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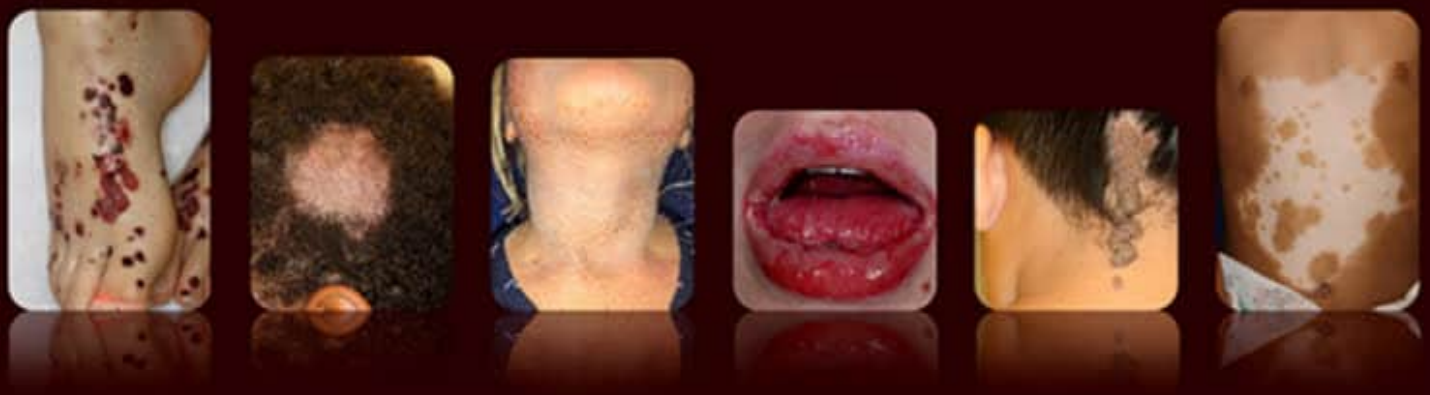
Paller and Mancini

Hurwitz

Clinical Pediatric Dermatology

A Textbook of Skin Disorders of Childhood and Adolescence



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A Textbook of Skin Disorders of Childhood and Adolescence

SIXTH EDITION

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Dedication

We again dedicate the text to our families,
whose ongoing patience, encouragement, support,
and personal sacrifice enabled us
to complete this project:
To Etahn, Josh, Max, Laura, and Ben, and
to Nicki, Mallory, Christopher, Mackenzie, and
Alexander: thank you.

We also dedicate this sixth edition
to Sidney Hurwitz, MD,
the epitome of a role model in academic
pediatric dermatology.

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. We have advanced this text to be evidence based but full of our tips for the diagnosis and treatment of pediatric skin diseases in the four editions since Dr. Hurwitz "passed the baton" after writing the first and second editions. In this Paller/Mancini text, we have maintained the focus on educating and enlightening pediatricians, dermatologists, family practitioners, medical students, residents, fellows, nurses, and other allied pediatric care providers with a book that is practical, relevant, and user friendly in both its online and paper formats.

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 continue to be elucidated, and several new disease and syndrome associations have been described. The therapeutic armamentarium for cutaneous disease has broadened, with many new forms of pathogenesis-based therapy available for patients, including through new classes of drugs. We have strived to maintain a book that represents a balance between narrative text, useful tables, and vivid clinical photographs.

Several new features have been added to this sixth edition, including a downloadable e-book with the printed edition and more than 350 new clinical images. We have updated the sections on atopic dermatitis, psoriasis, connective tissue diseases, and autoinflammatory disorders to reflect our growing armamentarium of new medications. Our sections on the ichthyoses, hair and ectodermal dysplasias, genetic blistering disorders, and mosaic gene disorders have grown based on so many new discoveries of underlying causes. New directions, such as the use of stem cell and cell therapy, as well as recombinant protein, for treating epidermolysis bullosa are also mentioned.

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 infection with human herpesviruses and enteroviruses. There are expanded discussions of mycoplasma-associated disorders and updated sections on congenital syphilis, toxoplasmosis, and pediatric melanoma. A discussion of congenital Zika virus infections has been added, as have expanded discussions of therapy for infantile hemangiomas, newer approaches for other vascular tumors and malformations, and the expanding spectrum of genetic mutations and clinical presentations of vascular disorders and syndromes. We have expanded the discussions of pediatric vasculitides, as well as factitial disorders and delusional infestation in children.

Several new tables have been added or updated in this edition, including the evaluation of suspected neonatal infection with herpes simplex virus, a discussion of monitoring for comorbidities in psoriasis, new classifications for ectodermal dysplasias and epidermolysis bullosa that focus on a molecular basis, fixed-dose combination therapies for acne vulgaris, contraindications to combined oral contraceptives, clinical features of polycystic ovary syndrome, the RASopathies, gene polymorphisms and pigmentation, the epidermal necrolysis classification, diagnostic criteria for hemophagocytic lymphohistiocytosis, an update on the contemporary classification of pediatric histiocytoses, consensus-derived PHACES syndrome criteria, the updated ISSVA classification of vascular anomalies, updated treatment recommendations for herpes simplex virus infections, revised Jones criteria for acute rheumatic fever, and features of juvenile dermatomyositis.

As with our last edition, the references have again 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 Charlotta Kryhl, Melissa Rawe, Kathleen Nahm, and Janish Paul, 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 (especially Dr. Ayelet Ollech), nurses, and office staff (especially Melissa Jones and Giuliana Wells), who contributed enormously through assistance with literature searches and the taking and archiving of our many clinical photographs; and to our families, whose understanding, sacrifice, support, and unconditional love made this entire endeavor possible.

Contents

1 An Overview of Dermatologic Diagnosis and Procedures

CHAPTER OUTLINE

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, annular 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, bullous dermatosis of childhood, and sometimes epidermolysis bullosa simplex.

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 inflamed, dry skin with a tendency to thickening, oozing, vesiculation, and/or crusting; although atopic dermatitis is a classic eczematous disorder, other examples of eczema are contact, nummular, and dyshidrotic forms.

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 clones of embryonic epidermal 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.

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Table 1.1 Glossary of Dermatologic Terms

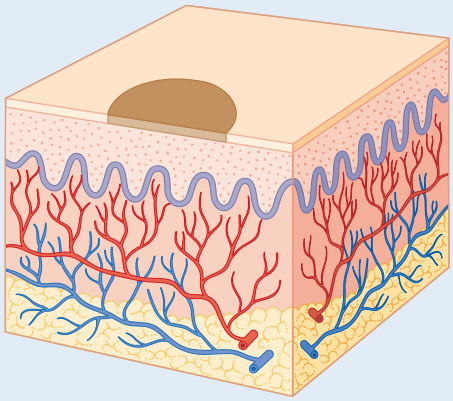
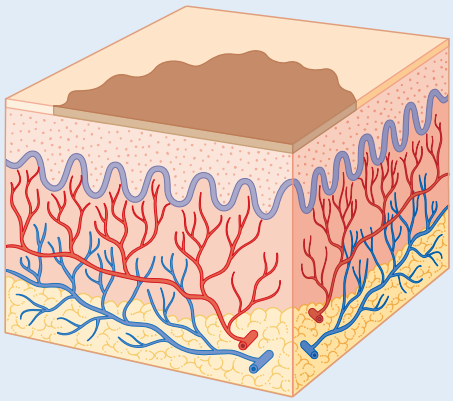
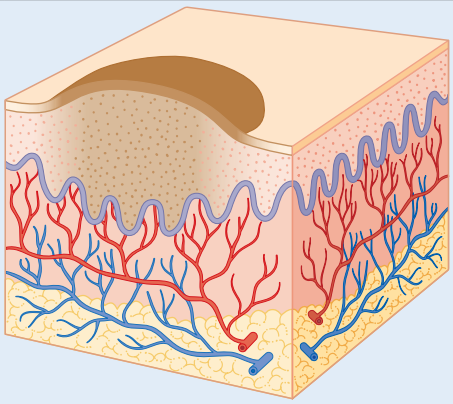
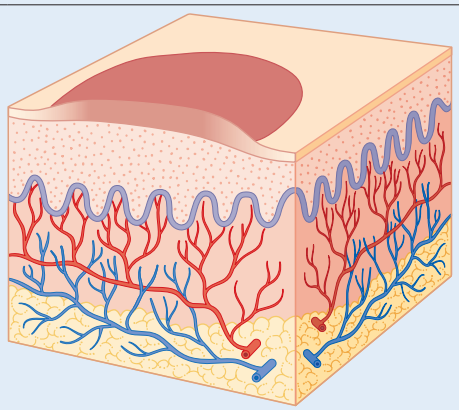
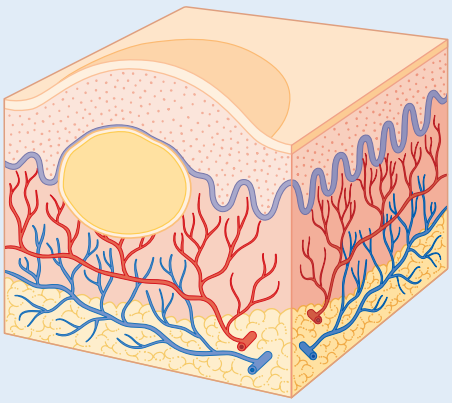
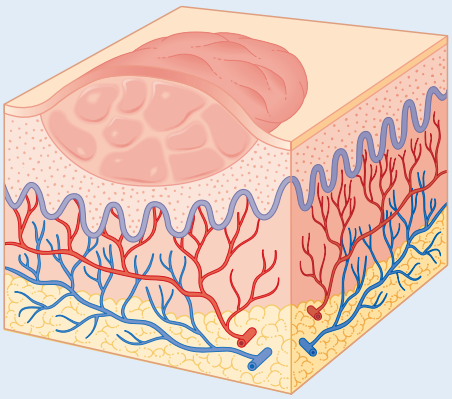
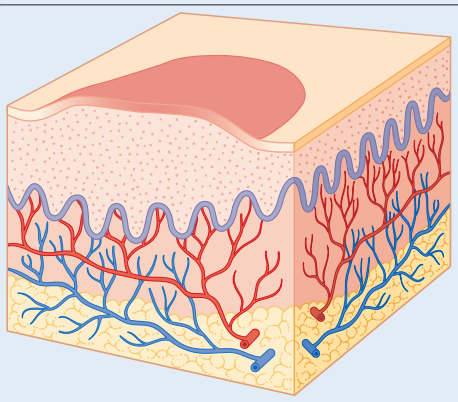
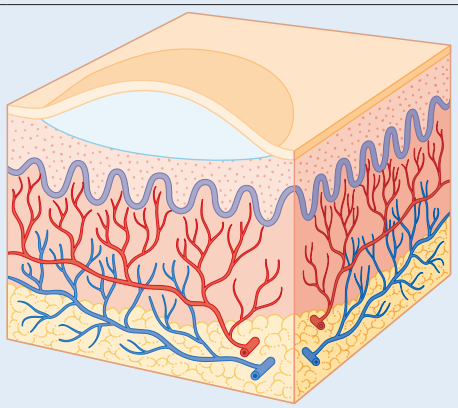
Lesion	Description	Illustration	Examples
PRIMARY LESIONS			
The term *primary* refers to the most representative, but not necessarily the earliest, lesions; it is distinguished from the cutaneous features of secondary changes such as excoriation, eczematization, infection, or results of previous therapy.			
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. 11.45); flat nevus (see Fig. 9.1); and tinea versicolor (see Fig. 17.40)
Patch	Flat, circumscribed lesion with color change that is >1 cm in size.		Congenital dermal melanocytosis (see Fig. 11.65); port wine stain (see Fig. 12.63); nevus depigmentosus (see Fig. 11.24); larger café-au-lait spot (see Fig. 11.49); and areas of vitiligo (see Figs. 11.2–11.10)
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. 15.20); molluscum contagiosum (see Fig. 15.40); perioral dermatitis (see Fig. 8.23); and individual lesions of lichen planus (see Fig. 4.54)
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. 4.6); lichen simplex chronicus (neurodermatitis, see Fig. 3.43); granuloma annulare (see Fig. 9.62); nevus sebaceus (see 9.43–9.46); and lesions of lichen planus (see Fig. 4.55)

Table 1.1 Glossary of Dermatologic Terms (Continued)

Lesion	Description	Illustration	Examples
Nodule	Circumscribed, elevated, usually solid lesion that measures 0.5–2 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 Fig. 20.45); pilomatricoma (see Figs. 9.50 and 9.51); subcutaneous granuloma annulare (see Fig. 9.64); and nodular scabies (see Figs. 18.9 and 18.10)
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. 12.8) and plexiform neurofibroma (see Fig. 11.56)
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. 9.59); urticarial vasculitis (see Fig. 21.15); and various forms of urticaria (see Figs. 20.2–20.7)
Vesicle	Sharply circumscribed, elevated, fluid-containing lesion that measures ≤1 cm in diameter.		Herpes simplex (see Figs. 15.8 and 15.12); hand-foot-and-mouth disease (see Fig. 16.32); pompholyx (see Fig. 3.47); varicella (see Fig. 16.1); and contact dermatitis (see Fig. 3.65, *B*)

Continued on following page

Table 1.1 Glossary of Dermatologic Terms (Continued)

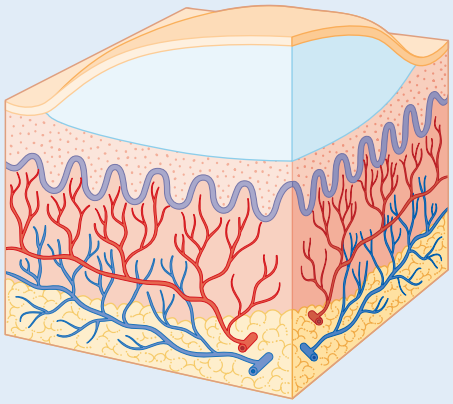
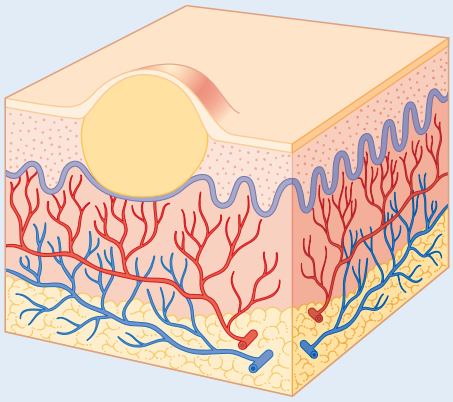
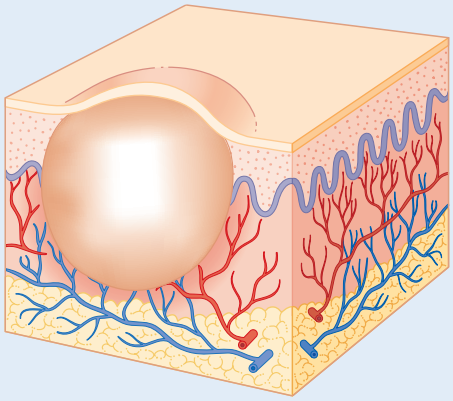
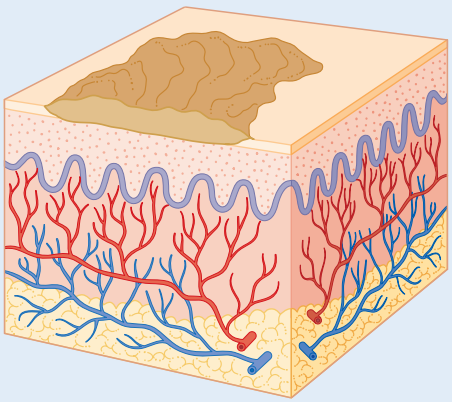
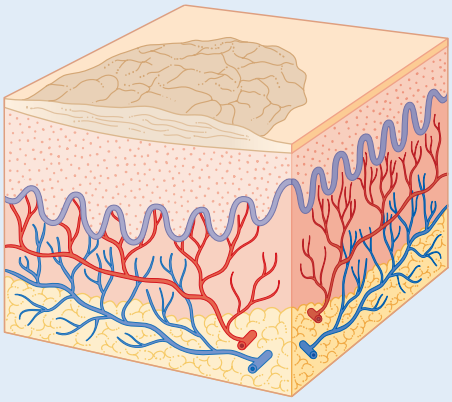
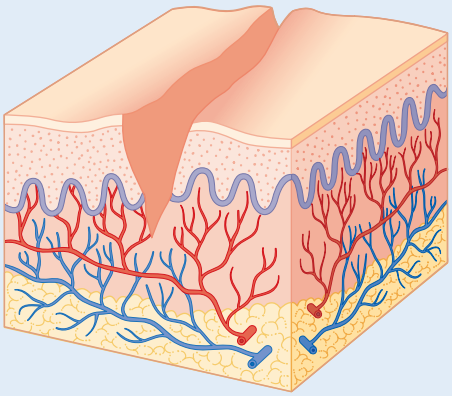
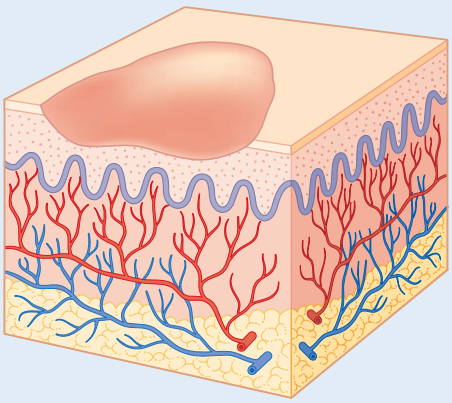
Lesion	Description	Illustration	Examples
Bulla	Larger, circumscribed, elevated, fluid-containing lesion that measures >1 cm in diameter.		Blistering distal dactylitis (see Fig. 14.22); bullous pemphigoid (see Fig. 13.33); chronic bullous disease of childhood (see Fig. 13.37); bullous flea bite reaction (see Figs. 18.33 and 18.34); 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. 2.22); pustular psoriasis (see Fig. 4.30); and neonatal cephalic pustulosis (see Fig. 2.16), neonatal *S. aureus* pustulosis (see Fig. 2.21), and infantile acropustulosis (see Fig. 2.24)
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. 3.41)
OTHER PRIMARY LESIONS			
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. 9.47)
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. 18.41)
Telangiectasia	Persistent dilation of superficial venules, capillaries, or arterioles of the skin.		Spider angioma (see Fig. 12.97); periungual lesion of dermatomyositis (see Figs. 22.26 and 22.29); CREST syndrome (see Fig. 22.45); and focal dermal hypoplasia (see Fig. 6.18)

