6 to 12 months of age, concurrent with the waning of the maternally derived antibodies. In a few patients, however, the cutaneous lesions disappeared within 1 month, and the eruption has lasted up to the age of 26 months. Affected individuals may show residual telangiectasia, dyspigmentation, atrophy, and/or scarring<sup>183,184</sup>; however, most cutaneous lesions clear without sequelae. Appropriate treatment of NLE includes avoidance of sun exposure and treatment of visceral complications, which may necessitate administration of systemic corticosteroid therapy. Low-to mid-potency topical steroids or topical calcineurin inhibitors can be used to treat the cutaneous lesions, but lesions clear spontaneously, and the use of topical anti-inflammatory agents has not been shown to affect residua.<sup>184</sup>

Patients with NLE do not show an increased risk of developing lupus and other autoimmune disorders beyond that of their siblings, suggesting that the small increased risk in this group of patients reflects their familial tendency, not the previous occurrence of NLE.<sup>185</sup>

Mothers who have had a child with NLE, however, have a 36% overall risk of having a second affected child.<sup>149</sup> The risk of cutaneous manifestations in the second child is 23%, and the risk of cardiac issues is almost 13%, sixfold higher than the overall risk congenital heart block in a first affected baby. A mother with a previous baby with NLE involving skin can have a subsequent baby with congenital heart block and vice versa. Fetal echocardiograms (weekly to every other week) between 16 and 26 weeks' gestational age, the peak period of cardiac injury, are recommended for at-risk pregnancies. Systemic corticosteroids administered during pregnancy may decrease the risk of first- or second-degree heart block<sup>186</sup> but have not been shown to prevent the progression toward third-degree heart block, which can occur quickly *in utero*.<sup>187-189</sup> Antimalarials, particularly hydroxychloroquine, are not teratogenic<sup>190</sup> and have been found to decrease the risk of cardiac, although not noncardiac, manifestations of NLE.<sup>191</sup> The combination of steroids with intravenous Ig and plasmapheresis is under investigation.<sup>192</sup>

## Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (APS) is an autoimmune thrombotic disorder, characterized by venous and/or arterial thrombosis and the persistence of at least one circulating aPL antibody. aPLs are a heterogeneous group of autoantibodies reactive against either negatively charged phospholipids (e.g. phosphatidyl serine and cardiolipin) or proteins that are complexed with them (e.g.,  $\beta$ 2 glycoprotein I). aPL antibodies are commonly found after bacterial and viral infections in children, leading to the requirement that two levels of aPL antibodies be tested at least 12 weeks apart for diagnosis.<sup>193,194</sup>

In approximately half of affected pediatric patients, APS is a primary syndrome. The disorder can also occur secondarily, most commonly in children with SLE (38% of children overall).<sup>193,194</sup> However, 30% of the patients with SLE and APS initially have primary APS, with a mean duration of 1.2 years before the onset of SLE.<sup>193,194</sup> The age of onset is significantly younger in children with primary APS (8.7 vs. 12.7 years), and 45% of tested children also have one or more inherited thrombophilic risk factors. These inherited prothrombotic disorders include methylenetetrahydrofolate reductase C677T polymorphism, factor V Leiden, protein S or protein C deficiency, prothrombin G20210A heterozygosity, and antithrombin III deficiency.

Manifestations may range from headache or livedo reticularis to stroke or severe tissue necrosis (Box 22-3).<sup>195-198</sup> The most common cutaneous manifestations of APS in children are livedo reticularis and Raynaud phenomenon, each occurring in approximately 6% of affected children. Livedo reticularis is characterized by prominent reticulated cutaneous vasculature, most commonly noted on the lower extremities (see Fig. 22-10 and Chapter 12, Fig. 12-81). Thrombosis, is the most serious manifestation (see Box 22-3), and venous thromboses involving the lower extremities occur most commonly. Recurrent thromboses occur in approximately 20% of children,<sup>193,194,199</sup> especially with inadequate anticoagulant therapy and with an underlying inherited thrombophilia. The clinical triad of livedo reticularis, hypertension, and cerebrovascular disease, or Sneddon syndrome, is linked to aPL antibodies in individuals and has rarely been described in children.<sup>200</sup>

Five percent of children have life-threatening thrombotic disease with the rapid occurrence of thrombosis involving at least three organ systems (catastrophic APS).<sup>201,202</sup> Affected children are likely to be female and suffer from primary APS (each about 70%). The catastrophic event is often the first sign of APS in children (87%). Infections are often a precipitating factor (61%) and peripheral vessel thrombosis occurs in 52% of affected children.

aPL antibodies have been associated with a high risk of miscarriage in pregnant women. In successful pregnancy, transplacental passage of maternal aPL antibodies can rarely lead to neonatal thrombosis,<sup>199</sup> most commonly manifesting as stroke. The risk may be increased in aPL-positive neonates by acquired thrombotic risk factors such as central lines, sepsis, prematurity and heart disease, or the hereditary prothrombotic diseases previously mentioned. Neonates with stroke may have persistently elevated aPL titers for years that show no concordance with maternal aPL levels.<sup>203</sup>

### Box 22-3 Antiphospholipid Antibody Syndrome in Children

#### Cutaneous and Subcutaneous Features

Livedo reticularis  
Raynaud phenomenon  
Palpable purpura/leukocytoclastic vasculitis  
Superficial vein thrombosis  
Deep venous thrombosis with ulceration  
Pyoderma gangrenosum-like ulceration  
Degos-like disease  
Gangrene

#### Noncutaneous Features\*

Thromboses\*  
Pulmonary thromboembolism, hypertension  
Strokes, transient ischemic attacks  
Transverse myelopathy  
Cerebral venous sinus thrombosis  
Retinal vein thrombosis  
Renal artery thrombosis  
Hematologic abnormalities (38%)  
Evans syndrome  
Thrombocytopenia  
Leukocytopenia  
Autoimmune hemolytic anemia  
Neurologic abnormalities, nonthrombotic (16%)  
Migraine headaches  
Chorea  
Seizures  
Hepatomegaly, enzyme elevation

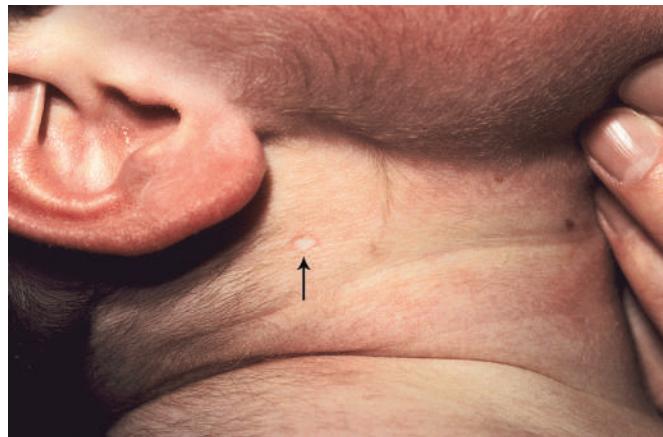
\*Venous thromboses occur in 60% of patients; arterial thromboses in 32% (45% of patients with primary antiphospholipid antibody syndrome [APS] and 18% with secondary APS); mixed thromboses in 3% of patients; and small vessel thromboses, particularly leading to digital infarctions in 6% of patients.

aPL antibodies in APS are thought to be pathogenic, rather than merely a serologic marker. Anticardiolipin, lupus anticoagulant, and anti-β2 glycoprotein I antibodies are found in 81%, 72%, and 67% of patients, respectively, without a significant difference between primary and secondary types of APS. Only 33% of pediatric patients have all three aPL subtypes, and 48% have two simultaneously, emphasizing the need to evaluate all three antibodies for diagnosis. Of note, having more than one aPL antibody does not increase the risk of thrombosis. ANAs and anti-ds DNA antibodies are detected much more commonly in children with secondary APS (86% vs. 35% and 59% vs. 6%, respectively).

Despite the established association between aPL antibodies and thromboses, most individuals with circulating aPL antibodies do not show evidence of thrombosis. As such, it remains controversial whether to treat individuals prophylactically who show persistently positive aPL antibody levels but have no history of thromboses. There is currently no evidence to support the routine administration of low-dose aspirin in individuals with IgM or low titers of IgG antibodies; however, anticoagulants (e.g., aspirin at 1 to 3 mg/kg per day or an 81 mg tablet) should be considered in patients with higher levels of aPL antibodies, especially patients who will be immobilized or undergoing surgery. Administration of hydroxychloroquine may be protective against the development of thrombosis in aPL+ children with SLE.<sup>204</sup> In addition, at-risk adolescents should be discouraged from smoking or treatment with estrogen-containing oral contraceptives. Children with aPL antibodies and thrombosis require anticoagulant therapy, but the use of these medications should be weighed in very active children and noncompliant adolescents because of the greater risk of hemorrhage. Children with catastrophic APS are treated with intravenous anticoagulation, plasmapheresis, and sometimes rituximab.<sup>202</sup>

## Degos Disease

Degos disease, also known as *malignant atrophic papulosis*, is an often-fatal disorder characterized by multiple infarcts in the skin and viscera



**Figure 22-21** Degos disease. Note the atrophic, porcelain-white center surrounded by telangiectasia. Note the hypertrichosis in this young boy from administration of prednisolone.

owing to a thrombotic vasculopathy of unknown cause. Altered platelet function or fibrinolysis have been noted in some patients. The condition is particularly rare in children but has been reported to occur in infants as young as 1 day of age.<sup>205</sup> Typical lesions are asymptomatic 3- to 10-mm papules with an atrophic, porcelain-white center surrounded by an erythematous, telangiectatic border (Fig. 22-21). Lesions may appear in crops and typically involve the trunk and extremities; one adolescent with cutaneous Degos-like lesions has been described with localized unilateral involvement of the abdomen.<sup>206</sup> Biopsy of lesional skin shows a characteristic acellular, ischemic wedge-shaped area of dermis underlying an atrophic but hyperkeratotic epidermis. The GI tract<sup>207</sup> and CNS<sup>208</sup> are the most commonly affected organs. Although involvement of the GI tract is most typical, of the 25 reported pediatric cases of Degos disease, 56% showed CNS involvement and 48% had GI involvement. Acute hematemesis, abdominal pain, dyspepsia, abdominal distension, diarrhea, and constipation are signs of GI tract involvement, and patients may develop peritonitis, bowel infection, or perforation.<sup>209</sup> CNS manifestations include fatal hemorrhagic or ischemic strokes, polyradiculoneuropathy, and nonspecific neurologic symptoms, especially headache. In most cases, the skin lesions precede the occurrence of other manifestations by months to years. Most affected patients die within 2 to 3 years, particularly from sepsis from peritonitis, CNS bleeding, or pleural or pericardial involvement. Approximately 36% of affected children have a more benign course without evidence of systemic involvement,<sup>206</sup> in contrast to 15% of patients of all ages. Familial cases have been described.<sup>210</sup> Degos-like lesions have been described in patients with aPL antibodies and/or SLE and, less commonly, dermatomyositis,<sup>197</sup> suggesting that Degos disease is a distinctive disease pattern rather than a unique entity.<sup>211</sup> In patients with SLE and dermatomyositis, the lesions tend to be more telangiectatic and show more mucin deposition. Administration of medications that inhibit increased platelet aggregation (especially aspirin and dipyridamole) may be helpful in some cases. Immunosuppression may worsen the skin lesions of Degos disease.

## Juvenile Dermatomyositis

Juvenile dermatomyositis (JDM) is an inflammatory disorder with an incidence of three per million children per year that primarily affects the skin, striated muscles, and occasionally other internal organs (Box 22-4).<sup>212-216</sup> In cases in which cutaneous changes are absent, the term *polymyositis* is used. Because the clinical and pathologic features of involved skin and muscles are similar, dermatomyositis and polymyositis are believed to be variants of the same disease process; however, 85% to 95% of children with an inflammatory myopathy have JDM.<sup>217</sup>

The criteria to make a diagnosis of JDM were originally described in 1975<sup>218</sup> and remain largely the same today, except that

#### Box 22-4 Clinical Features of Juvenile Dermatomyositis

##### General

Fever  
Lethargy  
Adenopathy

##### Skin, Subcutaneous, Mucosae

Heliotrope rash  
Gottron papules  
Nailfold capillary changes  
Malar or facial eruption  
Mouth ulcers  
Gingival telangiectasia, bleeding gingivae  
Skin ulcers  
Limb edema  
Xerosis and pruritus of skin, including scalp  
Poikiloderma  
Calcinosis  
Lipodystrophy

##### Muscle

Muscle tenderness and myalgias  
Muscle weakness

##### Joints

Arthralgia  
Arthritis  
Contractures

##### Gastrointestinal

Dysphagia/dysphonia  
Gastrointestinal symptoms, especially pain

##### Pulmonary

Dyspnea from interstitial lung disease

##### Cardiac

Murmurs, cardiomegaly, pericarditis  
Rarely, myocarditis, conduction abnormalities

#### Box 22-5 Diagnostic Criteria for Juvenile Dermatomyositis

- Progressive symmetric weakness of the proximal muscles (limb girdle and anterior neck flexors), with or without dysphagia or respiratory weakness
- Muscle biopsy evidence of myositis and necrosis
- Elevation of muscle-derived serum enzyme levels
- Evidence of myopathy on electromyography/magnetic resonance imaging
- Typical cutaneous findings of dermatomyositis

A definitive diagnosis of dermatomyositis can be made when specific skin findings and three of the above criteria (excluding the rash) are present; a probable diagnosis of dermatomyositis requires two of the above criteria plus the rash.

electromyographs, which are painful and technically challenging, have largely been replaced by magnetic resonance imaging (MRI) evaluation (Box 22-5). Muscle biopsies, although performed to diagnose the disease in only 61% of patients, provide important diagnostic and prognostic information<sup>212</sup> and are critical if the cutaneous features are not typical.

JDM occurs more often in girls than boys (2.3:1) and shows a bimodal age distribution, with one peak between 2 and 5 years of age and another at 12 to 13 years of age, giving a mean age of onset of 7 years of age; 35% of children have the onset of JDM before 5 years of age.<sup>219</sup> Overall approximately 25% of all individuals afflicted with dermatomyositis are younger than 18 years of age at the time of onset. Malignancy is associated with adult dermatomyositis in about 20% of cases but is rare in pediatric patients.<sup>220</sup> In contrast to adults, children

tend to have more inflammation and necrosis of muscle, calcinosis, periungual and gingival telangiectasias, ulceration, and small vessel vasculopathy, but fewer myositis-specific antibodies, less interstitial lung disease and amyopathic disease, and a lower mortality rate.<sup>215</sup> The histologic features in muscle and IFN gene signature of JDM are similar in both adult and childhood disease.

The immune alterations that drive the small-vessel occlusive vasculopathy of JDM are still poorly understood, but recent studies suggest important roles for environmental triggers, immune dysfunction, and specific tissue responses. Although the onset shows seasonality and many children have preceding infectious features, no evidence of an associated infectious agent has been discovered. Maternal microchimerism has also been implicated in causing JDM, and has been noted in 70% of peripheral blood T lymphocytes and 80% to 100% of muscle tissue samples from patients.<sup>221,222</sup> The major histocompatibility complex alleles HLAB8, HLADQA1\*0501, HLADQA1\*0301, HLADRB\*0301, and HLADPB1\*0101 confer increased risk. In addition, several other polymorphic gene loci have been shown to be risk factors.<sup>212</sup> A polymorphic variant of the TNF- $\alpha$  promoter that increases TNF- $\alpha$  expression (TNF-308A), including in response to UV light, is associated with a higher risk of calcinosis, ulcerations, and disease chronicity.<sup>223,224</sup> Polymorphisms in IL-1 and the IL-1 receptor antagonist also increase the risk of the development of calcinosis and JDM, respectively.<sup>225,226</sup>

The onset of JDM is insidious in approximately 50% of affected children with subtle weakness, anorexia, malaise, abdominal pain, and the gradual development of a rash. In about 30% of children, the onset of the disorder is fulminant, with fever, profound weakness, and severe multisystemic involvement. The remainder have a subacute onset, often with the cutaneous eruption preceding the appearance of constitutional symptoms or evidence of myopathy by 3 to 6 months, although occasionally by as long as several years; hypomyopathic disease occurs in the presence of skin signs but subclinical muscle disease. An amyopathic form, characterized by typical cutaneous manifestations without clinical or laboratory evidence of myositis for at least 6 months, is less common in children than in adults. In one study, 26% of these children with "amyopathic JDM" develop evidence of myositis during a mean follow-up period of 3.9 years, and the 4% who developed calcinosis all developed myositis, suggesting that children without myositis can be treated with antimalarials and topical anti-inflammatory medications, but may not need aggressive immunosuppressive management.<sup>227,228</sup> However, given the known increased risk of calcinosis without early intervention, there is continued controversy about management of amyopathic disease.

The cutaneous features of JDM may be striking or so minor that they might be easily overlooked. A variety of cutaneous findings may be noted (see Box 22-4). Characteristic cutaneous lesions are inflammatory and telangiectatic and are found in 75% of affected children at presentation. A purplish-red erythema occurs on the face, especially on the eyelids, and is called the *heliotrope rash*, because it matches the color of reddish purple flower of the heliotrope plant (Fig. 22-22). The eruption can also be seen on the upper cheeks, forehead, temples, and ears (Fig. 22-23). Sometimes the facial lesions are very edematous, leading to a periorbital and cheek edema. The facial edema and discoloration may be asymmetric, reflecting asymmetric disease activity; JDM has also first manifested in a Blaschkoid facial distribution with later involvement in a generalized distribution.<sup>229</sup> Violaceous, often confluent, telangiectatic erythema with fine scaling may also appear at the hairline of the scalp, nape of the neck, extensor surfaces of the arms and shoulders, the elbows and knees, and the shoulder and center of the upper anterior trunk (the shawl sign) (Fig. 22-24). These telangiectatic eruptions are often accentuated when the affected area is dependent (e.g., with lowering the face for facial lesions). The distribution of the eruption and the common sparing of sun-protected areas suggest photosensitivity; UV light exposure is known to trigger both cutaneous and muscle signs.

Periungual telangiectasia (Fig. 22-25) is a characteristic feature of JDM and provides a good indication of cutaneous, rather than muscle, disease activity.<sup>230</sup> Viewing the nailfold area through a dermatoscope, ophthalmoscope, or otoscope to magnify the area after local application of mineral oil improves visualization. Nailfold capillary microscopy has shown that the periungual telangiectasia represents bushy



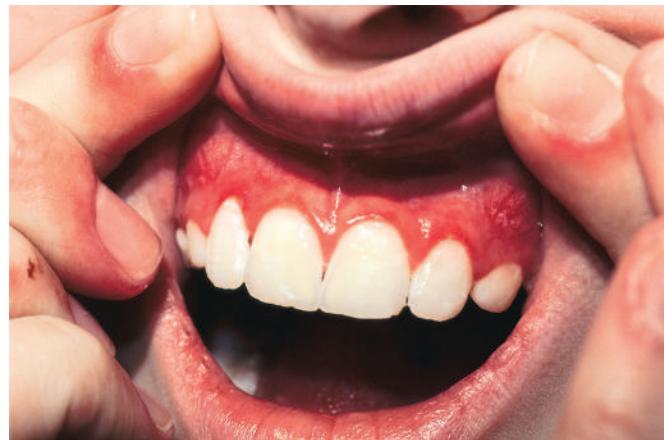
**Figure 22-22** Juvenile dermatomyositis. Telangiectasia and inflammation of the face. Note the sparing of the infraorbital, sun-shielded area.



**Figure 22-25** Juvenile dermatomyositis. Periungual telangiectasia with cuticular hypertrophy.



**Figure 22-23** Juvenile dermatomyositis. Facial inflammation and telangiectasia. Note the involvement of the ear.



**Figure 22-26** Juvenile dermatomyositis. Telangiectasias of the gingivae are commonly associated. Note the periungual telangiectasia as well.



**Figure 22-24** Juvenile dermatomyositis. Telangiectasia and atrophy induced by sun exposure in this young girl, whose relatively uninvolved area was covered by her bathing suit.

capillary loops adjacent to avascular areas, perhaps a form of compensatory neovascularization. Erythema of the cuticle at the base of the nails commonly accompanies the periungual telangiectasia. At times, the cuticles may also be thickened, hyperkeratotic, and irregular, giving an appearance of excessive picking or manicuring. Pitted

ulcerations of the fingertips, pressure points such as the elbows, lateral aspects of the trunk, axillae, and lateral ocular canthi are usually seen at presentation or with disease flares.<sup>214</sup> Thought to be a marker of severe disease, these ulcers leave residual atrophic scars. Even though not exposed to sun, the mucous membranes often show telangiectatic involvement, with erythema of the palate and buccal mucosa, with or without ulceration, and telangiectasia of the gum margin (Fig. 22-26).

Telangiectatic erythema may overlie the dorsal interphalangeal joints (Gottron sign), and when a component of a flat-topped papule, is a pathognomonic sign of JDM (Gottron papule) (Fig. 22-27). Coupled with the facial eruption, these inflammatory lesions on the dorsum of the hand may be misdiagnosed as contact dermatitis. When the papule resolves, atrophy, telangiectasia, and hypopigmentation may persist (Fig. 22-28). Inverse Gottron papules have also been described with papules on the palmar surface; in one report these were the only cutaneous feature and were associated with interstitial lung disease.<sup>231</sup>

Other cutaneous features include palmar erythema and thickening, which can be mistaken for dermatitis and sometimes has so much hyperkeratosis and fissuring that it has been compared with a mechanic's hand.<sup>232</sup> A more generalized hyperkeratotic disorder that resembles pityriasis rubra pilaris, and generalized erythroderma with scaling, have also been described.<sup>233,234</sup>

Sclerodactyly may be seen in children with overlap syndrome that includes SSc. Panniculitis may manifest clinically as tender, indurated



**Figure 22-27** Juvenile dermatomyositis. Gottron papules overlying the joints of the hands. Note the telangiectasia and cuticular hypertrophy of the periungual areas.



**Figure 22-28** Juvenile dermatomyositis. Atrophy, telangiectasia, and depigmentation are residual signs after clearance of the Gottron papules in this patient with chronic skin changes.

plaques and nodules, especially on the arms, thighs, and buttocks; however, panniculitis is often observed in biopsy specimens and is not noted clinically. Limb edema is noted in some patients at presentation, but anasarca is rare and should prompt consideration of nephritic syndrome.<sup>235</sup>

Several cutaneous features of JDM are seen more commonly with disease chronicity. Many children and adolescents with chronic disease have intensely pruritic, xerotic skin that shows poikiloderma (Fig. 22-29), which is the combination of cutaneous atrophy, telangiectasia, and dyspigmentation (see Chapter 11). The scalp is dry, scaling, and pruritic as well.

Cutaneous calcinosis develops in 18% to 24% of children,<sup>217,236,237</sup> in contrast to the up to 70% incidence of earlier reports. This decreased incidence of calcinosis can be attributed to both earlier diagnosis and to more aggressive, earlier treatment (see below). Nevertheless, calcinosis is a major cause of morbidity in JDM and is linked to younger age at disease onset, more persistent disease activity, and the presence of anti-NXP2 (anti-p140) autoantibodies before the calcinosis develops, which are found overall in 20% of JDM patients.<sup>238</sup> Most commonly seen at sites of trauma, particularly on the buttocks, elbows, knees, and fingers, and around the shoulders, subcutaneous calcium deposits may produce local pain and can be extruded, leading to



**Figure 22-29** Juvenile dermatomyositis. Poikilodermatos changes on the legs, characterized by telangiectasia, atrophy, and subtle reticulated hyperpigmentation.

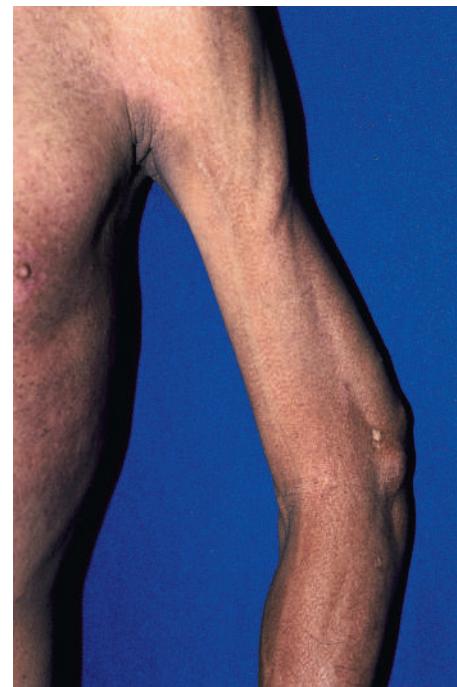


**Figure 22-30** Juvenile dermatomyositis with multiple calcifications. Even small calcifications over a joint may be exquisitely painful.

ulcers, sinuses, or cellulitis (Fig. 22-30). Ulcerations may also appear in children with dermatomyositis without calcifications, especially over joints (Fig. 22-31). Calcifications (see Chapters 9 and 23) appear as hard, irregular nodules that may drain a whitish, chalky material through their openings to the surface that resembles gritty toothpaste. The mean time to occurrence of calcinosis after onset is 2.5 to 3.4 years, although 3% of patients have calcinosis at diagnosis,<sup>239</sup> even



**Figure 22-31** Juvenile dermatomyositis. Note calcinosis on the fingertips.



**Figure 22-33** Juvenile dermatomyositis (JDM). Profound lipodystrophy on the limbs of a young adult with a history since elementary school of JDM.



**Figure 22-32** Juvenile dermatomyositis (JDM). Facial lipoatrophy and persistent telangiectasia in an older adolescent. The onset of her JDM was 8 years earlier; although the myositis has been controlled, she had residual disfiguring cutaneous and subcutaneous manifestations with extensive, problematic calcifications.



**Figure 22-34** Juvenile dermatomyositis. Acanthosis nigricans of the axillary area.

without evidence of myositis. Sometimes patients have widespread calcification along fascial planes, encasing muscles (universal form) or even appearing as an exoskeleton on radiographic examination.

Contractures have been associated with the calcinosis and occur in 17% to 30% of patients with JDM. Lipodystrophy is a common feature in children with chronic disease, especially if poorly controlled and of longer duration, overall occurring in 9.7% of patients<sup>236</sup> (Figs. 22-32 and 22-33). The lipodystrophy may be generalized or partial and is characterized by a slowly progressive symmetric loss. The lipodystrophy is associated with insulin resistance and hyperlipidemia (hypertriglyceridemia and low levels of high-density lipoprotein [HDL]).<sup>240</sup> These cardiac risk factors can be present in patients with chronic disease, even without the lipodystrophy. Acanthosis nigricans has been described in 10% of patients later in the disease course (Fig.

22-34). The insulin resistance correlates with muscle atrophy, proinflammatory circulating cytokines, and a family history of diabetes, but not with corticosteroid use.<sup>241</sup>

The myopathy of JDM affects primarily the proximal groups of muscles, especially the triceps and quadriceps, usually in a symmetric distribution. Muscle tenderness or stiffness is not uncommon but usually occurs later in the course rather than as a presenting sign. Affected children often complain of great fatigue and are unable to do

simple tasks, such as rising, squatting, walking, or reaching. In young children, muscle weakness may manifest as more demanding behavior. Physical therapists may be helpful as assessors of muscle strength, particularly in younger children. Speech may become nasal because of nasopharyngeal muscle weakness, and approximately 10% to 15% of patients complain of difficulty with swallowing.

A nondestructive, generally nondeforming arthritis occurs in approximately half of affected children at some time during the disorder, most commonly an asymptomatic arthritis of the knees; large and small joint polyarthritis has also been described.<sup>239</sup> Vasculopathy of the GI tract may lead to ulceration, perforation, pneumatoisis intestinalis, or hemorrhage. D-xylose absorption has been decreased in patients with JDM, suggesting the decreased absorption of nutrients and medications, including oral corticosteroids, and leading to the suggestion that the disorder be treated with intravenous methylprednisolone for acute cases.<sup>242</sup> Dysphagia from impaired muscle function may lead to esophageal reflux and aspiration pneumonia, requiring intravenous feeding. Children with JDM have occasionally been described with hepatomegaly, cholestasis, or pancreatitis.

The majority of patients with JDM show a reduced ventilatory capacity without respiratory complaints, probably owing to respiratory muscle weakness and poor chest wall compliance. Decreased diffusion capacity and evidence of interstitial lung disease is uncommon, but may present with dyspnea on exertion. Cardiac disease is rare in children with JDM, and mainly involves murmurs and cardiomegaly. Although pericarditis occurs, conduction defects and acute myocarditis are uncommon but severely damaging. Nevertheless, systolic dysfunction has recently been noted after long-term follow-up study (16.8 years) and is correlated with skin disease scores, not muscle disease activity.<sup>243</sup> Central or peripheral nervous system disease is very rare, in contrast with SLE. Similarly, other than conjunctival vessel tortuosity, eye disease is usually limited to cataracts from administration of systemic corticosteroids. IgA nephropathy has been described, but renal disease is not generally a feature of JDM.<sup>244</sup>

The presence of arthritis, significant dysphagia, renal disease, Raynaud phenomenon, or neuropathy should also prompt consideration of evaluation for overlap disease. Up to 10% of children with JDM show an overlap syndrome with features of SLE, SSc, or JIA.

The diagnosis of JDM is suspected on clinical grounds, based on the typical cutaneous manifestations and evidence of muscle weakness and/or tenderness. Increased levels of muscle enzymes and the demonstration of increased signal intensity on fat-suppressed T2-weighted MRI scans<sup>245</sup> provide evidence of muscle inflammation,<sup>237</sup> and whole body MRIs have been advocated to estimate total inflammatory burden.<sup>246</sup> The increased signal intensity on MRI scans relates to accumulated extracellular water content. It is indistinguishable from other inflammatory myopathies or rhabdomyolysis but can be differentiated from muscular dystrophies. Several enzyme levels should be assessed concomitantly (serum aldolase, aspartate aminotransferase, lactic dehydrogenase, and serum creatine phosphokinase levels); aldolase is most commonly elevated and serum creatine phosphokinase is normal in about 35% of affected children with active disease.<sup>237</sup> Muscle biopsy of a site shown to be affected by clinical examination or MRI testing can be performed to confirm the presence of perifascicular and perivascular lymphocytic infiltration with atrophy, necrosis, and late fibrosis of the muscle fibers. Skin biopsy is usually not valuable.

Children with active JDM are often lymphopenic but show a relative increase in the percentage of B cells, as defined by anti-CD19 monoclonal antibody binding. Overall, 70% of children with JDM have one or more detectable myositis-specific and myositis-associated antibody if full serologic testing is performed.<sup>212</sup> The high incidence in adults of myositis-specific antibodies, particularly anti-Jo-1, is a distinguishing feature between adult and pediatric disease. Indeed, anti-Jo-1 antibodies (against histidyl-tRNA synthetase) are found in fewer than 3% of patients with JDM, and anti-Mi-2 antibodies (against a DNA helicase) have been found in about 5%. However, other more recently recognized autoantibodies targeting intracellular proteins (anti-TIF1-γ, anti-NXP2, and anti-MDA5) have been found in JDM and are useful biomarkers for defining distinct clinical subsets and predicting prognosis.<sup>216,247,248</sup> Anti-TIF1-γ(p155) antibodies are detected in approximately 25% of children and are linked to more severe cutaneous involvement with generalized lipodystrophy. Anti-NXP2 (also called

*anti-MJ* or *anti-p140*) antibodies, found in about 20% of patients, are associated with a substantially increased risk of greater disease severity, and of developing calcinosis<sup>238</sup> and contractures.<sup>249</sup> Anti-MDA5 (also called *anti-CADM*) antibodies, noted in 7.4% of JDM patients, predict a distinct phenotype that includes skin and oral ulcers, arthritis, milder and shorter duration muscle disease activity, and, in a minority of patients, interstitial lung disease.<sup>250-252</sup>

Children with overlap disease may have anti-PM-Scl (5% to 7%) or anti-U<sub>1</sub>RNP (<6%) antibodies. ANAs are also present in 60% to 70% of newly diagnosed children, usually in a coarse speckled pattern.

The course of JDM can be monophasic (lasting remission within 1 or 2 years, 37%), chronic (60%), or polyphasic (3%).<sup>253</sup> Of JDM patients observed into adulthood (median time from diagnosis, 16.8 years), 90% of patients had persistent damage to the skin (77%), muscle (65%), and skeletal (57%) systems.<sup>254</sup> Unfortunately, prediction of disease course has been a challenge, although inadequate treatment is a strong predictor of poor outcome. A shorter duration of untreated disease and a lower JDM skin disease activity score at onset of disease are correlated with a monocyclic course.<sup>230</sup> The presence of persistent skin eruptions (especially Gottron papules) 3 months after initiation of treatment predicts a longer time to remission, and if Gottron papules and nailfold capillaroscopy are both abnormal at 6 months after initiation, the outcome is particularly poor.<sup>253</sup> Organ damage 6 months after onset of treatment is also a predictor for poor prognosis.<sup>254</sup> By 36 weeks, persistent nailfold capillary changes, which correlate with skin disease rather than muscle disease, also predict a nonmonocyclic disease.<sup>230</sup>

During the active phase of dermatomyositis, children are particularly at risk for sudden, overwhelming Gram-negative sepsis, sometimes masked by corticosteroids. Hospitalization may be advisable in the acute stage, especially if the disease involves palatal-respiratory muscles, to prevent aspiration and to ensure adequate respiration, including by feeding intravenously and using mechanical ventilation if necessary. A high index of suspicion must be maintained for aspiration because of weak palatal-respiratory function or perforation of a viscus, and early aggressive therapy must be instituted when necessary. Nevertheless, the mortality rate, formerly about 30%, generally because of these complications, has been markedly reduced by intervention, and most recently was found to be 3% to 4%.<sup>217,236</sup>

The course of JDM can be classified as monophasic in 47%, polyphasic in 18%, and chronic in 35%.<sup>237</sup> The Pediatric Rheumatology International Trials Organisation (PRINTO) criteria and a Myositis Disease Activity Assessment Tool (MDAAT) have been developed to define disease activity versus inactivity.<sup>255,256</sup> In one cohort with a median follow-up period of 16.8 years after symptom onset, 50% to 73% of patients had continuing disease activity, most commonly in the skin (59%).<sup>257</sup>

Most JDM is treated with high-dosage corticosteroid therapy, and many specialists now initiate pulsed intravenous steroids (30 mg/kg or up to 1.5 g), administered every 24 to 48 hours until laboratory values normalize.<sup>258</sup> Usage of pulse steroids, followed by oral corticosteroids or intermittent pulses if needed for continued control, has been shown to decrease the duration of rash, cause less functional impairment, and markedly reduce calcifications in comparison with those children treated with oral corticosteroids only. Side effects are not increased with pulse steroids, and the overall dosage of required corticosteroids tends to be less than that with oral treatment.

Some patients may fail to respond even to very large doses of corticosteroids. Methotrexate is generally the second-line treatment for JDM, when the disease is recalcitrant or corticosteroid usage is problematic. Treatment of severe JDM early in the course with both intravenous methylprednisolone and methotrexate appears to be more useful than with either agent alone,<sup>259</sup> and patients with milder cases have responded to methotrexate (or intravenous immunoglobulin [IVIG]) alone.<sup>260</sup> Methotrexate can be administered orally or, preferably, by subcutaneous injection at a dosage of 1 mg/kg per week with a maximum of 40 mg/week. Intravenous gammaglobulin has also been found to be an effective steroid-sparing agent, especially for cutaneous manifestations. Other cytotoxic agents such as azathioprine in dosages of 1 to 3 mg/kg (up to 200 mg/day) or cyclosporine (5 mg/kg per day) may be used in severe life-threatening forms of dermatomyositis, or when the disease cannot be adequately managed with

prednisone alone. However, biologics, and particularly rituximab, are showing promise. Rituximab has been generally well tolerated, with infections and infusion reactions as the main adverse events. Although the onset of action can be slow, the response is good, including with more than one course.<sup>216,261,262</sup> TNF- $\alpha$  has been implicated in the pathogenesis and severity of JDM, and some patients have shown benefit, especially with administration of infliximab<sup>263</sup>; however, other patients have not responded, particularly with etanercept, or have even worsened on a TNF- $\alpha$  antagonist. Disease that is refractory to immunosuppressants, including rituximab, can be treated with autologous stem-cell transplantation.<sup>264</sup>

The response of the cutaneous features of JDM to treatment may not correlate with the response of muscle; skin manifestations may persist for years despite resolution of other signs of disease. Oral antimalarial agents, especially hydroxychloroquine (generally 5 to 6.5 mg/kg per day), have been helpful in controlling the cutaneous manifestations of dermatomyositis. Topical corticosteroids and calcineurin inhibitors do little to reverse the skin signs of JDM, although topical flucinolone 0.01% in oil has been helpful with the pruritus of chronic scalp involvement. Counseling about sun protection is critical (see discussion for SLE).

The problematic calcinoses may gradually disappear but can cause considerable morbidity. Despite the long list of medications that have been used successfully in anecdotal reports in an effort to hasten clearance, no agent has been helpful in the majority of cases. Nevertheless, bisphosphonates in combination with aggressive immunosuppression have led to dramatic improvement in some patients.<sup>265,266</sup> Sodium thiosulfate can help clear calcinoses when given intravenously, orally, or even topically, but it is often poorly tolerated (e.g., oral administration may lead to severe diarrhea).<sup>267</sup> The combination of abatacept and sodium thiosulfate reduced the muscle and ulcerative skin disease activity, as well as calcifications.<sup>268</sup>

Surgical procedures may also be useful in selected situations.<sup>269</sup> Occlusive dressings (such as DuoDerm) over joint areas, particularly when areas are ulcerated and draining, have promoted healing. Physiotherapy is important for patients with or at risk for contractures to prevent deformity and increase muscle strength. MRI evaluations, myometry, and blood studies did not show increased muscle inflammation after exercise, suggesting that a moderate exercise program is acceptable with active myopathy.<sup>270</sup>

## Systemic Sclerosis (Scleroderma)

Fewer than 5% of patients with SSc have their onset before the age of 16 years. Juvenile SSc (jSSc) has a mean age of onset of 8 years but has been observed in children as young as 0.4 years of age. On average it requires 1 to 4 years to make the diagnosis, because the onset is often insidious.<sup>271</sup> As in adult-onset SSc, jSSc predominantly affects females (female/male ratio of 2.1 to 10.5 : 1), including in prepubertal patients.<sup>272–276</sup> jSSc features pathologic thickening and tethering of skin, as well as visceral fibrosis and small vessel vasculopathy. jSSc is classified into three major groups: diffuse cutaneous (dc) SSc, with diffuse and rapidly progressive skin thickening of the extremities to the elbows and knees, which is associated with early organ involvement (lungs, heart, kidneys); limited cutaneous (lc) SSc, with limited and nonprogressive skin thickening of the distal extremities, in which visceral disease (largely pulmonary arterial hypertension and malabsorption) occurs late; and overlap SSc, in which the dcSSc or lcSSc is associated with another connective tissue disease, such as SLE or JDM.<sup>277,278</sup> Other scleroderma-like disorders include chronic graft-versus-host disease (see Chapter 25), eosinophilic fasciitis, scleroderma from toxins, nephrogenic systemic fibrosis (NSF), and sclerodermatosus plaques in progeria, Werner syndrome (Chapter 6) and phenylketonuria (Chapter 24). In the neonate, stiff skin syndrome (Chapter 6) can be confused with SSc.

Major and minor criteria for jSSc<sup>279</sup> are shown in Box 22-6, with symmetric proximal skin sclerosis/induration being the major criterion for diagnosis. This classification distinguishes jSSc from overlap disease, which is more common in children than in adults (29% vs. 9%).<sup>280</sup> dcSSc occurs in 90% to 100% of patients with jSSc. The organs involved (lung, kidney, joint, muscle, and heart) are similar in children

### Box 22-6 Proposed Criteria for Diagnosis of Juvenile Systemic Sclerosis

Must be younger than 16 years at onset

**Major Criterion (Required)**

Skin induration/thickening proximal to the MCP or MTP joints

**Minor Criteria (2 Required) (Scleroderma-Specific Organ Involvement)**

Cutaneous	Sclerodactyly
Peripheral vascular	Digital-tip ulcers Nailfold capillary changes (megacapillaries and avascular areas) Raynaud phenomenon
Gastrointestinal	Dysphagia Gastroesophageal reflux
Cardiac	Arrhythmias Cardiac failure
Renal	Scleroderma renal crisis New arterial hypertension
Respiratory	Decreased DLCO Pulmonary arterial hypertension (echocardiography; primary or secondary to interstitial lung disease) Pulmonary fibrosis (chest radiograph or high-resolution CT)
Neurologic	Neuropathy Carpal tunnel syndrome
Musculoskeletal	Tendon friction rubs Arthritis Myositis
Serologic	Antinuclear antibody SSc-selective autoantibodies (antitopoisomerase 1 [Scl-70], anticentromere, anti-RNA polymerase III, anti-PM-Scl)

CT, Computed tomography; DLCO, diffusing capacity for carbon monoxide; MCP, metacarpophalangeal; MTP, metatarsophalangeal; RNA, ribonucleic acid; SSc, systemic sclerosis.



**Figure 22-35** Raynaud phenomenon. Note the blue discoloration of the thumbs and fingers with the sharply demarcated white coloration of the distal aspect of the third finger.

and adults with SSc.<sup>281</sup> In comparison with adults, jSSc has less visceral involvement but a greater prevalence of arthritis and myositis.<sup>282</sup> Some children have a rapidly progressive and fatal illness with cardiac involvement, but more commonly children have a chronic course with less overall mortality.<sup>283</sup>

Raynaud phenomenon is seen in 70% at onset and ultimately in virtually all affected children (Fig. 22-35). The condition may occur



**Figure 22-36** Systemic scleroderma. Smooth atrophic skin, pinched nose, and fixed grimace are evident on the face of this adolescent.

in children as young as 1 year of age. In jSSc, it is associated with vascular intimal hyperplasia and fibrosis that manifests as dilated, sausage-shaped capillary loops and avascular areas. Capillary microscopy of the nailfolds can be performed with an ophthalmoscope, otoscope, or dermatoscope after a drop of mineral oil is placed on the nailfold area. The capillary changes are indistinguishable from those of patients with JDM, distinct from those of SLE, and not seen in patients with isolated Raynaud disease, acrocyanosis, or morphea. Raynaud phenomenon is precipitated by cold or emotional stress, and is characterized by pallor, cyanosis, and hyperemia with pain, burning, numbness, tingling, swelling, and hyperhidrosis of the affected fingers or toes. Rarely, Raynaud phenomenon affects the nose, lips, cheeks, or ears. Nail changes in which the distal portion of the nailbeds adheres to the ventral surface of the nail plate and obliterates the space that normally separates these two structures have also been described. Digital infarcts affect 10% to 28% of children and calcinosis up to 18%.

Overall, 69% of children with Raynaud phenomenon have primary disease (without an underlying collagen vascular disease).<sup>284</sup> In both primary and secondary forms of Raynaud phenomenon, girls predominate (80%). The age of onset, presence of livedo reticularis, and presence of aPL antibody cannot distinguish secondary from primary disease, but a positive ANA test and abnormal capillary pattern correlate strongly with the presence of an underlying disease.<sup>284</sup> Primary Raynaud phenomenon is also not associated with digital tip pitting and/or ulceration. Raynaud phenomenon must be differentiated from acrocyanosis, which is common in thin adolescent girls as a purplish discoloredation. The discoloration of acrocyanosis tends to affect the toes more than the fingers, to be mottled, and to largely persist with warming. Nailfold capillary changes are absent in acrocyanosis, but distal pulses may be faint. Raynaud phenomenon must also be distinguished from blue toe syndrome induced by mixed amphetamine salts, thought to be a reversible vasoconstrictive phenomenon.<sup>285</sup>

At onset, 60% of children have the characteristic early edema, sclerodactyly, and induration of the hands (53% have both Raynaud phenomenon and skin induration of the hands). The hands become shiny, with tapered fingertips and, ultimately, restricted movements as the tendons become shortened. Rarely, the more proximal extremities, trunk, or face are involved at onset. With time, however, the face may develop a characteristic appearance. The forehead becomes smooth and cannot be wrinkled, and atrophy and tightening of the skin give a characteristic appearance because of a fixed stare, pinched nose, prominent teeth, pursed lips, reduced oral aperture, and a perpetual grimace-like facies (Fig. 22-36). Skin thickness is scored serially (modified Rodnan score), leading to a skin thickness progression rate. Telangiectases (especially with calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia [CREST syndrome]), calcification (Fig. 22-37), ulceration (Fig. 22-38), and dyspigmentation may also be seen with chronic disease. The pigmentary



**Figure 22-37** Systemic scleroderma. Calcinosis on the finger. Note the tightness of the skin.



**Figure 22-38** Systemic scleroderma. Ulceration overlying a joint.



**Figure 22-39** Systemic scleroderma. Speckled depigmentation on the upper chest in this boy with systemic scleroderma.

changes in jSSc may be homogeneously hypopigmented or hyperpigmented, or may have a “salt and pepper”-like appearance because of retained perifollicular hyperpigmentation in areas of hypopigmentation (Fig. 22-39).

Early scleroderma is often associated with arthralgias and limited joint mobility. Patients may complain initially of weight loss, fatigue, GI symptoms, and exertional dyspnea. Muscle weakness is seen in up to 40% of children and often is associated with evidence of myositis. Overall, GI manifestations have been described in up to 75% of children. In addition to the acid reflux<sup>286</sup> and decreased esophageal motility, patients have reported constipation, bloating, discomfort,



**Figure 22-40** CREST syndrome. Telangiectatic mats on the face. This adolescent boy showed myriads of calcifications, Raynaud phenomenon, esophageal dysmotility, and sclerodactyly as well.

regurgitation, weight loss, and malabsorption. Cardiac and pulmonary abnormalities are usually screened by chest X-ray, pulmonary function tests, and echocardiogram. Pulmonary function testing usually shows restrictive lung disease (54% of children), even if clinically silent.<sup>287</sup> High-resolution computed tomography (CT) scanning can capture the early alveolitis that precedes pulmonary fibrosis. Pulmonary function testing reveals the decrease in forced air capacity and diffusing capacity for carbon monoxide that are particularly concerning.<sup>288</sup> Cardiac disease (occurring in 15%) is the major cause of pediatric mortality. It may be secondary to pulmonary hypertension or may be primary (pericarditis, arrhythmia, cardiac failure). Severe cardiomyopathy has been described in children with SSc/myositis overlap.<sup>289</sup> Up to 60% of children have shown evidence of renal involvement, usually the result of renal vasculopathy and during the first 3 years of diffuse scleroderma. However, fewer than 5% develop renal failure (scleroderma renal crisis) and 0.7% experience scleroderma renal crisis. Regular monitoring of blood pressure is critical to identify rapid progression and hypertensive renal crisis. CNS involvement affects only 3% of affected children.

CREST syndrome (Fig. 22-40), a form of lcSSc, is quite rare in children. Patients generally have a more slowly progressive form of the disease and have anticentromere antibodies. Although some patients with the CREST syndrome may develop severe pulmonary hypertension, more extensive cutaneous lesions, and visceral involvement, the patients with this subset generally tend to have a relatively benign course.

The diagnosis of SSc is easily established when cutaneous sclerosis of the face and hands is present, particularly when it is associated with Raynaud phenomenon, nailfold telangiectasia, and visceral involvement. Laser Doppler imaging can help visualize the microvascular abnormalities.<sup>290</sup> Symptoms or signs of dysphagia or gastroesophageal reflux help confirm the diagnosis. A new severity score (J4S) grades general, vascular, skin, osteoarticular, muscle, GI, respiratory, cardiac and renal features as normal (0) to end stage (5).<sup>291,292</sup>

The presence of autoantibodies correlates with disease subset. Antitopoisomerase antibody (Scl70) is found in 20% to 34% of children and predicts rapid skin disease progression and interstitial lung disease, but not poorer survival in children. In contrast, anticentromere antibody (ACA) is found in only 2% to 16% of patients and is associated with lcSSc and pulmonary arterial hypertension. Anti-U<sub>1</sub>RNP and polymyositis-scleroderma (PM-Scl) antibodies are also detected in 2% to 16% of children and often described with overlap syndromes and in association with myositis and arthritis. RNA polymerase III (POL3) antibody, which portends the risk for scleroderma renal crisis, is rare in children, but is found in 30% of adult-onset SSc. Most children with SSc have ANAs (81% to 97%), often of the speckled or nucleolar configuration; about 20% to 23% of children with SSc have a positive ANA test with a scleroderma-related autoantibody.

The 10-year survival rate for jSSc is 98%, considerably better than in adults with SSc (75%).<sup>272,279</sup> Most deaths result from cardiac (most common), pulmonary, or renal disease. Treatment of SSc in children is challenging and similar to that in adults. Early treatment before the occurrence of the irreversible fibrotic damage to tissue is ideal. General measures include avoidance of factors producing vasospasm (tension, fatigue, stress, cold weather, and smoking in adolescents) and minimizing trauma to the hands. Heated gloves are available, and emollients and dressings can be applied to ulcerated cutaneous sites. Calcium channel blockers such as nifedipine or nicardipine, which reduce smooth muscle contraction by reducing the uptake of calcium, are considered first-line therapy for Raynaud phenomenon. Pentoxifylline, which lowers blood viscosity, thus increasing blood flow, can also help control the severity of Raynaud phenomenon and digital ulcers. Intravenous infusion of iloprost or other prostacyclins are used for severe jSSc-related Raynaud phenomenon and digital ulcers. Physiotherapy is important to limit contractures.

The arthritis may respond to NSAIDs or salicylates. Proton pump inhibitors (e.g., omeprazole and lansoprazole) are the treatment of choice for reflux esophagitis. General measures for treating reflux include elevating the head of the bed, staying upright after eating, a bland diet, and restricting the size of meals. Prokinetic drugs such as domperidone may improve motility, and antibiotics administered in rotation may decrease the risk of malabsorption from bacterial overgrowth. Intravenous pulse therapy cyclophosphamide has been recommended at a dosage of 0.5 to 1 g/m<sup>2</sup> every 4 weeks for at least 6 months for interstitial lung disease. Good hydration and frequent voiding are important to decrease the risk of cystitis. Endothelin receptor antagonists or phosphodiesterase inhibitors, followed by intravenous infusions of prostacyclin analogues have been used for the pulmonary artery hypertension.<sup>293</sup> Oxygen, antibiotics, and diuretics may also be required for lung disease, especially with congestive heart failure.

Immunosuppression with methotrexate or mycophenolate mofetil has been shown to improve the skin manifestations and have been particularly useful for children with overlap disorders. Corticosteroids do not appear to help the sclerodermatosus process and may trigger renal crisis; however, systemic steroids may be used with caution to treat severe disabling arthritis or myositis. ACE inhibitors such as losartan and captopril are critical in controlling hypertension and stabilizing renal function. The renal disease may require dialysis. Several children who have not responded to other therapies have been treated with autologous stem cells with improvement in clinical signs and stabilization of pulmonary function.<sup>294,295</sup> Bosentan has been helpful for pulmonary hypertension in jSSc<sup>296</sup> and, in adults with SSc, for promotion of healing of cutaneous ulcerations.<sup>297</sup>

The pathogenesis of SSc involves alterations in the immune system, vasculature, and connective tissue. Cytokine mediators, such as transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF) and connective tissue growth factor (CTGF), are particularly important in inducing fibroblast activation and differentiation to myofibroblasts,<sup>298</sup> triggering collagen synthesis. An imbalance between matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases may also play a role. Also of major importance are the presence of autoantibodies and the vasospastic phenomena with endothelial damage that precede digital, pulmonary, and renal fibrosis. Imatinib, which targets TGF-β/Smad<sup>299</sup> and PDGF<sup>300</sup> signaling, has shown some benefit. Support groups for patients with scleroderma are the Scleroderma Foundation ([www.scleroderma.org](http://www.scleroderma.org)); the Scleroderma Society ([www.sclerodermasociety.co.uk](http://www.sclerodermasociety.co.uk)), and the Scleroderma Society of Canada ([www.scleroderma.ca](http://www.scleroderma.ca)).

## Eosinophilic Fasciitis

Eosinophilic fasciitis (diffuse fasciitis with eosinophilia) is a sclerodermatosus disease characterized by diffuse infiltration of the skin of the extremities and trunk without visceral involvement or Raynaud phenomenon (Box 22-7).<sup>301,302</sup> Seen rarely in children, eosinophilic fasciitis may evolve into generalized or localized morphea (localized scleroderma),<sup>303-306</sup> suggesting that the disorder is a deep variant within the spectrum of severe morphea.<sup>307</sup> In contrast to adults with

### Box 22-7 Eosinophilic Fasciitis

- Scleroderma-like disease without Raynaud phenomenon or visceral involvement
- Painful swelling and induration of skin and subcutaneous tissue
- Usually acute onset after trauma, stress, or strenuous physical activity
- Cobblestone or puckered appearance; may resemble scleroderma later
- Eosinophilia and hypergammaglobulinemia common; occasional elevation in antinuclear antibodies or aldolase
- Usually good initial response to systemic corticosteroids

eosinophilic fasciitis, the childhood form has a better prognosis and shows a female predominance, more muscle involvement, common involvement of the hands with painless contractures and sclerosis, and is associated with arthritis in only 25% of cases (vs. 44% of adults).<sup>308</sup> The hematologic abnormalities that have been noted in adults (aplastic anemia, thrombocytopenic purpura) have not been described in children. However, renal involvement, especially IgA nephropathy, has been noted.

