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Pediatric Dermatology



Bernard A. Cohen

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Pediatric Dermatology

FOURTH EDITION

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Preface

Since I began taking clinical photographs during my residency training over 30 years ago, I have been impressed by the virtually unlimited variation in the expression of skin disease. However, with careful observation, clinical patterns that permit the development of a reasonable differential diagnosis emerge. In the fourth edition, I have been able to use over 600 images, a third of which are new, to demonstrate the diverse variations and common patterns that are fundamental to an understanding of skin eruptions in children. Moreover, since I have catalogued all new images on our online dermatology webAtlas at dermatlas.org, which is the source of most of the new images in this edition, the reader is referred to this site to view additional images and more detailed discussion of specific clinical cases. There are over 500 contributors to dermAtlas, and you are invited to participate.

Pediatric Dermatology is designed for the pediatric and primary care provider with an interest in dermatology and the dermatology practitioner who cares for children. The text is organized around practical clinical problems, and most chapters end with an algorithm for developing a differential diagnosis. This book should not be considered an encyclopedic text of pediatric dermatology; it should be used in conjunction with the further reading suggested at the end of Chapter 1. Classic papers and more recent literature are included in the further reading lists at the end of each chapter.

At Hopkins, we have been fortunate to have oral pathologists on the dermatology faculty in the roles of teacher and consultant. With their help, the importance of recognizing oral lesions in the care of children is reflected in Chapter 9, which is devoted to oral pathology. Although the focus of this chapter is on primary lesions of the oral mucosa, a discussion of clues of systemic disease is included. Chapter 2, which is devoted to dermatologic disorders of newborns and infants, remains the longest chapter in the book due to the continued blossoming of neonatology as a respected pediatric discipline. I never cease to be amazed by how human beings manipulate their skin accidentally, deliberately, secretly, and/or therapeutically. With this in mind, Chapter 10, Factitial Dermatoses, concludes with several disorders that are triggered, exacerbated, or caused primarily by external factors.

Finally, the format of the text should be user-friendly. The pages and legends have been numbered in a standard textbook fashion, and the index is again revised to include all of the disorders listed in the text as well as the legends. The text and images incorporate advances made in diagnosis, evaluation, and treatment during the last 7 years, since the publication of the third edition. I only hope that students of pediatric dermatology will enjoy reading the book as much as I enjoyed writing and illustrating it.

Bernard A. Cohen
2012

Acknowledgments

This book would not have been possible without the help of the children and parents who allowed me to photograph their skin eruptions, and the practitioners who referred them to me. I am particularly indebted to the faculty, residents, nurse practitioners, nurses, physicians assistants, and students at the Johns Hopkins Children's Center and the Departments of Pediatrics and Dermatology at the Johns Hopkins University School of Medicine for their inspiration and support. I would again like to thank my friends at the Children's Hospital of Pittsburgh where this book was first conceived.

I have a new group of over 500 friends and contributors, most of whom I have met through an ever-expanding online dermatology image project 'dermatlas'. My association with dermatlas as one of the founding Editors gives me access to an incredible national and international repository of cutaneous images. It was my honor to work with Editor emeritus and medical informatics maven Christoph Lehmann, a neonatologist who probably knows more dermatology than any other neonatologist in the country. My son, Michael Cohen, a young and rising computer science wizard is in the process of rewriting and modernizing the platform, which hopefully will be completed by the time this new edition of Pediatric Dermatology is published.

I am also indebted to the oral pathology faculty at Hopkins who call dermatology their home. They have taught me to seek clues for dermatologic and systemic disease from evaluation of the mucous membranes, and to respect oral pathology in its own right. Without them, the conception of Chapter 9 and the most recent updates would not have been possible.

I continue to be grateful for the persistent prodding and sensitive guidance of the editors at Elsevier who are responsible for completion of this book in a timely fashion. I would also like to thank Tracy Shuford for keeping the lines of communication open between the Publisher and my office, despite the 6-hour time difference.

Special thanks go to Kate Puttgen, my colleague in crime in pediatric dermatology at the Children's Center; John Mavrolopoulos, a rising dermatology resident star at the School of Medicine, and my wife Sherry Cohen, Family Practice Nurse Practitioner, who still works in dermatology in spite of me, and all of whom have contributed significantly to this edition.

I would like to thank the residents in dermatology and pediatrics, who by their questions and consultations, have helped me prioritize topics for inclusion in this book.

Finally, I would like to again acknowledge Dr Nancy Esterly, who contributed the foreword to the second edition (reprinted in the third edition). I think of her often and would like to honor her by using her foreword in this edition as well. Dr Esterly taught me that pediatric dermatology could be exciting and academically challenging. As a role model and friend, she continues to guide all of us in pediatric dermatology. I would also like to acknowledge Dr Frank Oski who brought me home to Baltimore, where he incorporated pediatric dermatology into the pediatric training program. Hopefully, we can live up to the high standards which he demanded.

Figure Credits

The following figures have been reprinted from Zitelli BJ, Davis HW (eds). Atlas of pediatric physical diagnosis, 3rd edn. Mosby, St Louis, 1997:

4.10, 7.8, 7.9, 8.1, 8.15, 8.49, 10.5, 10.7, 10.8, 10.11, 10.13

I am grateful for the use of images from: www.dermatlas.org, and to Dr Russ Corio and Dr Gary Warnock Associate Professor of Dermatology at the Johns Hopkins University School of Medicine, for contributing additional images to the chapter on the Oral Cavity (Ch. 9).

Dedication

To Sherry for her continued patience, love, understanding, and encouragement during the revision of this book, which took longer than I thought!

To Michael, Jared, and Jennie for keeping me young and laughing. It has been exciting to see them mature into young adults who now contribute to the care of children and adults in their own ways.

To all of the children who made this project possible.

Foreword

NOTE FROM DR COHEN

I have asked the managing editor to reprint the Foreword from the second edition (also reprinted in the third edition) written by Dr. Nancy Esterly to honor her for her contributions to pediatric dermatology, the training of many practitioners of the specialty, and my own career. In the spring of 1983 when I was desperately searching for a mentor in pediatric dermatology, Nan adopted me during my elective month at Childrens's Memorial Hospital in Chicago.

Dr. Esterly has been the quintessential practitioner of pediatric dermatology since her pediatric and dermatology training in Baltimore over 40 years ago. She was one of the founders of the Society for Pediatric Dermatology and embodies the tripartite mission of pediatric dermatology of patient care, resident teaching, and clinical research.

FOREWORD TO THE SECOND EDITION

It isn't often that one encounters a single author textbook that is outstanding in both text and illustrations. But, once again, Bernard Cohen has crafted an exceptional basic pediatric dermatology text liberally illustrated with photographs depicting a wide range of skin problems in infants and children.

In this fourth edition of Pediatric Dermatology, the text has been expanded to include a 20 page chapter devoted entirely to mucosal lesions and accompanied by more than 50 new photographs of patients with problems ranging from the common herpes simplex infection to the uncommon ectodermal dysplasias. In keeping with the very successful style of previous editions, the requisite algorithm, diagrams of the oral cavity and up-to-date references are included in this chapter. In addition, new photographs have been added and some old ones replaced throughout the book.

For beginners in this discipline, Dr. Cohen's text is an excellent place to start. For those of us who practice pediatric dermatology, there is still much to be learned from a well-put-together text such as this one.

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Chapter 1

Introduction to Pediatric Dermatology

Bernard A. Cohen

ANATOMY OF THE SKIN

Most of us think of skin as a simple, durable covering for the skeleton and internal organs. Yet skin is actually a very complex and dynamic organ consisting of many parts and appendages (Fig. 1.1). The outermost layer of the epidermis, the stratum corneum, is an effective barrier to the penetration of irritants, toxins, and organisms, as well as a membrane that holds in body fluids. The remainder of the epidermis, the stratum granulosum, stratum spinosum, and stratum basale, manufactures this protective layer. Melanocytes within the epidermis are important for protection against the harmful effects of ultraviolet light, and the Langerhans cells and other dendritic cells are one of the body's first lines of immunologic defense and play a key role in systemic and cutaneous diseases such as drug reactions.

The dermis, consisting largely of fibroblasts and collagen, is a tough, leathery, mechanical barrier against cuts, bites, and bruises. Its collagenous matrix also provides structural support for a number of cutaneous appendages. Hair, which grows from follicles deep within the dermis, is important for cosmesis, as well as protection from sunlight and particulate matter. Sebaceous glands arise as an outgrowth of the hair follicles. Oil produced by these glands helps to lubricate the skin and contributes to the protective function of the epidermal barrier. The nails are specialized organs of manipulation that also protect sensitive digits. Thermoregulation of the skin is accomplished by eccrine sweat glands as well as changes in the cutaneous blood flow regulated by glomus cells. The skin also contains specialized receptors for heat, pain, touch, and pressure. Sensory input from these structures helps to protect the skin surface against environmental trauma. Beneath the dermis, in the subcutaneous tissue, fat is stored as a source of energy and also acts as a soft protective cushion.

EXAMINATION AND ASSESSMENT OF THE SKIN

The skin is the largest, and most accessible and easily examined organ of the body, and it is the organ of most frequent concern to the patient. Therefore, all practitioners should be able to recognize basic skin diseases and dermatologic clues to systemic disease.

Optimal examination of the skin is best achieved in a well-lit room. The clinician should inspect the entire skin surface, including the hair, nails, scalp, and mucous membranes. This may present

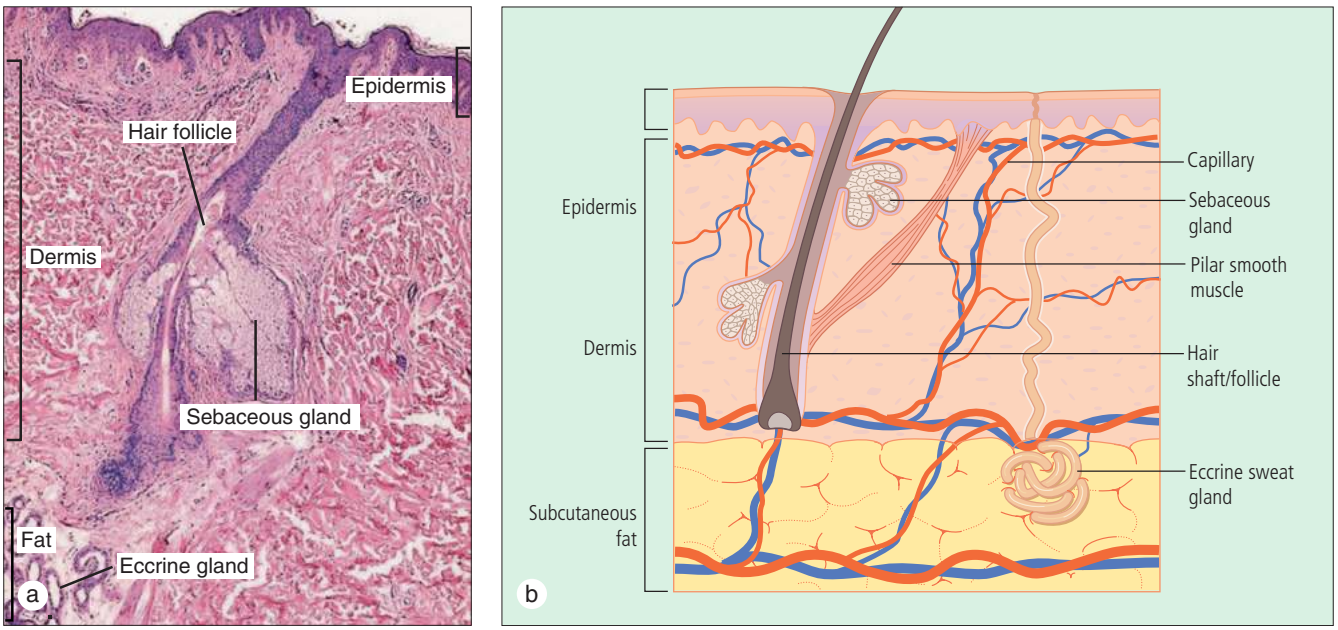


Fig 1.1 (a) Skin photomicrograph and **(b)** schematic diagram of normal skin anatomy.

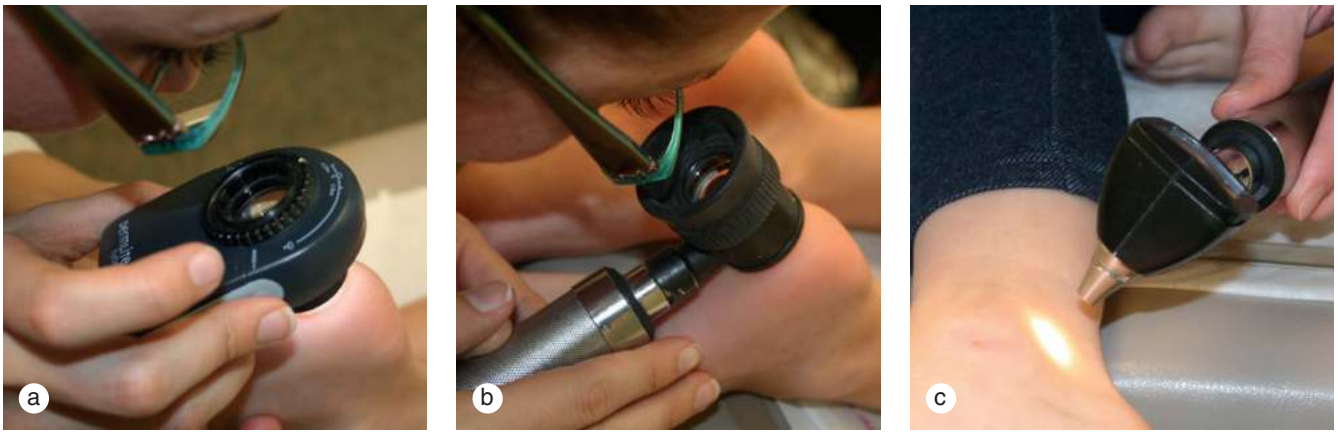
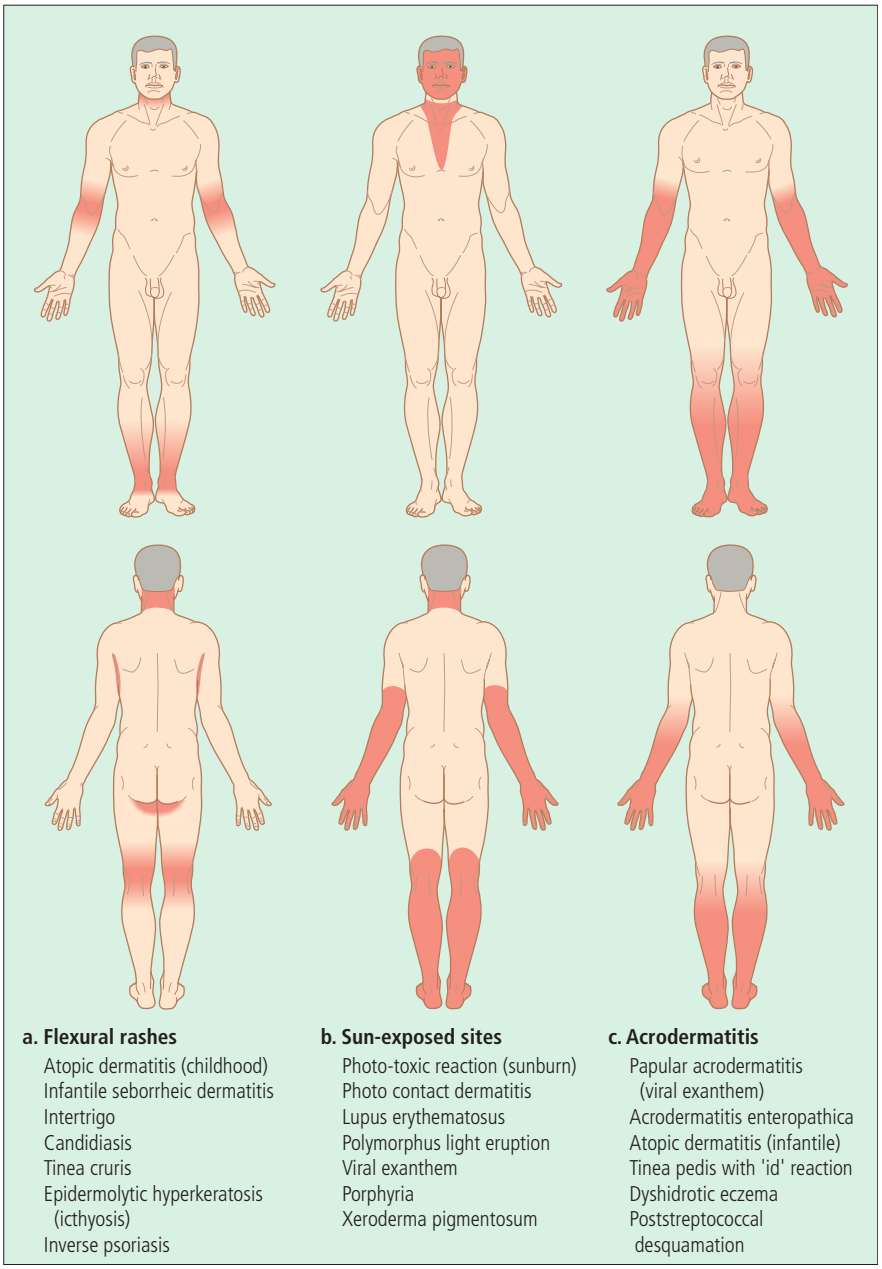


Fig 1.2 Examination of pigmented nevi with **(a)** DermLite II Hybrid by 3Gen, **(b)** Welch Allyn Episcope Skin Surface Microscope, and **(c)** Welch Allyn Otoscope.



a. Flexural rashes
- Atopic dermatitis (childhood)
- Infantile seborrheic dermatitis
- Intertrigo
- Candidiasis
- Tinea cruris
- Epidermolytic hyperkeratosis (icthyosis)
- Inverse psoriasis

b. Sun-exposed sites
- Photo-toxic reaction (sunburn)
- Photo contact dermatitis
- Lupus erythematosus
- Polymorphus light eruption
- Viral exanthem
- Porphyria
- Xeroderma pigmentosum

c. Acrodermatitis
- Papular acrodermatitis (viral exanthem)
- Acrodermatitis enteropathica
- Atopic dermatitis (infantile)
- Tinea pedis with 'id' reaction
- Dyshidrotic eczema
- Poststreptococcal desquamation

Fig 1.3 (a–h) Pattern diagnosis.