Table 1.1 Glossary of Dermatologic Terms (Continued)

Lesion	Description	Illustration	Examples
SECONDARY LESIONS			
Secondary lesions represent evolutionary changes that occur later in the course of the cutaneous disorder. Although helpful in dermatologic diagnosis, they do not offer the same degree of diagnostic aid as that afforded by primary lesions of a cutaneous disorder.			
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. 15.5); weeping eczematous dermatitis (see Fig. 3.1); and dried honey-colored lesions of impetigo (see Fig. 14.1)
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 Fig. 3.3); psoriasis (silvery and mica-like, see Fig. 4.1); lichen striatus (fine and adherent, see Fig. 3.52); and lamellar ichthyosis (large and adherent, see Fig. 5.16)
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. 17.46) and dermatitis on the palmar aspect of the fingers (see Fig. 3.58) or the plantar aspect of the foot (see Fig. 3.69)
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. 3.31 and 15.3); epidermolytic ichthyosis in a neonate (see Fig. 5.6); and superficial forms of epidermolysis bullosa (see Fig. 13.5)

Continued on following page

Table 1.1 Glossary of Dermatologic Terms (Continued)

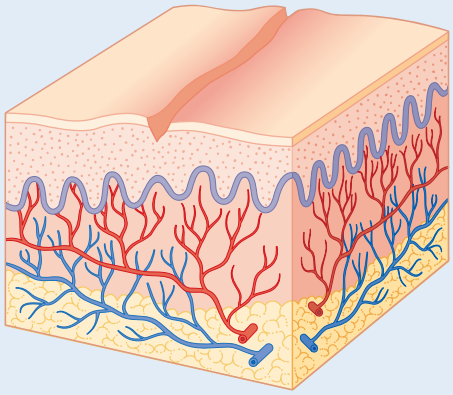
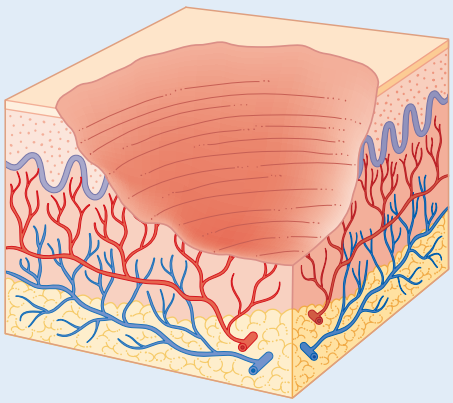
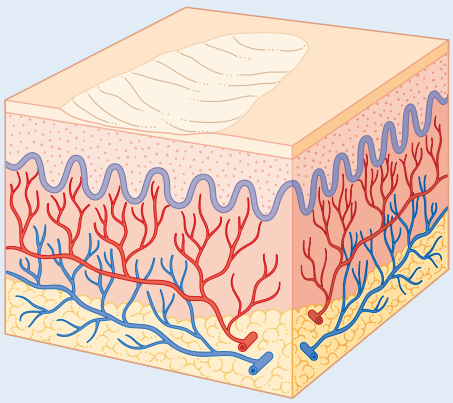
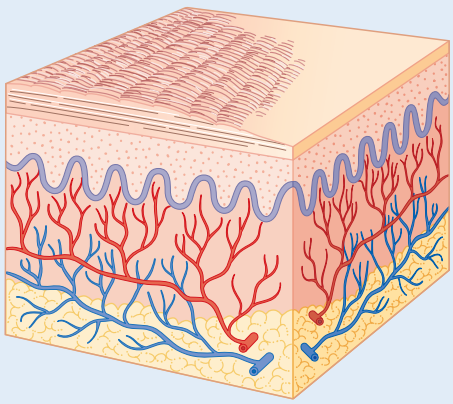
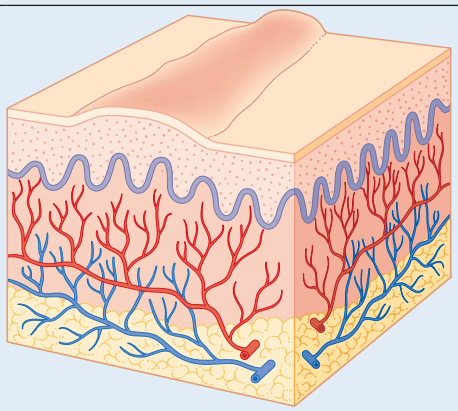
Lesion	Description	Illustration	Examples
Excoriation	Traumatized or abraded (usually self-induced) superficial loss of skin caused by scratching, rubbing, or scrubbing of the cutaneous surface.		Atopic dermatitis (see Fig. 3.9) and acne excoriée (see Fig. 8.22)
Ulcer	Necrosis of the epidermis and part or all of the dermis and/or the underlying subcutaneous tissue.		Pyoderma gangrenosum (see Fig. 25.18) 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. 22.63); morphea (see 22.54 and 22.56); steroid-induced atrophy (see Fig. 3.36); and focal dermal hypoplasia (see Fig. 6.19)
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. 3.61, *B*); and lichen simplex chronicus (see Fig. 3.43)

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 6–12 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. 9.93); healed areas of recessive dystrophic epidermolysis bullosa (see Fig. 13.26); post-hemangioma scarring (see Fig. 12.21); congenital erosive and vesicular dermatosis with reticulated supple scarring (see Fig. 2.21, *B*); and amniocentesis scars (see Fig. 2.4)

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, urticaria multiforme, early Henoch–Schönlein purpura, and polymorphous light eruption.

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

Polycyclic 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 reticulated 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.

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 8.8).

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 3.11).

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. 20.35 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 15.14). Herpes zoster generally has a dermatomal or nerve-like distribution and is usually but not necessarily unilateral (see Figs. 15.15 through 15.17). 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. 4.54, 4.55, and 4.58). 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 22.4). 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. 15.41 through 15.47). 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, 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, phototoxic reactions, 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 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 Fig. 4.49). After an interval of days to 2 weeks, affected individuals develop a generalized symmetric 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* (see Figs. 4.50, 4.51, and 4.53). A common variant, inverse pityriasis rosea, often localizes in the inguinal region (see Fig. 4.52), but the parallel nature of the long axis of lesions remains characteristic.

Psoriasis classically consists of round, erythematous, well-marginated 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 4.16). 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 18.12). 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. 3.3, 3.44, and 3.45). 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. 15.19 through 15.37). 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 (see Chapter 11). 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 congenital dermal melanocytosis, 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 Black and other darker-skinned children varies in several ways from that of lighter-skinned children based on genetic background and customs (see Chapter 11). 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 Black children commonly has a purplish tinge that can be confusing to unwary observers. The skin lesions in several inflammatory disorders such as in atopic dermatitis, pityriasis rosea, and syphilis commonly show a follicular pattern in Black 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 Black individuals; lichen planus is reported to be more severe, leaving dark postinflammatory hyperpigmentation. Vitiligo is particularly distressing to patients with darker skin types, whether Black or Asian, because of the easy visibility in contrast with surrounding skin.

Although darker skin may burn, 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) generally have an extremely low incidence in Blacks 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 Blacks, although the presence of six or more should still raise suspicion about neurofibromatosis. Dermatosis papulosa nigra commonly develop in adolescents, especially those who are 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 Voigt–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. Black 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 Blacks than in other groups. Tinea capitis is particularly common in prepubertal Blacks; 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 cornrow braids. The use of other hair grooming techniques such as chemical straighteners, application of hot oils, and 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.

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 caused by 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 blend in with surrounding skin during diascopy and do not refill when the slide is lifted after diascopy (as do the surrounding normal areas).

Magnification using a lens or lighted devices such as the otoscope, ophthalmoscope, or dermatoscope 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.[1,2] Indeed, *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,[3] visualization of vascular lesions, and hair disorders ranging from shaft defects to alopecia areata.[4–8] Reflectance confocal microscopy[9–11] is a noninvasive technology for in vivo imaging of skin at nearly histologic resolution. Although largely used currently to distinguish benign lesions from skin cancer, it has also been used to identify skin accumulation of cysteine for diagnosis of infantile nephropathic cystinosis.[12]

Several diagnostic techniques involve procedures to obtain scales or discharge (by scraping or swabbing) for analysis. Scraping can be performed with a sterile surgical blade, Fomon blade, or even less costly small metal spatula. An endocervical brush (Cytobrush)[13] or moistened swab 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,[13] 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. 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), many important potential allergens are missing; thus 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 Langerhans 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/UVA1 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 close to the lesion 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 warmer 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 vesiculation after application to molluscum contagiosum lesions (see Chapter 15). Although traditionally requiring compounding and administration using a wooden applicator, a single-use applicator with cantharidin is in development. Because the extent of blistering cannot be controlled (with some children developing extensive blisters and others virtually none), lesions near the eyes, on mucosae, and near other sensitive areas should not be treated with

cantharidin. In addition, lesions should not be occluded. Blistering occurs in 24 to 48 hours, and crusting clears within about a week. Associated discomfort is variable, but application is painless.

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). Many pediatric dermatologists avoid the 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 parents and child is important to allay concerns and manage expectations. If possible, the area to be biopsied, excised, or injected with anesthesia can be treated initially with a topical anesthetic cream (e.g., 4% lidocaine or 2.5% lidocaine/2.5% prilocaine) under a clear occlusive film (e.g., waterproof transparent dressing [Tegaderm] or Glad Press'n Seal wrap, which adheres more effectively than traditional plastic cling wrap). 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, watching a video, or applying vibrations to a contiguous area can also allay fear at almost any age. Punch biopsy is most useful for removing lesions smaller than 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; however, shave removal 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 that are 3 mm or less can be left to heal via secondary intention after hemostasis (including with insertion of Gelfoam), 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 they are generally not recommended. Deep sutures are often required to close the deeper space of larger or 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. Adhesive wound closure strips such as 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, and hematoma (especially on the scalp). Contact dermatitis may also occur, especially in reaction to adhesives or topical antibiotics; many surgeons use petrolatum alone after skin surgery to avoid the risk of contact dermatitis. 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.[13]

By far the most common laser used 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. PDL has also been used (with more variable response) for inflammatory linear verrucous epidermal nevus, erythematous striae, warts[14,15], acne,[16] 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 (e.g., central facial stains classically respond less to PDL therapy than lesions on the forehead or peripheral face, in part likely related to the more superficial depth of laterally located dilated capillaries),[17] 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.[18] Port wine stains located on the extremities tend to require more treatments than those located elsewhere, and those associated with early-onset hypertrophy have a poorer response and higher complication rate after PDL treatment.[19] Recent studies in adults with facial port wine stains suggest that the effect of the combination of topical rapamycin and PDL may be greater and more persistent than PDL alone.[20]

Other lasers used in pediatric patients include neodymium:yttrium-aluminum-garnet (Nd:YAG; 1064 nm),[21] alexandrite (755 nm),[22] 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).[13,23] 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 to be useful in psoriasis, vitiligo, nevus depigmentosus, pityriasis alba, and postinflammatory hypopigmentation.[24–28]

The complete list of 28 references for this chapter is available online at http://expertconsult.inkling.com.

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2 Cutaneous Disorders of the Newborn

CHAPTER OUTLINE

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.[1] 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.[2] However, in extremely low-birthweight infants, this process may take up to 4 to 8 weeks.[3] 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.[4–7]

The risk of percutaneous toxicity from topically applied substances is increased in infants, especially those born prematurely.[8,9] 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.[10] Although its function is not completely understood, it may act as a natural protectant cream to "waterproof" the fetus *in utero*, where it is submerged in the amniotic fluid.[11] 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.[12]

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.[13] 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. Recommendations for "first bathing" of the newborn suggest timing it according to local culture, performing it only after the newborn is physiologically stable and able to appropriately thermoregulate, considering the use of water alone or water and an appropriately formulated pH neutral (or acidic) liquid cleanser such as a synthetic detergent (syndet) or liquid baby cleanser, and considering the use of gloves by healthcare workers if performing the initial bath.[14–16]

There is no single method of umbilical-cord care that has been proven to limit bacterial colonization and disease, and cord care practices are quite variable in relation to cultural beliefs and healthcare disparities. Several methods have been reported, including 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.[17] A recent clinical review suggests consideration of application of antimicrobial agents

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_3 analog	Hypercalcemia, hypercalcemic crisis
Chlorhexidine	Topical antiseptic	Systemic absorption but no toxic effects
Corticosteroids	Topical antiinflammatory	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*-diethyl-*m*-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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for infants born at home or otherwise outside of birthing centers or hospitals in resource-limited settings but highlights that their use in high-resource countries or the setting of in-hospital delivery has not been found to provide clear benefit.[18]

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 vasospasm, 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.

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 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)

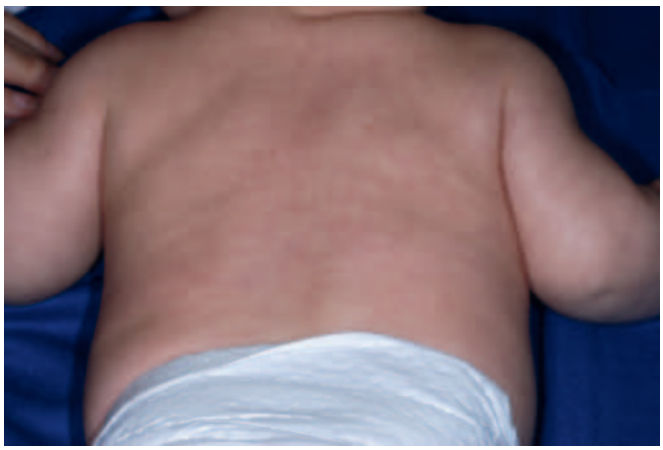


Fig. 2.1 Cutis marmorata. Reticulate bluish mottling that resolves with rewarming.

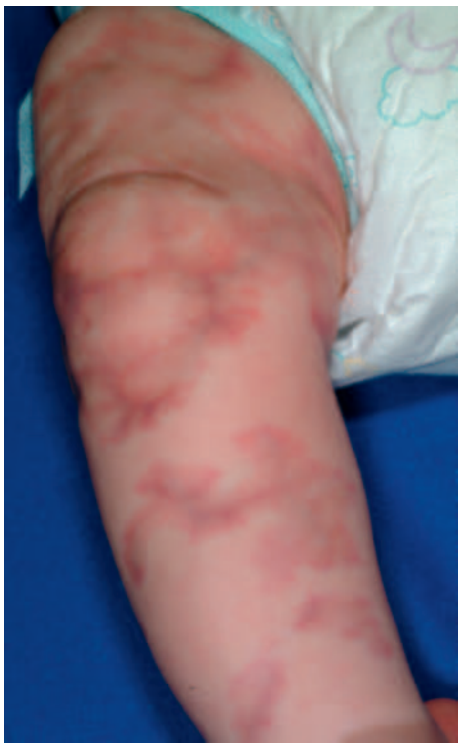


Fig. 2.2 Cutis marmorata telangiectatica congenita. Violaceous, reticulate patches with subtle atrophy. These changes did not resolve with rewarming and were associated with mild ipsilateral limb hypoplasia.

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, a form of vascular autonomic dysregulation not to be confused with harlequin ichthyosis (see Chapter 5), is occasionally observed in full-term infants but classically described 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 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. Some medications, including anesthetics and prostaglandin E, may exacerbate the condition.[19] Although the peak frequency of attacks of harlequin color change generally occurs between the second and fifth days of life, attacks may occur anywhere from the first few hours to as late as the second or the third week of life.[20]

INFANTILE TRANSIENT SMOOTH MUSCLE CONTRACTION OF THE SKIN

Believed to be a primitive reflex or autonomic phenomenon, *infantile transient smooth muscle contraction of the skin* refers to a transient rippling of the skin of otherwise-healthy infants, often triggered by cold or blowing air exposure. In a series of nine full-term newborns with this phenomenon, the authors noted several asymptomatic episodes occurring daily for brief periods (usually <1 minute), with completely normal–appearing skin in between episodes. Histologic examination was unremarkable in the skin biopsy specimens from three patients, and the episodes spontaneously resolved over 18 to 24 months. This condition appears to be related to transient arrector pili smooth muscle contraction, without features to suggest smooth muscle hamartoma.[21]

BRONZE BABY SYNDROME

Bronze baby syndrome (BBS) 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.[22–24] Infants who develop BBS usually have modified liver function, particularly cholestasis, of various origins.[25] Although very few babies with cholestasis develop BBS during phototherapy, those who do should be investigated for underlying liver disease.[26] 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, or "carbon baby" syndrome),[27] and chloramphenicol intoxication ("gray baby" syndrome).[28] Although early recognition of BBS suggests further evaluation for associated disorders, it does not appear to be a contraindication to ongoing phototherapy for hyperbilirubinemia.[29] 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.[30] This condition, however, is unlikely to be confused with BBS.