The disorder is characterized by a sudden onset of usually painful swelling, induration, and scleroderma-like changes of the skin with marked thickening of the subcutaneous fascia. The skin has a cobblestone or puckered appearance and often has a yellowish or erythematous color. It is indurated, taut, and bound down without pigmentary change; the “groove sign,” in which a vein is depressed, is seen in up to 50% of patients and is a clue to diagnosis, reflecting the depth of involved fascia. The hands, forearms, feet, and legs are most commonly affected initially, although the disease may progress to the trunk and face. When painless (which is unusual), the disorder has been mistaken for angioedema.<sup>309</sup> In the majority of patients, the onset of the disorder follows trauma or excessive physical exertion. Although systemic changes are usually absent in affected children, patients show peripheral eosinophilia early in the disease, hypergammaglobulinemia, and an elevated sedimentation rate. The ANA test may be positive during the course, but is usually negative, especially at onset. A deep biopsy to include fascia may be necessary to confirm the diagnosis, but MRI is also helpful in demonstrating the depth of the inflammatory involvement. Sections show edema and infiltration of the lower subcutis and deep fascia by lymphocytes, plasma cells, and histiocytes. Eosinophils may be detected in early lesions; thick, sclerotic dermis is characteristically seen late in the disorder.

Patients usually show a good initial response to oral or pulse intravenous systemic corticosteroids, sometimes in combination with methotrexate, with resolution of soft-tissue induration and correction of laboratory abnormalities.<sup>310</sup> However, gradual progression during one or more years to cutaneous fibrosis and/or painless flexion contractures, especially of the hands and feet, occurs in the majority of affected children.<sup>303</sup> Younger age at onset (<7 years of age) and greater disease severity have been correlated with a higher risk of progression to residual fibrosis. Physiotherapy is important adjunctive therapy. In children who do not respond to systemic corticosteroids, other broadly immunosuppressive medications, IVIG,<sup>311</sup> dapsone,<sup>312</sup> infliximab,<sup>309,313</sup> rituximab,<sup>314</sup> retinoids, and UVA1 irradiation<sup>307,315</sup> may be considered. Eosinophilic fasciitis must be distinguished from eosinophilia-myalgia syndrome, which has rarely been described in children and results from oral ingestion of contaminated L-tryptophan.<sup>316</sup> These patients show pronounced eosinophilia with myalgias, especially centrally, and vasculitis of the skin and other organs (Fig. 22-41). The associated myopathy and sometimes elevated muscle enzymes can lead to confusion with an overlap autoimmune syndrome (of scleroderma and dermatomyositis).<sup>310,317</sup> Cutaneous lymphoma and hypereosinophilia syndrome must also be considered.

## Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF; previously known as *nephrogenic fibrosing dermopathy*) has increasingly been recognized as a sclerosing disorder predominantly seen in patients with renal dysfunction who receive gadolinium-based contrast media as part of MRI testing.



**Figure 22-41** Eosinophilic fasciitis. This girl has swelling, induration and cobblestoning of the skin of the arms, hands, legs and feet. Although many respond to systemic steroids, this girl required several other systemic immunosuppressants for response.

Although NSF was first described in 2000,<sup>318</sup> the first pediatric cases were reported in 2003<sup>319</sup>; in total, 23 pediatric cases have been described.<sup>320</sup> The signs of NSF may develop 2 to 75 days after exposure to the gadolinium.<sup>321</sup> Lesions are characterized by indurated papules and plaques, brawny thickening of skin with a *peau d'orange* appearance, and sometimes joint contractures. The extremities, buttocks, and trunk are usually involved, and the face is typically spared. Patients usually complain of associated pruritus, burning, and pain. Biopsy sections of skin show widened septae in with subcutaneous tissue with increased collagen and fibroblasts. Calcinosis cutis and perforating collagenosis may be seen concomitantly in biopsy sections. The disorder must be distinguished from scleroderma, scleromyxedema, and scleredema. The US Food and Drug Administration (FDA) warns against the use of all gadolinium agents in patients with glomerular filtration rates (GFRs) less than 30 mL/min, and the European guidelines specify a GFR of 30 to 60 mL/min.<sup>322</sup> The most successful treatment is renal transplantation or recovery of the acute renal injury to improve renal function.

## Scleredema

Scleredema (scleredema adultorum of Buschke) is a rare disorder of diffuse large areas of induration of skin that must be distinguished from scleroderma.<sup>323</sup> The condition most commonly occurs in adults with diabetes, but 29% of described cases are in children, half of these cases during the first decade of life.<sup>324,325</sup> Although scleredema may begin spontaneously, 65% to 95% of patients have the onset of their disorder within a few days to 10 weeks after an acute febrile illness. Of these, 58% of the infections are streptococcal; scleredema may also follow infections from influenza, measles, mumps and varicella.<sup>326,327</sup>

The skin changes usually begin suddenly on the neck and then gradually spread to the upper trunk, and occasionally the arms and face, as nonpitting thickening. The abdomen and lower extremities, if involved, tend to show less thickening than the upper half of the body. The texture of skin has been described as brawny or woody, and children with facial involvement may show a mask-like facies. Although affected individuals are usually asymptomatic, some patients display a prodromal period with fever, malaise, and myalgias. In general the condition is benign, although involvement of the skeletal and cardiac muscles has been reported. Tachycardia, arrhythmias, and pericardial effusions have been noted.<sup>328</sup> In addition, the tongue has been involved, making protrusion and mastication difficult. The thickening results from deposition of acid mucopolysaccharide, largely hyaluronic acid, which can easily be detected with colloidal iron or Alcian blue stains of lesional biopsies. The mechanism by which infection triggers scleredema in children is unclear. Therapy is generally unsuccessful,

although high-dosage intravenous corticosteroids may have been helpful in one affected child.<sup>329</sup> Lesions usually resolve spontaneously within months to 2 years. Scleredema has rarely been described in a generalized form in sick neonates (sclerema neonatorum) and must be distinguished from subcutaneous fat necrosis of the newborn in this age group (see Chapter 2).

## Morphea

Morphea is an autoimmune disorder characterized by localized areas of cutaneous sclerosis.<sup>277,278,330–334</sup> Although sometimes termed *localized scleroderma*, use of the term *morphea* decreases the potential confusion with SSc, or scleroderma, a disorder with significantly greater morbidity that shares similar pathogenic features of immune activation and increased collagen production.<sup>308,335,336</sup> The presence of sclerodactyly and/or Raynaud phenomenon should alert the physician to consider a systemic form of scleroderma, rather than morphea.

Morphea has been divided into five subgroups based on pattern and lesional depth: circumscribed, linear, generalized, mixed, and pansclerotic (Padua criteria<sup>337</sup>) (Box 22-8). In children, linear morphea (or linear scleroderma) is most common (42% to 65%), followed by the relatively localized circumscribed type (26% to 37%); in contrast, the circumscribed type of morphea is the most common form (60%) in adults.<sup>338–340</sup> Circumscribed morphea now includes deep morphea forms (morphea profunda, subcutaneous morphea). The development of bullae within lesions is very rare. Linear scleroderma includes the *en coup de sabre* and Parry–Romberg syndrome forms, in which facial involvement occurs. Morphea can be more extensive in distribution (generalized morphea, 7% to 11%) or depth (disabling pansclerotic morphea, extending from the dermis to the bone). Patients may show more than one type concurrently, most commonly linear and circumscribed types (mixed type, 8% to 15%).

The incidence of morphea is 0.4 to 1:100,000 individuals, occurring more often in Caucasians than other racial groups.<sup>338,339</sup> In children, morphea occurs at least 10 times more often than SSc.<sup>287</sup> The disorder occurs primarily in children and young adults with a 2 to 3:1 female-to-male ratio. The mean age in children is 5.2 to 8.2 years of age,<sup>338,340,341</sup> but morphea has been described in infants and even neonates. A family history of rheumatic or autoimmune disorders is reported in the first- or second-degree relatives of 12% to 24% of children, but only 2% of relatives have morphea. Of individuals with childhood-onset morphea, 5% developed a concomitant autoimmune disorder, including skin-localized disorders (psoriasis, alopecia areata, vitiligo).<sup>339</sup>

The unilateral nature of the disorder in most patients and the patterning of lesions have led investigators to hypothesize that affected patients have genetically susceptible cells in this distribution that are triggered by environmental exposure to develop morphea. Some

patterns of morphea seem to follow lines of Blaschko, but others are clearly distinct. The potential link with *Borrelia* infection in European patients remains controversial.<sup>342</sup> Administration of valproic acid was thought to trigger morphea in two patients.<sup>343</sup> Trauma, including from vaccination,<sup>344,345</sup> has also been postulated to trigger lesions of pediatric morphea, and this possibility is supported by the rate of activation of morphea when corrective procedures are performed;<sup>346</sup> however, trauma is so common in children that controlled studies would be required to further consider its role.

The onset of circumscribed morphea is insidious, and superficial plaque-type lesions begin as flesh-colored, erythematous or lilac-colored patches that evolve during weeks to months into firm, hyperpigmented or ivory plaques, with or without a surrounding lilac or violaceous inflammatory zone. The ivory plaques may resemble lesions of lichen sclerosus et atrophicus (LSA) but tend to evolve with the development of hyperpigmentation (Fig. 22-42). Occasionally, patients have 1- to 3-mm papules of morphea (guttate morphea). Affected areas, in order of decreasing incidence, are the trunk, neck, extremities, and face. Morphea may also show localized areas of atrophy and resemble atrophoderma of Pasini and Pierini (Fig. 22-43), a disorder that many experts consider within the morphea spectrum<sup>347</sup> and may be indurated or associated with classic lesions of morphea.<sup>348</sup> The atrophoderma usually begins on the trunk during the late teens or early 20s but may even be congenital.<sup>349–351</sup> The atrophic patches extend very slowly with a depressed center and a “cliff-drop” border. Lesions of atrophoderma of Pasini and Pierini tend to increase in number for 10 years or more, primarily on the trunk, neck, and proximal extremities, and then generally persist without apparent change.



**Figure 22-42** Morphea. (A) Ivory-colored, indurated plaque with surrounding active violaceous border and residual hyperpigmentation. (B) Central depigmentation with peripheral hyperpigmentation. Note the evidence of residual atrophy, including venous prominence.

### Box 22-8 Subsets of Morphea (Localized Scleroderma)

- Circumscribed morphea (round and oval lesions)
  - Superficial (limited to epidermis and dermis)
    - Plaque-type morphea
    - Guttate morphea
    - Atrophoderma of Pasini and Pierini
    - Lichen sclerosus-like
  - Deep morphea (subcutaneous)
- Linear morphea/linear scleroderma (can be deep to muscle and bone)
  - Linear morphea
  - En coup de sabre*
  - Progressive hemifacial atrophy (Parry–Romberg)
- Generalized morphea (>4 plaques, each >3 cm in diameter, involving at least 2 of 7 anatomic areas: head/neck, right and left upper extremities, right and left lower extremities, anterior and posterior trunk)
- Mixed morphea (combination of 2 or more of the above subtypes)
- Pansclerotic morphea (circumferential limb involvement to all depths of skin, including muscle and bone; tends to spare digits)



**Figure 22-43** Morphea. Atrophodermic patches in a girl with generalized morphea. Some of the lesions on the upper shoulders demonstrate the “cliff drop” depression of lesions.



**Figure 22-44** This girl with generalized morphea and uncomfortable sclerosis of the chest had resultant deformity of the breasts. Note the taut breasts, areolar prominence, and shininess from skin atrophy.

In the plaque type, lesions typically vary from a few centimeters to several inches in diameter; fusion of many plaques may result in the more generalized form of morphea. Circumscribed deep morphea feels indurated at a deep level; the skin surface may appear slightly puckered or hyperpigmented, but often appears normal.

Linear lesions (linear scleroderma) generally affect the limbs (occasionally the head or trunk). Their clinical appearance is similar to that of circumscribed plaque-like forms, but the violaceous peripheral ring is inconspicuous or only present at the advancing border. Lesions usually present as broad linear bands of induration with dyspigmentation (both hyperpigmentation and hypopigmentation). Much less commonly, a thin linear band of involvement with atrophy and hyperpigmentation may occur and is sometimes called *linear atrophoderma of Moulin*. Associated atrophy of the skin and underlying subcutaneous tissue leads to a puckered or indented appearance with prominent veins; atrophy may also affect the underlying muscles, fascia, and bones. Linear scleroderma involving an extremity is associated with a risk of undergrowth, both linear and circumferential, of the affected limb, and involvement of the breast area can lead to undergrowth and severe deformity in female adolescents (Fig. 22-44). Impaired joint mobility and contractures (Fig. 22-45) are additional risks when the sclerodermatosus area overlies a joint. Occasionally, roughening of one surface of the long bones underlying a linear area of morphea may be noted. This disorder, termed *melorheostosis*, is characterized radiographically by a picture suggesting that of wax flowing down the side of a candle. Calcinosis is occasionally present in plaques of linear scleroderma, and the underlying muscle may show an interstitial myositis.

Linear scleroderma involving the frontal or frontoparietal region of the scalp (with or without associated facial hemiatrophy) is called *en coup de sabre* (“cut of a saber”). Although usually unilateral, bilateral cases of *en coup de sabre* have rarely been described.<sup>352,353</sup> This variant begins with a purplish to brown patch that becomes sclerotic and often progresses to a linear depressed groove. The initial presentation may be confused with a port wine stain if purplish in color without induration or depression,<sup>354</sup> but pulsed dye laser does not lead to improvement.<sup>355</sup> With loss of subcutaneous tissue, it thus resembles a saber wound or cut on the frontoparietal scalp (Fig. 22-46). The groove may extend downward into the cheek, nose, and upper lip, and, at times, may involve the mouth, gum, chin, or neck. Extension to the scalp or periocular area leads to associated alopecia of the scalp in a linear distribution (Fig. 22-47) or local loss of eyebrow or eyelashes.

The *en coup de sabre* variety may represent a more superficial form of progressive facial hemiatrophy (the Parry–Romberg syndrome), a condition of slowly progressive atrophy of the soft tissue of half of the face with (Fig. 22-48, A) or without (Fig. 22-48, B) associated dermal sclerosis. Either *en coup de sabre* or Parry–Romberg syndrome may be accompanied by alopecia, seizures, headaches, trigeminal neuralgia, enophthalmos, myopathy of external eye muscles, and atrophy of the



**Figure 22-45** Linear scleroderma. Flexion contraction of the hand in a girl with linear scleroderma. This is the extent to which she can straighten her fingers.

ipsilateral half of the upper lip, gum, and tongue. Of these manifestations, headaches are most common, occurring in 67% of patients<sup>356</sup> and often meeting the criteria for migraines.<sup>357</sup> Intracerebral atrophy, white matter hyperintensity, and calcifications may be seen on MRI and CT evaluations of affected patients,<sup>352,358–360</sup> especially in patients with neurologic abnormalities.<sup>356</sup> The severity of *en coup de sabre* morphea does not correlate with neuroimaging changes.<sup>356</sup>

Severe, generalized involvement which may extend to bone has been termed *disabling pansclerotic morphea*.<sup>361</sup> This variant, usually



**Figure 22-46** *En coup de sabre*. Extensive soft-tissue atrophy in a linear pattern on the forehead.



**Figure 22-47** *En coup de sabre*. Note the extension into the scalp, leaving cicatricial alopecia.

affecting girls from 1 to 14 years, tends to have a relentless disabling course and may produce marked disability. Nonhealing ulcers and squamous cell carcinoma may develop at sites of involvement.<sup>362,363</sup>

In most pediatric patients, the diagnosis of localized scleroderma is made clinically. However, histologic evaluation of lesional skin shows early inflammation with edema, subsequent sclerosis, and eventual atrophy. The dermis progressively thickens, and dermal appendages are lost. In contrast to SSc, there is more inflammation and more sclerosis of the papillary dermis. Although the development of the cutaneous sclerosis occurs in both morphea and SSc, the clinical features and prognosis of these two autoimmune disorders differs. Raynaud phenomenon and nailfold capillary dilation and dropout are seen in SSc, but rarely in morphea. Arthralgias occur in 15% to 24% of children affected by morphea<sup>338,364</sup> and have been described more commonly with linear scleroderma, generalized morphea, and circumscribed deep morphea. Dysphagia is not uncommon, and ocular (especially anterior segment inflammation)<sup>365</sup> and renal<sup>366</sup> abnormalities have also been described. However, the restrictive pulmonary and esophageal complications of SSc very rarely arise in morphea.<sup>338</sup> Children with extracutaneous manifestations other than as noted for *en coup de sabre* morphea tend to have more severe skin disease (e.g., pansclerotic morphea, extensive linear scleroderma, generalized morphea). Morphea may also occur in patients with other collagen vascular disorders as part of an overlap syndrome (4.9%).<sup>339</sup>



**Figure 22-48** Parry–Romberg syndrome. Hemifacial atrophy, with (A) or without (B) induration of the overlying skin. In (A) the superficial sclerosis and atrophy is clearly visible.

Several laboratory tests may be abnormal in individuals with morphea, although to date they do have no significant diagnostic or prognostic value. ESR may be increased, especially in children with linear and deep morphea.<sup>340</sup> Eosinophilia is seen in 15% overall, most often in the deep type.<sup>340</sup> ANA positivity, especially speckled and nucleolar patterns, occurs in 30% to 42% of affected children,<sup>339,367</sup> and RF is positive in 16% of patients. Autoantibodies (ANA, ssDNA, antihistone antibodies) are correlated with more extensive body surface area involvement, functional limitations, and higher skin scores in linear morphea.<sup>367</sup> Antitopoisomerase II antibodies have been detected in 76% of patients with localized scleroderma (and 85% in generalized morphea); these antibodies (in contrast to Scl70 antibodies) have been found in 14% of patients with SSc and are detectable in less than 10% of normal children and children with SLE or JDM.<sup>368</sup> Serum levels of B-cell activating factor (BAFF) are increased in morphea (as well as in SSc and SLE), but not in autoimmune blistering disorders such as pemphigus or pemphigoid.<sup>369</sup> In addition, antimatrix



**Figure 22-49** Linear scleroderma with limb length discrepancy. Severe circumference and linear hypotrophy of the bone and soft tissue of the affected leg led to gait disturbance and compensatory scoliosis.

metalloproteinase-1 antibodies are markedly increased in about 50% of patients with morphea or SSc, suggesting that decreased collagen I degradation may contribute.<sup>370</sup> Finally, IP-10 has been detected in both the serum and tissue of pediatric morphea.<sup>371</sup>

Morphea lesions can be subtle in their appearance and difficult to monitor for activity. Active lesions may show erythema, skin induration, and enlargement, but these characteristics can be subtle and difficult to appreciate. Skin thickening (especially centrally), atrophy, and dyspigmentation are part of the damage left behind. A Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) has been used to track clinical changes.<sup>372</sup> Thermography, laser Doppler flowmetry, and high-frequency ultrasound have been recommended as sensitive and noninvasive means for evaluating disease activity and risk of further tissue damage.<sup>277,373-375</sup>

Plaque type morphea lesions tend to improve within 3 to 5 years, but the residual hypopigmentation, hyperpigmentation, and occasional atrophy may persist indefinitely. Lesions of linear scleroderma tend to last longer, even having long periods of quiescence followed by reactivation.<sup>376</sup> In one study, 31% of patients reported disease activity after 10 years.<sup>377</sup> Virtually all patients show residual persistent atrophy and dyspigmentation, especially of the atrophy of the *en coup de sabre*/facial hemiatrophy variant, and 38% with linear scleroderma have functional limitations.<sup>377</sup> Sequelae can be serious and range from significant cosmetic impairment to functional disability from joint contractures, limb length discrepancies (Fig. 22-49), loss of skin adnexae, calcinosis in linear lesions, and ocular or CNS dysfunction.

Treatment for morphea depends on the extent of involvement, activity of the disease, and cosmetic or functional ramifications. Potent topical or intralesional corticosteroid therapy may hasten resolution of lesions but can result in localized atrophy. Calcipotriene ointment is the topical treatment of choice and has been shown to stop the progression of morphea and linear scleroderma when used early in the course, especially twice daily under occlusion,<sup>378</sup> but does not reverse tissue loss. Calcipotriol-betamethasone dipropionate<sup>379</sup> and imiquimod<sup>380</sup> have also shown benefit. The combination of physiotherapy, massage, warm baths, and exercise are often helpful for patients with linear morphea in whom the involvement overlies a joint because of the risk of contractures.

The first-line systemic therapy for disfiguring or disabling morphea/linear scleroderma is the combination of methotrexate and corticosteroids.<sup>381,382</sup> Systemic corticosteroids (1 mg/kg per day) are given (either orally or pulse intravenous) for the first 2 to 3 months, and methotrexate 0.3 to 0.6 mg/kg or 15 mg/m<sup>2</sup> per week (either orally or subcutaneously) is given initially and on a continuing basis. Approximately 75% of children show disease improvement that is usually maintained on medication for a mean of more than 2 years.<sup>383-385</sup> In one trial of 10 patients with localized scleroderma, all patients responded to this therapy and skin lesions became inactive.<sup>381</sup> The mean time to response was 3 months, and relapses were seen after the methotrexate was discontinued. Mycophenolate mofetil has more recently been used in individuals who have failed to respond to steroids and methotrexate or in combination with methotrexate for greater effect. In a study of 10 patients, all patients treated with 600 to 1200 mg/m<sup>2</sup> per day experienced improvement that allowed withdrawal or reduction in steroid and methotrexate within 3 to 6 months.<sup>386</sup> There is also anecdotal evidence of improvement with rituximab<sup>387</sup> and IVIG.<sup>388</sup> In one child, the addition of imatinib to steroids and methotrexate achieved control.<sup>389</sup> Oral calcitriol has also led to significant improvement in some children with linear scleroderma,<sup>390</sup> but is limited by its risk of excessive urinary excretion of calcium, leading to renal calcium stones. Dietary calcium must be restricted, and serum calcium and phosphorus as well as the calcium/creatinine ratio in a 24-hour collection of urine must be monitored. In children, the starting dosage is 0.25 mcg/day with increases to a maximum of 0.75 mcg/day in children and 1.5 mcg/day in adolescents.

Psoralen plus UVA light (PUVA) has been shown to be efficacious for morphea, but its toxicity restricts its use in children. Medium-dose (70 J/cm<sup>2</sup>) UVA1 (340 to 400 nm) significantly reduces the skin thickness of morphea.<sup>391</sup> Although UVA1 light has been thought to work best in lighter skin, good effects are seen as well in darker skin.<sup>392</sup> Home therapy may be an option in children without other UVA1 access. Twice-daily application of calcipotriol ointment combined with UVA1 phototherapy has led to significant softening and repigmentation of morphea lesions, but it is unclear whether these results are superior to topical calcipotriol or UVA1 therapy alone.<sup>393</sup>

Successful repair of contractures may be performed by release and coverage with grafts.<sup>394</sup> Leg-shortening procedures to the normal leg may be performed after full growth is achieved, when the affected leg is significantly shortened by linear scleroderma. Orthodontic devices can assist in craniofacial development and minimize the progressive asymmetry of the lower face from Parry-Romberg syndrome.<sup>395</sup> For residual lesions with atrophy, excision can be considered if the affected area is small or the site can be hidden (such as the scalp). Facial lesions can be corrected by transplants of fat, bone, or cartilage, introduction of fillers, and pedicled or free flaps. Laser has been used to lighten the associated hyperpigmentation.<sup>396</sup> Fat transplants have been most successful for forehead lesions, with a mean of 51% to 75% improvement after at least a year, but have a poorer outcome on the chin, infraorbital, and nose areas.<sup>396</sup> In one study in adolescents with facial linear scleroderma (mean age, 15 years), 65% of whom had undergone multiple procedures, 90% were satisfied with their intervention and 100% would recommend surgical intervention to other patients.<sup>397</sup> Ideally, repair should be delayed until the lesion is inactive.

## Lichen Sclerosus et Atrophicus

Lichen sclerosus et atrophicus (LSA; LS&A) is a disorder primarily of females (85% to 90%) with a prevalence of greater than 1 in 900 girls.<sup>398-401</sup> It has its onset before 13 years of age in 10% to 15% of affected individuals; 70% of these childhood cases occur before 7 years of age, and the condition has been described during the first weeks of life. The mean age at development of symptoms is 5 years, with a mean age at diagnosis of 6.7 years. Mosaic distribution of extragenital lichen sclerosus has been described.<sup>402</sup> The Koebner phenomenon has been documented in cases of LSA in childhood; lesions may develop in surgical scars or sites of vaccination, and exacerbations of quiescent lesions may occur after local trauma or irritation. Lesions of LSA, usually extragenital, occur in 6% of patients with morphea, although



**Figure 22-50** Lichen sclerosus et atrophicus. Ivory atrophic plaque in a girl who also showed genital area involvement.

more commonly in affected adults,<sup>403</sup> and overall 15% have another autoimmune disease. Autoantibodies have been demonstrated against extracellular matrix protein-1 and, more recently, against BP180.<sup>404</sup> Autoimmune disease in a parent or grandparent has been found in 65%.<sup>405,406</sup>

The eruption of LSA is characterized by sharply defined, small, pink to ivory white, slightly raised, flat-topped papules a few millimeters in diameter that aggregate and coalesce into plaques of various sizes (Fig. 22-50). As the condition progresses, atrophy and delling (fine follicular plugs on the surface of macules) may become highly diagnostic features of the disorder. In fact, white comedo-like openings are seen by dermoscopy.<sup>407</sup>

The anogenital region is involved in 75% of affected children. Of those who have extragenital lesions, up to 42% have anogenital involvement as well. Exogenous lesions are asymptomatic and may begin asymmetrically but eventually become distributed in a symmetric manner, primarily on the trunk, neck, and extremities.<sup>408</sup>

In females the anogenital lesions commonly tend to surround both the vulvar and perianal regions in an hourglass or figure-8 pattern (Fig. 22-51). LSA in children most commonly presents in the genital area in girls with itching (70%), soreness (80%), pain with urination (43%), and bleeding (61%) from the vulvar and perianal areas; constipation occurs in more than 10%.<sup>398,409</sup> In studies of girls with vulvar disease or vulvar pruritus, 18% and 11% have lichen sclerosus, respectively.<sup>410,411</sup> A vaginal discharge from the lichen sclerosis may precede the vulvar lesions in about 20% of affected girls, but secondary bacterial vaginosis has also been described.<sup>412</sup> Anogenital lesions uncommonly extend to include the skin on the inner aspect of the thighs. In many girls, erythema, purpuric areas (Figs. 22-52), blistering, and excoriations predominate, especially on the labia minora and clitoris.

When seen on the dorsum of the glans penis in males, the disorder has been termed *balanitis xerotica obliterans*.<sup>413,414</sup> Clinical evidence of lichen sclerosus of the genital area in boys is less common than in girls, but lichen sclerosis is found in biopsy sections in 15% to 35% of circumcisions and has been blamed for 60% of cases of acquired phimosis.<sup>415,416</sup> Perianal involvement in boys is rare. Lichen sclerosus of the lips tends to be asymptomatic and less destructive, resembling vitiligo.<sup>417</sup>

Lichen sclerosus is often misdiagnosed when present in the genital area of girls as irritant dermatitis because of the associated itching and erythema, or as sexual abuse, owing to the purpura and bleeding. The associated white coloration may lead to confusion with vitiligo or postinflammatory hypopigmentation (Fig. 22-52). The anal pruritus often raises the possibility of pinworm infestation, and the inflammation and discharge should cause one to consider candidiasis or bacterial vulvovaginitis.<sup>412</sup> The associated constipation or dysuria often leads to unnecessary GI or urinary tract investigations as well. Lichen sclerosus has been described in girls with an infantile perianal



**Figure 22-51** Lichen sclerosus et atrophicus. Whitening, atrophy, inflammation, and purpura of the labia.



**Figure 22-52** Lichen sclerosus et atrophicus (LSA). This dark-skinned girl with advanced LSA shows partial obliteration of the clitoris. Note the associated purpura and depigmentation.

pyramidal protrusion (see Chapter 15, Fig. 15-34), a benign tag-like lesion that has been associated with constipation in many patients.<sup>418-420</sup> Although biopsies of lesional skin show characteristic epidermal atrophy with subepidermal vacuolization, a hyalinized superficial dermis, and a band-like infiltration of lymphocytes beneath

it, the diagnosis of lichen sclerosus is usually made on clinical grounds and confirmatory biopsy is both traumatic and unnecessary.

Application of clobetasol for 6 to 12 weeks is the treatment of choice to alleviate symptoms, followed by a taper in potency or frequency and intermittent use as needed.<sup>421</sup> Eighty-three percent of patients experience remission after initial treatment. In one study, relapses after initial treatment with clobetasol occurred in more than 40% and required an average of 3 years of intermittent maintenance therapy.<sup>422</sup> In prepubertal boys with phimosis, skin stretching and application of potent topical corticosteroids twice daily for 6 weeks led to a retractable prepucle, including in 67% of the boys with clinically detectable lichen sclerosus.<sup>416</sup> Topical tacrolimus 0.1% ointment has been used successfully to clear lichen sclerosus in girls, both as initial treatment and to promote continued remission.<sup>423–425</sup> Complete circumcision is the treatment of choice in boys with phimosis, but 7% to 19% require late surgery for meatal stenosis.<sup>426</sup> Precircumcision topical steroids<sup>426</sup> or topical tacrolimus ointment 0.1% ointment for 3 weeks after therapeutic circumcision may help decrease the rate of later meatal pathology and maintain control.<sup>427</sup> Plastic surgery may be required to correct labial fusion or clitoral obliteration from scarring. Treatment of extragenital lichen sclerosus is much more challenging than treatment of genital region disease. Although topical steroids and retinoids are occasionally helpful,<sup>428</sup> UVA light treatment (especially UVA1) and systemic medication used to treat morphea, such as methotrexate or mycophenolate mofetil (see Morphea section) may be required.<sup>429,430</sup>

Lichen sclerosus has been reported to improve or disappear at puberty in 60% of affected girls, although a recent study suggested that signs of the disease persisted in 75% postpubertally.<sup>431</sup> In females, atrophy of the clitoris and labia minora may occur, with fusion of the latter and stricture of the introitus. In patients in whom improvement has taken place, the disorder may be reactivated years later by trauma, pregnancy, or the administration of anovulatory drugs.

Although vulvar LSA in childhood does not predispose a patient to neoplasia, the incidence of lesional squamous cell carcinoma in adult cases has been estimated as 4.4%. Patients with cases persisting beyond puberty or having onset after puberty should be observed at intervals of 6 to 12 months for the possibility of leukoplakia or carcinoma. Newly arising nodules, erosions, or ulcers in lesions of LSA that persist for more than a few weeks require histologic examination. Development of genital carcinoma has been reported in an adult after clearance of lichen sclerosus during childhood.<sup>432</sup>

## Anetoderma

Anetoderma (from the Greek, meaning *relaxed skin*) describes an idiopathic atrophy of the skin characterized by oval lesions of thin, soft, loosely wrinkled, depigmented outpouchings of skin that result from weakening of the connective tissue of the dermis.<sup>433</sup> The disorder may be classified as primary macular anetoderma, which arises from apparently normal skin, or as secondary macular anetoderma, which follows previous inflammatory and infiltrative dermatoses. Some of these dermatoses include lupus erythematosus and other collagen vascular disorders, secondary syphilis, sarcoidosis, leprosy, tuberculosis, urticarial lesions, purpura, lichen planus, acne vulgaris, urticaria pigmentosa, molluscum contagiosum,<sup>434</sup> varicella,<sup>435</sup> juvenile xanthogranuloma,<sup>436</sup> and pilomatrixomas.<sup>437,438</sup> A peculiar laxity of the eyelid (blepharosclerosis) may also follow chronic or recurrent dermatitis of the eyelids. When eyelid changes are seen in association with adenoma of the thyroid and progressive enlargement of the lips resulting from inflammation of the labial salivary glands, the disorder is termed *Ascher syndrome*.

Based on whether an inflammatory reaction occurred before the appearance of the atrophy, two types of primary macular anetoderma have been described: anetoderma of Jadassohn–Pellizzari, in which the atrophic lesions are preceded by inflammation; and anetoderma of Schweninger–Buzzi, in which there is no evidence of inflammation. Although the underlying etiopathogenesis of primary anetoderma has not been established, serologic and direct immunofluorescent findings suggest that immunologically mediated mechanisms play a role in the elastolytic process seen in individuals with this disorder.



**Figure 22-53 Anetoderma.** Well-demarcated circles of cutaneous atrophy developed progressively over 3 years on the anterior trunk and neck of this young boy. aPL antibodies were negative.

Anetoderma of Jadassohn–Pellizzari is characterized by crops of round or oval pink 0.5- to 1-cm macules that develop on the trunk, shoulders, upper arms, thighs, sacral area, and occasionally face or scalp (Fig. 22-53). Usually seen in females in their teens to 30s, and occasionally in children, the anetoderma begins with a sharply defined red spot that grows peripherally and becomes round or oval and slightly depressed. As the redness disappears, the characteristic atrophic, wrinkled, and pale herniation ensues. The herniation yields on pressure, admitting the finger through the surrounding ring of normal skin. Much like an umbilical hernia, the bulge reappears when the finger is released, and, at times, fatty tissue may infiltrate the lesions, giving them a more firm, soft, tumor-like appearance.

Anetoderma of Schweninger–Buzzi is manifested by the sudden appearance of large numbers of bluish-white macules, some of which are protuberant, without any preceding inflammatory eruption. Women are affected more commonly than men. Lesions are generally seen on the trunk, neck, face, shoulders, extremities, and back, and range from 10 to 20 mm in diameter. Seen during childhood or adult life, the disease is slowly progressive, and new lesions appear one by one or in groups, a few at a time, over several years. The essential difference in this form of anetoderma is a lack of inflammation and the relative absence of coalescence of lesions.

Anetoderma has also been described in premature infants after use of gel electrocardiographic electrodes, perhaps because of local hypoxemia from the pressure of the electrodes (see Chapter 2).<sup>439,440</sup> More widespread congenital anetoderma of unclear cause has also been described.<sup>441</sup> Drug-induced anetoderma has been described after administration of penicillamine, particularly in patients with Wilson disease. Prothrombotic abnormalities and aPL antibodies have been detected in the majority of patients in more than one investigation, and criteria for the diagnosis of APS have been fulfilled in some patients.<sup>198,442,443</sup> A hereditary form has rarely been described<sup>444</sup> and can manifest with skin lesions alone or in association with bony, neurologic, and ocular anomalies; the disorder most likely is autosomal dominant with incomplete penetrance, but the underlying pathogenesis is unclear. In all forms of macular anetoderma, the primary histopathologic feature is the destruction and loss of elastic fibers. No therapy is effective.

## Relapsing Polychondritis

Relapsing polychondritis is an uncommon disorder in children characterized by inflammation of cartilage.<sup>445,446</sup> Most patients have demonstrated circulating antibodies against type II collagen and matrillin-1, both components of cartilage, suggesting an autoimmune pathomechanism with a strong IFN pathway component.<sup>447</sup> This concept is supported by the report of an infant with transient

disease born to a woman with the condition.<sup>448</sup> Some patients have, or develop, concomitant collagen vascular disorders, especially lupus erythematosus.<sup>449</sup>

Erythema, swelling, and pain of the ear is the most common manifestation (90%), with typical involvement of the auricle but sparing of the earlobe. With chronic disease, the ear cartilage is destroyed, resulting in a scarred "cauliflower" ear. Nasal cartilage inflammation occurs in 70% of affected individuals and can eventuate in a saddle nose deformity. Nonerosive arthritis has been described in approximately 80% of patients, particularly involving the sternoclavicular, sternomanubrial, and costochondral joints. Approximately 65% of patients have ocular inflammation (conjunctivitis, episcleritis, uveitis, corneal ulceration, or inflammation of the optic nerve).

The most serious potential feature is respiratory tract involvement.<sup>450</sup> Patients may show hoarseness, dyspnea, cough, wheezing, or anterior neck tenderness with palpation of the trachea. Secondary pulmonary infection, airway collapse, or airway obstruction may ensue. Renal and cardiac manifestations have rarely been described. A variety of dermatologic features have been associated, among them aphthous ulcerations, palpable purpura, panniculitic nodules, pyoderma gangrenosum,<sup>451</sup> livedo reticularis, and neutrophilic disorders of skin, such as Sweet syndrome.

In children, the most commonly seen disorder to be considered in the differential is otomelalgia (red ear syndrome), a condition characterized by erythema, swelling, and pain of the entire ear that does not spare the earlobe. The condition is short-lived, responds to application of ice, and is episodic, rather than persistent (see Chapter 12; Fig. 12-83). Red ear syndrome can be associated with migraines.

The treatment of choice for relapsing polychondritis is systemic corticosteroids (1 mg/kg per day initially) and NSAIDs. TNF inhibitors, dapsone, and methotrexate have been used as steroid-sparing agents.<sup>452</sup> Rituximab has been successful in treating resistant pediatric cases.<sup>453</sup> Emergency tracheostomy and/or airway stents may be required for upper respiratory tract involvement.<sup>450,454</sup> One child responded to oral ingestion of type II collagen as a tolerogen.<sup>455</sup>

## Sjögren Syndrome

Sjögren syndrome is a chronic autoimmune disorder of unknown etiology that is uncommon in children.<sup>456</sup> Characteristic features are keratoconjunctivitis sicca (inflammation of the cornea and the conjunctiva with dryness and atrophy), xerostomia (dryness of the mouth from lack of normal secretion), and enlargement of the salivary and lacrimal glands (as a result of lymphocytic and plasma cell infiltration) (Box 22-9). Sjögren syndrome can occur alone (primary) or in association with virtually any other autoimmune disorder (secondary), although the most common are JIA and SLE. The manifestations of Sjögren syndrome may precede the onset of another autoimmune disorder by years.

### Box 22-9 Sjögren Syndrome

#### Major Clinical Features

- Inflammation and chronic enlargement of salivary glands
- Keratoconjunctivitis sicca (dryness and atrophy of cornea and conjunctiva)
- Xerostomia (dryness of mouth)
- Fatigue
- May be associated with other autoimmune disorders, especially juvenile idiopathic arthritis

#### Cutaneous Features

- Dryness and scaling of skin (with partial or complete loss of perspiration)
- Sparse, dry, brittle hair
- Hypergammaglobulinemic purpura (usually lower extremities)
- Raynaud phenomenon

#### Laboratory Abnormalities

- Positive antinuclear antibodies; rheumatoid factor, anti-Ro, anti-La antibodies in majority
- Tests to show decreased tear formation and salivary flow

In a review of 39 pediatric cases, the female/male ratio in children was greater than 3:1, with a mean age at onset of 8 years.<sup>457</sup> In children, the presenting sign is usually parotitis (62.5% vs. 13% in adults) with parotid gland enlargement, which may be bilateral.<sup>458–460</sup>

Bacterial parotitis and lymphoproliferative disease must be included in the differential diagnosis. Almost 10% of the children have an extraglandular manifestation, and 51% experience at least one extraglandular manifestation during the course of the disease. The most common extraglandular feature is leukopenia (35%) with or without splenomegaly. Arthritis occurs in 15% of children (vs. 38.5% of adults). Purpura and intense residual hyperpigmentation, especially on the lower extremities (hypergammaglobulinemic purpura), is the most common cutaneous manifestation (12% of children) (Fig. 22-54). Annular erythema, erythema nodosum, mesangial proliferative glomerulonephritis,<sup>461</sup> and lipodystrophy have also been described.

The most prominent mucosal manifestations are associated with dryness of the gingiva and mucous membranes of the mouth and, at times, the conjunctivae, nose, pharynx, larynx, vagina, and respiratory tract.<sup>462</sup> The tongue may become smooth, red, and dry, and in severe cases there may be difficulty in swallowing dry food. The lips may be cracked, fissured, or ulcerated, particularly at the corners of the mouth; the teeth commonly undergo rapid and severe decay; the eyes may be reddened and moist; and thick, tenacious secretions formingropy mucous strands in the inner canthi may be noted (particularly when the patient first arises in the morning). Other ocular manifestations include a burning sensation, as if a foreign body is present in the eye, and the inability to produce tears in response to irritants or emotion.

A positive ANA test has been seen in 67% of children (vs. 92% of adults), and RF in 71%. Positive anti-Ro and/or anti-La antibodies are detected in 73% of children with Sjögren syndrome, but the minority of children with these antibodies develop Sjögren syndrome.<sup>463</sup> Patients may show a decreased stimulated salivary flow rate and positive Schirmer (<5 mm wetting of a strip of filter paper inserted under the lower eyelid) and rose bengal (conjunctival staining) tests of the eyes. Sialography, ultrasound,<sup>464</sup> and CT scans of the parotid glands may show evidence of enlargement and inflammation.

Although no criteria for diagnosis have been established for pediatric Sjögren syndrome, which is more difficult to diagnose, in adults



**Figure 22-54** Hypergammaglobulinemic purpura. Recurrent episodes of purpuric lesions on the lower extremities left darkly hyperpigmented macules that persisted. Joint pain and high levels of anti-Ro and anti-La antibodies as well as immunoglobulin G were associated. Administration of hydroxychloroquine eliminated joint pain and dramatically suppressed cutaneous flares, leading to gradual fading of the hyperpigmentation.

### Box 22-10 Mixed Connective Tissue Disease (Kasukawa Criteria)

**Criteria: Must Meet All Three to be Diagnosed with MCTD**

Raynaud phenomenon and/or swollen fingers or hands  
Positive anti-RNP antibody  
Must have at least one abnormal finding from two or more groups of findings  
SLE-like findings (facial eruption, polyarthritides, serositis, lymphadenopathy, leukopenia, thrombocytopenia)  
Scleroderma-like findings (sclerodactyly, pulmonary fibrosis, vital capacity <80% of normal, carbon monoxide diffusion <70% of normal, decreased esophageal motility)  
Polymyositis-like findings (muscle weakness, elevated serum levels of muscle enzymes, myogenic pattern on EMG)

**Mucocutaneous Features**

Alopecia  
Heliotrope rash  
Hypopigmentation and/or hyperpigmentation  
Livedo reticularis  
Lupus-like lesions, including malar telangiectasia and/or erythema  
Mucosal dryness  
Periungual telangiectasia  
Photosensitivity  
Raynaud phenomenon  
Sclerodactyly

**Musculoskeletal Features**

Arthritis or arthralgia  
Proximal muscle weakness  
Tapered or sausage-shaped fingers

**Gastrointestinal Features**

Abnormal esophageal motility

**Cardiac Features**

Aortic insufficiency  
Congestive heart failure  
Pericarditis/myocarditis

**Pulmonary Features**

Abnormal pulmonary function tests  
Pulmonary fibrosis

**Neurologic Features**

Headache  
Peripheral neuropathy  
Seizures

**Renal Features**

Glomerulonephritis

**Laboratory Abnormalities**

Elevated anti-RNP titer  
Speckled ANA

Mier RJ, Shishov M, Higgins GC, et al. Pediatric-onset mixed connective tissue disease. *Rheum Dis Clin North Am* 2005;31:483–96, vii.  
ANA, Antinuclear antibody; MCTD, mixed connective tissue disease; RNP, ribonuclear protein; SLE, systemic lupus erythematosus.

they include: 1) positive serum anti-SSA/Ro and/or anti-SSB/La or positive RF and ANA titer at least 1:320; 2) labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis; and 3) keratoconjunctivitis sicca, with specific criteria for the biopsy features and severity of the keratoconjunctivitis that may not be applicable to children.<sup>465</sup> The management of Sjögren syndrome includes treatment of the dry skin, keratoconjunctivitis, and xerostomia with lubricants, and therapy for the associated collagen vascular disorder if present. Although systemic corticosteroids are capable of reducing the swelling of the salivary glands, they usually do not improve the function of affected glands, and their use is reserved for severely affected patients. Rituximab has been shown benefit for the mucosal dryness and systemic manifestations in adults.<sup>466</sup>

## Mixed Connective Tissue Disease

Only 0.6% of all pediatric patients with rheumatologic disease have mixed connective tissue disease (MCTD; overlap syndrome), which begins before 16 years of age in 23% of individuals with MCTD.<sup>467</sup> At least 85% are female, and the earliest age of onset described has been 2 years of age (mean onset at age 9.5 to 12 years).<sup>468</sup> The disease is characterized by the combination of clinical features and laboratory data similar to those of SLE, scleroderma, and dermatomyositis (Box 22-10). The most common presenting features of pediatric-onset MCTD are fatigue and pain (polyarthralgias, myalgias) and Raynaud phenomenon (mean, 73% of children).<sup>469</sup> In one study, myositis was the most common manifestation at onset, with SLE-like features least common.<sup>467</sup> Although some patients with MCTD have deforming arthritis, an evanescent nonerosive, nondeforming polyarthritides similar to that seen in patients with SLE is more common.

Approximately two-thirds of children with MCTD have cardiovascular involvement, including pericarditis, myocarditis, congestive heart failure, aortic insufficiency, and/or pulmonary arterial hypertension<sup>470</sup>; about 10% have clinical evidence of renal disease (more by biopsy evaluation);<sup>471</sup> and about 10% of individuals have neurologic abnormalities (trigeminal sensory neuropathy, vascular headaches, seizures, multiple peripheral neuropathies, and cerebral infarction or hemorrhage). Severe thrombocytopenia appears to be limited to

childhood forms, and the incidence of renal and cardiac involvement is higher in children than in adults.<sup>471</sup> However, the course is more slowly progressive, overall shows a lower risk of renal disease, and responds to lower doses of steroids than SLE or scleroderma. Progression toward scleroderma can be predicted by changes on capillaroscopy.

The distinguishing laboratory marker for this disease is the demonstration of serum antibody specific for nRNP (U<sub>1</sub>RNP), a ribonuclease-sensitive component of extractable nuclear antigen (ENA). In addition, most patients with MCTD have high serum titers of ANA in a speckled pattern. Up to 50% of patients show a high titer of RF.

Immunosuppressive medications, particularly systemic corticosteroids, hydroxychloroquine and methotrexate, are most commonly used as therapy. Immunoabsorption onto protein A in combination with low-dosage systemic steroids and bosentan led to remission in a recalcitrant patient.<sup>472</sup> Long-lasting remission occurs in only 3% of patients; inflammatory manifestations (fever, arthritis, skin eruption) are most responsive to treatment, whereas the sclerodermatous features (sclerodactyly, esophageal disease) and vasculopathy (including Raynaud disease) tend to persist. In one study with 12 children, 92%, 79%, and 52% were free of organ involvement at 2, 5, and 10 years, respectively.<sup>468</sup> Mortality is lower in children than in adults, especially if organ involvement can be detected and treated early.

The complete list of 472 references for this chapter is available online at <http://expertconsult.inkling.com>.



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Endocrinologic diseases often display cutaneous features that may provide diagnostic clues, and patients with these disorders may be more susceptible to a variety of mucocutaneous problems. Some of these conditions and their therapy, where applicable, are reviewed here. A thorough discussion of all endocrine disorders and their treatment is beyond the scope of this chapter.

## Thyroid Disorders

Patients with hyperthyroidism or hypothyroidism may show a variety of skin findings. In some cases associated hair or nail defects may also be seen. Some of these findings are related to the imbalance in thyroid hormone, which may play a role in skin homeostasis via its influence on proteoglycan synthesis, epidermal differentiation, hair formation, and sebum production.<sup>1</sup>

### HYPERTHYROIDISM

**Box 23-1** summarizes the various cutaneous changes that may be seen in hyperthyroidism. This disorder is most often caused by an autoimmune thyroid disease, Graves disease. It may also be associated with a hyperfunctioning thyroid nodule, thyroid multinodular goiters, non-Graves thyroiditis, excessive thyroxine intake, or hypersecretion of thyroid-stimulating hormone (TSH). Cutaneous features occur most commonly in association with Graves disease, and these manifestations may more often be the result of autoimmune mediation rather than direct effects of thyroid hormones.<sup>2</sup>

The clinical features of hyperthyroidism include nervousness, emotional lability, tachycardia and palpitation, heat intolerance, weakness, fatigue, tremors, hyperactivity, increased appetite, weight loss, increased systolic and pulse pressure, accelerated growth, sleep disturbances, school problems, vomiting, diarrhea and occasionally exophthalmos. An enlarged thyroid gland is often present. Specific findings that suggest Graves disease include thyroid ophthalmopathy, pretibial myxedema (PTM), and acropachy. The ophthalmopathy is secondary to periorbital deposition of glycosaminoglycans and may present with proptosis, ocular paralysis, or lid lag.

#### Pretibial Myxedema

Pretibial myxedema (PTM; also known as *thyroid dermopathy*) is manifested as plaques on the anterior tibial surfaces and is related to localized accumulation of acid mucopolysaccharides. Other locations of involvement are occasionally reported, including the dorsal feet. The majority of patients with PTM have ophthalmopathy.<sup>3,4</sup> The onset of PTM usually follows the diagnosis of hyperthyroidism. Examination reveals nonpitting edema, nodules, and plaques with pink to yellow-brown discoloration. The overlying epidermis is thin with a waxy and sometimes translucent quality. Hypertrichosis with dilated hair follicles and a “peau d’orange” appearance may be noted. Polypoid or elephantiasis forms occur less commonly.<sup>3</sup> Although the pretibial surfaces are most commonly involved, other areas including the face, scalp, upper extremities, and trunk may reveal similar changes. The differential diagnosis may include cellulitis, trauma, erythema nodosum, or other mucinoses, and PTM can be confirmed by tissue examination of skin-biopsy material in conjunction with laboratory findings. Histologic evaluation may reveal mucin deposition and reduced elastic fibers.

#### Thyroid Acropachy

Thyroid acropachy is more common in adults with hyperthyroidism, only occasionally occurs in children, and classically presents as the

triad of digital clubbing, soft-tissue swelling of the hands and feet, and periosteal changes. Examination reveals thickening of the soft tissues over the distal extremities and (secondary to diaphyseal periosteal proliferation) of the distal bones. Drumstick-like clubbing, enlargement of the hands and feet, and radiographic changes (fluffy, spiculated, or homogeneous subperiosteal thickening with new bone formation) may be seen. Associated extremity and joint pain may be reported, and nail clubbing may also be seen. Thyroid acropachy and diabetic dermopathy (DD) are indicators of more severe Graves ophthalmopathy.<sup>5,6</sup>

Less specific cutaneous changes in hyperthyroidism include skin that is warm, velvety, moist, and smooth. Hair may be fine and thin. Facial flushing, increased sweating (particularly of the palms and soles), and palmar erythema are common, especially in the advanced state of the disease, called *thyrotoxicosis*. The nails grow rapidly, are shiny, and may reveal onycholysis (separation or loosening of the nail plate from the nailbed) with distal upward curvature (Plummer nails). Koilonychia (spoon-shaped nails; **Fig. 23-1**) and clubbing may also be noted. Chronic urticaria and generalized pruritus are uncommon manifestations of thyrotoxicosis, and chronic active hyperthyroidism can be complicated by Addison disease-like hyperpigmentation. However, the hyperpigmentation of hyperthyroidism is distributed differently, primarily on the shins (**Fig. 23-2**), posterior feet, and nailbeds.<sup>7</sup> Patients with hyperthyroidism may also have an increased incidence of alopecia areata and/or vitiligo.<sup>8,9</sup> Gynecomastia may be present in males and may be caused by increased conversion of testosterone to estradiol. Scleromyxedema, a condition marked by white-yellow papules, weight loss, monoclonal gammopathy, esophageal dysmotility, myopathy, and Raynaud phenomenon, has also been reported in patients (mainly adults) with hyperthyroidism.<sup>10</sup>

### HYPOTHYROIDISM

**Box 23-2** summarizes the various mucocutaneous changes that may be seen in hypothyroidism. Hypothyroidism in pediatric patients may be congenital or acquired. Clinical features of congenital hypothyroidism are shown in **Box 23-3**. Symptoms may be subtle in both forms of hypothyroidism, but decreased linear growth is an important indicator of both types of disease. Hypothermia, lethargy, and poor feeding are all characteristic of congenital disease, which is most often diagnosed on routine newborn screening examinations. Children with acquired hypothyroidism tend to be quiet and well behaved and as a result often receive high grades in school.