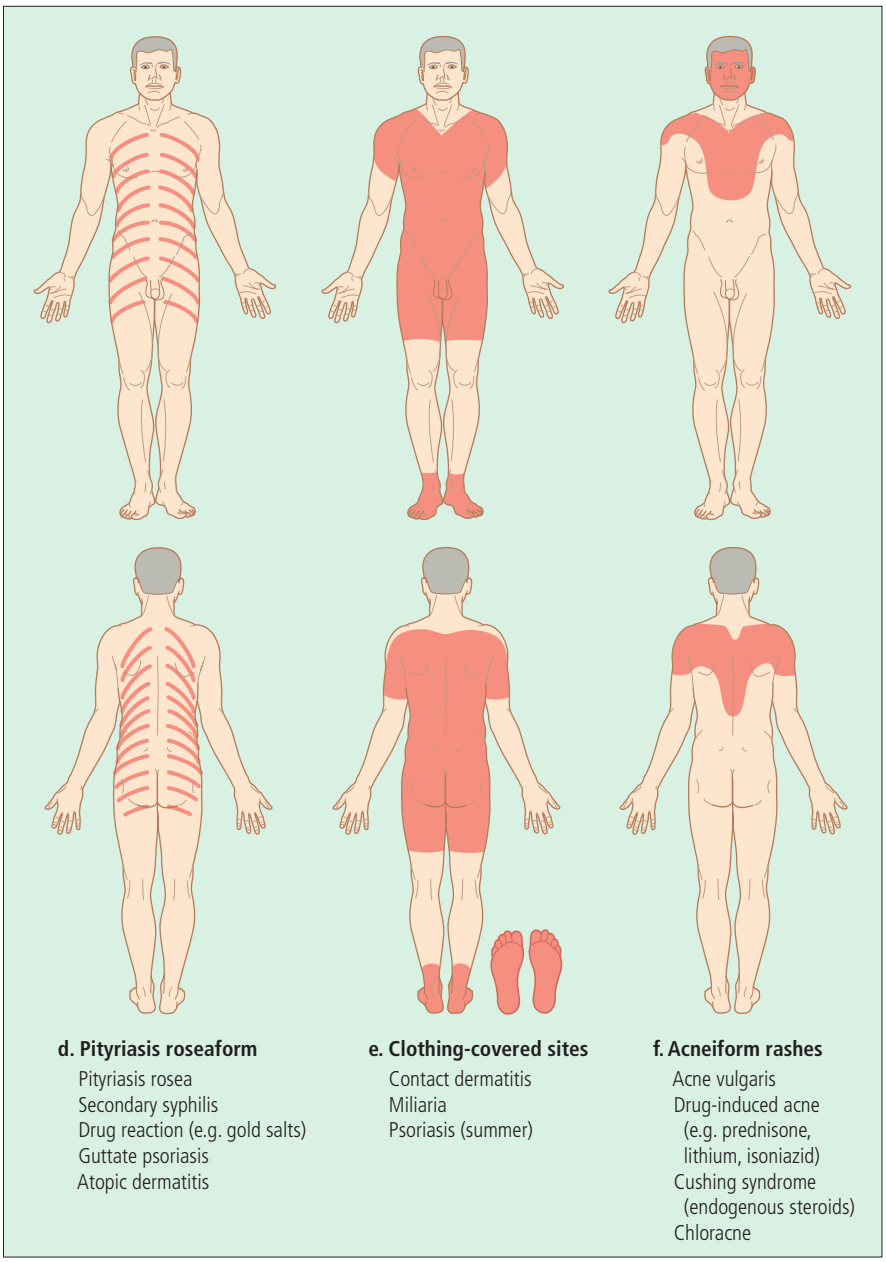


Fig 1.3 Continued.

particular problems in infants and teenagers, since it may be necessary to examine the skin in small segments to prevent cooling or embarrassment, respectively. Although no special equipment is required, a hand lens and side-lighting are useful aids in the assessment of skin texture and small discrete lesions. In many offices, the otoscope can be adapted for this purpose by removing the plastic speculum.

There are also a number of relatively inexpensive portable dermatoscopic devices, which can also be used to enhance the examination (also known as epiluminescence microscopy). These instruments have traditionally provided a magnified (×10) view of the skin with a non-polarized light source, a transparent plate, and a liquid medium between the dermatoscope and the skin. This allows for a view of the skin without interference from surface reflections. Dermatoscopic heads can be purchased for otoscope/ophthalmoscope handpieces, and mineral oil or alcohol gel can be applied directly to the skin lesion. Newer devices achieve the same view without the liquid medium by using polarized light (Fig. 1.2).

Despite the myriad of conditions affecting skin, a systematic approach to the evaluation of a rash facilitates and simplifies the process of developing a manageable differential diagnosis. After assessing the general health of a child, the practitioner should obtain a detailed history of the cutaneous symptoms, including the date of onset, inciting factors, the evolution of lesions, and the presence or absence of pruritus. Recent immunizations, infections, drugs, and allergies may be directly related to new rashes. The family history may suggest a hereditary or contagious process, and the clinician may need to examine other members of the family. A review of nursery records and photographs will help to document the presence of congenital lesions.

Attention should then turn to the distribution and pattern of the rash. The distribution refers to the location of the skin findings, while the pattern defines a specific anatomic or physiologic arrangement. For example, the distribution of a rash may include the extremities, face, or trunk, while the pattern could be flexural or intertriginous areas (Fig. 1.3a). Other common patterns include

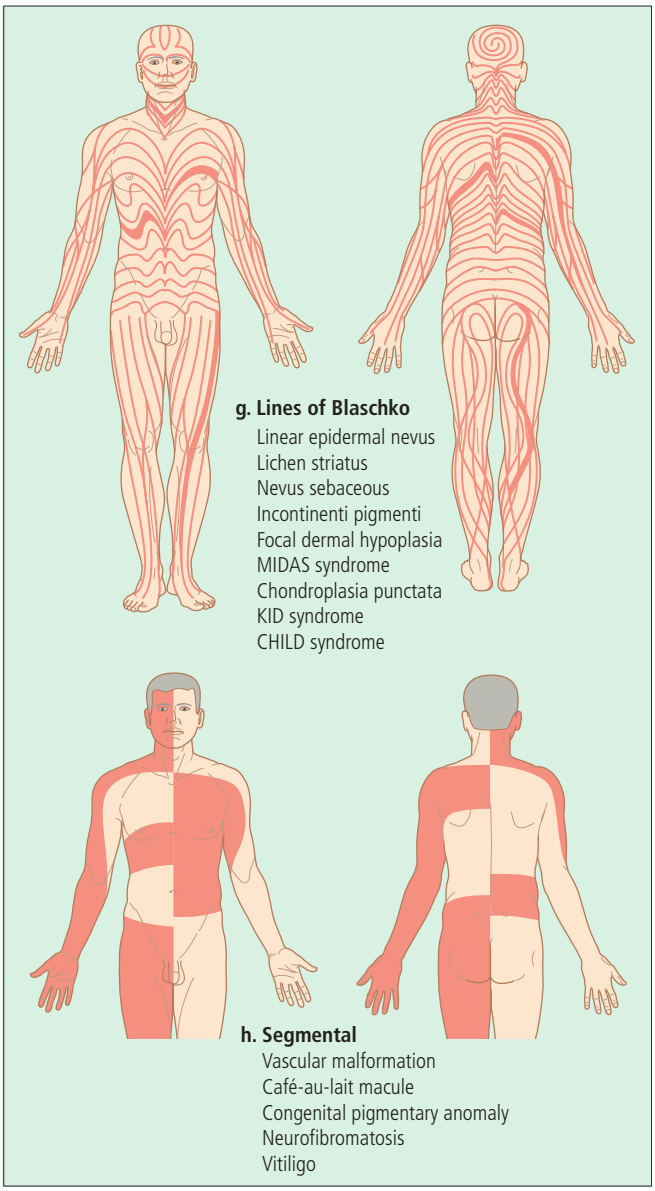


Fig 1.3 Continued.

sun-exposed sites, acrodermatitis (predilection for the distal extremities), pityriasis rosea (truncal, following the skin cleavage lines), clothing-protected sites, acneiform rashes, Blaschko lines, and segmental lesions (Fig. 1.3b–g).

Next, the clinician should consider the local organization and configuration of the lesions, defining the relationship of primary and secondary lesions to one another in a given location (Table 1.1) and the shape of the lesions. Are the lesions diffusely scattered or clustered (herpetiform)? Are they dermatomal, linear, serpiginous, circular, annular, or reticulated?

The depth of the lesions in the skin, as noted by both observation and palpation, may also give further clues (Table 1.2). Disruption of the normal skin markings by scale, papules, vesicles, or pustules points to the involvement of the epidermis. Alterations in skin color alone can occur in epidermal and dermal processes. In disorders of pigmentation, the color of the pigment may suggest the anatomic depth of the lesion. Shades of brown are present in flat junctional nevi, lentigines, and café-au-lait spots, where the increased pigment resides in the epidermis or superficial dermis. In Mongolian spots and nevus of Ota, the Tyndall effect results in bluish-green to gray macules from melanin in the mid-dermis. If the epidermal markings are normal but the lesion is elevated, the disorder usually involves the dermis. Dermal lesions have well-demarcated firm borders. Nodules and tumors deep in the dermis or subcutaneous tissue can distort the surface markings, which are otherwise intact. Some deep-seated lesions can only be appreciated by careful palpation.

Lesion color can provide important clues for diagnosis and the pathophysiology of the underlying process (Table 1.3). Brown, blue, gray, bronze and black lesions are associated with disorders that alter normal pigmentation, while white lesions may be associated with loss of normal pigmentation or the accumulation of scale, crust, or exudates. Red and blue lesions are associated with inflammatory and vascular processes. Non-blanching blue or purple lesions should suggest the presence of purpura. Yellow lesions occur when the skin is infiltrated with inflammatory or tumor cells containing lipid. Other pigments from topical agents (e.g. silver, gold), oral medications (e.g. minocycline, amiodarone), foreign bodies (e.g. asphalt, tattoo pigments), and infectious agents (e.g. *Pseudomonas* species, *Corynebacterium* species) may impart specific colors to cutaneous lesions.

Finally, the clinician may develop a differential diagnosis using the morphology of the cutaneous lesions. Primary lesions (macules, papules, plaques, vesicles, bullae, pustules, wheals, nodules, and tumors) arise *de novo* in the skin (Fig. 1.4). Secondary lesions (scale, crust, erosions, ulcers, scars with atrophy and/or fibrosis, excoriations, and fissures) evolve from primary lesions or result from scratching of primary lesions by the patient (Fig. 1.5).

The practitioner who becomes comfortable with dermatology will integrate all of these approaches into their evaluation of a child with a skin problem. This will be reflected in the clinically focused format of this text.

Each chapter will finish with an algorithm that summarizes the material in a differential diagnostic flow pattern. The limited bibliography includes comprehensive, historically significant, and/or well-organized reviews of the subject. Readers may also find some of the texts and online further reading listed at the end of this chapter useful.

DIAGNOSTIC TECHNIQUES

Potassium hydroxide preparation

There are a number of rapid, bedside diagnostic procedures in dermatology. One of the most useful techniques is a wet mount of skin scrapings for microscopic examination (Fig. 1.6). Potassium hydroxide (KOH), 20%, is used to change the optic properties of skin samples and make scales more transparent. The technique requires practice and patience.

The first step is to obtain the material by scraping loose scales at the margin of a lesion, nail parings, subungual debris, or the small pearly globules from a molluscum body. Short residual hair stubs (black dots in tinea capitis) may also be painlessly shaved off the scalp with a #15 blade. Scale is placed on the slide and moved to the center with a cover slip. One or two drops of KOH are added and gently warmed with a match or the microscope light. Boiling the specimen will introduce artifact and should be avoided. Excess KOH can be removed with a paper towel applied to the edge of the cover slip. Thick specimens may be more easily viewed after gentle, but firm pressure is applied to the cover slip with a pencil eraser. Thick scale will also dissolve after being set aside for 15–20 min.

View the preparation under a microscope, with the condenser and light at low levels to maximize contrast, and with the objective at ×10. Focus up and down as the entire slide is rapidly scanned.

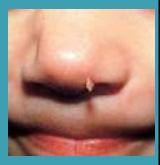
Organization and configuration of lesions							
							
Linear	**Dermatomal**	**Serpiginous**	**Annular**	**Herpetiform**	**Reticulated**	**Filiform (thread-like)**	**Geographic**
Epidermal nevi Lichen striatus Contact dermatitis Warts Ichthyosis Psoriasis Porokeratosis Incontinentia pigmenti	Herpes zoster Vitiligo Nevus depigmentosus Becker nevus Café-au-lait spot Port-wine stain	Psoriasis Erythema marginatum Cutaneous larvae migrans Elastosis perforans serpiginosa	Ringworm Granuloma annulare Subacute cutaneous lupus Atopic dermatitis Erythema annulare centrifugum Erythema chronicum migrans Erythema marginatum	Herpes simplex infection Herpes zoster Dermatitis herpetiformis	Cutis marmorata Livedo reticularis Congenital phlebectasia Reticulated and confluent papillomatosis Erythema ab igne	Wart Dermatosis papulosa nigra Syringocystadenoma papilliferum Skin tag Pigmented nevus	Psoriasis Geographic tongue Nummular eczema Erythema annulare centrifugum

Table 1.1 Organization and configuration of lesions

Anatomic depth of lesions			
Cutaneous structure	**Physical findings**	**Specific skin disorder**	
Epidermis	Altered surface markings Scale, vesicle, crust Color changes (black, brown, white)	Impetigo Café-au-lait spot Atopic dermatitis Vitiligo Freckle	
Epidermis + dermis	Altered surface markings Scale, vesicle, crust Distinct borders Color changes (black, brown, white, and/or red) Edema	Psoriasis Atopic dermatitis Cutaneous lupus erythematosus	
Dermis	Normal surface markings Color changes Altered dermal firmness	Urticaria Granuloma annulare Hemangioma Blue nevus	
Subcutaneous tissue	Normal surface markings Normal or red skin color Altered skin firmness	Hematoma Cold panniculitis Erythema nodosum	

Table 1.2 Anatomic depth of lesions

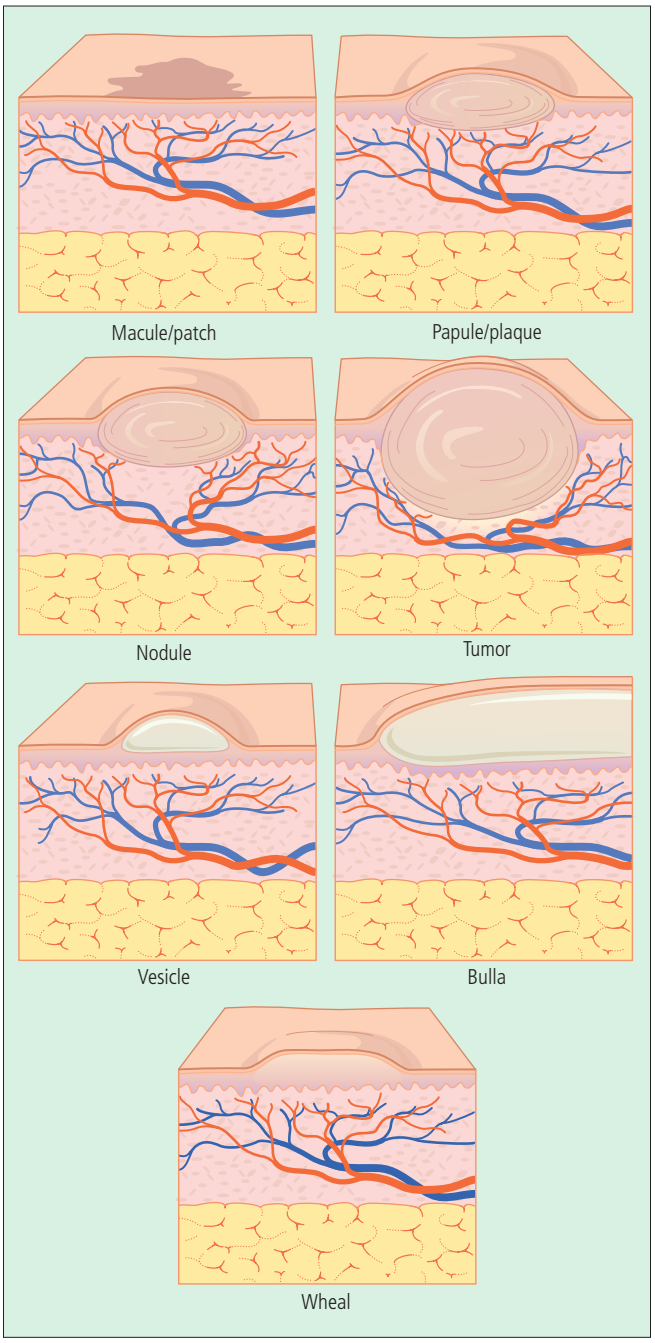


Fig 1.4 Primary skin lesions. Macule: a small (usually = 1 cm), flat lesion showing an alteration in color or tone. Large macule is a patch. Papule: a small (= 1 cm), sharply circumscribed, elevated lesion. An elevated lesion over 1 cm is referred to as a plaque. Nodule: a soft or solid mass in the dermis or subcutaneous fat. Tumor: a large nodule, localized and palpable, of varied size and consistency. Vesicle: a blister containing transparent fluid. Bulla: a large blister. Wheal: an evanescent, edematous, circumscribed elevated lesion that appears and disappears quickly. (Adapted from CIBA.)

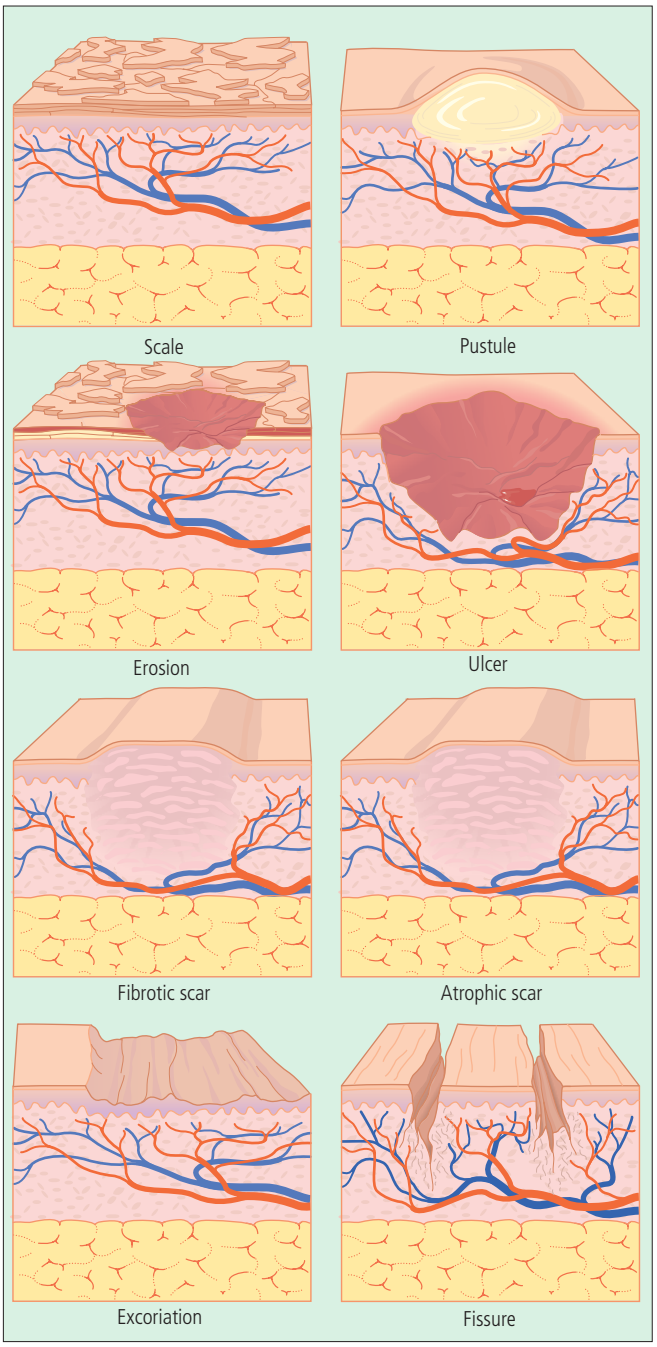


Fig 1.5 Secondary skin lesions. Scale: dry and/or greasy fragments of adherent epidermis. Pustule: a sharply circumscribed lesion containing free pus. Crust: a dry mass of exudate from erosions or ruptured vesicles/pustules, consisting of serum, dried blood, scales, and pus. Erosion: well-defined partial-thickness loss of epidermis. Ulcer: a clearly defined, full-thickness loss of epidermis that may extend into the subcutis. Scar: a permanent skin change resulting from new formation of connective tissue after destruction of the epidermis and cutis. When the loss of dermis and/or fat is prominent the lesion may be atrophic. Fibrosis may result in firm thickened papules or plaques. Excoriation: any scratch mark on the surface of the skin. Fissure: any linear crack in the skin, usually accompanied by inflammation and pain. (Adapted from CIBA.)