Cephalohematoma

A cephalohematoma is a subperiosteal hematoma overlying the calvarium. These lesions are more common after prolonged labor, 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 distinguish them from caput succedaneum (see the next section). Occasionally, a cephalohematoma may occur over a linear skull fracture. Other potentially associated complications include calcification (which may persist radiographically for years), osteomyelitis, hyperbilirubinemia, and infection. Signs of an infected cephalohematoma, usually caused by *Staphylococcus aureus* or *Escherichia coli*, include erythema, increasing size, and fluctuance.[31] Although infected lesions (which are rare) may require aspiration,[32] most lesions require no therapy, with spontaneous resorption and resolution occurring over several weeks to months.

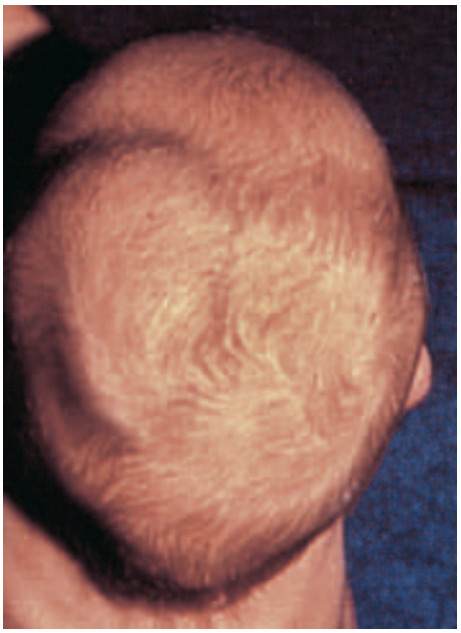


Fig. 2.3 Cephalohematoma. Note the sharp demarcation at the midline.

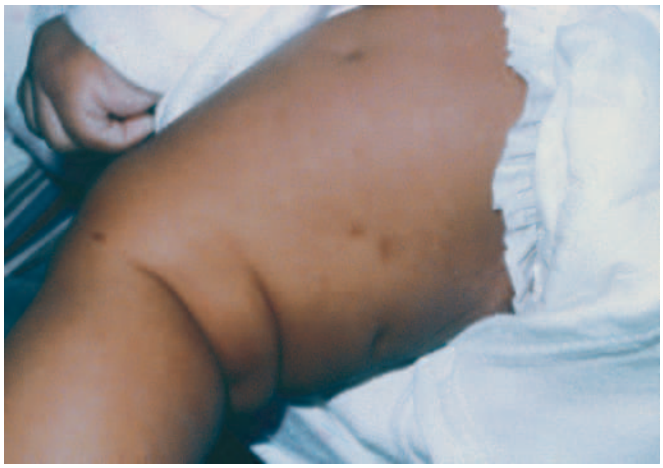


Fig. 2.4 Amniocentesis scars. Multiple depressed scars on the thigh of an infant born to a mother who had an amniocentesis during pregnancy. (Courtesy Lester Schwartz, MD.)

Fig. 2.5 Staphylococcal scalp abscess. Fluctuant, erythematous nodule on the scalp of this 9-day-old infant as a complication of intrauterine fetal monitoring.

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 primigravidas. 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.[33] 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, dimples, or round depressed scars on any cutaneous surface of the newborn (Fig. 2.4).[34–36]

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%, 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).[37–39] 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 (Fig. 2.6).[40] In a large series of vacuum-assisted deliveries, occurrence of head injury did not correlate with duration of vacuum application or the number of pop-offs or pulls.[41]

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, 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.[42,43]

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.[44,45]

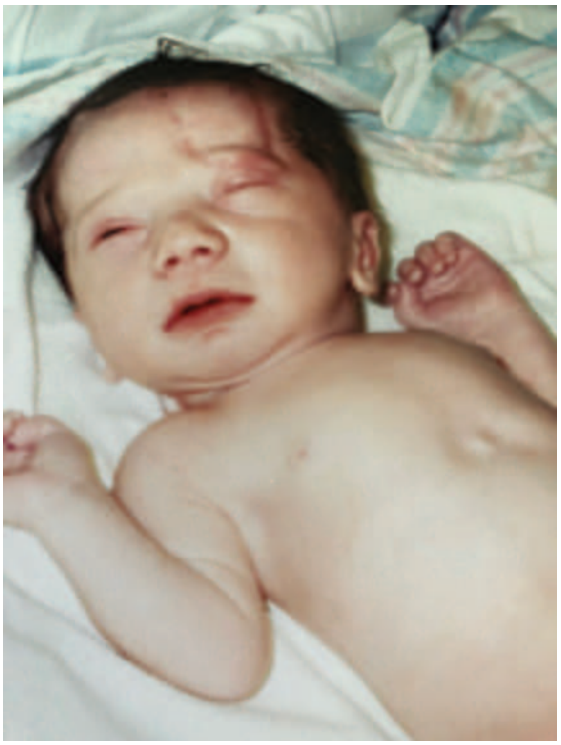


Fig. 2.6 Forceps-induced ecchymoses. This newborn boy was delivered vaginally with forceps assistance and developed this bruising, which conforms to the shape of the forceps blade.

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, *heel-stick calcinosis* refers to calcified nodules that usually begin as small depressions on the heels. It is considered a form of dystrophic calcinosis cutis (see Chapter 9). With time, generally after 4 to 12 months, tiny yellow or white papules appear (Fig. 2.7, *A*), gradually enlarge to form nodular deposits, migrate to the cutaneous surface, extrude their contents ("transepidermal elimination") (Fig. 2.7, *B*), 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. Rarely, persistent or symptomatic cases may require surgical excision.[46] 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.[47,48]

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 birthweight), 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.

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 and may rarely present after several months of life.[49] The disorder, usually associated with a serious underlying condition such as sepsis or other infection, congenital heart disease, respiratory distress, intracranial hemorrhage, diarrhea, or dehydration, is characterized by a diffuse nonpitting woody induration of the involved tissues. The process is symmetric, usually starting on the legs and buttocks, and may progress to involve all areas except the palms, soles, and genitalia.[50] 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 large percentage of cases, die.

Although the cause of this disorder is unknown, it appears to represent a nonspecific sign of severe illness rather than a primary

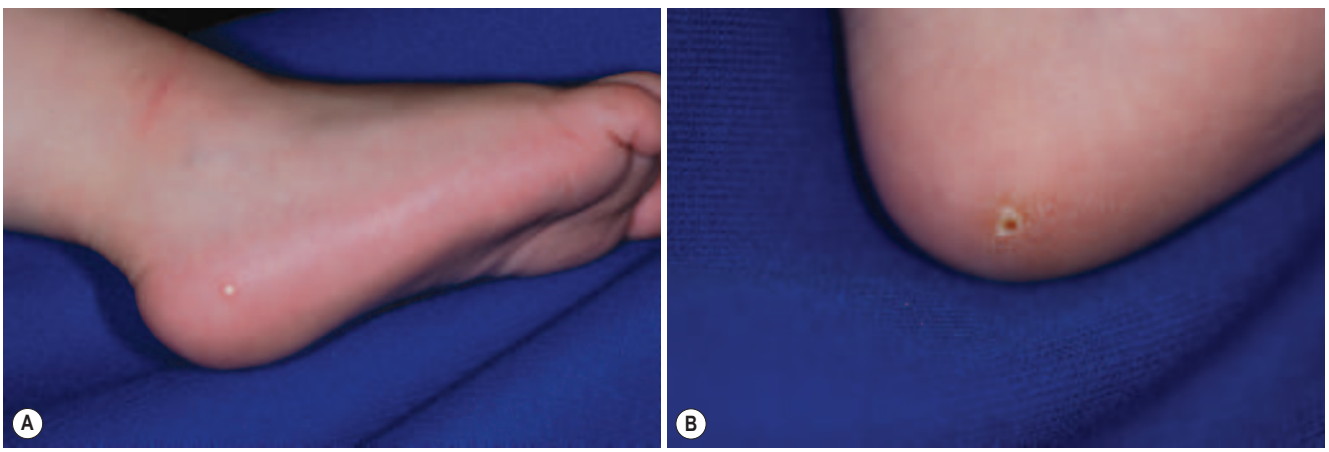


Fig. 2.7 Heel-stick calcinosis. **(A)** Firm, yellow-white papule on the lateral plantar heel of an infant who had multiple heel sticks as a newborn. **(B)** Hyperkeratotic firm papule on the heel of another infant, with early transepidermal elimination before resolution.

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 Also seen in infants with history of therapeutic cooling for HIE
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

HIE, Hypoxic-ischemic encephalopathy.

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.[51]

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 infants with 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%.[52] In infants who survive, the cutaneous findings resolve without residual sequelae. There is no specific therapy, although steroids and exchange transfusion have been used.[50]

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. 2.8). The cause of this disorder remains unknown but appears to be related to perinatal trauma, asphyxia, hypothermia, and, in some instances, hypercalcemia.[53,54] 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 of 11 infants with SCFN had been delivered via emergency cesarean section for fetal distress, and 9 of the 11 had meconium staining of the amniotic fluid.[55] The relationship among SCFN, maternal diabetes, and cesarean section, if any, is unclear. SCFN after ice-bag application for treatment of supraventricular tachycardia has been reported,[56] and it has also been observed after selective head or generalized cooling for hypoxic-ischemic encephalopathy.[57,58] In a review of neonates with hypoxic-ischemic encephalopathy in Switzerland, 2.8% of all cooled neonates developed SCFN, which occurred independently of the cooling method used and the number of temperature measurements outside the target temperature range.[59]

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 (Fig. 2.9). Many lesions have an uneven lobulated surface with an elevated margin separating it from the surrounding normal tissue. Histologic examination of skin biopsy tissue reveals larger-than-usual fat lobules and an extensive inflammatory infiltrate, needle-shaped clefts within fat cells, necrosis, and calcification. Fine-needle aspiration biopsy has been reported as a useful and less invasive method for diagnosis.[60] Magnetic resonance imaging (MRI), although rarely performed, reveals decreased T1 and increased T2 signal intensity in affected areas.[61]

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 an association observed in up to 56% to 63% of infants in larger series,[62,63] 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.[64,65] Infants should be monitored for several months after delivery, because the onset of hypercalcemia can be delayed.[55,66] Other rare systemic complications may include thrombocytopenia, hypoglycemia, and hypertriglyceridemia, all of which tend to be mild or self-limited.

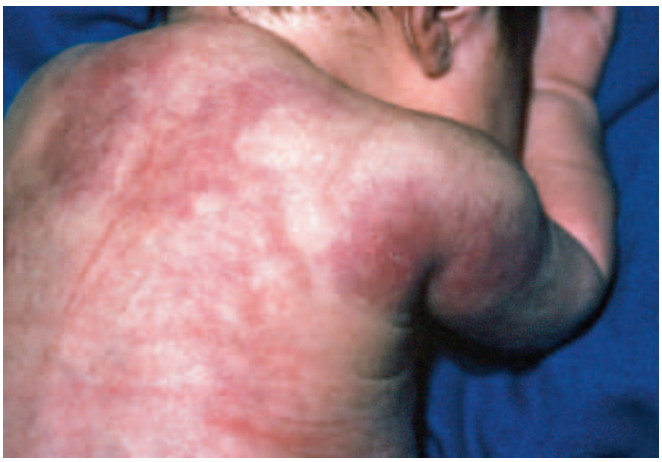


Fig. 2.8 Subcutaneous fat necrosis. Indurated, erythematous plaques on the shoulders and back of this 1-week-old boy.

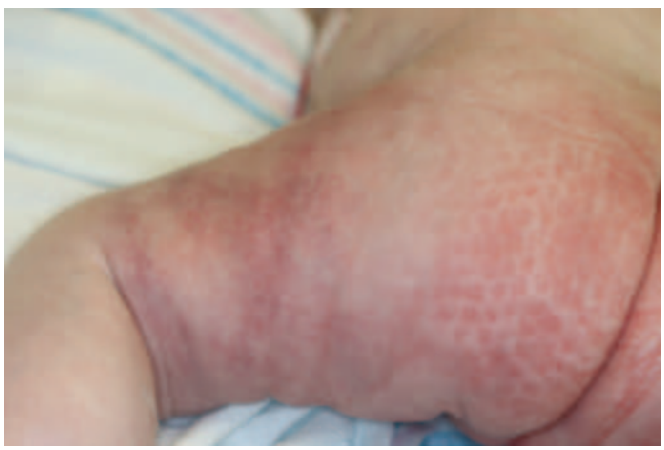


Fig. 2.9 Subcutaneous fat necrosis. This 20-day-old girl presented with firm, indurated erythematous plaques and nodules on the thighs and had been delivered via emergency cesarean section with a history of meconium aspiration, respiratory distress, and hypoglycemia. Her serum ionized calcium was found to be markedly elevated and required therapy with pamidronate.

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 pathophysiologic 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 (Fig. 2.10)
2. Miliaria rubra (prickly heat), representing a deeper level of sweat gland obstruction and characterized by small discrete erythematous papules, vesicles, or papulovesicles (Fig. 2.11)

The incidence of miliaria is greatest in the first few weeks of life because of 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.[67]

Therapy for miliaria is directed toward avoidance of excessive heat and humidity. Lightweight cotton clothing, cool baths, and air conditioning are helpful in the management and prevention of this disorder. Avoidance of emollient overapplication (e.g., 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 (Fig. 2.12) and are often grouped, in which case they have been termed *milia en plaque* (Fig. 2.13). 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. Milia en plaque may occur in a congenital fashion, although they most often occur outside the newborn period, where they may be secondary to skin injury (e.g., abrasions) or blistering disorders.[68] Persistent milia in an unusual or widespread distribution, particularly

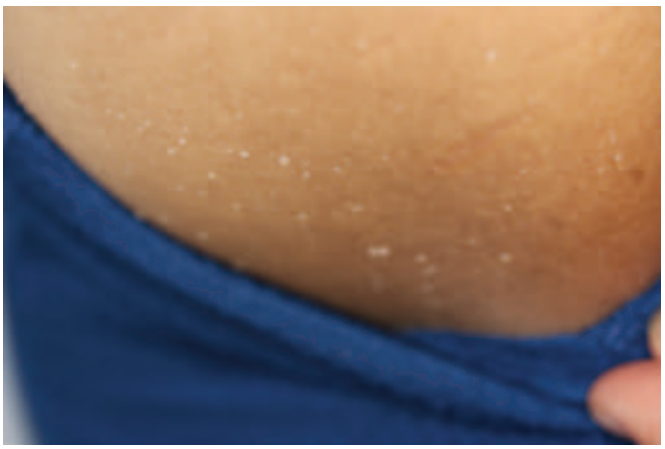


Fig. 2.10 Miliaria crystallina. Note clear, noninflammatory vesicles on the medial thigh of a hospitalized, febrile child.

Fig. 2.12 Milia. Multiple small white papules on the cheek of a girl; similar lesions are often noted on the face of healthy newborns.

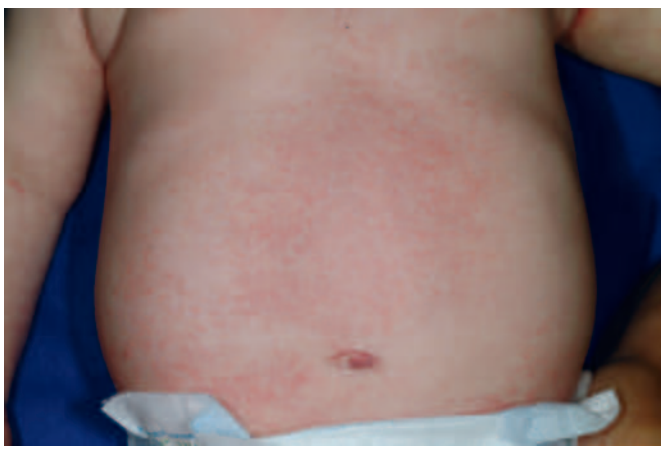


Fig. 2.11 Miliaria rubra. Multiple, erythematous, pinpoint macules and papules in an infant with atopic dermatitis who was being treated with overapplication of greasy emollients.

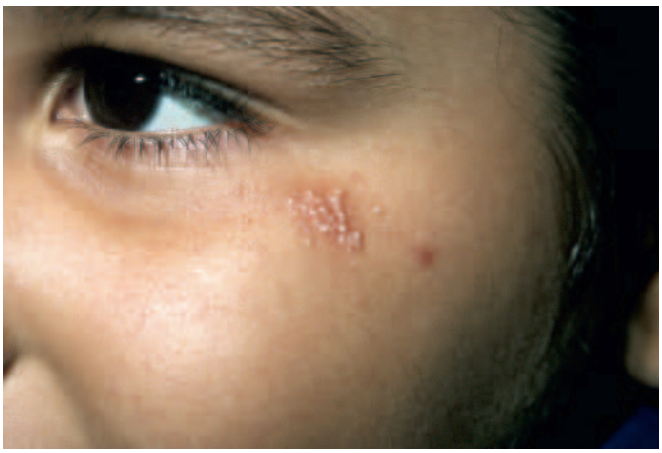


Fig. 2.13 Milia en plaque. Clustered, small, white papules on the lateral cheek.

when seen in association with other defects, may be a manifestation of hereditary trichodysplasia (Marie-Unna hypotrichosis), dystrophic forms of epidermolysis bullosa, Bazex or Rombo syndromes, or type I oral-facial-digital syndrome.