Congenital hypothyroidism may develop as a result of agenesis or dysgenesis of the thyroid gland (the most common cause); defective synthesis of thyroid hormone caused by an enzymatic defect; the presence of antithyroid antibodies in a pregnant mother; the lack of maternal iodine during pregnancy (endemic goiter); or the ingestion of antithyroid medications such as propylthiouracil or methimazole by a pregnant woman being treated for thyrotoxicosis. Iodine toxicity from iodine-containing skin antiseptic solutions has been implicated as a potential cause of transient hypothyroidism in newborn infants, although recent studies refute this association.<sup>11,12</sup> Acquired hypothyroidism in children younger than 5 or 6 years of age may be caused by a delayed failure of thyroid remnants (with thyroid dysgenesis); by inborn defects of thyroid-hormone synthesis; by ingestion of antithyroid agents; by thyroidectomy or ablation after radiation; or by chronic thyroiditis or hypothalamic-pituitary disease. After the age of 5 or 6 years, although the same etiologies may be involved, chronic lymphocytic thyroiditis (Hashimoto thyroiditis) is the most common cause. Although iodine deficiency is the most common cause of hypothyroidism worldwide, it is uncommon in the United States.

### Box 23-1 Cutaneous Manifestations of Hyperthyroidism

Warm, velvety, moist, erythematous, smooth skin  
 Thin, fine hair; diffuse nonscarring alopecia  
 Hyperpigmentation (especially of palmar creases, soles, gingivae, buccal mucosa)  
 Facial flushing  
 Palmar erythema  
 Increased sweating  
 Nail changes (onycholysis, curvature, koilonychia, clubbing, yellow nails)  
 Pretibial myxedema  
 Periorbital edema  
 Chronic urticaria  
 Generalized pruritus  
 Thyroid acropachy (clubbing)  
 Increased incidence of vitiligo, alopecia areata  
 Gynecomastia (in men)

### Box 23-2 Mucocutaneous Manifestations of Hypothyroidism

Dry, coarse, pale, cool skin  
 Dull, brittle hair with thinning  
 Cutis marmorata  
 Generalized myxedema (especially hands, feet, periorbital)  
 Carotenoderma  
 Nail changes (ridged, brittle, grow slowly)  
 Alopecia (diffuse, lateral eyebrows)  
 Hypertrichosis (back and shoulders usually)  
 Easy bruising  
 Ichthyosis  
 Eruptive or tuberous xanthomas  
 Livedo reticularis  
 Periorbital edema  
 Dermatitis herpetiformis (has been reported with Hashimoto thyroiditis, atrophic variant)  
 Protuberant lips  
 Macroglossia  
 Urticaria  
 Pruritus

### Box 23-3 Clinical Features of Congenital Hypothyroidism

Puffy (myxedematosus) facies  
 Sallow complexion  
 Wide anterior fontanel and sutures  
 Macroglossia and thick lips  
 Hypertelorism, depressed nasal bridge  
 Coarse, brittle hair  
 Hoarse cry  
 Translucent ("alabaster") ears  
 Umbilical hernia and abdominal distention  
 Heart murmur  
 Hypotonia and slow reflexes  
 Short stubby fingers and broad hands  
 Short lower extremities  
 Scalp seborrhea, purpura  
 Prolonged relaxation phase of tendon reflexes  
 Cold, mottled, or jaundiced skin  
 Sluggishness and inactivity  
 Delayed motor development, mental retardation  
 Lack of coordination and ataxia  
 Poor weight gain, stunted growth  
 Subnormal body temperature, poor circulation, and intolerance to cold  
 Delayed/defective dentition  
 Myxedema (some cases)



**Figure 23-1** Koilonychia. These spoon-shaped nails may occur in disease states (such as hyperthyroidism) or as a normal variant in young children, as in this infant.



**Figure 23-2** Hyperpigmentation of hyperthyroidism. Diffuse hyperpigmentation of the lower extremities was present in this young Hispanic female with Graves disease.

occur in hypothyroidism, again as a result of mucopolysaccharide deposition in skin. It most commonly occurs in the hands, feet, and periorbital locations and may also be deposited in the tongue, giving rise to macroglossia. Generalized puffiness may be present, and the skin may take on a yellow hue as a result of carotenemia (Fig. 23-3). The hair is dull and brittle, and nails are ridged, brittle, and grow very slowly. Patients may have a dull, expressionless facies. Hypertrichosis of the back and shoulders may be seen, and alopecia may involve the lateral portions of the eyebrows (termed *madarosis*) or occur in a more diffuse pattern.<sup>13</sup> A collodion baby with concomitant congenital hypothyroidism has been reported.<sup>14</sup>

## Parathyroid Disorders

Disorders of the parathyroid glands (hyperparathyroidism and hypoparathyroidism) may affect the skin in various ways and often present

Cutaneous features of hypothyroidism are a reflection of the hypometabolic state with reduced body temperature and reflex vasoconstriction. Patients often have dry, coarse, pale, and cool skin. Cutis marmorata (physiologic mottling) may be prominent. Hypohidrosis may lead to acquired palmoplantar keratoderma.<sup>10</sup> Myxedema may



**Figure 23-3** Carotenemia. This yellow-orange skin coloration (carotenoderma) is especially prominent on the palms and soles. It may be seen in association with disease states (i.e., hypothyroidism) or with high intake of  $\beta$ -carotene-containing foods such as prepared baby foods containing orange vegetables, as in this healthy infant.

with cutaneous features that can assist the primary or consulting physician in diagnosis and management. Although primary parathyroid disease is uncommon in children, these glands play a major role in the regulation of calcium and phosphorus metabolism, and associated abnormalities manifest distinctive clinical patterns. Parathyroid hormone (PTH) is one of the two main calcitropic hormones (the other one being calcitriol); these hormones regulate phosphate and calcium homeostasis.

### HYPERPARATHYROIDISM

Primary hyperparathyroidism, one of the least common endocrine disorders of infancy and childhood, is rarely diagnosed in children younger than 16 years of age. When seen, it is usually the result of a familial, genetically determined hyperplasia of the parathyroid, which may present as an isolated hyperparathyroidism or as the hyperparathyroidism-jaw-tumor syndrome, in which case ossifying tumors of the maxilla or mandible are present.<sup>15</sup> A malignant neoplasm of the parathyroid, or an association with some other disease such as is seen in patients with multiple endocrine adenomatosis (multiple endocrine neoplasia [MEN]; see below) or chronic renal insufficiency may also result in hyperparathyroidism.<sup>16,17</sup>

The majority of cases of hyperparathyroidism are sporadic, most often being caused by a single adenoma in the parathyroid gland. The clinical features of hyperparathyroidism include systemic effects of hypercalcemia: failure to thrive, muscular weakness, lethargy, anorexia, vomiting, fever, headache, constipation, weight loss, polydipsia, polyuria, mental retardation, metastatic calcification, and with marked hypercalcemia, stupor or death. Of these, metastatic calcification is the most common cutaneous manifestation, and in patients with sporadic hyperparathyroidism, this may be the only cutaneous finding. Hypercalcemia may also produce an ophthalmologic finding known as *band keratopathy*, which is the result of calcium and phosphate deposition beneath the Bowman capsule. Band keratopathy appears as a superficial corneal opacity resembling frosted or ground glass in a band-like configuration with white flecks or "holes" in the band resulting in a "Swiss cheese"-like appearance. It is not specific for hyperparathyroidism but may also be seen as a manifestation of hypercalcemia secondary to vitamin D intoxication, uremia, or sarcoidosis. It is not commonly found in patients with hyperparathyroidism when serum phosphorus levels are low and glomerular function is maintained.

Patients with chronic renal failure may experience several types of cutaneous manifestations. The skin of the patient with uremia may be pruritic, dry, scaly, sallow, and hyperpigmented; the sallow appearance is partially caused by anemia, and the hyperpigmentation appears to be the result of decreased renal clearance of melanocyte-stimulating hormone (MSH). Hyperparathyroidism secondary to chronic renal failure results from impaired synthesis of 1,25-

dihydroxyvitamin D<sub>3</sub>, which leads to hypocalcemia from impaired intestinal calcium absorption and ultimately increased levels of PTH. Hyperphosphatemia may result in a high serum calcium phosphate product and produce secondary calcification of the skin. This calcinosis cutis (see Chapter 9) manifests as hard calcium deposits in skin and subcutaneous tissues, especially in periarticular locations. These lesions may resolve spontaneously with correction of the serum calcium and phosphate levels. In addition to being seen in hyperparathyroidism, it may also be noted in association with paraneoplastic hypercalcemia, milk alkali syndrome, sarcoidosis, and hypervitaminosis D.

When the calcification is more progressive and involves blood vessels, ischemic necrosis of skin and soft tissues occurs and is termed *calciphylaxis*. This rare (especially in children) and life-threatening condition results from vascular calcification and is most commonly reported in patients with end-stage renal disease. Clinically, it is manifested as ecchymotic or infarcted areas of skin, bullous lesions, and plaques of calcinosis with periodic extrusion of calcium. Lesions of pediatric calciphylaxis are most commonly noted on the upper and lower extremities.<sup>18</sup> They are very painful, and mortality related to gangrene and sepsis is high. Extensive calcification in the heart and lungs may result in cardiorespiratory failure.<sup>19</sup> Parathyroidectomy is often, but not always, useful in this setting.<sup>20-22</sup> Histologically, calciphylaxis shows calcification of the walls of small and medium-sized blood vessels in the dermis and subcuticular regions.

The diagnosis of hyperparathyroidism is established by consistent elevations of total serum calcium above 12 mg/dL, the reduction of serum phosphorus concentrations below 4 mg/dL, and elevated levels of PTH. High alkaline-phosphatase levels usually indicate bone disease. This complication of hyperparathyroidism may be demonstrated radiographically by generalized demineralization of bones, destructive changes at the growing ends of long bones, subperiosteal erosions (particularly in the phalanges, metacarpals, and lateral portions of the clavicles), and in more advanced disease, generalized rarefaction, cysts, tumors, fractures, and deformities. Radiographs of the abdomen may reveal renal calculi or nephrocalcinosis, and ultrasonography and radioisotope scanning can confirm the diagnosis of primary hyperparathyroidism associated with an isolated parathyroid adenoma. In infants with parathyroid hyperplasia, cupping and fraying at the ends of long bones and ribs may suggest rickets, and severe demineralization and pathologic fractures are common.

### HYPOPARATHYROIDISM/DIGEORGE SYNDROME

Hypoparathyroidism is characterized by hypocalcemia and inappropriate response of the parathyroid glands or, less often, with elevated PTH levels and lack of response to the hormone (see Pseudohypoparathyroidism section). In childhood, hypoparathyroidism may develop as a congenital idiopathic disorder but usually appears in the neonatal period, in later infancy, or during childhood or as an acute condition after inadvertent removal or damage of the parathyroid glands during thyroid surgery. Congenital hypoparathyroidism may occur alone; may be seen as an autoimmune disorder, where it may occur alone or with other endocrine disorders; or may be a hereditary condition associated with an increased familial incidence of other endocrinologic disorders (Addison disease, pernicious anemia, and Hashimoto thyroiditis), candidiasis, and/or vitiligo. When associated with hypoplasia of the thymus and immunologic defects, the condition is known as *Digeorge syndrome* (see below).

Idiopathic or congenital hypoparathyroidism usually is first manifested by tetany or seizures and in 25% to 50% of patients, ectodermal defects. The skin of affected individuals is rough, dry, thick, and scaly; the hair and eyebrows are sparse; and the nails are short and thin with brittleness, crumbling, or longitudinal grooving. When hypoparathyroidism occurs during tooth development, pitting, ridging, absence of dental enamel, and absence or hypoplasia of the permanent teeth may result. Extensive calcification of skin and subcutaneous tissues has been reported in an infant with congenital primary hypoparathyroidism, although this is exceedingly rare.<sup>23</sup> Other clinical manifestations include convulsions, carpopedal spasm, muscle cramps and twitching, numbness or tingling of the extremities, laryngospasm or bronchospasm, exfoliative dermatitis, mental retardation, chronic diarrhea (especially in infants), photophobia, keratoconjunctivitis,

blepharospasm, and cataracts. Mucocutaneous candidiasis is seen as a complication in 15% of patients with idiopathic hypoparathyroidism. Electrocardiography may reveal prolongation of the QT interval, and head imaging may show calcifications of the basal ganglia.<sup>15</sup> The combination of candidiasis, endocrinopathy, and ectodermal dysplasia has been termed *autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy (APECED)* as well as *autoimmune polyglandular syndrome (APS) type 1* or *autoimmune polyendocrinopathy syndrome type 1* and is discussed in more detail below in the section Autoimmune Polyglandular Syndromes (see also Chapter 17).

The cutaneous manifestations of hypoparathyroidism associated with surgical removal or injury of the parathyroid glands differ from those seen in patients with idiopathic or congenital hypoparathyroidism. These include thinning or loss of hair, the development of horizontal grooves (Beau lines) in the nails, or a complete loss of nails after episodes of tetany (these abnormalities revert to normal when hypocalcemia is controlled). Hyperpigmentation (predominantly on the face and distal extremities) may resemble melasma, pellagra, or Addison disease and also may occur in cases of postthyroidectomy hypoparathyroidism. Although cutaneous calcification has been noted, this complication is relatively uncommon. In a series of 21 patients with acquired hypoparathyroidism, the most common cutaneous manifestations were hair loss (especially axillary and pubic), coarsening of body hair, and dry skin.<sup>24</sup>

DiGeorge syndrome is a T-cell deficiency disorder that develops as a result of faulty embryologic development of the thymus and the parathyroid glands (a congenital malformation of the third and fourth pharyngeal pouches and the surrounding arches). The classic triad consists of cardiac malformation, hypocalcemia, and T-cell immunodeficiency. Defects of the great vessels may include truncus arteriosus, interrupted aortic arch, double aortic arch, or aberrant subclavian artery. Oral candidiasis is an almost constant finding in patients with this disorder, and overwhelming fungal, viral, or bacterial infection usually leads to death early in infancy. Hypocalcemia and tetany may occur at an early age, and other features include chronic diarrhea, interstitial pneumonia, failure to thrive, micrognathia, hypertelorism, low-set ears, bifid uvula, shortened philtrum, bowed mouth, chronic purulent rhinitis, mental retardation, calcification of the central nervous system, and nephrocalcinosis.<sup>25</sup>

DiGeorge syndrome is associated with a deletion in the long arm of chromosome 22, and is also referred to as a *chromosome 22q11.2 deletion syndrome* or *velocardiofacial syndrome*.<sup>26</sup> The candidate gene for this disorder is termed *TBX1*, which encodes the T-box transcription factor 1. Approximately half of patients with DiGeorge syndrome are hemizygous for 22q11, and they have occasionally been found to have overlapping deletions in the 10p13/14 boundary.<sup>27,28</sup> These patients are at increased risk for developing psychiatric disorders, with one in four developing schizophrenia and one in six developing major depressive disorders.<sup>29</sup> Other reported psychiatric morbidities include attention-deficit/hyperactivity disorder, oppositional defiant disorder, and anxiety disorders.<sup>30</sup> When the immunodeficiency is severe, thymic or bone marrow transplantation should be considered.<sup>31</sup>

### PSEUDOHYPOPARATHYROIDISM/ALBRIGHT HEREDITARY OSTEODYSTROPHY

Pseudohypoparathyroidism (PHP) is a hereditary disorder in which there is decreased target tissue responsiveness in the receptor tissues, particularly the kidneys and skeletal system, to PTH (rather than a true deficiency). PHP is subclassified into types Ia, Ib, Ic, and type II (which involves a different mechanism of resistance to PTH). *Albright hereditary osteodystrophy (AHO)* refers to PHP in conjunction with a clinical constellation of physical features, including short stature, central obesity, brachydactyly, ectopic ossification, and variable degrees of mental retardation.<sup>32,33</sup>

*Pseudopseudohypoparathyroidism (PPHP)* is a term used to describe individuals with AHO who have normal end-organ responsiveness to PTH. These patients do not develop hypocalcemia and tetany. PHP and PPHP are caused by different types of mutations in the *GNAS* gene, and presence of genetic imprinting may lead to quite diverse clinical phenotypes.<sup>32,34</sup> Specifically, maternal inactivating mutations result in PHP-Ia, whereas paternal inactivating mutations result in PPHP and the disorder progressive osseous heteroplasia (POH), a disease of



**Figure 23-4** Osteoma cutis. These rock-hard papulonodules revealed ectopic ossification microscopically.

severe heterotopic ossifications of the subcutaneous tissues, skeletal muscles, and deep connective tissues (see Chapter 9).<sup>35</sup>

Patients with PHP have hypocalcemia, hyperphosphatemia, and elevated serum levels of PTH. Hypothyroidism secondary to TSH resistance may be seen in PHP-Ia. Ectopic calcification is common, and intracranial lesions usually involve the basal ganglia and occasionally other regions. Calcinosis cutis may occur and presents with multiple small papules, plaques, or nodules with a predilection for the scalp, hands and feet, periarticular regions, and chest wall.<sup>35</sup> Soft-tissue ossification (osteoma cutis) may be present at birth or develop during infancy or childhood (Fig. 23-4) and is often a presenting feature of the disease, along with hypothyroidism.<sup>36</sup> The subcutaneous calcifications or ossifications may occasionally present very early in life (even by 2 weeks of age) and in those patients may be vital to early recognition and diagnosis of PHP.<sup>37</sup> Dermal or subcutaneous hypoplasia may occasionally be noted in areas of cutaneous calcification.<sup>38</sup>

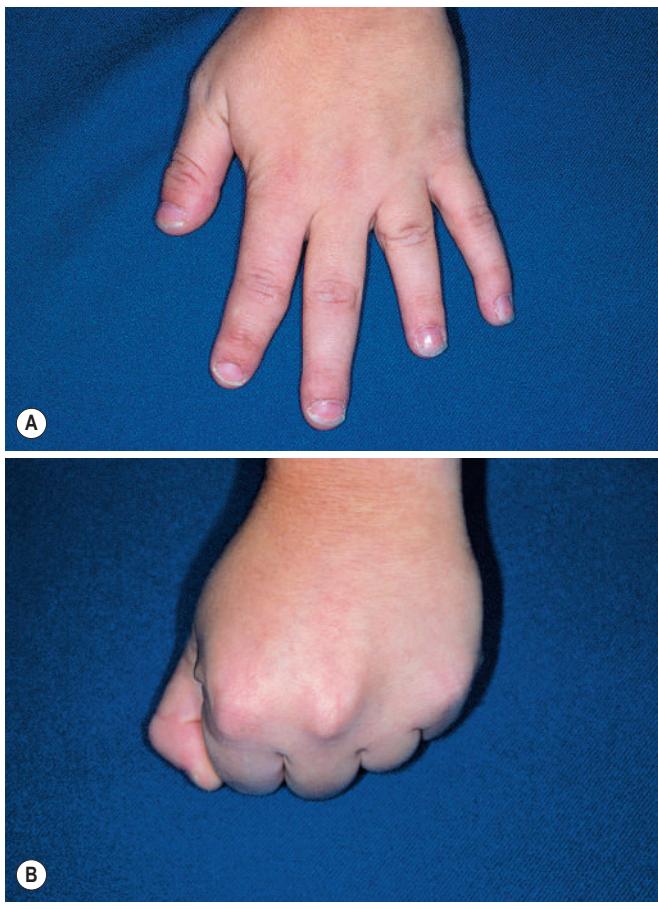
The characteristic features of AHO include short stature, obesity, and characteristic facial features, including round face, flat nasal bridge, and a short neck. Brachymetaphalangism refers to shortening of the fourth and fifth metacarpals and may be recognized by knuckle dimples when the patient makes a clenched fist.<sup>35</sup> In addition, the fourth and fifth fingers and toes may appear shortened (Fig. 23-5).<sup>39</sup> Plain radiography may confirm this feature when the clinical findings are subtle. Mental retardation may be present and may be less common with aggressive and early treatment for the hypocalcemia.

## Disorders of the Adrenal Glands

Adrenal gland dysfunction may result in a variety of systemic effects with various cutaneous manifestations. Those of particular interest to the pediatrician, dermatologist, and pediatric dermatologist are Addison disease, Cushing syndrome (CS), and the adrenogenital syndrome (discussed under Disorders of Androgen Excess).

### ADDISON DISEASE

Addison disease (primary adrenal insufficiency) is caused by the absence of glucocorticoids and mineralocorticoids despite an increased concentration of adrenocorticotrophic hormone (ACTH), and characterized by weakness, anorexia, weight loss, hypotension, decreased serum sodium and chloride, increased serum potassium, hypoglycemia, and hyperpigmentation of the skin and mucous membranes. Sporadic and recurrent "flu-like" episodes may provide a clinical clue to the diagnosis, especially in the setting of pigmentary alterations.<sup>40</sup> Hyperpigmentation in Addison disease is the result of increased production of proopiomelanocortin, which is cleaved to form MSH and ACTH.<sup>41</sup> This overproduction in the pituitary gland occurs as a compensatory phenomenon associated with decreased cortisol production by the adrenal glands. The hyperpigmentation of Addison disease occurs in the setting of primary adrenocortical failure as opposed to



**Figure 23-5** (A) Brachymetaphalangism in a girl with pseudohypoparathyroidism, with shortened fourth and fifth metacarpals. (B) The “knuckle, knuckle, dimple, dimple” sign when she makes a fist. (Reprinted with permission from Schachner LA, Hansen RC, editors. Pediatric dermatology. 3rd ed. Edinburgh: Mosby; 2003.)

secondary adrenal insufficiency, in which case ACTH levels are low and mineralocorticoid production remains relatively intact.<sup>42</sup>

The pigmentation of Addison disease is most intense in the flexures, at sites of pressure and friction, in the creases of the palms and soles (Fig. 23-6), in the nails, in sun-exposed areas, and in normally hyperpigmented areas such as the genitalia and areolae. Pigmentation of the conjunctivae and vaginal mucous membranes is common, and pigmentary changes of the oral mucosae (Fig. 23-7) include spotty or streaked blue-black to brown hyperpigmentation of the gingivae, tongue, hard palate, and buccal mucosa. In addition, increased pigmentation may be noted in existing nevi.<sup>43</sup> The pigmentation may in some children be quite diffuse.<sup>40</sup> Labial pigmentation and longitudinal pigmentary streaks of the fingernails similar to those in Laugier-Hunziker syndrome have been observed.<sup>44</sup> Because the pigmentation may in some cases be subtle, comparison of the patient to other family members may be useful in highlighting the clinical findings.<sup>42</sup> In one series of 18 pediatric patients with primary adrenal insufficiency at one institution, 12 (67%) exhibited cutaneous hyperpigmentation.<sup>45</sup> Primary adrenal insufficiency without hyperpigmentation has been reported and may result in a delay in the diagnosis of Addison disease.<sup>46</sup> Loss of body hair may be another cutaneous finding in this disorder.

The diagnosis of chronic adrenocortical insufficiency is suggested by the clinical features and confirmed by serum electrolyte studies and cortisol level determinations after stimulation by ACTH (the ACTH-stimulation test). A morning serum-cortisol (“AM cortisol”) level is a convenient and simple test but may be insensitive as a screening tool.<sup>42</sup> There are multiple potential causes of Addison disease, including adrenal dysgenesis (which may be related to a variety of



**Figure 23-6** Hyperpigmentation of Addison disease. Increased pigmentation of the palmar creases in this male with Addison disease. (Courtesy of Anne Lucky, MD.)



**Figure 23-7** Oral mucosa pigmentation of Addison disease. Note hyperpigmentation of the tongue and buccal mucosa in this patient with Addison disease.

gene mutations), diseases resulting in adrenal destruction, or impaired steroidogenesis (disorders of cholesterol or steroid biosynthesis, including several forms of congenital adrenal hypoplasia). Although the majority of cases of Addison disease in the past century were attributed to tuberculosis, autoimmune disease currently accounts for most cases presenting outside of the newborn period.<sup>47</sup> APS (autoimmune polyendocrinopathy syndrome) types 1 and 2 may both present with this disorder as one component. Other nonautoimmune causes include infection, metabolic and infiltrative or metastatic diseases, and drug-induced damage.<sup>48</sup> The incidence of Addison disease is elevated in vitiligo probands and their first-degree relatives.<sup>49</sup> When these two disorders occur concurrently, patients may have a striking presentation of hypopigmentation and hyperpigmentation.

## CUSHING SYNDROME

Cushing syndrome (CS) is a rare disorder caused by long-term glucocorticoid excess, which may be caused by a variety of different etiologies. It is divided into ACTH-dependent types (including pituitary-dependent Cushing disease, ectopic ACTH syndrome, and adrenal hyperplasia) and non-ACTH-dependent types (including adrenal adenoma, adrenal carcinoma, and adrenal hyperplasia).<sup>50</sup> The most common form is pituitary-dependent bilateral adrenal

#### Box 23-4 Cutaneous Features of Cushing Syndrome

- Facial plethora and telangiectasias
- Hirsutism, fine lanugo hair growth
- Violaceous striae (especially over the abdomen, flanks, and upper arms)
- Acne
- Bruising
- Poor wound healing
- Skin atrophy
- Thin, translucent skin
- Hyperpigmentation (seen only in ACTH-dependent form)
- Acanthosis nigricans
- Frequent fungal infections (i.e., tinea corporis, pityriasis versicolor, candidiasis)
- Male-pattern alopecia (in females)

ACTH, Adrenocorticotrophic hormone.

hyperplasia, termed *Cushing disease*. Endogenous CS is fairly uncommon in children, and the lack of classic features of hypercortisolism in pediatric patients may delay diagnosis and treatment. In all patients with CS, there is loss of diurnal variation of ACTH and cortisol secretion, which leads to sustained hypercortisolism.<sup>51</sup> Growth retardation to complete linear growth arrest is the hallmark of the disease in children and growing adolescents.<sup>52</sup> CS may also result from the systemic administration of exogenous glucocorticoids (including oral, parenteral or rarely, topical) or ACTH, and should be suspected by the findings of suppressed ACTH and cortisol with no response to corticotropin-releasing hormone (CRH) or ACTH, respectively.<sup>50</sup> CS has occurred after intralesional corticosteroid injections for keloids in a child.<sup>53</sup> The authors have observed CS in a few children after topical application of ultrapotent corticosteroids for extensive alopecia areata/totalis and severe atopic dermatitis.

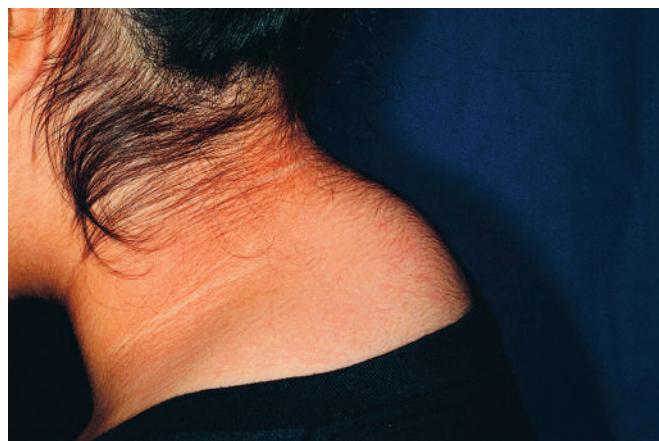
The clinical findings in CS are multiple and usually suggest the presence of hypercortisolism. Noncutaneous signs and symptoms include truncal obesity, marked diminution of the linear growth rate, diabetes mellitus or glucose intolerance, gonadal dysfunction, hypertension, muscle weakness, fatigue, mood disorders, sleep disturbances, menstrual irregularities, osteoporosis, delayed or accelerated bone age, edema, polydipsia, polyuria, and fungal infections.<sup>50,54</sup> The typical growth chart in a child with CS reveals a severely diminished linear growth curve, with continued weight gain across percentiles. This is in distinction to the growth chart in a child with exogenous obesity, which reveals increasing linear growth.<sup>55,56</sup>

The cutaneous features of CS are listed in Box 23-4. Addison disease-like pigmentation (particularly on the face and neck) has been noted in 6% to 10% of patients and is seen primarily in the ACTH-dependent forms of the disease. Other skin findings include a characteristic plethoric “moon” facies with telangiectasias over the cheeks; increased fine lanugo hair on the face and extremities; purplish striae (stretch marks, see below) at points of tension such as the lower abdomen, flanks, thighs, buttocks, upper arms, and breasts; fragility of dermal blood vessels with an increased tendency toward bruising at sites of minimal trauma; poor wound healing; and steroid acne. The latter usually presents as red papules or small pustules distributed primarily on the upper trunk (Fig. 23-8), arms, neck, and to a lesser degree, the face. There is a tendency to develop cutaneous fungal infections (i.e., tinea corporis, onychomycosis, candidiasis, pityriasis versicolor), and disseminated mycobacterial infection has been reported.<sup>57</sup> Patients with CS classically have fatty deposits over the back of the neck, termed the *buffalo hump* (Fig. 23-9).

CS is diagnosed based on suspicious clinical findings and the results of laboratory testing. A 24-hour urinary free-cortisol test is a widely used assay for diagnosing hypercortisolism and has a very high specificity and sensitivity.<sup>50,51</sup> Other diagnostic studies include plasma-cortisol measurement (limited by diurnal variation), low-dose dexamethasone suppression test (excellent sensitivity but requires overnight hospitalization), high-dose dexamethasone suppression test, ACTH measurement (useful for discriminating between ACTH-dependent and ACTH-independent forms), late night salivary cortisol measurement, inferior petrosal sinus sampling, and the CRH stimulation test.<sup>51,58,59</sup> Radiographic imaging may be useful for



**Figure 23-8** Steroid acne. Erythematous papules and papulopustules on the chest and upper arms.



**Figure 23-9** Buffalo hump. This finding consisting of fatty deposits over the posterior neck and upper back may be associated with either endogenous or exogenous Cushing syndrome.

assessing for pituitary or adrenal tumors. The treatment options for CS depend on the etiology and may include transsphenoidal pituitary surgery, external pituitary radiotherapy, excisional surgery (adrenal tumors), and mitotane (an adrenocytolytic agent). With the exception of striae, the cutaneous effects of CS most often completely heal after successful therapy.<sup>60</sup> After treatment, glucocorticoid replacement and stress dosing of cortisol are often required.

Striae distensae (stretch marks), mentioned earlier, are linear depressions of the skin that are initially pink (Fig. 23-10) or purple and later become more flesh-colored, translucent, and atrophic (Fig. 23-11). They are most commonly seen in areas subject to stretching such as the lower back, buttocks, thighs, breasts, abdomen, and shoulders. Striae may develop physiologically in up to 35% of girls and 15% of boys between the ages of 9 and 16 years. Causes of striae include stretching exercises, rapid growth, obesity, adolescence, pregnancy, CS, and prolonged use of systemic or potent topical corticosteroids. They may be seen in patients with anorexia nervosa, mainly the restrictive (vs. the bulimic) form.<sup>61</sup> They can occasionally be mistaken for nonaccidental injury or physical abuse.<sup>62</sup> Although the precise cause of striae is unknown, their formation appears to be related to stress-induced rupture of connective tissue, alteration of collagen and elastin, and dermal scarring in which glucocorticoids suppress fibroblastic activity and newly synthesized collagen fills the gaps between ruptured collagen fibers.<sup>63</sup> Elastic fibers are fine in early lesions and thickened in older lesions of striae.<sup>64</sup> Treatment of striae is challenging, and most therapies are generally unsatisfactory. Many of the lesions that occur during adolescence tend to become less noticeable with time. It has been suggested that topical tretinoin cream may be



**Figure 23-10** Striae distensae. These early lesions appear as pink, linear depressions in the skin.



**Figure 23-11** Striae distensae. These older lesions appear as flesh-colored, linear, atrophic bands.

helpful for some patients, although the results are mixed. Other topical agents reportedly effective in some patients include glycolic and trichloroacetic acid peels and topical hyaluronic acid preparations.<sup>65</sup> The flashlamp-pumped pulsed-dye laser has also been used for treating these lesions, but data suggest that this modality should be reserved for patients with the more fair skin phenotypes (types II to IV).<sup>66-68</sup> Other treatment modalities that have been reported for striae include intense pulsed light, excimer laser, copper-bromide laser, fractional photothermolysis, and microdermabrasion.<sup>65,69,70</sup>

## Disorders of Androgen Excess

Patients with androgen excess may initially present with a variety of skin-related conditions, including hirsutism, acne, and alopecia. Hyperandrogenism may be related to benign or malignant ovarian, testicular, or adrenal tumors; functional overproduction of androgens by the adrenal glands or ovaries; or exogenous androgens. The clinical findings of hyperandrogenism may vary depending upon the pubertal

### Box 23-5 Clinical Features of Hyperandrogenism

Prepubertal
Precocious sexual development:
Sex appropriate (males)
Sex inappropriate (females)
Rapid linear growth
Accelerated bone age
Axillary and pubic hair development
Acne
Hirsutism
Neonate:
Hyperpigmentation of the genitalia
Ambiguous genitalia
Postpubertal
Acne
Hirsutism
Androgenetic alopecia
Amenorrhea or irregular menses
Infertility
Other virilizing signs (deep voice, increased muscle mass, male habitus)
Early cardiovascular disease

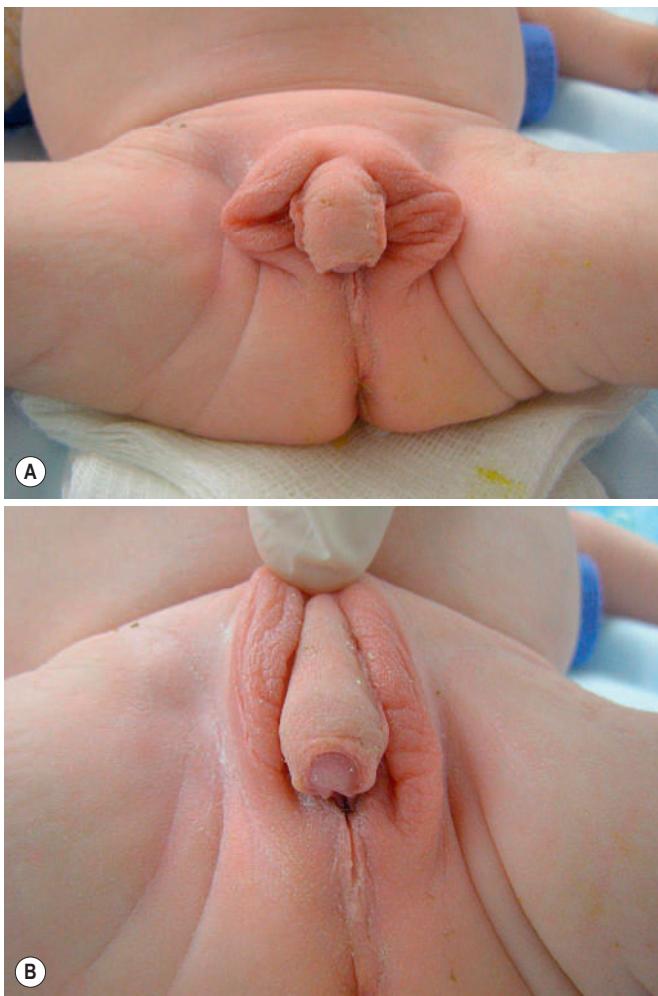
development of the child, and these are summarized in **Box 23-5**. The two disorders to be discussed in this section are congenital adrenal hyperplasia (CAH) and polycystic ovary syndrome (PCOS).

A brief mention of exogenous androgen excess is in order, in light of the expanding US market for testosterone-replacement therapies. These products are the standard of care for androgen deficiency and are available as depot injectables, subcutaneously implanted pellets, transdermal patches, topical gels, and buccal tablets.<sup>71</sup> Inadvertent drug transfer to spouses and/or children (secondary exposure) may occur in association with use of the topical agents and may present with precocious puberty in young children or virilization in exposed adult females.<sup>71-73</sup> Although skin-to-skin contact is presumed to be the primary mode of transfer, spread via shared linens may also be possible. These reports highlight the importance of adequate education in contact precautions when topical androgens are prescribed, as well as vigilance on the part of pediatric practitioners, with recognition of this potential cause for precocious puberty. The United States Food and Drug Administration (FDA) added a box warning about the risks of secondary transfer to topical testosterone product labels in 2009.<sup>74</sup>

## CONGENITAL ADRENAL HYPERPLASIA

*Congenital adrenal hyperplasia (CAH; also known as adrenogenital syndrome)* is a term used to describe a constellation of diseases characterized by impaired steroid metabolism in the adrenal cortex. The most common cause of CAH is 21-hydroxylase deficiency, and other enzymes that may be defective include 11 β-hydroxylase and 3 β-hydroxysteroid dehydrogenase.<sup>75</sup> 21-Hydroxylase deficiency occurs in about one in 10,000 to one in 15,000 live births worldwide.<sup>76</sup> It is inherited in an autosomal recessive fashion, and the gene (*CYP21A2*) is located in the HLA class III region on the short arm of chromosome 6p.<sup>77,78</sup> Owing to the defect in cortisol synthesis, the adrenal cortex in these disorders is stimulated by corticotropin, and overproduction of cortisol precursors occurs, some of which are diverted toward synthesis of sex hormones. This androgen excess leads to clinical signs of hyperandrogenism, and concomitant aldosterone deficiency may result in salt-wasting, failure to thrive, hypovolemia, and in some cases, shock.<sup>79</sup>

One of the most classic presenting features of female children with CAH (21-hydroxylase deficiency) is ambiguous genitalia (Fig. 23-12). Because of exposure to high systemic levels of adrenal androgens during gestation, affected girls are born with a large clitoris, rugated and partially fused labia majora, and a common urogenital sinus in place of a separate urethra and vagina.<sup>79</sup> The degree of virilization is variable and may range from simple clitoromegaly to the appearance of a penile urethra. In severe forms, important features in distinguishing the virilized female genitalia from true male genitalia include the absence of testicles and the presence of normal internal sex organs.<sup>80</sup> Affected boys generally have no obvious physical signs



**Figure 23-12** Congenital adrenal hyperplasia. This newborn has ambiguous genitalia. Note the marked clitoral enlargement (resembling a penis), the rugated and partially fused labia majorae (**A**) and the common opening between the vagina and the urethra (urogenital sinus) (**B**). (Courtesy of Marleta Reynolds, MD.)

of the disorder, although subtle hyperpigmentation and/or penile enlargement may be present. Some forms of CAH, such as 17 $\alpha$ -hydroxylase/17,20-lyase deficiency, may result in ambiguous or female-appearing external genitalia in males, identical to the androgen insensitivity syndrome.<sup>81</sup>

In patients who are not treated or in whom therapy is inadequate, long-term exposure to these androgens results in rapid somatic growth, advanced skeletal age, and premature development of secondary sexual characteristics, including development of pubic and axillary hair, clitoral growth, and penile growth in males. Although linear growth may be accelerated during childhood, these patients often ultimately have short stature because of premature epiphyseal closure. Centrally mediated precocious puberty may occur. Hirsutism is a common feature in patients with nonclassic (partial) 21-hydroxylase deficiency, and when menstrual irregularity and acne also occur, the presentation may simulate that of PCOS (see below). Patients with nonclassic CAH do not have ambiguous genitalia at birth and usually have premature adrenarche and advanced skeletal maturation.<sup>82</sup>

Abnormalities of reproductive function are common in CAH, and infertility is often present. Affected males have fewer problems with reproductive function. Salt-wasting is seen in up to 75% of patients with classic 21-hydroxylase deficiency, owing to decreased synthesis of aldosterone. These patients are prone to hyponatremia, hyperkalemia, hypovolemia, dehydration, and shock. Hyperpigmentation, most notably of skin creases and the genitalia, may occur as an early

sign of adrenal insufficiency. Classic 21-hydroxylase deficiency is diagnosed by the finding of markedly elevated levels of serum 17-hydroxyprogesterone, the main substrate for the enzyme; this is the measurement utilized in newborn-screening protocols. The cosyntropin (corticotropin)-stimulation test is useful for differentiating this disorder from other steroidogenic enzyme defects. Molecular-based genetic testing is available for CAH, and prenatal diagnosis is possible using chorionic villus and amniotic fluid cells for deoxyribonucleic acid (DNA) analysis.<sup>83</sup> Fetal DNA harvested from maternal plasma has also been investigated as a noninvasive approach to prenatal diagnosis. Management for CAH consists of glucocorticoid and mineralocorticoid replacement, supplemental sodium chloride, and surgical management of ambiguous genitalia, which is generally recommended between 2 and 6 months of life.<sup>79</sup> When the diagnosis is known, dexamethasone administered to the mother before the ninth week of gestation may prevent the development of genital ambiguity.<sup>84</sup>

## POLYCYSTIC OVARY SYNDROME

Poly cystic ovary syndrome (PCOS; also called Stein–Leventhal syndrome) is the most common androgen disorder of ovarian function<sup>85</sup> and among the most common endocrine disorders in women.<sup>86</sup> It is estimated to affect between 6% and 15% of women, depending on the diagnostic criteria utilized.<sup>87</sup> Patients with PCOS have increased androgen production and disordered gonadotropin secretion, resulting in amenorrhea or severe oligomenorrhea, increased testosterone levels, and enlarged polycystic ovaries on ultrasound examination. Women with PCOS also have metabolic derangements related to insulin resistance and an increased risk of type 2 diabetes mellitus. The hormonal dysregulation seen in PCOS usually begins during adolescence.<sup>88</sup> The pathophysiology of PCOS is multifactorial, and it has been found to cluster in families with a history of PCOS, non-insulin-dependent diabetes mellitus (NIDDM), cardiovascular disease, and breast cancer.<sup>89</sup>

Three sets of diagnostic criteria have been utilized for adult women, including the 1990 National Institutes of Health criteria (which requires chronic oligoovulation plus clinical or biochemical signs of hyperandrogenism), the 2003 Rotterdam criteria (which requires two of three criteria: chronic oligoovulation or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries), and the criteria of the Androgen Excess Society (which defines PCOS as hyperandrogenism manifested as hirsutism and hyperandrogenemia, and ovarian dysfunction based on chronic oligoovulation or anovulation and polycystic ovaries).<sup>87,90,91</sup> There are no formal diagnostic criteria in adolescents, and this may present a challenge given the potential clinical overlap between features of normal puberty and PCOS.

Hirsutism and acne vulgaris are the most common manifestations of PCOS and in fact, the leading cause of hirsutism in adolescence is PCOS (see Chapter 7).<sup>92</sup> Hair growth occurs in androgen-dependent areas including the face, neck (Fig. 23-13), chest, back, and lower abdomen. It may be less noticeable in adolescents (given their shorter duration of hyperandrogenism) and is less common in some ethnic backgrounds such as Asians.<sup>88</sup> Acne is a common finding, and in one study of 119 women with acne but without menstrual disorders, obesity, or hirsutism, PCOS was found on ultrasound in 45%.<sup>93</sup> These findings suggest that PCOS is common in women with acne even in the absence of other suggestive clinical findings.

Acanthosis nigricans (AN) (see below in Acanthosis Nigricans section) is another common cutaneous finding in patients with PCOS. It presents with hyperpigmented, velvety plaques of the neck folds, axillae, and other intertriginous areas. AN is a marker for insulin resistance, although the latter appears to be only one factor leading to its development.<sup>94</sup> Other important components of PCOS include menstrual irregularity and obesity. Anovulation or oligoovulation commonly occur, although women with PCOS can ovulate spontaneously. Secondary amenorrhea, oligomenorrhea, and dysfunctional uterine bleeding may all occur, and delayed menarche may be seen in girls.<sup>95</sup> Adolescent females with oligomenorrhea secondary to PCOS may be difficult to distinguish from those with physiologic anovulation. Obesity is often present, with a centripetal weight distribution and



**Figure 23-13 Hirsutism.** The hair growth in this adolescent female with polycystic ovary syndrome occurs in androgen-dependent areas and is accompanied by acne.

increased waist-to-hip ratio of greater than 0.85.<sup>95</sup> Some patients with PCOS display a metabolic pattern of atherogenic lipid profile, glucose intolerance, and increased fasting insulin level, with an increased incidence of type 2 diabetes mellitus and cardiovascular disease.<sup>85</sup> Studies of adult women with type 2 diabetes mellitus show a prevalence of PCOS higher than that reported in the general population.<sup>96</sup>

The clinical presentation of PCOS and its associated features have overlap with other entities described in the literature. The association of hyperandrogenism, insulin resistance, and AN has been called *HAIR-AN syndrome*. Although the potential causes of hyperandrogenism in this syndrome are multiple, PCOS may be present in many patients. It is possible that the etiology of insulin resistance (and resultant hyperinsulinemia) could produce both polycystic ovaries and hyperandrogenism.<sup>97</sup> *Syndrome X* is a term that has been used to describe a systemic disease notable for hyperinsulinemia and hyperandrogenism. More recently, *metabolic syndrome* has been the terminology used to describe patients with abdominal obesity, dyslipidemia, glucose intolerance, and often, PCOS.<sup>98</sup> These patients are also prone to hypertension, hyperuricemia, fatty liver disease, chronic inflammation, endothelial dysfunction, and coagulopathy.<sup>98</sup> Importantly, there is a threefold increase in the risk of coronary heart disease and stroke. Sleep disorders such as obstructive sleep apnea and excessive daytime sleepiness have been increasingly recognized in patients with PCOS.

The diagnosis of PCOS is suggested by the clinical features of hyperandrogenism and prolonged menstrual irregularity and confirmed by finding elevated serum androgens and excluding other potential causes. The ultrasound finding of polycystic changes is common, but such changes may also be seen in normally menstruating adolescents or in other conditions, and so this must be kept in appropriate context during the evaluation. In addition, some adolescents with PCOS may not have polycystic ovaries. Screening for glucose intolerance and diabetes mellitus should be performed in all patients with PCOS, as should fasting lipid levels. **Box 23-6** lists the recommended diagnostic testing for adolescents suspected of having PCOS.<sup>99</sup>

Treatments for the condition are primarily directed at symptoms and lifestyle modifications, and include hormonal regulation, weight reduction via nutritional changes and physical exercise, and treatment for hirsutism and acne. A serious attempt at weight loss and increased physical activity should be first-line therapy; weight loss itself has been associated with decreased testosterone, increased sex-hormone binding globulin, normalization of menses, and improved fertility in females with PCOS.<sup>100</sup> Combined estrogen-progestin contraceptives provide regular withdrawal bleeds, contraception, and improvement in hirsutism and acne. Antiandrogen medications such as spironolactone may also be of benefit. The use of insulin-sensitizing drugs such as metformin may be effective for anovulation and may benefit the associated metabolic derangements.<sup>101</sup> Other options for treatment of hirsutism include mechanical hair removal (i.e., plucking, waxing, shaving, chemical depilatories, and laser therapy), topical

### Box 23-6 Recommended Testing for Adolescents Suspected of Having Polycystic Ovary Syndrome

#### Laboratory

- Human chorionic gonadotropin (HCG) (urine or serum)
- Follicle-stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Estradiol
- Thyroid-stimulating hormone (TSH)
- Prolactin
- Testosterone (total and free)
- Dehydroepiandrosterone sulfate (DHEA-S)
- Androstenedione
- 17-hydroxyprogesterone

#### Radiologic

- Pelvic ultrasonography (transabdominal if virginal, or transvaginal)

#### If PCOS Confirmed:

- Fasting glucose and insulin
- 2-hour oral glucose tolerance test
- Fasting lipid panel

Modified from Rackow BW. Polycystic ovary syndrome in adolescents. *Curr Opin Obstet Gynecol* 2012;24:281–7, and Nicandri KF, Hoeger K. Diagnosis and treatment of polycystic ovarian syndrome in adolescents. *Curr Opin Endocrinol Diabetes Obes* 2012;19:497–504.

PCOS, Polycystic ovary syndrome.

inhibitors of ornithine decarboxylase (eflornithine), and gonadotropin-releasing hormone agonists.

## Gonadal Dysgenesis/Turner Syndrome

Gonadal dysgenesis, or Turner syndrome (TS), is a condition characterized by short stature and ovarian dysgenesis. Patients are females with either a missing X chromosome (45, X) or an abnormality of one of the X chromosomes. It occurs in 1 in 2000 to 1 in 5000 female live births.<sup>102</sup> Genomic imprinting, whereby allelic genes or chromosomes are expressed differently depending on the parent of origin, has been implicated in TS in which up to 80% of patients have retained the maternal X chromosome.<sup>103</sup> The rate of spontaneous fetal loss for 45, X fetuses is high; TS may occur in up to 3% of all fetuses and may cause up to 10% of all spontaneous fetal loss (the majority terminating during the first and second trimesters).<sup>104</sup>

In addition to short stature and ovarian failure, patients with TS may have lymphatic abnormalities, skeletal abnormalities (micrognathia, broad “shield” chest, kyphoscoliosis, Madelung deformity), hearing and cardiac defects, renal abnormalities, and endocrinopathies (most notably involving the thyroid and glucose metabolism). Congenital cardiovascular disease is present in approximately 50% of girls with TS, the most common being bicuspid aortic valve; aortic coarctation (10%) and hypertension (25% of adolescents and 50% of adults) may also occur.<sup>105</sup> Characteristic physical findings also include a low posterior hairline, cubitus valgus, unusual rotation of the ears, downward displacement of the lateral canthus, epicanthal folds, inverted or hypoplastic nipples, and shortened fourth and fifth metacarpals and metatarsals. Learning deficits occur in the majority of patients with TS, and psychiatric conditions may be more common.

Abnormalities of the lymphatic system include cystic hygroma (macrocystic lymphatic malformation), which when occurring *in utero*, may result in neck webbing or pterygium colli (Fig. 23-14). Transient lymphedema of the distal extremities, mainly the hands and the feet, may occur, and nail dysplasia may be seen as a result of intrauterine peripheral lymphedema.<sup>106</sup> This lymphedema usually resolves by 2 years of age. Deep furrows of the scalp, similar to what has been termed *cutis verticis gyrata*, may also be the result of preceding lymphedema.<sup>107</sup>

The nails in patients with TS are characteristic, revealing hypoplasia and hyperconvexity (Fig. 23-15).<sup>39</sup> Increased numbers of melanocytic nevi are commonly noted, although clinical atypia is not necessarily more prominent.<sup>108</sup> Despite the increased numbers of melanocytic



**Figure 23-14** Pterygium colli in Turner syndrome. This neck webbing is likely the result of *in utero* cystic hygroma.



**Figure 23-16** Cutis verticis gyrata. This coarse furrowing of the skin on the scalp may be associated with hyperpituitarism or as part of a disorder called *pachydermoperiostosis*.



**Figure 23-15** Nail changes in Turner syndrome. Note the hypoplastic, hyperconvex toenails and hypoplasia of the fourth and fifth metatarsals in this girl with gonadal dysgenesis. (Reprinted with permission from Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 3rd ed. Edinburgh: Mosby; 2003.)

nevi, there appears to be a lower-than-expected incidence of malignant melanoma in patients with TS, possibly reflecting the relationship between sex hormones and melanoma development.<sup>109,110</sup> Multiple pilomatricomas, including giant lesions, have been reported in girls with TS.<sup>111,112</sup>

## Pituitary Disorders

### HYPERPITUITARISM

The pituitary gland, an endocrine organ located in a bony cavity (the sella turcica) at the brain base, is divided into anterior and posterior portions. Both portions secrete a variety of hormones under the influence of the hypothalamus. These hormones include growth hormone (GH), TSH, ACTH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, antidiuretic hormone (ADH, vasopressin), and oxytocin. Skin manifestations of hyperpituitarism include those related to excess GH, glucocorticoids (see Cushing Syndrome section), and prolactin (not discussed here). Most GH-secreting pituitary tumors are eosinophilic adenomas. Excessive secretion of GH by pituitary-gland tumors produces gigantism in children whose epiphyses have not yet closed and acromegaly in individuals whose normal bone growth has ceased. Acromegaly is rare in children, but transitional acromegalic features at times may be seen in affected adolescents. Soft-tissue overgrowth of the hands, feet, face, and nasal tip occur. Patients may have a large furrowed tongue, thick lips,

lantern jaw, broad spade-like hands with squat fingers, hypertrichosis, and hyperpigmentation in a pattern similar to that observed in patients with Addison disease. Although the cause of the hypertrichosis is not well understood, the hyperpigmentation is related to increased secretion of MSH. Other cutaneous manifestations of acromegaly include excessive sweating, oily skin, acrochordons (skin tags), heel-pad thickening, eyelid swelling, and AN.<sup>113</sup> Early noncutaneous complaints in patients with acromegaly may include headache, visual disturbances, weakness, and paresthesias, and impaired glucose tolerance may be present.<sup>114</sup>

Cutis verticis gyrata (coarse furrowing of the skin on the posterior aspect of the neck and the vertex of the scalp; Fig. 23-16) is caused by an increase in dermal collagen; as a result, excessive skin buckles and forms furrows and ridges that resemble gyri of the cerebral cortex (hence the terminology). In addition to being an occasional manifestation of hyperpituitarism, cutis verticis gyrata may occasionally occur as a primary disorder without other associated abnormalities. It has been reported in association with TS (see earlier) and Noonan syndrome.<sup>115-118</sup> It may also be seen as part of a disorder called *pachydermoperiostosis*, which is manifested by thickening of the skin of the face and scalp, clubbing of the fingers, and periostosis of the long bones. Severe progressive arthritis has rarely been reported in association with this syndrome.<sup>119</sup>

### HYPOPITUITARISM

*Pituitary insufficiency (hypopituitarism)* refers to a group of disorders resulting from a deficiency in secretion of one or more hormones derived from the pituitary gland. These include idiopathic hypopituitarism (panhypopituitarism, Simmonds disease), Sheehan syndrome (pituitary deficiency usually arising as a result of hemorrhage or infarct), pituitary tumors (especially craniopharyngioma, Langerhans cell histiocytosis), autoimmune disorders, trauma, infections (i.e., tuberculosis), congenital abnormalities, or ablation of the pituitary gland by surgery or radiation used for the treatment of local tumors. Systemic manifestations of hypopituitarism may include those related to mineralocorticoid and glucocorticoid deficiencies (see Addison Disease section), hypothyroidism, GH and gonadotropin deficiency, and diabetes insipidus secondary to ADH deficiency.