Lesion color							
							
Red	**Purple**	**Brown**	**Gray**	**Blue**	**Bronze**	**Green**	**Yellow**
Inflammatory disorders such as eczema, psoriasis, urticaria, erythema chronicum migrans and other figurate erythemas	Purpura, vascular malformations, hemangiomas, hematoma	Pigmented nevus, post-inflammatory hyperpigmentation, lentigo, ephiled (freckle), café-au-lait spot, epidermal nevus	Mongolian spot, graphite tattoo, nevus of Ota	Tattoo, vascular malformation, hemangiomas, blue nevus, Mongolian spot	Progressive pigmented purpuric dermatosis, resolving hematoma, phyto-photodermatitis	Tattoo, pseudomonas infection, deposition of minocycline, Mongolian spot, resolving hematoma	Xantho-granuloma, xanthoma, sebaceous hyperplasia, epidermal inclusion cyst

Table 1.3 Lesion color

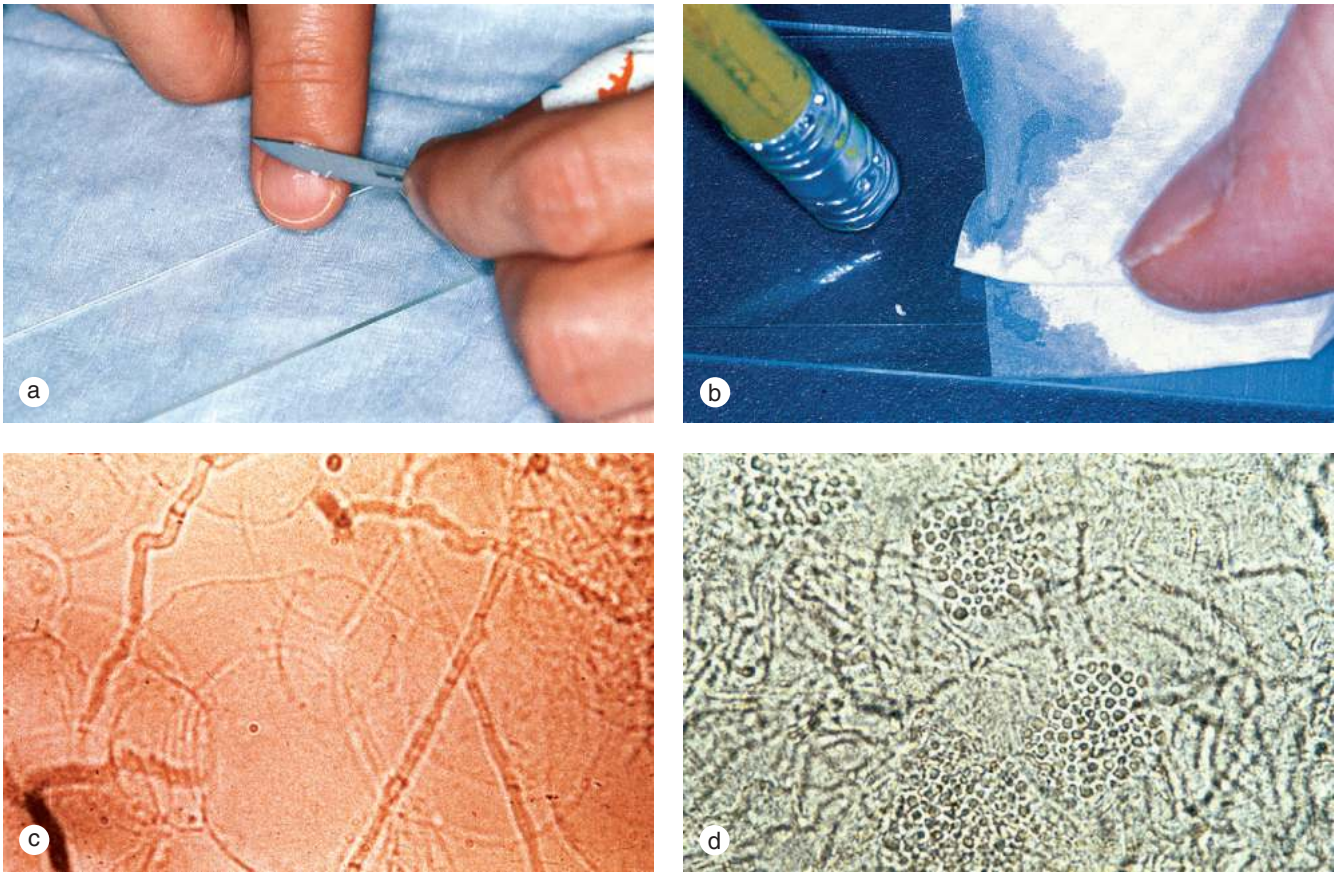


Fig 1.6 Potassium hydroxide (KOH) preparation. **(a)** Small scales are scraped from the edge of the lesion onto a microscopic slide. **(b)** The scales are crushed to form a thin layer of cells in order to visualize the fungus easily. **(c)** In this positive KOH preparation of skin scrapings, fungal hyphae are seen as long septate, branching rods at the margins and center of the scales. **(d)** Pseudohyphae and spores typical of tinea versicolor give the appearance of spaghetti and meatballs.

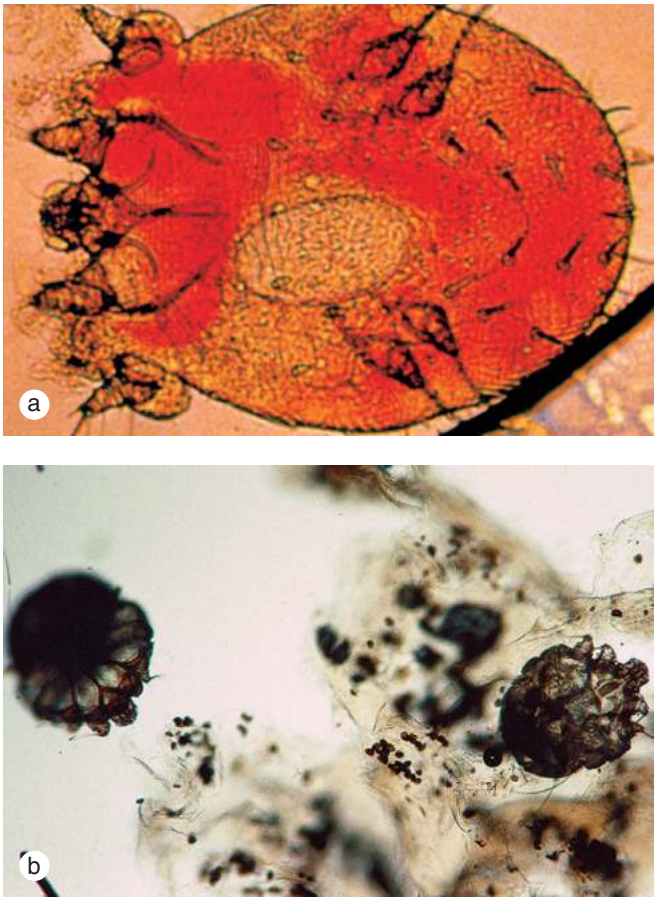


Fig 1.7 (a) Microscopic appearance of the adult scabies mite. Note the small oval egg within the body. **(b)** Scraping from an adolescent with crusted scabies shows two mites and multiple fecal pellets.

True hyphae are long branching green hyaline rods of uniform width that cross the borders of epidermal cells. They often contain septae. False positives may be vegetative fibers, cell borders, or other artifacts. Yeast infections show budding yeast and pseudohyphae. Molluscum bodies are oval discs that have homogeneous cytoplasm and are slightly larger than keratinocytes. In hair fragments, the fungi appear as small round spores packed within or surrounding the hair shaft (see Fig. 8.19e). Hyphae are only rarely seen on the hair.

Scabies preparation

A skin scraping showing a mite, its egg, or feces is necessary to diagnose infestation with *Acarus scabei*, because many other skin rashes resemble scabies clinically (Fig. 1.7). The most important factor for obtaining a successful scraping is the choice of site. Burrows and papules, which are most likely to harbor the mite, are commonly located on the wrists, fingers, and elbows. In infants, primary lesions may also be found on the trunk, palms, and soles. A fresh burrow can be identified as a 5–10 mm elongated papule with a vesicle or pustule at one end. A small dark spot resembling a fleck of pepper may be seen in the vesicle. This spot is the mite and it can be lifted out of its burrow with a needle or the point of a scalpel. Usually, it is best to hold the skin taut between the thumb and index finger while vigorously scraping the burrow. Although this may induce a small amount of bleeding, if performed with multiple, short, rapid strokes, it is usually painless. A drop of mineral oil should be applied to the skin before scraping to ensure adherence of the scrapings to the blade. The scrapings are then

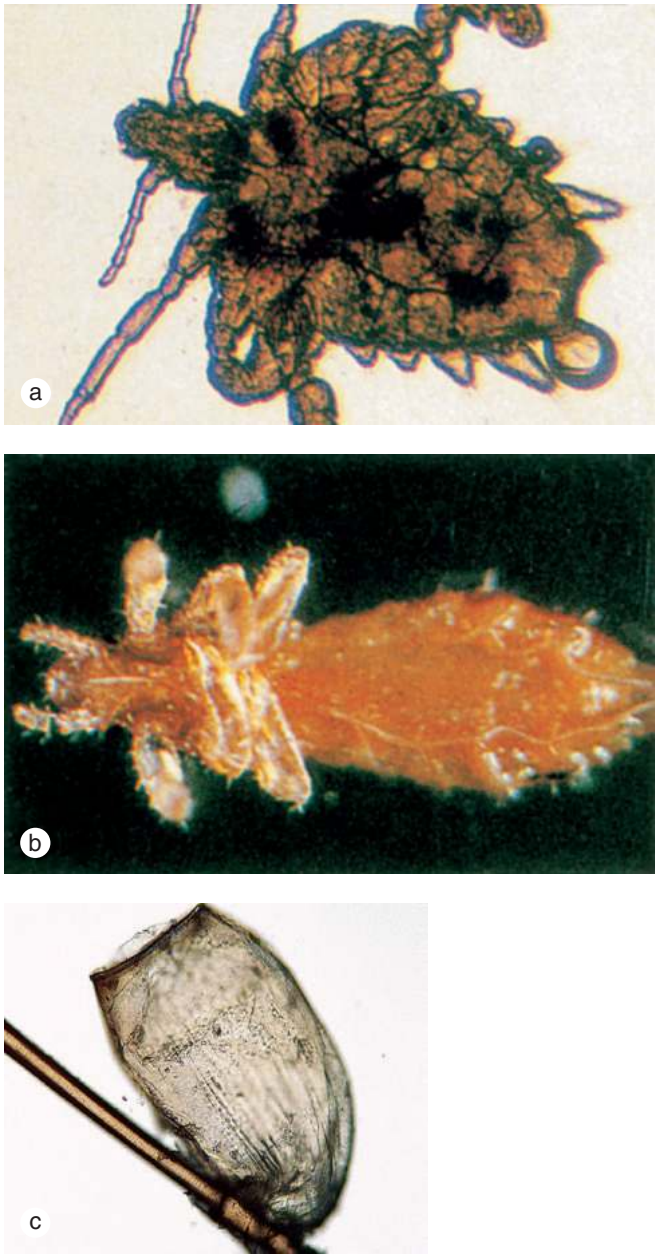


Fig 1.8 Microscopic appearance of lice. **(a)** The crab louse has a short, broad body, with claws spaced far apart. **(b)** The head louse has a long, thin body, with claws closer together. **(c)** A hatched nit is tightly cemented to the hair shaft.

placed on the slide, another drop of mineral oil is added, and a cover slip is applied. Gentle pressure with a pencil eraser may be used to flatten thick specimens.

Mites are eight-legged arachnids easily identified with the scanning power of the microscope. Care must be taken to focus through thick areas of skin scrapings so as not to miss any camouflaged mites. The presence of eggs (smooth ovals, approximately one half the size of an adult mite) or feces (brown pellets, often seen in clusters) are also diagnostic. If eggs or feces are found first, perusal of the entire slide usually reveals the adult mite.

Lice preparation

Lice are six-legged insects visible to the unaided eye that are commonly found on the scalp (Fig. 1.8), eyelashes, and pubic areas. Pubic lice are short and broad, with claws spaced far apart for

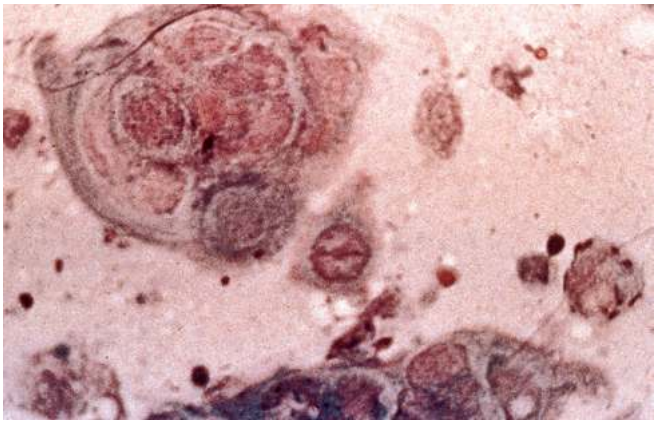


Fig 1.9 Tzanck smear. Note the multinucleated giant cells characteristic of viral infection with herpes simplex and varicella/zoster.

grasping the sparse hairs on the trunk, pubic area, and eyelashes, whereas scalp lice are long and thin, with claws closer together to grasp the denser hairs found on the head. The lice are best identified close to the skin, where their eggs are more numerous and more obvious. Diagnosis can be made by identifying the louse, or by plucking hairs and confirming the presence of its eggs or 'nits' by microscopic examination.

Tzanck smear

The Tzanck smear is an important diagnostic tool in the evaluation of blistering diseases. It is most commonly used to distinguish viral diseases, such as herpes simplex, varicella, and herpes zoster, from non-viral disorders (Fig. 1.9). It is important to note that Tzanck smears from vesicles of vaccinia and smallpox do not demonstrate multinucleated giant cells. The smear is obtained by removing the 'roof' of the blister with a curved scalpel blade or scissors, and scraping the base to obtain the moist, cloudy debris. The material is then spread onto a glass slide, air dried, and stained with Giemsa or Wright stain. The diagnostic finding of viral blisters is the multinucleated giant cell. The giant cell is a syncytium of epidermal cells, with multiple overlapping nuclei; it is much larger than other inflammatory cells. A giant cell may be mistaken for multiple epidermal cells piled on top of each other.

Wood light

Wood light is an ultraviolet source that emits at a wavelength of 365 nm. Formerly, its most common use was in screening patients with alopecia for tinea capitis, as the most common causative organisms, *Microsporum* (*M.*) *audouinii* and other *Microsporum* species, were easily identified by blue-green fluorescence under Wood light. However, today *Trichophyton tonsurans* is the most common fungus associated with tinea capitis, but it does not fluoresce. In the USA, fewer than 10% of cases are caused by *M. canis* and other *Microsporum* species. In Europe, Africa, and Asia, organisms that cause ectothrix scalp infection and which fluoresce include *M. ferrugineum*, *M. audouinii*, and *M. canis*.

Wood light is still of value in diagnosing a number of other diseases. Erythrasma is a superficial bacterial infection of moist skin in the groin, axilla, and toe webs. It appears as a brown or red flat plaque, and is caused by a *Corynebacterium* that excretes a pigment which contains a porphyrin. This pigment fluoresces coral red or pink under Wood light. Tinea versicolor, a superficial fungal infection with hypopigmented macules and plaques on the trunk, also fluoresces under Wood light with a green-yellow color. *Pseudomonas* infection of the toe web space and colonization of the skin in burn patients will fluoresce yellow-green. Patients with porphyria cutanea tarda excrete uroporphyrins in their urine, and examination of a urine specimen will show an orange-yellow fluorescence. Adequate blood levels of tetracycline produce yellow fluorescence in the opening of hair follicles, while lack of fluorescence indicates poor intestinal absorption or poor patient compliance. Positive fluorescence in the skin is diagnostically useful, but many of the pigments which fluoresce are water soluble and readily removed by swimming or bathing.

Wood light also emits purple light in the visible spectrum. This wavelength can be used to accentuate subtle changes in pigmentation. The purple light is absorbed by melanin in the epidermis, and variably reflected by patches of hypopigmentation and depigmentation. It can be helpful to distinguish increased pigmentation in the epidermis which will be enhanced by the purple light from increased pigmentation in the dermis which does not enhance. Purple light may be particularly useful in evaluating light-pigmented individuals with vitiligo or ash leaf macules (congenital hypopigmented macules).

DERMATOLOGIC THERAPEUTICS

General principles

Single component generic preparations are often effective and inexpensive. Fixed multiple component preparations are occasionally useful and may increase adherence to the treatment regimen, but the practitioner must be aware of all the constituent agents and the increased risk of adverse drug reactions. Specially formulated medications are often prohibitively expensive and seldom indicated in general practice.

The practitioner must calculate the quantity of medication required for the patient to comply with instructions. In a child, 15–30 g of an ointment is needed to cover the entire skin surface once. This quantity will vary with the vehicle used and the experience of the individual applying the preparation.

Topical vehicles

Two variables are particularly important in the selection of effective topical therapy: the active medication and the vehicle. No matter how effective the active medication, adherence to the recommended regimen will require that the clinician consider the selection of a vehicle carefully. In infants and young children, ointments tend to be better tolerated than other vehicles, while in older children, adolescents, and young adults, more elegant vehicles (e.g. creams, foams, sprays, solutions) that are free of lingering odors, color residues, or tackiness, will encourage adherence.

Ointments

In general, ointments are occlusive and allow for high transcutaneous penetration of the active drug. Ointments are stable for long periods and require few preservatives and bacteriostatic additives. As a consequence, they are least likely to cause contact allergy or irritation. These vehicles are well tolerated when the skin is cracked or fissured particularly in young children with chronic skin disease (e.g. atopic dermatitis, psoriasis). Unfortunately, ointments tend to be messy and may stain clothing, so they are not often welcome by older children and adolescents.

Open wet dressings

Open wet dressings, using tap water or normal saline, provide symptomatic relief by cooling and drying acute inflammatory lesions. They cleanse the skin by loosening exudates and crusts that can be painlessly removed before the dressing dries. Various astringents and antiseptics, such as vinegar or 5% aluminum acetate

solution (e.g. Burrow solution), may be added to compression solutions in a 1:20–40 dilution.

Powders and lotions

Powders promote drying and are especially useful in the intertriginous areas. Lotions are powders suspended in water (e.g. calamine lotion). When these preparations dry, they cool the skin and provide a uniform covering of the suspended agent. The clinician should warn patients and parents against the use of combination products that might result in irritation or percutaneous absorption of the active ingredients (e.g. calamine and diphenhydramine).

Gels

Gels are aqueous preparations that liquefy on contact with the skin and leave a uniform film on drying. Gels are well tolerated in hair-bearing areas. Water-based gels are best tolerated by children, while alcohol-containing products are more likely to cause burning or irritation. Gels are well tolerated in hair-bearing areas.

Aerosols

Aerosols and sprays act in a manner similar to lotions and gels. Active ingredients are incorporated into an aqueous phase. A convenient delivery system usually allows for easy dispersion over the skin surface. Aerosols are also particularly useful on the scalp.

Creams

Traditional creams are suspensions of oil in water. As the proportion of oil increases, the preparation approaches the consistency of an ointment, which is the most lubricating vehicle. Creams are water washable and hygroscopic. They may be drying and occasionally sensitizing.

Pastes

Pastes, which are mixtures of powder in ointment, are messy and may be difficult to remove from the skin. They are used to protect areas prone to irritation, such as the diaper area. Pastes can be removed with mineral oil.

Foams

Foams represent a novel vehicle, which enhances percutaneous absorption of medication in a cosmetically acceptable elegant preparation. Foams remain stable until applied to the skin where warming from natural body heat results in volatilization of inert contents with deposition of the active medication on the skin surface. Because foams contain minimal solid ingredients, there is little residue, making them particularly attractive vehicles for products designed for the scalp and intertriginous areas. A number of topical steroid foams have been approved for the treatment of atopic dermatitis and psoriasis while other agents have been approved for seborrheic dermatitis and ichthyosis.

Shampoos and washes

Short contact therapy with medicated shampoos and washes may also enhance adherence, particularly in adolescents with busy schedules and little time for topical therapy. These formulations contain insoluble particulate drugs such as benzoyl peroxide, salicylic acid, corticosteroids, and antifungal agents, some of which remain after showering or washing. Shampoos and washes may also be particularly useful when longer periods of contact are likely to result in burning or irritation.

Topical corticosteroids

Topical steroids are available in every type of vehicle. A good approach is to become familiar with one or two products in each of the potency ranges (Table 1.4). A check of local pharmacies is useful in determining the availability and cost of medications.