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. 2.14). 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. 2.15). Clinical examination typically reveals erythematous papules, pustules, and occasionally comedones (although the latter are more common in infantile acne; see Chapter 8). Although the cause 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, benzoyl peroxide, a topical retinoid, 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. 2.16). A correlation may exist between the clinical severity of lesions and the colonization with this fungal saprophyte.[69,70] 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. 2.17), or a combination

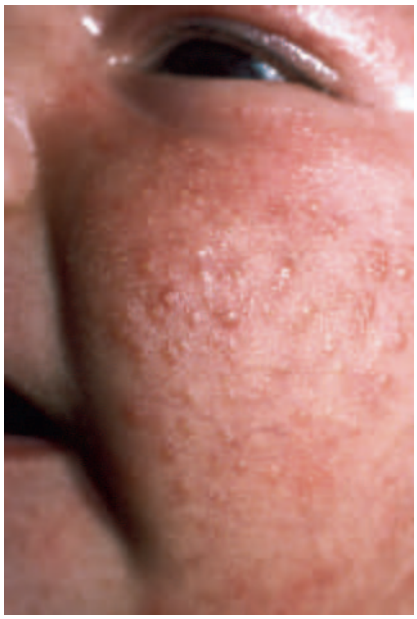


Fig. 2.15 Acne neonatorum. Erythematous papules and papulopustules on the cheek.

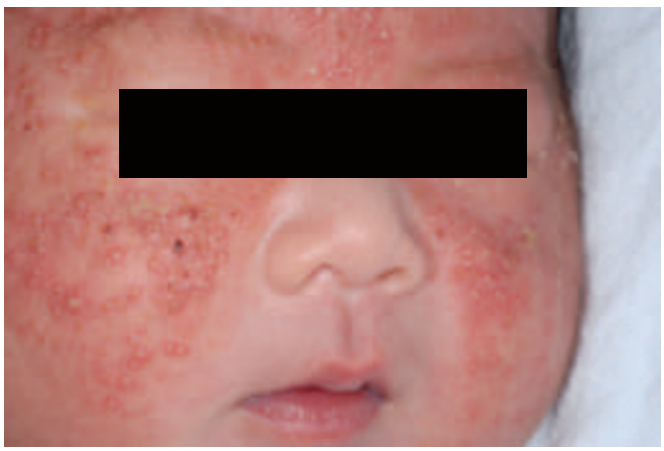


Fig. 2.16 Neonatal cephalic pustulosis. This 2-day-old boy had numerous small and large pustules on the forehead, cheeks, and chin. They cleared rapidly over 1 week with ketoconazole cream.

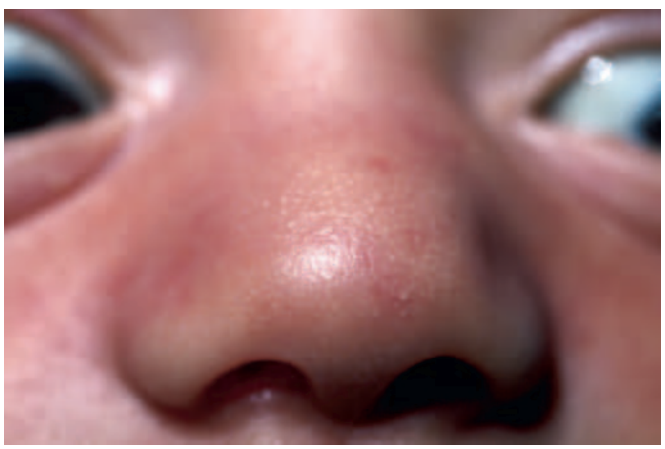


Fig. 2.14 Sebaceous gland hyperplasia. Yellow-white, pinpoint papules on the nasal tip of this 2-day-old boy.

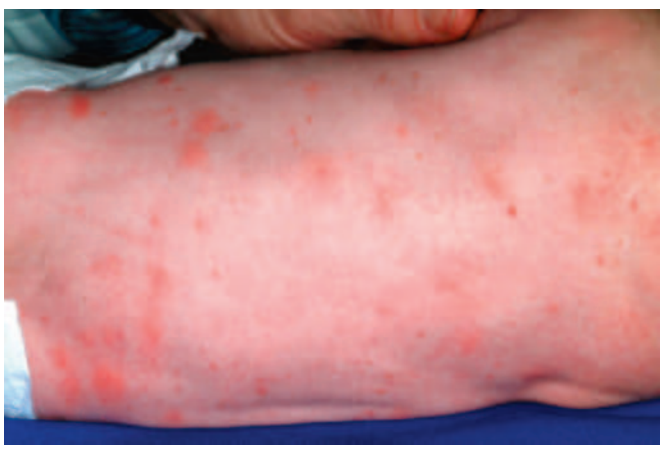


Fig. 2.17 Erythema toxicum neonatorum. Blotchy, erythematous macules and edematous papules.

of these, and may occur anywhere on the body, especially the forehead, face, trunk, and extremities. The fact that these lesions (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.[71] 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 cause of ETN remains obscure. One study suggested that it represents an immune response to microbial colonization of the skin at the hair follicle.[72] 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.[73] Two large prospective series of skin findings in newborns (one in the United States and one in Turkey) found incidences of 7% and 13.1%, respectively.[74,75] In a prospective 1-year multicenter study of more than 2800 neonates in Brazil, the prevalence of ETN was 21.3%, and it was primarily noted in term infants.[76] The incidence of ETN clearly appears to increase with increasing gestational age and birthweight of the infant.[77,76] 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 cause of this disorder to a hypersensitivity reaction, specific allergens have never been implicated or confirmed.

Because 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, milia, miliaria, and congenital infections such as candidiasis, herpes simplex, and 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.

Table 2.3 Differential Diagnosis of Vesicles or Pustules in the 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 (Fig. 2.18)
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	
Staphylococcus aureus	Superficial blisters rupture easily; look for peripheral collarettes (Fig. 2.19)
Listeria monocytogenes	
Pseudomonas aeruginosa	
Other Gram-negative organisms	
Fungal	
Candidiasis	Palms and soles involved; nail changes often present
Viral	
Herpes simplex	Three 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 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, and/or mouth; *XLD,* X-linked dominant.

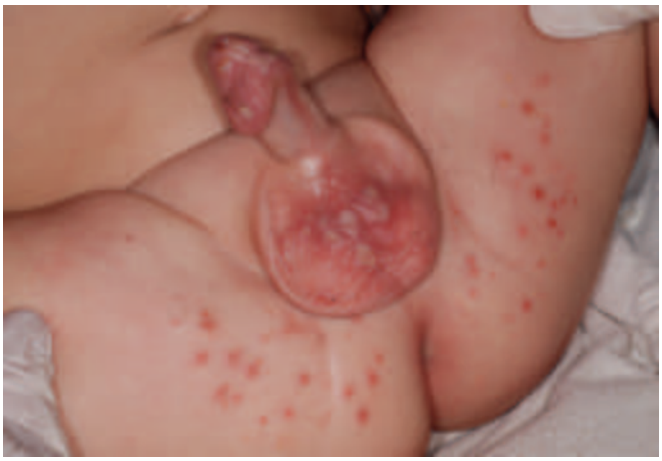


Fig. 2.18 Behçet syndrome. Shallow ulcerations on the scrotum, foreskin, and glans penis of an infant male with oral erosions and the human leukocyte antigen–B51 group genotype. Note the associated papulopustular lesions on the medial thighs and buttocks, another characteristic feature of Behçet syndrome.

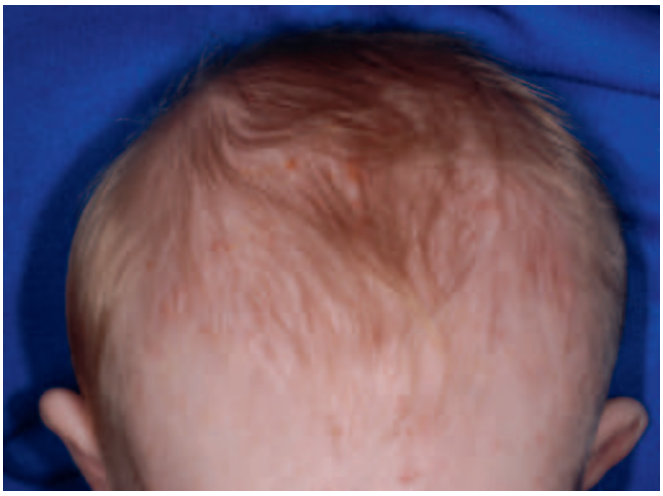


Fig. 2.20 Eosinophilic pustular folliculitis. Erythematous papules and pustules on the scalp of an infant girl, who was subsequently diagnosed with hyperimmunoglobulinemia E syndrome.

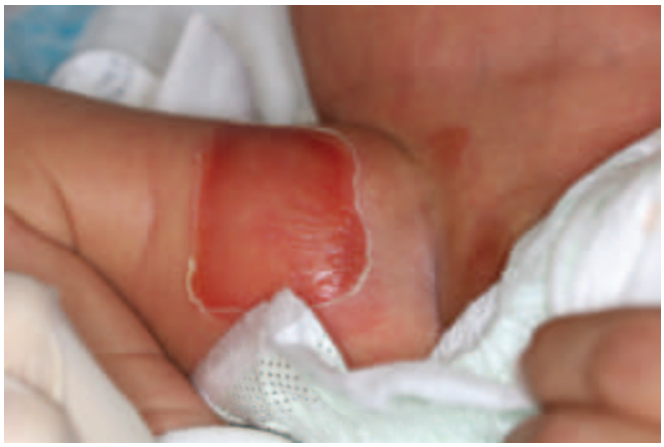


Fig. 2.19 Bullous impetigo. This 11-day-old boy developed flaccid vesicles and bullae that ruptured easily, leaving behind tender red patches with peripheral collarettes as seen here. Staphylococcus aureus grew in culture from the skin swab.

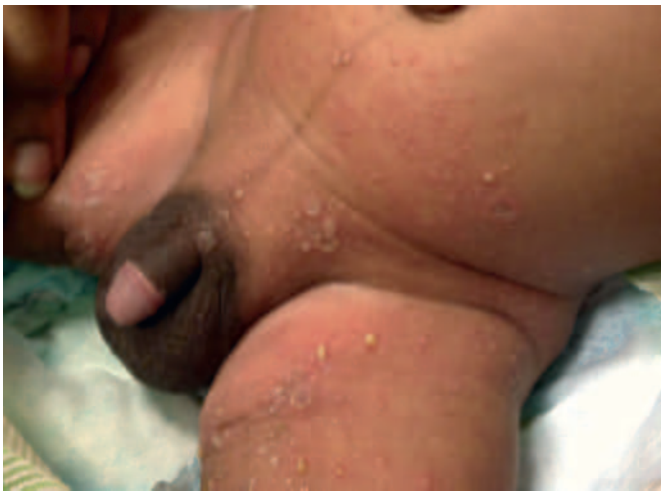


Fig. 2.21 Neonatal *Staphylococcus aureus* pustulosis with multiple pustules in the diaper region. Note some superficial erosions with peripheral collarettes of scale. The culture was positive for *S. aureus*.

EOSINOPHILIC PUSTULAR FOLLICULITIS

Eosinophilic pustular folliculitis (EPF) is an idiopathic dermatosis that occurs in both adults and children (particularly 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. 2.20). They tend to recur in crops, in a similar fashion to acropustulosis of infancy (see later), and some suggest that these conditions may be related.[78,79] 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.[80] 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.[81] 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.[80] Topical tacrolimus may be useful in patients who are unresponsive to topical corticosteroids.[82]

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 vesicular, pustular, or bullous lesion on an erythematous base. Vesicles and bullae are easily denuded, leaving a red, raw, and moist surface with a peripheral collarette (see Fig. 2.19), 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. 2.21), often distributed in the diaper region. The lesions denude easily on 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.[83] However, a complete blood cell count and blood culture are 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 cause characterized by superficial vesiculopustular lesions that rupture easily and evolve into hyperpigmented macules (Fig. 2.22). This disorder is seen in fewer than 1% of newborns[84] and occurs most commonly in infants with black skin. Lesions begin as superficial sterile pustules (Fig. 2.23) 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 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 to 48 hours, 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*.

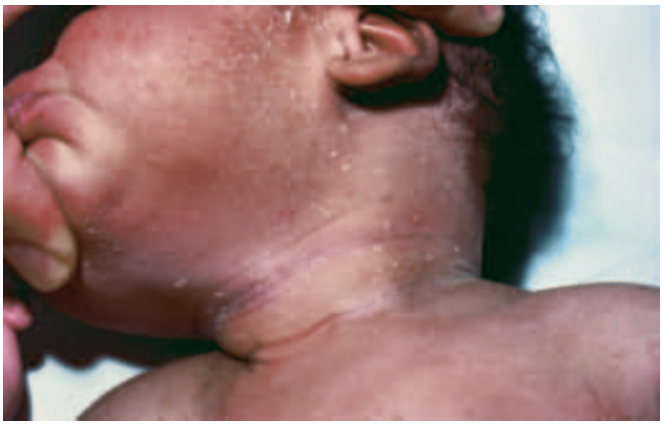


Fig. 2.22 Transient neonatal pustular melanosis. Papules and papulopustules rupture to leave a collarette of fine scales and eventual hyperpigmentation. (Courtesy Nancy B. Esterly, MD.)

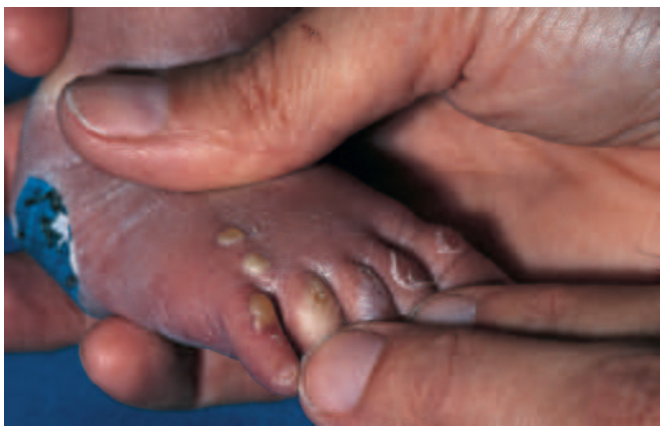


Fig. 2.23 Transient neonatal pustular melanosis. Tense pustules and collarettes of scale at sites of older lesions.

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 pruritic, vesiculopustular lesions that recur every few weeks to months. The lesions begin as pinpoint erythematous papules and enlarge into well-circumscribed discrete pustules.[85] They are concentrated on the palms (Fig. 2.24) and soles (Fig. 2.25) 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.[85–88] Although the etiology of IA remains unclear, several authors have noted a likely association with preceding scabies infestation.[89–91] IA appears to be common in internationally adopted children.[92]

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,[89] 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.

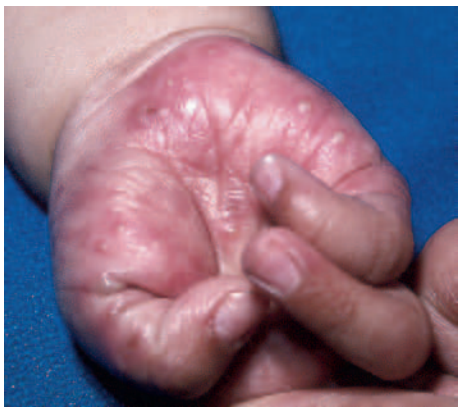


Fig. 2.24 Acropustulosis of infancy. Multiple tense erythematous papules and pustules on the palm of this 4-month-old girl.

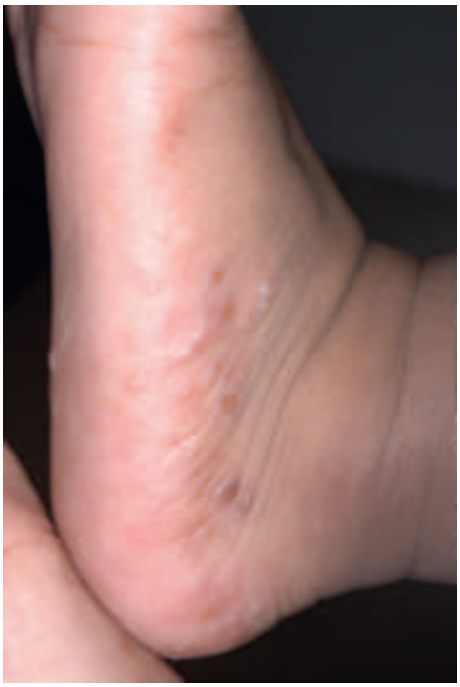


Fig. 2.25 Acropustulosis of infancy. Tense pustules, some of which have ruptured, on the plantar and lateral surfaces of the foot of a 14-month-old girl.