The most obvious skin manifestations of pituitary insufficiency are pallor secondary to anemia and decreased cutaneous blood flow, and a predisposition toward sunburn with decreased ability to tan (because of a decrease in melanin pigmentation secondary to diminished or absent secretion of MSH). Other features (and proposed causes) include smooth, fine skin (GH deficiency) or myxedematous, coarse,

**Table 23-1** Endocrine and Mucocutaneous Manifestations of Multiple Endocrine Neoplasia Syndromes

Syndrome (Gene)	Endocrine*	Mucocutaneous
MEN I (MEN-1)	Parathyroid Anterior pituitary Endocrine pancreas Thyroid Adrenal glands	Angiofibromas (facial) Collagenomas Hypopigmentation (confetti-like) Gingival papules Lipomas Café-au-lait macules Melanoma
MEN II (IIA) (RET)	Thyroid Parathyroid Pheochromocytoma	Lichen amyloidosis
MEN III (IIB) (RET)	Thyroid Pheochromocytoma Parathyroid (extremely rare)	Mucosal neuromas (lips, eyelids, tongue) Café-au-lait macules Lichen nitidus

MEN, Multiple endocrine neoplasia.

\*May be hyperplasia, benign tumors, malignant tumors.

dry skin (hypothyroidism and GH deficiency). The face may be slightly puffy and pale or yellowish (secondary to carotenoderma from hypothyroidism). Hair is thin and sparse with alopecia (hypothyroidism and androgen deficiency), and the nails grow slowly. Adolescent males may have a smooth scrotum with absence of hair and rugae (androgen deficiency).<sup>120</sup> Gonadotropin deficiency may result in loss of axillary, pubic, and body hair and micropenis in males.

## Multiple Endocrine Neoplasia Syndromes

The multiple endocrine neoplasia (MEN) syndromes are familial disorders characterized by benign and malignant tumors of multiple endocrine glands. Cutaneous manifestations may also be found in these disorders. The clinical manifestations of MEN syndromes are inconsistent and reflect the variable involvement of hormone-producing tissues. These disorders are inherited in an autosomal dominant fashion. The endocrine and cutaneous manifestations of the MEN syndromes are summarized in Table 23-1.

MEN 1 (Werner syndrome) is characterized by tumors of the parathyroid glands, endocrine pancreas, and anterior pituitary. Thyroid and adrenal gland tumors may also be seen, as may foregut carcinoid tumors.<sup>121</sup> Clinical manifestations may be related to primary hyperparathyroidism, gastrinoma, tumors secreting neuroendocrine peptides and prolactinomas. There is an increased risk of malignant endocrine tumors, including parathyroid, thymic, bronchial (carcinoid), and enteropancreatic neuroendocrine tumors.<sup>122</sup> The gene for MEN 1 (*MEN1*) was initially mapped to chromosome 11q13, and genetic testing is available.<sup>122,123</sup> This gene encodes a protein called *menin*, which functions as a tumor suppressor protein and in whose absence cellular replication, hyperplasia, and tumorigenesis are increased.

Cutaneous manifestations of MEN 1 include lipomas, angiofibromas, collagenomas, confetti-like hypopigmented macules, and gingival papules.<sup>121</sup> Café-au-lait macules may also occur, although not in the high numbers usually associated with neurofibromatosis. The multiple facial angiofibromas (Fig. 23-17) are clinically and histologically indistinguishable from those that occur in the setting of tuberous sclerosis, although they tend to present later in life in MEN 1, usually during the third or fourth decade.<sup>121,124</sup> In addition, they may involve the upper lip and vermillion border. Nonetheless, facial angiofibromas, which were once felt to be pathognomonic for tuberous sclerosis (and traditionally referred to as *adenoma sebaceum*), can no longer be considered a specific marker for that disorder. In one series of patients with MEN 1, 88% had facial angiofibromas.<sup>121</sup> Collagenomas, which are hamartomas of connective tissue, tend to be more discrete and papular



**Figure 23-17** Facial angiofibromas. These pink to red, dome-shaped smooth papules occur most commonly on the cheeks, nasolabial folds, and chin and may be seen in the setting of MEN 1 or tuberous sclerosis. They may occasionally be confused with lesions of acne vulgaris.

in MEN 1 than the histologically similar lesions ("shagreen patch") seen in patients with tuberous sclerosis.<sup>121</sup> Protuberant collagenomas have been reported, with rapid growth after surgery to remove an endocrine tumor.<sup>125</sup> Melanoma may occur with increased incidence in patients with MEN 1.<sup>126</sup> Patients who have a cluster of tumors suggestive of the syndrome or with single proliferative disorders with a high correlation such as prolactinoma or multigland parathyroid hyperplasia, or with facial angiofibromas in the absence of stigmata of tuberous sclerosis, should be screened for MEN 1.<sup>127</sup>

MEN 2A (Sipple syndrome) is a rare autosomal dominant disorder caused by a point mutation in the *RET* protooncogene. Clinical findings include medullary thyroid carcinoma, pheochromocytoma, and parathyroid hyperplasia. Hirschsprung disease may also occur with increased incidence. Cutaneous manifestations are not a significant feature of MEN 2A. The one that has received the most attention is lichen amyloidosis, which presents as multiple infiltrated papules overlying a well-demarcated plaque on the upper back (especially the interscapular region) or extensor surfaces of the extremities.<sup>128,129</sup> These lesions often begin with intense pruritus, with the subsequent development of brown-colored papules on the skin<sup>130</sup> and the histologic finding of amorphous material in the papillary dermis that stains as amyloid.<sup>131,132</sup>

MEN 2B (MEN III, mucosal neuroma syndrome) is characterized by medullary thyroid carcinoma, pheochromocytoma, ganglioneuromatosis, a Marfanoid body habitus, and only very occasional parathyroid hyperplasia. Medullary thyroid carcinoma is the initial presentation in most patients with MEN 2B (as well as those with MEN 2A) and remains the major cause of morbidity.<sup>133</sup> This disorder is also caused by an activating mutation in the *RET* protooncogene.

Mucocutaneous manifestations of MEN 2B include multiple mucosal neuromas that are often present by the preschool years. These ganglioneuromas involve the anterolateral tongue and lips and may also be located on the conjunctiva and eyelids.<sup>134,135</sup> Lip involvement results in diffusely enlarged lips with a fleshy, bubbled appearance. The upper lip is usually more involved than the lower lip. The tongue lesions are usually limited to the anterior third of the surface and appear as pink-white, somewhat translucent papules and nodules (Fig. 23-18). They may be congenital or noted during the first few years of life and are an important feature, because they may be the initial marker of the syndrome. Although multiple mucosal neuromas are nearly pathognomonic for this disorder, they may rarely occur without other clinical, biochemical, or molecular evidence of MEN 2B.<sup>136</sup> Multiple lesions of lichen nitidus have also been observed.<sup>137</sup>

Ocular involvement may involve the limbus of the conjunctivae and the eyelids, in which case it results in thickening of the lid margin and distortion or displacement of the eyelashes (Fig. 23-19). Nasal, laryngeal, and gingival neuromas may also be present, and skin lesions are



**Figure 23-18** Mucosal neuromas in multiple endocrine neoplasia 2B. Characteristic lingual neuromas and protuberant fleshy lips are present in this 16-year-old male with mucosal neuroma syndrome.



**Figure 23-20** Oral candidiasis. White plaques of the lateral tongue (thrush) in a young female with chronic mucocutaneous candidiasis and diabetes mellitus.



**Figure 23-19** Eyelid changes in multiple endocrine neoplasia 2B. Neuromas of the eyelid margins result in thickening and displacement of the lashes.



**Figure 23-21** Perlèche (angular cheilitis). In this condition, which can occur as a component of chronic mucocutaneous candidiasis, candidal infection presents as erythema, fissures, and maceration at the mouth angles.

occasionally seen. Café-au-lait macules may also be a cutaneous component of the syndrome. Intestinal ganglioneuromatosis (distinct from Hirschsprung disease) is another feature of MEN 2B, presenting with intermittent intestinal obstruction, gas formation, diarrhea, and failure to thrive.<sup>134</sup> Musculoskeletal features of Marfan syndrome are common, including tall stature, elongated limbs, pes cavum, and pectus excavatum, but cardiac or ocular abnormalities typical of that disorder are absent.

Genetic testing for *RET* gene mutations should be performed early in life for individuals with a known family history of MEN 2A or 2B and can identify young carriers at an early stage, often before the development of cancer.<sup>129</sup> In primary relatives of patients affected by medullary thyroid carcinoma with no identified *RET* mutation, linkage analysis and biochemical testing for MEN should be performed. Total thyroidectomy is recommended for all patients at risk.<sup>134,138</sup>

## Autoimmune Polyglandular Syndromes

Autoimmune polyglandular syndromes (APSs) are a group of disorders in which multiple endocrine and nonendocrine defects occur together. The best characterized of these syndromes is APS1, also known as *APECED syndrome*. This autosomal recessive condition is defined by the presence of two of three conditions: adrenocortical failure (Addison disease), hypoparathyroidism, and mucocutaneous candidiasis.<sup>139</sup>

It occurs with increased incidence in Finnish, Iranian, Jewish, and Sardinian populations.<sup>140</sup> APS2, the most common APS, is characterized by Addison disease in conjunction with thyroiditis and/or diabetes mellitus. APS3 has been defined as autoimmune thyroid disease in conjunction with other autoimmune endocrinopathy excluding adrenal disease. More recently, immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome has been recognized as a rare disorder caused by mutations in the *FOXP3* gene and resulting in overwhelming autoimmunity and absence or dysfunction of regulatory T cells<sup>141</sup> (see Chapter 3). Children with this syndrome often die early in life without prompt diagnosis and bone marrow transplantation.

The symptoms of APS1 commonly begin in infancy, although studies of affected individuals reveal marked heterogeneity in clinical features and age of onset of manifestations.<sup>142</sup> In addition to hypoparathyroidism and adrenal failure, other associations may include insulin-dependent diabetes mellitus, gonadal failure, autoimmune thyroiditis, chronic active hepatitis, malabsorption, and parietal-cell atrophy.<sup>143,144</sup> Autoimmune hepatitis may occur and can be one of the presenting features.<sup>145</sup> Candidiasis is seen in nearly all patients, and in the majority of patients it appears first before the endocrinologic manifestations.<sup>146,147</sup> Oral candidiasis (thrush; Fig. 23-20) tends to be chronic and has a peak incidence during the first 2 years of life.<sup>148</sup> Candidal infection may also take the form of angular cheilitis (perlèche; Fig. 23-21), hyperplastic or atrophic oral candidiasis, candidal esophagitis, diaper or perianal candidiasis, scalp infection, intertrigo,



**Figure 23-22** *Candida* onychodystrophy. Nail thickening, subungual debris, and culture positivity for *Candida albicans* were present in this young girl with chronic mucocutaneous candidiasis and endocrinopathy.

or nail infection. These changes, taken together, are also referred to as *chronic mucocutaneous candidiasis* (see Chapter 17). When chronic candidal infection occurs in the esophagus or larynx, stricture formation may result. Nail involvement leads to thickening (Fig. 23-22), brittleness, and discoloration with associated inflammation of the periumgual areas (paronychia). Many postpubertal female patients may experience candidal vulvovaginitis.<sup>148</sup> Generalized candidiasis in these patients is rare, but serious lung infection may occasionally occur. Mucocutaneous candidal infections that are unresponsive to topical therapy should be considered an alerting sign for possible APS1.<sup>142</sup>

Alopecia areata occurs in around one-third of patients with APS1,<sup>144</sup> often presents in childhood, and may progress to alopecia universalis. It tends to begin around the peripubertal years. Vitiligo occurs in some patients and is quite variable in extent. The most consistent cutaneous features are those representing ectodermal dysplasia. APS1 patients often have enamel hypoplasia of permanent teeth, and nail dystrophy with pitting affects around half of the patients.<sup>148</sup> They are more prone to dental caries, abscesses, and tooth loss.<sup>149</sup>

The gene mutated in patients with APS1 is termed *AIRE*, for “autoimmunity regulator.” It is localized to the short arm of chromosome 21 and may act as a transcriptional regulator.<sup>140,143</sup> Mutations in *AIRE* result in loss of central tolerance to a number of self-antigens, with impaired clonal deletion of self-reactive thymocytes, which may subsequently attack a variety of host organs.<sup>141,150</sup> Treatments for APS1 include hormone replacement, aggressive treatment for mucocutaneous candidiasis, and close surveillance for the development of additional autoimmune conditions.

## McCune–Albright Syndrome

McCune–Albright syndrome (MAS) is defined clinically as the triad of fibrous dysplasia of bones (polyostotic fibrous dysplasia), patchy cutaneous pigmentation, and various endocrinopathies, most notably precocious puberty. Other associated endocrine disorders include pituitary adenomas (resulting in GH excess), hyperthyroid goiters, and adrenal hyperplasia.<sup>151</sup> Renal phosphate wasting with or without rickets/osteomalacia as well as hepatic and cardiac involvement have also been reported.<sup>152</sup> The endocrinopathies of MAS are all characterized by autonomous excessive hyperfunction of hormonally responsive cells, which respond to signals through activation of the adenylate cyclase system.<sup>153</sup> Activating mutations in the guanine nucleotide-binding (G) protein gene *GNAS*, which encodes a subunit of the G protein that stimulates adenylate cyclase, have been identified in patients with MAS.<sup>154</sup> A postzygotic somatic mutation leads to a mosaic distribution of cells bearing the defect.<sup>151</sup> As mentioned earlier in this chapter, germline inactivating mutations of this same gene are present in patients with AHO (PHP).



**Figure 23-23** Café-au-lait lesions in McCune–Albright syndrome. Well-demarcated tan patches with a ragged border involved the labia majora, thigh, leg, and foot in this 18-month-old female.

The pigmentary lesions of MAS, which are seen in approximately 50% of patients, present as one or more *café-au-lait* macules or patches with a distinct distribution pattern: they rarely extend beyond the midline, and the majority are on the same side of the body as the skeletal lesions.<sup>154</sup> The most common sites of involvement are the buttocks and lumbosacral regions, and lesions may follow the lines of Blaschko. These *café-au-lait* lesions have irregularly ragged or serrated borders (Fig. 23-23) that are described as resembling the “coast of Maine,” in contrast to the *café-au-lait* spots of neurofibromatosis, where the smooth borders are said to resemble the “coast of California.” They are usually present early in life and often are the first sign of this disorder. Bilateral involvement and lack of respect for the midline may occasionally be observed.<sup>155</sup> Diffuse scalp alopecia with histologic features of fibrous dysplasia has been reported.<sup>156</sup>

Fibrous dysplasia is a rare bone disorder that results in bone pain, fractures, bony deformity, and occasionally neurologic compression. It occurs most often as a bone-limited process, and fewer than 5% of patients have concomitant endocrine dysfunction.<sup>157</sup> Most patients with MAS have either solitary or multiple fibrous dysplasia lesions of bone, which tend to develop during the first decade. Although any bone can be involved, the proximal femurs, pelvis, and skull base are most common, and progressive deformity with fractures may occur. Radiographic studies reveal lytic lesions with scalloped borders and a “ground-glass” pattern. Computed tomographic imaging or bone biopsy may be required to confirm the diagnosis in questionable cases. Precocious puberty is a common initial manifestation in girls with MAS (much less common in boys) and is recognized by the development of secondary sexual characteristics before 9 years of age.<sup>154</sup> In males, testicular tumors associated with penile enlargement may be present, and Leydig- and/or Sertoli cell tumors or hyperplasia are common.<sup>152</sup>

## Disorders Associated with Diabetes Mellitus

Diabetes mellitus is a common, chronic disease, and up to 30% of patients with diabetes mellitus may have some form of cutaneous disorder. The exact influences of plasma-glucose homeostasis, insulin resistance, elevated body mass index (BMI), and/or components of

### Box 23-7 Some Cutaneous Associations with Diabetes Mellitus

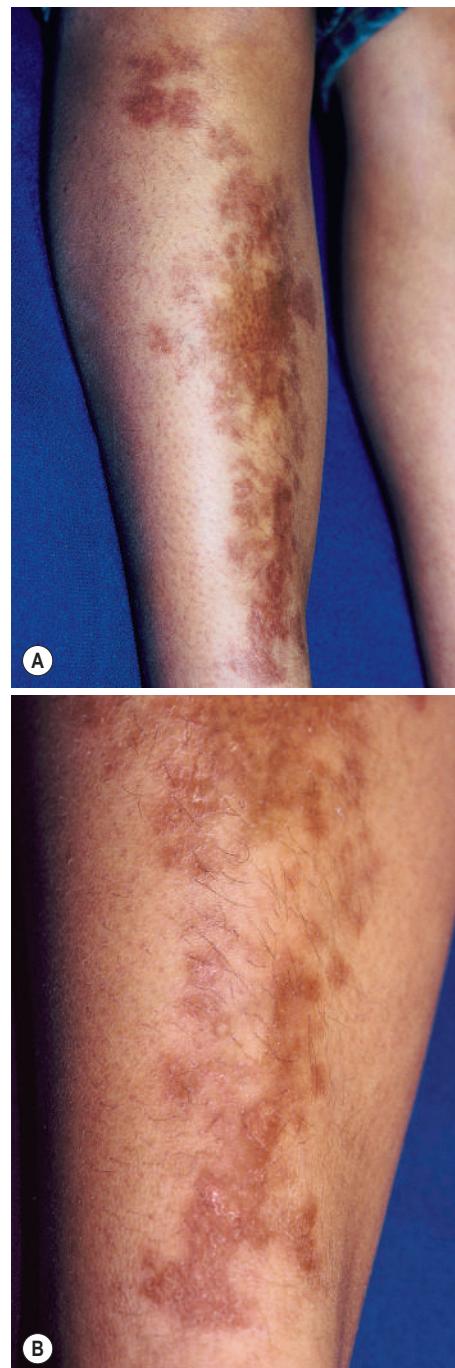
- Established or probable association
  - Necrobiosis lipoidica (NL) diabetorum
  - Diabetic dermopathy
  - Diabetic bullae
  - Acanthosis nigricans
  - Acrochordons (skin tags)
  - Scleredema diabetorum
  - Limited joint mobility and waxy skin syndrome
  - Partial lipodystrophy
  - Malignant otitis externa
  - Neuropathic leg ulcers
  - Perforating disorders
  - Eruptive xanthomas
  - Hemochromatosis
  - Carotenemia
  - Pruritus
  - Xerosis and anhidrosis
  - Yellow nails, koilonychia
- Increased susceptibility to infections:
  - Candida albicans*
  - Staphylococcus aureus*
  - Group A  $\beta$ -hemolytic streptococcus
  - Pseudomonas aeruginosa*
  - Dermatophytes (tinea pedis, onychomycosis)
  - Corynebacterium minutissimum* (erythrasma)
- Possible association
  - Disseminated granuloma annulare
  - Vitiligo

metabolic syndrome on these cutaneous findings are, in many instances, unclear. Some skin findings associated with diabetes mellitus include poor wound healing, necrobiosis lipoidica (NL), DD, diabetic bullae, acrochordons, AN, and the syndrome of limited joint mobility and waxy skin.<sup>158–160</sup> For some skin conditions, the exact association between the disorder and diabetes mellitus is uncertain, and for many, pathogenesis remains unproven. Box 23-7 lists some potential cutaneous associations with diabetes mellitus. A select number of these disorders will be discussed here. The glucagonoma syndrome, which may be associated with mild diabetes mellitus and cutaneous manifestations, is discussed separately in the next section.

### NECROBIOSIS LIPOIDICA DIABETICORUM

Necrobiosis lipoidica (NL; also known as *necrobiosis lipoidica diabetorum*) is a fairly distinct clinical entity that, although not the most common, is the best recognized cutaneous marker of diabetes mellitus.<sup>158</sup> It may be seen outside of the setting of diabetes mellitus, although up to three-quarters of patients with NL have or will have diabetes mellitus; among patients with diabetes mellitus, it occurs in fewer than 1% of patients.<sup>161,162</sup> NL is predominantly seen in females and has an average age of onset of 34 years.<sup>158,163</sup> However, it may occur in children, and its presence may suggest a higher risk for diabetic nephropathy and retinopathy.<sup>164</sup> In up to one-third of patients with NL, these cutaneous lesions may precede the diagnosis (by up to several years) or present simultaneously with diabetes mellitus. NL is most commonly seen in patients who are insulin dependent. The etiology is unclear but may relate to microangiopathy resulting from glycoprotein deposition in the vasculature.

Lesions of NL typically occur in the pretibial areas and are usually asymptomatic. They present as slowly enlarging, irregularly bordered, red to yellow-brown to violaceous plaques (Fig. 23-24). The center often becomes atrophic and more yellow, and there may be superficial telangiectasias, especially later in the course. Older lesions may be primarily brown in color. Multiple lesions are usually present, and ulceration may occur in up to one-third of patients with NL. Skin biopsy can be useful for diagnosis, revealing degeneration of collagen with inflammation and granuloma formation. However, it is preferable to avoid surgical procedures in this location in patients who have diabetes mellitus when possible. The diagnosis is usually strongly suggested in the presence of sharply demarcated, waxy plaques with a red



**Figure 23-24** Necrobiosis lipoidica diabetorum. Waxy, yellow-brown plaques (**A**) were present in this young girl with diabetes mellitus, with subtle atrophy present on closer inspection (**B**).

or violaceous border on the anterior tibial surfaces of a patient with diabetes mellitus. The cause of NL is unclear but may relate to microangiopathy, endarteritis, vasculitis, or delayed hypersensitivity.

The treatment of NL is challenging, and there is no established gold standard of care, because the clinical response to various treatments is quite variable. When there is no ulceration and lesions are relatively asymptomatic, watchful waiting and protection from injury is appropriate.<sup>169</sup> The influence of strict diabetic control on the lesions of NL is controversial. Many have suggested that glucose control has no effect on the appearance or clinical course of NL, whereas others support the opposite hypothesis.<sup>110,161,165</sup> Cosmetic cover-ups are useful for patients in whom the appearance of lesions is

bothersome. Active therapy of lesions has included topical and intralesional corticosteroids, aspirin, dipyridamole, pentoxifylline, clofazimine, cyclosporine, mycophenolate mofetil, systemic corticosteroids, chloroquine, topical tretinoin, hyperbaric oxygen, and topical psoralen plus ultraviolet A (PUVA) light therapy.<sup>163,166–171</sup> Local corticosteroid products should be used with caution, because they may contribute to further atrophy or ulceration. Antiplatelet therapy with aspirin is reportedly quite effective and well tolerated, although this observation has not been confirmed by randomized clinical trials.<sup>165</sup> Pulsed-dye laser has been used and may benefit the telangiectatic and erythematous components.<sup>172</sup> Ulcerated lesions of NL are treated with local wound care, semipermeable wound dressings, and topical or systemic antibiotics. Surgical excision with split-thickness skin grafting may be useful.<sup>173</sup>

### DIABETIC DERMOPATHY

Diabetic dermopathy (DD; also called spotted leg syndrome, shin spots) is the most common cutaneous marker for diabetes mellitus. It is considered by some to be a pathognomonic sign of diabetes mellitus.<sup>174</sup> DD is seen most often in older patients with diabetes mellitus and only occasionally in children. It presents as multiple, well-circumscribed, brown macules and patches with a tendency toward bilateral involvement of the pretibial surfaces. The lesions often become atrophic and take on the appearance of scars. They are occasionally scaly and measure from several millimeters up to 2 cm. Lesions of DD may occasionally occur on the scalp, forearms, or trunk, but the pretibial surfaces are the most common site of involvement in the majority of patients. The etiology of these lesions is unclear, but some have suggested that their presence may be a clinical sign of an increased likelihood of retinopathy, nephropathy, and neuropathy.<sup>175</sup> It may also be associated with large-vessel (i.e., coronary artery) disease.<sup>174</sup> In a histopathologic study of 14 skin biopsies from DD, taken at the time of autopsy in patients with diabetes mellitus, the most common findings were melanin and hemosiderin deposition with arterial or arteriolar wall thickening seen in a minority of specimens.<sup>176</sup>

Lesions of DD are in large part uninfluenced by treatment. Because the condition is asymptomatic, it requires no therapy aside from protection from trauma and supportive wound care should lesions become inflamed or infected. Although lesions may resolve spontaneously, others may appear individually or in asymmetric crops.<sup>153</sup>

### DIABETIC BULLAE

Diabetic bullae are an uncommon association with diabetes mellitus and present as spontaneously arising large blisters with a predilection for the distal extremities. Diabetic bullae are felt to be a distinct marker for diabetes mellitus. The most common location for these bullae is the dorsal and lateral surfaces of the lower legs and feet (Fig. 23-25). Occasionally, patients may have lesions on the hands or forearms.<sup>158</sup> They range in size from less than 1 cm to several centimeters. There is usually no history of trauma, and the lesions usually have no surrounding erythema. These lesions are generally asymptomatic, and healing occurs over several weeks with supportive wound care. They often heal without scarring, although in some patients, atrophy and scarring typical of dystrophic epidermolysis bullosa may result.<sup>163,177</sup>

### ACANTHOSIS NIGRICANS

Acanthosis nigricans (AN) is a symmetric cutaneous eruption consisting of brown, velvety plaques that involve primarily the skin folds. It may be associated with several different clinical settings, including obesity, insulin resistance, various syndromes, malignancy, and medications, as well as occurring as "benign" and mixed types.<sup>178</sup> Table 23-2 summarizes the various clinical associations with AN. The discussion here will focus primarily on AN associated with obesity, insulin resistance, and diabetes mellitus.

AN presents as dark brown, velvety thickening of the skin involving the axillae (Fig. 23-26) and the neck, especially the posterior and lateral neck folds (Fig. 23-27). The initial change is hyperpigmentation followed by eventual thickening with intensification of skin markings.<sup>179</sup> In addition to the characteristic areas of involvement,



**Figure 23-25** Diabetic bullae. These large, painless, tense bullae may occur in the setting of diabetes mellitus, often with no history of preceding trauma.

**Table 23-2** Clinical Associations with and Variants of Acanthosis Nigricans

Association	Comments
"Benign"	Form of epidermal nevus; may be autosomal dominant; associated with multiple nevi
Obesity	Most common type; insulin resistance common; increased incidence of type II diabetes mellitus
Malignancy	Usually adults, rarely observed in children; sudden onset and rapid spread; especially abdominal adenocarcinoma
Syndromes	Multiple syndrome associations, including Bloom, Crouzon, Prader-Willi, Lawrence-Seip, PCOS, Beare-Stevenson; also lupus erythematosus, dermatomyositis, scleroderma
Medications	Niacin, corticosteroids, oral contraceptives, diethylstilbestrol, others
Acral type	Dorsal hands, fingers, feet
Unilateral type	Unilateral distribution or "nevroid"; may persist unchanged or progress to bilateral involvement
Mixed type	Two of the above types occurring together

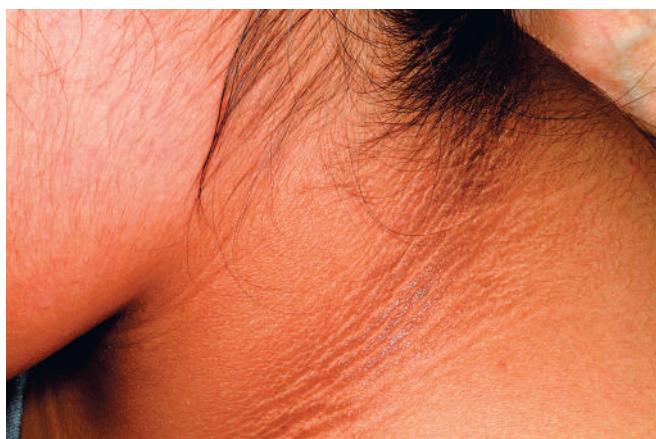
Modified from Schwartz RA. Acanthosis nigricans. J Am Acad Dermatol 1994;31(1):1–19.  
PCOS, Polycystic ovary syndrome.



**Figure 23-26** Acanthosis nigricans. Velvety hyperpigmentation involves the axillae in this patient.



**Figure 23-28** Acanthosis nigricans. Hyperpigmentation with verrucous changes may occasionally occur overlying the knuckles.



**Figure 23-27** Acanthosis nigricans. Velvety hyperpigmentation is present on the lateral and posterior neck folds of this obese teenaged female.

there may be verrucous hyperkeratosis of the knuckles (Fig. 23-28), genitalia, perineum, face, thighs, breasts, and flexural regions of the elbows and knees. Occasionally the eruption of AN may become generalized,<sup>180,181</sup> and mucosal involvement may occur, manifested as thickening and papillomatosis of eyelids, conjunctivae, lips, and oral mucosa. The differential diagnosis of AN may include epidermal nevi, lichen simplex chronicus, postinflammatory hyperpigmentation, erythrasma, and endocrine disorders with hyperpigmentation (Addison disease).

Hyperinsulinemia appears to predispose individuals to AN, and patients with inactivating insulin receptor mutations often have severe involvement.<sup>182</sup> Children with AN often have greater body weight and body fat mass, greater basal and glucose-stimulated insulin levels during oral-glucose tolerance testing, and lower insulin sensitivity. Importantly, after adjusting for body-fat mass and age, the differences in glucose metabolism and insulin studies were less significant in some studies, suggesting that increased BMI should still suggest the possibility of hyperinsulinemia whether or not AN is present.<sup>182</sup> However, other studies have disputed this finding, showing

that AN is associated with hyperinsulinemia and impaired glucose metabolism independent of BMI.<sup>183,184</sup> In a study of 149 overweight Caucasian children, those with AN had greater BMI, waist circumference, and total body fat, but after correcting for age and BMI, there was no evidence for increased abdominal fat.<sup>185</sup> Among African-Americans, AN is strongly associated with obesity and insulin resistance and identifies a subset with a much higher prevalence of NIDDM than is present in African-Americans in the general population.<sup>186</sup> AN is associated with obesity in every ethnic group but occurs with greatest incidence (within the obese population) in Native Americans, followed by African-Americans, Hispanics, and Caucasians.<sup>187</sup> It should be considered a clinical surrogate for laboratory-determined hyperinsulinemia and indicates a high risk for NIDDM.<sup>187,188</sup> As mentioned earlier in this chapter, AN and insulin resistance may also be associated with hyperandrogenism as part of the HAIR-AN syndrome, which may also have as a feature PCOS.

The pathogenesis of AN is unclear. In patients with hyperinsulinemia, insulin may bind to insulin-like growth factor receptors in the epidermis, resulting in papillomatosis (thickening with folding). There are no successful therapies for AN, and the primary focus should be on treatment for the underlying condition. In obesity-associated disease, weight reduction itself seems to reduce the findings of AN. Topical or oral retinoids may benefit some patients, and lactic acid-containing emollients (i.e., LactiCare, AmLactin, Lac-Hydrin) or other keratolytic agents (salicylic acid, urea) may also be useful.

#### Confluent and Reticulated Papillomatosis

Confluent and reticulated papillomatosis (CARP) of Gougerot and Carteaud is briefly discussed here because of its clinical overlap with AN. CARP is a rare disorder characterized by hyperpigmented papules confluent in the center and reticulated at the periphery. They have a characteristic distribution involving the intermammary region (Fig. 23-29) most commonly, as well as the epigastric area (Fig. 23-30) and upper back. Less commonly, the neck, face, and shoulders may be involved. The differential diagnosis may include AN and tinea versicolor. This disorder is seen primarily in adolescents and young adults, and females are involved twice as often as males.

The cause of CARP remains unknown, although there are several speculative theories. An association with insulin resistance has been hypothesized, and the condition has been reported in patients with concomitant AN, obesity, and hyperinsulinemia.<sup>189</sup> However, in most patients, no such association exists. An abnormal host immune response to *Pityrosporum orbiculare* (*Malassezia furfur*) has also been suggested given clinical resemblance to tinea versicolor and the occasional response of patients to treatment with topical or oral antifungal agents, although this association remains controversial.<sup>190,191</sup> Potassium hydroxide examinations on skin scrapings for fungal elements are negative in the majority of patients.<sup>192</sup> A hypopigmented variant of CARP has been described and may be challenging to differentiate clinically from tinea versicolor.<sup>193</sup>



**Figure 23-29** Confluent and reticulated papillomatosis. Hyperpigmented papules and plaques with a reticulate appearance around the periphery involving the intermammary region.



**Figure 23-30** Confluent and reticulated papillomatosis. Reticulate tan papules, patches, and plaques involving the epigastrium, inframammary areas, and sternum.

Treatment of CARP is often but not always successful. A significant proportion of patients seem to respond to minocycline or doxycycline,<sup>194-197</sup> although the mechanism of action is unclear. Minocycline in conjunction with a topical lactic acid-containing emollient is often useful. Other reported therapies of variable effectiveness include topical selenium sulfide shampoo, oral or topical retinoids, oral and topical antifungal agents, topical vitamin D analogues, topical salicylic acid, and topical urea.

## Scleredema Diabeticorum

Scleredema (see Chapter 22) is a rare disorder characterized by diffuse and symmetric induration of the skin. There are two forms: scleredema of Buschke (which tends to occur after upper respiratory infection, especially streptococcal) and the diabetes mellitus-associated form. Scleredema diabetorum occurs most often in middle aged, obese men, although it has been reported in childhood and even in a congenital form.<sup>198</sup> The most common sites are the neck and upper back, but eventual extension to other areas may occur, including the face, scalp, chest, and arms. The skin in affected areas is firm and indurated without pitting and cannot be wrinkled or pressed into folds.<sup>158</sup> The surface appears taut and shiny with loss of normal surface markings. Scleredema is painless but may be uncomfortable for patients given the textural changes and limitation of movement. Occasionally, involvement of the tongue, pharynx, and esophagus may result in dysarthria and dysphagia. Rare associations include pleural, pericardial, or peritoneal effusion, skeletal muscle dysfunction, and paraproteinemia. Histologic evaluation of biopsy tissue characteristically reveals collagen bundles separated by mucin deposits. The course of scleredema diabetorum is variable. It may improve

with control of the diabetes mellitus,<sup>199</sup> although this is inconsistent; in some patients it persists for many years. Therapy is challenging, and the results are often disappointing. Treatments reported include antibiotics, corticosteroids, steroid-sparing immunosuppressant agents, chemotherapy, radiation, light therapy, physiotherapy, and attention to glycemic control.<sup>200,201</sup>

## The Glucagonoma Syndrome

Patients with glucagon-secreting, pancreatic islet  $\alpha$ -cell tumors may have a distinctive dermatosis termed *necrolytic migratory erythema* (NME). The glucagonoma syndrome is characterized by the triad of this cutaneous eruption, a glucagon-secreting tumor, and diabetes mellitus.<sup>202</sup> Weight loss, anemia, and stomatitis are common. Patients with this syndrome are generally middle-aged to elderly, with only rare reports of affected adolescents or young adults.

The cutaneous findings of NME are a hallmark of this syndrome. These skin changes may be present for several years before the diagnosis of glucagonoma is made. Characteristic features include erythema that most often begins in the groin, perineum, and buttocks, with eventual extension to the extremities and perioral areas. The erythematous lesions develop into well-demarcated, annular plaques with scaling, vesicles, and bullae. Erosions and pustules may develop (the latter occasionally studding the periphery of the plaques), and crusting is common. Induration, psoriasisiform changes, lichenification, and bronze pigmentation may occur. The skin lesions of NME evolve sequentially from erythema to blistering to crusting to resolution and are characterized by a pattern of spontaneous remissions and exacerbations.<sup>202</sup> Secondary superinfection with *Staphylococcus aureus* or *Candida* (especially at perineal sites) is common. Patients often appear ill and may have venous thromboses and alopecia. The average 5-year survival rate is less than 50%.<sup>203</sup> The differential diagnosis of NME may include several nutritional deficiency-related dermatoses, staphylococcal scalded-skin syndrome, psoriasis, and toxic epidermal necrolysis.

The diagnosis of NME is suggested by the histologic finding of necrosis of the upper layers of the epidermis. The diagnosis of glucagonoma syndrome is confirmed by finding an elevated serum glucagon level or identifying the neuroendocrine tumor radiographically or histologically. Complete surgical resection of the tumor, when feasible, is the treatment of choice and is usually associated with complete to near-complete resolution of the cutaneous eruption.

The complete list of 203 references for this chapter is available online at <http://expertconsult.inkling.com>.



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The inborn disorders of metabolism are a group of primarily autosomal recessive hereditary disorders that result in metabolic and clinical defects. (More comprehensive discussion of some of these topics is covered elsewhere: disorders of tyrosine metabolism [Richner–Hanhart syndrome], Gaucher syndrome, and multiple sulfatase deficiency are mentioned in Chapter 5; Menkes syndrome in Chapter 7; alkaptonuria in Chapter 11; Fabry disease and fucosidosis in Chapter 12; and Hartnup disease in Chapter 19.) Most developed countries have instituted comprehensive screening programs during the first week of life that allow detection of many of these defects, among them biotinidase deficiency, aminoacidopathies, urea cycle defects, and organic acid disorders.<sup>1</sup>

### **Phenylketonuria**

Phenylketonuria (PKU; phenylpyruvic oligophrenia) is an autosomal recessive disorder of amino acid metabolism characterized by mental retardation, diffuse hypopigmentation, seizures, dermatitis, and photosensitivity (Table 24-1).<sup>2-4</sup> The classic form is caused by a deficiency of phenylalanine hydroxylase or its cofactor, tetrahydrobiopterin. Its incidence has been estimated to be 1 in 10,000 births. Because of mandatory screening in the neonatal period, the disorder is detected early in developed countries, and the clinical features do not appear if early dietary control is achieved. Screening is achieved by a variety of different tests ranging from a semiquantitative bacterial inhibition assay (Guthrie test) to mass spectrometry assays. If missed in the neonatal period by screening, the diagnosis depends on the demonstration of elevated serum levels of phenylalanine (20 mg/dL or higher, 10 to 50 times that of normal), normal or elevated levels of plasma tyrosine (normal is approximately 1 mg/dL), or elevated urinary levels of phenylpyruvic acid. The latter can be detected by a characteristic green or blue color that results when a few drops of urine are added to a 10% solution of ferric chloride. The normal phenylalanine/tyrosine ratio is 1 : 1; in PKU it is greater than 3 : 1. The observed pigmentary dilution is thought to result from the inhibitory effect of phenylalanine on tyrosinase.

Most commonly seen in individuals of northern European ancestry, 90% of affected individuals are blond, blue-eyed, and fair-skinned, given the important role of phenylalanine and its derivative tyrosine in pigment formation. A peculiar musty odor, attributable to decomposition products (phenylacetic acid or phenylacetalddehyde) in the urine and sweat, and early intractable vomiting are characteristic. Infants appear to be normal at birth and if untreated, develop manifestations of delayed intellectual development sometime between 4 and 24 months of age. Seizures, attention-deficit/hyperactivity disorder, hypertonicity, hyperreflexia, a peculiar gait, speech delay, and self-destructive behavior have been described. Skeletal changes include microcephaly, short stature, pes planus, and syndactyly. The dermatitis appears in 10% to 50% of untreated patients and resembles atopic dermatitis; sclerodermoid changes of the proximal extremities, sparing the hands and feet, may present during the first 2 years of life.<sup>5,6</sup> These changes regress with appropriate treatment.

Management consists of a diet low in phenylalanine content, starting at as early an age as possible. This can be initiated by the use of formula from which most of the phenylalanine has been removed or a synthetic amino acid preparation devoid of phenylalanine. Restriction of phenylalanine leads to reversal of the seizures, dermatitis, and pigmentary dilution, but the effect on intellectual function depends on the age at which therapy is initiated. Little benefit for intellectual function can be achieved if therapy is initiated after 2.5 years of age, and optimal benefit is achieved if it is initiated by 2 months of age. It should

be remembered that phenylalanine is high in many foods and is a metabolite of the sweetener aspartame. Children and adolescents with PKU who achieve dietary control early in life are well adjusted and have an excellent quality of life.<sup>7</sup> Sapropterin dihydrochloride may reduce phenylalanine levels in patients who do not adequately adhere to the prescribed diet<sup>8</sup> and has been shown to significantly improve within 4 weeks the attention-deficit hyperactivity disorder and executive function of patients.<sup>9</sup>

Although there is some controversy about continuation of phenylalanine restriction in later childhood and adults, lack of dietary control during the 1st trimester of pregnancy of affected mothers (>600 µM or 10 mg/dL phenylalanine) has led to cardiac defects in 15% of offspring, particularly coarctation of the aorta and hypoplastic left heart.<sup>10</sup> Optimal levels during pregnancy of 120 to 360 µM/L are recommended. Some patients maintain low levels of phenylalanine as adults without dietary manipulation.

### **Disorders of Tyrosine Metabolism**

Clinical disorders of tyrosine metabolism include neonatal tyrosinemia, tyrosinemia I, and tyrosinemia II (Richner–Hanhart syndrome). Of these, only Richner–Hanhart syndrome exhibits cutaneous manifestations and is described in Chapter 5. These include palmoplantar keratoderma with painful erosions and photophobia with corneal erosions.

### **Cobalamin Deficiency**

In a single patient, a metabolic disorder of vitamin B<sub>12</sub> (cobalamin), called *cbfJ*, resulted from biallelic mutations in *ABCD4*, which encodes an ABC transporter involved in the intracellular processing of cobalamin.<sup>11</sup> Features were prominent, diffuse progressive skin hyperpigmentation, but hair lightening, with macrocytic anemia and cobalamin deficiency. Treatment with oral cobalamin (3 mg daily for this 12-year-old) led to metabolic correction and some reduction in the skin hyperpigmentation.

### **Homocystinuria**

Homocystinuria is an autosomal recessive disorder of methionine metabolism that results from an absence or deficiency of cystathione β-synthase, the pyridoxine-dependent hepatic enzyme that catalyzes the formation of cystathione from homocysteine and serine.<sup>12</sup> Based on biochemical testing, the disorder is most common in Ireland (1 in 65,000 births) and has a worldwide incidence of 1 in 344,000.<sup>13</sup> However, a study in Norway using genotyping showed an estimated birth prevalence of 1 in 6400.<sup>14</sup>

The disorder affects predominantly the eyes, central nervous system, blood vessels, and bones (see Table 24-1). Subluxation of the ocular lenses (ectopia lentis) occurs in 82% of patients by 15 years of age<sup>15</sup> and is usually present by 10 years of age. Developmental delay is evident during infancy and most untreated patients develop seizures and significant retardation. Bony abnormalities include a body habitus similar to that seen in Marfan syndrome (see Chapter 6), and generalized osteoporosis, which is seen radiographically in 50% of affected individuals by 15 years of age. Platyspondylia (congenital flattening of the vertebral bodies) and hollowing out of the vertebral bodies by pressure of the vertebral disks are also seen radiographically, and kyphoscoliosis, pectus carinatum, and genu valgum are common.

**Table 24-1** Errors of Protein Metabolism

<b>Disorder</b>	<b>Inheritance</b>	<b>Defect</b>	<b>Clinical Features</b>	<b>Diagnosis</b>	<b>Treatment</b>
Phenylketonuria	AR	Phenylalanine hydroxylase	90% are blond, blue-eyed, and fair-skinned; musty odor; sclerodermatosus plaques; eczematous dermatitis; photosensitivity; retardation; microcephaly; short stature	Guthrie test, ferric chloride test	Low phenylalanine diet; sapropterin dihydrochloride
Homocystinuria	AR	Cystathione synthetase	Ectopia lentis, myopia, arachnodactyly, seizures, mental retardation, cerebrovascular accidents, sparse light or blond easily friable hair, malar flush, wide-pored facies, livedoid rash, "Charlie Chaplin-like" gait and "rocker-bottom" feet	Cyanide nitroprusside test	Low methionine diet with pyridoxine (vitamin B <sub>6</sub> )
Alkaptonuria (ochronosis)	AR	Homogentisic acid oxidase	Dark urine; blue to brownish-black pigment on nose, malar region, sclerae, ears, axillae, genitalia; staining of clothing ("beads of ink" perspiration); arthritis; contractures; rupture of Achilles tendon; mitral and aortic valvulitis and/or calcific aortic stenosis	Ferric cyanide reduction	Nitisinone
Trimethylaminuria	AR	Flavin mono-oxygenase type 3	Odor of rotting fish	Trimethylamine in urine	Dietary avoidance of choline
Wilson disease (hepatolenticular degeneration)	AR	ATP7B; ceruloplasmin metabolism	Kayser–Fleischer rings, hyperpigmentation, azure lunulae, neurologic and liver dysfunction	Aminoaciduria, decreased ceruloplasmin	Chelating agents (BAL, versenate, or D-penicillamine; trientine has fewer side effects, but is weaker and more expensive); zinc to sequester copper
Lesch–Nyhan syndrome	X-LR	HPRT deficiency	Mental retardation, spastic cerebral palsy, choreoathetosis, self-mutilation	Increased uric acid, orange uric acid crystals in diaper	Allopurinol

AR, Autosomal recessive; BAL, British antilewisite or dimercaprol; HPRT, hypoxanthine-guanine phosphoribosyl transferase; X-LR, X-linked recessive.

Some patients have rocker-bottom feet and most have a shuffling toe-out "Charlie Chaplin-like" gait. Megaloblastic anemia has also been described.<sup>16</sup>

The vascular complications can be life-threatening; the chance of a vascular event during childhood is 25% to 30% and increases to 50% by 30 years of age. These include pulmonary embolism, myocardial infarction, transient ischemic attacks, cerebrovascular accidents, abdominal aortic aneurysm, and venous thromboses. Cutaneous features include sparse, light or blond, coarse hair that can darken and become softer with treatment; a malar flush; coarse, wide pores on facial skin; and a reticulated livedoid vasculopathy (*cutis reticulata*) on the face and extremities.

The presence of homocystinuria is suggested by the clinical features and can be confirmed by a urinary cyanide or sodium nitroprusside testing (turns a beet-red color) and by amino acid chromatography of the serum and urine. The presence of homocystine in the urine establishes the diagnosis. In the blood, homocysteine and methionine are elevated, whereas cysteine levels are decreased. Unfortunately, there are no neonatal manifestations of homocystinuria, and not all newborns with this disorder have increased blood methionine levels.

In at least 50% of patients, the disease is responsive to pyridoxine and can be controlled with the combination of pyridoxine (vitamin B<sub>6</sub>; 150 mg/day for an infant to 500 mg/day for an adolescent), folic acid, and vitamin B<sub>12</sub> (cobalamin). For those who do not respond to vitamins alone, a methionine-restricted, cystine-supplemented diet is required as well.<sup>17</sup> Betaine, a methyl donor that remethylates homocysteine to methionine, has been used as an adjunct to treatment, especially in patients who do not respond to vitamin therapy. As with PKU, early institution of therapy dramatically reduces the risk of complications.

## Trimethylaminuria

Trimethylaminuria (the fish odor syndrome) is a metabolic disorder in which accumulation of trimethylamine in the sweat and urine gives rise to an unpleasant "rotting fish" odor to the skin, sweat, and urine. There are no visible cutaneous changes, but one-third of patients with an unexplained intermittent malodor were shown to be positive for the disorder using a standard choline challenge.<sup>18</sup>

The disorder results from mutations in the flavin-containing monooxygenase type 3 (*FM03*) gene.<sup>19</sup> The liver is unable to convert the trimethylamine generated in the intestinal tract by bacterial degradation of choline- and lecithin-containing foods such as saltwater fish and seafood, egg yolk, liver, kidney, soy beans, meat, broccoli, cauliflower, cabbage, Brussels sprouts, wheat germ, milk (from wheated cows), and yeast to the nonodorous oxide metabolite.<sup>20</sup> The psychosocial effects of the condition can be devastating, including disruption of schooling, clinical depression, and attempted suicide. Treatment is best accomplished by avoidance and limitation of choline-containing foods,<sup>17,21</sup> although administration of metronidazole has also led to a clinical and biochemical response.<sup>22</sup>

## Wilson Disease (Hepatolenticular Degeneration)

Wilson disease is an autosomal recessive disorder that results from mutations in *ATP7B*, which encodes a copper-transporting adenosinetriphosphatase (ATPase).<sup>23</sup> Deficiency leads to an inability to

synthesize normal amounts of ceruloplasmin.<sup>24,25</sup> Patients show abnormal hepatic excretion of copper and toxic accumulations of copper in the liver, brain, and other organs. The clinical triad that results consists of progressive neurologic dysfunction, hepatic cirrhosis, and pathognomonic pigmentation of the corneal margins (Kayser–Fleischer ring) (see Table 24-1).

The disorder can be detected as early as 4 years of age but usually manifests during adolescence. The clinical signs at presentation can be quite varied. Although initial signs of the disorder are often neurologic (intention tremors, dysarthria, ataxia, incoordination, personality changes, psychiatric problems, and worsening school performance and handwriting), signs of liver insufficiency (jaundice, ascites, hepatomegaly, hematemesis, and cutaneous spider angiomas) are present at onset in 40% to 50% of affected individuals.<sup>26</sup>

Hyperpigmentation of the anterior lower legs, genital region, or even in a generalized distribution<sup>27</sup> may be the presenting sign and may be misinterpreted as Addison disease. In addition, patients may manifest a vague greenish discoloration on the skin of the face, neck, and genitalia. Increased melanin deposition, but not copper or iron, is seen in cutaneous biopsy specimens. Blue or azure lunulae of the nails have been reported in individuals with this disorder, but also have been observed in normal individuals as a complication of phenolphthalein or quinacrine ingestion, and in argyria. White discoloration of the nails has also been noted.<sup>28</sup> Xerosis has been described in 45.7% of affected children.<sup>28</sup>

Kayser–Fleischer rings are seen as dense golden brown or greenish brown pigmentation localized near the limbus of the cornea. Occurring in about 95% of patients with this disorder and best visualized by side lighting and slit-lamp examination, this discoloration is produced by the deposition of copper in the Descemet membrane at the periphery of the cornea. Kayser–Fleischer rings may also be seen in other copper overload states such as primary cirrhosis, intrahepatic cholestasis of childhood (Byler syndrome), and chronic active hepatitis.

Hepatolenticular degeneration is a progressive disease, and if untreated, is inevitably fatal. Death usually results from infection, hepatic disease, or liver failure. Treatment depends on removal of accumulated copper deposits in the body. Chelating agents such as D-penicillamine or trientine (triethylene tetramine dihydrochloride)<sup>29</sup> and elemental zinc (1 to 3 mg/kg per day divided three times daily) are helpful. Because discontinuation of therapy can result in rapid deterioration, treatment is life long. Penicillamine can produce allergic or toxic reactions, fever, cutaneous rashes, leukopenia, thrombocytopenia, elastosis perforans serpiginosa<sup>30</sup> (see Chapter 6; Fig. 6-13), other dermal disorders,<sup>31</sup> and immunobullous skin disease.<sup>32</sup> Because penicillamine inhibits pyridoxine-dependent enzymes, patients should also be given daily supplements of pyridoxine (12.5 to 50 mg/day). In an effort to minimize copper deposition, patients should be encouraged to limit their ingestion of copper-rich foods such as liver, nuts, chocolate, cocoa, mushrooms, brain, shellfish, dried foods, and broccoli. Liver transplantation can be life saving for patients with hepatic failure.<sup>33,34</sup>

## Lesch–Nyhan Syndrome

Lesch–Nyhan syndrome, an X-linked recessive disorder of purine metabolism, is characterized by mental retardation, choreoathetoid movements, and self-mutilation.<sup>35</sup> The condition is caused by a deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT),<sup>36</sup> which leads to an overproduction of uric acid and the clinical features associated with this disorder (Table 24-1). Patients appear normal at birth and may develop normally for 6 to 8 months. The first recognizable sign of the disease is often orange uric acid crystals (resembling grains of sand) in the diaper or as hematuria during the early months of life.