Most childhood skin eruptions requiring topical steroids can be readily managed with twice-daily applications of low- or medium-potency preparations. Moreover, a number of studies have shown that twice-daily applications of mid-potency agents can be applied to most areas of the skin in children for long periods of time safely. With few exceptions, low-potency medications should be used on the face and intertriginous areas, because more potent preparations may produce atrophy, telangiectasias, and hypopigmentation. Regardless of the potency of a medication, patients should be followed carefully for steroid-induced changes, even though they are only rarely produced by therapy restricted to 2–4 weeks. Patients receiving chronic therapy to sensitive areas should take frequent 'time-outs' from their topical steroids (e.g. 1 week per month) and should taper them when possible. Tapering may be achieved by decreasing the frequency of application as well as by mixing the active preparation with a bland emollient such as petrolatum.

Steroids may mask infections and suppress local and systemic immune responses. Consequently, they are contraindicated in most patients with viral, fungal, bacterial, or mycobacterial infections.

Topical calcineurin inhibitors

The new topical non-steroidal anti-inflammatory agents, pimecrolimus (Elidel) and tacrolimus (Protopic), provide an alternative for the treatment of atopic dermatitis. These calcineurin inhibitors selectively suppress the release of inflammatory mediators from lymphocytes without compromising the function of melanocytes, fibroblasts, or endothelial cells. As a consequence, they are not associated with the development of pigment alteration, atrophy, or telangiectasias. They can be applied at any site including the genital skin, breasts, and face. However, they are contraindicated in erythrodermic conditions where significant percutaneous absorption may occur.

The non-steroidal agents are approved for use in children over 2 years of age, but recent studies on a large number of patients from 3 months to 2 years old demonstrate safety and efficacy similar to older children.

A black box warning cautions prescribers and patients against using these agents in children under 2 years of age and long term in any patient. However, when used judiciously they offer a safe alternative to topical steroids particularly in sensitive areas of the skin. Before using these agents, it is imperative that the practitioner discuss the black box warning and the rationale for prescribing them.

Emollients (lubricants)

Any preparation that reduces friction and leaves a smooth, occlusive film that prevents drying is classified as a lubricant (Table 1.5). In patients with chronic dermatitis, ointments (or water-in-oil-based products) provide the best lubrication, especially during the dry winter months. Less oily preparations (oil-in-water creams, lotions, foams, aerosols) are often preferred by patients during the spring and summer. More elegant products should be considered in older children and young adults especially for use on the scalp or intertriginous areas. Cultural preferences should also be taken into account when selecting a lubricant. Preparations containing topical sensitizers such as fragrance, neomycin, and benzocaine should be avoided, particularly in patients with inflamed skin.

Sun protective agents

These agents (Table 1.6) include sunscreens (light-absorbing compounds) and sunblocks (inert compounds which reflect light). Although the long-awaited guidelines from the Food and Drug Administration have not yet been released, most experts recommend the use of broad-spectrum sun protective agents (protective

Topical corticosteroids					
	Generic name	**Trade name**		**Generic name**	**Trade name**
Super High Potency Topical Steroids – Class 1	Betamethasone dipropionate augmented 0.05%	Diprolene ointment 0.05%		Hydrocortisone probutate 0.1%	Pandel cream 0.1%
	Clobetasol propionate 0.05%	Clobex lotion, spray, shampoo 0.05%		Hydrocortisone valerate 0.2%	Westcort ointment 0.2%
		Cormax cream, solution 0.05%		Mometasone furoate 0.1%	Elocon cream, lotion 0.1%
		Dermovate 0.05%		Prednicarbate 0.1%	Dermatop ointment 0.1%
		Embeline E 0.05%		Triamcinolone acetonide 0.1%, 0.025%	Kenalog ointment 0.1%, 0.025%
		Olux E foam 0.05%, Olux foam 0.05%			
		Temovate cream, ointment, solution 0.05%	Topical Steroids – Class 5	Betamethasone dipropionate 0.05%	Diprosone lotion 0.05%
	Diflorasone diacetate 0.05%	ApexiCon E Cream 0.05%		Betamethasone valerate 0.1%	Valisone cream, lotion 0.1%
		Nerisone forte 0.3% (UK)			
	Fluocinonide 0.1%	Vanos cream 0.01%		Fluocinolone acetonide 0.025%	Synalar 0.025%, cream 0.01%
	Halobetasol propionate 0.05%	Ultravate cream, ointment 0.05%		Flurandrenolide 0.05%	Cordran cream, lotion 0.05%
High Potency Topical Steroids – Class 2	Amcinonide 0.1%	Cyclocort ointment 0.1%		Fluticasone propionate 0.05%	Cutivate cream, lotion 0.05%
	Desoximetasone 0.25%, 0.05%	Topicort cream, ointment 0.25%, gel 0.05%		Hydrocortisone butyrate 0.1%	Locoid Lipocream, ointment, lotion, solution 0.1%
	Diflorasone diacetate 0.05%	Apexi E cream 0.05%		Hydrocortisone valerate 0.2%	Westcort cream 0.2%
		Florone cream 0.05%		Prednicarbate 0.1%	Dermatop ointment, cream 0.1%
		Maxiflor ointment 0.05%		Triamcinolone acetonide 0.1%	Kenalog cream, lotion 0.1%
		Psorcon cream 0.05%, ointment 0.05%			
	Halcinonide 0.1%	Halog, Halog E ointment, cream 0.1%	Topical Steroids – Class 6	Alclometasone dipropionate 0.05%	Aclovate ointment, cream 0.05%
	Fluocinonide 0.05%	Lidex cream, ointment 0.05%			Modrasone ointment, cream 0.05%
		Metosyn cream, ointment 0.05%		Desonide 0.05%	DesOwen ointment, cream, lotion 0.05%
	Mometasone furoate 0.1%	Elocon ointment 0.1%			Desonate Gel 0.05%
Topical Steroids – Class 3	Amcinonide 0.1%	Cyclocort cream, lotion 0.01%			Tridesilon cream 0.05%
	Betamethasone dipropionate 0.05%	Diprosone cream 0.05%		Fluocinolone acetonide 0.01%	Synalar cream, solution 0.1%
					Derma-Smoothe/FS oil
	Betamethasone valerate 0.1%	Valisone ointment 0.1%			
		Betacap 0.1% (UK)	Topical Steroids – Class 7	Hydrocortisone 2.5%	Hytone cream, lotion 2.5%
	Clobetasone butyrate 0.05%	Eumovate ointment, cream 0.05% (UK)			Cobadex 1%
	Fluocinonide 0.05%	Lidex ointment, cream, gel 0.05%			Dioderm 0.1%
	Fluocinonide 0.05%	Cutivate ointment 0.05%			Mildison 1%
					Hydrocortisyl 1%
Topical Steroids – Class 4	Betamethasone valerate 0.12%	Luxiq foam 0.12%			Hytone ointment 1%
				Dexamethasone	Hexadrol cream 0.04%
	Clocortolone pivalate 0.1%	Cloderm cream 0.1%		Methylprednisolone acetate	Medrol ointment 0.25%
	Desoximetasone 0.05%	Topicort LP cream 0.05%		Prednisolone	Meti-derm cream 0.5%
	Fluocinolone acetonide 0.025	Synalar ointment 0.025%	Topical Steroids – Class 8	Hydrocortisone 0.5%	Cortoid cream 0.5%
	Flurandrenolide 0.05%	Cordran ointment, lotion, tape 0.05%			

Table 1.4 Topical corticosteroids

Emollients		
Types of skin	**Moisturizing base type**	**Product name**
1. Extremely dry skin	Ointment or oil-based	Bag Balm Blue Star ointment Elta Swiss skin cream Johnson's Baby Oil Palmer's Cocoa Butter Theraplex Emollient Vaseline Petroleum Jelly Mineral Oil A and D ointment Alpha Keri Moisture Rich Baby Oil Aquaphor Healing ointment
2. Dry	Water in oil emulsion	A and D ointment with Zinc Oxide Acid Mantle cream Elta Light moisturizing cream Eucerin Original moisturizing cream/lotion Jergens All Purpose Face Cream Olay Body lotion Restoraderm lotion St Ives Swiss Formula products Sween Cream Theraplex Clear lotion Vanicream Vaseline Intensive Care lotion
3. Normal to dry	Oil in water	Alpha Hydroxy cream/lotion Aqua Care cream Biore Balancing Moisturizer Normal to Dry Caress Body Silkening lotion Carmol 40 cream Complex 15 lotion Curel Moisturizing lotion Cutemol cream Gold Bond Moisturizing Body Lotion Jergens Original Scent lotion Keri lotion LactiCare lotion Lubriderm Skin Therapy Moisturel cream/lotion Neutrogena lotion Nivea Body Creamy Conditioning Oil Nutraderm lotion Olay Active Hydrating Original Cream Pacquin Plus skin cream Ponds Age Defying lotion/cream Purpose Alpha Hydroxy Moisture cream/lotion Sarna lotion
4. Normal to oily	Oil free	Carmol 10 Deep Moisturizing lotion CeraVe lotion or cream Cetaphil lotion or cream Corn Husker's lotion Epilyt lotion Gerber Baby Lotion Johnson's Baby Lotion Lubriderm Skin Therapy Neutrogen Combination Skin Moisture Olay Regenerist Facial Moisturizer Wallgreens Glycerin and Rosewater

Table 1.5 Emollients

Sun protection		
Sunlight type	**Ultraviolet spectrum (nm)**	**Sun protection agent**
Visible light	>400	Titanium dioxide Zinc oxide Iron Oxide
UVA	320–400	Butylmethoxy dibenzylmethane (avobenzone or Parsol 1789) Dioxybenzone (up to 350 nm) Titanium dioxide Zinc oxide Iron Oxide Mexoryl SX (290–400 nm) (available in Canada and Europe) Mexoryl XL (290–400 nm) (available in Europe) Micronized zinc oxide (290–380) Anthelios 40 (Helioblock SX-contains 3% ecamsule, 2% avobenzone, 10% octocrylene, 5% titani
UVB	290–320	PABA and PABA esters (para-aminobenzoic acid, padimate O) Benzophenones (oxybenzone, dioxybenzone, sulisobenzone) – full UVB protection Cinnamates (cinoxate, octylmethoxycinnamate, octocrylene) – full UVB protection Titanium dioxide Zinc oxide Iron oxide Methoxycinnamate
UVC	<290	Filtered out by ozone, does not reach the Earth's surface

Table 1.6 Sun protection

against both ultraviolet A and B light) with an SPF of at least 30. Parents should also be counseled to purchase products that are water resistant. See Chapter 7 Photodermatoses, for further discussion of these agents.

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USEFUL WEBSITES

DermAtlas: www.dermatlas.org
An interactive, user-friendly clinical and histologic dermatology atlas and atlas of physical findings, edited by Dr Bernard Cohen (Pediatrics and Dermatology) and Dr Christoph Lehmann (Medical Informatics and Neonatology), Johns Hopkins University School of Medicine
www.dermnetnz.org
A good resource for skin diseases, conditions, and treatments
www.emedicine.com
General medical reference with data from a number of medical texts
www.ncbi.nlm.nih.gov
National Center for Biotechnology
www.ncbi.nlm.nih.gov/omim
OMIN Online Mendelian Inheritance in Man: a Johns Hopkins University initiated database that catalogs human genes and genetic disorders
www.ncbi.nlm.nih.gov/pubmed
PubMed: National Library of Medicine reference journal database

Chapter 2

Neonatal Dermatology

Katherine B. Püttgen and Bernard A. Cohen

INTRODUCTION

The skin of the newborn differs from that of the adult in several ways (Table 2.1). It is less hairy, has less sweat and sebaceous gland secretions, is thinner, has fewer intercellular attachments, and fewer melanosomes. These differences are magnified in the preterm neonate. As a consequence, newborns are not as well equipped to handle thermal stress and sunlight, have increased transepidermal water loss and penetration of toxic substances and medications, and are more likely to develop blisters or erosions in response to heat, chemical irritants, mechanical trauma, and inflammatory skin conditions. An algorithmic approach to diagnosis for neonatal dermatology is summarized at the end of the chapter (see below, Fig. 2.95).

BARRIER PROPERTIES AND USE OF TOPICAL AGENTS

The barrier properties of the skin reside primarily in the stratum corneum, the compact layer of flattened keratinocytes that cover the surface. Although keratinization begins at 24 weeks, it is not complete until close to term. Transepidermal water loss and drug absorption through the epidermis at term are similar to those in older children and adults. Skin barrier properties in babies of gestational age 36 weeks, approximate those of term infants within several days, but may be delayed by 14–21 days in children of gestational age less than 32–34 weeks. Barrier maturation may be further delayed when epidermal injury, inflammation, or hyperemia are present. Sepsis, ischemia, and acidosis in the severely ill newborn may also compromise barrier function. Moreover, even in healthy term infants, the increased surface-to-volume ratio compared with older children and adults may result in relatively high transcutaneous penetration of topical agents.

Percutaneous absorption of toxic substances in newborns, particularly preterm infants and term infants with disruption of barrier function, has been well documented. Aniline dyes used to mark diapers have caused methemoglobinemia and death. Topical corticosteroids may produce adrenal suppression and systemic effects. Vacuolar encephalopathy has been demonstrated in infants bathed with hexachlorophene, particularly premature infants exposed repeatedly.

Structural and functional differences of adult, term, and preterm infant skin

	Adult	Term	Preterm (30 weeks)	Significance
Epidermal thickness	50 μm	50 μm	27.4 μm	Permeability to topical agents ↑ Transepidermal water loss
Cell attachments (desmosome, hemidesmosome)	Normal	Normal	Fewer	↑ Tendency to blister
Dermis	Normal	↓ Collagen and elastic fibers	↓↓ Collagen and elastic fibers	↓ Elasticity ↑ Blistering
Melanosomes	Normal	Fewer Delayed activity for 1–7 days	One-third term infant	↑ Photosensitivity
Eccrine glands	Normal	↓ Neurologic control for 2–3 years	Total anhidrosis	↓ Response to thermal stress
Sebaceous glands	Normal	Normal	Normal	Barrier properties? Lubricant? Antibacterial?
Hair	Normal	↓ Terminal hair	Persistent lanugo	Helpful in assessing gestational age

Table 2.1 Structural and functional differences of adult, term, and preterm infant skin



Fig 2.1 Vernix caseosa covered the skin surface of this healthy newborn at delivery.

Pentachlorophenol poisoning occurred in 20 infants who were accidentally exposed to this chemical in nursery linens. Topical application of povidone-iodine to the perineum before delivery and the umbilical cord after delivery has resulted in elevated plasma iodine levels and thyroid dysfunction in the neonate. Other substances, which include isopropyl alcohol, ethyl and methyl alcohol, and chlorhexidine, are readily absorbed and may produce toxic reactions.

In general, topical agents should be used in newborns and infants only if systemic administration of the agent is not associated with toxicity. Antiseptic agents must be used only with great caution and to limited areas of the skin, particularly in premature infants under 30 weeks' gestational age during the first several weeks of life. Injuries to the skin induced by tape, monitors, adhesives, and cleansing agents must be kept to a minimum, as these tend to compromise barrier function. When lubrication is necessary, small amounts of petrolatum or other fragrance-free, bland emollients are adequate. Some investigators advocate the routine use of barrier products (petrolatum, Eucerin cream, Aquaphor) in tiny, premature infants to reduce heat and insensible water loss. Bubble blankets and humidified air also help to minimize energy requirements.

At birth, the skin is covered with a greasy white material of pH 6.7–7.4 (Fig. 2.1). Although the function of this vernix caseosa is unknown, it may have lubricating and antibacterial properties. Beneath the vernix, the skin has a pH of 5.5–6.0. Overwashing of the baby, particularly with harsh soaps, may result in irritation, alkaline pH, and a decrease in normal barrier function of the stratum corneum. As a consequence, bathing is done gently several times a week with tap water, and mild soaps are restricted to areas in which cutaneous bacteria are most numerous, such as the umbilicus, diaper area, neck, and axillae. In ill newborns, bathing may be limited to saline compresses of areas of irritated, macerated skin, which occur commonly in intertriginous areas.

Thermoregulation

Cold stress is the major risk to naked preterm infants nursed in a dry incubator. Decreased epidermal and dermal thicknesses result in increased heat loss from radiation and conduction. Minimal subcutaneous fat and an immature nervous system also decrease the premature infant's ability to respond to cooling. Although heat loss may be minimized by increasing ambient humidity and temperature and by covering the child with a plastic bubble, increasing postnatal age and weight approaching 2000 g are associated with maintenance of normal body temperature.

In growing premature and full-term infants hyperthermia may be a problem in warm climates, particularly when additional thermal stresses such as insulated clothing and phototherapy are present. Although sweat glands are anatomically complete at 28 weeks' gestation, they may not be fully functional until several weeks after delivery, even in the full-term neonate. At birth, sweating has been demonstrated in response to thermal stress in term babies. However, it may not be detectable in infants under 35 weeks' gestational age for several weeks. Consequently, sweating may not be an effective mechanism for thermoregulation in term or premature infants for at least several weeks, so thermal stress must be minimized.

Pigmentation and photoprotection

Although melanocytes are actively synthesizing and transferring pigment to epidermal keratinocytes by 20–24 weeks of intrauterine life, the skin surface tends to be less pigmented during the first few postnatal months than in later childhood. As a consequence, infants have less natural protection from sunlight and are more likely to develop sunburn.

Several investigators have expressed concern about using sunscreens in children under 6 months of age. However, as these infants are not ambulatory, sun avoidance and protective clothing are effective barriers to excessive sun exposure. If, however, sun exposure cannot be strictly avoided it is likely best to use a sunscreen that is fragrance free and which contains the physical sun block ingredients zinc oxide or titanium dioxide.

Certain children are particularly sensitive to sunlight, and for these prolonged sun avoidance beyond infancy and aggressive use of sunscreens may be mandatory (see Chapter 7, pp. 193–196). Hereditary porphyrias, xeroderma pigmentosum, Bloom syndrome, Cockayne syndrome, and a number of other photosensitivity disorders may present with exaggerated sunburn reactions in infancy. In some infants, tingling and burning of the skin may occur after sun exposure with no obvious physical findings. In neonatal lupus erythematosus the skin rash is often triggered by sun exposure. Although some of these children benefit from broad-spectrum sunscreens or sunscreens with sun protective factors above 30, photoreactions may be caused by wavelengths of light that are not absorbed by currently available sunscreens. A number of new products achieve broad-spectrum coverage and high sun protection factors by incorporating new cosmetically elegant formulations of inert physical blocking agents such as zinc oxide and titanium dioxide.

CUTANEOUS COMPLICATIONS OF THE INTENSIVE CARE NURSERY

Scars and burns are inevitable complications of nursery care and monitoring. Careful management of the skin in the nursery and after discharge minimizes the risk of serious functional impairment and cosmetic disfigurement.

Surgical scars

Wounds from subclavian and jugular venous lines generally heal with barely noticeable scars. Occasionally, scars are more obvious, but usually they fade over the first 2 years of life, particularly if the wounds conform to the normal skin lines. However, dimpling may result from sutures used to keep the lines in place (Fig. 2.2). Scarring and dimpling may also be minimized by gentle massage of the area.

Frequently, chest tubes are placed in emergencies with little time taken to consider optimal site selection. Unnecessary scars or injury

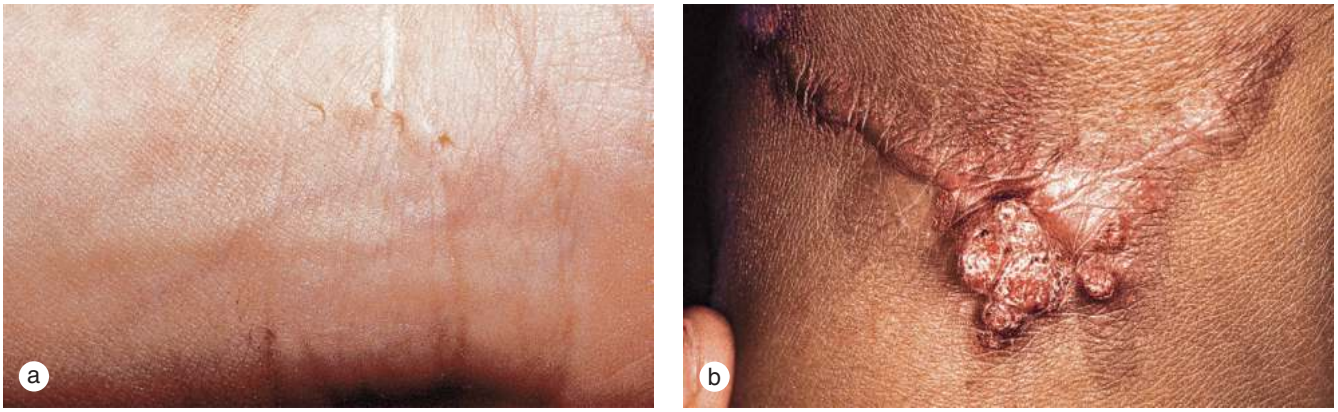


Fig 2.2 Effect of surgical scars. **(a)** Scar from an arterial cut down site. Recurrent drainage ended after a small fistulous tract in the scar was excised from the wrist of this 2-year-old girl. **(b)** This 6-year-old girl has a hypertrophic scar in the right antecubital space. She developed prurigo nodules in the center of the scar from chronic scratching.

to sensitive breast tissue may result in later surgical repair. Lateral placement beyond the breast tissue may eliminate the need for later surgery. Gentle massage after removal may prevent the formation of adhesions and dimpling. As with other surgical scars, these lesions tend to improve spontaneously over the first several years of life.