CONGENITAL EROSIVE AND VESICULAR DERMATOSIS

Congenital erosive and vesicular dermatosis (CEVD) healing with reticulated supple scarring is an uncommon disorder characterized by erosive and 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. There are several reports of CEVD occurring in association with neonatal herpes simplex virus infection.[93,94] The disorder generally involves skin of the trunk, extremities, scalp, face, and occasionally the tongue, with sparing of the palms and soles.

CEVD occurs most often in premature infants and presents with extensive cutaneous ulcerations (Fig. 2.26, *A*) and intact vesicles that develop crusting and then heal during the first month of life. Occasionally, blistering may continue to occur beyond infancy.[95,96] Generalized, supple, reticulated scars occur with alternating elevated and depressed areas (see Fig. 2.26, *B*). 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.[97,98] 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.[98–100] Facial involvement was present in roughly 50% of published cases in one review.[101] 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.[95,97] Some patients have also been found to have neurologic defects, including mental and motor retardation, hemiparesis, microcephaly, pachygyria, cerebral palsy, and seizures.[97,101]

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. 2.27) 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 (Fig. 2.28). (For a more detailed discussion of seborrheic dermatitis and its therapy, see Chapter 3.)

LEINER DISEASE

The term *Leiner disease*, rarely used in the current era, 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 at risk for 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.[102–106]

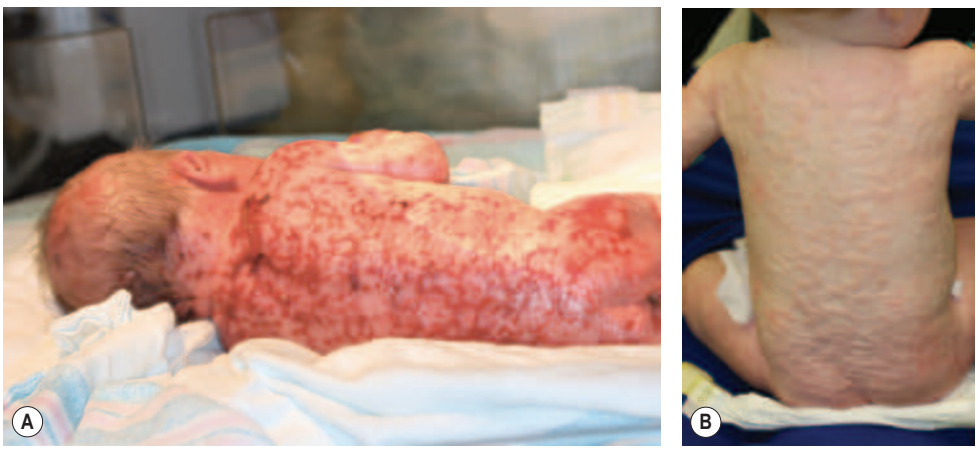


Fig. 2.26 Congenital erosive and vesicular dermatosis healing with reticulated supple scarring. **(A)** Diffuse reticulated erythematous erosions and atrophic plaques involved most of the skin surface in this female infant at 37 weeks' gestational age. **(B)** At age 8 months, prominent generalized reticulate supple scars were distributed on the trunk, face, scalp, and extremities.

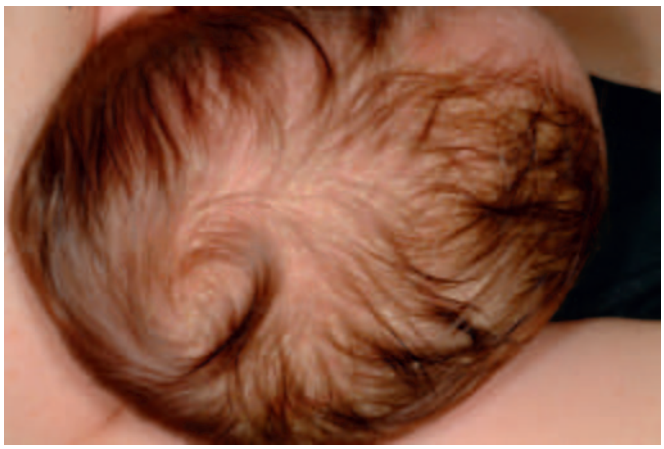


Fig. 2.27 Seborrheic dermatitis of the scalp (cradle cap). Erythema and greasy yellow scales involving the scalp of an infant boy who also had similar changes in the eyebrows.

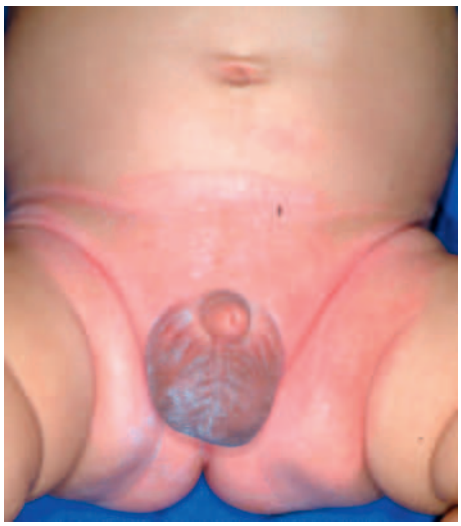


Fig. 2.28 Seborrheic dermatitis. Erythema of the medial thighs, suprapubic region, and buttocks. This presentation can be difficult to distinguish from infantile psoriasis, but the scaling tends to be more mild and the response to topical antiinflammatory therapy more brisk. The whitish debris in this child represents the barrier cream that his parents had applied rather than scaling.

DIAPER DERMATITIS

Diaper dermatitis is perhaps the most common cutaneous disorder of infancy and early childhood. The term is used to describe an acute 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.[107–109] The practice of diapering has evolved through the ages and varies according to local culture, geography, and tradition. Although the earliest materials included beaded cloths, peat moss with animal skin, and dried grass held in place by cloth, technological advancements led to refinement of the cloth diaper and diaper laundry services and eventually development of the disposable diaper in the early 1940s.[110]

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.

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 (e.g., acrodermatitis enteropathica, cystic fibrosis, biotin deficiency)
Allergic contact dermatitis
Atopic dermatitis
Granuloma gluteale infantum
Langerhans cell histiocytosis
Burns
Child abuse
Epidermolysis bullosa
Congenital syphilis
Varicella/herpes
Tinea cruris
Chronic bullous dermatosis of childhood
Bullous mastocytosis

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. 2.29). 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.

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 causal agent of most diaper dermatoses.[111] 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.[112,113]

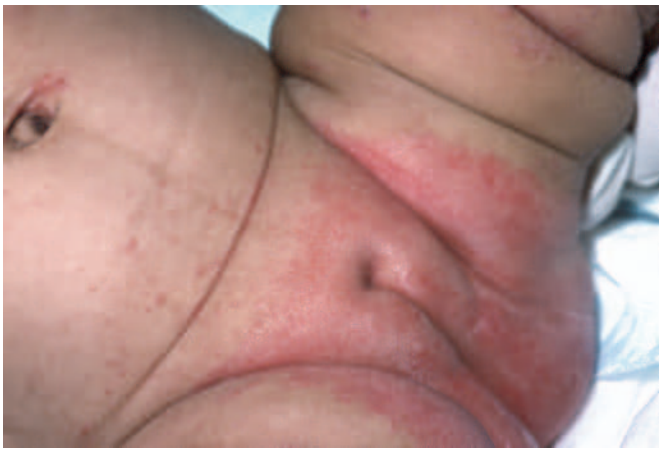


Fig. 2.29 Irritant contact diaper dermatitis. Erythema of the vulva, buttocks, and medial thighs. The inguinal creases were relatively spared.

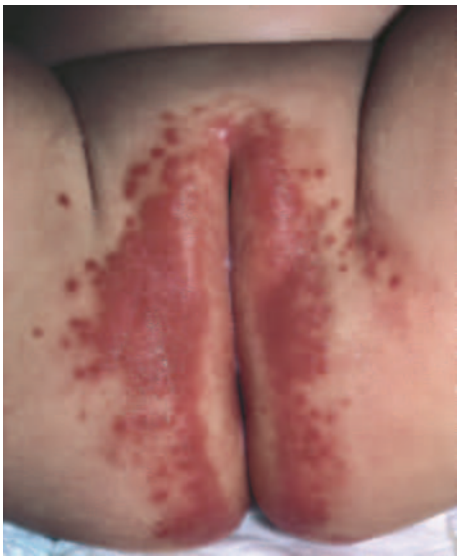


Fig. 2.30 Diaper candidiasis. Beefy-red, erythematous plaques with multiple red satellite papules and papulopustules.

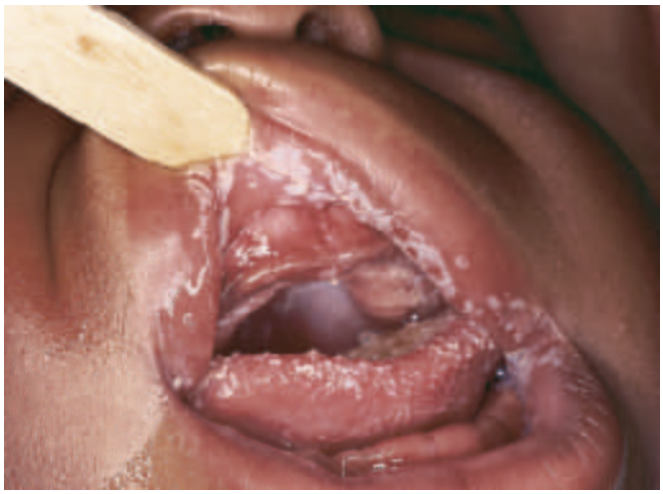


Fig. 2.31 Oral candidiasis (thrush). Gray-white, cheesy patches and plaques of the buccal mucosa, tongue, and gingiva.

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.[114] Other innovations have included nonirritating disposable diaper wipes and diapers designed to deliver petrolatum-based formulations to the skin.[115]

A blistering, erosive contact dermatitis has been observed after oral ingestion (either intentional or accidental) of senna-containing laxatives.[116,117] 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 (e.g., via overnight wearing of the diaper) is often reported. In some countries in the Middle East, such as Jordan and Turkey, where the application of table salt to the skin of infants *(salting)* is a tradition believed to prevent excessive sweating and body odor as an adult, severe erosive dermatitis of the diaper region with ulcerations on the scrotum has been reported, as has associated hypernatremia, which can be fatal.[118,119]

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).[120,121] In a report of six nondiapered children with recalcitrant perianal and buttock dermatitis, all tested positive to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), a combination preservative found in the wet wipes that were being used for cleansing, with complete clearance on discontinuation of the products.[122] In a review of potential allergens found in diapering products, botanical extracts, α-tocopherol, fragrances, propylene glycol, parabens, and lanolin were among the potential allergens identified.[123] Disperse dyes, which are used to impart color to synthetic fabrics, can also be contact sensitizers and are found in some disposable diapers. When allergic contact dermatitis in the diaper region is suspected in infants, a modified patch testing series (containing fewer allergens than a standard test, given patch test limitations in this population) has been proposed.[124]

Diaper Candidiasis

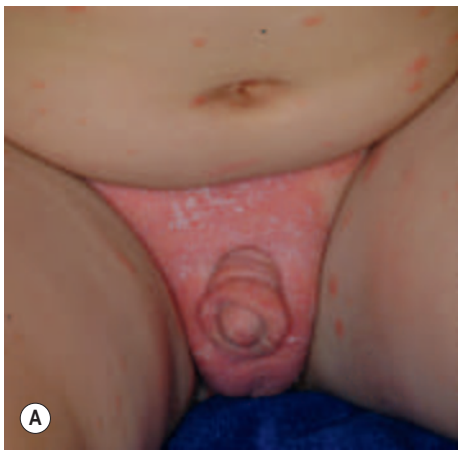
Candidal (monilial) diaper dermatitis is a commonly overlooked disorder and should be suspected whenever a diaper rash fails to respond to usual therapeutic measures. Cutaneous candidiasis is a possible sequela of systemic antibiotic therapy and should be considered in any diaper dermatitis that develops during or shortly after antibiotic administration.[125]

Candidal diaper dermatitis presents as a widespread, beefy-red erythema on the buttocks, lower abdomen, and inner aspects of the thighs. Characteristic features include a raised edge, sharp marginalization with white scales at the border, and pinpoint pustulovesicular satellite lesions (the diagnostic hallmark) (Fig. 2.30). Although cutaneous candidiasis commonly occurs in association with oral thrush (Fig. 2.31), 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



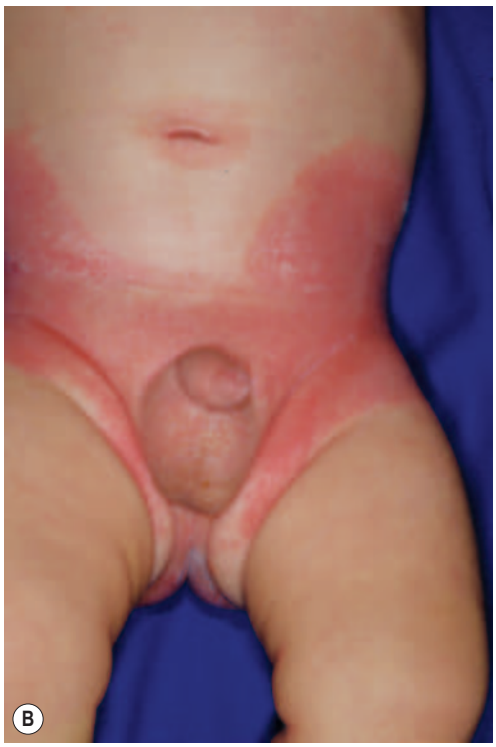


Fig. 2.32 Psoriasis (diaper). **(A)** Sharply demarcated, erythematous, scaly plaques involving the genitals and suprapubic region in this infant boy. **(B)** Thin, scaly, very well demarcated plaques over the diaper area, flanks, and umbilical region of a 3-month-old boy.

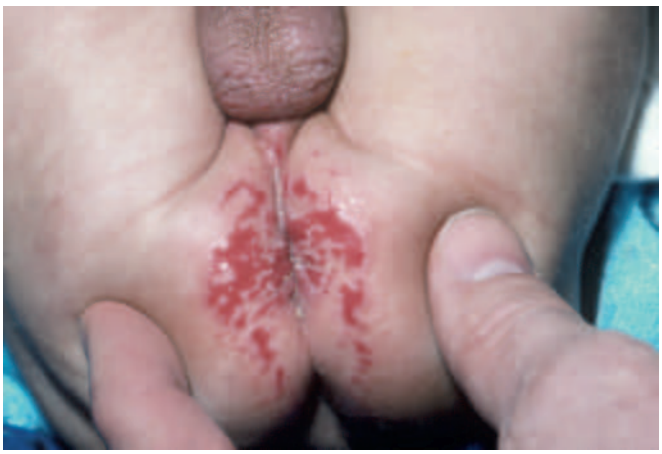


Fig. 2.33 Jacquet dermatitis. Severe diaper area erythema with ulcerated papules and islands of reepithelialization.

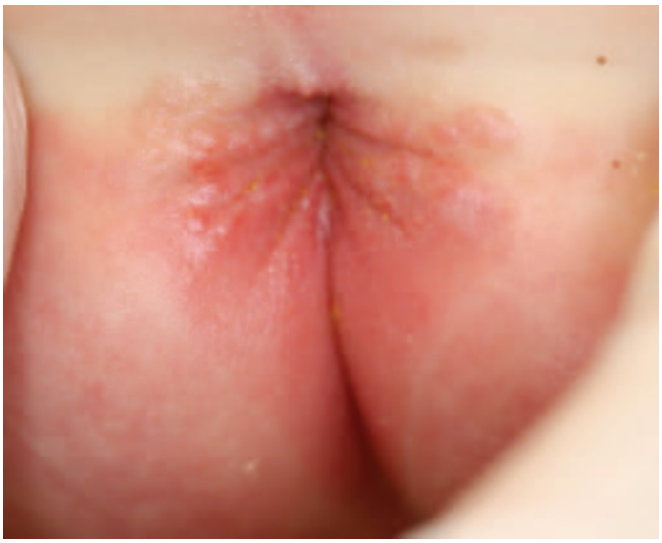


Fig. 2.34 Perianal pseudoverrucous papules and nodules. This 7-week-old boy developed these perianal verrucous papules after a period of severe irritant contact diaper dermatitis/Jacquet dermatitis.

and a predilection for intertriginous areas (see earlier). Coincident involvement of the scalp, face, neck, and postauricular and flexural areas helps establish the diagnosis. Seborrheic dermatitis of the diaper region may be difficult to distinguish from psoriasis.

Psoriasis

Psoriasis of the diaper area must also be considered in persistent diaper eruptions that fail to respond to otherwise seemingly adequate therapy (Fig. 2.32). 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-marginated 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. 2.33). 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 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 (Fig. 2.34) 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

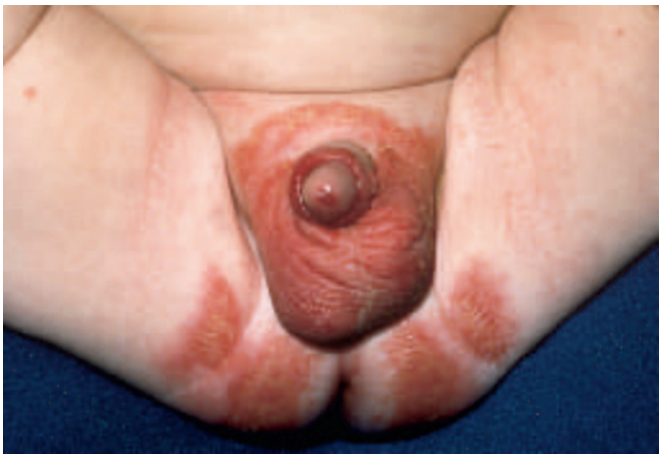


Fig. 2.35 Acrodermatitis enteropathica. Eroded, erythematous patches and plaques in this 4-month-old boy with zinc deficiency. Note the associated balanoposthitis.