The onset of cerebral manifestations may be subtle, with difficulty in sitting or standing without help, involuntary movements, dystonia, spasticity, and increased deep tendon reflexes. Although mental retardation may vary in degree, it usually is severe, and abnormal behavior remains a striking characteristic of the disease. The main clinical feature of this disorder is a loss of tissue about the mouth or fingers that occurs, not because of an inability to feel pain, but as a result of

the child's habit of compulsive self-destructive biting of these areas. In time, without adequate restraints, all of the lower lip accessible to the teeth may be chewed away. The face, fingers, and wrists may also be mutilated, and because young children commonly bite others, caution should be exercised when handling children with this disorder. Other destructive behaviors include head banging, extension of arms when being wheeled through doorways, tipping of wheelchairs, eye-poking, fingers in wheelchair spokes, and rubbing behaviors. Other manifestations of hyperuricemia, such as tophaceous deposits, nephropathy, and gouty arthritis, occur later. Reticulated pigment changes in a variant form have been described.<sup>37</sup>

Not to be confused with familial dysautonomia (Riley–Day syndrome) and congenital insensitivity to pain with anhidrosis (see Chapter 8), other conditions characterized by biting and self-mutilating behavior, Lesch–Nyhan syndrome can be confirmed by the clinical presentation and laboratory demonstration of increased levels of uric acid in the blood and urine.<sup>38</sup> Heterozygous females are asymptomatic. Management includes the use of allopurinol (in dosages of 10 mg/kg per day or, if >10 years of age, 600 to 800 mg/day divided twice daily) in an effort to control uric acid levels. Physical restraints (hand bandages and elbow splints) may be used to help control the self-mutilating behavior of patients.<sup>35</sup> Lip biting may require extraction of deciduous teeth, but permanent teeth should be spared, because lip biting usually diminishes with age.

## Dermatitis From Nutritional Abnormalities

### ACRODERMATITIS ENTEROPATHICA

Acrodermatitis enteropathica is an autosomal recessive disorder that generally appears in early infancy and is characterized by a triad of acral and periorificial skin lesions (vesiculobullous, pustular, and eczematous), diarrhea, and alopecia (Table 24-2).<sup>39-41</sup> The condition first becomes manifest days to weeks after birth if an infant is bottle-fed and shortly after weaning if breastfed. The disorder results from mutations in *SLC39A*, which encodes an intestinal zinc transporter ZIP4.<sup>42</sup>

The basic cutaneous lesion of acrodermatitis enteropathica is an erythematous, scaling, crusted, psoriasiform, eczematous, or vesiculobullous eruption (see Fig. 2-29). Lesions tend to be localized around the body orifices (mouth, nose, ears, eyes, and perineum; Fig. 24-1) and symmetrically located on the buttocks (Fig. 24-2) and extensor surface of major joints (elbows, knees, hands, and feet), the scalp, and the fingers and toes (hence the term *acrodermatitis*). On the face, the eroded and crusted peribuccal plaques may appear impetiginized, and



**Figure 24-1** Acrodermatitis enteropathica. Moist, sharply marginated psoriasiform plaques around the mouth, nose, and eyes of an infant.

**Table 24-2** Genetic and Acquired Nutritional Disorders

Disorder	Cause	Features	Evaluation	Therapy
Zinc deficiency	Acrodermatitis enteropathica Decreased zinc in breast milk Malabsorption Zinc-poor IV hyperalimentation	Periorificial dermatitis, stomatitis, glossitis, alopecia, irritability, diarrhea, failure to thrive, candidal infection, photophobia	Zinc levels, serum alkaline phosphatase; zinc levels in maternal breast milk	Zinc supplementation
Biotin deficiency	Holocarboxylase deficiency Biotinidase deficiency Malabsorption Ingestion of egg whites Biotin-poor IV hyperalimentation	Periorificial dermatitis, conjunctivitis, blepharitis, alopecia, candidal infections, metabolic acidosis, vomiting, lethargy, developmental delay, seizures, ataxia, optic atrophy, hearing loss	Urinary organic acids, plasma ammonia and lactate, serum biotin, specific enzyme activity	Biotin supplementation
Deficiency of vitamin B <sub>12</sub> or isoleucine from restrictive diets	Organic acidurias Citrullinemia Maple syrup urine disease Methylmalonic acidemia Propionic acidemia	Periorificial dermatitis, alopecia, candidal infections, metabolic acidosis, vomiting, failure to thrive, lethargy, developmental delay, hypotonia, pancytopenia	Urinary organic acids; plasma ammonia and glycine levels, plasma isoleucine levels	Dietary manipulation (results from effects of low-protein diet; some respond to vitamin B <sub>12</sub> supplementation)
Cystic fibrosis	Deficiency of CFTR	Periorificial and truncal dermatitis, occasionally alopecia, failure to thrive, diarrhea, irritability, edema	Sweat test, serum albumin, gene analysis, mutational analysis of <i>CFTR</i> gene	Pancreatic enzymes, vitamin and zinc supplementation
Essential fatty acid deficiency	Inadequate dietary intake	Generalized scaling with underlying erythema, intertriginous erosions, alopecia, decreased pigmentation of hair, failure to thrive, thrombocytopenia, and anemia	Plasma linoleic, linolenic, arachidonic and icosatrienoic acid levels; check for other deficiencies	Supplementation of essential fatty acids
Kwashiorkor	Inadequate protein; often infants taken off milk protein for allergies or dietary fads without adequate replacement	Superficial desquamation with erosion (flaky paint), edema with moon faces and pallor, hyperpigmentation and hypopigmentation, ecchymoses, sparse, dry lusterless hair with decreased pigmentation and "flag sign", cheilitis, dry mucosae, irritability and failure to thrive, irritability and apathy, secondary skin infections, diarrhea, hepatomegaly	Serum albumin, good dietary history	Slow supplementation with protein, correction of electrolyte imbalances

*CFTR*, Cystic fibrosis transmembrane conductance regulator; *IV*, intravenous.



**Figure 24-2** Acrodermatitis enteropathica. Sharply marginated psoriasis-like plaques of the perianal area and buttock.

secondary infection with *Candida albicans* is common. When the fingers and toes are involved, there is marked erythema and swelling of the paronychial tissues, often with subsequent nail deformity. If unrecognized or untreated, acrodermatitis enteropathica follows an intermittent but relentlessly progressive course, and as a consequence of general disability, infection, or both, commonly ends in death.

Typically, infants with acrodermatitis enteropathica are listless, anorexic, and apathetic. Many infants show frequent crying, irritability, and restlessness. Tissue wasting is present with an associated failure to thrive. During periods of exacerbation, frothy, bulky, foul-smelling diarrheal stools are present. Other findings include conjunctivitis, photophobia, stomatitis, perlèche, nail dystrophy, recurring candidal or bacterial infection, and alopecia of the scalp, eyelashes, and/or eyebrows.<sup>43</sup> Children suffering from this disorder exhibit a striking uniformity of appearance, mainly because of the alopecia and periorificial lesions.

In addition to the classic inherited disease, zinc deficiency with signs mimicking acrodermatitis enteropathica may also occur in babies who are breastfed by mothers with inadequate secretion of zinc in the maternal milk.<sup>44</sup> Maternal mutations in *SLC30A2* (*ZnT-2*), which

encodes a protein required for zinc secretion, have been found.<sup>45</sup> Zinc deficiency with clinical manifestations may also be seen in individuals receiving long-term parenteral nutrition with inadequate zinc supplementation, patients who have had intestinal bypass procedures, premature infants with low zinc storage (particularly those fed exclusively with human milk), in patients with Crohn disease,<sup>46</sup> in infants with human immunodeficiency virus (HIV) infection and diarrhea (causing inadequate absorption of zinc), in patients with cystic fibrosis with poor zinc absorption,<sup>47,48</sup> patients with celiac disease,<sup>49</sup> chronic alcoholics or patients with anorexia nervosa,<sup>50</sup> in individuals on zinc-deficient vegetarian diets, and in patients with low pancreatic enzyme levels resulting in poor intestinal absorption of zinc.<sup>41,51</sup> In babies with cystic fibrosis, the manifestations of zinc deficiency typically are noted at 3 to 5 months of age, before any evidence of pulmonary disease. The low serum albumin level and abnormal sweat test can confirm the diagnosis. An acrodermatitis enteropathica-like eruption can be seen with biotin deficiency and kwashiorkor.

The diagnosis of acrodermatitis enteropathica is based on the clinical features and low serum zinc levels (50 mcg/dL or lower). It should be noted, however, that zinc contamination of glass tubes and rubber stoppers often occurs; blood samples should be collected in acid-washed sterile plastic tubes with the use of acid-washed plastic syringes. Low serum alkaline phosphatase levels (even when the serum zinc level is normal), low serum lipid levels, and defective chemotaxis may be found. Skin biopsy is not diagnostic but may be useful in some patients. Zinc levels can also be measured in maternal milk.

Zinc sulfate supplementation is provided at 5 to 10 mg/kg per day, which usually provides approximately 1 to 2 mg/kg per day elemental zinc, although the dosage may differ to provide sufficient elemental zinc if other formulations are used. When given in divided doses two or three times a day, improvement in temperament and decrease in irritability can generally be noted within 1 or 2 days; the appetite improves in a few days, and diarrhea and skin lesions begin to respond within 2 or 3 days after the initiation of therapy. Hair growth begins after 2 to 3 weeks of therapy, and increase in the growth of the infant generally occurs within approximately 2 weeks. After the patient's condition appears to be stabilized, zinc levels should be monitored at periodic (6-month) intervals, followed by the adjustment of supplemental zinc to the lowest effective dosage schedule. Because foods may have an effect on the absorption of zinc, zinc supplementation should be administered 1 or 2 hours before meals. Zinc supplementation can cause gastrointestinal upset (nausea, vomiting, gastric hemorrhage); zinc gluconate tends to cause fewer gastrointestinal problems. Less zinc supplementation may be required for acquired or dietary zinc deficiency. In infants who have zinc deficiency as a result of defective maternal mammary zinc secretion, zinc supplementation can be discontinued after weaning.

## Disorders That Resemble Acrodermatitis Enteropathica

### BIOTIN DEFICIENCY/ORGANIC ACID DISORDERS

A dermatitis resembling acrodermatitis enteropathica, often in association with alopecia and changes in hair texture, has been described in patients with biotin deficiency and in certain organic acid disorders.<sup>52,53</sup> The cutaneous features resembling acrodermatitis enteropathica have been described in methylmalonic aciduria,<sup>54</sup> propionic acidemia,<sup>54</sup> glutaric aciduria type I,<sup>55</sup> maple syrup urine disease,<sup>56</sup> ornithine transcarbamylase deficiency,<sup>57</sup> and citrullinemia,<sup>58</sup> because of dietary restriction and deficiency of amino acids, especially isoleucine (Fig. 24-3).<sup>59,60</sup> Acrodermatitis enteropathica-like eruptions have also been reported in children with Hartnup disease (see Chapter 19).<sup>61,62</sup>

Biotin, part of the vitamin B complex, is required for the function of four carboxylase enzymes<sup>51</sup>:

1. 3-Methyl crotonyl-CoA carboxylase, essential for the catabolism of leucine
2. Propionyl CoA carboxylase, essential for the catabolism of isoleucine, threonine, valine, and methionine



**Figure 24-3** Methylmalonic aciduria. **(A)** This patient developed the typical erosive and desquamative eruption while on a restricted diet. **(B)** Isoleucine deficiency was discovered, and the eruption cleared within a week when isoleucine was added to the diet.

3. Pyruvic acid carboxylase, required for the gluconeogenesis and regulation of carbohydrate metabolism
4. Acetyl CoA carboxylase, an enzyme of long-chain fatty acid synthesis that contains biotin.

Biotin deficiency may be induced by a biotin-deficient diet; that is, a diet in which patients ingest large quantities of raw egg white (which contains the protein avidin that binds to biotin, thus preventing its absorption in the intestine) and/or prolonged parenteral nutrition to which biotin has not been added (see Table 24-2). The resulting deficiency is manifested by anorexia, lassitude, a pale tongue, grayish pallor of the skin, atrophy of the lingual papillae, hair loss, anemia, muscle pains, dryness of the skin, and a scaly dermatitis, all of which disappear after biotin administration or by cooking, boiling, or steaming of egg white (which causes avidin to lose its biotin-binding capacity). Decreased biotin levels have also been noted in patients who have been administered antiepileptics (phenytoin, carbamazepine), and may result in seborrheic dermatitis and alopecia.<sup>63,64</sup>

Several autosomal recessive disorders may manifest as an acrodermatitis enteropathica-like eruption, because they require biotin as a cofactor. Cheilitis and diffuse erythema with erosions and desquamation are features of methylmalonic aciduria before therapeutic amino acid restriction.<sup>65</sup> Inherited biotin deficiency also occurs in two forms of multiple carboxylase deficiency, one of which presents acutely during the neonatal period (neonatal form), and the other that



**Figure 24-4** Biotin deficiency. Scaly, periorificial dermatitis in a child with biotin-responsive carboxylase deficiency.<sup>67</sup>



**Figure 24-5** Kwashiorkor. Sharply marginated raised edge of reddish-brown scaling (flaky paint dermatosis) on the arm of an infant with severe hypoalbuminemia from dietary deficiency.

presents during early infancy (juvenile form).<sup>66</sup> These disorders occur in up to 1 : 40,000 births. Both forms usually show a sharply marginated, brightly erythematous scaling eruption of the periorificial areas, scalp, eyebrows, and eyelashes (Fig. 24-4).<sup>67</sup> Alopecia can manifest as hair thinning or total alopecia. Secondary candidiasis is not uncommon.<sup>68</sup> The neonatal form, which results from deficiency of holocarboxylase synthetase, appears in the first few weeks of life with metabolic acidosis, ketosis, and rarely, cutaneous manifestations. Patients show feeding and breathing difficulties, seizures, hypotonia, and lethargy; without early diagnosis and treatment, they usually die. The juvenile form of the disorder, which first manifests at 2 months of age or older, is the result of deficiency of biotinidase, which is required for recycling of endogenous biotin. Patients have low levels of biotin in the blood and urine and impaired biotin absorption and/or transport. In addition to the cutaneous features, the juvenile form is characterized by seizures (especially myoclonic spasms that respond partially to antiepileptics), hyperventilation or apnea, recurrent infections (including candidal skin infections), keratoconjunctivitis, ataxia, hypotonia, glossitis, and life-threatening acidosis and massive ketosis. More than 50% of patients whose disease is not recognized early have hearing loss that does not improve with biotin therapy.

The diagnosis of biotin deficiency can be established by a decreased concentration of plasma biotin. Deficiencies of biotinidase or holocarboxylase synthetase also show an increase in the urinary metabolites 3-hydroxyisovaleric acid, 3-methylcrotonyl-glycine, 3-hydroxypropionic acid, methylcitric acid, and lactic acid. Biotin deficiency can be treated by intravenous multivitamins containing 60 mcg of biotin or by the oral administration of 5 to 10 mg of biotin daily. Higher concentrations of biotin may be required for holocarboxylase synthetase deficiency.<sup>69</sup> Skin and neurologic signs tend to improve within a few weeks, although neurologic dysfunction can be permanent if treatment is delayed.

## KWASHIORKOR

Kwashiorkor is a severe form of protein deficiency in which edema, hypoalbuminemia, and dermatosis predominate.<sup>70</sup> Seen primarily in underdeveloped countries, several cases of kwashiorkor have been described in developed countries as well.<sup>71,72</sup> Cases in developed countries have been described because of nutritional ignorance, food allergen avoidance, food fads, and child abuse.<sup>73</sup> Particularly common is the substitution of rice "milk," which has only a minuscule content of protein and is not a milk substitute.<sup>74</sup> In children with chronic protein and caloric malnutrition, particularly from Africa, signs usually present during the second or third year of life with the onset of



**Figure 24-6** Kwashiorkor. Note the brown, peeling, "flaky paint" appearance of the posterior aspect of the upper thighs.

weaning from breastfeeding. In contrast, patients in developed countries most commonly show features during the first year of life with a rapid onset of edema. Kwashiorkor has also been described with malabsorption disorders, including infantile Crohn disease<sup>75</sup> and cystic fibrosis.<sup>76</sup>

The clinical picture consists of a blanching erythema with an overlying reddish-brown scale that shows a sharply marginated raised edge. This edge resembles paint that is lifting up and about to peel off, leading to the term *flaky paint dermatosis* (Figs. 24-5 and 24-6). In contrast to lesions of pellagra, the dermatosis seldom appears on areas exposed to sunlight and tends to spare the feet and dorsal areas of the hands. Photosensitivity, purpura, and excessive bruising may also be present. Other associated features include changes in mental behavior, anorexia, apathy, irritability, growth retardation, and fatty infiltration of the liver with hypoproteinemia. As a result of the hypoalbuminemia, affected children show edema of the face (moon facies) (Fig. 24-7), feet, and abdomen (potbelly appearance).

In mild cases the cutaneous eruption is associated with a superficial desquamation; in severe cases there are large areas of erosion that have been mistaken for Stevens-Johnson syndrome and/or toxic epidermal necrolysis.<sup>77</sup> As the disease progresses, the entire cutaneous surface develops a reddish or coffee-colored hue. Other associated



**Figure 24-7** Kwashiorkor. Moon facies and generalized dermatosis.



**Figure 24-8** Kwashiorkor. The hair often loses its coloration and may become gray or straw-colored.

features include circumoral pallor, loss of pigmentation (especially after minor trauma), and depigmentation of the hair. In darker haired children, the hair color can change to a reddish-brown hue or even gray or straw color (Fig. 24-8). The dyschromia with hypopigmentation has been attributed to deficiency of tyrosine, which is critical for melanin synthesis. When periods of malnutrition alternate with intervals of adequate dietary intake, alternating bands of light and dark color (the flag sign) are produced in the hair.

The condition may be difficult to distinguish from acrodermatitis enteropathica, and in fact, children may have concomitant zinc deficiency as well. The hypoalbuminemia and edema are helpful signs to distinguish kwashiorkor from acrodermatitis enteropathica and other disorders of nutritional deficiency. Children with marasmus have both protein and caloric deficiency. They appear emaciated (vs. the edematous appearance of children with kwashiorkor), have dry, scaling skin that may show follicular hyperkeratosis, and often have thin, sparse hair.

Children afflicted with kwashiorkor are extremely ill, and if they are not treated, the mortality rate can be 30% or more, primarily resulting from infection (impairment of immunity) and electrolyte imbalance

with diarrhea. In underdeveloped countries where the disorder is common, breastfeeding should be continued for as long as possible to prevent the protein malnutrition. Treatment of affected individuals with gradual administration of a high-protein diet, vitamin supplementation, and correction of dehydration and electrolyte imbalance leads to resolution of the clinical abnormalities.

### ESSENTIAL FATTY ACID DEFICIENCY

Essential fatty acid deficiency (EFA) can also be manifested by periorificial dermatitis and a generalized xerotic or eczematous dermatitis (see Table 24-2).<sup>78</sup> Failure to thrive, alopecia with lightly colored hair, and thrombocytopenia are other signs that may occur. The condition usually occurs in patients receiving parenteral nutrition without lipid supplementation, in association with severe fat malabsorption from gastrointestinal disorders, or with surgery of the gastrointestinal tract. EFA has also been described in patients with cystic fibrosis, anorexia nervosa, and acrodermatitis enteropathica. Decreased plasma levels of linoleic, linolenic, arachidonic, and icosatrienoic acid, as well as an icosatrienoic/arachidonic acid ratio of greater than 0.4 confirms the diagnosis. The treatment consists of oral or parenteral fat emulsions. If these cannot be administered, topical application of 2 to 3 mg/kg soybean or safflower oil may be sufficient to restore plasma levels of linoleic acids but may not maintain stores in the liver or other tissues.<sup>79</sup>

## The Hyperlipidemias

The hyperlipidemias (hyperlipoproteinemias) represent a group of metabolic diseases characterized by persistent elevation of plasma cholesterol levels, triglyceride levels, or both. Because plasma lipids circulate in the form of high molecular-weight complexes bound to protein, the term *hyperlipidemia* also indicates an elevation of lipoproteins, hence justification for the term *hyperlipoproteinemia* for this group of disorders. The dermatologic manifestation is the xanthoma, which may also be seen in metabolic disorders with normal levels of lipids (sitosterolemia and cerebrotendinous xanthomatosis) and disorders with deficiencies in high-density lipoproteins. Xanthomas can provide a clue that a child has a serious lipid abnormality and is at risk for other abnormalities, particularly vascular disease.

Lipid levels can be assayed in blood samples taken after a 12-hour fast. Plasma lipoproteins differ significantly in electrostatic charges, thus permitting their separation by electrophoretic mobility techniques into four major fractions: chylomicrons and  $\beta$ -, pre- $\beta$ -, and  $\alpha$ -lipoproteins. By means of ultracentrifugation it is also possible to separate the plasma lipoproteins into four major groups: chylomicrons and very low-density lipoproteins (VLDL; including the pre- $\beta$ -mobility lipoproteins), low-density lipoproteins (LDL, the  $\beta$ -mobility lipoprotein), and high-density lipoprotein (HDL; the  $\alpha$ -mobility lipoprotein), which correlate well with those separated by electrophoresis. Triglycerides are the major core lipids of chylomicrons and VLDLs. Cholesterol esters predominate in the core of LDLs. HDLs, remnants of VLDLs (also known as *intermediate-density lipoproteins* or *IDLs*), and chylomicrons. Apolipoproteins mediate the binding of lipoproteins to their receptors in target organs and activate enzymes that metabolize lipoproteins (Table 24-3). The levels of lipoproteins allow classification of the familial hyperlipidemias into five groups, designated as hyperlipoproteinemias I through V (World Health Organization [WHO]/Frederickson classification system), each with its own specific clinicopathologic, prognostic, and therapeutic features (Tables 24-4 and 24-5). Of these, types I and II most commonly present during childhood.

Lipoproteins can be synthesized from dietary intake or made endogenously in the liver. Dietary triglycerides are degraded by pancreatic lipase and bile acids to fatty acids and monoglycerides, but they are repackaged after intestinal absorption with cholesterol esters to form the central core of a chylomicron. This core is surrounded by free cholesterol, phospholipids, and apolipoproteins (see Table 24-3). In the circulation, this triglyceride core is hydrolyzed by lipoprotein lipase (LPL), leaving a chylomicron remnant of predominantly cholesterol ester and releasing fatty acids to peripheral tissues; LPL is activated by apolipoprotein C-II and requires hormones such as insulin. The

**Table 24-3** Apolipoproteins and Their Function

Apolipoprotein	Association with Lipoprotein	Function
ApoA1	HDL, chylomicrons	Main protein of HDL; activates lecithin/cholesterol acyltransferase
ApoA3	VLDL, HDL, chylomicrons	Interacts with LDL receptor and affects lipoprotein metabolism
ApoB48	Chylomicrons	Only in chylomicrons; ApoB100 without LDL receptor-binding domain
ApoB100	LDL, VLDL	Main protein of LDL; binds to LDL receptor
ApoC2	HDL, VLDL, chylomicrons	Activates lipoprotein lipase
ApoC3	VLDL	Inhibits lipoprotein lipase and hepatic lipase to delay catabolism of triglyceride-rich particles
ApoE2, E3, E4	HDL, VLDL, chylomicron remnants	Binds to LDL receptor

HDL, High-density lipoprotein; LDL, low-density lipoprotein, VLDL, very low-density lipoprotein.

endogenous pathway of lipid synthesis begins in the liver with the formation of VLDLs from hepatic triglycerides and circulating free fatty acids.

Xanthomas are lipid-containing papules, plaques, nodules, or tumors that may be found anywhere on the skin and mucous membranes.<sup>80,81</sup> Although the mechanism of their formation is not completely understood, it appears that serum lipids infiltrate the tissues where they are phagocytized by macrophages to form lipid-laden foam cells. They are then deposited, particularly in areas subjected to stress and pressure. Depending on their morphology, anatomic location, and mode of development, xanthomas can be categorized as *plane*, *eruptive* or *papuloeruptive*, *tendinous*, or *tuberous*. Recognition of these types of lesions, in addition to biochemical testing and physical examination, provides clues to possible metabolic abnormalities and diagnosis of specific metabolic diseases. Of note, juvenile xanthogranuloma (JXG; see Chapter 10), the most common xanthomatous skin lesion seen in children, does not have an association with systemic hyperlipidemias or other metabolic abnormalities.

### PLANE (PLANAR) XANTHOMAS

Plane (planar) xanthomas range from soft, yellow-orange, and brown-yellow macules to slightly elevated plaques (Fig. 24-9). They are generally seen on the face, sides of the neck, upper trunk, buttocks, elbows, and knees, but they may occur anywhere on the body and have a marked predilection for surgical or acne scars and the palmar creases.<sup>82</sup> Commonly seen plane xanthomas are xanthelasmas, which occur on or near the eyelids and are rarely seen in children or adolescents. Xanthelasmas in pediatric patients, in contrast with those in adults, are almost always associated with an underlying lipid abnormality. Intertriginous plane xanthomas, as in the antecubital fossae or the web spaces of the fingers, are usually associated with homozygous familial hypercholesterolemia.<sup>67</sup> Plane xanthomas of the palmar creases (xanthoma striatum palmarum) suggest the diagnosis of dysbetalipoproteinemia, especially when the child also has tuberous xanthomas. Plane xanthomas also occur in children with cholestasis from biliary atresia or primary biliary cirrhosis (Box 24-1), because of the accumulation of circulating unesterified cholesterol, and in patients with an underlying monoclonal gammopathy, such as in Castleman disease.



**Figure 24-9** Plane xanthomas in a girl with homozygous type II hyperlipoproteinemia.



**Figure 24-10** Xanthomas in hyperlipidemia. Eruptive xanthomas in a boy with nephritic syndrome. More commonly, eruptive xanthomas are grouped. Biopsy confirmed the diagnosis of xanthoma.

### ERUPTIVE (PAPULOERUPTIVE) XANTHOMAS

Eruptive (papuloeruptive) xanthomas appear in crops of multiple 1- to 4-mm, red to yellow-orange papules (Fig. 24-10) and are often surrounded by an erythematous base. Although they may involve the trunk and oral mucosa, they have a predilection for sites subjected to pressure or trauma, particularly the extensor surfaces of the arms, legs, and buttocks. Papuloeruptive xanthomas are almost always associated with hypertriglyceridemia (often to levels of >3000 mg/dL).<sup>83,84</sup> They can result from deficiency of LPL activity, as in patients with LPL deficiency (type I hyperlipoproteinemia), dysfunctional apolipoprotein C-II, (impaired insulin activity); or from overproduction by the liver of triglyceride-rich lipoproteins (as in endogenous familial hypertriglyceridemia [type IV hyperlipoproteinemia] or the elevations of both chylomicrons and VLDLs of type V hyperlipoproteinemia). Environmental factors and underlying diseases can also significantly elevate triglyceride levels. Among these are obesity, alcohol abuse, diabetes mellitus, nephrotic syndrome, and therapy with estrogens or

**Table 24-4** Laboratory Findings in Lipid Disorders

<b>Disorder</b>	<b>Inheritance</b>	<b>OMIM No.</b>	<b>Prevalence</b>	<b>Cholesterol</b>	<b>Triglycerides</b>	<b>VLDL</b>	<b>Chylomicrons</b>	<b>LDL</b>	<b>HDL</b>	<b>Serum</b>	<b>Cause</b>
Type I a: Familial hyperchylomicronemia	AR	239600, 246650, 615947	1/million	↑	↑↑↑	↑	↑	↓	↓↓↓	Creamy top	a: Deficiency from mutations in lipoprotein lipase; <i>LPL/HBPI</i>
b: Familial apoprotein C2 or A-V deficiency		207750, 133650									b. Deficient ApoC2 or ApoA5 (see Type 5)
c: —		118830									c. LP lipase inhibitor in blood
Type II a: Familial hypercholesterolemia	AD	143890, 144010, 603776	1 in 500 for heterozygotes	↑	NI or ↑	↑	NI	↑	↓	Clear	LDL receptor defect in 60%–80%; <i>APCB</i> , <i>PCSK9</i> , each <5% <i>LDLRAP1</i>
b: Familial combined hyperlipidemia	AR	603813 144250	AD, AR 1 in 100								Polygenic Decreased LDL receptor and ApoB100 dysfunction
Type III Familial dysbetaipoproteinemia	AR	107741	1 in 10,000	↑	↑	↑	↑	↓	NI	Turbid	ApoE2 synthesis
Type IV Familial hypertriglyceridemia	AD	144600	1 in 100	↑	NI ↑	↑	NI	↓	↓↓	Turbid	Renal disease, diabetes
Type V	AR	144650	Very rare	↑	↑↑↑	↑	↑	↓	↓↓↓	Creamy top, turbid bottom	Apo A-V (ApoA5) deficiency

AD, Autosomal dominant; AR, autosomal recessive; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LP, lipoprotein; NI, normal; OMIM, Online Mendelian Inheritance in Man; VLDL, very low-density lipoprotein; ↑, increased; ↓, decreased.

**Table 24-5** Disorders of Lipids: Clinical Findings and Management

<b>Disorder</b>	<b>Xanthomas</b>	<b>Cardiovascular</b>	<b>Gastrointestinal</b>	<b>Neurologic</b>	<b>Ophthalmologic</b>	<b>Other Findings</b>	<b>Management</b>
Type I	Eruptive, tendinous, xanthomas	None	Acute abdomen, hepatosplenomegaly, pancreatitis	None	Lipemia retinalis, retinal vein occlusion	Diabetes, lipemic plasma	Diet, plasmapheresis
Type II	Planar, especially intertriginous, tendinous, tuberous	Generalized atherosclerosis	None	None	Arcus cornea	None	Type IIa: bile acid sequestrants, statins, niacin, fish oil Type IIb: statins, niacin, fibrate
Type III	Planar, especially palmar, tuberous	Atherosclerosis	None	None	None	Abnormal glucose tolerance, hyperuricemia	Statins, fibrate
Type IV	Eruptive, tuberous	Atherosclerosis	Acute abdomen, hepatosplenomegaly, pancreatitis	None	Lipemia retinalis	Obesity	Statins, fibrate, niacin
Type V	Eruptive, tuberous	Atherosclerosis	Acute abdomen, hepatosplenomegaly, pancreatitis	None	Lipemia retinalis	Obesity, hyperinsulinemia	Niacin, fibrate
Tanger	Macular rash, foam cells in biopsies	Atherosclerosis	Acute abdomen, hepatosplenomegaly	Peripheral neuropathy	Corneal infiltration	Enlarged orange tonsils, lymphadenopathy	
Apolipoprotein A-I and C-III deficiency	Planar and tendon xanthomas, foam cells in biopsies	Atherosclerosis	Normal	Normal	Corneal clouding	None	
HDL deficiency with planar xanthomas	Planar xanthomas, foam cells in biopsies	Atherosclerosis	Hepatomegaly	Normal	Corneal opacity	None	

HDL, high-density lipoprotein.

### Box 24-1 Potential Causes of Secondary Hyperlipidemia in Pediatric Patients

Endocrine
Anorexia nervosa
Diabetes mellitus
Hypopituitarism
Hypothyroidism
Lipodystrophy
Pregnancy
Hepatic
Cholestasis
Biliary atresia
Biliary cirrhosis
Hepatitis
Renal
Chronic renal failure
Hemolytic-uremic syndrome
Nephrotic syndrome
Storage disease
Cystine storage disease
Gaucher disease
Glycogen storage disease
Neimann-Pick disease
Tay-Sachs disease
Medications
Alcohol
Anabolic steroids
Highly active antiretroviral therapy
Oral contraceptives
Corticosteroids
Retinoids
Others
Burns
Common variable immunodeficiency
Klinefelter syndrome
Progeria
Werner syndrome

retinoids (see Box 24-1). The mechanism for retinoid-induced hypertriglyceridemia is by elevation of hepatic VLDL production.

### TENDINOUS XANTHOMAS

Tendinous xanthomas are skin-colored or yellowish, smooth, freely movable subcutaneous nodules and tumors.<sup>85</sup> They have a predilection for the extensor tendons of the elbows, knees, heels (Fig. 24-11), hands, and feet. These nontender, firm nodules measure 1 cm or more in diameter. They usually are seen or palpated on the Achilles tendon and the tendons on the dorsal aspect of the hands. They are most commonly seen in either heterozygotes or homozygotes with familial hypercholesterolemia (type II hyperlipidemia), but may also be seen in individuals with familial defective apolipoprotein B-100, cerebrotendinous xanthomatosis, and sitosterolemia.

### TUBEROUS (TUBEROERUPTIVE) XANTHOMAS

Tuberous (tuberoeruptive) xanthomas are large, firm, nodular, sessile or pedunculated, flesh-colored or yellowish to red xanthomas (Fig. 24-12). They occur on the palms and extensor surfaces subject to stress or trauma, particularly the elbows, knees, hands, and buttocks. Located in the dermis and subcutaneous layers, they can enlarge to 5 cm or more in diameter, and in contrast to tendon xanthomas, are not attached to underlying structures. These lesions are found in patients with hypercholesterolemia, particularly with familial hypercholesterolemia (type II hyperlipoproteinemia)<sup>86</sup>; hepatic cholestasis; or dysbetalipoproteinemia (type III hyperlipoproteinemia). Some 80% of individuals with dysbetalipoproteinemia have tuberous xanthomas. Tuberous xanthomas are also found in sitosterolemia.<sup>87</sup>

### OTHER XANTHOMAS

Other xanthomas, not part of the hyperlipoproteinemia spectrum, include *xanthoma disseminatum*, an uncommon clinical entity charac-



**Figure 24-11** Xanthomas in hyperlipidemia. Tendinous xanthomas in adolescent with type II hyperlipoproteinemia.



**Figure 24-12** Xanthomas in hyperlipidemia. Tuberous xanthomas in a boy with Alagille syndrome.

terized by red-yellow or mahogany-colored papular and nodular lesions with a predilection for the flexural creases (see Chapter 10), and *verruciform xanthomas*, a rare disorder manifested by solitary, 0.2- to 2-cm, verrucous papillary or flat to lichenoid, gray to reddish-pink, sessile, occasionally pedunculated lesions most commonly seen on the oral mucosa and lips and occasionally on the penis, scrotum, vulva, groin, digits, nostrils, and areas of epidermal hyperplasia such as in congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD syndrome; see Chapter 5), lymphedema,<sup>88</sup> or epidermolysis bullosa (see Chapter 13).

The five major types of hyperlipoproteinemas are summarized in Tables 24-4 and 24-5. Type I hyperlipoproteinemia (Bürger-Grütz disease, familial LPL deficiency, and familial hyperchylomicronemia syndrome) is usually discovered accidentally because of lactescence

(manifested by a creamy or chocolate appearance of whole blood)<sup>89</sup> in an infant or child with bouts of abdominal pain, which may be caused by lipid accumulations in the liver and spleen, splenic infarct, or pancreatitis. The risk of atherosclerosis is not increased in this form. About two-thirds of children with type I disease have eruptive xanthomas, primarily localized to the buttocks, shoulders, and extensor surfaces of the extremities.<sup>90</sup> Eruptive xanthomas occur when the serum triglyceride level exceeds approximately 2000 mg/dL. The disorder results from LPL or apolipoprotein C-II deficiency, or is a result of the presence of an LPL inhibitor. Increased levels of chylomicrons can also be found in familial hypertriglyceridemia or in patients with diabetes or hypothyroidism, or in those undergoing therapy with retinoids, glucocorticoids or estrogens.

Type II hyperlipoproteinemia (familial hypercholesterolemia) is the most common and best understood disorder of the lipoprotein disorders in pediatric patients.<sup>91,92</sup> Heterozygotes (1 in 500 individuals) have plasma concentrations of total cholesterol and LDL cholesterol that are increased by twofold to threefold.<sup>93</sup> Homozygotes have levels five to six times normal values from birth to early childhood. Children with homozygous disease may have planar xanthomas at birth or by the first decade (including intertriginous xanthomas), and tendon and tuberous xanthomas by 15 years of age.<sup>94–97</sup> Rarely, tuberous xanthomas are the first manifestation.<sup>98</sup> Arcus cornea (lipid deposits around the edge of the cornea), angina pectoris, and myocardial infarction often present during the second decade. Carotid plaque has been noted as early as 4 years of age,<sup>99</sup> and coronary artery bypass or aortic valve replacement may be required during childhood.<sup>100–102</sup> Ten percent to 15% of heterozygous individuals develop tendon xanthomas during the second decade of life, particularly involving the Achilles tendon and the extensor tendons of the hands, but only rarely show angina pectoris during late teenage years. Approximately 5% of families have a mutation in *ApoB100* (see Table 24-3), and lack tendon xanthomas.

Type III hyperlipoproteinemia (also known as *dysbetalipoproteinemia* or *broad β disease*) is usually first diagnosed in adulthood, but sometimes first manifests during childhood.<sup>103</sup> Most affected individuals are homozygotes for the *ApoE2* allele, which is seen in 1 in 100 individuals; clinical expression is thought to be triggered by environmental factors, such as hormonal abnormalities, obesity, or medications, because only 1 in 2000 individuals are known to have the disorder. Some 75% of patients have plane xanthomas of the palms and/or tuberous xanthomas. Type IV disease (endogenous familial hypertriglyceridemia) is usually not seen before the age of 20 years, although it may appear in children with renal disease or in patients with diabetes who have become ketotic. Type V disease (seen in familial hyperchylomicronemia with hyperprebetalipoproteinemia or occasionally *ApoC2* deficiency) occasionally presents in preadolescent children. Patients are usually obese and have acute abdominal pain. Eruptive xanthomas are most common. Diabetes, glycogen storage disease, ingestion of contraceptives, and alcohol abuse may trigger manifestations.

Treatment of hyperlipidemias is type-specific but may include dietary modification, statins (hydroxymethylglutaryl [HMG]-CoA reductase inhibitors, which also decrease LDL levels by increasing LDL receptor expression and thus hepatic reuptake of LDL), cholesterol lowering agents (fibrates, which act on *PPARα* to decrease free fatty acid production; cholestyramine, which is a bile acid sequestrant; and niacin), and/or ezetimibe (selectively inhibits the absorption of cholesterol).<sup>104–106</sup> Apheresis<sup>107</sup> and even liver transplantation<sup>108</sup> have been used for recalcitrant cases of homozygous hypercholesterolemia. Successful therapy can lead to dramatic shrinkage or clearance of xanthomas.

## ALAGILLE DISEASE

Hyperlipidemia with hypercholesterolemia and xanthomas is also a feature of Alagille syndrome (arteriohepatic dysplasia, Watson-Alagille syndrome),<sup>109,110</sup> an autosomal dominant disorder caused by mutations in *JAG1*, which encodes a ligand for the Notch receptor and is critical for determination of cell fates in early development.<sup>111</sup> The most characteristic feature is congenital intrahepatic biliary hypoplasia with cholestasis and pruritus. Most patients show an unusual facies with a prominent forehead, hypertelorism, eyes deeply

set in orbits, atrophy of the iris, a pointed, bulbous, or saddle-shaped nose, and a sharply pointed chin, even in relatives without other features.<sup>112</sup> Other features may include vertebral anomalies, cardiovascular disease (generally pulmonic stenosis or aneurysms), renal abnormalities, hypogonadism, and physical and mental retardation.<sup>113</sup> The xanthomas have been described in approximately 30% of affected children, may appear as early as the first year of life, and are associated with high cholesterol levels.<sup>110</sup> The xanthomas are most often tuberous (see Fig. 24-12) and are often widespread, especially over extensor surfaces and fold areas. They may form confluent plaques, especially on the elbows and knees. Secondary eczematization is not uncommon, given the intense pruritus from cholestasis. Early photosensitivity with sunburn and residual facial scars resembling erythropoietic protoporphyria have rarely been described.<sup>114,115</sup> Death before 5 years of age as a result of cardiac failure, renal failure, or both has occurred, but the prognosis of children with Alagille syndrome is generally better than that of patients with congenital biliary atresia, in whom survival to 2 years of age is unusual. Transplantation and other means to lower cholesterol result in clearance of the xanthomas.<sup>110</sup>

## SITOSTEROLEMIA

Individuals with this autosomal recessive disorder have 30- to 100-fold elevations in plasma levels of plant sterols<sup>116</sup> and often have increased cholesterol levels owing to mutations in two adjacent sterol adenosine triphosphate (ATP)-binding cassette transporters, ABCG5 (encoding sterolin-1) or ABCG8 (encoding sterolin-2).<sup>117</sup> These proteins are thought to prevent dietary noncholesterol sterols from being retained by the body and for cholesterol excretion into bile. Affected children show tuberous and tendinous xanthomas during the first decade of life, as well as arthritis, premature vascular disease with a high risk of fatal cardiac events during teenage years, and sometimes hemolysis and thrombocytopenia.<sup>87,118,119</sup> Treatment with ezetimibe, which inhibits cholesterol absorption, reduces the plasma concentrations of plant sterols in patients.<sup>120</sup> The combination of ezetimibe and cholestyramine has also been used successfully to clear the xanthomas.<sup>119,121,122</sup>

## CEREBROTENDINOUS XANTHOMATOSIS

Cerebrotendinous xanthomatosis is an autosomal recessive disorder caused by mutations in *CYP27A1* (sterol 27-hydroxylase).<sup>123,124</sup> As a result, large amounts of cholestanol, the 5-α-dihydro derivative of cholesterol, accumulate in virtually every tissue, leading to tendinous xanthomas, juvenile cataracts, diarrhea, and atherosclerosis.<sup>125</sup> Patients may develop cataracts, and neurologic signs include dementia, psychiatric disturbances, seizures, progressive paresthesias, mental retardation, and cerebellar problems.<sup>126</sup> Replacement therapy with chenodeoxycholic acid (750 mg/day) reduces cholestanol synthesis and concentrations. If started early enough (the neurologic manifestations can be seen during infancy), therapy improves neurologic function and clears the xanthomas.<sup>123</sup>

## DEFICIENCIES IN HIGH-DENSITY LIPOPROTEIN

Low levels of HDL cholesterol are most commonly seen in disorders of triglyceride metabolism, but may occur in the presence of otherwise normal levels of lipids and be associated with xanthomas. These disorders are Tangier disease, apolipoprotein A-I and C-III deficiency, and HDL deficiency with planar xanthomas (with decreased levels of *ApoC3*).

## TANGIER DISEASE

Tangier disease (familial HDL deficiency) is an autosomal recessive disorder characterized by hypcholesterolemia (50 to 125 mg/dL), an almost complete absence of plasma HDL, and massive deposition of cholesterol esters in tissues. The disorder results from homozygous mutations in the ATP-binding cassette (ABCA1) transport protein, which mediates the efflux of cellular cholesterol to the HDL particle in plasma for transport to the liver.<sup>127,128</sup> Triglyceride levels may be normal or slightly elevated (150 to 250 mg/dL), and plasma ApoA1

**Table 24-6** The Mucopolysaccharidoses

Disorder	Inheritance	Enzyme	Storage	Clinical Features
MPS I-H Hurler	AR	$\alpha$ -Iduronidase	DS, HS	Severe retardation, corneal clouding, hepatosplenomegaly, chondrodstrophic dwarfism, generalized mongolian spots; early death
MPS I-S Scheie	AR			Bone and joint involvement, retinopathy, corneal clouding, sometimes cardiac abnormalities; normal intelligence
MPS II Hunter	X-LR	Iduronate 2-sulfatase	DS, HS	Cutaneous papules and nodules on scapula, posterior axillae, thigh, buttocks, atypical retinitis pigmentosa; normal cornea
MPS III Sanfilippo	AR	Several subtypes*	HS	Aggressive behavior, severe neurologic involvement, mild somatic changes
MPS IV Morquio	AR	A: Galactose-6-sulfatase B: $\beta$ -galactosidase	KS	Striking dwarfism but not dysmorphic, corneal opacity, severe osteoporosis, extreme short stature; atlantoaxial dislocation leads to chronic cervical myelopathy and progressive paresis; restrictive respiratory disease usually leads to death; normal intelligence
MPS VI Maroteaux-Lamy	AR	Galactosamine-4-sulfatase	DS	Dwarfism, severe corneal, and bony lesions; cardiac involvement, respiratory obstruction; normal intelligence
MPS VII Sly	AR	$\beta$ -glucuronidase	HS, DS	Often born with hydrops fetalis, severe Hurler-like phenotype if survive
MPS IX	AR	Hyaluronidase	HA	One patient; short stature, periaricular soft-tissue masses

AR, Autosomal recessive; DS, dermatan sulfate; HA, hyaluronic acid; HS, heparan sulfate; KS, keratan sulfate; MPS, mucopolysaccharidosis; X-LR, X-linked recessive.

\*A: heparan N-sulfatase; B: N-acetylglucosaminidase; C: acetyl-CoA: glucosamine N-acetyltransferase; D: N-acetylglucosamine-6-sulfatase.

levels are less than 3% of normal. The disorder commonly manifests during childhood. The tonsils are enlarged and show distinctive alternating bands of red, orange, or yellowish white striations overlying the normal red mucosa.<sup>129</sup> Lipid deposits in the skin and other organs may be accompanied by a persistent maculopapular eruption over the trunk and abdomen, hepatosplenomegaly, lymph node enlargement, infiltration of the cornea in adults, and alterations in the intestinal and rectal mucosa. Several patients have had recurrent peripheral neuropathy.

## The Mucopolysaccharidoses

The mucopolysaccharidoses (MPSs) are inherited disorders of lysosomal hydrolases that catabolize glycosaminoglycan (GAG), a sulfated component of connective tissue.<sup>130</sup> As a result, dermatan sulfate, heparin sulfate, and/or keratan sulfate accumulate within cells and are excreted in excess amounts in the urine. First described by Hunter in 1917 (and labeled *gargoylism* in 1936), these disorders can now be divided into at least seven subtypes that share clinical features, mode of inheritance, and nature of the accumulated mucopolysaccharide. Affected individuals are normal in appearance at birth but, as with all lysosomal storage disorders, progressively show features with advancing age, beginning during infancy. Patients with any of the MPSs can show hypertrichosis, especially over the back and extremities, and thickened, roughened, taut inelastic skin, especially over the fingers because of the accumulation of GAG. Only individuals with Hunter syndrome (MPS type II, iduronate-2-sulfatase deficiency) have specific cutaneous features (papulonodules), although extensive, persistent Mongolian spots have rarely been described in children with Hunter<sup>131</sup> and Hurler<sup>132,133</sup> syndromes.

The disorders tend to present because of dysmorphic features or psychologic and learning difficulties, or as severe bony dysplasia. Considerable heterogeneity within subgroups has been described. Urinary screening tests for GAG should be followed by specific enzyme assays. Hunter syndrome (MPS II) is an X-linked recessive disorder; all others are autosomal recessive. Hurler syndrome, or MPS I, is presented as the prototype MPS; Hunter syndrome is also discussed in detail because it is the one form of MPS that shows a distinctive cutaneous feature: dermal papules and nodules. Table 24-6 summarizes the clinical and biochemical features of all of the MPSs.

## HURLER SYNDROME

Hurler syndrome (MPS I-H, MPS I in McKusick's original classification) is the most common of this group of disorders.<sup>134,135,136</sup> Seen in approximately 1 in 100,000 births, it appears in the first year of life. MPS I is a particularly grave disorder, with death occurring in almost all cases before the age of 10 years, usually from cardiac failure or respiratory infection.

Patients are usually diagnosed toward the end of the first year of life because of their coarse facial features (Fig. 24-13). Many have umbilical and inguinal hernias at presentation and recurrent respiratory infections before diagnosis. Other cardinal features of the Hurler syndrome include coarse hair; macrocephaly with frontal bulging; premature closure of the sutures with hyperostosis, commonly leading to a scaphocephalic skull; flattened nasal bridge with a saddle-shaped appearance; hypertelorism; protuberant tongue; short neck; protuberant abdomen because of hepatic and splenic enlargement; deformity of the chest; shortness of the spine; laxity of the abdominal wall with inguinal and umbilical hernias; broad hands with stubby fingers; a claw hand due to stiffening of the phalangeal joints (Fig. 24-14); limitation of extensibility of the joints; severe, progressive mental retardation; and marked retardation of growth. Although most affected infants are normal or above normal in length during the first year of life, the growth rate starts to decrease by 2 years of age. By age 3, almost all patients are below the third percentile for stature. Clouding of the cornea develops in all patients with Hurler syndrome and is best seen by side-lighting of the cornea; if severe visual loss occurs, however, it is usually related to retinal involvement. Deafness is almost always a feature, and cardiac involvement may range from severe early life-threatening cardiomyopathy to progressive valve disease. Approximately 40% of affected individuals have hydrocephalus, and a large head circumference, even without hydrocephalus, is often noted. Dysplasia of the odontoid process increases the risk of atlantoaxial subluxation and acute spinal cord damage. Upper respiratory tract obstruction and sleep apnea related to the large tongue and midfacial hypoplasia may require corrective surgery.<sup>137</sup> MPS I is the most common metabolic disorder associated with generalized mongolian spots during the first decade of life.<sup>132,138</sup>

There is a wide range of heterogeneity in severity and manifestations of Hurler syndrome. At the other end of the spectrum is Scheie syndrome (MPS I-S, formerly MPS V), which also results from mutations in the gene encoding ( $\alpha$ )-L-iduronidase. Patients with Scheie



**Figure 24-13** Hurler syndrome. Coarse facial features, macrocephaly, scaphocephalic skull, flattened nasal bridge, hypertelorism, short neck, chest deformity, and protuberant abdomen in a girl with Hurler syndrome (MPS I).



**Figure 24-14** Hurler syndrome. Broad hands with stubby fingers and limited joint extension. Note the hypertrichosis.

syndrome have normal intelligence and may have a normal lifespan, with predominantly bone and joint problems. Carpal tunnel syndrome occurs commonly, and corneal transplantation may be considered for corneal clouding (assuming lack of concurrent retinopathy as a cause of visual loss). Cardiac valvular insufficiency may develop and require surgery.

### HUNTER SYNDROME

Hunter syndrome (MPS II) is distinguished from Hurler syndrome by an X-linked recessive inheritance, longer survival, lack of corneal clouding, and the different biochemical defect with deficiency of the lysosomal enzyme iduronate-2-sulfatase.<sup>139,140</sup> As with Hurler syndrome, patients show coarse, straight scalp hair. Some patients develop papules and nodules on the upper back and sides of the upper arms, which are pathognomonic. Mental retardation progresses at a slower rate, and humping of the lumbar area (gibbus) does not occur.



**Figure 24-15** Hunter syndrome. Distinctive, firm, flesh-colored papules and nodules on the buttocks (a cutaneous marker of Hunter syndrome, or MPS II).

Progressive deafness is a feature of 50% of patients and can impair speech development. A mild form of MPS II (type IIB) may show only mild skeletal abnormalities, and skin lesions may be the presenting feature.<sup>141</sup>

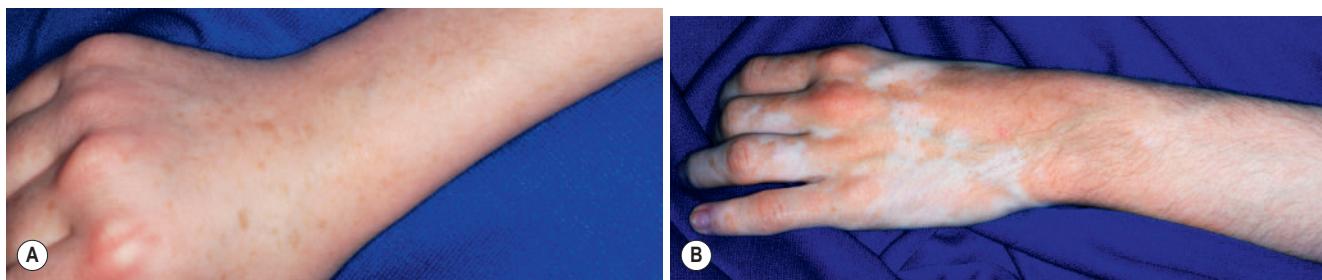
The distinctive cutaneous changes are found in the minority of affected boys. They consist of firm flesh-colored to ivory-white papules and nodules that often coalesce to form ridges or a reticular pattern in symmetric areas between the angles of the scapulae and posterior axillary lines, the pectoral ridges, the nape of the neck, buttocks (Fig. 24-15), and/or the lateral aspects of the upper arms and thighs. They appear before age 10 years and can spontaneously disappear.