Arterial catheters

In addition to local scarring, arterial catheters may be associated with serious systemic and cutaneous complications in the areas distal to their placement. Extensive ischemia and necrosis of the genital and buttock skin is an unusual complication of umbilical artery spasm and thromboembolism. Ensuing ulcerations may take months to heal and require surgical repair (Fig. 2.3). Radial artery catheters have rarely been associated with the necrosis of digits. However, more subtle findings, such as discrepancies in hand size, may not be evident for a year.



Fig 2.3 Several hours after an umbilical artery catheter was removed from this infant a purple area developed unilaterally on the scrotum, perineum, and perirectal skin. After 1 day, the area became ulcerated. Note the formation of granulation tissue and early scarring 1 week later.

Chemical and thermal burns

Infiltration of the soft tissues by intravenous fluids often produces cutaneous inflammation and necrosis. Hypertonic fluids, such as glucose and calcium, may result in full-thickness sloughing of the skin and in contractures (Fig. 2.4). These lesions usually heal over weeks to months and may require splinting, physical therapy, and surgical repair, particularly if they are located over joints.

Removal of adhesives used with dressings, of endotracheal and nasotracheal tubes, and of monitor leads results in extensive trauma to the skin (Fig. 2.5). Although full-thickness sloughs may rarely develop, postinflammatory hyperpigmentation and hypopigmentation are common. Pigmentary changes may persist for years, particularly in dark-pigmented individuals, but usually

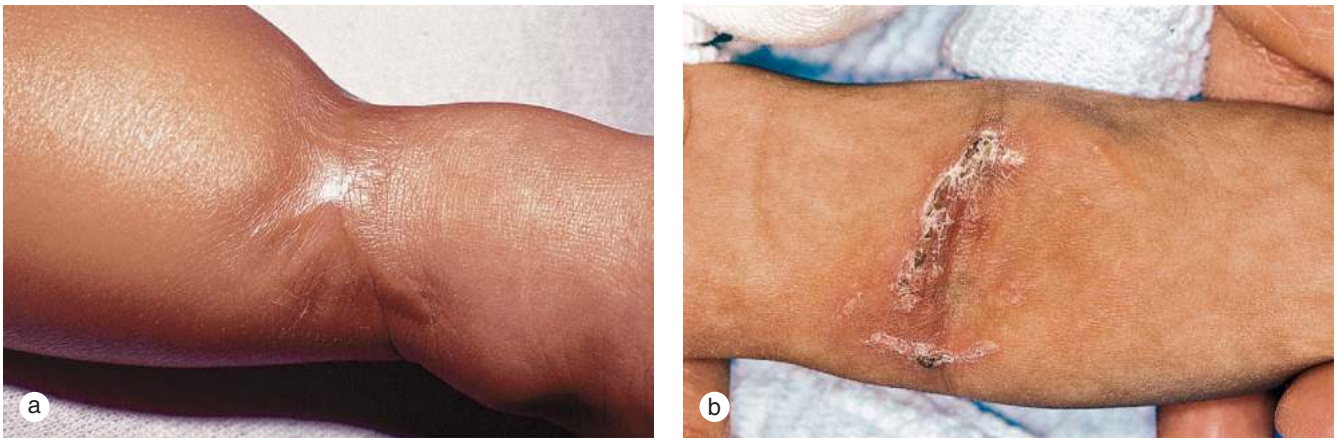


Fig 2.4 (a) Infiltration of the antecubital skin with 20% glucose resulted in an ulcer that healed with severe scarring. The scar was surgically revised at 4 years of age. **(b)** Infiltration of calcium resulted in a painful red patch which healed with an annular red calcified plaque.



Fig 2.5 Repeated trauma from removal of monitor leads produced a round, atrophic patch on the lower abdominal wall of this 29-week premature infant. Note the wrinkling of the skin, prominent vessels, and purpura (which was present before a biopsy was taken).

fade markedly within the first year of life. Other topical agents, such as iodophors, soaps, detergents, and solvents, may produce severe irritant reactions, particularly in premature infants or children with an antecedent cutaneous injury (Fig. 2.6).

Accidental thermal burns have been reported following exposure to heated water beds, radiant warmers, transcutaneous oxygen monitors, and heated, humidified air. Although cold stress must be minimized in the small premature infant, extensive burns that have cutaneous and airway involvement may be prevented by close monitoring of these devices.

Heel-stick nodules

Repeated blood sampling from the heel leads to the formation of papules and nodules in many graduates of the neonatal intensive care unit (Fig. 2.7a). Although the most prominent lesions occur in children who have had frequent heel sticks, these scars are also detected in infants who have had only a few. Lesions may be palpable at the time of discharge from the nursery. Over a period of several months, they generally become more superficial and resemble milia. Papules typically calcify over the ensuing months and

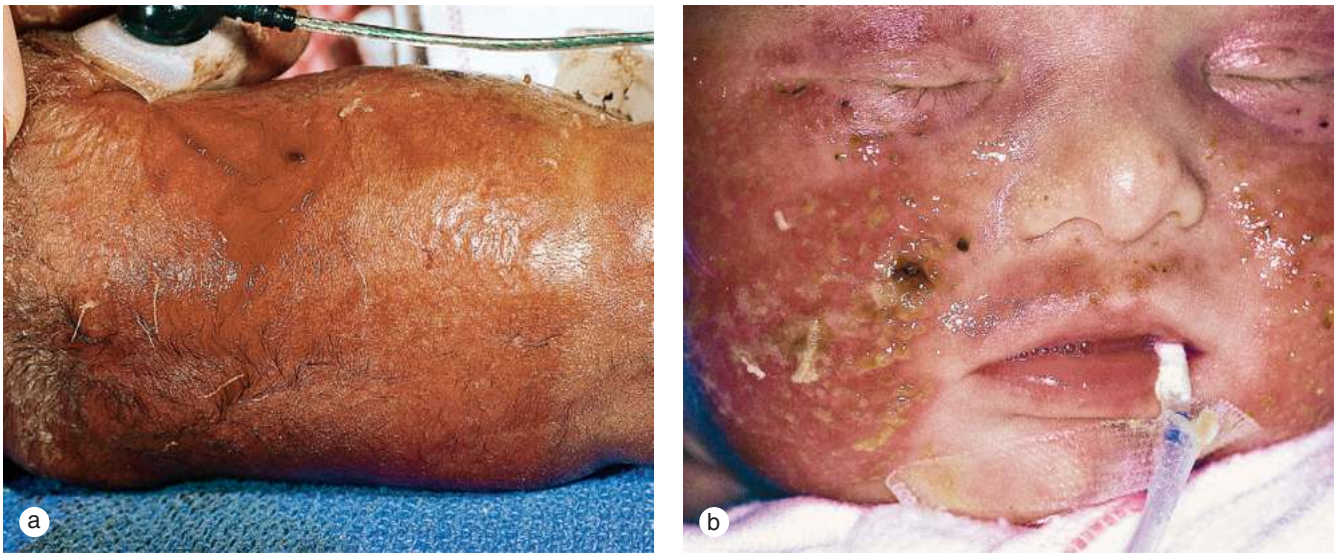


Fig 2.6 Severe irritant reactions. **(a)** Application of a solution containing topical iodophor produced an erosive irritant dermatitis on the flank of a premature infant in the intensive care nursery. Fortunately, this area healed with only minimal scarring. **(b)** A chemical burn resulted from a solvent that was applied to this child's face to remove adhesive tape.

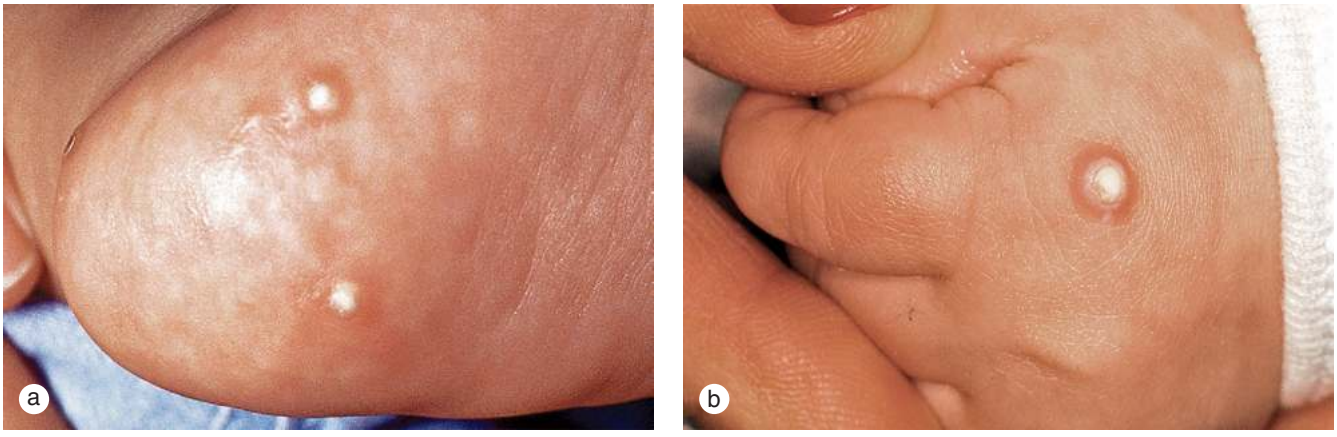


Fig 2.7 Calcinosis cutis. **(a)** Heel-stick papules developed at 3 months of age on the feet of this graduate of the intensive care nursery. They cleared 9 months later without treatment. **(b)** This calcified nodule was present on the hand of a healthy newborn at birth.



Fig 2.8 Cutis marmorata. The diffuse, reticulated erythema disappeared with warming of this newborn.

resolve spontaneously in 18–30 months. During this time most infants are asymptomatic, and walking is not delayed.

Similar lesions occur from injuries at other sites (Fig. 2.7b). Isolated calcified nodules (calcinosis cutis) may be present at birth, and probably result from incidental intrauterine trauma to the skin. They are most common on the face and extremities.

TRANSIENT ERUPTIONS OF THE NEWBORN

A number of innocent rashes occur in infants. Although they are usually transient, they may be very dramatic and a major source of parental anxiety. Early recognition is important to differentiate these lesions from more serious disorders and to provide appropriate counseling to parents.

Transient vascular phenomena

During the first 2–4 weeks of life, cold stress may be associated with acrocyanosis and cutis marmorata (Fig. 2.8). In acrocyanosis, the hands and feet become variably and symmetrically blue in color without edema or other cutaneous changes. Cutis marmorata is identified by the characteristic reticulated cyanosis or marbling of the skin, which symmetrically involves the trunk and extremities. Both patterns usually resolve with warming of the skin, and recurrence is unusual after 1 month of age. Acrocyanosis is readily differentiated from persistent central cyanosis (cyanosis of the lips, face, and/or trunk), which occurs in association with pulmonary or cardiac disease. Cutis marmorata that persists beyond the neonatal period may be a marker for trisomy 18, Down syndrome, Cornelia de Lange syndrome, hypothyroidism, or other causes of central nervous system-induced neurovascular dysfunction.

Cutis marmorata telangiectatica congenita (CMTC) or congenital phlebectasia (Fig. 2.9) may mimic cutis marmorata. However, the lesions are persistent in a localized patch on the trunk or extremities. Location on the legs is most common, followed by truncal involvement. The eruption may extend in a Blaschkoid pattern, and occasionally widespread lesions and reticulated cutaneous atrophy are present. Although CMTC may be an isolated cutaneous finding, it may also occur in association with other mesodermal and neuroectodermal anomalies; reports of associated anomalies range from 20% to 70% of cases. Hypotrophy or hypertrophy of the affected site may occur.

The harlequin color change is noted when the infant lies horizontally and the dependent half of the body turns bright red in contrast to the pale upper half (Fig. 2.10). The color shifts when the infant is rolled from side to side. This phenomenon lasts from seconds to 20 min, and recurrences are common until 3–4 weeks of life. The cause is unknown, and it is not associated with serious underlying disease.

Benign pustular dermatoses

Several innocent pustular eruptions must be differentiated from potentially serious infectious dermatoses.

Erythema toxicum neonatorum

Erythema toxicum neonatorum (ETN) is the most common pustular rash; it occurs in up to 70% of full-term infants (Fig. 2.11). Although lesions usually appear on the second or third day of life, onset has been reported up to 2–3 weeks of age. Typically, ETN



Fig 2.9 Cutis marmorata telangiectatica congenita. **(a)** An otherwise healthy infant with extensive CMTC affecting the right arm, trunk and leg with sharp midline cutoff. **(b)** The right leg of an affected infant demonstrating extensive marbling and some atrophy. (a, Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure. b, Reprinted with permission from Bernard A. Cohen© DermAtlas, Johns Hopkins University; 2000–2012.)

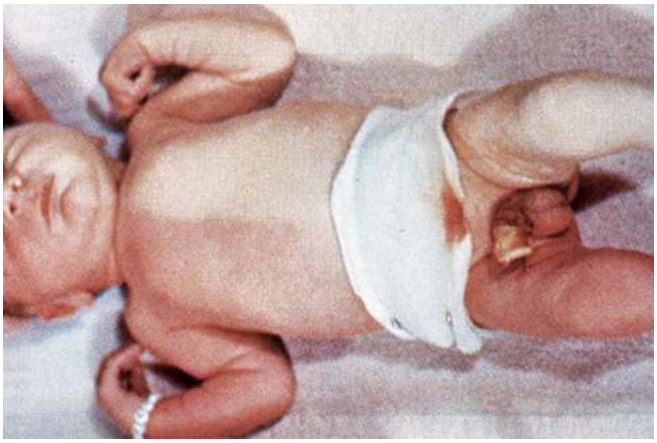


Fig 2.10 The dependent side is bright red in this infant with the harlequin color change.

begins with 2–3 mm diameter erythematous, blotchy macules and papules, which may evolve over several hours into pustules on a broad erythematous base to give affected infants a 'flea-bitten' appearance. Lesions may be isolated or clustered on the face, trunk, and proximal extremities, and usually fade over 5–7 days. Recurrences, however, may occur for several weeks. A Wright stain of the pustule contents reveals sheets of eosinophils and occasional neutrophils, and 15–20% of patients have a circulating eosinophilia.

Transient neonatal pustular melanosis

Transient neonatal pustular melanosis (TNPM) occurs in 4% of newborns, particularly in black male infants (Fig. 2.12). Unlike ETN, lesions are usually present at birth and probably evolve in many children prenatally. Characteristically, TNPM appears as 2–5 mm diameter pustules on a non-erythematous base on the chin, neck, upper chest, sacrum, abdomen, and thighs. Over several days, lesions develop a central crust, which desquamates to leave a hyperpigmented macule with a collarette of fine scale. Lesions at different stages of development may be present simultaneously.



Fig 2.11 Erythema toxicum neonatorum. Numerous yellow papules and pustules are surrounded by large, intensely erythematous rings on the trunk of this infant.

Often the only manifestation of the eruption is the presence of brown macules with a rim of scale at birth. However, in light complected newborns, little or no hyperpigmentation remains. A Wright stain of the pustular smear shows numerous neutrophils and rare eosinophils.

Acropustulosis of infancy

Acropustulosis of infancy is a chronic, recurrent pustular eruption that appears on the palms and soles, but may also involve the scalp, trunk, buttocks, and extremities (Fig. 2.13). Onset may occur during the newborn period or in early infancy, and episodes typically last 1–3 weeks with intervening remissions of 1–3 weeks. Disease-free periods tend to lengthen until the rash resolves by 2–3 years of age. During flares infants are usually fussy and pruritus is severe.

Although the cause is unknown, in some infants scabies infestation may precede the onset of the eruption. Histopathology of the lesions reveals sterile, intraepidermal pustules. A Wright stain shows numerous neutrophils and occasional eosinophils. Although oral dapsone (1–3 mg/kg per day) suppresses lesions and symptoms in 24–48 h, brief courses of moderate- to high-potency topical corticosteroids to the palms and soles may provide safe temporary relief.

Eosinophilic pustular folliculitis

Eosinophilic pustular folliculitis (EPF), or Ofuji disease, is a rare, self-limiting vesiculopustular eruption of infancy characterized by recurrent episodes of 2–3 mm diameter follicular white vesicles and pustules on a red base on the scalp and forehead (Fig. 2.14). Occasionally, lesions spread to the trunk. It occurs almost exclusively in boys of age 5–10 months and can recur for months to years. Several neonatal cases have also been described. Although affected infants experience intense pruritus and irritability, EPF is not associated with systemic disease, and treatment is symptomatic. Wright stain preparations of material from pustules show large numbers of eosinophils, but no evidence of bacterial, fungal, or viral organisms. The strong association of EPF with human immunodeficiency virus infection seen in adults has not been noted in infants. EPF may be an early presenting feature in cases of hyper IgE syndrome. The clinical findings and course may overlap with some cases of ETN and acropustulosis of infancy. Reported treatments include topical corticosteroids, oral erythromycin, dapsone, colchicine, indometacin, and cyclosporine.

Other papulopustular rashes

Benign pustular dermatoses can be differentiated from herpes simplex infection by the absence of multinucleated giant cells on Wright-stained smears of pustular contents. Negative Gram-stain and potassium hydroxide preparations exclude bacterial and candidal infection. However, in seriously ill infants viral and bacterial cultures may be required to confirm the clinical impression. Serologic studies for syphilis and scrapings for ectoparasites exclude syphilis and scabies in children with acropustulosis.

The benign pustular dermatoses may also be confused with several other innocent papulopustular rashes, which include sebaceous gland hyperplasia, miliaria, milia, and acne.

Sebaceous gland hyperplasia

Sebaceous gland hyperplasia is a common finding over the nose and cheeks of term infants (Fig. 2.15). Lesions consist of multiple 1–2 mm diameter yellow papules that result from maternal or endogenous androgenic stimulation of sebaceous gland growth. Parents are counseled that the eruption resolves within 4–6 months.

Miliaria

Miliaria results from obstruction to the flow of sweat and rupture of the eccrine sweat duct. In miliaria crystallina, superficial,



Fig 2.12 Transient neonatal pustular melanosis. **(a)** Numerous tiny pustules dot the forehead and scalp of this light-pigmented neonate. **(b)** Healing pustules leave marked hyperpigmentation and scale on the chin of this dark-pigmented baby. **(c)** Dry, hyperpigmented crusts cover the back of this Asian newborn. **(d)** Healing pustules and brown macules dot the lower back and sacrum of this child at birth. Note the Mongolian spot on his gluteal cleft.



Fig 2.13 Acropustulosis of infancy. Multiple 2–3 mm pustules covered the hands and feet of this otherwise healthy infant. Lesions recurred episodically until this child was 3 years old. (Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure.)



Fig 2.14 Pruritic vesicles and pustules recurred on the scalp of a healthy 5-month-old boy for over a year. Histologic findings revealed eosinophilic folliculitis.



Fig 2.15 Sebaceous gland hyperplasia. Note the yellow papules on the nose, forehead, and cheeks of this healthy newborn who also had a nodule that demonstrated the typical changes of Langerhans cell histiocytosis on histopathology. He had no evidence of systemic disease, and the nodule resolved without treatment over the 1st month of life.