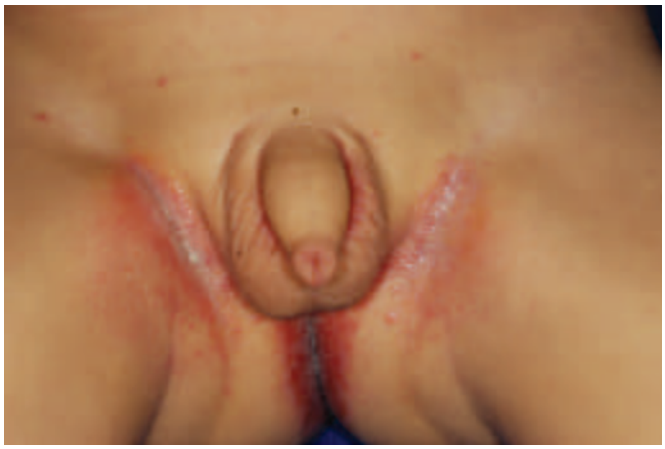


Fig. 2.36 Langerhans cell histiocytosis. Red-brown, eroded plaques in the inguinal creases in an infant male with multiorgan involvement. Note the presence of skin lesions also in the perineum and on the anterior scrotal surface, as well as a few scaly crusted papules on the lower abdomen.

urinary incontinence.[126–128] 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. 2.35) but also may involve the perioral 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 (Fig. 2.36) or purpuric qualities. 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 cause 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.[129]

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 (after defecation), exposure to air whenever possible, and the judicious use of topical therapy may be sufficient in most cases. Parents should be educated that minimal to no cleansing is required after urination only. Zinc oxide and petrolatum-based formulations tend to be most effective in forming a barrier to further skin contact with urine and feces; ointments and pastes are generally accepted as the most helpful vehicles. Other useful ingredients may include lanolin, white soft paraffin, and dimethicone. These products should be applied at every diaper change when acute dermatitis is present. Parents should be taught that cleansing the diaper area is necessary only when stool is present, because overwashing in itself can lead to irritation. A low-potency, nonfluorinated topical corticosteroid (e.g., 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 (e.g., nystatin, clotrimazole, ketoconazole, oxiconazole, econazole, miconazole). It is important to avoid use of topical antifungals such as terbinafine and naftifine, which lack effectiveness against *Candida*.[130] 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, at a dosage of 6 mg/kg per day given once daily for 2 to 4 weeks, 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.[131,132] 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. Recalcitrant diaper candidiasis may be an initial sign of chronic mucocutaneous candidiasis (see Chapter 17).

GRANULOMA GLUTEALE INFANTUM

Granuloma gluteale infantum is a benign disorder of infancy characterized by purple-red nodules on the skin of the groin, lower abdomen, and inner thighs (Fig. 2.37). 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.[133] Histologic evaluation of biopsy tissue from granuloma gluteale infantum reveals a nonspecific inflammatory infiltrate, sometimes with giant cells.[134,135]

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

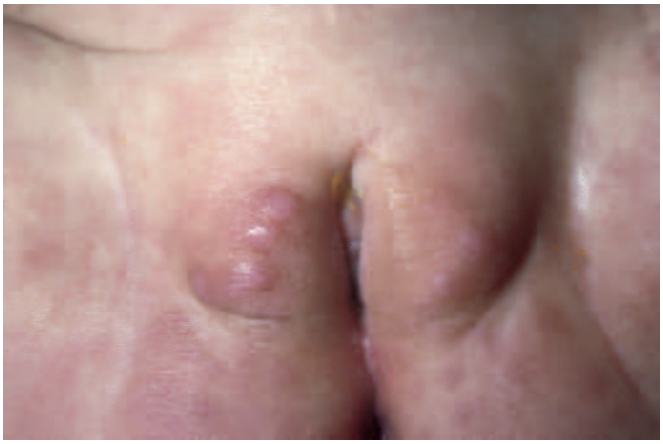


Fig. 2.37 Granuloma gluteale infantum. Erythematous to violaceous papulonodules on the labia majora of this infant with a history of potent topical corticosteroid use in the diaper region.

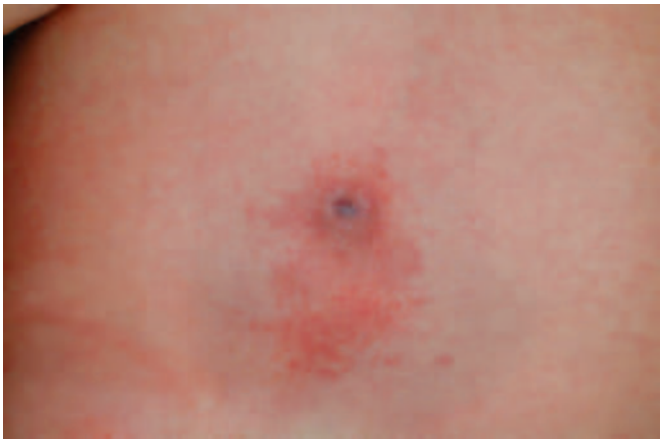


Fig. 2.38 Lumbosacral port wine stain associated with occult spinal dysraphism. Note the associated central depression in this boy who also had an underlying tethered spinal cord.

congenital spinal-cord anomalies.[136] Because occult spinal dysraphism (OSD) can lead to irreversible neurologic complications from tethered cord syndrome, 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. 2.38), atypical sacral dimples (Fig. 2.39), sinuses, appendages (skin tag, tail), ACC, and melanocytic nevi.[137] Gluteal cleft asymmetry or deviation is another useful finding. The presence of multiple findings increases the risk of OSD.[138,139] 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).[140] 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.[141]

The majority of simple midline dimples are not associated with OSD. Patients with atypical dimples (>5 mm in size, further than 2.5 cm from the anal verge), on the other hand, have a significant risk of associated OSD.[138] 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

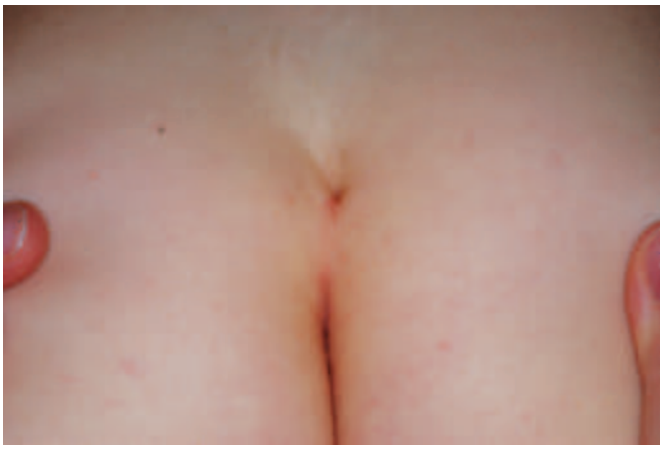


Fig. 2.39 Prominent sacral dimple. This young girl was found to have this prominent dimple superior to the gluteal cleft in association with mild gluteal cleft deviation. Imaging for associated spinal dysraphism was unremarkable.

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.[142] 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,[137] 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%.[140] Ultrasound may occasionally be associated with false-positive findings, as reported in a study of 439 newborns in whom the study was performed because of cutaneous stigmata. A total of 39 of 439 had abnormal findings, with subsequent MRI revealing unremarkable findings in 17 of them.[143]

In infants with low-risk lesions such as simple dimples or gluteal cleft deviation and without other high-risk findings (e.g., 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.[144] 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 later).

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

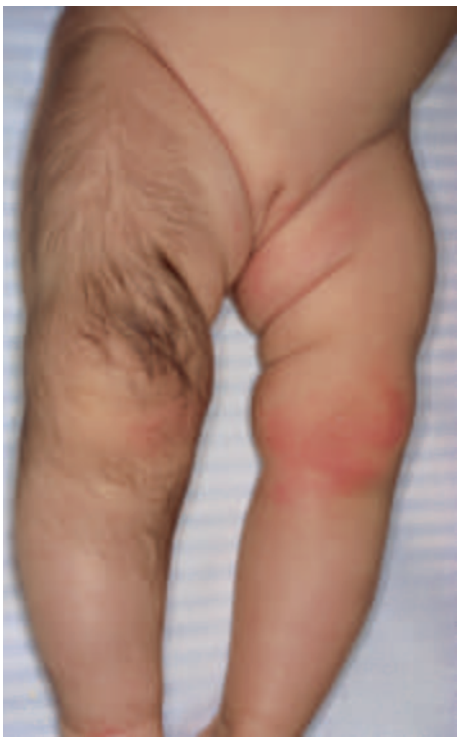


Fig. 2.40 Congenital hemihypertrophy with hypertrichosis. (From Hurwitz S, Klaus SN. Congenital hemihypertrophy with hypertrichosis. Arch Dermatol 1971;103:98–100. ©1971 American Medical Association. All rights reserved.)

(Fig. 2.40). Body temperature and sweating differences have also been reported in patients with this disorder.[145]

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.[146] 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 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.[147]

ACC classically presents as solitary or multiple, sharply demarcated, weeping or granulating, oval to circular, stellate defects ranging from 1 to 3 cm in diameter. Some 70% of scalp lesions are isolated and 20% are double, and in 8% of patients three or more defects may be present.[148] The most common location for ACC is the scalp, and in those cases 80% occur in close proximity to the hair whorl.[149] Although aplasia cutis may also affect the occiput, the postauricular areas, and the face, involvement of these areas appears to be relatively uncommon.

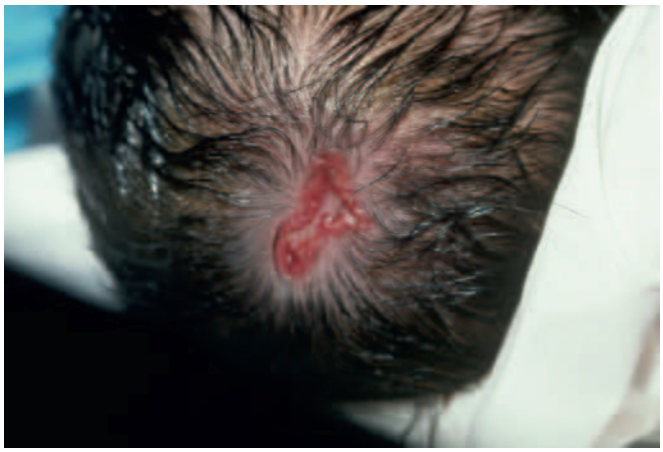


Fig. 2.41 Aplasia cutis congenita. Sharply demarcated ulceration on the scalp of an infant with this disorder.

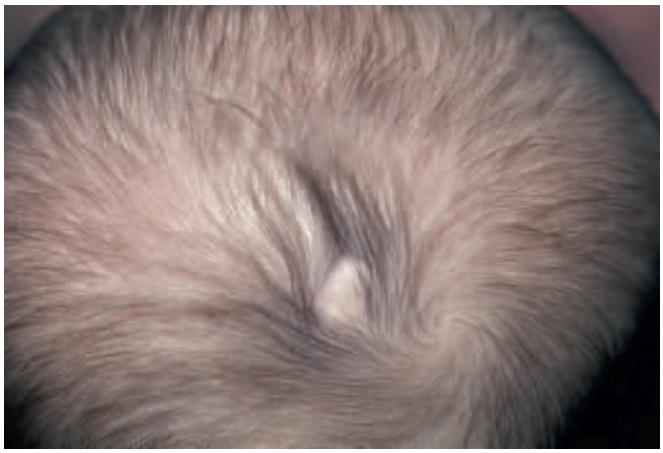


Fig. 2.42 Aplasia cutis congenita. Healed scar with alopecia near the hair whorl in this 8-month-old girl.

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^2) 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. 2.41) to a superficial erosion or even a well-formed scar. As healing of open lesions occurs, the defect is replaced by smooth, hairless scar tissue (Fig. 2.42), 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"; Fig. 2.43) may represent a forme fruste of a neural tube defect.[150] This membranous form of ACC may have a recognizable appearance on prenatal sonography as a round hypoechoic defect.[151]

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.[147] Adams–Oliver syndrome (AOS), a malformation syndrome caused by mutations in the *ARHGAP31, DLL4, RBPJ,* or *NOTCH1* (autosomal dominant) genes or *DOCK6* or *EOGT* (autosomal recessive) genes, is the association of ACC with transverse terminal limb defects and cardiac and CNS abnormalities.[152–155] The limb defects may include

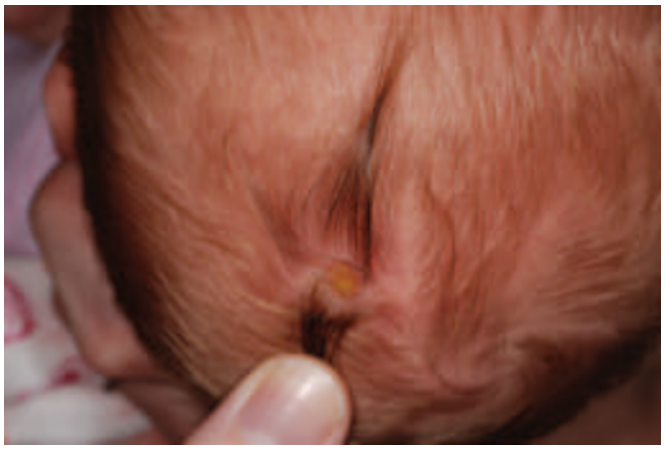


Fig. 2.43 Aplasia cutis congenita, membranous type, with hair collar sign. Note the hairs surrounding the defect in this infant girl, which are longer and darker than her other hair. Magnetic resonance imaging revealed a small tract down to calvarium, without any intracranial or intradural extension.

brachydactyly, syndactyly, loss of terminal phalanges, nail agenesis, or complete absence of the digits, hand, foot, or limb.[156] The cardiac malformations in AOS may include ventricular septal defects, tetralogy of Fallot, left-sided obstructive lesions, and truncus arteriosus.[157] Cutis marmorata telangiectatica congenita (see Chapter 12) is present in nearly 20% of patients with AOS.[158] 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.[159,160] 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.[161] Aplasia cutis of the scalp can also be a feature of scalp-ear-nipple (SEN) syndrome, an autosomal dominant disorder resulting from mutations in *KCTD1*, encoding a protein that affects a transcription factor (AP-2α) that is important in development.[162] Other features of SEN syndrome are minor anomalies of the external ears, digits, nails, and breasts.

The cause 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.[163] 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.[164] 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.[165] A heterozygous missense mutation in *BMS1* (which affects ribosomal function) has been identified in autosomal dominant ACC.[166]

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. Large split-thickness skin grafting has been reported in infants with more extensive defects with good results but can be complicated by hypertrophic scarring and partial skin graft necrosis.[167] Emergency (within the first hours of life) split-thickness skin grafting has been recommended for infants with large ACC defects or defects with large veins or sagittal sinus exposure in an effort to minimize the risks of hemorrhage and infection.[168]

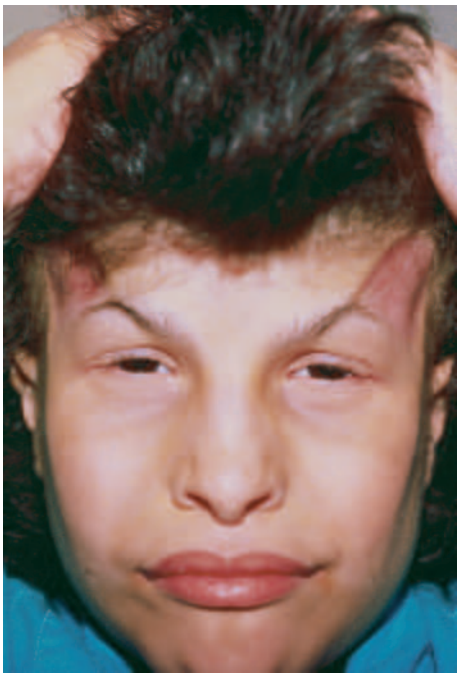


Fig. 2.44 Setleis syndrome. A child with bilateral depressed oval areas on the temples, upwardly slanting eyebrows, narrowed palpebral fissures, and large lips. (Courtesy Seth Orlow, MD.)

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.[169] 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. 2.44; see Chapter 6). 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.[170]

Reports of Setleis syndrome have suggested both autosomal recessive and autosomal dominant modes of inheritance,[170,171] and variable expressivity and reduced penetrance may be observed.[172] Setleis syndrome is considered by some to be a form of focal facial dermal dysplasia (see Chapter 6).[173] Homozygous nonsense, missense, and frameshift mutations in *TWIST2* (encoding a basic helix-loop-helix transcription factor) or *de novo* genomic duplication or triplication at 1p36.22p36.21 have been confirmed in some cohorts with the Setleis phenotype.[174–185]

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. Because 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.