### THERAPY FOR MUCOPOLYSACCHARIDOSES

Palliative therapy for the hydrocephalus and joint stiffness and pain are appropriate, but surgical correction of the skeletal or cardiac abnormalities is not, given the limited life expectancy. Hematopoietic stem cell transplantation is standard treatment and can stabilize cognitive improvement when performed before 9 to 24 months of age.<sup>142,143</sup> Other effects are unpredictable but can include softening of coarse hair and facial features, and improvement in corneal clouding, hepatomegaly, upper airway obstruction, and cardiomyopathy (but not the constellation of bony defects [dysostosis multiplex] or cervical instability). Enzyme replacement therapy with  $\alpha$ -L-iduronidase (iduronidase) can also reduce GAGs and improve respiratory and cardiac function, as well as the hepatomegaly and joint mobility in patients with MPS I.<sup>134,144,145</sup> Enzyme replacement therapy (ERT) with idurafuse, recombinant lysosomal iduronate-2-sulfatase, has been noted to improve the skin texture, as well as the hepatosplenomegaly, bronchitis, and physical activity of Hunter syndrome.<sup>146,147</sup> However, ERT cannot pass the blood-brain barrier to improve neurocognitive function.<sup>144,148–150</sup> The combination of ERT and transplantation may benefit patients with more severe manifestations.<sup>134</sup>

### Other Storage Disorders

Several other storage disorders may show cutaneous features, particularly angiokeratomas and pigmentary changes. Among these are the mucolipidoses (sialidosis II or mucolipidosis I and mucolipidosis II), the sphingolipidoses (Fabry disease, Farber lipogranulomatosis, Gaucher disease, GM1 gangliosidosis, salt and pepper syndrome/GM3 synthase deficiency (Fig. 24-16),<sup>151–153</sup> and multiple sulfatase deficiency) and other storage disorders of carbohydrate metabolism (aspartylglycosaminuria, fucosidosis, galactosialidosis,  $\alpha$ -mannosidosis, Salla disease, and Schindler disease).<sup>154–160</sup> The features of these storage disorders, their cutaneous manifestations, and their underlying causes are summarized in Table 24-7. (Fabry disease and fucosidosis are discussed in



**Figure 24-16** Dyspigmentation with GM3 synthase deficiency. **(A)** Hyperpigmented macules, especially acrally, begin late in childhood and give GM3 synthase deficiency the name *salt and pepper syndrome*. **(B)** Vitiliginous lesions tend to appear in late adolescence and can become extensive.

**Table 24-7** Other Storage Disorders with Cutaneous Manifestations during Childhood

Disorder	Inheritance	Enzyme	Cutaneous Features	Clinical Features
Aspartylglycosaminuria	AR	Aspartylglycosaminidase	Angiokeratomas	Speech delay, otitis media, behavioral change resembling MPS III
Fabry	X-LR	$\alpha$ -Galactosidase	Angiokeratomas, hypohidrosis	Acroparesthesias, progressive renal disease (see Chapter 12)
Farber lipogranulomatosis	AR	Ceramidase	Painful subcutaneous nodules, especially over joints	Hydrops fetalis, chronic pulmonary disease with granulomatous infiltration of the lungs, hepatosplenomegaly, neurodegeneration; granulomatous infiltration of the mucosae with hoarse cry, recurrent vomiting, dysphagia
Fucosidosis	AR	$\alpha$ -Fucosidase	Angiokeratomas, sweating abnormalities, purple nail bands	Neurodegeneration, dysostosis, respiratory infections, hepatosplenomegaly, growth retardation, resembles MPS (see Chapter 12)
Galactosialidosis	AR	Defective protective protein/cathepsin A; proteolysis of both $\beta$ -galactosidase and neuraminidase	Angiokeratomas	Hydrops fetalis, skeletal abnormalities, myoclonus, cherry-red macular spots, ataxia, mild mental retardation
Gaucher, type II	AR	$\beta$ -Glucocerebrosidase	Collodion baby	Severe neurologic involvement, marked hepatosplenomegaly (see Chapter 5)
GM1 gangliosidosis	AR	$\beta$ -Galactosidase	Angiokeratomas, extensive mongolian spots	Dysostosis multiplex, hepatosplenomegaly, early neurologic degeneration, corneal clouding
Mannosidosis	AR	$\alpha$ -Mannosidase	Angiokeratomas	Middle ear and respiratory infections; may have mild learning difficulties to severe MPS I-like phenotype and seizures
Multiple sulfatase deficiency	AR	Posttranslational processing of multiple sulfatases	Ichthyosis (recessive X-linked)	Hepatosplenomegaly, dysostosis, progressive neurologic deterioration (see Chapter 5)
Mucolipidosis I (sialidosis type II)	AR	Neuraminidase I	Angiokeratomas	MPS I phenotype; dysostoses multiplex, progressive retardation
Mucolipidosis II (I-cell disease)	AR	N-acetylglucosaminyl-1-phosphotransferase	Malar telangiectasia, puffy eyelids, prominent periorbital veins; thick, rigid skin	MPS I phenotype; gingival hypertrophy, dysostosis multiplex, stiff joints, respiratory tract infections, cardiac failure
Salla disease (infantile sialic acid storage)	AR	Sialic acid transporter	Hypopigmentation	Hydrops fetalis, recurrent infections, failure to thrive, dysostosis multiplex, cardiac disease, coarse facies, learning disabilities
Salt and pepper syndrome	AR	GM3 synthase	Small acral pigmented macules; vitiliginous lesions	Severe intellectual disability, seizures, choreoathetosis, spasticity, scoliosis, dysmorphic facies
Schindler	AR	$\alpha$ -N-acetylgalactosaminidase	Angiokeratomas	Variable; may have myoclonus, spasticity, progressive dementia

AR, autosomal recessive; X-LR, X-linked recessive; MPS, mucopolysaccharidosis.

more detail in Chapter 12.) The neonatal form of Gaucher disease, type II, may present as a collodion baby, whereas multiple sulfatase deficiency (mucosulfatidosis) is phenotypically identical to recessive X-linked ichthyosis (see Chapter 5). All of these conditions are inherited in an autosomal recessive fashion, except for Fabry disease, which is X-linked recessive.

 The complete list of 160 references for this chapter is available online at <http://expertconsult.inkling.com>.

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## Primary Immunodeficiency Disorders

Recurrent infections, including those involving the skin, raise the possibility that a child has an immune deficiency. The most common cause of immunodeficiency in children is acquired immunodeficiency resulting from human immunodeficiency virus (HIV) infection (see Chapter 15). Less commonly, children with evidence of an immunodeficiency have an inherited disorder.<sup>1–6</sup> Genetic immunodeficiency disorders may show a variety of cutaneous abnormalities, some of which are unique and characteristic of the disorder, and others, such as dermatitis, that are shared by other immunodeficiencies and other disorders.

Some of these immunodeficiencies are discussed elsewhere because of their manifestations. Wiskott–Aldrich syndrome and hyperimmunoglobulinemia E (Hyper-IgE) syndrome are discussed in Chapter 3, owing to the common presence of dermatitis. Chediak–Higashi and Griscelli syndromes, the silvery hair syndromes associated with immunodeficiency, are reviewed in Chapter 11 with the disorders of pigmentation. The telangiectasias that allow ataxia-telangiectasia to be distinguished from other forms of ataxia are described in Chapter 12. Complement deficiencies are mentioned in Chapter 14 because individuals with a deficiency of a late complement component have an increased risk of nosocomial infection, in Chapter 20 because hereditary angioedema (HAE) can be confused with angioedema, and in Chapter 22 because deficiency of the early components of complement may lead to a lupus-like disorder. Given its characteristic recurrent and recalcitrant candidal infections, chronic mucocutaneous candidiasis is reviewed in Chapter 17.

Signs that should raise the suspicion of acquired or hereditary immunodeficiency are listed in **Box 25-1**. Screening laboratory tests for a patient with recurrent cutaneous infections suspected of having an immunodeficiency are suggested in **Table 25-1**.

### IMMUNOGLOBULIN DEFICIENCIES

Children with deficiencies of immunoglobulins (Igs) primarily manifest with bacterial infections beginning at 3 to 6 months of age, at a time when transplacentally derived maternal Igs wane.<sup>7,8</sup> In general, the treatment of hypogammaglobulinemia is antibody replacement by intravenous infusions of immune serum globulin and vigorous antibiotic therapy.<sup>9</sup>

The most common Ig deficiency is selective IgA deficiency, found in 1 in 500 individuals, of which 10% to 15% show clinical manifestations. About 5% of patients with IgA deficiency have mutations in TACI, which encodes a tumor necrosis factor (TNF) receptor family member. B cells in individuals with TACI mutations have impaired isotype switching and do not produce IgA and often IgG in response to TACI ligand. The most common features are sinopulmonary bacterial infections and *Giardia* gastroenteritis. Approximately one-third of patients with clinical manifestations develop immune-mediated disorders, some of which involve the skin. These include an atopic-like dermatitis, lupus erythematosus with selective IgA deficiency (recently linked to mutations in *IFIH1*),<sup>10</sup> vitiligo, recurrent candidal infections, lipodystrophy, and idiopathic thrombocytopenic purpura. Two percent of individuals with celiac disease have full or partial selective IgA deficiency; this subgroup of patients has more concomitant autoimmune disorders and may have persistent elevation of IgG serologies, even with disease improvement.<sup>11</sup> The risk of allergy is also increased with selective IgA deficiency, including asthma, cow's milk allergy, and allergic rhinoconjunctivitis.

In addition to their decreased levels of IgA, 30% to 50% of affected individuals have serum anti-IgA IgG antibodies, leading to a risk of fatal anaphylactic reactions upon administration of blood products with IgA-bearing lymphocytes; if intravenous immunoglobulin (IVIG) is necessary, only IVIG with low IgA content should be administered.<sup>12</sup>

IgA deficiency may transition into (and is seen with increased incidence in families with) combined variable immunodeficiency (CVID),<sup>13</sup> a heterogeneous group of disorders with decreased Ig levels (IgG, IgA, and sometimes IgM) and variable functional T-cell abnormalities.<sup>14–17</sup> Patients with CVID most commonly show pyoderma, extensive warts, widespread dermatophyte infections, and dermatitis. They are predisposed to pyogenic infections of the upper and lower respiratory tract, as well as gastrointestinal infections, particularly those caused by *Giardia*. Noncaseating granulomas of the lungs, liver, spleen, and/or skin have been described and are not associated with microorganisms. Individuals with CVID also have an increased risk of autoimmune diseases, including vitiligo (Fig. 25-1), alopecia areata, and vasculitis. The incidence of lymphoma is increased 400-fold, and that of cancer overall 8- to 13-fold. CVID is primarily a disorder of adults, with the mean age of onset 23 to 33 years<sup>18</sup>; however, 25% of cases are diagnosed before 21 years of age, with a peak incidence in children aged 5 to 10 years and a minimum age of 4 years used to exclude patients with other primary immunodeficiency disorders.<sup>19</sup> Death in patients with CVID usually results from lymphoma, hepatitis, respiratory insufficiency, or gastrointestinal disease.

Most cases of panhypogammaglobulinemia in children represent X-linked hypogammaglobulinemia (also called *X-linked agammaglobulinemia*), a disorder caused by mutations in *BTK*, which encodes a tyrosine kinase that regulates the conversion of pre-B cells to B cells able to differentiate and produce Igs.<sup>20</sup> Less commonly, pediatric patients may have a transient form during infancy with early failure to thrive, protracted diarrhea, sinopulmonary infections, pyoderma, and cutaneous abscesses, but with reversal when Ig is produced at 18 to 30 months of age. Approximately 10% have an autosomal recessive form of panhypogammaglobulinemia.

Boys with X-linked hypogammaglobulinemia develop recurrent bacterial infections in the first year of life and have an increased susceptibility to hepatitis B and enteroviral infections. Furuncles and cellulitis are the most common infections. An atopic-like dermatitis is common, and noninfectious cutaneous granulomas have been described. There is an increased predisposition to the development of pyoderma gangrenosum, which has been recently linked to Warthin–Starry-positive *Helicobacter bilis* infection; although difficult to grow, the *Helicobacter* organisms are detectable by polymerase chain reaction (PCR) and electrospray ionization time-of-flight mass spectrometry.<sup>21</sup> A small percentage of patients develop a dermatomyositis-like disorder with slowly progressive neurologic involvement, usually related to echoviral meningoencephalitis. Up to 6% of patients develop lymphomas.

Patients with X-linked hypogammaglobulinemia with hyper-IgM (HIM) tend to have deficiencies of IgA, IgE, and IgG with neutropenia, but increased levels of IgM and isohemagglutinins.<sup>22</sup> Rather than a primary B-cell defect, affected individuals have a primary T-cell defect. Cross-linking of CD40 on B cells induces switching of Ig classes from IgM to IgG, IgA, or IgE. Mutations in X-linked HIM lead to a dysfunction of the ligand for CD40 (CD40L). B cells from patients with HIM express functional CD40, but the T cells express the defective CD40 ligand and cannot bind CD40.<sup>23,24</sup> Three other forms of HIM are autosomal recessive; these result from deficiency of CD40

### Box 25-1 Signs of Immunodeficiency

#### History of infections

- Increased frequency, severity, and duration
- Unusual manifestations
- Unusual infecting agents
- Chronic infections, incomplete clearing
- Poor response to appropriate agents
- Severe viral infections
- Recurrent osteomyelitis

#### Failure to thrive

Diarrhea, vomiting, malabsorption

#### Clues to specific types of immunodeficiency

- Hematologic abnormalities (e.g., Wiskott–Aldrich syndrome)
- Arthritis (e.g., Wiskott–Aldrich syndrome or early complement deficiency)
- Paucity of lymph nodes (e.g., SCID) or lymphadenopathy (e.g., CGD)
- Hepatosplenomegaly (e.g., CGD, Omenn syndrome, or Wiskott–Aldrich syndrome)
- Poor wound healing (e.g., leukocyte adhesion deficiency)
- Silvery hair (e.g., Chediak–Higashi or Griscelli syndromes)

*CGD*, Chronic granulomatous disease; *SCID*, severe combined immunodeficiency.

**Table 25-1** Screening Laboratory Testing for the Child with Recurrent Infections

Test	Primary Immunodeficiency
Complete blood count with differential, platelet count and examination of smear	Giant leukocyte granules (Chédiak–Higashi syndrome) Thrombocytopenia (Wiskott–Aldrich syndrome) Leukocytosis (chronic granulomatous disease and leukocyte adhesion deficiency)
Quantitative immunoglobulins	Selective IgA deficiency Transient hypogammaglobulinemia X-linked hypogammaglobulinemia Hypogammaglobulinemia with hyper-IgM Common variable immunodeficiency Wiskott–Aldrich syndrome Hyperimmunoglobulin E
Flow cytometry (T and B cells)	Severe combined immunodeficiency Leukocyte adhesion defect (CD18 deficiency) Chronic granulomatous disease

*IgA*, Immunoglobulin A; *IgM*, immunoglobulin M.



**Figure 25-1** Common variable immunodeficiency (CVID). Individuals with CVID or IgA deficiency have an increased incidence of autoimmune disorders, as evidenced in this adolescent with CVID and vitiligo.



**Figure 25-2** Hyperimmunoglobulinemia syndrome. Extensive warts are a commonly observed cutaneous manifestation of boys with this form of immunodeficiency.

itself,<sup>25</sup> activation-induced cytidine deaminase (AICD), or uracil-N-glycosylase (UNG),<sup>26</sup> the latter two being signaling components downstream of the CD40 receptor that are critical to B-cell differentiation and class switching. A rare form of X-linked immunodeficiency, sometimes associated with HIM, is associated with hypohidrotic ectodermal dysplasia (see Chapter 7), and has been linked to mutations in the *NEMO* gene, the same gene that is mutated in incontinentia pigmenti (see Chapter 11). Patients with HIM often seek treatment during infancy with bacterial and sometimes fungal or opportunistic sinopulmonary infections (most common feature), pyoderma, and gastrointestinal infections (especially with opportunistic infections such as *Cryptosporidium*), hepatosplenomegaly, cervical adenitis, autoimmune disorders (especially thyroiditis, and hemolytic anemia),<sup>27</sup> and an increased risk of lymphoma.<sup>25,28</sup> Numerous, widespread warts (Fig. 25-2), oral and perianal area ulcerations, and sclerosing cholangitis are additional features.<sup>29</sup> Extensive warts are also a feature of warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome, which results from mutations in the chemokine receptor CXCR4<sup>30</sup>; EVER1 and EVER2 deficiency; DOC8 deficiency (see Hyperimmunoglobulinemia E section in Chapter 3); Netherton syndrome (Chapter 5); GATA2 deficiency<sup>31</sup>; and STK4 deficiency.<sup>32,33</sup>

X-linked lymphoproliferative disease (XLP) is characterized by an abnormal response to Epstein–Barr virus infection because of mutations in either *SH2D1A*, which encodes signaling lymphocytic activation molecule (SLAM)-associated protein (SAP) (XLP-1), or *XIAP* (XLP-2), critical proteins for cytotoxic T-cell function.<sup>34–36</sup> Affected boys are healthy until they first develop infectious mononucleosis during childhood or adolescence. Fever, pharyngitis, maculopapular rash, lymphadenopathy, hepatosplenomegaly, purpura, jaundice, and hemorrhagic colitis, and often hypogammaglobulinemia are typical features. The virus stimulates a rapidly progressive B-cell lymphoma, often with superimposed bacterial sepsis, which leads to death in 70% of affected boys, especially with hemophagocytic lymphohistiocytosis and without transplantation.<sup>37</sup>

## CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease (CGD) is a group of disorders characterized by severe recurrent infections resulting from an inability of phagocytic leukocytes to generate oxidative metabolites and activate neutrophil granule elastase and cathepsin G, thus blocking the killing of intracellular bacteria and fungi.<sup>38,39</sup> In all forms of CGD the function of the nicotinamide dinucleotide phosphate (NADPH) oxidase complex is reduced. The disorder usually presents with recurrent pneumonias, hepatosplenomegaly, and lymphadenopathy. Patients develop granulomas, primarily of the lungs, liver, skin, and

genitourinary and gastrointestinal tracts, as an abnormal immune response.<sup>40–43</sup>

The most common form of CGD is X-linked recessive and results from mutations in the membrane-bound component of NADPH oxidase gp91<sup>phox</sup> (*phox* is short for *phagocyte oxidase*), and 90% of affected individuals are male. Autosomal recessive forms (30% of patients) are due to mutations in other components of phagocyte NADPH oxidase, p22<sup>phox</sup> and the cytoplasmic components p47<sup>phox</sup> and p67<sup>phox</sup>.

The skin, lungs, and perianal area are most often the sites of infection. Early lesions are usually cutaneous staphylococcal pyoderma and abscesses of the face and perianal area, not uncommonly associated with purulent dermatitis and regional lymphadenopathy. Seborrheic dermatitis, Sweet syndrome, scalp folliculitis, perioral and intraoral ulcerations that resemble aphthous stomatitis. Female carriers of gp91<sup>phox</sup> mutations may show aphthous stomatitis and lupus-like eruptions,<sup>44,45</sup> but rarely these have been described in affected patients with recessive form or administered Voriconazole.

The organisms associated with CGD are usually *Staphylococcus aureus* and opportunistic Gram-negative bacteria, including *Serratia*,<sup>46</sup> *Klebsiella*, *Pseudomonas*, and *Escherichia coli*. These organisms all require oxidative metabolism for intracellular killing. Other organisms that may cause infection in patients with CGD with increased incidence are *Aspergillus*, *Candida*, *Cryptococcus*, *Fusarium*, and *Nocardia*.<sup>47</sup> Bronchopneumonia and suppurative lymphadenitis are the most prevalent noncutaneous infections, and respond to appropriate antibacterial therapy and, in some cases, surgical drainage. The extracutaneous organs most commonly involved in CGD are the lymph nodes, lungs, liver, spleen, and gastrointestinal tract (Box 25-2). CGD has been misdiagnosed as Crohn disease because of the overlap in features (failure to thrive, diarrhea, colitis, bowel obstruction, perianal ulcerations and fistulas, anemia, and hypoalbuminemia),<sup>48</sup> and as hyper-IgE syndrome because of associated elevation of IgE levels in a case with selective IgA deficiency.<sup>49</sup>

Patients with CGD commonly show leukocytosis, anemia, elevated erythrocyte sedimentation rate (ESR), and hypergammaglobulinemia. Skin tests for delayed hypersensitivity, phagocytosis, and chemotaxis are normal. Carrier and affected patients are often detected by quantitative dihydrorhodamine flow cytometry,<sup>50</sup> and the nitroblue tetrazolium (NBT) screening assay is now rarely performed (in which the oxidized yellow form of NBT is reduced to a blue formazan precipitate). Ferricytochrome C reduction assay is a quantitative assay that shows absence of the respiratory burst. Immunoblots can detect the selective loss of membrane phagocyte oxidase components. However, mutations that lead to deficiency of gp91<sup>phox</sup> or p22<sup>phox</sup> cannot be differentiated by immunoblotting, because both are components of cytochrome b<sub>558</sub>, and the entire cytochrome is absent if one is deficient; gene sequencing is required to confirm the mutation in gp91<sup>phox</sup> or p22<sup>phox</sup>.

#### Box 25-2 Signs and Symptoms in Patients with Chronic Granulomatous Disease

Seen in more than 50% of patients

- Lymphadenopathy, lymphadenitis
- Hepatosplenomegaly
- Bronchopneumonia
- Failure to thrive

Seen in 25% of patients or less

- Persistent diarrhea
- Pleuritis or empyema
- Septicemia or meningitis
- Hepatic or perihepatic abscess
- Osteomyelitis

Seen in fewer than 25% of patients

- Perianal abscess
- Periorificial dermatitis
- Aphthous stomatitis
- Conjunctivitis
- Lung abscess
- Peritonitis
- Obstructive granulomas

Antibiotic treatment of infection with surgical intervention as needed, and prophylactic trimethoprim-sulfamethoxazole and itraconazole therapy<sup>51</sup> have been used in most affected individuals.<sup>52</sup> Short courses of systemic corticosteroids have been helpful for patients with obstructive visceral granulomas. Stem-cell therapy has led to reversal of the immunodeficiency in severe cases with fewer infections and better linear growth, but management of CGD without transplantation similarly prolongs survival during childhood.<sup>53–55</sup>

#### LEUKOCYTE ADHESION DEFICIENCIES

The leukocyte adhesion deficiencies (LADs) are a group of three autosomal recessive disorders that affect the ability of neutrophils, cytolytic T lymphocytes, and monocytes to be mobilized into extravascular sites of inflammation.<sup>56</sup> In most affected individuals (LAD1), mutations in CD18 occur, leading to deficiency or dysfunction of the β<sub>2</sub> subunit of integrins. The principal ligand for these integrins is ICAM1, which participates actively in neutrophil and monocyte chemotaxis and phagocytosis. More than 75% of patients with severe disease die by 5 years of age; more than half of the patients with moderate deficiency die between the ages of 10 and 30 years.

Patients with LAD have frequent skin infections (especially facial cellulitis and perianal infection), mucositis, and otitis, with a 5- to 20-fold increase in peripheral blood leukocytes. Poor wound healing is characteristic and leads to paper-thin or dysplastic cutaneous scars. Minor skin wounds may become large ulcerations that resemble pyoderma gangrenosum (Fig. 25-3), especially if secondarily infected. Periodontitis is a typical feature, and if severe, may lead to loss of teeth. Bacterial and fungal infections may be life-threatening. Delayed separation of the umbilical cord is a common historic clue to the diagnosis. Psoriasis has been described in affected individuals with mild disease.<sup>57</sup>

A second form of LAD (LAD2) is an autosomal recessive disorder caused by mutations in FUCT1. FUCT1 encodes a GFP-fucose transporter that is required for formation of sialyl-Lewis X, a ligand for selectins on the surface of neutrophils.<sup>58</sup> In addition to their elevated leukocyte counts and recurrent bacterial infections, patients have short stature, a distinctive facies, and developmental delay. A third type of LAD, which features a bleeding tendency, is caused by a mutation in FERMT3, which encodes kindlin-3 and prevents activation of β1, β2, and β3 integrins.<sup>59</sup> Dermal hematopoiesis, leading to the “blueberry muffin” presentation, has been described in affected infants and children.<sup>60</sup>

Therapy of the soft-tissue infections includes antimicrobial agents and, as appropriate, debridement of wounds. Scrupulous dental



**Figure 25-3** Leukocyte adhesion deficiency. Small wounds can lead to large ulcerations that may resemble pyoderma gangrenosum. The ulceration on this boy's leg, initiated by a scratch from his sister, eventually extended to several centimeters in diameter and required a graft. (Reprinted with permission from Schachner LA, Hansen R, editors. Pediatric dermatology. London: Churchill Livingstone; 1995.)

**Table 25-2** Classification of Severe Combined Immunodeficiency

Disorder	Gene Location	Gene	Diagnostic Tests	Cells
ADA deficiency*	20q12-13	ADA	Red cell ADA levels and metabolites	T-/B-/NK-
Artemis deficiency	10p13	Artemis	Defects in V(D)J recombination; increased sensitivity to radiation	TB-/NK <sup>+</sup>
CD45 deficiency	1q31-32	CD45	CD45 expression	T-/B <sup>+</sup> /NK
IL-7 receptor deficiency	5p13	IL-7 receptor $\alpha$	IL-7 receptor $\alpha$ expression	T-/B <sup>+</sup> /NK <sup>+</sup>
JAK3 deficiency	19p13	JAK3	JAK3 expression/signaling	T-L/B <sup>+</sup> /NK
MHC class II deficiency	16p13 1q21 13q13	CIITA RFX5 RFXAP	HLA-DR expression	T <sup>+</sup> /B <sup>+</sup> /NK <sup>+</sup>
PNP deficiency	14q11	PNP	Red cell PNP levels and metabolites	T-/B-/NK-
RAG deficiency, Omenn syndrome	11p13	RAG1 and RAG2	Defects in V(D)J recombination; T- and B-cell clonal analysis	T-/B-/NK <sup>+</sup>
T-cell receptor deficiency	11q23	CD3g	CD3 expression	T-/B <sup>+</sup> /NK <sup>+</sup>
X-linked SCID <sup>†</sup>	Xq13	Common $\gamma$ chain	$\gamma_c$ expression by FACS	T-/B <sup>+</sup> /NK-
ZAP70 deficiency	2q12	ZAP-70	ZAP-70 expression	T-/B <sup>+</sup> /NK <sup>+</sup>

ADA, Adenosine deaminase; IL, interleukin; HLA-DR, human leukocyte antigen DR; MHC, major histocompatibility complex; PNP, purine nucleoside phosphorylase; RAG, recombinase activating gene; SCID, severe combined immunodeficiency; V(D)J, variable (diversity) joining.

\*Most common autosomal recessive form.

<sup>†</sup>Most common X-linked recessive form (46% overall).

hygiene reduces the severity of the periodontitis. Death usually occurs by 2 years of age in patients with severe LAD unless successful bone marrow transplantation or cord blood transplantation is performed.<sup>61</sup> Oral fucose has been helpful for some patients with LAD2.

### SEVERE COMBINED IMMUNODEFICIENCY

Severe combined immunodeficiency (SCID) is a group of disorders with similar clinical manifestations and immune dysfunction, but different biochemical, cellular, and molecular features (Table 25-2).<sup>62-65</sup> Overall, 75% of affected patients are boys. The majority of cases are autosomal recessive. Approximately 46% have the X-linked recessive form resulting from mutations in gene that encodes  $\gamma_c$ , which leads to an absence of T and natural killer (NK) cells but normal B-cell numbers.<sup>66</sup> This  $\gamma_c$  chain is a component of several interleukin receptors and is critical for T- and NK-cell function. Mutations in adenosine deaminase (ADA) lead to the second most common form of SCID. Accumulation of adenosine when its deaminase is missing is toxic to lymphocytes. Omenn syndrome usually results from deficiency of recombination activating gene (RAG) proteins, which mediate the deoxyribonucleic acid (DNA) double strand breaks that allow variable (diversity) joining (V[D]J) recombination and Ig diversity.<sup>67-69</sup>

Infants may present have a generalized seborrheic-like dermatosis, a morbilliform eruption, or exfoliative erythroderma with alopecia. Extensive cutaneous inflammation is a characteristic of 98% of infants with Omenn syndrome, a subset of SCID with reticuloendothelial cell proliferation. Patients with Omenn syndrome typically show hepatosplenomegaly (88%), lymphadenopathy (80%), alopecia (57%), eosinophilia, and a high serum IgE level.<sup>67</sup> Oral and genital ulcers are characteristic of defects in patients with an *Artemis* mutation, especially in Athabaskan-speaking American Indian children.<sup>70</sup> Multicentric dermatofibrosarcoma protuberans<sup>71</sup> and pulmonary alveolar proteinosis<sup>72</sup> have recently been described in association with ADA deficiency.

Acute graft-versus-host disease (GVHD) from maternal cell engraftment or nonirradiated transfusions should also be considered in an infant with an extensive cutaneous eruption.<sup>73</sup> Biopsy will allow differentiation. A more chronic form of GVHD (often with the acute form *in utero*) may also present as lesions that resemble lichen planus, lamellar ichthyosis, or scleroderma.

Recurrent infections, diarrhea, and failure to thrive are apparent by 3 to 6 months of age. The most common early infections are candidal infections and pneumonia caused by bacteria, viruses, or *Pneumocystis jiroveci*. Patients with SCID usually lack tonsillar buds, thymus, and

palpable lymphoid tissue, despite recurrent infections. Nearly all patients with SCID have a profound deficiency of T lymphocytes and a low absolute lymphocyte count. Patients are further classified by the results of fluorescent activated cell sorter (FACS) analysis into those with B lymphocytes (T-/B<sup>+</sup> SCID) and those without B lymphocytes (T-/B- SCID). Further subclassification can be made according to the presence or absence of NK cells (see Table 25-2). The specific diagnosis is confirmed primarily by direct gene analysis and flow cytometric analysis of peripheral blood mononuclear cells with antibodies directed against specific proteins missing from the cell surface, such as JAK3 or  $\gamma_c$ . The natural outcome for SCID is poor, and most patients die by 2 years of age without intervention. Hematopoietic stem-cell transplantation in infants is the treatment of choice<sup>74</sup> and leads to survival of 95% of infants if performed in the first 3 months of life. Bone marrow-derived CD34+ cells transduced with the SIN- $\gamma_c$  modified  $\gamma$ -retrovirus vector without preparative conditioning led to T-cell recovery without evidence of leukemia development after 12.1 to 38.7 months of follow-up study in nine boys with X-linked SCID.<sup>75</sup> Early diagnosis of SCID is critical, preferably before the administration of live vaccines, nonirradiated blood products and, in countries where applicable, bacille Calmette-Guérin (BCG). Patients with SCID have a high risk of BCG-associated complications (34% disseminated and 17% localized) and subsequent death, especially if they are given the vaccination at 1 month of age or younger and with T-cell numbers of 250/mcL or less at diagnosis.<sup>76</sup> In a United Kingdom-based study, diagnosis at birth because of a positive family history significantly improved outcome with survival of greater than 90% related to reduced rate of infection and improved transplantation outcome, suggesting that neonatal screening for SCID will also improve outcome.<sup>77</sup> Perinatal screening is now mandatory in several states.<sup>78-80</sup>

### Graft-Versus-Host Disease

The *host-versus-graft reaction* occurs when a graft or transplant (skin, heart, or kidney) is placed in a normal individual and the host's circulating immune cells react against the foreign tissue, causing graft or transplanted tissue destruction. In GVHD, the reverse happens.<sup>81</sup> The inflammation from conditioning regimens is thought to activate host antigen-presenting cells and chemokines that recruit donor leukocytes into host target organs.<sup>82</sup> Activated donor T cells stimulate dendritic cells, leading to further T-cell stimulation and expansion and culminating in target organ apoptosis and dysfunction. GVHD most commonly occurs in children with malignancy suppressed by

radiation and chemotherapy, who receive hematopoietic stem-cell transplantation, or in immunodeficient children who receive nonirradiated blood products. The risk of both acute GVHD (aGVHD) and chronic GVHD (cGVHD) is greater in males who receive female donor cells because of responses to H-Y minor histocompatibility antigens.<sup>83</sup> It has been estimated that moderate to severe GVHD occurs in 10% to 50% of patients given an allogeneic transplant from a human leukocyte antigen (HLA)-identical donor and much more commonly in patients given a transplant from a partially matched family donor or an unrelated volunteer.<sup>84</sup> *In utero* GVHD may occur in immunodeficient babies exposed to maternal antigens.<sup>73</sup> GVHD can occur in recipients of solid-organ transplants, especially multiorgan transplants, and reflects donor T-cell chimerism.<sup>85–87</sup>

The response to the host can be early (acute) or late (chronic). aGVHD classically develops during the first 100 days (usually 2 to 4 weeks) but can be persistent, recurrent or late onset, and usually involves the skin, gastrointestinal tract, and liver (in that order of incidence).<sup>88</sup> Patients who receive autologous transplants may have a mild cutaneous form of aGVHD that occurs 1 to 3 weeks after transplantation and resolves spontaneously. Reactions to transfusions often occur 7 to 10 days after the transfusion.<sup>89</sup> The most common cutaneous manifestation of aGVHD is erythematous macules and maculopapules that often begin on the ears, face, neck, palms, and soles and then become generalized (Figs. 25-4 and 25-5). The cutaneous eruption may become confluent and desquamate. Mild to moderate aGVHD most often presents with a nonspecific cutaneous eruption and thus can be confused with infection (especially viral), drug reaction,<sup>90</sup> and

reactions related to the transplant (e.g., the self-limited eruption of lymphocyte recovery, engraftment syndrome (which is characterized by associated fever and vascular leak with weight gain, edema, ascites, pulmonary infiltrates and hypotension),<sup>91</sup> and toxic erythema of chemotherapy (which is painful and usually localized to the palms, soles and intertriginous areas. Severe aGVHD may resemble exfoliative erythroderma or toxic epidermal necrolysis. Patients with aGVHD may complain of nausea or crampy abdominal pain and have watery or bloody diarrhea, hepatomegaly, and hepatic function abnormalities. Many patients are anorexic and have fever.

Milder forms of aGVHD may be difficult to distinguish from an infection (especially viral) or drug reaction. Abnormalities seen in biopsy specimens reflect the clinical severity of the cutaneous manifestations and range from nonspecific changes to basal keratinocyte vacuolization with scattered necrotic keratinocytes surrounded by lymphocytes (the characteristic "satellite cell necrosis") to severe epidermal necrosis. As such, biopsies are not helpful for patients with milder disease and do not tend to affect treatment decisions.<sup>92</sup> Laboratory tests may show eosinophilia and elevation of bilirubin and hepatic transaminase levels.

GVHD occurs in 6% (matched sibling cord blood) to 65% (matched unrelated donor peripheral blood stem-cell transplants) of pediatric patients. It typically presents 6 to 18 months after allogeneic stem-cell transplantation. Patients may have previous aGVHD that resolves or progresses directly into cGVHD, or may have no history of preceding aGVHD. cGVHD is now defined based on clinical and histopathologic signs of presentation, rather than time of onset since transplantation (formerly ≥100 days) and can be subclassified as *mild*, *moderate*, or *severe* based on number of sites, disability, and lung involvement.<sup>93,94</sup> An overlap syndrome with features of both aGVHD and cGVHD has been described. cGVHD often resembles autoimmune disorders and in contrast to aGVHD, can affect virtually any organ, leading to significant morbidity with decreased quality of life and overall survival.<sup>95</sup> Decreased survival of patients with cGVHD has been associated with thrombocytopenia, progressive onset, extensive cutaneous involvement, gastrointestinal involvement and a low Karnofsky performance status at diagnosis.<sup>92</sup>

cGVHD often manifests with generalized cutaneous involvement<sup>92</sup> (Table 25-3). Early lesions may resemble lichen planus with flat-topped violaceous papules and plaques (including mucosal changes of lichen planus) (Figs. 25-6 and 25-7) (see Chapter 4). Lichenoid lesions may be localized to Blaschko lines or to the site of previous herpes zoster infection.<sup>96</sup> Some patients with cGVHD manifest acquired ichthyosis that resembles ichthyosis vulgaris (Fig. 25-8) or lichen sclerosus (Fig. 25-9). Later changes of cGVHD include generalized xerosis, patchy dyspigmentation (Fig. 25-10), progressive poikiloderma, sclerodermatous changes<sup>97,98</sup> with joint contracture and ulcerations<sup>99</sup> (Figs. 25-10 through 25-13), cicatricial alopecia (Fig. 25-14), and nail dystrophy resembling that of dyskeratosis congenita (see Chapter 7, Fig. 7-63).<sup>100</sup> Disseminated porokeratosis has also been described after stem-cell transplantation and may respond to acitretin administration.<sup>101</sup>



**Figure 25-4** Acute graft-versus-host disease. Involvement of the scalp, ears, palms, and soles is common.



**Figure 25-5** Acute graft-versus-host disease. Almost confluent eruption of erythematous macules and papules in an immunodeficient neonate treated with extracorporeal membrane oxygenation (ECMO) and transfusion of nonirradiated blood.



**Figure 25-6** Chronic graft-versus-host disease (GVHD), lichenoid. After bone marrow transplantation, this boy had acute GVHD and subsequently developed cutaneous scaling papules and plaques typical of lichen planus.



**Figure 25-7** Chronic graft-versus-host disease (GVHD), lichenoid. Note the white coloration on the lips and tongue of this girl with early chronic GVHD.



**Figure 25-8** Chronic graft-versus-host disease (GVHD), ichthyotic. The ichthyotic changes of chronic GVHD resemble those of ichthyosis vulgaris.



**Figure 25-9** Chronic graft-versus-host disease (GVHD). The changes of chronic GVHD can resemble those of other autoimmune skin disorders. In this case, the cutaneous plaques resembled those of morphea/lichen sclerosus et atrophicus.

<b>Table 25-3</b> Features of Chronic Graft-Versus-Host Disease		
Location	Characteristic Features	Other Features
Skin	Lichen planus-like Sclerotic (or lichen sclerosus-like) Poikilodermatous Ichthyotic Vaginal scarring, stenosis	Depigmentation Genital erosions, ulcers, fissures
Hair		Alopecia, nonscarring, or cicatricial
Nails		Ridging, onycholysis, loss, pterygium
Oral	Lichen planus-like Keratotic plaques Sclerosis with restricted opening	Mucosal atrophy Xerostomia Ulceration Mucocele
Eyes		Dry eyes Cicatricial conjunctivitis Keratoconjunctivitis sicca Punctate keratopathy
Joints/ muscle	Contracture from sclerosis Fasciitis, arthritis	Myositis
GI	Chronic diarrhea Upper esophageal strictures, stenosis, webbing Hepatomegaly	
Lungs	Bronchiolitis obliterans Interstitial fibrosis	

Affected individuals may have dry eyes (as in Sjögren syndrome; see Chapter 22) and desquamative esophagitis with stricture formation. Weight loss can result from dysphagia and mucositis. Other manifestations are chronic diarrhea, hepatomegaly, lymphadenopathy, myositis, arthritis, pleural and pericardial effusions, and pulmonary fibrosis.

Patients with cGVHD show evidence of immune dysfunction and have recurrent infections. The majority of patients with cGVHD have eosinophilia and hypergammaglobulinemia. Many have thrombocytopenia and increased titers of a wide variety of autoimmune



**Figure 25-10** Chronic graft-versus-host disease. Hypopigmented and hyperpigmented scaling, indurated plaques in a generalized distribution, is seen here on her back.

antibodies, especially antinuclear antibodies (ANAs).<sup>92</sup> Liver function testing may show evidence of cholestasis. Pulmonary function tests are abnormal in approximately 50% of patients, and chest radiographs may reveal interstitial fibrosis. Biopsies of skin lesions show changes consistent with the clinical picture. For example, patients



**Figure 25-11** Chronic graft-versus-host disease. Sclerodactyly and subtle telangiectasia overlying knuckles, as seen in patients with systemic scleroderma and juvenile dermatomyositis.



**Figure 25-14** Chronic graft-versus-host disease. Note the extensive alopecia of the scalp with dyschromia and numerous sclerodermatosus plaques of the scalp and back.



**Figure 25-12** Chronic graft-versus-host disease. Note the cutaneous atrophy and nail dystrophy, including onycholysis and pterygium formation resembling the nails of lichen planus.



**Figure 25-13** Chronic graft-versus-host disease (GVHD). Sclerodactyly and generalized scaling were noted at birth in this girl with immunodeficiency and *in utero* GVHD. Her skin softened considerably with high dosages of thalidomide.

with lichenoid lesions have the histologic changes of lichen planus (see Chapter 4), often with satellite cell necrosis. Patients with sclerosis tend to show band-like inflammation at the dermal–epidermal junction and dermal sclerosis with obliteration of adnexae. Direct immunofluorescence analysis of skin specimens often shows the linear deposition of immunoreactants at the dermal–epidermal junction.

The mortality rate of GVHD ranges from 12% for mild aGVHD to 55% for severe aGVHD, usually because of infection.<sup>102</sup> The mortality of cGVHD is 25%, usually from infection, hepatic failure, and malnutrition. Having aGVHD is a major risk factor for development of cGVHD (11-fold increased risk), emphasizing the importance of preventing aGVHD. Other risk factors are an unrelated or mismatched donor, use of peripheral blood stem cells, older age of donor or recipient, use of total body irradiation, male recipient with a female donor, and malignant disease.<sup>103</sup> For patients with myeloablation (full-intensity conditioning, which eliminates all malignant and marrow hematopoietic cells), prophylaxis usually involves 2 to 12 months of tacrolimus (or cyclosporine), with or without a short course (about 1 month) of methotrexate. With reduced intensity conditioning before transplant, which does not fully eradicate malignant and hematopoietic cells and instead relies on immunologic antihost and antitumor effects, a calcineurin inhibitor and mycophenolate mofetil (MMF) (or, instead, corticosteroid) are generally used prophylactically. In both situations, anti-T-cell serotherapy with either antithymocyte globulin or alemtuzumab (Campath) is usually added for unrelated donor transplants and also reduces graft rejection; for haploididentical donors, T-cell depletion or CD34 selection is often performed. Environmental isolation, bowel rest through hyperalimentation, irradiation of blood products, and prevention of infection are other protective measures.

If grade II through IV aGVHD develops, the first-line therapy is continuing prophylactic immunosuppression (optimizing calcineurin inhibitor levels) and adding methylprednisolone 1 to 2 mg/kg per day.<sup>94</sup> For skin GVHD, topical steroid and/or tacrolimus may be added, with oral administration of budesonide for gastrointestinal GVHD. Patients who fail to respond to corticosteroid alone after 5 to 7 days can be treated with salvage therapy, such as MMF,<sup>104–106</sup> anti-TNF antibodies (e.g., infliximab), mammalian target of rapamycin (mTOR) inhibitors (e.g., sirolimus/ rapamycin),<sup>107–109</sup> anti-interleukin



**Figure 25-15** Orofacial granulomatosis. Granulomatous infiltration limited to the lip(s) is called *cheilitis granulomatosa*.



**Figure 25-16** Orofacial granulomatosis as part of Melkersson–Rosenthal syndrome. Scrotal tongue.

(IL-2) 2 antibodies (e.g., daclizumab),<sup>110</sup> or extracorporeal photopheresis (ECP).<sup>111–113</sup> Responses in general are poor if initial steroid treatment is not successful, and the risk of infection is high. If at least two second-line treatments fail, alternatives are alemtuzumab (Campath), methotrexate, pentostatin,<sup>114,115</sup> and mesenchymal stem cells.<sup>88,116–119</sup>

Similar regimens have been used to treat cGVHD, although there is no proven standard, with prednisone and calcineurin inhibitors most commonly used for first-line therapy.<sup>92</sup> The mean duration of therapy for patients with cGVHD is 3 years, with about half of the patients able to discontinue therapy 5 years after transplantation. Second-line treatment (steroid-resistant or steroid-sparing) includes one of more of the following: ECP (which gives the best result for skin, oral or liver cGVHD), rituximab,<sup>120</sup> imatinib mesylate (increases range of motion with sclerotic cGVHD),<sup>121–123</sup> mTOR inhibitors, and pentostatin. Third-line treatment includes pulsed high-dose intravenous methylprednisolone, MMF, or methotrexate. Overall, the 5-year survival rate is 50% for those who respond to therapy for GVHD and 30% for those with no or an incomplete response. Mucocutaneous manifestations of GVHD may also benefit from administration of thalidomide, acitretin, application of topical tacrolimus, or treatments with narrowband ultraviolet B (UVB) light, psoralen plus ultraviolet A light, or UVA1 light.<sup>124–128</sup> Supportive intervention for cGVHD includes supplemental nutrition (usually parenteral), scrupulous care of wounds, physical therapy to prevent joint contractures and disability, artificial tears, cutaneous emollients and sunscreens, and prophylaxis against *Pneumocystis* infection with trimethoprim-sulfamethoxazole.

### Orofacial Granulomatosis

Orofacial granulomatosis (OFG; also called *cheilitis granulomatosa* or *granulomatous cheilitis*) (Fig. 25-15) is characterized by face and lip swelling (macrocheilitis). It is the most common manifestation (93% with facial swelling and 66% with lip swelling) of Melkersson–Rosenthal syndrome, which also includes recurrent facial paralysis and a furrowed or “scrotal” tongue (lingua plicata) (Fig. 25-16).<sup>129,130</sup> Furrowing of the tongue and facial palsy have each been reported to occur in approximately 30% of patients. No prodrome warns of attacks, and patients experience no associated erythema, pain, or pruritus. The disorder is more prevalent in males and has a mean age of onset of 11 years.<sup>131</sup> The swelling can increase the size of the lip by twofold to threefold, leading to chapping from exposure of the mucosa. Both lips may be involved, and the swelling may be bilateral or unilateral. In addition to the swelling of the lips and other oral mucosal structures, the eyelids may be swollen. The attacks usually disappear within days or weeks but commonly tend to persist after several recurrences. Facial palsy usually occurs on the side of the facial swelling and tends to resolve spontaneously.<sup>132</sup>

The cause is unknown. Attacks usually start during adolescence with paralysis of a facial nerve, repeated severe headaches, edema of the circumoral tissue of the upper lip or cheeks, and occasionally edema of the gingivae, sublingual area, and lower lip. The edema is

usually asymmetric, but the whole face may be involved. Associated signs include hyperhidrosis, loss of taste, and visual impairment. Biopsy specimens show noncaseating granulomas in an edematous stroma that may be indistinguishable from the granulomas of Crohn disease,<sup>133</sup> and the relationship between Crohn disease and OFG remains controversial. In one systematic review, gastrointestinal signs were present in 26% at time of OFG diagnosis, and 40% of children received a concomitant diagnosis of Crohn disease, with OFG preceding signs of Crohn disease in more than 50%.<sup>131</sup> Concomitant perianal disease and a family history of Crohn disease are associated with a higher risk of Crohn disease.

Intralesional injections of triamcinolone or systemic administration of corticosteroids can control the facial and mucosal swelling; intermittent application of topical clobetasol gel may also lead to improvement. Minocycline, with or without corticosteroids, and sometimes macrolides have also been helpful.<sup>134,135</sup> Other therapies include thalidomide, dapsone, azathioprine, clofazimine, and TNF- $\alpha$  inhibitors, particularly infliximab.<sup>136–138</sup> Wedge resection of the inner lip should be reserved for patients who fail to respond to other options. The recurrent facial palsy tends to be more persistent than recurrent Bell palsy,<sup>139</sup> and transmastoid subtotal facial nerve decompression can lead to improvement in most cases.<sup>140</sup>

### Crohn Disease

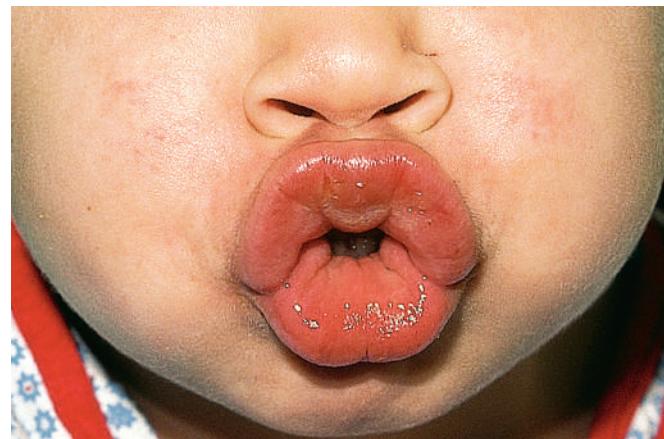
Crohn disease is a granulomatous disorder of the intestinal tract that usually has its onset between 15 and 30 years of age but has been described in young children.<sup>141,142</sup> Approximately one-third of pediatric patients have small intestinal disease, one-third have ileocolitis, and one-third have colitis. Total colitis is more common than segmental or isolated proctitis.<sup>142</sup> Growth failure,<sup>143,144</sup> delayed pubertal development, and osteopenia<sup>145</sup> are important complications of Crohn disease.

The pathogenesis of Crohn disease is complex. The disorder is thought to occur in genetically predisposed individuals when the intestinal mucosal immune function is altered by exogenous agents, such as infectious organisms, or host factors, such as intestinal barrier function, vascular supply, or stress.<sup>146</sup> The disorder occurs twofold to fourfold more often in Ashkenazi Jews and has been linked to certain HLA alleles (DR3, DQ2, DR103), as well as to mutant alleles of NOD2/CARD15. The CARD15 protein senses bacterial peptidoglycan and regulates nuclear factor (NF)- $\kappa$ B signaling.<sup>147,148</sup> Granulomatous colitis is also a feature of a subset of individuals with Hermansky–Pudlak syndrome (see Chapter 11).<sup>149</sup>

Skin manifestations may occur before, concomitantly, or after other evidence of disease.<sup>150</sup> Perianal skin tags are found in 75% to 80% of patients with Crohn disease (Fig. 25-17) and occur before gastrointestinal manifestations in 25% of patients. In addition to tags, skin and mucosal findings have been noted in 22% to 44% of patients (Table 25-4) and occur more often in patients with colonic versus small intestinal disease. Several mucocutaneous manifestations of Crohn disease also are features of ulcerative colitis. Erythema nodosum (see



**Figure 25-17** Crohn disease. Perianal tags are an early manifestation and seen in most affected children.



**Figure 25-19** Crohn disease. Note the infiltration of the lips, which showed noncaseating granulomas in biopsy sections.



**Figure 25-18** Crohn disease. Pyoderma gangrenosum on the vulva of an affected girl. Pyoderma gangrenosum is more commonly seen in individuals with ulcerative colitis than in those with Crohn disease.

**Table 25-4** Mucocutaneous Manifestations of Crohn Disease

	Specific	Nonspecific
Cutaneous	Extraintestinal cutaneous Crohn disease	Erythema nodosum Pyoderma gangrenosum Polyarteritis nodosa Erythema multiforme Vasculitis
Anogenital	Perianal fissures and tags Sinus tracts Labial or scrotal edema	
Oral	Orofacial granulomatosis Cobblestoning Mucosal tags	Aphthous stomatitis Angular cheilitis

Chapter 20) occurs in up to 15% of patients with Crohn disease and has been shown to correlate with the presence of arthritis.<sup>151</sup> Pyoderma gangrenosum occurs less often in Crohn disease<sup>152</sup> (approximately 1% of patients) (Fig. 25-18) than in ulcerative colitis (up to 5% of pediatric patients), occasionally precedes the development of bowel symptoms, and has a course unrelated to the activity of the bowel

disease. Oral aphthous ulcers have been described in greater than 50% of pediatric patients with Crohn disease.<sup>153</sup> Pyostomatitis vegetans, erythematous pustular lesions associated with erosions and ulcerations, is considered a marker for inflammatory bowel disease. Cutaneous changes related to nutritional deficits (particularly acrodermatitis enteropathica caused by zinc deficiency) can occur as well.