1–2 mm diameter vesicles appear on non-inflamed skin when the duct is blocked by keratinous debris just beneath the stratum corneum (Fig. 2.16). Small papules and pustules are typical of miliaria rubra (prickly heat), in which the obstruction occurs in the mid epidermis (Fig. 2.17). Deep-seated papulopustular lesions of miliaria profunda occur only rarely in infancy, when the duct ruptures at the dermal–epidermal junction.

Miliaria occurs frequently in term and preterm infants after the first week of life in response to thermal stress. Lesions erupt in crops in the intertriginous areas, scalp, face, and trunk. In older infants, lesions appear most commonly in areas of skin occluded by tight-fitting clothing. Cooling the skin and loosening clothing results in prompt resolution of the rash.

Milia

Milia appear as pearly, yellow, 1–3 mm diameter papules on the face, chin, and forehead of 50% of newborns (Fig. 2.18a). Occasionally, they erupt on the trunk and extremities (Fig. 2.18b). Although milia usually resolve during the first month of life without treatment, they may persist for several months. Histology



Fig 2.16 Miliaria crystallina. Tiny, thin-walled vesicles quickly desquamated when this child was placed in a cooler environment. (Reprinted with permission from Bernard A. Cohen© DermAtlas, Johns Hopkins University; 2000–2012.)



Fig 2.17 Miliaria rubra. The red papules of prickly heat are readily visible on this infant.

demonstrates miniature epidermal inclusion cysts that arise from the pilosebaceous apparatus of vellus hairs. Large numbers of lesions distributed over a wide area or persistence beyond several months of age suggest the possibility of the oral-facial-digital syndrome (Fig. 2.18c) or hereditary trichodysplasia (Marie Unna hypotrichosis). Increasing numbers of lesions, particularly in areas of normal trauma such as the hands, knees, and feet, may occur in patients with mild variants of scarring epidermolysis bullosa where blistering is subtle.

Neonatal acne

Mild acne develops in up to 20% of newborns with an average onset at 3 weeks of age. Lesions may be present at birth or appear in early infancy. Inflammatory red papules and pustules predominate and cysts may rarely occur. Absence of typical comedones distinguishes this condition from adolescent acne (Fig. 2.19). While neonatal acne was once thought to be due to androgen stimulation of sebaceous glands by maternal hormones, most now favor the term neonatal cephalic pustulosis, to highlight that this condition in neonates is unlikely to be true acne. It has been suggested that colonization of the skin with *Malassezia* spp. causes an inflammatory reaction, though a direct correlation between burden and *Malassezia* and disease severity has been questioned.

Treatment is usually unnecessary as lesions involute spontaneously within 1–3 months. However topical acne preparations can be used with minimal risk in persistent or severe cases. Use of ketoconazole cream may also be of help. Risk of acne in adolescence does not seem to be increased.

Infantile acne

Occasionally, the onset of acne is delayed until 3–6 months of age when it is referred to as infantile acne and is more common in boys. Lesions tend to be more pleomorphic and inflammatory papules and pustules are common. Although infantile acne usually resolves by 3 years of age, lesions may rarely persist until puberty. Unlike neonatal acne, infantile acne is probably triggered by endogenous androgens and open and closed comedones are seen. Children with early-onset, persistent disease, and a positive family history of severe acne tend to have a more severe course with resurgence at puberty. Severe infantile acne should prompt a search for other signs of hyperandrogenism and an abnormal endogenous or exogenous source of androgens.

Subcutaneous fat necrosis of the newborn

Fat necrosis is a rare, self-limited process that usually occurs in otherwise healthy full-term and post-mature infants (Fig. 2.20).

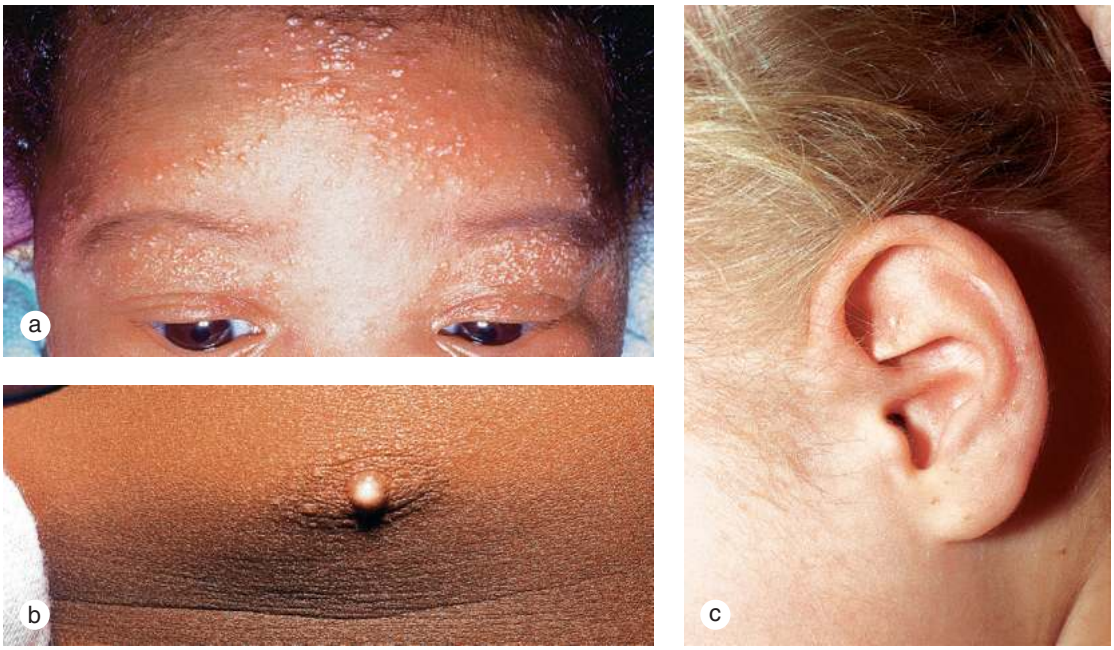


Fig 2.18 Milia. **(a)** Widespread milia were noted on the forehead and eyelids of this vigorous newborn. The white papules resolved spontaneously before the 2-month pediatric check-up. **(b)** The milium on this infant's nipple also cleared without treatment. **(c)** Multiple congenital persistent milia on the sides of the cheeks and ears of this toddler were an early marker of oral-facial-digital syndrome.

It has been reported to occur after total body cooling for treatment of hypoxic ischemic encephalopathy. Discrete firm red or hemorrhagic nodules and plaques up to 3 cm in diameter appear most commonly over areas exposed to trauma, such as the cheeks, back, buttocks, arms, and thighs, during the first few weeks of life. Lesions are usually painless, but marked tenderness may be present. Although the cause is unknown, difficult deliveries, hypothermia, perinatal asphyxia, and maternal diabetes predispose to the development of fat necrosis, suggesting a role for mechanical, cold, and hypoxic injury to fat.

Nodules usually resolve without scarring in 1–2 months. However, lesions occasionally become fluctuant, drain, and heal with atrophy. Variable amounts of calcification develop and can be appreciated radiographically. Even in uncomplicated cases and occasionally after the lesions have resolved, hypercalcemia can develop 1–4 months after the initial detection of subcutaneous fat necrosis. Infants may present with nephrocalcinosis, poor weight gain, irritability, and seizures. Consequently, calcium should be monitored for the first 4–6 months of life in these infants at an interval of every 2–4 weeks. More rarely, thrombocytopenia, hyperlipidemia, and hyperglycemia may also occur.

Histopathology demonstrates necrosis of fat with a foreign body giant cell reaction. Remaining fat cells contain needle-shaped clefts, and calcium deposits are scattered throughout the subcutis. Occasionally, early lesions of sclerema neonatorum are confused with subcutaneous fat necrosis. However, in a severely



Fig 2.19 Neonatal acne. **(a)** Red papules and pustules covered the face of this 4-week-old boy. **(b)** Acne spread to the trunk of this healthy infant. In both children the eruption cleared by 4 months of age.

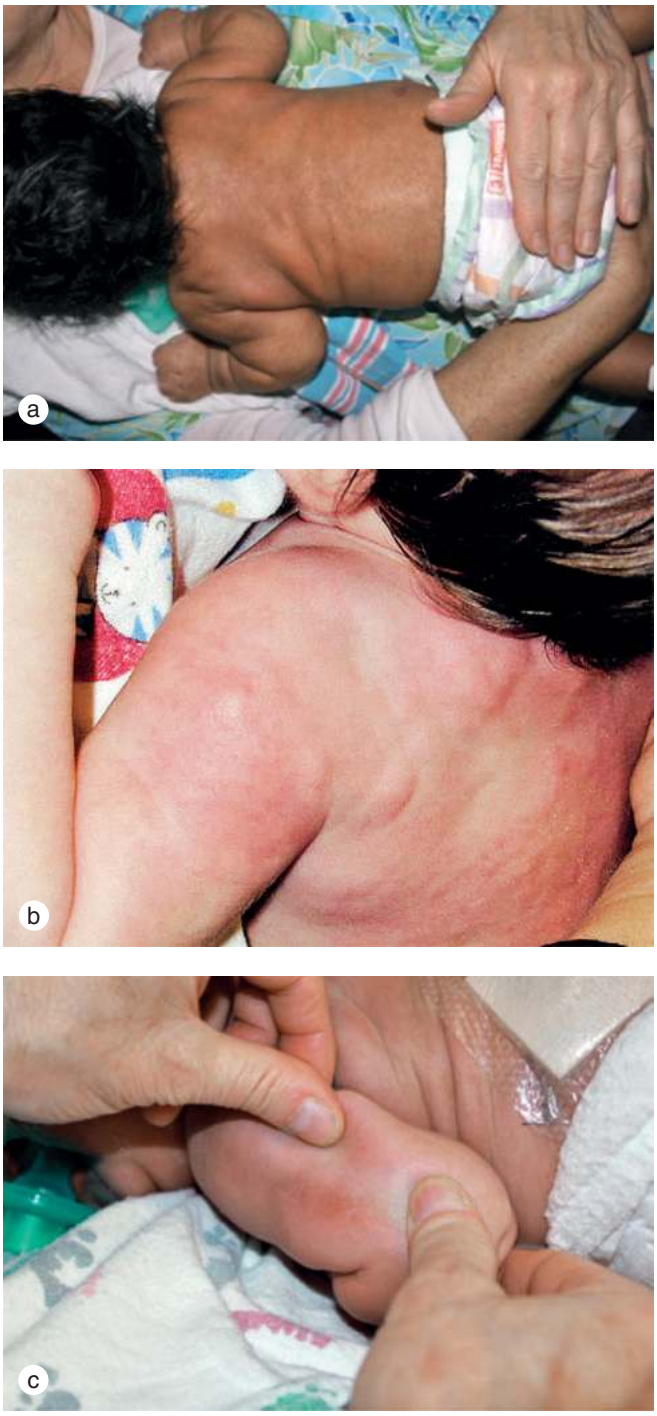


Fig 2.20 Subcutaneous fat necrosis. **(a)** Red nodules are evident on the back of this neonate. **(b)** Multiple nodules covered the upper back of this newborn who developed hypercalcemia at 3 months of age as the lesions were resolving. **(c)** A deep reddish nodule on the left upper arm best appreciated on palpation. (a, Reprinted with permission from Bernard A. Cohen© DermAtlas, Johns Hopkins University; 2000–2012. c, Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure.)

ill newborn, sclerema is usually differentiated from fat necrosis by the presence of diffuse, wax-like hardening of the skin. Unlike subcutaneous fat necrosis, skin biopsy shows only minimal inflammation in the fat. Thickening of the skin occurs from the increased size of fat cells and interlacing bundles of collagen in the dermis and subcutis.

MINOR ANOMALIES

Minor anomalies occur in up to half of all newborns and are of no physiologic consequence. Their presence, particularly in association with other minor anomalies, prompts an evaluation for more serious multisystem disease.

Dimpling

Dimpling is a common finding over bony prominences, particularly the sacral area (Fig. 2.21a–c). Although skin dimples may be the first sign of several dysmorphic syndromes, these lesions are usually of only cosmetic consequence (Fig. 2.21d). Spinal anomalies should be excluded when deep dimples, sinus tracts, or other cutaneous lesions (such as lipomas, hemangiomas, nevi, and tufts of hair) involve the lumbosacral spine. This area is readily visualized by ultrasound during the first 8–12 weeks of life; after this time ultrasound may suffice but magnetic resonance imaging (MRI), which requires sedation, is typically necessary to obtain a clear view of the area of interest to exclude malformations.

Periauricular sinuses, pits, tags, and cysts

Periauricular sinuses, pits, tags, and cysts occur when brachial arches or clefts fail to fuse or close normally (Fig. 2.22). These lesions develop along a line from the preauricular area to the corner of the mouth. Defects may be unilateral or bilateral and are occasionally associated with other facial anomalies and rarely more complex malformation syndromes such as Goldenhar (oculoauriculovertebral) syndrome or branchio-oto-renal syndrome. Although occult lesions may be discovered when they present with secondary infection, many of these anomalies are noted at birth and readily excised during childhood.

Supernumerary digits

Supernumerary digits appear most commonly as rudimentary structures at the base of the ulnar side of the fifth finger (Fig. 2.23). They are usually familial and asymptomatic. Histology demonstrates bundles of peripheral nerves extending in various directions and sharply demarcated from dermal connective tissue. A good cosmetic result is best achieved by local surgical excision.

Supernumerary nipples

Supernumerary nipples may appear unilaterally or bilaterally anywhere along a line from the mid-axilla to the inguinal area (Fig. 2.24) and may develop without areolae, which results in their misdiagnosis as congenital nevi. Malignant degeneration rarely occurs, and many are excised for cosmetic purposes. Some studies have demonstrated a relationship between accessory nipples and renal or urogenital anomalies, while other investigators have found no association. Ultrasound should be considered if clinical concern or physical findings warrant further evaluation.

Umbilical granulomas

Umbilical granulomas occur commonly during the first few weeks of life. Normally, the cord dries and separates in 7–14 days. The

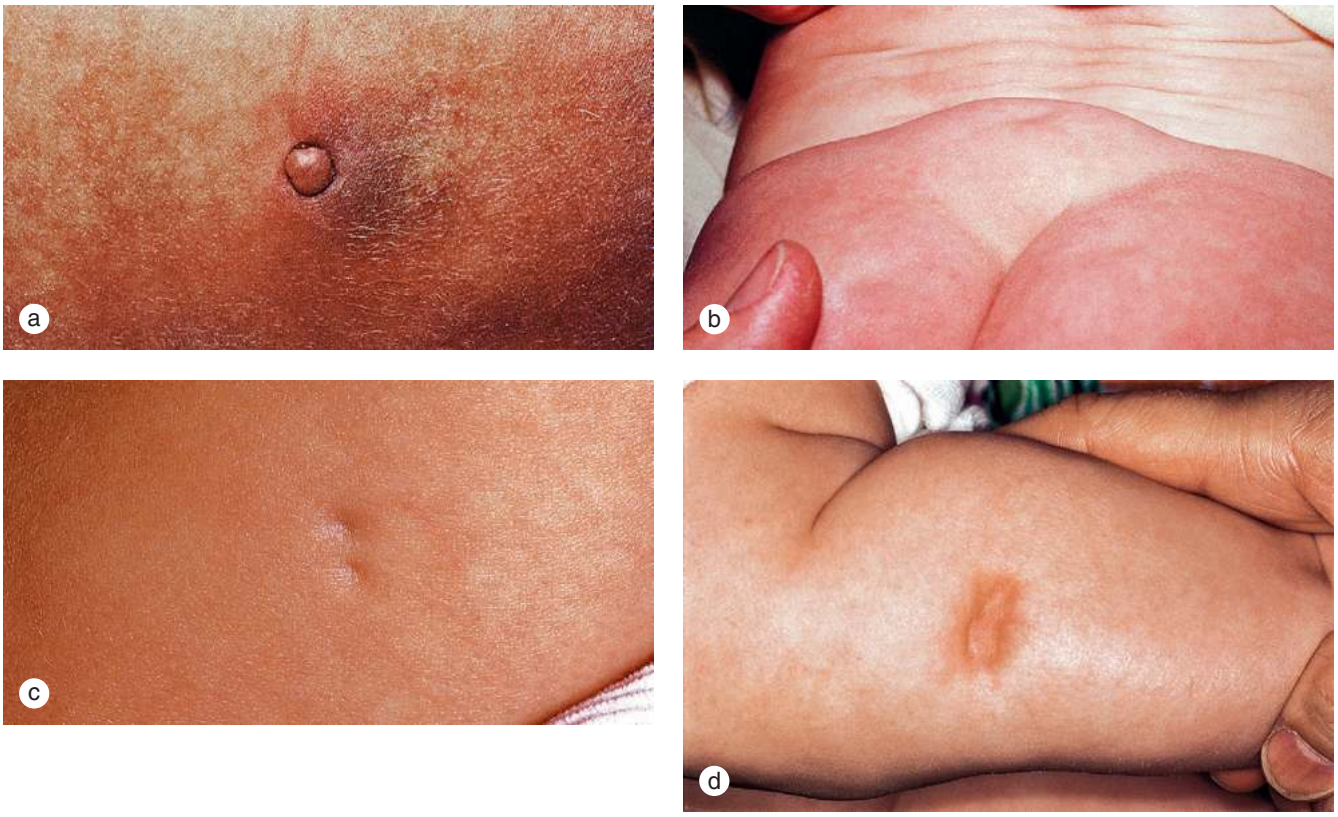


Fig 2.21 Dimples. **(a)** A sacral dimple was noted in this healthy infant. Computed tomography scan of the lumbosacral spine was normal. **(b)** At birth a spongy mass was palpable in the sacral area of this baby. A magnetic resonance image of this tumor revealed a lipoma and normal spine. **(c)** These dimples on the thigh of an otherwise healthy infant may have resulted from amniocentesis-induced trauma. **(d)** The cause of an isolated pit on the calf of this healthy infant was unknown. There was no history of amniocentesis.

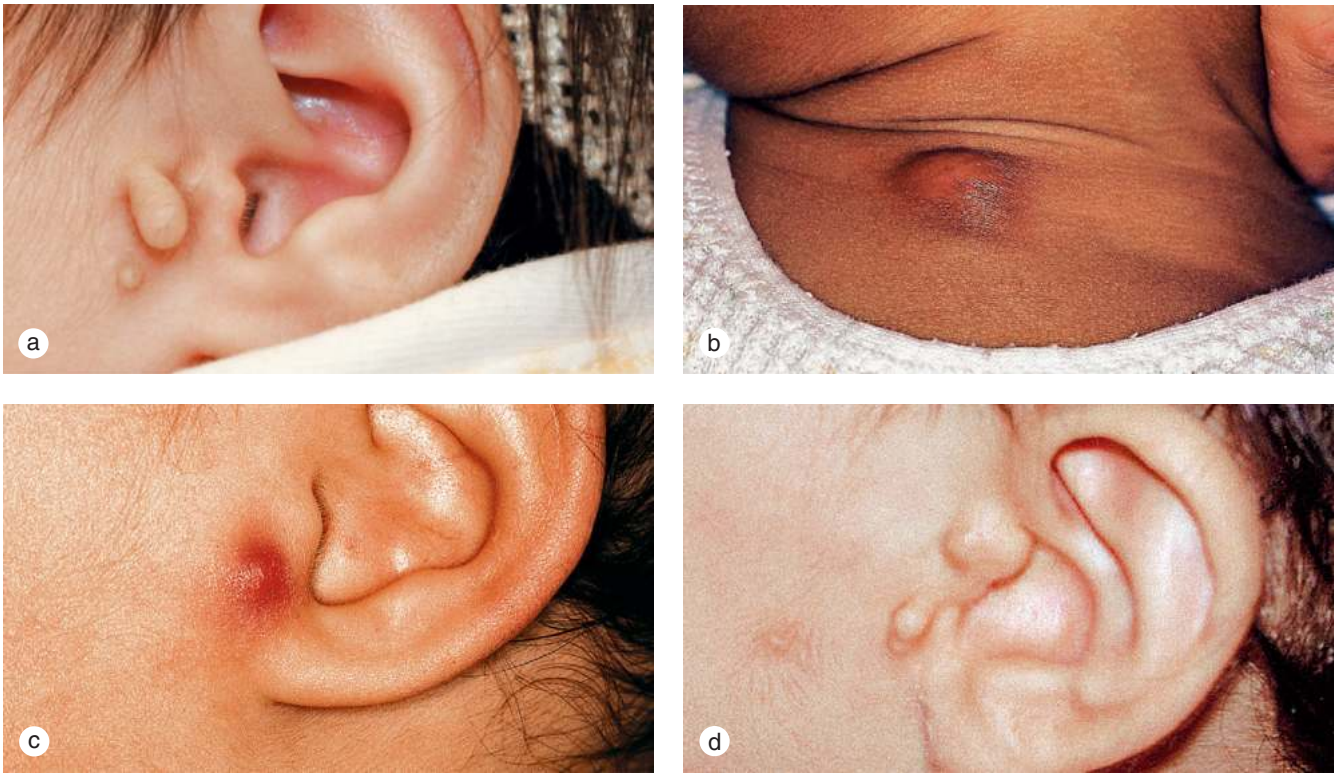


Fig 2.22 Skin tags and cysts. **(a)** This preauricular skin tag was tied off in the nursery (a, Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure). **(b)** Congenital cyst on the supraclavicular area. **(c)** Congenital cyst on the preauricular area. The cysts on these children became apparent when they became infected. Both required surgical excision. **(d)** This healthy toddler exhibits two preauricular skin tags (accessory tragi). The lesions were broad based and were eventually excised by a pediatric plastic surgeon.