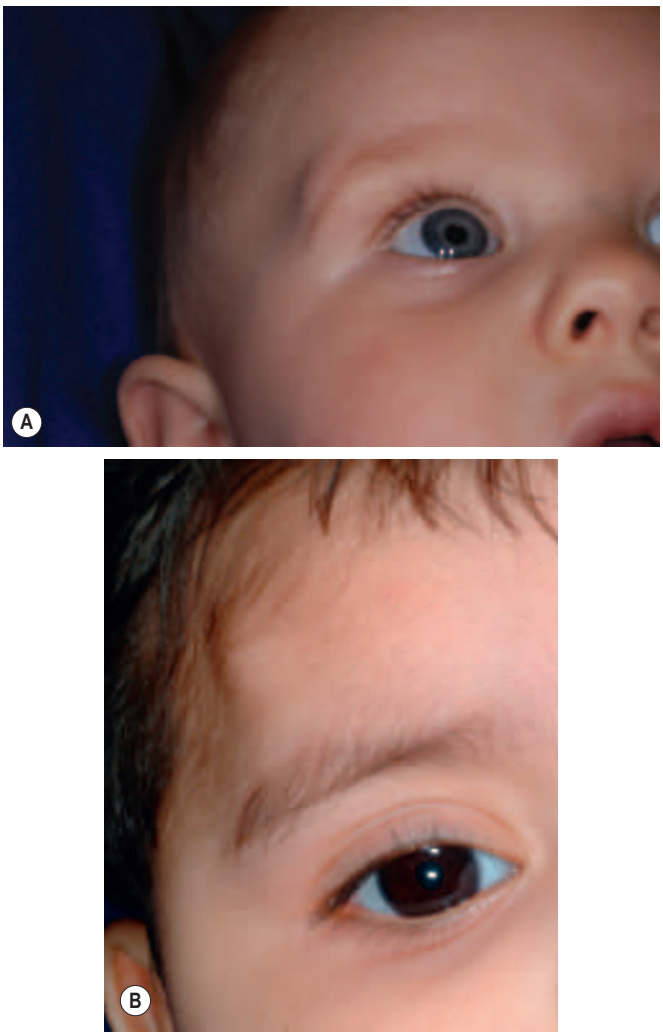


Fig. 2.45 Dermoid cysts. **(A)** A congenital mobile subcutaneous nodule over the lateral eyebrow. **(B)** This mobile, nontender, subcutaneous nodule was present at birth in this 5-month-old girl. The lateral midforehead distribution is slightly higher than most dermoids, which present most often in the lateral eyebrow region.

Dermal sinus openings may be difficult to visualize, particularly in the occipital scalp region where they may be hidden by hair. A 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. 2.45). In this location, there is no association with deep extension. About 3% of dermoids are located in the nasal midline[137] (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. 2.46). Presence of such a pit may indicate a higher likelihood of intracranial extension.[176] 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.

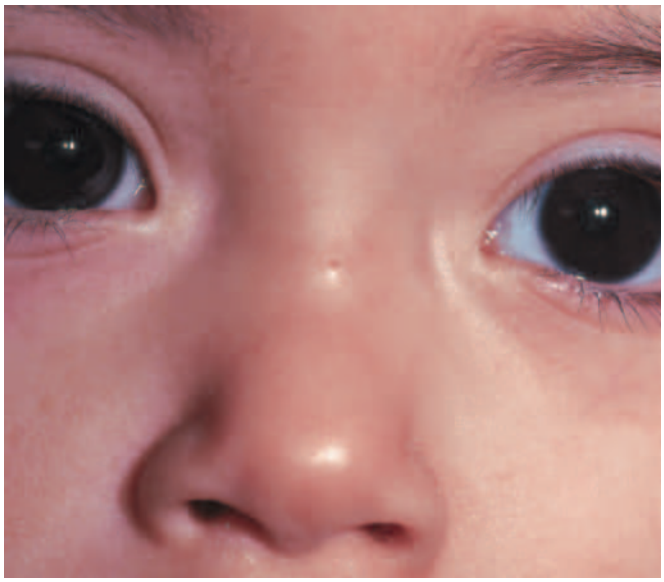


Fig. 2.46 Dermoid sinus. Small sinus ostium at the superior nasal bridge. This patient had no intracranial extension.

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.[137] 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 (called the *Furstenberg sign*). 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.[177] 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.[178,179] 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 vermilion 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.

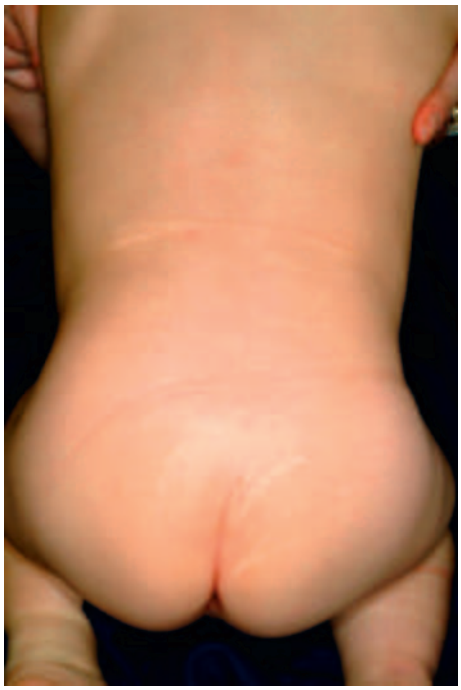


Fig. 2.47 Acquired raised bands of infancy. Numerous linear raised bands on the back of an infant who had similar bands on the extremities. (Courtesy Sarah L. Chamlin, MD.)

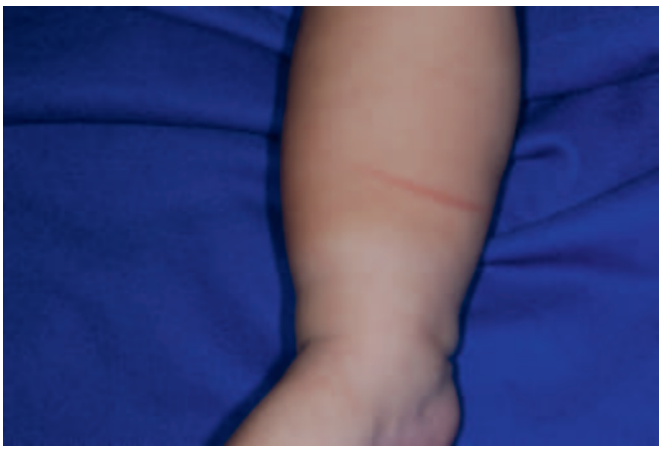


Fig. 2.48 Sock-line hyperpigmentation. Erythematous to hyperpigmented curvilinear streak on the lower leg of a 1-year-old girl whose mother noted the changes shortly after dressing her in tight-fitting socks.

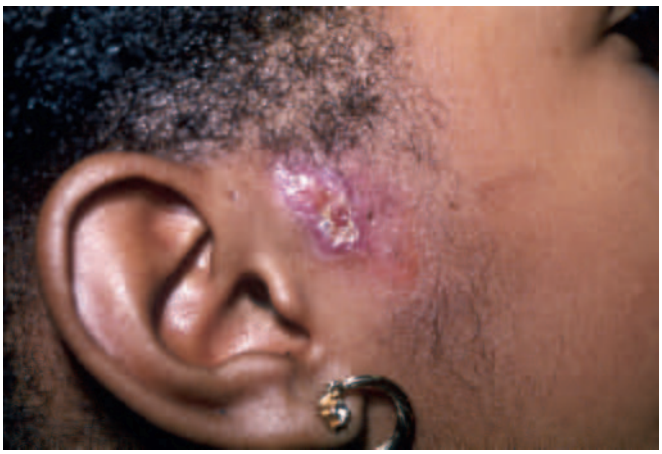


Fig. 2.49 Preauricular sinus with ulceration. This lesion was at risk for recurrent inflammation and infection and ultimately was surgically excised.

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).[180]

Skin dimpling defects (depressions, deep pits, or creases) in the sacral area (see earlier) 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 (cerebrohepatorenal), 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 amnion with formation of fibrous bands that encircle fetal parts and produce permanent constriction of the underlying tissue.[181] The most commonly affected areas are the extremities, followed by the umbilical cord, abdomen, and limb–body wall complex.[182] Acquired raised bands of 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. 2.47). They may also occasionally occur on the trunk. Although some argue that these findings are distinct from amniotic constriction bands,[183] coexistence with congenital constriction bands[184] and prenatal ultrasound observation of amniotic bands[185] 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. 2.48) 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.[186] 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.[187] These lesions have also been observed on the posterior heel of infants after wearing heel-length socks.[188] Damage to adipose tissue with inflammation and secondary postinflammatory changes have been hypothesized as the cause.

Preauricular pits, cysts, 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. 2.49), 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. 2.50, *A*) or multifocal, occurring along the embryologic migration line extending from the preauricular cheek to the mouth angle (see Fig. 2.50, *B*). Although generally seen as an isolated congenital defect, they may be associated with other branchial arch syndromes (e.g., oculoauriculovertebral or Goldenhar syndrome). The prevalence of preauricular pits and tags is estimated at around 0.5% to 1.0%.[189,190]

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, including eustachian tube dysfunction and sensorineural

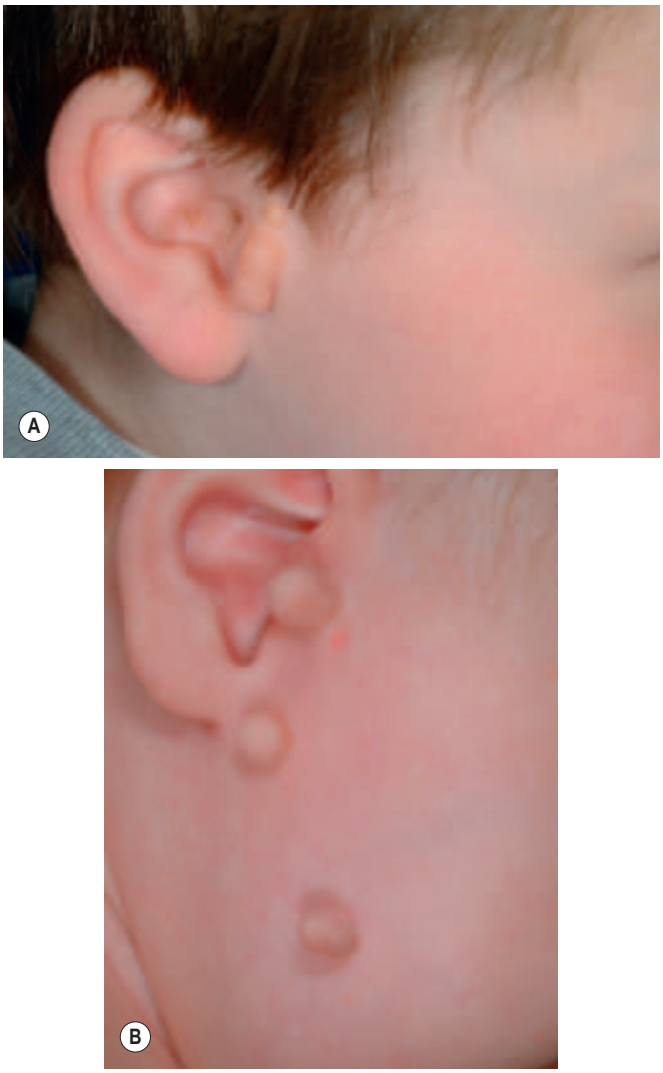


Fig. 2.50 Accessory tragi. These fleshy papules may present in a solitary or localized fashion **(A)** or in a multifocal form, occurring along the embryologic migration line extending from the preauricular cheek to the mouth angle **(B)**.

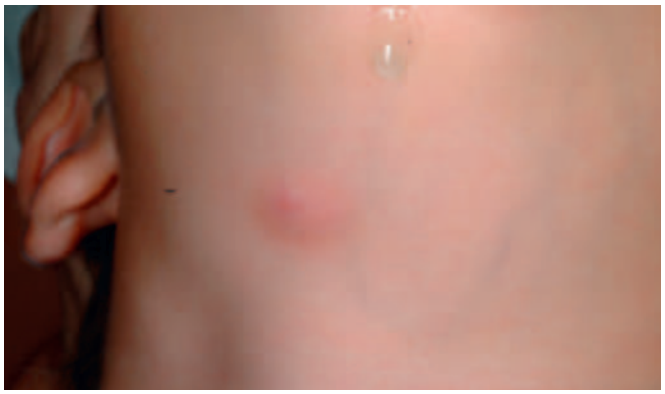


Fig. 2.51 Thyroglossal duct cyst. This congenital nodule of the anterior midline neck was noted to move upward with swallowing.

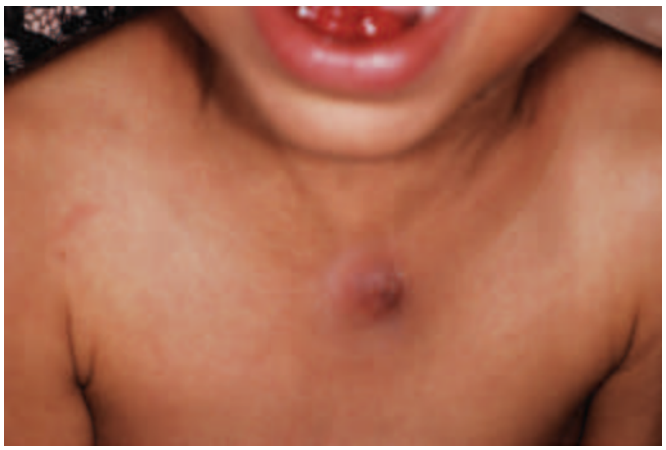


Fig. 2.52 Bronchogenic cyst. This congenital nodule, adjacent to the suprasternal notch, became recurrently inflamed and tender. It was ultimately treated by surgical excision.

hearing loss, suggesting that audiologic evaluation should be performed in these infants.[191–194] The data regarding genitourinary malformations are more controversial, with studies both supporting and refuting an association with preauricular pits or tags.[190,195] 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. 2.51). 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 to prevent postoperative hypothyroidism.

Bronchogenic cysts present early, usually at birth, as a nodule (Fig. 2.52) 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. Fig. 2.53 shows the locations of several types of congenital neck cysts. Small superficial midline neck cysts that appear similar to a giant milium near the sternal notch (Fig. 2.54) have also been observed and appear to be another type of midline developmental anomaly. These lesions have recently been termed *midline anterior neck inclusion cysts (MANICs)*.[196]

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), and multiple pterygium syndromes; trisomy 18; short-limbed dwarfism; and combined immunodeficiency disease.

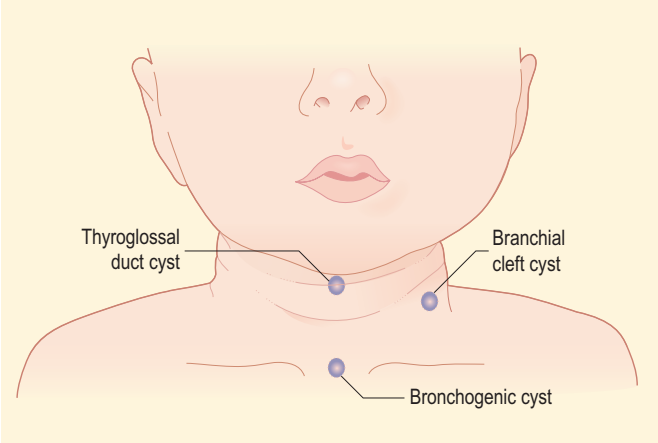


Fig. 2.53 Congenital sinuses of the neck.

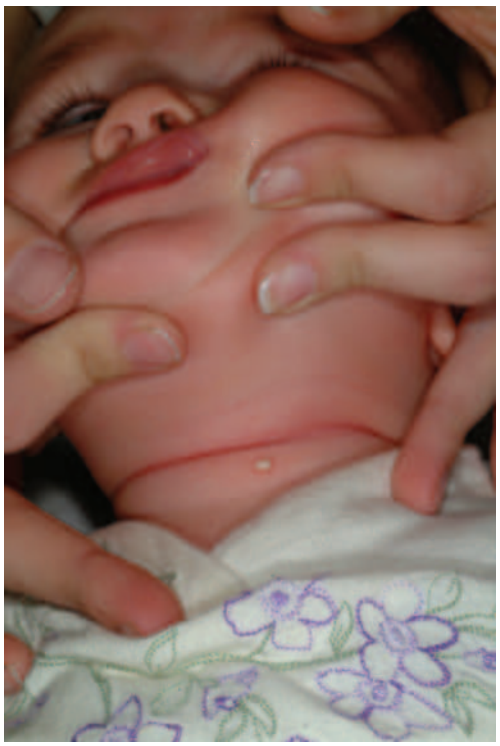


Fig. 2.54 Anterior neck inclusion cyst. This white exophytic cyst was present over the midline anterior neck at birth in this 7-month-old girl.

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 (Fig. 2.55). They are most common on the chest or upper abdomen and occasionally occur at 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.[197–199]

A variety of developmental anomalies 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 Zika virus infection is briefly discussed, given increasing recognition of its untoward effects on the human fetus.