Other mucocutaneous manifestations are more specific for Crohn disease.<sup>142</sup> Cobblestoning of the buccal mucosa is seen in up to 20% of affected individuals. Painless swelling of the lips, resembling OFG, may be the initial presentation of Crohn disease in a child or adolescent<sup>154</sup> and may precede the gastrointestinal symptoms by several years (Fig. 25-19).<sup>155-159</sup> Similarly, the vulva may show erythema, swelling, and fissuring,<sup>160,161</sup> and the scrotum and penis may be swollen and erythematous.<sup>162-164</sup> Perianal lesions may extend onto the adjacent perineum, abdomen, or buttocks with fissures, and sinus tracts are common.<sup>165,166</sup> Nasal perforation<sup>167</sup> and chronic granulomatous otitis externa<sup>168</sup> have been described. Abdominal surgical sites may also be loci for cutaneous involvement. Biopsy provides the clue to diagnosis, although the noncaseating granulomas resemble those of Melkersson–Rosenthal/cheilitis granulomatosa and sarcoidosis. Special stains (periodic acid–Schiff, Ziehl–Nielsen and Gram) are important to consider infectious causes of granulomas. These granulomatous lesions of the lips and anogenital area are considered “contiguous” Crohn disease because of their proximity to the gastrointestinal tract. Granulomatous lesions elsewhere are considered extraintestinal (sometimes called *metastatic*) cutaneous Crohn disease.<sup>169,170</sup> These lesions typically are dusky red, swollen/indurated plaques, most commonly found on the genital region of children, lower extremities, abdomen, or trunk; lesions less commonly show no erythema or are ulcerating.<sup>171</sup>

Barium contrast studies are particularly important for investigating small bowel disease, but endoscopy and colonoscopy are important tools for upper and lower bowel disease, respectively. Initial treatment involves administration of systemic corticosteroids and aminosalicylates, with the early addition of azathioprine or 6-mercaptopurine as steroid-sparing alternatives for maintenance therapy.<sup>172</sup> TNF- $\alpha$  inhibitors (etanercept, adalimumab, and infliximab) are very helpful as well, and reduce the need for surgery.<sup>173-177</sup> The development of psoriasisiform dermatitis is common in patients with Crohn disease treated with TNF- $\alpha$  inhibitors and often manifests in periorificial and genital areas, scalp, hands and feet<sup>178-180</sup> (see Chapter 4; Fig. 4-25). The mechanism for the common occurrence of psoriasisiform dermatitis is unclear but has been linked to IL-23 receptor polymorphism.<sup>181</sup> Azathioprine-induced Sweet syndrome has also been described in association with Crohn disease.<sup>182</sup> Oral metronidazole has been used for extraintestinal cutaneous Crohn disease<sup>183,184</sup>; intralesional or topical applications of potent topical corticosteroids or tacrolimus<sup>185</sup> have helped clear the ulcerations of pyoderma gangrenosum. Colectomy in Crohn disease does not prevent recurrence and should be used selectively.<sup>186,187</sup>

## Sarcoidosis

Sarcoidosis is a systemic granulomatous disorder of unknown etiology with CD4+ Th1 cell and monocyte activation, leading to hypergammaglobulinemia, sarcoidal granulomas (predominantly affecting the lungs, eyes, skin, and reticuloendothelial system), and ultimately fibrosis. The condition presents most often in adults between the ages of 20 and 40 years. In pediatric patients, it is most commonly seen in adolescents between 9 and 15 years of age, in which manifestations resemble those of adult patients. In a US series of pediatric sarcoidosis, 72% to 81% among older children were African-Americans (vs. only 7% to 28% in young children).<sup>188</sup>

There is no single reliable test for sarcoidosis. Because the clinical picture may be mimicked by other diseases, histologic confirmation is advisable. In typical lesions, the characteristic histopathologic finding consists of islands of large, pale-staining epithelioid cells containing few if any giant cells intermingled with histiocytes and lymphocytes. Sarcoidosis must also be distinguished from infectious granulomatous conditions, particularly mycobacterial and fungal infections, but cultures and special stains of biopsy sections are negative. Cutaneous anergy is common, but children should be tested for reactivity to tuberculin.

### SARCOIDOSIS IN OLDER CHILDREN AND ADOLESCENTS

Adolescents and older children may have fever and weight loss.<sup>189</sup> Cutaneous involvement occurs in 15% to 25% of pediatric patients and in older children.<sup>190</sup> Several specific and nonspecific lesions have been described, although no lesion is pathognomonic.<sup>191</sup> Most typical are yellow-brown to red flat-topped papules, infiltrated plaques, and nodules that show an apple-jelly color when diascopy (pressure applied with a glass slide) is performed, a characteristic sign of granulomas. Scaling is sometimes associated. These granulomatous lesions are most commonly localized to the face, and an annular configuration of lesions around the nares, lips, and eyelids is highly characteristic, although any site, including the mucosae, palms, and soles, may be involved. Lesions often occur in areas of trauma or scarification. Other cutaneous manifestations of sarcoidosis include subcutaneous, often painful nodules (Darier-Roussy sarcoidosis), ichthyosis (ichthyosiform sarcoidosis, usually most prominent on the lower extremities), generalized erythroderma with scaling, and hypopigmentation. More than 20% of affected children have erythema nodosum (see Chapter 20), which is often manifested at onset and is a good prognostic sign<sup>188</sup> that usually portends clearance of the adenopathy. The combination of erythema nodosum, bilateral hilar adenopathy, uveitis, and fever has been called *Löfgren syndrome*. Lupus pernio is a variant of sarcoidosis in which soft, infiltrated, violaceous plaques are located on the nose, cheeks, ears, forehead, and on the dorsal aspects of the hands, fingers, and toes (Fig. 25-20). This variant can cause significant scarring and deformity and is a marker for upper respiratory involvement, including the larynx.

The lung is the most commonly involved site in older children and adolescents, as in adults. A dry, hacking cough is the most common



**Figure 25-20** Sarcoidosis. The lupus pernio form of sarcoidosis shows infiltrated violaceous plaques on the nose, cheeks, and ears. This girl had hoarseness owing to her laryngeal involvement with sarcoidosis, and was left with severe scarring after treatment.

complaint, but patients may have dyspnea and develop parenchymal lung disease. Lymphadenopathy may be generalized, but typically involves the hilar nodes and is symmetric. More than 90% show an abnormal chest X-ray at onset. Clinical evidence of liver involvement is detected in approximately one-third of patients, although more than half show granulomas when the liver is biopsied. Splenic enlargement has been associated with extensive visceral fibrosis and a poor prognosis. Granulomatous infiltration of the heart may lead to arrhythmias, and infiltration of the lung to congestive heart failure. Some patients with renal involvement will show hypercalciuria, renal stones, and ultimately renal failure from excessive production of 1,25-dihydroxyvitamin D<sub>3</sub>, with or without hypercalcemia; calciphylaxis has also been reported in association with end-stage renal disease, manifesting as painful violaceous plaques, retiform purpura, or subcutaneous nodules, which can progress to nonhealing ulcers and cutaneous gangrene.<sup>192</sup>

Although more common in young children, arthritis is a component of sarcoidosis in older children and can be the presenting feature in more than 10%. Overall, up to 74% of pediatric patients have eye involvement, particularly anterior segment uveitis (Fig. 25-21). Conjunctival granulomas are often seen on biopsy, and lacrimal gland inflammation is not uncommon. Chorioretinitis, keratitis, and glaucoma may occur as well, resulting in blindness. Neurologic manifestations are associated with a poorer prognosis, and overall affect 5% to 10% of older patients, most commonly facial nerve paralysis. The combination of uveitis, facial nerve palsy, parotid gland enlargement, and fever has been called *uveoparotid fever* or *Heerfordt syndrome*. Lytic lesions of the distal bones rarely occur and are asymptomatic.

Thorough evaluation also includes ophthalmologic examination with slit-lamp testing, chest radiographs (with chest computed tomography [CT] scanning if needed), pulmonary function testing, electrocardiogram, and 24-hour urine calcium measurements. Many affected patients have hyperglobulinemia, especially African-Americans. Patients may show hypercalcemia (7% to 24% and usually transient), leukopenia, eosinophilia (>50% of children), and usually an increased ESR. The angiotensin-converting enzyme (ACE) level is often elevated but may be increased in other granulomatous disorders as well and has a 40% false-negative rate.

The natural course of sarcoidosis in childhood is insidious, and the condition often regresses completely after many years, especially in those with an acute onset. Chronic, progressive sarcoidosis has a poorer prognosis and rarely involutes. Features that portend a worse prognosis include chronicity; lupus pernio; symptoms lasting longer than 6 months; black race; involvement of more than three organ systems; and later stage pulmonary disease.<sup>193</sup> The overall mortality rate is 1% to 5%.

Corticosteroids (1 mg/kg per day initially with tapering as possible) can suppress the acute manifestations of the disorder.<sup>194</sup> However, given the hazards of prolonged systemic corticosteroid therapy and



**Figure 25-21** Sarcoidosis. Uveitis in a teenager with sarcoidosis since early childhood. She had ichthyosiform scaling overlying granulomatous papules and arthritis.

**Table 25-5** Common Features of Sarcoidosis in Older Versus Younger Children

Older Children and Adolescents	Preschool-Aged Children
Fever, weight loss	Low-grade fever
Skin lesions	Polyarthritides
Cough, dyspnea	Skin lesions
Lymphadenopathy	Iridocyclitis with uveitis
Hepatomegaly	Parotid gland enlargement
Splenomegaly	Lymphadenopathy, especially peripheral
Arrhythmias	
Congestive heart failure	
Renal stones (hypercalciuria)	
Uveitis	
Facial paralysis	Splenomegaly

the common spontaneous resolution of sarcoidosis, the administration of systemic corticosteroids is best reserved for rapidly progressive and disfiguring skin lesions, ocular disease, and significant visceral abnormalities (persistent hypercalcemia; joint involvement; lesions of the nasal, laryngeal, and bronchial mucosa; severe, debilitating, or rapidly progressing lung disease; central nervous system lesions; persistent facial palsy; myocardial involvement; and hypersplenism). Methotrexate is the most commonly used steroid-sparing systemic agent for pediatric sarcoidosis, and MMF and TNF- $\alpha$  inhibitors (particularly infliximab) have also been used successfully.<sup>195</sup> Ophthalmic steroid preparations may be used adjunctively for eye disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used for the arthritis, and hydroxychloroquine and allopurinol have been used successfully for skin lesions.

### SARCOIDOSIS IN PRESCHOOL CHILDREN/BLAU SYNDROME

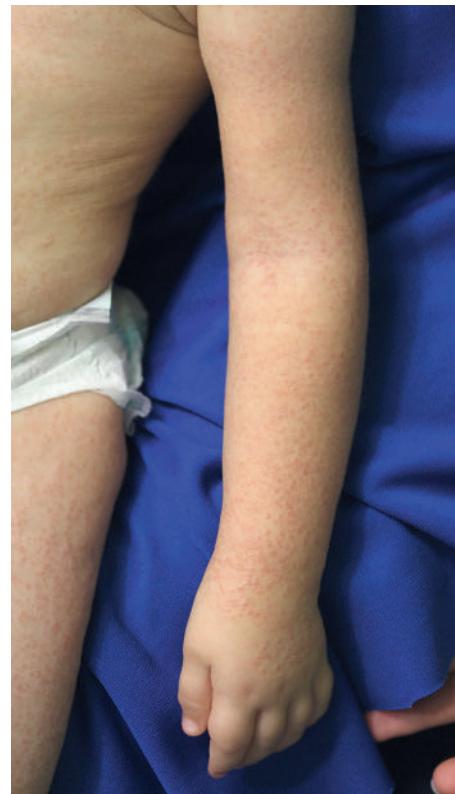
Sarcoidosis in preschool-age children differs from that of older children, adolescents, and adults,<sup>188,196,197</sup> and is characterized by polyarthritis and severe uveitis (commonly suggesting a diagnosis of juvenile idiopathic arthritis [JIA]),<sup>198</sup> cutaneous manifestations, and a conspicuous absence of pulmonary abnormalities (Table 25-5).<sup>199,200</sup> The majority of young children with this presentation (also called *early-onset sarcoidosis* [EOS]) have been found to have heterozygous mutations in *CARD15*. As such, EOS is considered to be the sporadic form of Blau syndrome, an autosomal dominant disorder with the cutaneous granulomas and other features of EOS.<sup>201–203</sup> Blau syndrome/EOS is associated with increased flaring and morbidity and a poorer prognosis than sarcoidosis in older children and adults. The complete classic triad (skin eruption, arthritis, and recurrent uveitis) occurs in 42% of patients with Blau syndrome,<sup>204,205</sup> and cutaneous features are usually the first to appear.<sup>206</sup> Generalized asymptomatic small erythematous papules on the trunk and extremities are most commonly seen (Figs. 25-22 and 25-23), often leaving small pitted scars as sequelae. However, the cutaneous lesions have variably been described as eczematous, ichthyosiform (misdiagnosed as ichthyosis vulgaris), or lichenoid.<sup>207,208</sup> Relapses and remission are common. Erythema nodosum is the second most common skin manifestations of Blau syndrome, and leukocytoclastic vasculitis involving skin has also been described.

Boggy synovitis and tenosynovitis of the wrists, fingers, knees, and ankles are characteristic and show symmetric nonerosive arthritis radiographically.<sup>209</sup> Despite the chronicity, joint destruction is uncommon, and range of motion is usually not reduced, in contrast to the arthritis of JIA. However, the proximal interphalangeal joints disproportionately develop contractures, leading to camptodactyly (usually congenital flexion contracture of a finger).<sup>210</sup> Bone dysplasia can also be seen.

Ocular involvement is extremely common in children,<sup>211</sup> especially an insidious bilateral granulomatous iridocyclitis with uveitis that involves not just the anterior uveitis (as in JIA), but also posterior uveitis. The mean age of onset of ocular disease is 4 years, and it ultimately develops in 80% of patients.<sup>201</sup> Keratitis, retinitis, optic



**Figure 25-22** Blau syndrome. Discrete, erythematous papules were present in a generalized distribution in this young boy with arthralgias. Biopsy showed noncaseating granulomas.



**Figure 25-23** Blau syndrome/early-onset sarcoidosis. Erythematous granulomatous papules on the arm, trunk, and thigh of a 5-year-old boy with a *CARD15* mutation.

atrophy, glaucoma, cataracts, retinal detachment, and involvement of the eyelids and lacrimal glands may also occur. Of those with ocular involvement, 11% show moderate visual impairment and 16% become blind.

Other manifestations are noted in about one-third of patients. In addition to the erythema nodosum, low-grade fever, and sialadenitis with parotid gland enlargement, splenomegaly and lymphadenopathy are relatively common. Other signs are large vessel vasculitis, cranial (but not central) neuropathy, interstitial lung disease, interstitial nephritis, pericarditis, and hepatomegaly without abnormal hepatic function.

The susceptibility gene for Blau syndrome, also known as *familial granulomatous arthritis*, is *CARD15* (also known as *NOD2*).<sup>212</sup> Mutations in *CARD15* lead to constitutive activation of NF-κB signaling. Mutations in *CARD15/NOD2* have also been associated with the development of Crohn disease, but mutations that increase the susceptibility to Crohn disease versus Blau syndrome are in regions.<sup>213,214</sup> The cutaneous granulomatous papules may respond to chronic administration of erythromycin but may leave tiny atrophic macules. Methotrexate and TNF-α inhibitors are most often used for extracutaneous manifestations; thalidomide and IL-1 inhibition have also been reported to be effective.<sup>215,216</sup>

## Auto-Inflammatory Disorders

### HEREDITARY PERIODIC FEVER SYNDROMES

The auto-inflammatory disorders are a group of monogenic inherited disorders characterized by intermittent or fluctuating degrees of inflammation, particularly of the abdomen, skin, and joints, without evidence of high-titer autoantibodies or antigen-specific T cells (Table 25-6).<sup>217-220</sup> One group of auto-inflammatory disorders, inflammasomopathies, results from abnormalities of the inflammasome. The inflammasome is a macromolecular complex that senses microbial products and endogenous “danger signals” to activate caspase-1 and ultimately IL-1β, key steps in the innate immune response. Some of these are intrinsic defects of the inflammasome, such as the cryopyrinopathies (defective cryopyrin leads to familial cold auto-inflammatory syndrome [FCAS], Muckle–Wells syndrome [MWS], and neonatal onset multisystemic inflammatory disorder). Others result from abnormalities or deficits in proteins that interact directly or indirectly with the inflammasome, such as pyrin (hereditary periodic fever syndromes) and PSTPIP1 (pyogenic sterile arthritis, pyoderma gangrenosum, and acne [PAPA] syndrome). The hereditary periodic fever syndromes (familial Mediterranean fever [FMF], mevalonate kinase deficiency, and TNF receptor-associated periodic syndrome) show recurrent episodes of fever, often in association with a cutaneous eruption, serositis (peritonitis, pleuritis), arthritis, and lymphadenopathy. Progressive amyloidosis of the liver and kidneys has been reported in association with several types of periodic fever syndromes and may be life-threatening.

The pyogenic auto-inflammatory disorders include PAPA; periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA); and synovitis, acne, palmoplantar pustulosis and psoriasis, hyperostosis, and osteitis (SAPHO) syndromes (see Chapter 8) and deficiencies of the IL-1 receptor antagonist (DIRA) and interleukin-36 receptor antagonist (DITRA); they feature neutrophilic infiltration, with clinical features that include pyogenic arthritis, aphthous ulcerations, pyoderma gangrenosum-like lesions, and pustular skin eruptions.<sup>221,222</sup> Auto-inflammatory disorders such as Crohn disease and Blau syndrome (see Sarcoidosis section) are related to sequence variations in *NOD2/CARD15*, which plays a central role in the NF-κB activation response to microbial products. Among other disorders considered auto-inflammatory are Behcet syndrome and systemic onset JIA (see Chapter 22).<sup>223-226</sup>

### HEREDITARY PERIODIC FEVER SYNDROMES

#### Familial Mediterranean Fever

Familial Mediterranean fever (FMF; benign paroxysmal peritonitis, familial paroxysmal polyserositis, familial recurrent polyserositis, Armenian disease) is the prototype of the hereditary auto-inflammatory disorders.<sup>227-229</sup> An autosomal recessive disorder, FMF results from loss-of-function mutations in *MEFV* (Mediterranean fever gene), which encodes pyrin (or marenostatin).<sup>230</sup> Pyrin is thought to act as an anti-inflammatory molecule of polymorphonuclear leukocytes and cytokine-activated monocytes. The disorder is most commonly seen in individuals of Arabic, Turkish, or non-Ashkenazi Jewish descent, in which the gene is carried in one of five persons.

The acute attacks of high fever and serositis (peritonitis, pleuritis, and synovitis, with abdominal, chest, and articular pain) begin during the first decade in 67% of cases and by the second decade in 90%. The attacks typically last 1 to 3 days. The erysipelas- or cellulitis-like



**Figure 25-24** Familial Mediterranean fever. Erythematous nodules on the dorsal aspect of the foot and pretibial area of an affected child. (Courtesy of James E. Rasmussen, MD; reprinted from Hurwitz S. The skin and systemic disease in children. Chicago: Year Book Medical Publishers, 1985.)

lesions, the most common cutaneous manifestations, occur in almost 10% of patients (Fig. 25-24).<sup>231</sup> Of importance, these painful, warm, swollen erythematous, well-defined plaques can occur in children without a history of fevers, although acute phase reactants are increased.<sup>232</sup> Both the skin signs and the arthritis may be precipitated by trauma. Other cutaneous manifestations include urticaria, erythematous papules, vesicles, bullae, and subcutaneous nodules histologically resembling periarteritis nodosa or vasculitis. Skin lesions usually appear on the calves, around the ankles, and on the dorsal aspects of the feet.

Usually a single organ is affected during an attack. Attacks last from a few hours to 4 days and recur throughout life with variable periodicity. Asymptomatic intervals may last as long as several years. Although symptoms of the monoarticular joint inflammation persist longer than episodes of peritonitis, sometimes for several months, chronic residual manifestations are rare.

Amyloidosis occurs in about 25% of untreated patients and causes death in 90% of individuals affected with amyloid-induced renal dysfunction before the age of 40. The risk of developing amyloidosis is a function of the duration between disease onset and diagnosis, and of

**Table 25-6** Auto-Inflammatory Disorders

<b>Disorder</b>	<b>Inheritance</b>	<b>Gene Defect</b>	<b>Gene Product</b>	<b>Associated Features</b>
<b>GRANULOMATOUS</b>				
Blau syndrome	AD	<i>NOD2/CARD15</i>	CARD15	Onset usually <5 years old Granulomatous dermatitis, uveitis, synovitis Good response to TNF inhibitors
<b>PERIODIC FEVERS</b>				
Familial Mediterranean fever	AR	<i>MEFV</i>	Pyrin (marenostrin)	Recurrent fever of short duration (24–48 h) Serositis with abdominal pain, pleuritis and chest pain Pericarditis, scrotal swelling, splenomegaly, erysipelas-like eruption in minority of patients High risk of renal amyloidosis if untreated Good response to colchicine, IL-1 blockade
TNF receptor-associated periodic syndrome (TRAPS)	AD	<i>TNFRSF1A</i>	P55 TNF receptor	Recurrent fevers that are prolonged (1–3 weeks) Serositis, rash, conjunctivitis, periorbital edema, arthritis 10% to 25% incidence of renal amyloidosis Response to etanercept and IL-1 blockade
Mevalonate kinase deficiency (MVK)	AR	<i>MVK</i>	Mevalonate kinase	Early onset (usually first year) Periodic fever lasting 4–5 days
Hyper-IgD syndrome (HIDS)				Urticular eruption (>90%), abdominal pain with vomiting and diarrhea, arthritis Headache, hepatosplenomegaly, painful cervical adenopathy, aphthous stomatitis, leukocytosis, high levels of IgD Response to steroids, NSAIDs, simvastatin, IL-1 blockade Often improves by adulthood Amyloidosis rare*
<b>CRYOPYRINOPATHIES</b>				
Familial cold auto-inflammatory syndrome (familial cold urticaria)	AD	<i>CIA1</i>	Cryopyrin	Cold-induced nonpruritic urticaria, arthritis, fever and chills, leukocytosis Responds to IL-1 blockade
Muckle–Wells syndrome	AD	<i>CIA1</i>	Cryopyrin	Recurrent urticaria, sensorineural hearing loss, amyloidosis Responds to IL-1 blockade
Neonatal onset multisystem disease (NOMID) <sup>†</sup>	AD	<i>CIA1</i>	Cryopyrin	Neonatal onset urticaria, chronic aseptic meningitis, arthropathy and bone deformities, fever, ocular changes and hearing loss Responds to IL-1 blockade
<b>PYOGENIC</b>				
Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome	AD	<i>PSTPIP1/C2BP1</i>	PSTPIP1/C2BP1	Pyogenic (sterile, destructive) arthritis, pyoderma gangrenosum, acne, myositis
Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome	Unknown	Unknown	Unknown	Periodic fevers, aphthous stomatitis, pharyngitis, and cervical adenitis Malaise, headache
Majeed syndrome	AR	<i>LPIN2</i>	Lipin-2	Multifocal osteomyelitis, congenital dyserythropoietic anemia, inflammatory dermatosis Responds to IL-1 blockade
Deficiency of the IL-1 receptor antagonist (DIRA)	AR	<i>IL1RN</i>	IL-1 receptor antagonist	Fetal distress, joint swelling with periosteal inflammation, severe osteopenia, lytic bone lesions, respiratory involvement, thromboses, aphthae, pyoderma gangrenosum, pustulosis Responds to IL-1 blockade
Deficiency of the IL-36 receptor antagonist (DITRA)	AR	<i>IL36RN</i>	IL-36 receptor antagonist	Usually generalized pustules, fever and malaise May have palmoplantar pustulosis or AGEP-like disorder Nail dystrophy, arthritis, cholangitis
CARD14-mediated pustular psoriasis (see Ch. 4)	AD	<i>CARD14</i>	CARD14	Pityriasis rubra pilaris, plaque psoriasis, erythroderma with pustular psoriasis Usually responds to ustekinumab May respond to methotrexate TNF inhibitor
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome (see Ch. 20)	AR	<i>PSMB8</i>	Proteasome subunit β type	Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (fever), lymphadenopathy, purpuric patches and nodules, arthralgias Same as Nakajo–Nishimura syndrome May respond to JAK inhibitor
STING-associated vasculopathy with onset in infancy (SAVI) syndrome	AD	<i>TMEM173</i>	STING	Acral telangiectatic vasculopathy with soft tissue loss, sometimes large pustules Fevers, adenopathy, interstitial lung fibrosis May respond to JAK inhibitor

AD, Autosomal dominant; AGEP, acute generalized exanthematous pustulosis; AR, autosomal recessive; Ig, immunoglobulin; IL, interleukin; NSAID, nonsteroidal anti-inflammatory drug; STING, stimulator of interferon genes; TNF, tumor necrosis factor.

\*Amyloidosis is unusual in Blau, HIDS, PAPA and PFAPA syndromes.

<sup>†</sup>Also called chronic infantile neurologic cutaneous and articular (CINCA) syndrome.

the frequency of episodes of chest pain, arthritis, and erysipelas-like erythema.<sup>233</sup>

The diagnosis of FMF is dependent on clinical features and, as needed, genetic testing. Colchicine (1 to 2.5 mg/kg per day) prevents the recurrence of attacks and the amyloidosis<sup>234,235</sup>; once daily usage may be as effective and safe as two to three divided daily doses.<sup>236</sup> Anakinra (directed against IL-1), interferon- $\alpha$ , corticosteroids, and cyclophosphamide have been used in rare patients who are unresponsive to colchicine.<sup>237,238</sup> FMF patients carrying a *CARD15/NOD2* mutation have a higher rate of erysipelas-like erythema and acute scrotum attacks, a trend for a higher rate of colchicine resistance, and a more severe disease as compared with patients without mutations.<sup>239</sup>

### TNF Receptor-Associated Periodic Syndrome

TNF receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disorder caused by mutations in the p55 TNF receptor (*TNFR1*), encoded by *TNFRSF1A*,<sup>240</sup> or defects in shedding of the receptor.<sup>241-244</sup> The febrile attacks tend to last longer than those of FMF, at least 5 days and sometimes up to 3 weeks (mean, 11 days with 70 symptomatic days per year).<sup>245</sup> They usually have no periodicity, despite the name, but are recurrent rather than continuous with flares in almost 90% of affected individuals.<sup>244</sup> Fever always occurs in children but is sometimes absent in adults. Only 25% of patients can identify triggers, and a minority have prodromal symptoms (periorbital edema, malaise, headache). Manifestations usually begin during childhood in more than 90% of patients (median age of symptom onset of 3 to 4 years old), and more than 75% of patients have cutaneous involvement.<sup>246</sup> Most typical is the erythematous swollen plaque with indistinct margins that is warm and tender to palpation. It is most commonly located on the extremities, where it may begin distally and migrate proximally during the attack. The eruption is described as maculopapular or urticarial, each in approximately 25% of patients. Localized or generalized serpiginous erythematous patches and plaques and pseudofolliculitis have also been described. Painful myalgias accompany the eruption in 70% of patients and may precede the appearance of cutaneous signs. Severe abdominal pain and arthralgias or occasionally arthritis occur in most patients, but thoracic and scrotal pain, orbital edema, and conjunctivitis are also common complaints. Amyloid deposition, especially in the kidneys and liver, is described in 10% to 25% of individuals with TRAPS at a median age of 43 years.

The diagnosis of TRAPS can be confirmed by gene testing. Corticosteroids are the most effective treatment, but daily administration has been required; NSAIDs provide symptomatic relief. TNF- $\alpha$  inhibitors (etanercept),<sup>247</sup> anakinra,<sup>248</sup> and tofacitinib have been efficacious in some patients, but infliximab and adalimumab may induce paradoxical inflammatory reactions,<sup>249,250</sup> which may be mutation dependent.

### Periodic Fever Associated with Mevalonate Kinase Deficiency (Hyperimmunoglobulin D Syndrome)

Periodic fever associated with mevalonate kinase deficiency (MKD, or hyper-IgD syndrome [HIDS]) is an autosomal recessive disorder that presents during the first 6 months of life in 60% of patients and by 5 years of age in 92%.<sup>251</sup> More than 90% of patients show the cutaneous eruption of erythematous maculopapules or papules. Fever is also often associated with lymphadenopathy (71%), diarrhea (69%), joint pain (67%), abdominal pain (63%), and splenomegaly (63%). The high serum level of IgD distinguishes this periodic fever from FMF.<sup>252</sup> Inflammatory attacks typically last approximately 1 week and recur every 4 to 8 weeks. Renal deposition of amyloid is rare.<sup>253</sup>

Mutations in MVK lead to deficient mevalonate kinase,<sup>254,255</sup> disruption of cholesterol biosynthesis, and a shortage of isoprenoid end products, leading to inflammasome activation and IL-1 mediated inflammation.<sup>256,257</sup> Complete deficiency of mevalonate kinase (vs. the 1% to 8% residual activity in MKD) results in mevalonic aciduria, which is associated with growth and mental retardation and morphologic abnormalities, in addition to recurrent fevers, rash, lymphadenopathy, and inflammation of the joints and gastrointestinal tract. Definitive diagnosis of HIDS cannot rely on the demonstration of high levels of IgD, because this has now been shown in some patients with

FMF and TRAPS, but rather depends on finding evidence of MKD or mevalonic aciduria.

Fevers respond dramatically to steroids, but the frequent recurrence of fevers makes steroid therapy untenable. IL-1 inhibitors are the treatment of choice.<sup>258</sup> However, other cytokines are activated as well,<sup>259</sup> and in patients in whom IL-1 inhibition is insufficient, TNF inhibitors<sup>260,261</sup> and tofacitinib may decrease the inflammation. Administration of simvastatin improves inflammatory attacks; simvastatin inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which precedes mevalonate kinase in the isoprenoid pathway.<sup>262</sup>

### THE CRYOPYRINOPATHIES: FAMILIAL COLD AUTO-INFLAMMATORY, MUCKLE-WELLS, AND CINCA/NOMID SYNDROMES

Although originally described as separate disorders, these three autosomal dominant syndromes are now known to be caused by mutations in the gene *NLRP3/CIA1* (cold-induced auto-inflammatory syndrome).<sup>263,264</sup> This gene encodes cryopyrin (or NALP3), which forms a complex that activates caspase 1. Caspase 1 cleaves the inactive IL-1 $\beta$  to the active form of IL-1 $\beta$ . The recent demonstration of IL-17-associated neutrophil recruitment suggests IL-1-induced activation of Th 17 cells and that IL-17/IL-17RA inhibitors may be new therapeutic targets.<sup>265</sup> The mutations that result in the different syndromes are largely distinct.

Recurrent urticarial-like eruptions are common to all three syndromes. In FCAS (familial cold urticaria), the mildest condition of the group, the urticaria is delayed in its onset, usually a few hours after exposure to cold, and persists for less than 24 hours. Fever, conjunctivitis, and arthritis are also seen in association.<sup>266</sup> FCAS must be distinguished from FCAS2, a newly described autosomal dominant disorder caused by mutations in *NLRP12* and responsive to IL-1 inhibition. FCAS2 is characterized by recurrent cold-induced episodes of fever, urticarial eruption, aphthous stomatitis, adenopathy, and abdominal discomfort. Dominant missense mutations in *PLCG2*, encoding phospholipase Cy2, lead to phospholipase Cy2-associated antibody deficiency and immune dysregulation (PLAID) syndrome, characterized by evaporative cold urticaria (see Chapter 20). The onset may be as early as the neonatal period with vesiculopustules and recurrent erythematous granulomatous plaques.<sup>266,267</sup> Other features may include interstitial pneumonitis and bronchiolitis, arthralgia, enterocolitis, ocular issues, and mild immunodeficiency.

MWS is an autosomal dominant auto-inflammatory disorder characterized by recurrent urticarial eruption, arthralgias, conjunctivitis, sensorineural hearing loss, and risk of reactive AA amyloidosis resulting from the progressive visceral accumulation of amyloid fibrils. Proteinuria or renal insufficiency from renal amyloidosis can be observed in up to 25% of patients. Female sex and hearing loss are risk factors for more severe disease.<sup>268</sup>

Chronic infantile neurologic cutaneous and articular (CINCA), or neonatal onset multisystemic inflammatory disease (NOMID), syndrome typically presents as fever and nonpruritic urticarial erythema during the first week of life.<sup>269,270</sup> The urticarial rash usually begins on the extremities and tends to migrate, even during examination. It has a waxing and waning course but never tends to resolve entirely.<sup>271</sup> Arthralgias and arthritis develop early during the first weeks of life and are thereafter persistent, leading to disabling destructive arthropathy during infancy. Bony deformities, especially of the knees, are characteristic, with distinctive radiographic findings of patellar and long bone ossification with overgrowth. Chronic aseptic meningitis has been associated with headaches in older children, and patients may have seizures, spasticity, and motor defects. Some affected children have developed brain atrophy during the neonatal period, which has been linked to developmental delay and retardation. Papillitis with optic atrophy and anterior uveitis are the most common ocular manifestations, with a mean age of onset of 4.5 years; severe visual loss occurs in 26% of patients with ocular disease.<sup>272</sup> Bilateral sensorineural progressive hearing loss is commonly associated as well. Most patients show a typical angelic facies with frontal bossing, a saddleback nose, and midfacial hypoplasia. Lymphadenopathy, splenomegaly, premature atherosclerosis,<sup>273</sup> increased ESR, eosinophilia,

leukocytosis, and hyperglobulinemia are features of chronic inflammation. Early death has been linked to infection, vasculitis, and amyloidosis.

IL-1 inhibitors such as anakinra and canakinumab usually lead to rapid resolution of inflammation in cryopyrin-associated autoinflammatory syndromes (CAPS).<sup>274–277</sup> Canakinumab administration every 8 weeks is well tolerated and leads to a complete response in 78% of treated individuals within 1 week and virtually all patients by 3 weeks of after administration.<sup>278,279</sup> Canakinumab has also been shown to improve kidney function in MWS with overt renal amyloidosis.<sup>280</sup> TNF inhibitors and stem-cell transplantation have been used for severely affected patients who fail to respond to IL-1 inhibition. MCC950, a small molecule inhibitor of NLRP3, reduced IL-1 $\beta$  and showed promise in a mouse model and *ex vivo* samples from individuals with MWS.<sup>281</sup>

### PERIODIC FEVER, APHTHOUS STOMATITIS, PHARYNGITIS, AND CERVICAL ADENITIS SYNDROME

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome (or Marshall syndrome) is the most common periodic fever syndrome and occurs primarily in children under 5 years of age.<sup>282</sup> Affected children have a mean of 4 to 5 days of fever greater than 39°C, which recurs regularly every 3 to 8 weeks. Pharyngitis has been described in almost 90% of patients, cervical adenitis in 78%, and stomatitis in 38% to 71%.<sup>283,284</sup> Attacks of mild abdominal pain, vomiting, headache, and malaise are common; arthralgias, genital ulceration,<sup>285,286</sup> erythematous cutaneous eruptions and neurologic signs are uncommon.

Familial cases are often described, but it is unclear if these cases reflect a genetic or environmental predisposition.<sup>282,287–289</sup> Approximately 20% of affected individuals have NLRP3 variants, suggesting that inflammasome-related genes might be involved.<sup>290</sup> IL-1 $\beta$  monocyte production is dysregulated in patients with PFAPA syndrome, with elevation in IP-10/CXCL10 chemokines.

Other inflammatory disorders with fever, including infectious disorders, must be considered. The fever tends to be poorly responsive to acetaminophen or ibuprofen. Short courses (one or two doses) of corticosteroids can be highly effective in controlling symptoms but may shorten the duration of remission.<sup>291</sup> Patients have been shown to respond to IL-1 inhibition.<sup>292</sup> Tonsillectomy has also been associated with improvement.<sup>293,294</sup> Tonsils of patients with PFAPA syndrome have shown significant increases in *Candida albicans* and biofilm formation compared with controls, but less *S. aureus*, *Varicella zoster*, and herpes simplex virus, and no difference in group A  $\beta$ -hemolytic *Streptococcus*.<sup>295</sup> In most patients, episodes tend to occur less often or disappear with advancing age, without any long-term sequelae.<sup>296</sup>

### Deficiency of the Interleukin-1 Receptor Antagonist

Deficiency of the IL-1 receptor antagonist (DIRA) is a recently described autosomal recessive disorder<sup>297,298</sup> in which IL-1 activity is markedly increased because of deficiency of an antagonist that also binds to the IL-1 receptor and prevents IL-1 activity.<sup>299</sup> Affected infants and young children show fetal distress, joint swelling with periosteal inflammation, severe osteopenia with lytic bone lesions, respiratory involvement, thrombotic episodes, oral mucosal and cutaneous pyoderma gangrenosum-like ulcerations, and a localized to generalized pustular eruption that resembles pustular psoriasis (Fig. 25-25). Fever occurs occasionally (not periodically) and only in a few patients. DIRA must be also be distinguished from Majeed syndrome, an autosomal recessive disorder that also features chronic recurrent multifocal osteomyelitis and an inflammatory dermatosis that can vary from a Sweet syndrome-like eruption to chronic pustulosis; Majeed syndrome features congenital dyserythropoietic anemia, results from mutations in *LPIN2*, encoding lipin-2, and responds well to IL-1 inhibition.<sup>300</sup> Administration of anakinra (2 mg/kg per day) dramatically reverses the inflammatory manifestations, whereas other systemic immunomodulators have largely failed to cause improvement.

### Deficiency of the Interleukin-36 Receptor Antagonist

Another rare autosomal recessive auto-inflammatory disorder associated with a pustular psoriasis-like eruption is deficiency of the IL-36



**Figure 25-25** Deficiency of IL-1 receptor antagonist. This Puerto Rican boy with failure to thrive and multifocal lytic lesions of bone showed numerous plaques of erythematous pustules.



**Figure 25-26** Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) syndrome. These two unrelated boys both show the acral telangiectatic vasculopathy of SAVI syndrome. One of these boys died at 14 years of age because of his pulmonary disease.

receptor antagonist (DITRA), caused by mutations in *IL36RN*, encoding the IL-36 receptor antagonist.<sup>217,301,302</sup> The IL-36 receptor antagonist inhibits NF- $\kappa$ B activation by IL-36 $\alpha$ ,  $\beta$ , and  $\gamma$ . The disorder may have its onset during infancy or childhood, or less commonly during adulthood, and should be considered in adult patients with generalized pustular psoriasis without a history of plaque psoriasis.<sup>303</sup> Rather than generalized pustules with high fevers and malaise, affected individuals may have pustules localized to the palms and soles that may even resemble acute generalized eruptive pustulosis (AGEP) (see Chapter 20). Nail dystrophy, arthritis, and/or cholangitis have been noted in the minority of patients.<sup>302</sup> Bacterial or viral infections and menstruation may be triggers. Patients often respond to systemic retinoids, but steroids, methotrexate, cyclosporine, and anakinra have also been used. DIRA and DITRA need to be distinguished from *CARD14*-mediated pustular psoriasis, an autosomal dominant disorder in which affected children may manifest symptoms of pityriasis rubra pilaris, plaque psoriasis, erythrodermic psoriasis, pustular psoriasis, or an overlap disorder (see Chapter 4).

### STING-Associated Vasculopathy with Onset in Infancy (SAVI) Syndrome

Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) syndrome is a recently described disorder characterized by the onset by 6 months of telangiectatic vasculopathy (Fig. 25-26)<sup>304</sup> with pustules and residual scarring and soft-tissue loss. Lesions are characteristically localized to the hands, feet, nose, cheeks, and ears with exacerbations in cold weather. Patients have systemic inflammation (increased ESR and C-reactive protein) with

intermittent low-grade fevers, hilar or paratracheal adenopathy, and interstitial lung fibrosis. The disorder results from heterozygous mutations in *TMEM173*, encoding STING.

## Pyoderma Gangrenosum

Pyoderma gangrenosum is a severe, chronic, inflammatory disorder of the skin characterized by a painful sloughing ulceration with purulent or vegetative base and an elevated dusky blue or reddish purple undermined border surrounded by a rim of inflammation (Fig. 25-27; see Fig. 25-18).<sup>305</sup> The lesion usually begins as a tender papulopustule or erythematous nodule that undergoes necrosis and ulcerates. The ulceration heals with cribriform scarring (Fig. 25-28). Lesions in older children and adolescents (as in adults) are most often found on the lower extremities (especially the anterior tibial surface) but can be seen anywhere on the body, including mucosal and peristomal sites.<sup>306</sup> The head, airway, and anogenital areas are more common sites of involvement in neonates, infants, and younger children.<sup>307–310</sup> Pustular, bullous, and superficial<sup>311</sup> variants have been described. The



**Figure 25-27** Pyoderma gangrenosum. Painful leg ulceration with an inflamed, undermined border. Note the pustule distal to the ulceration, often the earliest sign of a new site of involvement. The most common underlying condition in affected children is inflammatory bowel disease, although no underlying abnormality may be discovered.



**Figure 25-28** Pyoderma gangrenosum. Partial response to treatment with cyclosporine. Note the persistent inflammation and evidence of healing ulcerations with residual cribriform scarring. The pyoderma gangrenosum healed fully and remained quiescent while the child was given etanercept, but this young boy developed Takayasu disease several years after onset of the pyoderma gangrenosum despite ongoing inhibition of TNF- $\alpha$  activity.

bullous form may be difficult to distinguish from bullous Sweet syndrome (see Chapter 20). Pulmonary and splenic lesions have been described.<sup>312</sup> The diagnosis is based on clinical features. Biopsy findings are nonspecific, but special stains and cultures of biopsy specimens may help to distinguish pyoderma gangrenosum from other disorders, including vasculitis and infectious causes of ulceration.

Although virtually always described in adults, 4% of cases have occurred in infants and children.<sup>313,314</sup> Pathergy (the development of lesions at sites of minor trauma), which occurs in 20% of patients with this disorder, may be more common in childhood cases; in a recent report, an abused child developed pyoderma gangrenosum at multiple sites of physical abuse.<sup>315</sup> Although the disorder may occur without associated disease, including in siblings,<sup>316</sup> it usually develops in pediatric patients with any of a variety of systemic disorders. Most common in children is inflammatory bowel disease (especially ulcerative colitis; see Crohn Disease section), but immunodeficiency (especially HIV infection, leukocyte adhesion defect,<sup>317,318</sup> SCID,<sup>319</sup> CVID<sup>320</sup>), hematologic disorders (especially leukemia),<sup>321,322</sup> Takayasu disease with or without airway or pulmonary disease,<sup>323–325</sup> and rheumatic disorders (especially JIA, systemic lupus erythematosus, Henoch-Schönlein purpura, and in association with antiphospholipid antibodies)<sup>326,327</sup> have all been reported. Pyoderma gangrenosum can also be seen during adolescence in patients with PAPA syndrome, chronic recurrent multifocal osteomyelitis,<sup>328</sup> and SAPHO syndrome.<sup>329</sup> In children with the onset during infancy, Takayasu disease is the most common association and may occur years after the onset of the pyoderma gangrenosum.

Treatment of pyoderma gangrenosum involves use of systemic and topical anti-inflammatory medications to promote wound healing and decrease pain, as well as a vigorous attempt to control the underlying disease. Debridement and other mechanical trauma may worsen the ulcerations and should be avoided. Systemic corticosteroids are usually the initial drug of choice. Cyclosporine or systemic tacrolimus,<sup>330</sup> TNF- $\alpha$  inhibitors (etanercept, adalimumab, infliximab),<sup>331–336</sup> dapsone, clofazimine, MMF, and intravenous Ig<sup>337</sup> have been used successfully as steroid-sparing agents. Topical tacrolimus ointment applied a few times daily has improved ulcer healing<sup>338</sup>; intralesional steroid injections may be appropriate for adolescents.

## PYOGENIC STERILE ARTHRITIS, PYODERMA GANGRENOSUM, ACNE SYNDROME

This autosomal dominant disorder is characterized by pyoderma gangrenosum-like ulcerative lesions, usually in the second decade of life; severe cystic acne; and episodes of inflammatory arthritis that lead to significant joint destruction.<sup>339,340</sup> Pyoderma gangrenosum lesions are usually seen on the leg but may occur at acne sites (Fig. 25-29). Sterile abscesses have been described at sites of parenteral injections. Affected family members may show variable expressivity. Mutations occur in *PSTPIP1/CD2BP1*, which encodes CD2-binding protein 1, a protein that interacts with pyrin.<sup>341</sup> PAPA syndrome is treated with oral corticosteroids, and marked improvement has been noted with TNF inhibitors and anti-IL-1 treatment.<sup>225,342</sup> The acne can be controlled with isotretinoin administration.<sup>343</sup> Pyoderma gangrenosum and acne have also been associated with suppurative hidradenitis, comprising PASH syndrome.<sup>344–346</sup>

## Behçet Syndrome

Behçet syndrome is a chronic multisystemic auto-inflammatory disease characterized by recurrent oral and genital ulcerations and inflammatory disease of the eye.<sup>347</sup> Although even neonatal onset without maternal Behçet syndrome has been noted,<sup>348</sup> Behçet syndrome usually begins in patients between 10 and 45 years of age, with approximately 17% of cases beginning before 17 years of age.<sup>349</sup> Neonatal Behçet syndrome usually occurs in infants born to mothers with the disease and generally disappears spontaneously by the time the infants reach the age of 6 months. Characterized by aphthous stomatitis and skin lesions, affected neonates rarely have severe, life-threatening complications.<sup>350,351</sup> Although most studies have suggested that Behçet syndrome has a predilection for males,<sup>352</sup> including



**Figure 25-29** Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome. This 11-year-old boy had small inflammatory papules of acne, which rapidly became purulent plaques (as shown) and then ulcerated to form pyoderma gangrenosum, leaving residual scars. He also had arthritis. His disease was brought under control with golimumab (TNF inhibitor) and isotretinoin.



**Figure 25-30** Behçet syndrome. Major and minor aphthae on the tongue. Note the scalloping of the tongue border from past scarring lesions.

in pediatric patients, a recent international registry enrolled equal numbers of boys and girls.<sup>353</sup> In general, the disease is less severe and more delayed in its full manifestation in pediatric patients.<sup>354</sup>

The pathomechanism for Behçet disease is not understood, although the majority of patients in several studies carry HLA-B51 alleles, the strongest known risk factor.<sup>355,356</sup> Some 15% to 45% of children have an affected family member, in contrast to 8% of adults.<sup>349,357</sup> The demonstrated activation of inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 has lead to new therapeutic approaches.

Cutaneous and oral lesions are the most common clinical features of pediatric Behçet disease.<sup>357-359</sup> Oral lesions, noted at some point in the course of virtually every affected child, are the initial manifestation in 83% of pediatric patients<sup>358</sup> and occur approximately 8 years before other signs.<sup>360</sup> The ulcerations begin as erythema, and within 1 to 2 days become superficial erosions that range from smaller ulcerations, indistinguishable from aphthous stomatitis, to deeply punched-out necrotic ulcers on the lips, buccal mucosa, tongue (Fig. 25-30), and less commonly, the gingivae. They have regular sharp edges and vary from a few millimeters to a centimeter in diameter. Minor aphthae have a diameter of less than 1 cm, resolve in 7 to 10 days, do not scar, and are most common, whereas major aphthae are larger, deep, more painful, and tend to scar. Sometimes aphthae are grouped (herpetiform aphthae). The ulcer base is covered with a yellowish-gray exudate, and the margin is surrounded by a red halo. Oral lesions in recur at intervals varying from weeks to months; by definition, aphthae



**Figure 25-31** Behçet syndrome. Vulvar ulcerations.



**Figure 25-32** Behçet syndrome. Genital region ulcers on the glans penis and foreskin, in a boy with a positive family history of Behçet syndrome and HLA-B51 positivity.

must recur at least 3 times yearly. Features of Behçet syndrome and relapsing polychondritis have also been described as the mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome.

Genital ulcerations are seen in 60% of children with Behçet syndrome, and occur more often in girls than in boys. They are found on the vulva and vagina of females (Fig. 25-31) and the scrotum or base of the penis in males. They are similar in appearance to the oral ulcerations but less painful and may be overlooked. Perianal ulcerations are less common but have been noted more often in children than in adults (up to 30%). Genital ulcerations are usually deeper than oral ulcerations (Fig. 25-32) and may scar. As with oral ulcerations, they remit in 1 to 2 weeks and tend to recur.

Cutaneous lesions of Behçet syndrome present a varied picture. Seen in approximately 80% of affected children, they consist of folliculitis, pustules, pyoderma, acneiform lesions, furuncles, abscesses, ulcerations, erythema nodosum-like lesions, and palpable purpura (Fig. 25-33). Pathergy (the formation of an ulceration at an area of trauma, skin prick, or venipuncture) is typical.

Ocular lesions, seen in approximately 50% of boys but only 15% to 20% of affected girls, are less common than in adults, but associated with a worse prognosis. Conjunctivitis and photophobia may be early ocular findings, but bilateral panuveitis is the most common manifestation (more than 80% of children with eye findings)<sup>361</sup>; posterior uveitis is found more often than anterior uveitis. Retinal vasculitis and retinitis occur in the majority of children with ocular features, and cataracts, maculopathy and optic atrophy have been described.

Fever and constitutional symptoms are variable. Musculoskeletal complaints, especially arthralgia and arthritis, are found in up to 75%



**Figure 25-33** Behcet syndrome. Palpable purpura on the inner thighs and glans penis of this boy with Behcet syndrome. Superficial ulcerations were also noted on the penile shaft. Biopsy of affected areas showed leukocytoclastic vasculitis.

### Box 25-3 Proposed Criteria for Diagnosis of Pediatric Behcet Disease

Oral aphthous stomatitis, occurring at least three times yearly  
Plus at least one of the following:

- Genital ulceration
- Erythema nodosum
- Pustular/acneiform lesions
- Folliculitis
- Positive pathergy testing
- Uveitis
- Venous/arterial thrombosis
- Family history of Behcet disease

The diagnosis is usually definite with three or more features.

of affected children. Gastrointestinal complaints are more common in children than in adults<sup>362</sup> and may warrant endoscopic evaluation, especially in children under 10 years of age. They range from vague abdominal pain (up to 50%) and anorexia to diarrhea and hemorrhagic colitis. Central nervous system involvement, often the most severe prognostic feature of this disorder, is seen in 20% to 50% of patients, often manifests as headache, and most commonly involves cerebral venous sinus thrombosis.<sup>352</sup> Arterial or venous thrombosis can also affect the lower extremities and can be recurrent.<sup>363,364</sup> Renal involvement, an uncommon complication, may be seen with a spectrum ranging from asymptomatic abnormalities detected on urinalysis to a rapidly progressive glomerulonephritis and nephrosis. Other unusual findings in children include pericarditis, orchitis, and epididymitis.

The diagnosis of Behcet syndrome in a patient with the full triad of oral and genital ulcers and ocular inflammation is not difficult. Two or more major criteria (oral, genital, ocular, or cutaneous involvement) or a combination of major and minor criteria (vascular, neurologic, musculoskeletal, or intestinal involvement), however, allow diagnosis. Having three or more features of Behcet syndrome is highly associated with definitive diagnosis but is only present in 31% of children<sup>360</sup> (Box 25-3). Biopsy is usually not helpful, but having HLA-B51 positivity can be useful supporting evidence of the diagnosis. Although pathergy is common and a helpful criterion to the diagnosis, it may also be seen in children with pyoderma gangrenosum, leukemia, and bowel bypass syndrome (see Chapter 20); a negative pathergy test does not rule out the diagnosis.

Treatment of the aphthous ulcers with potent topical or intralesional corticosteroids, topical application of tacrolimus, oral rinses with elixir of diphenhydramine, or application of 2% viscous lidocaine can give symptomatic relief. For mucocutaneous ulcerations, colchicine is often helpful. Therapy is begun with a dosage of 0.6 mg twice

### Box 25-4 Cutaneous Signs of Anorexia Nervosa and Bulimia Nervosa

- Xerosis
- Generalized pruritus
- Loss of subcutaneous fat
- Carotenemia
- Acne
- Petechiae and purpura
- Edema, especially pretibial and pedal
- Calluses on the dorsum of the hand (Russell sign)
- Other self-inflicted injuries
- Poor wound healing
- Pellagra
- Scurvy
- Acrodermatitis enteropathica
- Seborrheic dermatitis
- Acral changes
  - Periungual erythema
  - Acrocyanosis
  - Acral coldness
  - Perniosis
- Oral changes
  - Cheilitis/perleche
  - Aphthous stomatitis
  - Gum recession
  - Enamel erosion and dental caries
- Hair changes
  - Telogen effluvium
  - Increased lanugo-like body hair
  - Dry hair
- Brittle, dystrophic nails
- Enlarged parotid and salivary glands (full cheeks despite malnutrition)
- Heating pad-induced erythema ab igne

daily for the first week. If the patient has no nausea, vomiting, or diarrhea, the dosage can be increased to three times a day, but colchicine is poorly tolerated by most pediatric patients. Thalidomide 50 to 100 mg once weekly to once daily has also led to improvement, but its use is limited by constipation, fatigue, and peripheral neuropathy, which may be irreversible. Dapsone can also be helpful, especially in children with recurrent oral ulcerations. In severe cases, corticosteroids, alone or in combination with immunosuppressive agents such as methotrexate, azathioprine, or TNF inhibitors,<sup>365–367</sup> are usually successful. For patients who do not respond, inhibitors of IL-1<sup>368</sup> (anakinra, canakinumab) and IL-6 (tocilizumab) activation, as well as rituximab, have been used<sup>369</sup> have also been used successfully. The overall mortality rate of Behcet disease in children is 3%; death usually results from large vessel vasculopathy (aneurysm, thrombosis), intestinal perforation, central nervous system involvement, or as a complication of therapy.