Fig 2.23 This rudimentary, supernumerary digit was present at birth. It was surgically excised at 6 months of age.



Fig 2.25 An umbilical granuloma responded to shave removal with light cautery. (Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure.)

open surface epithelializes and scars down in an additional 1–2 weeks. Excessive moisture and low-grade infection may result in the growth of exuberant granulation tissue to form an umbilical granuloma. Cauterization with silver nitrate or desiccation with repeated applications of isopropyl alcohol usually produces rapid healing of the granuloma. In some cases, a less friable, more firm nodule may be present (Fig. 2.25).

In some infants, secondary infection results in omphalitis (Fig. 2.26). Aggressive antibiotic therapy is necessary to prevent peritonitis and sepsis.

Umbilical granulomas must be differentiated from umbilical polyps, which result from persistence of the omphalomesenteric duct or urachus (Fig. 2.27). A mucoid discharge may occur at the tip of the firm, red polyp, which histologically demonstrates gastrointestinal or urinary tract mucosa. Surgical excision is necessary.



Fig 2.26 Omphalitis developed in this 10-day-old infant shortly after the cord separated from the umbilicus. The infection cleared after a 10-day course of parenteral antibiotics.

THE SCALY NEWBORN

At delivery, the skin is smooth, moist, and velvety. Desquamation begins at 24–36 h of age and may not be complete for 3 weeks (Fig. 2.28). As peeling progresses, the underlying skin appears normal and cracking and fissuring is absent. Desquamation at birth or during the first day of life is abnormal and suggests postmaturity, intrauterine stress, or congenital ichthyosis.



Fig 2.24 This accessory nipple was an incidental finding on a healthy teenager with tinea versicolor.



Fig 2.27 This 2-week-old infant had a broad umbilical stump and chronic watery (urine) discharge. At surgery the patent urachus was excised.



Fig 2.28 Scaling in a 1-week-old healthy infant. **(a)** Scaling was present on the trunk. **(b)** Similar scaling was present on the hands and feet. A week later the scaling had resolved completely.

Collodion baby

Collodion infants are born encased in a thick, cellophane-like membrane (Fig. 2.29). Although the collodion membrane may desquamate to leave normal skin, up to 70% of affected infants go on to develop autosomal recessive congenital ichthyosis (ARCI), most commonly lamellar ichthyosis. The congenital ichthyosiform erythroderma phenotype of ARCI may also occur. Less commonly, this membrane is a prelude to Netherton syndrome, Conradi–Hunermann syndrome, Sjögren–Larsson syndrome, or one of the ectodermal dysplasias – especially hypohidrotic ectodermal dysplasia. The association of collodion membrane with Type II Gaucher disease and X-linked ichthyosis is less clear.

Although the horny layer is markedly thickened in collodion babies, barrier function is compromised by cracking and fissuring. Increased insensible water loss, heat loss, and risk of cutaneous infection and sepsis are minimized by placing affected newborns in a high-humidity, neutrally thermal environment. Débridement of the membrane is contraindicated, and topical applications should be restricted to bland emollients such as petrolatum. Desquamation is usually complete by 2–3 weeks of life. A biopsy during the immediate newborn period prior to shedding of the membrane is not of value and biopsy should be deferred until the membrane has fully desquamated.

A severe variant of ichthyosis, harlequin ichthyosis, occurs rarely (Fig. 2.30). Although these infants may appear normal at birth, within minutes they develop a thick, generalized membrane, deep cracks and fissures, and marked ectropion and eclabium. Most infants succumb to respiratory distress or infection, but children who survive the neonatal period may develop scale reminiscent of lamellar ichthyosis. Oral retinoids may be of benefit in the neonatal period.

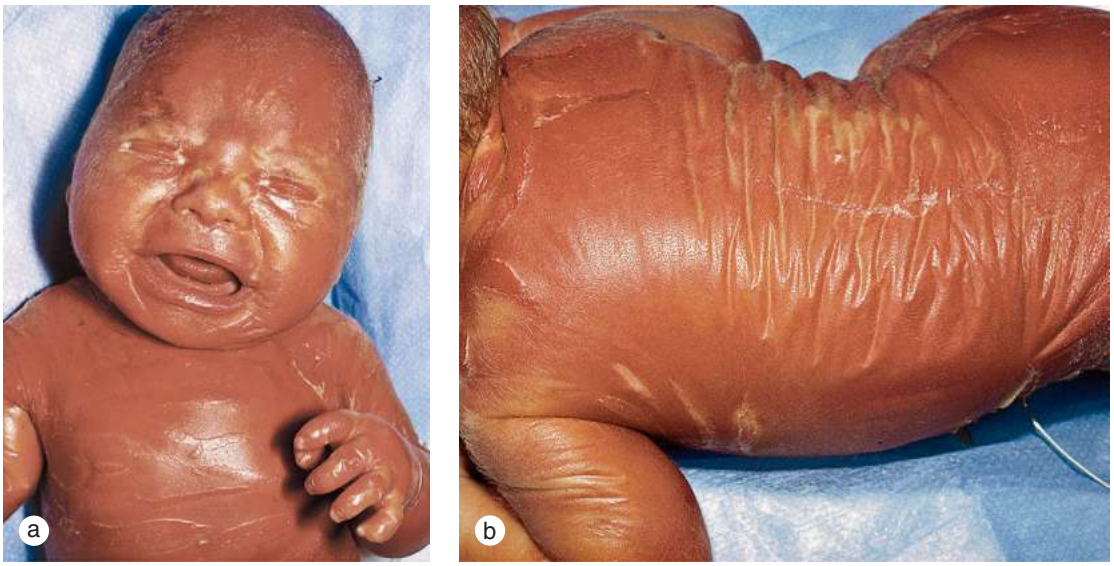


Fig 2.29 Collodion baby. **(a)** A shiny transparent membrane covered this baby at birth. **(b)** She later developed lamellar ichthyosis.



Fig 2.30 Harlequin baby. This baby developed thick, plate-like scales immediately after drying in the delivery room. Respiratory failure resulted in death during the first week. Note the ectropion and eclabium.

Ichthyosis

The ichthyoses are a heterogeneous group of scaling disorders that may be differentiated by mode of inheritance, clinical features, histology, biochemical markers, and in some cases genetic mutational analysis (Table 2.2). Rarely, ichthyosis is a marker of multisystem disease in the newborn (Table 2.3).

Autosomal recessive congenital ichthyosis

The phenotype of children with ARCI exists on a continuum from congenital ichthyosiform erythroderma (CIE) (Fig. 2.31) – which presents with erythema and fine scale – to lamellar ichthyosis (LI) (Fig. 2.32) – which presents with thick, brown scale involving the trunk, extremities, and flexural areas. Both CIE and LI present with a collodion membrane at birth. ARCI is rare and occurs in fewer than 1/100 000 deliveries. The erythroderma of congenital ichthyosiform erythroderma and the generalized, thick, brown scales of lamellar ichthyosis develop after the membrane desquamates at 2–4 weeks of age.

Epidermolytic hyperkeratosis

Infants with epidermolytic hyperkeratosis (also referred to as bullous congenital ichthyosiform erythroderma; Fig. 2.33) demonstrate widespread blistering at birth and may be misdiagnosed as having a primary blistering dermatosis such as staphylococcal scalded skin syndrome or epidermolysis bullosa. During the first

Ichthyoses

Variant	Genetics	Incidence	Clinical features	Onset
Congenital ichthyosiform erythroderma MIM #242100	Autosomal recessive TGM-1, ABCA12, NIPAL4 (ICHTHYIN) ALOX12B, ALOXE3	1/50 000–1/100 000	Collodion baby Fine white scale on trunk, face, and scalp Large scale on legs Variable erythroderma	Birth
Lamellar ichthyosis MIM #242300	Autosomal recessive TGM-1, ABCA12, NIPAL4 (ICHTHYIN), CYP4F22, LIPN	1/100 000	Collodion baby Generalized large, dark plate-like scale Ectropion, eclabium Mild palmoplantar keratoderma	Birth
Epidermolytic hyperkeratosis MIM #113800	Autosomal dominant (most common) Autosomal recessive, sporadic KRT1, KRT10	Rare	Widespread blisters at birth Increase erythema, scale with age Marked scale in intertriginous areas, palms, soles Malodor from bacterial overgrowth	Birth
Ichthyosis vulgaris MIM #146700	Autosomal dominant FILAGGRIN	1/250 (may be higher)	Generalized mild scale sparing flexures Improves with age	After 3 months
X-linked ichthyosis MIM #308100	X-linked recessive Steroid sulfatase gene	1/2000–1/6000 males	Large 'dirty' scales on trunk, extremities sparing flexures Variable in female carriers Corneal opacities in Descemet's membrane Cryptorchidism Placental sulfatase deficiency with prolonged maternal labor	Within first 3 months
Harlequin ichthyosis MIM #242500	Autosomal recessive ABCA12	Very rare	Thick plates of 'armor'-like scale in neonate Overall survival just over 50% Death in first 3 months of life most common	Birth

Table 2.2 Ichthyoses

Ichthyosis syndromes		
Syndrome/disease	**Genetics**	**Clinical features**
Netherton syndrome MIM #256500	Autosomal recessive SPINK5	Hair shaft anomaly (trichorrhexis invaginata most common), ichthyosis linearis circumflexa, severe atopic dermatitis, failure to thrive
Refsum disease, infantile MIM #266510	Autosomal recessive PEX1, PXMP3, PEX26	Retinitis pigmentosa, cerebellar ataxia, chronic polyneuritis with deafness, skin resembles ichthyosis vulgaris
Sjögren–Larsson syndrome MIM #270200	Autosomal recessive ALDH3A2 (fatty aldehyde dehydrogenase gene)	Spastic paralysis, mental retardation, seizures, glistening dots on retina, dental bone dysplasia, similar skin findings to congenital ichthyosiform erythroderma
Conradi–Hunermann syndrome (chondrodysplasia punctata type 2) MIM #302900	X-linked dominant EBP gene	Chondrodysplasia punctata, alopecia, skeletal anomalies, cataracts, dysmorphic facies, ichthyosiform erythroderma
KID (keratitis-ichthyosis-deafness) syndrome MIM #148210	Autosomal dominant (sporadic) GJB2 encoding connexin 26	Fixed keratotic plaques, keratoderma, atypical ichthyosis with prominent keratoses on extremities and head, neurosensory deafness, keratoconjunctivitis
CHILD syndrome MIM #308050	X-linked recessive NSDHL	Congenital hemidysplasia, unilateral ichthyosiform nevus (epidermal nevus), limb defects, cardiovascular and renal anomalies

Table 2.3 Ichthyosis syndromes



Fig 2.31 Congenital ichthyosiform erythroderma. **(a)** Congenital erythroderma persisted in this child. **(b)** Note the marked scaling on her hands. **(c)** Generalized erythema with fine scaling was noted on the first day of life. **(d)** Shortly after his first birthday, he developed a new pattern of migrating, scaly, erythematous plaques typical of Netherton syndrome. Microscopic examination of his hair revealed trichorrhexis invaginata (bamboo hair).



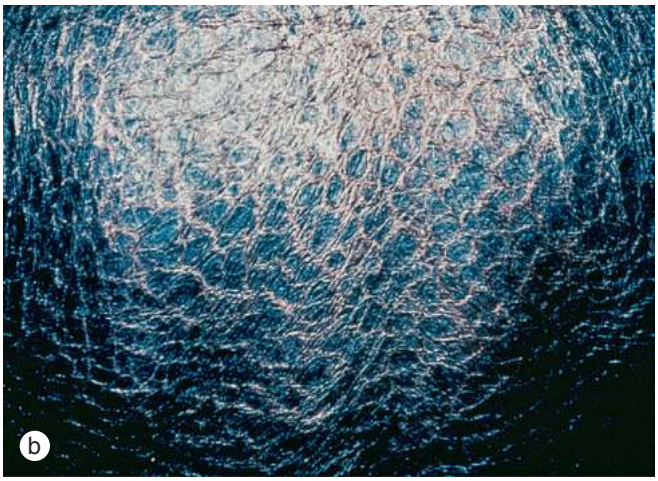




Fig 2.32 Lamellar ichthyosis. **(a)** Typical appearance. **(b)** Note the thick, brown scales that cover the entire skin. This child was born with a collodion membrane. **(c)** Example of axillary and truncal scale in a patient with autosomal recessive congenital ichthyosis. (Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure.)

few weeks and months of life, blisters give way to increasing hyperkeratoses, especially in intertriginous and flexural areas.

In these ichthyotic disorders, increased insensible water loss, temperature instability, and increased risk of infection may persist for weeks. Involvement of the face may result in ectropion formation, particularly in lamellar ichthyosis, and aggressive eye care is necessary to preserve visual acuity. Decreased sweating as a result of the obstruction of eccrine ducts in the epidermal scale often interferes with effective cooling of the skin. Aggressive management of fever, air conditioning, and cooling suits reduce the risk of hyperthermia associated with self-limited childhood illnesses and increased physical activity, especially during the summer.

Ichthyosis vulgaris and X-linked ichthyosis

Children with ichthyosis vulgaris (Fig. 2.34) and X-linked ichthyosis (Fig. 2.35) may not develop scaling until 3 months of age or later. The generally mild scales of ichthyosis vulgaris tend to spare the flexures and improve with age. The 'dirty' brown scales of X-linked ichthyosis also spare the flexures, but typically involve much of the body surface. The skin lesions do not usually impair epidermal barrier function.

Mild scaling responds well to lubricants, urea-containing preparations (Carmol®, Ureacin®), and α-hydroxy acids in emollients (lactic acid [LactiCare®, LacHydrin®], glycolic acid [Aqua Glycolic®, Glycolix®]). Irritation associated with these agents may be reduced by special formulation in bland vehicles such as petrolatum or hydrophilic ointment. Although topical salicylic acid and phenol are also potent keratolytics, their use is restricted to small areas because of the risk of transcutaneous absorption and systemic toxicity.

Oral retinoids (isotretinoin, acitretin, etretinate) have demonstrated marked improvement of cutaneous lesions in severe ichthyosis. However, clinical benefits must be weighed against the risk of systemic effects, particularly hepatic and skeletal toxicity, which can occur during prolonged use.

DIAPER DERMATITIS AND RELATED DISORDERS

The dermatitides are characterized by acute changes (erythema, edema, and vesiculation) and/or chronic changes (scale, lichenification, and increased or decreased pigmentation) in the skin. Microscopically, these disorders show infiltration of the dermis with inflammatory cells, variable thickening of the epidermis, and scale.

Irritant contact dermatitis

Diaper dermatitis is one of the most common skin disorders of infancy. In its most usual form, it is an irritant contact dermatitis (Fig. 2.36). The diaper area is a prime target for an irritant dermatitis, because it is bathed in urine and feces and occluded by diapers. Although ammonia from urine was first thought to play a leading role in the pathogenesis of diaper dermatitis, current evidence points to feces as the principal culprit. Once the epidermal barrier is disrupted, the skin may become sensitive to other irritants such as soap, powder, and detergents. Watery stools, particularly after antibiotic exposure or viral infections, often trigger severe dermatitis that is recalcitrant to conservative measures.

Red, scaly, and occasionally erosive irritant reactions are usually confined to convex surfaces of the perineum, lower abdomen, buttocks, and proximal thighs. The intertriginous areas are invariably spared. Gentle, thorough cleansing of the area and the application of lubricants (e.g. petrolatum) and barrier pastes (e.g. zinc oxide) usually result in clearing of the dermatitis. A



Fig 2.33 Epidermolytic hyperkeratosis in a 6-year-old girl. **(a,b)** Generalized, thick, greasy scales accentuate the normal skin markings on the extremities. Epidermolytic hyperkeratosis in a 6-year-old girl. **(c)** Similar scales on the trunk and neck. Flexures were most severely involved. **(d)** This adult with epidermolytic hyperkeratosis from birth developed a severe keratoderma of the hands and feet with constriction bands and autoamputation of several digits.

tapering course of low-potency topical corticosteroid ointment (e.g. hydrocortisone or desonide) in severe dermatitis may speed resolution of symptoms and clinical findings.

Allergic contact dermatitis

Although less common than irritant dermatitis, allergic contact dermatitis may account for occasional diaper rashes. Fragrances, preservatives, and emulsifiers such as mercaptobenzothiazole, fragrance mix, disperse dye, cyclohexylthiophthalimide, p-tert-butylphenol-formaldehyde resin, and sorbitan sesquioleate in topical baby products and diapers may be associated with allergic reactions in the diaper area, as well as on the face, trunk, and extremities. Avoidance of the offending agent, aggressive use of emollients, and judicious use of topical corticosteroids clear these reactions within several days.

Infected contact dermatitis

Contact diaper dermatitis is occasionally complicated by secondary staphylococcal infection, or pustules may appear as primary lesions, especially in the first few weeks of life (Fig. 2.37). The presence of thin-walled pustules on an erythematous base should alert the clinician to the diagnosis of staphylococcal pustulosis. Typically, the lesions rupture rapidly, and dry to produce a collarette of scale around a denuded red base. Gram-stain of pustule contents demonstrates Gram-positive cocci in clusters and neutrophils. Bacterial cultures are confirmatory.

Seborrheic dermatitis

Persistent diaper dermatitis may result from other disorders such as seborrheic dermatitis, infantile psoriasis, and candidiasis. In particular, these should be considered when the intertriginous areas are involved.

Seborrheic dermatitis is characterized by salmon-colored patches with greasy, yellow scale beginning in the intertriginous areas, especially the diaper area, axillae, and scalp (Fig. 2.38). Fissuring, maceration, and weeping develop occasionally. Thick, adherent scales on the occiput are referred to as 'cradle cap.' Although oval, red patches may spread to the trunk, proximal extremities, and





Fig 2.34 Ichthyosis vulgaris. **(a)** Typical fish-scale appearance on the lower extremities of a light-pigmented child. **(b)** The appearance on a dark-pigmented child. Both children had at least one parent with similar findings. **(c)** Xerosis and ichthyotic scale on the bilateral lower legs. (Reprinted with permission from Bernard A. Cohen© DermAtlas, Johns Hopkins University; 2000–2012.)



Fig 2.35 X-linked ichthyosis: 'dirty' tan scales are evident on the trunk of this infant.



Fig 2.36 Irritant contact dermatitis involves the convex surfaces and spares the creases in the diaper area.



Fig 2.37 Staphylococcal diaper dermatitis. Numerous, intact, thin-walled pustules surrounded by red halos are present, as well as multiple areas in which pustules have ruptured to leave a collarette of scaling around a denuded red base.

postauricular areas, affected infants remain healthy and asymptomatic. In dark-pigmented children, postinflammatory hypopigmentation is marked, but transient.

In the diaper area, red, greasy, scaly patches extend from the skin creases to involve the genitals, perineum, suprapubic area, and thighs. Secondary candidiasis or impetigo may mask the underlying process.