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.[200] It occurs after a maternal 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, 79 cases of rubella and six cases of CRS were reported in the United States and were either import associated or from unknown sources.[201] In 2014 an expert panel reported that since 2004 the incidence of CRS was less than 1 per 5,000,000 births, supporting virtual elimination of the disease from the United States.[202] In 2015 the Pan American Health Organization/World Health Organization declared the Americas region free of endemic transmission of rubella and CRS. Occasional rubella outbreaks, however, 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.[203,204] 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.[204,205] Importantly, rubella virus continues to circulate in other parts of the world (e.g., Africa, Asia) where rubella vaccination programs are not established and increases the risk of imported rubella in the United States and subsequent CRS.[201,202]

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.[206] 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.[207,208]

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 "blueberry muffin" lesions (Fig. 2.56). Blueberry muffin lesions are usually present at birth or within the first 24 hours, and new lesions rarely appear after age 2 days. 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

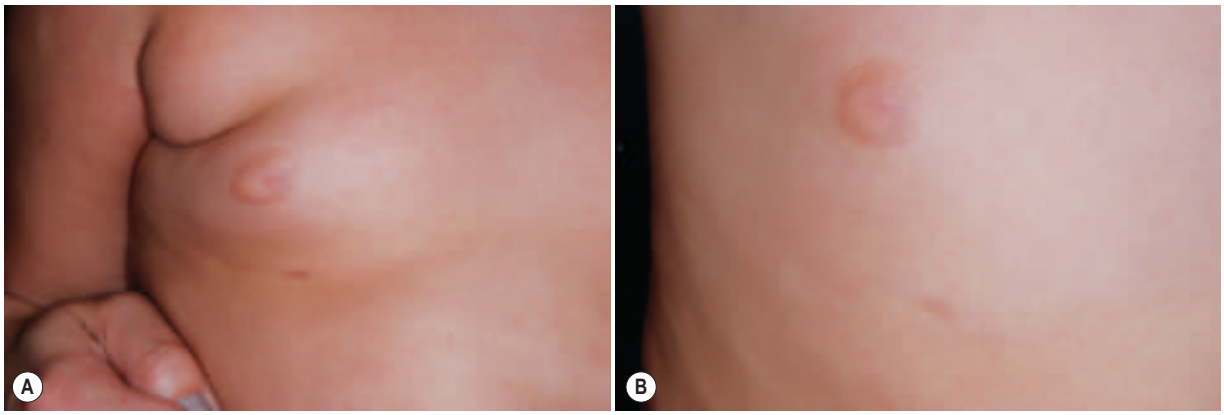


Fig. 2.55 (A) Supernumerary nipple. This papule, inferior and medial to the right breast, was present at birth in this young girl. **(B)** Closer inspection reveals an umbilicated, pink papule representing a well-formed nipple and surrounding areola.

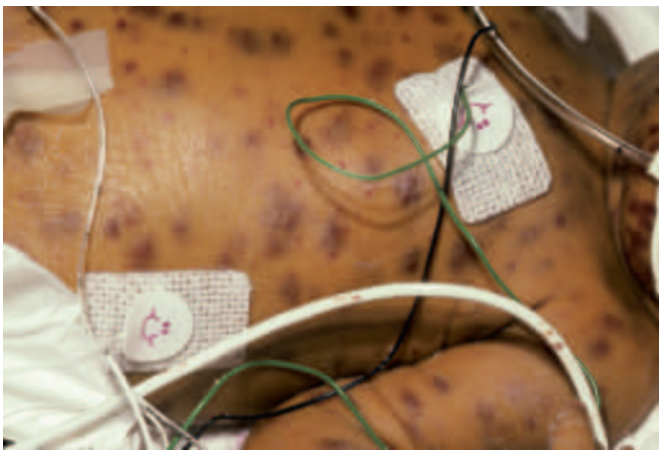


Fig. 2.56 Congenital rubella with blueberry muffin lesions. Multiple violaceous, infiltrative papules and nodules in this newborn with congenital rubella.

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

generalized nonspecific maculopapular eruption, reticulated 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.

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. Prenatal diagnosis of congenital infection can be pursued when maternal rubella is diagnosed and is based on detection of rubella virus IgM in fetal blood or detection of viral genome in amniotic fluid, fetal blood, or chorionic villus sampling.[209] Prenatal ultrasound findings most useful in evaluating for CRS include cardiac septal defects, pulmonary artery stenosis, microcephaly, cataracts, microphthalmia, and hepatosplenomegaly.[210]

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.[211]

Congenital rubella can be effectively prevented by immunization with live rubella virus vaccine, and universal vaccination is recommended. 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.[207] 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 given that the majority of women have acquired immunity by childbearing age.[212] 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.[213,214] Primary VZV infection in a pregnant woman most often results in the birth of a normal newborn, related to either 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.[213,215] 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.[216]

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.[212] 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 PCR-based testing of fetal blood or amniotic fluid.[217] Prenatal ultrasound may reveal disseminated organ calcifications.[218] Studies suggest that the use of varicella-zoster immunoglobulin (VariZIG) 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 women who are already pregnant should be counseled about avoiding contact with individuals who have chickenpox and about the availability of VariZIG 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. 2.57), with pneumonia, hepatitis, or meningoencephalitis and severe coagulopathy and a mortality rate of around 30%. In an effort to prevent neonatal varicella infection, VariZIG (or intravenous immunoglobin [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.[219]

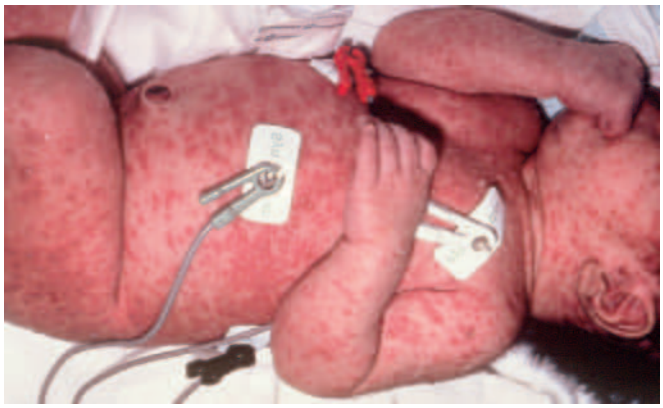


Fig. 2.57 Neonatal varicella. Disseminated, erythematous papules, vesicles, and erosions.

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 to range between 9.6 and 13.3 cases per 100,000 births.[220,221] Incidence rates likely vary by geographic region and race or ethnicity.[222] Traditionally, up to 70% of neonatal HSV infections were caused by type 2 ("genital") HSV, and the disease was acquired either by ascending *in utero* infection or by spread during delivery through an infected birth canal (perinatal transmission). More recently, type 1 HSV has evolved to be the predominant type causing genital herpes, and neonatal HSV infections in many parts of the world are now caused by HSV-1.[223] 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.[224–226] Of infants with neonatal HSV, 85% acquire their infection during birth (peripartum), 10% postnatally (postpartum), and 5% from *in utero* exposure.[227] 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.[228] 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).[229]

The risk of neonatal HSV infection in an infant born vaginally to a mother with primary genital infection is high (40% to 57%), 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.[230] 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

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	Multiple organs, including liver, lungs, adrenals, GI tract, and SEM; may progress to respiratory collapse, liver failure, and DIC

Adapted from Kimberlin DW. Herpes simplex virus infections in neonates and early childhood. Semin Pediatr Infect Dis 2005;16:271–81; Kimberlin DW. Herpes simplex virus infections of the newborn. Semin Perinatol 2007;31:19–25; James SH, Kimberlin DW. Neonatal herpes simplex virus infection. Clin Perinatol 2015;42(1):47–59.

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

*Approximate incidence out of all neonatal herpes patients.

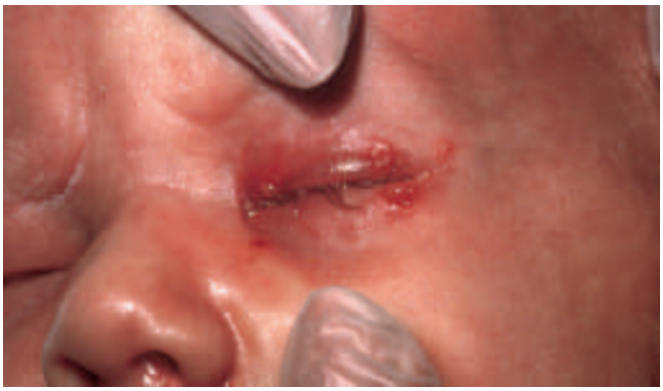


Fig. 2.58 Neonatal herpes simplex infection. Clustered vesicles on an erythematous base in this newborn with congenital herpes simplex infection, skin, eyes, and/or mouth (SEM) type.

Table 2.5 Recommended Evaluation for Suspected Neonatal HSV

Swab specimens from the mouth, nasopharynx, conjunctivae, and anus for HSV culture or PCR assay
Specimens of skin vesicles for HSV culture (if available) or PCR assay
CSF sample for HSV PCR assay
Whole blood sample for HSV PCR assay
Whole blood sample for measuring alanine transaminase (ALT)

From American Academy of Pediatrics. Herpes simplex. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red book: 2018 report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2018:437–49.

CSF, Cerebrospinal fluid; *HSV*, herpes simplex virus; *PCR*, polymerase chain reaction.

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; SEM and disseminated disease tend to present earlier (average 9 to 11 days postnatal age) than CNS disease (average 16 to 17 days postnatal age). 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.[231]

Presenting features of neonatal HSV include skin lesions, fever, respiratory distress, and CNS dysfunction. The latter includes seizures, lethargy, poor feeding, irritability, and hypotonia. In a retrospective series of 49 infants with neonatal HSV, 84% presented with seizures, vesicular skin eruption, or critical illness.[232] The skin eruption may vary from erythematous macules to individual or grouped vesicles (Fig. 2.58) 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 become 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.[233] 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.[231] 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. The recommended evaluation from the Committee on Infectious Diseases of the American Academy of Pediatrics is shown in Table 2.5. 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 and is rarely if ever performed in the present era. Direct fluorescent antibody study of skin lesion scrapings has a high sensitivity (80% to 90%), excellent specificity,[234] 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.[231] 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, for which they are the diagnostic method of choice. Skin biopsy is rarely indicated, but if it is performed, it 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.[235] Electroencephalography and neuroimaging with MRI should also be considered.[235]

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.[224] 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.[236] 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.[228] 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 handwashing 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 used, 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.[237]

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.[217] 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.[238] Toxicity was limited to transient neutropenia during therapy, suggesting the importance of monitoring absolute neutrophil counts. In a study of 89 infants with neonatal HSV treated with high-dose acyclovir, the most common clinical adverse events were hypotension and seizure, and the most common laboratory aberration observed was thrombocytopenia, which occurred in 25% of infants.[239] Treatment recommendations are for 14 days for SEM disease and 21 days for CNS and disseminated disease.[235,240] Oral acyclovir suppression for 6 months after acute therapy is recommended for surviving infants with CNS disease, given the demonstrated improved neurodevelopmental outcomes.[241] Algorithmic guidelines on the management of asymptomatic neonates born to women with active genital herpes lesions have been published.[242,243]

CONGENITAL PARVOVIRUS B19 INFECTION

Human parvovirus B19, the same virus that causes erythema infectiosum (fifth disease), may be transmitted by a gravid woman 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.[244] Overall, up to 65% of pregnant women are immune to B19 and therefore not at risk,[245] 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%.[246–248] The highest risk period for fetal loss is when maternal transmission occurs between 9 and 16 weeks' gestation.[249] Fetal B19 infection may result in severe anemia, high-output cardiac failure, generalized edema, pleural and pericardial effusions, and polyhydramnios. *Hydrops fetalis* refers to fluid accumulation in at least two of the following compartments: subcutaneous, pericardial, pleural, and abdominal.[249] Bony lucencies of long and axial bones noted on plain radiographs have been reported.[250] Although skin findings are not a major feature of congenital B19 infection, blueberry muffin lesions have been described.[251]

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.[252] 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. However, despite management with transfusion in severely anemic or hydropic fetuses with B19 infection, the mortality rate may still approach 25%.[253]

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.[254] In the United Kingdom, the number of babies reported with CS increased from 2 in 1996 to 14 in 2005.[255] 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.[256] Although the overall rate of CS in the United States decreased during the period from 2008 to 2012, during the years 2012 to 2014 it again increased from 8.4 to 11.6 cases per 100,000 live births.[257] 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.[258] The risk of CS increases with greater maternal spirochetemia and longer duration of maternal primary or secondary syphilis.[259] 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.[260] Of those who die from CS, more than 80% are stillbirths. Among affected live newborns, around 50% are symptom free.[261] Perinatal associations with CS include premature delivery, low birthweight, and small size for gestational age.[262]

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. Premature infants are more likely to display characteristic features of early CS, including skin findings, hepatosplenomegaly, thrombocytopenia, and radiographic findings in long bones as neonates, compared with full-term infants.[263]

The most common clinical manifestations of early CS are summarized in Table 2.6. 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 papulosquamous 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. 2.59). 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.

Table 2.6 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%–75% of patients
		Icterus, jaundice, ascites associated
Mucocutaneous	Papulosquamous lesions	Diffuse eruption
		Palms and soles red, fissured (Fig. 2.59)
		Bright pink-red, fades to coppery brown
		Rare vesiculobullous lesions
		Eventual widespread desquamation
	Condylomata lata	Flat, wart-like lesions in moist areas (especially anogenital, nares, mouth angles)
	Mucous patches	Present in 30%–35% of cases
		Weeping, fissuring at mucocutaneous junctions
		Extend out from lips in radiating fashion
		When deep, may leave scars (rhagades) of perioral region
Osseous	Osteochondritis	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
	Periostitis	Most pronounced at 2–6 months of life
		Usually diffuse
		Calcification and thickening of cortex may lead to permanent deformity (e.g., frontal bossing, anterior bowing of tibia or saber shins)
	Dactylitis	Affects small bones of hands and feet
CNS	CSF abnormalities	Increased protein, mononuclear pleocytosis, positive CSF-VDRL

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

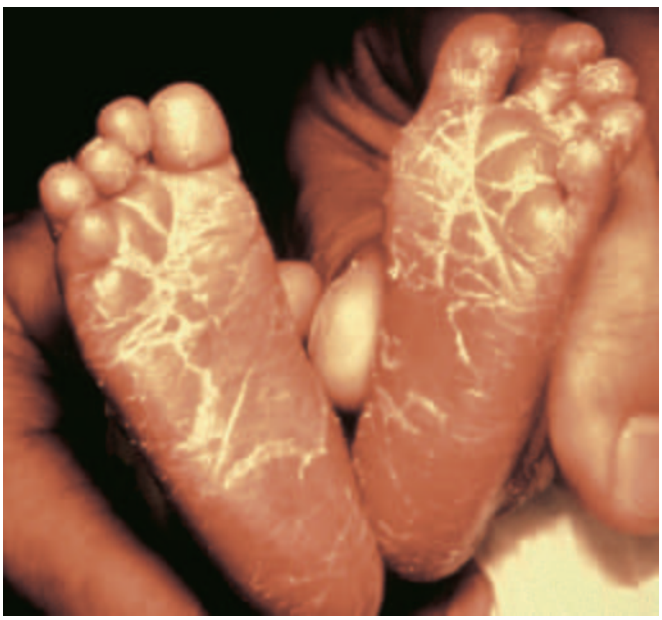


Fig. 2.59 Congenital syphilis. Erythema, scaling, and fissuring of the plantar surfaces in early congenital syphilis.

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.[264]

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 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. IgM immunoblotting and PCR assay on serum or CSF have been shown to be most predictive of CNS infection.[265] 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 infancy may go on to demonstrate marked residua with varying degrees of physical and mental retardation.

Late Congenital Syphilis

Late CS refers to 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 at risk for 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 because of 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. Because 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.

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

*Hutchison triad.

Diagnosis and Treatment of Congenital Syphilis

Determination of the maternal serologic status for syphilis is the standard of care in hospitals, and no newborn infant should be discharged without this information being known.[266] All infants born to mothers who are seropositive require a thorough clinical and laboratory examination, namely a quantitative nontreponemal syphilis test (e.g., Venereal Disease Research Laboratories [VDRL] or rapid plasma reagin [RPR]), and preferably the same as that performed on the mother so that the titers can be compared. In mothers with a reactive RPR or VDRL, important maternal history to consider, which will guide further testing or therapy, includes whether the mother received no therapy, received undocumented therapy, or received therapy less than 1 month before delivery; there is concern of maternal reinfection or relapse (fourfold or greater increase in maternal titers); the mother was treated with a nonpenicillin drug; or the partner was recently diagnosed with syphilis.[266] Confirmation of a reactive nontreponemal test is accomplished with a specific treponemal test, such as the fluorescent treponemal antibody absorption (FTA-ABS) test, the *T. pallidum* particle agglutination (TP-PA), 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 earlier in the Early Congenital Syphilis section), villous enlargement, and acute villitis.[267] 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, because maternal IgM antibodies do not cross the placenta, detection of IgM in the infant indicates active infection.[255] 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, CSF-VDRL, and cellular/protein analysis and complete blood cell and platelet counts; other tests that may be indicated include ophthalmologic evaluation, long-bone and chest radiographs, neuroimaging, liver function studies, and auditory brainstem response.[266]

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 intravenous aqueous crystalline penicillin G at a dosage of 50,000 units/kg every 12 hours for infants aged 1 week or younger, then every 8 hours for infants older than 1 week, for a total of 10 days of therapy. Procaine penicillin G at 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 ages 2, 4, 6, and 12 months and serologic nontreponemal tests performed every 2 to 3 months until results become