## Anorexia Nervosa and Bulimia

Anorexia nervosa and bulimia nervosa are severe disorders associated with potentially serious medical complications (Box 25-4).<sup>370,371</sup> Anorexia nervosa occurs in up to 3% of pubertal females and less commonly in prepubertal females or males. In both disorders, patients have an intense preoccupation with food and irrational concern about gaining weight. Bulimic patients tend to binge eat and attempt to lose weight by vomiting and abusing laxatives, diuretics, diet pills, or emetics. The cutaneous features, which reflect endocrinologic changes and malnutrition, usually occur when the body mass index drops to less than 16 kg/m<sup>2</sup>.<sup>372,373</sup> Affected individuals often show self-induced lesions as well, particularly the characteristic superficial ulcerations and hyperpigmented calluses or scars on the dorsal aspect of the second and third fingers (Russell sign), the result of repeated abrasion of the skin against the maxillary incisors during forced emesis.<sup>374,375</sup> Other emesis-associated complications include recurrent sore throat, hoarse voice, and dental erosions. Nutritional deficiency, such as zinc deficiency,<sup>376</sup> scurvy, and pellagra<sup>377</sup> have occurred, as has erythema ab igne from chronic use of a heating pad for warmth.<sup>378</sup> Because of

the potential severity of these disorders, it is important that physicians recognize the early signs and symptoms, particularly in view of the fact that patients tend to deny their illness or minimize the severity of their symptoms. The cutaneous manifestations are reversible when weight is gained. Many patients respond well to the combination of antidepressant and cognitive-behavioral therapy.

 The complete list of 378 references for this chapter is available online at <http://expertconsult.inkling.com>.

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# 26 Abuse and Factitial Disorders

## Child Abuse

*Child abuse* is a broad term used to describe a spectrum of nonaccidental trauma inflicted upon children. Kempe et al. are generally credited with emphasizing the prevalence and importance of this entity when they coined the term *battered child syndrome* in 1962.<sup>1</sup> This “syndrome” has subsequently been expanded to include an array of childhood abuses including physical abuse, sexual abuse, and neglect. Child abuse continues to be one of the most significant causes of childhood morbidity and mortality in the United States.<sup>2</sup> In one 10-year study of medical records submitted to the National Pediatric Trauma Registry, child abuse accounted for 10.6% of all blunt trauma to patients under 5 years of age.<sup>2</sup> Children who are abused tend to be younger, with the highest incidence seen in those under 3 years of age. High-risk groups include children with a history of prematurity, physical handicap, and behavioral problems. Factors that appear to be associated with an increased risk of abuse are summarized in Table 26-1.<sup>3–5</sup> Up to 75% of abuse may be missed in the acute care setting because of failure of recognition by medical professionals, and this may lead to lost opportunities to intervene.<sup>6</sup>

Various abusive patterns may be evident in families where abuse is an issue. These include parents who were the victims of abuse themselves, parents with emotional disturbances, stressful crises within the family unit (i.e., loss of job or financial distress), and lack of a close support network for the family (see Table 26-1).<sup>7</sup> Recognition of abuse is vital, because the trauma tends to be repeated (an abused child has up to a 50% chance of being abused again), and the risk of future injury or death is high. Instances in which there is a delay in reporting the injury, in which the degree and type of injury are at variance with the history offered, or in which the parents are evasive or vague as to the cause of injury are all suspicious and should lead to consideration for an abuse investigation. In evaluating the child with possible abuse, a detailed history is the most important component of the assessment.<sup>8</sup> Vital details include the alleged mechanism of the injury, developmental history of the child, past medical history (especially of any disorders that may mimic abuse, such as coagulopathy or skin disorders), history of prior injuries, social history, and family history. A complete physical examination should be performed and should include high-quality photography of cutaneous lesions.

Radiographic findings in child physical abuse are often useful in the evaluation and are not discussed in great detail here. Findings that may increase suspicion for abuse include the classic metaphyseal lesion (also known as “corner fracture” or “bucket-handle fracture”), skull and femur fractures, and healing fractures, although each of these findings must be considered in the appropriate context of the medical history and physical examination findings.<sup>9,10</sup>

Although abused children may exhibit multiple abnormalities on physical and radiographic examination, this section will focus primarily on the cutaneous stigmata.

### PHYSICAL ABUSE

Nonaccidental injuries in children may take many forms, and often the skin reveals pathologic findings. Cutaneous trauma may be seen in the form of ecchymoses, burns, lacerations, bite marks, abrasions, underlying hematomas, pigmentary changes, and scars.

Ecchymoses (bruises) are the most common type of skin injury seen in children who have been abused. Lesions on the hands and face, adult human bites, and lesions on the cheeks, mouth, lips, lower back, buttocks, or inner thighs are particularly suspect. Ecchymoses in

various different stages of healing are more suggestive of abuse. Ecchymoses on padded areas such as the buttocks, torso, face, and genitalia (Fig. 26-1, A) or uncommonly injured areas (earlobe, neck, lip, philtrum) are more concerning for possible abuse.<sup>3</sup> In a study of discriminating bruising characteristics in children who have been abused, characteristics that were more predictive of abuse included bruising on the torso, ear (Fig. 26-1, B), or neck (in a child ≤4 years of age, termed the *TEN region*) and bruising in any region in an infant younger than 4 months of age.<sup>6</sup> Abuse-associated bruising should be differentiated from accidental bruising, which is more common in ambulatory children and occurs most commonly over bony prominences such as the forehead and shins.<sup>3</sup> Any bruising in the noncruising infant under 9 months of age should raise significant suspicion for abuse. There are many potential mimics and non-abuse-related causes of ecchymoses, including Mongolian spots, hypersensitivity vasculitis (i.e., Henoch–Schönlein purpura or acute hemorrhagic edema of infancy), Ehlers–Danlos syndrome, vascular malformations, infantile hemangiomas, inks or dyes, and bleeding disorders.

The configurations of lesions in battered children are morphologically similar to the items or methods used to inflict the trauma and may be useful in the abuse investigation. Multiple evenly spaced markings (Fig. 26-2) or curvilinear loops and arcuate lesions (Figs. 26-3 and 26-4) such as those that may be induced by lashing with a doubled-over belt or electric cord are typical of these trauma-induced lesions. They are usually ecchymotic, but they may also present as abrasions, lacerations, or hyperpigmentation.

Belt-buckle imprints (ecchymotic or hyperpigmented) may result from intentional trauma with these items. Adjacent, small ecchymotic macules (Fig. 26-5) are typical of pinch marks. Shackles on the wrists, ankles, or neck leave easily identifiable rings that are red if fresh and hyperpigmented if longstanding. Ligature marks on the neck or extremities and grab or slap marks (fingertip bruises; Fig. 26-6) on the shoulders, hands, or legs are particularly suspicious and highly suggestive of deliberate trauma. Slapping injuries result in linear bruising that outlines the blunt objects (fingers) because of the breakage of superficial skin capillaries. *Çao gio* (“coining”) and cupping, Asian customs believed to treat a variety of ailments, may be confused with ecchymotic lesions of abuse and must be appropriately recognized (see below in *Cutaneous Mimickers of Abuse and Factitial Disorders* section).

Burns are a very common type of injury seen in abused children and result from thermal injury to the skin and subcutaneous tissues. Burns can also be electrical, chemical, or radiant in nature. Thermal burns may be inflicted with cigarettes, matches, scalding liquid, or other heated objects (Fig. 26-7) and are often mistaken for lesions of impetigo. Cigarette burns present as 8- to 10-mm, deep, round crusted ulcers that heal with scars and pigmentary changes (Figs. 26-8 and 26-9). Although they may be accidental, multiple lesions with deeper involvement and significant scarring are highly indicative of abuse, because this pattern is usually suggestive of prolonged contact. The differential diagnosis of cigarette burns includes ecthyma, cellulitis, herpes, and bullous impetigo.

Branding injuries occur after prolonged contact with a heated object, and they may take on the shape of the object used to inflict them. Burns inflicted with a hot iron (Figs. 26-10 and 26-11) reveal differing pigmentary changes between the heated metal surface and the steam vent openings. Figures 26-12 and 26-13 demonstrate burns inflicted by a heated metal spoon, with the shape of the spoon readily visible in the resultant skin markings. Dunking scald injuries are most commonly seen in infants and toddlers and present with a characteristic “stocking and glove” distribution on the extremities or

**Table 26-1** Factors Associated with an Increased Risk of Child Abuse

Child	Parent	Both
Prematurity	Partner violence within the family	Neighborhood factors
Mental retardation	History of past abuse or neglect	Crime
Disability	Substance abuse	Poor recreational activities
Congenital anomalies	Mental illness	Poverty
Clinging	Unemployment	Poor parent-child relationships
Excessive or inconsolable crying	Lack of external support	Substandard housing
Expectations inconsistent with normal child development	African-American child in single-parent household	Poor impulse control
Toilet training or toilet accidents (preschoolers)	Adolescent in age	Rely on children for emotional support

Modified from Swerdlin A, Berkowitz C, Craft N. Cutaneous signs of child abuse. *J Am Acad Dermatol* 2007;57:371–92; Peck MD, Priolo-Kapel D. Child abuse by burning: a review of the literature and an algorithm for medical investigations. *J Trauma* 2002;53:1013–22; and Dubowitz H, Bennett S. Physical abuse and neglect of children. *Lancet* 2007;369:1891–9.



(A)



(B)

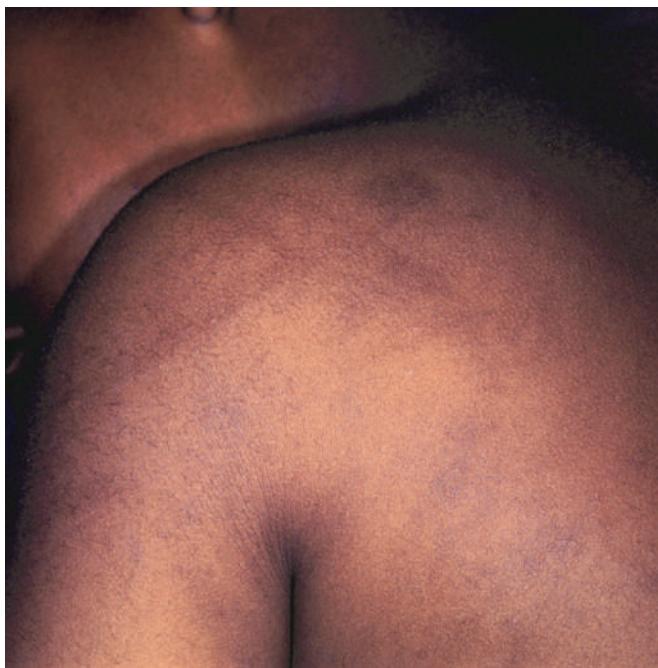
**Figure 26-1** Child abuse. Ecchymoses in certain locations such as these lesions noted on the genitalia (A) and superior ear (B) are more suggestive of nonaccidental trauma. Of ear ecchymoses, the most concerning location for abuse-associated bruising is the earlobe.



**Figure 26-2** Child abuse. The evenly spaced nature of these markings should arouse suspicion for an outside source of these skin findings.

with “doughnut-type sparing” that occurs when the child’s buttocks are held against the cooler tub or basin.<sup>7</sup> These patients have erythema and blistering indicative of a second-degree burn. It should be remembered that children will not stay in contact with a hot surface or scalding hot water. They normally test the heat of the water and step into the bath with one foot at a time. Accordingly, symmetrical burns on the feet, the buttocks, or the hands require careful investigation and evaluation. Stun-gun injuries have been observed in the setting of physical abuse and present as evenly spaced (4 to 5 cm apart), erythematous to hypopigmented papules and macules, usually occurring in multiples.<sup>11</sup>

Bite marks are another pathognomonic sign of nonaccidental trauma. The human bite is differentiated easily from the dog bite by the contusing and crushing characteristics of the latter; dog bites rip and tear the flesh. It is important to distinguish adult from child bite marks, since the former is more likely to be seen in an abusive setting. Adult bites are characterized by a dental arch width greater than 4 cm<sup>3</sup>, whereas the markings of a child’s bite tend to be significantly narrower (Fig. 26-14). The discovery of one bite mark necessitates a thorough examination of the child’s entire body for further evidence of bites or other findings of abuse.<sup>12</sup> Traumatic alopecia may occur when the parent pulls the child’s hair, since the hair provides a readily accessible “handle” that can be used to grab or jerk at the child. The resultant alopecia is an irregularly bordered area that may reveal hemorrhage, hair breakage, and scalp tenderness.



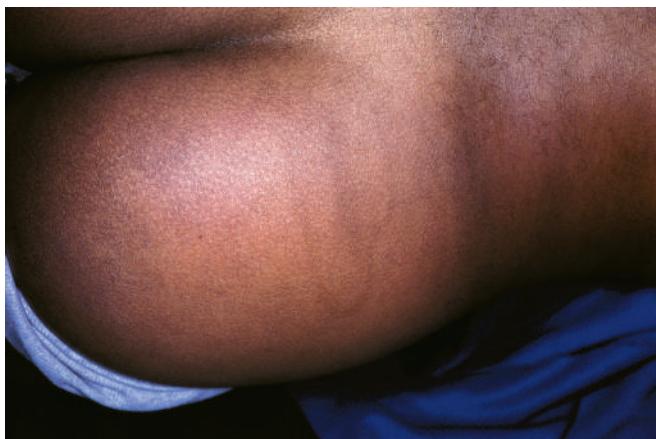
**Figure 26-3** Child abuse. These multiple, overlapping, linear and hyperpigmented patches were the result of postinflammatory changes at sites of whipping.



**Figure 26-4** Child abuse. These burns, the result of intentional contact with a hot wire, presented as curvilinear erosions.



**Figure 26-5** Child abuse. Adjacent, ecchymotic macules are typical of pinch marks.



**Figure 26-6** Child abuse. Fingertip bruises present as hyperpigmented patches in the shape of fingers at sites of excessive slapping or spanking.



**Figure 26-7** Child abuse. This geographically shaped burn was believed to have been inflicted with the heated metal end of a disposable cigarette lighter.

Oral injuries are another common feature in abused children. Findings may include tears of the labial or lingual frenulum caused by a blow to the mouth, forced feeding, or forced oral sex.<sup>12</sup> Other manifestations include burns or lacerations of the gingivae, tongue, or palate from overly hot food or utensils. Teeth may also be involved, including fracture, displacement, or avulsion.

A difficult situation arises when the physician observes recent skin injuries in the child who does not seek treatment for trauma. In one large series, 76% of children between 9 months and 17 years of age seen in a clinic for a reason other than trauma were found to have at least one recent skin injury. Injuries were more prevalent in the summer (in regions with a temperate climate) and were most commonly observed on the shins and knees.<sup>13</sup> The authors offered certain unusual characteristics that may suggest a greater risk of physical abuse (or bleeding disorder), and these include uncommon location, more than 15 injuries, bruises in a child younger than 9 months of age, numerous injuries elsewhere than the lower limbs, numerous injuries in cold seasons in a temperate climate, and injuries other than bruises, abrasions, or scratches.<sup>13</sup> In another series of infants aged 6 to 12 months, bruises were noted to be generally limited to the face, head, or shins, and there was a direct correlation between the number of bruises and increases in mobility.<sup>14</sup> In this group, the prevalence rate of bruises was 12%, and they were most often solitary.



**Figure 26-8** Cigarette burns. This patient has evidence of fresh lesions (erythematous eroded plaque) and older lesions in the forms of hyperpigmentation and scars.



**Figure 26-9** Cigarette burns. These burns demonstrate the classic abuse finding of lesions in various stages of healing.



**Figure 26-10** Iron burn. This hyperpigmented patch is studded with evenly spaced, normally pigmented regions that correlate with sites of steam vent openings.

## SEXUAL ABUSE

Sexual abuse has been defined in many ways, including “any exploitative sexual activity between a child and an adult”; “any sexual activity that a child cannot comprehend or give consent to, or that violates the law”; or “when a child is engaged in sexual activities that he/she cannot comprehend, for which he/she is developmentally unprepared



**Figure 26-11** Iron burn. This child's hand reveals the classic hyperpigmentation with evenly spaced macules of sparing that occur at sites of steam vent openings.



**Figure 26-12** Child abuse. This infant had burns inflicted with a heated metal spoon. Note the overlapping oval-shaped patches of pigmentation and crusting.

and cannot give consent, and/or that violates the law or social taboos of society.”<sup>7,15,16</sup> Some studies have suggested that 1% of children experience some form of sexual abuse each year.<sup>16</sup> It is important to realize that boys may be the victims of sexual abuse as well as girls, although the former tend to be less likely to disclose abuse, and thus it is likely underreported, underrecognized, and undertreated.<sup>17</sup> Adolescents are the perpetrators in up to 20% of reported cases of sexual abuse, and although women may be perpetrators, these allegations are significantly less likely than those involving males.<sup>16</sup> Up to one fifth of adolescents who regularly use the Internet have been solicited by strangers for sex through the Internet. Childhood sexual abuse may lead to a variety of physical and mental symptoms and disorders, including depression, suicidal ideation, eating disorders, low self-esteem, and posttraumatic stress disorder.<sup>18</sup>

The perpetrator of childhood sexual abuse is often well known, or related, to the victim. Activities involved in sexual abuse may include



**Figure 26-13** Child abuse. The same infant as that shown in **Figure 26-12** had these blistering burns on the plantar surfaces. They were inflicted with a heated metal spoon.



**Figure 26-14** Bite marks. These erythematous, petechial macules and papules revealed a dental arch width of 2.5 cm, more consistent with a child's bite. There were no other clinical features of (or concerns for) child abuse in this 2-year-old female.

oral-genital, genital, or anal contact by or to the child, as well as nonphysical abuses such as voyeurism, exhibitionism, or involvement of the child in pornography.<sup>16</sup> Sexual abuse should be differentiated from "sexual play" or age-appropriate exploratory behavior. The child who has been sexually abused may exhibit a variety of features including behavioral changes, school difficulties, regression, depression, eating disturbance, sexual acting-out, symptoms referable to the genitourinary or gastrointestinal tracts, pregnancy, various somatic complaints, or a sexually transmitted disease (STD).<sup>15</sup>

Mucocutaneous findings suggestive of sexual abuse are listed in **Table 26-2**. However, it should be noted that many children who have been sexually abused in the past may have a relatively normal physical examination. Many prepubescent patients seen in emergency departments for a sexual-abuse evaluation have not experienced recent abuse, in distinction to adolescents, who often come after the acute

**Table 26-2** Mucocutaneous Findings in Childhood Sexual Abuse

Finding	Comment
Hymenal changes	Attenuated hymenal tissue, disruption of hymenal contour; acute laceration or ecchymosis
Anal area changes	Boys and girls; changes in anal tone, hematomas, abrasions, lacerations; scarring, skin tags; dilation
Fossa navicularis scarring	
Posterior fourchette scarring	
Inner thigh changes	Abrasions, ecchymosis (concerning but not diagnostic)
Labia minora changes	Scarring or tears (concerning but not diagnostic)
Other genital injuries	Circumferential injuries to penile shaft or glans penis
Oral injuries or diseases	Unexplained erythema or petechiae of the palate; oral or perioral gonorrhea or syphilis (pathognomonic for sexual abuse in the prepubertal child)

**Table 26-3** Implications of Sexually Transmitted Diseases and Clinical Findings for the Diagnosis of Childhood Sexual Abuse

STD or Finding	Implication for Abuse	Suggested Action
Gonorrhea*	Diagnostic	Report
Syphilis*	Diagnostic	Report
HIV infection* <sup>‡</sup>	Diagnostic	Report
Chlamydia*	Diagnostic	Report
Trichomoniasis	Highly suspicious	Report
Anogenital warts* <sup>‡</sup>	Suspicious	Report
Genital herpes <sup>§</sup>	Suspicious	Report
Bacterial vaginosis	Inconclusive	Clinical follow-up care
Presence of sperm, semen, or acid phosphatase	Diagnostic	Report
Pregnancy	Diagnostic	Report

Modified from Swerdlin A, Berkowitz C, Craft N. Cutaneous signs of child abuse. *J Am Acad Dermatol* 2007;57:371–92, and Kellogg N, American Academy of Pediatrics Committee on Child Abuse and Neglect. The evaluation of sexual abuse in children. *Pediatrics* 2005;116(2):506–12. HIV, Human immunodeficiency virus; STD, sexually transmitted disease.

\*If not perinatally acquired.

<sup>‡</sup>If not transfusion acquired.

<sup>§</sup>Not uncommonly transmitted via benign mode; see discussion in Chapter 15.

Unless caused by autoinoculation.

assault.<sup>19</sup> A normal anogenital examination, therefore, does not preclude prior sexual abuse. The physical examination should be most focused on areas involved in sexual activity, including the mouth, breasts, genitals, perineum, buttocks, and anus. In females, a more thorough examination of the medial thighs, labia majora and minora, clitoris, urethra, hymen and hymenal opening, fossa navicularis, and posterior fourchette should be included.<sup>16</sup> In males, the thighs, penis, and scrotum should be closely examined.

Examinations for STDs should be performed when indicated. Factors to be considered include the possibility of oral, genital, or rectal contact and the child's symptomatology. **Table 26-3** summarizes the implications of various STDs and clinical findings for reporting



**Figure 26-15** Neglect. This toddler came to the clinic for a routine follow-up examination for eczema and was noted to have this blistering sunburn.



**Figure 26-16** Neglect. Dental neglect in this young boy presented as dental caries, periodontal disease, and aphthous ulcerations of the labial surfaces. This lesion was also culture-positive for herpes simplex virus.

childhood sexual abuse. Anogenital warts, which may be sexually transmitted in children, are often the result of benign, nonsexual transmission, especially in infants and young toddlers (see Chapter 15). Nonsexual modes of transmission include perinatal transmission, autoinoculation (child with common warts spreads them via skin-to-skin contact to his or her own anogenital region), heteroinoculation (caregiver with common warts spreads them via skin-to-skin contact to anogenital region of child), and possibly indirect spread from fomites. Importantly, molluscum contagiosum lesions involving the anogenital region in children are nearly always a result of benign transmission or autoinoculation and should not be considered as indicative of childhood sexual abuse. The details of the evaluation, treatment, and reporting of childhood sexual abuse are beyond the scope of this chapter but are well documented elsewhere. Importantly, however, when the diagnosis of childhood sexual abuse is being considered, review of the case with an expert in such evaluations (such as a child-abuse pediatrician) is advisable. Recent data suggest that five or more examinations per month may be required for ongoing competency in the interpretation of medical and laboratory findings in children in whom sexual abuse is suspected.<sup>20</sup>

## NEGLECT

Neglect may be either physical, emotional, or both. The former results when a parent or caretaker fails to provide necessities of life such as food, appropriate supervision shelter, clothing, or medical care.<sup>7</sup> General findings in the neglected child may include lack of immunizations, poor nutrition and growth, and developmental or behavioral problems. Potential cutaneous findings include poor hygiene, untreated injuries, infections, and infestations. Severe or extensive sunburns (Fig. 26-15) may be a sign of parental neglect, although several conditions and medications may make children more sensitive to ultraviolet light. It is important to bear these in mind whenever the possibility of neglect or abuse is being considered.

Physical neglect may also present as dental neglect, which is defined as the "willful failure of parent or guardian to seek and follow through with treatment necessary to ensure a level of oral health essential for adequate function and freedom from pain and infection."<sup>21</sup> Findings may include dental caries, periodontal disease (Fig. 26-16), and other oral conditions. When left untreated, these conditions can lead to significant pain, infection, and loss of function.<sup>21</sup>

## Factitious Skin Disorders

Factitious skin disorders (also called *self-inflicted skin lesions*) are a group of disorders characterized by self-inflicted lesions or artifacts on the skin. The individual cases vary in terms of the visible lesions and the

underlying motive that causes the patient to act. These disorders may be associated with a variety of psychopathologic conditions, and comanagement with a psychologist or psychiatrist is often necessary. Factitious skin disorders fall under the rubric of psychodermatologic conditions or psychocutaneous disorders, although these two classifications also include dermatologic conditions with secondary psychiatric sequelae (i.e., alopecia areata or albinism) and dermatologic conditions that may be aggravated by psychologic factors (i.e., acne, atopic dermatitis, psoriasis).<sup>22</sup> Diagnosis of factitious skin disorders is often delayed, and management is challenging, requiring the development of a therapeutic alliance between the physician and patient and treatment of any underlying psychiatric comorbid conditions. The diagnosis of factitious skin disorders largely remains a diagnosis of exclusion.<sup>23</sup> Treatment often requires a multidisciplinary approach that may include the pediatrician, dermatologist, psychologist, and/or psychiatrist.

## FACTITIOUS DERMATITIS/DERMATITIS ARTEFACTA

Factitious dermatitis is one type of factitious disorder that is caused by a conscious or subconscious behavior driven in response to internal psychologic stressors and not associated with secondary gain.<sup>23</sup> *Dermatitis artefacta* (DA) is often the terminology used to describe a disorder in which the skin is the purposeful target of self-inflicted injuries. In DA, the patient creates the lesions on the skin in order to satisfy a psychological need (of which he or she is often not consciously aware) and in the pursuit of secondary gain.<sup>23,24</sup> There appears to be the need to satisfy an internal emotional necessity—the need to be cared for.<sup>25,26</sup> The desired gain may be obvious or may not be readily evident. DA occurs predominantly among women, with a wide range in the quoted ratios of women to men, from 3 : 1 to 20 : 1.<sup>25</sup> It may have its onset at any time, although it most commonly occurs in teenagers and young adults. When it occurs in children, DA may be related to various stressors including school examinations, bullying, and discord in the home.<sup>27</sup> Several comorbid conditions may be present, including borderline personality disorder, disorders of impulse control, depression, anxiety, obsessive-compulsive disorder (OCD), and psychotic disorders.<sup>22,24,26,28</sup> It may also result from a transient maladaptive response to a recent psychosocial stressor(s). A past and/or current history of sexual abuse is common.<sup>25,29</sup> Patients with DA often have a close connection (either personally or through a close family member) with the healthcare field, and many have an "encyclopedic" grasp of medical knowledge and/or terminology. Some have suggested abandoning the terms *factitious dermatitis* and *DA* in favor of the terminology *factitious disorders in dermatology*.<sup>30</sup>

DA has a variety of presentation patterns. Importantly, the cutaneous features are often only one facet of the entire picture, because these patients often have involvement of other organ systems and have



**Figure 26-17** Suction purpura. This well-demarcated, petechial patch over the upper lip and philtrum area arose after this young girl repeatedly sucked air from a cup placed over her lips and upper chin.

visited numerous medical specialists for other bizarre or unexplained symptoms. The skin lesions themselves may consist of purpura, excoriations, abrasions, crusting, necrosis, blisters, ulcers, erythema, nodules, or scarring. When blisters are present (bullous DA), modes of injury often include thermal, electrical, or chemical injury.<sup>31</sup> The lesions of DA usually lack features of recognizable dermatoses. Notable features often include linearity, geometric arrangements, and sharp demarcation from the surrounding normal skin. The face, upper trunk, and upper extremities are the sites most often involved, and there is notable sparing of areas outside of the patients' reach (i.e., the middle back). There is often a prominence on one side, depending on the handedness of the patient. The lips may also be involved, presenting usually as persistent bleeding and crusting.<sup>32</sup> The lesions are often fully formed and are all in a similar stage of development. This inability of the patient to give details of evolutionary change has been termed *hollow history* and is quite typical of DA.<sup>24,25,33</sup>

Reported modes of injury include rubbing; scratching; picking; cutting; gouging; pinching; puncturing; biting; sucking; applying suction; applying heat, dye, or caustic substances; and injecting caustic materials or bodily secretions.<sup>22,24</sup> The differential diagnosis may be broad and depends on the nature of the inflicted injury. A clue to the diagnosis of DA is indifference or lack of concern on the part of the patient, who will often deny pain or discomfort despite the impressive physical findings.<sup>33</sup> Bullous DA caused by thermal injury may result after the “salt and ice challenge,” a trending dare contest in which participants sprinkle salt on the skin followed by compression with an ice cube.<sup>34</sup>

Factitious purpura, which is a form of mechanical purpura, may result in a detailed, lengthy investigation for other medical causes before the diagnosis is entertained. Patients may be entirely unaware that they are causing the skin lesions. A common form of factitious purpura is that caused by sucking air from a drinking glass placed over the chin and lower lip, resulting in a well-demarcated, circular area of purpura (Fig. 26-17).<sup>35</sup> Other forms may be caused by a variety of instruments or objects, with the purpuric lesions corresponding to the patterns of those objects. Figures 26-18 through 26-30 depict some various presentations of DA.

Malingering may present with lesions similar to DA, but in this setting the patient self-inflicts injury consciously, often with a secondary gain. These patients may exhibit “*la belle indifference*,” which refers to an apparent lack of frustration, despite the recurrent nature of their symptomatology.

Neurotic (psychogenic) excoriations are lesions self-inflicted by patients who have an irresistible urge to manipulate their skin.<sup>26</sup> It is often related to mood disorders, anxiety disorder, drug abuse, or OCD.<sup>36</sup> The cycle of neurotic excoriations may begin with a true physical stimulus such as pruritus or a skin lesion or irregularity such as an acne papule. The latter is referred to as *acne excoriée des jeunes filles*



**Figure 26-18** Dermatitis artefacta. Well-demarcated abrasions and hyperpigmentation in a 10-year-old male.



**Figure 26-19** Dermatitis artefacta. Sharply demarcated, eroded, erythematous plaques from chronic rubbing.



**Figure 26-20** Dermatitis artefacta. This localized discoloration of the hand had been caused by intentional exposure to fabric dye.

and occurs when even mild acne lesions (especially those on the forehead) are squeezed or excoriated (Fig. 26-31). This behavior may result in permanent scarring, and although some patients may fulfill diagnostic criteria for OCD, many do not. Patients with neurotic excoriations usually acknowledge the behavior and may have any of several comorbid conditions, including OCD, a personality disorder, anxiety, or depression. The picking activity is performed most often with the fingernails, although some patients may use an auxiliary tool



**Figure 26-21** Dermatitis artefacta. These evenly spaced, linear, hemorrhagic markings were self-induced.



**Figure 26-24** Dermatitis artefacta. Linear purpura is a common finding in factitious skin disease.



**Figure 26-25** Dermatitis artefacta. These linear and stellate purpuric patches were present in the same patient shown in [Figure 26-24](#). Note the associated resolving purpuric areas located on the arm.



**Figure 26-22** Dermatitis artefacta. This patient with underlying atopic dermatitis had acute worsening in these areas, which ultimately was found to be self-inflicted.



**Figure 26-26** Dermatitis artefacta. Linear purpura was present on both arms of this school-age boy.



**Figure 26-23** Dermatitis artefacta. These well-demarcated erosions are notable for their even spacing and sharp, linear borders.

such as the point of a knife.<sup>24</sup> The resultant skin lesions reveal erythema, erosions, weeping, crusting ([Fig. 26-32](#)), pigmentation, or scarring. There is often a notable sparing of the upper lateral back areas.

Prurigo nodularis (PN) is a condition characterized by firm papules and nodules with pruritus. It most typically presents with discrete, 2- to 10-mm, firm, lichenified hyperkeratotic papules that may reveal some central excoriation or crusting ([Figs. 26-33](#) and [26-34](#)). Common locations include the extremities and the upper and lower back, often with a zone of sparing noted in the middle back, which is a difficult location for the patient to reach. The cause of PN is unknown. It has been seen in a variety of settings, including bite reactions, atopic dermatitis (see [Fig. 3-16](#)), allergic contact dermatitis, folliculitis,



**Figure 26-27** Dermatitis artefacta. Irregularly shaped purpuric patches of the neck and face.



**Figure 26-28** Dermatitis artefacta. Purpuric patches with geometric and linear borders in the same patient shown in [Figure 26-27](#).

psychosocial disorders, thyroid disease, malignancy, iron-deficiency anemia, kidney failure, gluten sensitivity, obstructive biliary disease, and infections (including hepatitis, human immunodeficiency virus [HIV], and mycobacteria).<sup>37,38</sup> If generalized pruritis is reported by the patient, a laboratory investigation (including blood counts, kidney and liver function tests, and thyroid and parathyroid screening) may be warranted.<sup>38</sup> Skin biopsy may be useful if infection is included in the differential diagnosis. Treatment for PN is notoriously difficult and may include topical corticosteroids or calcineurin inhibitors (i.e., tacrolimus and pimecrolimus), topical capsaicin, ultraviolet phototherapy, and antihistamines. In severe cases, systemic agents such as cyclosporine, thalidomide, naltrexone, and etretinate have been used.<sup>37,38</sup> Psychological intervention is often necessary.



**Figure 26-29** Dermatitis artefacta. Well-demarcated linear purpuric macules.



**Figure 26-30** Dermatitis artefacta. These eroded and scarred plaques reveal irregular borders consistent with self-manipulation.



**Figure 26-31** Acne excoriée. Acne papules with erosions, scarring, and hyperpigmentation are typical of this condition.

## DELUSIONS OF PARASITOSIS

A delusional disorder is characterized by adherence to a possible yet implausible belief for which there is no supportive objective evidence.<sup>39</sup> Monosymptomatic hypochondriacal psychosis (MHP) is characterized by a delusional ideation that revolves around one concern, in contrast



**Figure 26-32** Neurotic excoriation. This adolescent female acknowledged her repeated picking and scratching, which resulted in these erythematous eroded and crusted papules on her bilateral breasts.



**Figure 26-34** Prurigo nodularis. Firm, lichenified, hyperpigmented papules were present on the arms and legs of this 9-year-old girl.



**Figure 26-33** Prurigo nodularis. This boy had numerous, discrete, lichenified firm papules on his upper and lower back, forearms, and lower extremities. Note the zone of sparing over the middle back, an area that was difficult for him to reach.

to schizophrenia, in which case patients have multifunctional deficits in mental functioning.<sup>40</sup> The most common type of MHP with dermatologic relevance is delusions of parasitosis. This disorder, also known as *delusional infestation*, is characterized by the conviction of an individual that he or she is infested with parasites in the absence of any objective evidence. Patients with delusions of parasitosis, most often older adult females, complain of having the sensation of crawling, burrowing, and biting insects or worms on their skin. They may resort to self-mutilation in an attempt to remove the offending arthropods. A history of psychiatric illness can be elicited in most patients with this disorder.<sup>41</sup> This discussion is focused on primary delusions of parasitosis; a secondary form may arise from certain medical conditions such as stroke, cardiovascular disease, vitamin (especially B<sub>12</sub>) deficiency, diabetes, or psychiatric diagnoses such as schizophrenia or depression.<sup>42</sup>

Patients with delusions of parasitosis often attend the clinic with spurious samples of the “parasite” that when microscopically examined turns out to be lint, skin cells, scabs, or other debris. Skin findings may include excoriations, lichenification, pigmentary alteration, and

scarring. Treatment of the disorder is challenging, with the anti-psychotic medication pimozide being the most often utilized pharmacologic agent. Other utilized agents have included aripiprazole, olanzapine, and risperidone.<sup>42,43</sup> Before therapy, however, exclusion of true skin disorders (i.e., scabies, dermatitis herpetiformis, or insect-bite reactions) should be considered.<sup>44</sup>

*Morgellons disease* is a term that initially began to surface in 2002 and whose name was taken from the label, given in 1674 in France by Sir Thomas Browne, to children who had hair-like skin extrusions and sensations of movement.<sup>45</sup> This terminology provides an alternative to the decades-old nomenclature of *delusions of parasitosis*, although many consider the two disorders to be part of the same spectrum.<sup>46–50</sup> Patients with Morgellons disease complain of cutaneous dysesthesias, resulting in skin manipulations in an effort to extract the “organisms,” thin fibers, or foreign materials. They may experience itching or crawling sensations, and many report the sense that bugs or worms are stinging or biting them. The examination findings may include excoriations, ulcers, lichenification, and prurigo nodules. Patients with Morgellons disease, much like those with delusions of parasitosis, may bring samples or debris in bottles, jars, or bags to the appointment. Examination of these contents often reveals lint, hair, debris, fuzz, dead skin, material fibers, or bugs.<sup>47</sup> Management of the condition is difficult and includes establishing good rapport, excluding skin or other organic conditions, consideration for the use of psychotropic medications, and treatment of secondary skin infection when necessary. Long-term antibiotic therapy has reportedly been useful.<sup>48,51</sup> Collaborative care with a psychiatrist or a psychodermatology clinic is strongly encouraged for both Morgellons disease and patients with delusions of parasitosis.

## OBSESSIVE-COMPULSIVE DISORDERS

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions (recurrent thoughts or images experienced as intrusive or senseless) or compulsions (repetitive, intentional behaviors performed to diminish discomfort or future harm and felt to be unreasonable or excessive).<sup>52</sup> The essential features required for diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* 5 is that the obsessions or compulsions are severe enough to significantly impact the daily routine and social or work functioning and the patient does not realize that they are excessive or unreasonable.

The expression of OCD may take the form of a dermatologic disorder. Entities that may fall into this spectrum are listed in Table 26-4. Clinical features that may suggest an OCD-related spectrum disorder include a heightened concern for cleanliness, fear of contamination, excessive worry about life-threatening illnesses or STDs, inappropriate concerns about body odor, and worries regarding an unattractive appearance or hair loss.<sup>22,53</sup>

OCD often begins in childhood or early adulthood, and most patients have a waxing and waning course. Comorbid conditions are common,



**Figure 26-35** Obsessive-compulsive disorder. This 6-year-old boy has features of onychophagia (nail biting; note shaggy, uneven, and short distal nail plates) and onychotillomania (nail picking; note damage to cuticles). The associated nail pitting was felt to be related to underlying twenty-nail dystrophy of childhood.

**Table 26-4** Obsessive-Compulsive Disorder and Some Possibly Associated Dermatologic Conditions

Disorder	See Chapter Number for Details
Acne excoriée	8
Body dysmorphic disorder	Current
Irritant dermatitis (hand-washing)	3
Lichen simplex chronicus	3
Lip-licker dermatitis	3
Neurotic (psychogenic) excoriations	Current
Onychophagia/onychotillomania	Current
Rhinotillexomania (pathologic nose-picking)	Current
Prurigo nodularis	3
Trichotillomania	7

including depression and anxiety disorders. Childhood OCD may be associated with Tourette syndrome, tics, family history of OCD, developmental delay, and hyperactivity.<sup>54</sup> The most common cutaneous presentations are trichotillomania (see Chapter 7), onychophagia, onychotillomania (Fig. 26-35), and acne excoriée (see Chapter 8).<sup>53,55</sup> *Onychophagia* refers to the compulsive habit of nail biting, which becomes pathological when excessively time consuming or associated with social avoidance.<sup>50</sup> *Onychotillomania* refers to picking of the cuticle or removal of the nail. More recently, *rhinotillexomania* (compulsive nose picking) has been recognized as a potential manifestation of OCD when it becomes socially compromising or physically harmful. Nasal-septum perforation has been reported in some patients. Importantly, patients with pediatric OCD experience chronicity and intractability of the disorder despite multiple interventions.<sup>56</sup>

*Body dysmorphic disorder (BDD)* is defined as preoccupation with an imagined defect in appearance. BDD, which falls into the OCD spectrum of disorders, may present with dermatologic symptoms or concerns. These include concerns about an unattractive appearance, acne scarring, hair thinning, early skin aging, hirsutism, greasy skin, body odor, large nose, small genitalia, or blushing.<sup>53,55,57</sup> Patients with BDD may spend many hours a day worrying about their obsession and visually inspecting the “abnormality,” which may impact on social and professional functioning. BDD occurs at high rates in patients with eating disorders. Tanning addiction has been classified as one subtype of BDD.<sup>58</sup>

Treatment of OCD spectrum disorders includes both behavioral and pharmacologic therapies, most notably the tricyclic antidepressants and selective serotonin reuptake inhibitors.



**Figure 26-36** Psychogenic purpura. This young female with a history of anxiety disorder complained of recurrent, spontaneous ecchymoses. Examination revealed ecchymotic patches with superimposed abrasions.

### PSYCHOGENIC PURPURA/GARDNER-DIAMOND SYNDROME

Psychogenic purpura (autoerythrocyte sensitization syndrome, Gardner–Diamond syndrome) is a rare disorder characterized by recurrent episodes of painful ecchymoses (Fig. 26-36) in various locations. The patients are most often young adult females with emotional disturbances, and the lesions commonly occur after trauma, surgery, or severe emotional stress.<sup>59,60</sup> The individual lesions resolve over 2 weeks. Psychiatric associations include depression, OCD, hypochondriasis, hysterical and borderline personality disorders, and anxiety.<sup>59–61</sup> Gardner and Diamond, in 1955, suggested that the disorder was associated with autoreactivation of patients to their own blood.<sup>62</sup> Traditionally the diagnosis was confirmed by intradermal injection of the patient’s own erythrocytes, which may result in reproduction of the clinical lesions.

The skin lesions of Gardner–Diamond syndrome are often consistent with a factitious dermatosis given their purpuric nature, irregular distribution, peculiar morphology, and erratic onset. However, confirmation of a self-inflicted process is often difficult, if not impossible. During the prodromal stage, nonspecific symptoms such as malaise and fatigue may be reported. The skin lesions develop rapidly after sensations of burning and stinging and evolve over 1 or 2 days from erythematous to ecchymotic. They resolve over 7 to 10 days. Associated findings such as hematuria, epistaxis, or menorrhagia are occasionally noted. Histologic evaluation of skin-biopsy samples reveals nonspecific features including perivascular inflammation (without frank vasculitis), erythrocyte extravasation, and pigment deposition.<sup>63</sup> Avoidance of confrontation with the patient, establishment of rapport, and psychiatric evaluation and therapy are indicated. Psychotropic medications and hypnotherapy have occasionally been utilized.<sup>63</sup>

### CAREGIVER-FABRICATED ILLNESS

Caregiver-fabricated illness (also known as *Munchausen syndrome by proxy*, *pediatric condition falsification*, *fictitious disorder by proxy*, *child abuse in the medical setting*, and *medical child abuse*) is a form of child maltreatment caused by a caregiver who falsifies and/or induces a child’s illness, leading to unnecessary and potentially harmful medical

investigations and/or treatment.<sup>64</sup> Munchausen syndrome is the traditional designation for a form of factitious disorder characterized by dramatic presentations with factitious complaints, exaggerated lying, and “physician shopping.” Patients have recurrent feigned symptoms and often have borderline or antisocial personality types. Caregiver-fabricated illness occurs when a parent or caregiver creates an illness in a child and is a form of child abuse inflicted most often by the mother. The stereotype of a mother involved in caregiver-fabricated illness is one who works in the healthcare field, is estranged from the child’s father, is quite friendly with the medical staff, and seems relatively unconcerned when the physician is unable to render a diagnosis.<sup>65</sup> The perpetrators are often quite familiar with medical terminology and diseases and usually have pathologic attachments to their children.<sup>66</sup> A history of working in a daycare setting is also common.<sup>65</sup>

The classic four criteria set forth for caregiver-fabricated illness are medical illness in a child that is fabricated by a parent; the child is brought for repeated medical evaluation or treatment and often undergoes multiple medical procedures; the perpetrator denies the actions; and acute symptoms and signs resolve when the child and caregiver are separated.<sup>33</sup> Two circumstances should be present for this diagnosis to be confirmed: harm or potential harm to the child involving medical care, and a caregiver who is causing it to happen.<sup>67</sup> Features of the clinical scenario usually include persistent symptoms that defy medical explanation, involvement of an adult caregiver (usually the biologic mother), and an involved physician who is eager to piece together the presentation and ameliorate the patient’s confusing symptoms.<sup>68</sup> Potential indicators of caregiver-fabricated illness in a child are listed in Box 26-1.

There are a variety of clinical symptoms or features that may be seen in the child victim of caregiver-fabricated illness. These include infant or sleep apnea, factitious coagulopathy, bruising, failure to thrive, hypoglycemia, abnormal urinalysis, seizures and other neurologic symptoms, cyanosis, vomiting and diarrhea, recurrent infections, sepsis, lethargy, behavior problems, fever, melena or hematochezia, electrolyte abnormalities, and bone and joint problems.<sup>33,64–67,69</sup> The dermatologic aspects of this disorder may invariably be referred to as *factitious dermatitis by proxy* or *DA by proxy*. Skin findings have been reported in 3% to 9% of cases of caregiver-fabricated illness.<sup>69</sup> These lesions may present with any of the morphologies discussed earlier for factitious dermatitis/DA, including erythema, blistering, burns, lacerations, puncture wounds, and dermatitis.

The diagnosis of caregiver-fabricated illness can be very challenging. The three forms of presenting signs or symptoms include covert injury induced in secret by the caregiver, fabrication of symptoms by the perpetrator, and symptoms neither induced nor fabricated but exaggerated by the caregiver.<sup>70</sup> The former is rendered when there is unquestionable evidence of commission such as capturing the act during covert videotape surveillance (CVS) in the hospital setting.<sup>71</sup> Some experts believe that such CVS is required in order to make a definitive and timely diagnosis in most cases of caregiver-fabricated illness.<sup>65</sup> When used, adequate safeguards including continuous surveillance and an agreed-upon plan of action must exist in order to

#### Box 26-1 Potential Red Flags for Caregiver-Fabricated Illness in a Child

- Persistent symptoms that defy medical explanation
- Unusual signs or symptoms (case often considered “atypical”)
- Symptoms out of proportion to physical findings
- Caregiver is neither satisfied or reassured when informed of positive progress
- History is inconsistent
- Caregiver encourages additional investigations or consultations
- Signs and symptoms consistently occur in presence of same caregiver
- Lack of response (or unusual response) to established therapies
- Caregiver with history of somatization disorders

Modified from Flaherty EG, MacMillan HL. Caregiver-fabricated illness in a child: a manifestation of child maltreatment. Pediatrics 2013;132:590–7, and Squires JE, Squires RH. A review of Munchausen syndrome by proxy. Pediatr Ann 2013;42(4):e67–71.

prevent further injury to the child.<sup>67</sup> The use of CVS remains controversial, with some arguing that it is an invasion of a parent’s right to privacy or constitutes entrapment. If utilized, hospital-implemented protocols that guide its use are encouraged.<sup>64</sup> A diagnosis of exclusion is occasionally rendered when all other possible explanations for the child’s condition have been considered and excluded.<sup>71</sup> Consultation with all colleagues who have cared for the child and a “separation test,” in which the child is demonstrated to be free of disease outside the care of the mother, are useful.<sup>72</sup> Child protective services should be involved and the perpetrator referred to a professional with significant experience in caregiver-fabricated illness. Long-term morbidity or permanent disability is common in survivors.

#### Cutaneous Mimickers of Abuse and Factitious Disorders

Although child abuse or factitious disorders should always be considered in the child with unusual skin marks or injuries, there are several potential mimickers that must be kept in mind. These are summarized in Table 26-5.<sup>73,74</sup> Although they are not each discussed in detail here, it is important to recognize potential cutaneous mimickers in order to reduce the erroneous diagnosis of child abuse.<sup>75</sup>

There are a number of cultural practices that may be confused with abuse, given the trauma-induced skin lesions that result from these practices. With the increasing influx of Asian immigrants entering the United States, such traditional East Asian medicine methods are being practiced with increasing incidence. The philosophy of East Asian medicine is to achieve a state of balance and equilibrium, including proper flow of energies within “channels” or “meridians.”<sup>76</sup> The goal of traditional folk remedies is to facilitate this energy balance. It is important for the pediatric practitioner to be familiar with these culturally based therapies, which include coining/spooning, cupping, moxibustion, gridding, blood letting, and warm-needle acupuncture.<sup>76–78</sup> The former three entities will be briefly discussed here.

Coining is also known as spooning, coin rubbing, skin scraping, or *cao gio*. It is an ancient Vietnamese folk remedy performed by applying heated, mentholated oil to the back, chest, and shoulders and then vigorously rubbing a coin on selected parts of the body in order to produce linear petechiae or ecchymoses (Fig. 26-37).<sup>79</sup> Other items that may be used include a ceramic Chinese soup spoon, water-buffalo horn, piece of jade or ginger root, or edge of a jar cap. Whereas a coin is traditionally used by the Vietnamese, a spoon is commonly the instrument used by the Chinese, in which case the practice is referred to as *quat sha*.<sup>80</sup> Those who utilize coining believe it to be useful for a variety of complaints including headache, fever, pain,



**Figure 26-37** Coining. These linear and stellate purpuric patches were caused by the vigorous rubbing of a coin on the skin, termed *coining*, or *cao gio*. (Courtesy of Jean Hlady, MD.)

**Table 26-5** Potential Mimickers of Abuse or Factitial Disorders

Disorder	Chapter/Comment
Accidental burns	Various, including enuresis blanket, acetic acid, objects heated by sun (i.e., bike seats, car upholstery)
Allergic contact dermatitis	Ch. 3; may be confused with abuse, especially when vesicular or bullous
Anal fissures	Most commonly associated with constipation, passage of hard stools; however, occasionally associated with sexual abuse
Autoimmune bullous disease	Ch. 13; vulvar pemphigoid, linear IgA bullous disease of childhood
Behçet syndrome	Ch. 25
Berloque dermatitis	Ch. 19; phototoxic reaction to fragrance products
Bullous impetigo	Ch. 14; may be confused with cigarette burns
Crohn disease	Ch. 25; may present with perianal erythema, fissures, skin tags, bleeding, scarring, swelling
Ecthyma	Ch. 14; confused with cigarette burns; usually caused by GABHS
Ehlers–Danlos syndrome	Ch. 6; may have poor wound healing, scarring, easy bruising
Enlarged hymenal opening	Important reassuring features include intact hymenal tissue at posterior rim, lack of laceration/deep notching/bruising/bleeding <sup>73</sup>
Epidermal nevus	Ch. 9; perianal lesions may be confused with anogenital condylomata <sup>74</sup>
Epidermolysis bullosa	Ch. 13; especially dominant dystrophic or simplex varieties
Fixed drug eruption	Ch. 20
Folk remedies	Current chapter; see text
Hematologic disorders	Various, including hemophilia, von Willebrand disease, leukemia, ITP, vasculitis
Herpes zoster	Ch. 15; may be confused with abuse when involves genital (S2, S3) dermatomes
Incontinentia pigmenti	Ch. 11; vesicular and pigmentary lesions with bizarre patterning
Labial adhesions	
Lichen sclerosus et atrophicus	Ch. 22; genital variant confused with sexual abuse; may be bullous
Mongolian spots	Ch. 11
Netherton syndrome	Ch. 5; dermatitis, ichthyosis, failure to thrive, and alopecia may be confused for abuse
Nevus of Ota or Ito	Ch. 11
Normal bruising	Most commonly children 2–5 years of age; consider distribution, developmental status, history
Osteogenesis imperfecta	Ch. 6; frequent fractures, osteoporosis, short stature, frontal bossing, blue sclerae
Perianal pyramidal protrusion	Ch. 15
Perianal streptococcal dermatitis	Ch. 14
Phytophotodermatitis	Ch. 19; phototoxic reaction to psoralens (lemons, limes, celery, parsley, dill)
Vaginal foreign body	May result in vaginal discharge, bleeding
Xeroderma pigmentosum	Ch. 19; severe sunburn may be confused with neglect

GABHS, Group A β-hemolytic streptococci; IgA, immunoglobulin A; ITP, idiopathic thrombocytopenic purpura.

and inflammation. Although serious injury is rare, minor and even major burns (resulting from ignition of the oil in the skin) have been reported.<sup>79</sup>

Cupping is an ancient technique dating back to the fourth century BC in Egypt.<sup>81</sup> It is practiced in the United States most often by Russian immigrants but is also utilized within Asian and Mexican-American cultures (where it is referred to as *ventosas*).<sup>80</sup> It is used to relieve such symptoms as abdominal pain, abscesses, stroke paralysis, lower back pain, indigestion, menstrual irregularities, fever, congestion, and poor appetite. With this remedy, a cup or jar is immediately placed on the skin after a cotton-ball soaked with alcohol has been ignited within the cup to create a suction vacuum. The procedure results in circular ecchymotic lesions (Figs. 26-38 and 26-39) with eventual hyperpigmentation. In Middle-Eastern cultures, the skin may be initially lanced, with some blood drawn into the cup during the procedure. This has been referred to as *wet cupping*.

Moxibustion is another folk remedy utilized primarily in Asian cultures for a variety of complaints including enuresis, behavioral disorders, asthma, and pain.<sup>76,80</sup> It has also been utilized for correction of breech presentation<sup>82</sup> and for treatment of tennis elbow.<sup>83</sup> In moxibustion, the moxa herb (mugwort herb, *Artemisia vulgaris*) is rolled into a cone or cigar, ignited, and placed on the appropriate body part (either directly or indirectly with a medium separating the moxa from the skin). It is allowed to burn to the point of pain, and the resulting skin



**Figure 26-38** Cupping. This 7-year-old girl (right) who was brought to the clinic for an unrelated skin complaint was noted to have this round, ecchymotic lesion on her back. Examination of her mother (left) revealed multiple such lesions that were being induced by cupping in hopes of treating her rheumatoid arthritis. The family performed the procedure on the girl at her request.



**Figure 26-39** Cupping. Close-up image of the ecchymotic lesion seen in the female patient in [Figure 26-38](#).

lesions vary from transient redness to second-degree burns that resemble cigarette burns on acupuncture sites and may scar. As with all folk remedies, these lesions may be confused with intentional child abuse. Indirect moxibustion, in which the lit moxa stick is held near (not on) the skin until it turns red, is less painful and less often results in scarring.<sup>84</sup>

The complete list of 84 references for this chapter is available online at <http://expertconsult.inkling.com>.

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