The cause of seborrheic dermatitis is unknown. However, the yeast *Pityrosporum* has been implicated in adult seborrhea and identified in the scalp of infants with 'cradle cap.' This organism tends to proliferate in areas where sebaceous glands are most numerous and active, which probably explains the timing and distribution of the eruption. Seborrheic dermatitis may clear without treatment by 2–3 months of age, but often persists until 8–12 months. Mild keratolytics found in antiseborrheic shampoos (zinc pyrithione, sulfur, and salicylic acid) are helpful in the management of 'cradle cap.' Emollients and low-potency topical corticosteroids hasten the resolution of cutaneous lesions. Topical ketoconazole has been approved for treating adult seborrheic dermatitis and may be useful in infants, particularly in patients with associated candidiasis.



Fig 2.38 Seborrheic dermatitis. **(a)** The slightly greasy, red, scaling eruption typically begins in the groin creases and spreads throughout the diaper area. **(b, c)** In florid cases, the dermatitis involves the trunk, face, and creases of the neck and extremities. **(d)** 'Cradle cap' consists of thick, tenacious scaling of the scalp. **(e)** Postinflammatory hypopigmentation may be marked, particularly in darkly pigmented individuals.





Fig 2.39 Psoriasis. This diaper dermatitis failed to respond to routine topical therapy. **(a)** A skin biopsy demonstrated histologic changes of psoriasis. **(b)** In some infants with psoriasis, thick, disseminated plaques appear. **(c)** Confluent, beefy red and pink plaques in the diaper area consistent with psoriasis; the eruption required short courses of mid- to high-potency topical steroids to control it. (Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure.)

Psoriasis

Psoriasis occasionally begins as a persistent diaper dermatitis (Fig. 2.39), and there may be considerable clinical overlap with seborrheic dermatitis. Although lesions may disseminate to the trunk and extremities, the rash may continue in the diaper area alone for months. The eruption is typically bright red, scaly, and well-demarcated at the diaper line. Although topical corticosteroids result in temporary improvement, lesions tend to persist or recur for months, and occasionally short-term use of mid- to high-potency topical corticosteroids is necessary. The topical calcineurin inhibitors approved for atopic dermatitis, pimecrolimus (Elidel) and tacrolimus (Protopic), are helpful in treating psoriasis at sensitive sites such as the diaper area. Infants remain well, and the eruption may be asymptomatic. Skin biopsy is the only way to confirm the diagnosis, though clinical impression guides management of most cases.

Candidiasis

Candidiasis appears as a brilliant red eruption with sharp borders, satellite red papules, and pustules (Fig. 2.40). Lesions typically involve the skin creases. *Candida* is a common complication of systemic antibiotic therapy, seborrheic dermatitis, psoriasis, and chronic irritant dermatitis. Examination of material from a pustule by Gram-stain or potassium hydroxide preparation reveals pseudohyphae and/or budding yeast. Diaper candidiasis may be accompanied by oral thrush, candidal paronychia of the fingers or toes, and



Fig 2.40 Diaper candidiasis. The eruption is bright red, with numerous pinpoint satellite papules and pustules. The urethra and intertriginous areas are prominently involved.

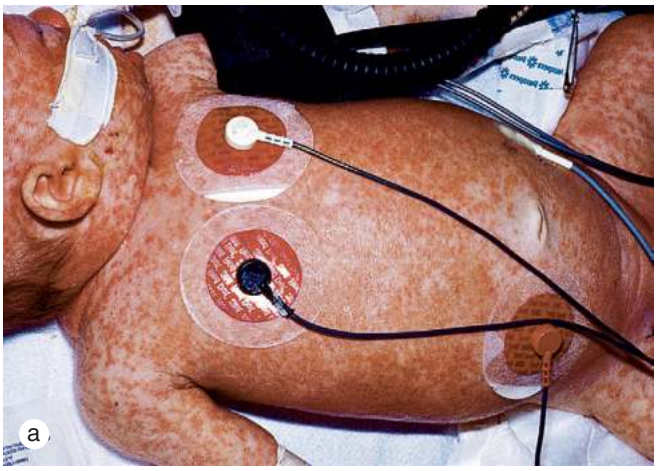






Fig 2.41 Langerhans cell histiocytosis (LCH). **(a)** A hemorrhagic diaper dermatitis rapidly generalized to the entire skin surface in this 3-week-old infant with diarrhea, poor weight gain, lymphadenopathy, and hepatosplenomegaly. This child died of disseminated LCH at 6 weeks of age. **(b)** This toddler with chronic LCH had an episodic, erosive diaper dermatitis associated with papules and plaques in the scalp. **(c)** This young child had petechial papules and diaper dermatitis classic for LCH. (Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure.)

candidiasis of other intertriginous areas such as the neck and axillae. Diaper candidiasis responds rapidly to topical antifungals such as nystatin, ciclopirox olamine, and the imidazoles (miconazole, clotrimazole, econazole, sulconazole, ketoconazole). Although a brief course of topical corticosteroids (1–2 times a day for 3–4 days) may speed clinical improvement, high-potency agents can produce atrophy in a short period of time. Several products that incorporate a combination of moderate- to high-potency topical corticosteroids and antifungal agents are available, and should be avoided.

Langerhans cell histiocytosis

Severe multisystem disease may begin with a progressive diaper dermatitis. A severe seborrheic dermatitis-like eruption is characteristic of Langerhans cell histiocytosis (LCH) (Fig. 2.41). The rash tends to become hemorrhagic and erosive, particularly in the diaper area. Scaly, crusted, purpuric plaques also develop on the scalp, trunk, and extremities. LCH is rare, with an incidence of 2–9 cases/million children under the age of 18, although the majority of affected children are 1–3 years of age at diagnosis. Diagnostic skin biopsies demonstrate infiltrates of atypical S-100 protein OKT6-positive histiocytes containing Langerhans cell (Birbeck) granules. Similar infiltrates may involve the bone marrow, liver, lungs, kidneys, and nervous system, resulting in severe organ dysfunction and death. Up to 50% of infants presenting with skin disease will go on to develop internal organ involvement. Close follow-up is mandatory.

Benign cephalic histiocytosis

A non-Langerhans cell histiocytosis, benign cephalic histiocytosis is characterized by scattered yellow-brown papules and macules concentrated on face, scalp, neck, and upper trunk that appear in the first 2 years of life, though typically after birth. No systemic involvement occurs. It has been proposed that benign cephalic histiocytosis (BCH) may be a variant of micronodular juvenile xanthogranulomas with early onset. BCH lacks markers typical for LCH, such as S100 and Birbeck granules. No treatment is necessary as lesions regress over the first few years of life, though there can be scar tissue left behind in some cases (Fig. 2.42).

Acrodermatitis enteropathica

Acrodermatitis enteropathica (AE) classically presents with an erosive diaper dermatitis, diarrhea, and hair loss during the first few months of life (Fig. 2.43). Weeping, crusted, erythematous patches also appear in a periorificial, acral, and intertriginous distribution. Affected infants are irritable, grow poorly, and are prone to infection and septicemia.

Since AE is an autosomal recessive disorder of zinc metabolism, affected infants have either defective or low levels of a zinc-binding protein in the gastrointestinal tract and resultant zinc malabsorption. Breast milk contains a compensatory zinc-binding ligand that facilitates absorption. Consequently, breast-fed infants do not develop symptoms until nursing is discontinued. Zinc is stored in the fetal liver, particularly during the last month of gestation. As a result, affected premature infants who are not breastfed become zinc deficient quickly. Normal infants who require hyperalimentation, as well as those with zinc losses from other malabsorption states (e.g. cystic fibrosis, chronic infectious diarrhea, short bowel syndrome), also develop an AE-like rash if they do not receive zinc supplementation. Rare cases of zinc-deficient breast

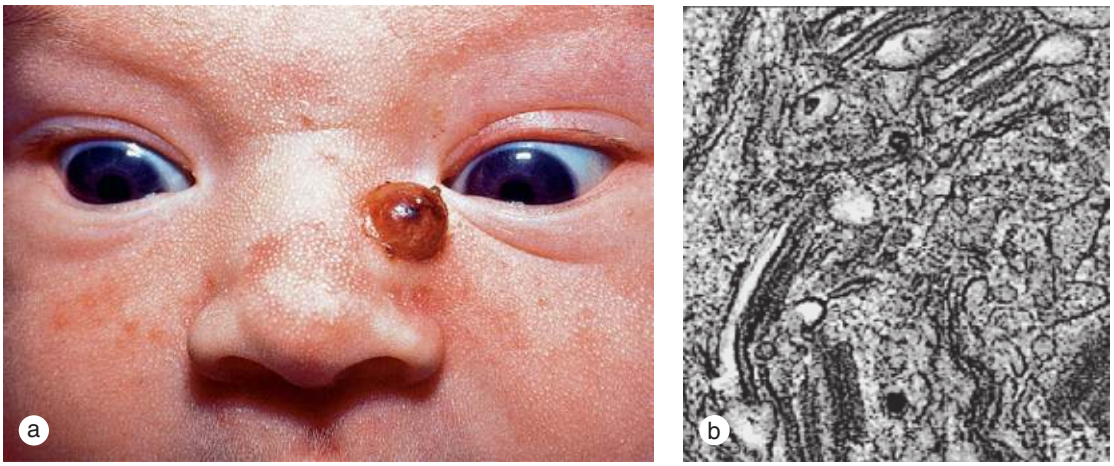


Fig 2.42 Benign cephalic histiocytosis. **(a)** This healthy newborn with multiple congenital crusted papules was initially treated for herpes simplex infection. When the lesions did not respond to parenteral aciclovir a skin biopsy which showed the typical changes of LCH on routine pathology and **(b)** electron microscopy was performed. Note the tennis racket shaped Bierback granules diagnostic of LCH. The lesions resolved without treatment within 2 weeks.

milk resulting in a zinc-deficiency eruption have been reported. Similar rashes have also been described with biotin deficiency, essential fatty acid deficiency, and urea enzyme cycle defects, which result in essential amino acid deficiency.

AE responds dramatically to high doses of oral or intravenous zinc within several days. Although dietary zinc without supplementation may be adequate in older children with AE, these patients require close monitoring of growth and development. Some patients require lifelong zinc supplements.

CONGENITAL SYPHILIS

Although the incidence of neonatal syphilis decreased in the 1970s and 1980s, a resurgence has occurred, particularly in urban centers. Infants born to mothers who contract syphilis late in pregnancy are at high risk for contracting the disease. Between 2005 and 2008, the rate of congenital syphilis increased 23%.

Although clinical manifestations of syphilis may be delayed until puberty (known as late congenital syphilis), common findings in early congenital syphilis, which encompasses disease diagnosed in children <2 years of age, include mucocutaneous lesions, prematurity, poor growth, and hepatosplenomegaly. Occasionally, severe systemic disease presents with generalized lymphadenopathy, pneumonitis, nephritis, enteritis, pancreatitis, osteochondritis, hematologic abnormalities, and meningitis. The bones, teeth, and central nervous system are the most common sites of extracutaneous involvement.

Mucocutaneous lesions usually appear between 2 and 6 weeks of age. The most common finding in the skin is a papulosquamous eruption beginning on the palms and soles and spreading over the extremities, face, and trunk (Fig. 2.44). These lesions are comparable with the secondary syphilitic eruption of adults and may be associated with vesiculation, ulceration, and desquamation. Moist, warty excrescences may develop in the intertriginous and perioriﬁcial areas. Smooth, round, moist mucous patches are characteristic of early neonatal syphilis and commonly involve the mouth and perianal area. Such lesions are highly infectious. 'Snuffles' or rhinitis with profuse and occasionally bloody rhinorrhea is invariably present in symptomatic babies.

Diagnosis may be confirmed by darkfield examination (though darkfield microscopy has limited availability now) of mucocutaneous lesions and serologic studies of the serum and cerebrospinal fluid. Screening of babies at risk for syphilis should include both specific *Treponema* (fluorescent treponemal antibody absorption tests) and non-treponemal (rapid plasma reagin or Venereal Disease Research Laboratory) studies. The most sensitive serologic method

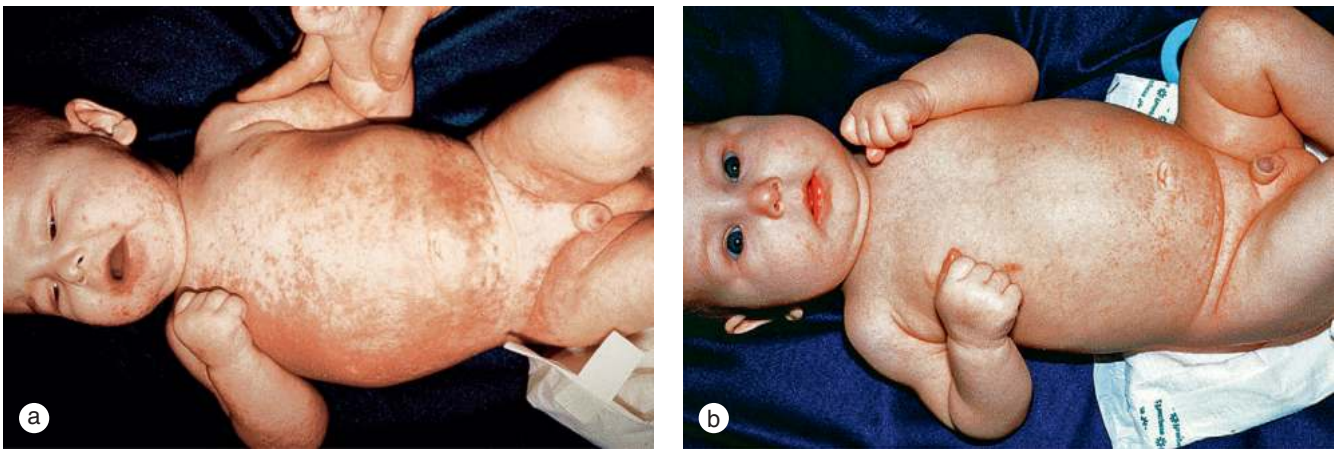


Fig 2.43 Acrodermatitis enteropathica. **(a)** A bright red, scaling dermatitis spread to the intertriginous areas, face, and extremities of this 4-week-old infant. **(b)** After 4 days of zinc supplementation, many lesions were healing with desquamation.



Fig 2.44 Neonatal syphilis. **(a,b)** A scaly eruption reminiscent of the lesions of secondary syphilis appeared on the face, trunk, and extremities of these infants.

is detection of specific IgM, though a negative test does not exclude possible infection. IgM can be detected in newborns using either 19S FTA-ABS tests, IgM immunoblots, or IgM ELISAs. Early diagnosis and treatment with high-dose penicillin prevents late complications of syphilis, including skeletal and dental anomalies, neurologic deterioration, eighth nerve deafness, and ophthalmologic disease.

VESICULOPUSTULAR DERMATOSES

Vesiculobullous and pustular eruptions may present a confusing clinical picture. Their diagnosis is critical, and early therapeutic intervention may be life-saving.

Infections and infestations

Viral infections, including herpes simplex and varicella-zoster, produce characteristic vesiculopustular eruptions. Herpes simplex is a common cause of self-limited oral and cutaneous lesions in toddlers and older children. However, in neonates there is a high risk of dissemination. Varicella is less common, but if lesions appear during the 1st week of life, the risk of mortality approaches 30%.

Neonatal herpes simplex infection

Herpes simplex infection occurs in 1 out of 3500 deliveries. Inoculation occurs from ascending infection *in utero* (5% of cases) or



Fig 2.45 Herpes simplex. **(a)** The eroded vesicles at the corner of the mouth were the first signs of herpes infection in this neonate. **(b)** An infant with respiratory distress and hepatitis developed herpetic vesicles on the face, scalp, and ear.

from lesions on the cervix or vaginal area during delivery (85% of cases). However, the disease may be acquired postnatally from nursery personnel and family members (10% of cases). The incubation period varies from 2 to 21 days and peaks at 6 days. Consequently, infants may appear normal in the nursery and develop lesions after discharge home. Manifestations vary from subclinical disease to widely disseminated infection and death. Of infected babies, 70% develop the skin rash. Between 70 and 85% of cases are due to HSV2. The risk of transmission to an infant born during new maternal genital HSV infection is between 25 and 50%, as compared to a rate of transmission of less than 1% if recurrent genital HSV is active during vaginal delivery. New maternal genital HSV infection accounts for 50–80% of neonatal HSV. The majority of mothers are asymptomatic at delivery. HSV has a higher incidence of transmission than syphilis, toxoplasmosis, and rubella.

Cutaneous lesions typically begin as 1–2 mm diameter, clustered, red papules and vesicles, which may become pustular, denuded, crusted, and hemorrhagic over the following 2–3 days (Fig. 2.45). The first lesions commonly develop on the face and scalp in head deliveries and on the feet or buttocks after breech presentation.

Neonatal HSV can occur as skin, eyes and mouth (SEM) disease – which accounts for 45% of neonatal HSV, central nervous system disease – which accounts for 30% of neonatal HSV, or disseminated disease – which accounts for 25% of neonatal HSV. It is important to note that overlap does exist between these subtypes and infants who present with skin disease only are at risk for dissemination to the CNS or other organs at any time during the acute infection. Infants with CNS and disseminated disease have a predictably worse outcome.

Blisters reveal multinucleated giant cells when their contents are prepared on a glass-slide with Giemsa or Wright stain. Viral cultures from blister fluid or denuded areas of skin often demonstrate

a cytopathic effect within 12–24 h. Diagnosis can be rapidly confirmed by double fluorescent antibody (DFA), or polymerase chain reaction (PCR) studies in some medical centers. Early intervention with parenteral acyclovir may decrease the risk of disseminated disease, and of morbidity and mortality when dissemination has already occurred. Skin lesions are gently cleansed and excess blister fluid absorbed with a gauze pad to reduce cutaneous spread. Skin lesions may recur throughout childhood; recurrence prompts a trial of oral acyclovir, particularly when recurrences are frequent and skin lesions frighten caretakers at home or in a day care. Recent evidence suggests that a 6-month course of oral acyclovir after the acute infection may improve neurodevelopment scores in infants at 12 months of age.

Congenital varicella syndrome

Early exposure during the first 20 weeks' gestation – with highest risk between weeks 13 and 20 – leads rarely to the development of the neonatal varicella syndrome, with linear scars, limb anomalies, ocular defects, and central nervous system involvement (Fig. 2.46).

Neonatal varicella

When a mother has varicella within 3 weeks of delivery, her baby has a 25% risk of acquiring the disease during the neonatal period.

When neonates develop the rash before 5 days of life or mothers develop lesions at least 5 days before delivery, the disease in neonates tends to be mild because of the presence of protective transplacental antibody. Infection acquired by the mother <5 days prior to delivery to 2 days after delivery, or lesions that develop in the newborn between days 5 and 10 of life tend to have more severe infection and are at risk for dissemination with resulting pneumonitis, encephalitis, purpura fulminans, widespread bleeding, hypotension, and death.

Varicella-zoster immune globulin and parenteral acyclovir may improve the outcome and should be considered early in the course. As with herpes simplex, the Tzanck smear shows multinucleated giant cells. These two viral infections can only be definitively differentiated by culture of the blister contents or by molecular studies (DFA, PCR).

Impetigo and staphylococcal scalded skin syndrome

Several common bacterial infections present with vesiculopustular eruptions in infancy. The rash tends to be localized in impetigo (see Fig. 4.12) and generalized in staphylococcal scalded-skin syndrome (SSSS) (Fig. 2.47, see also Fig. 4.13).

In classic streptococcal impetigo, honey-colored crusts overlie infected insect bites, abrasions, and other skin rashes, such as diaper dermatitis. Bullous impetigo, however, is characterized by slowly enlarging, blistering rings that surround central, umbilicated crusts. Lesions may appear anywhere on the skin surface. However, in young infants, areas prone to trauma, such as the diaper area, circumcision wound, and umbilical stump, are frequent sites of primary infection. Bullous lesions are caused by certain epidermal toxin-producing types of *Staphylococcus*, which produce exfoliative toxin A and exfoliative toxin B. Although lesions may remain localized, they are highly infectious and may be inoculated to multiple sites on the patient as well as on other family members. In newborns and young infants, dissemination of the toxin may result in widespread erythema and blistering typical of SSSS (Fig. 2.47). Gentle pressure on the skin causes the upper epidermis to slide off, leaving a denuded base (Nikolsky sign).

In localized impetigo, bacteria are identified in Gram-stained material obtained directly from the rash. In SSSS, the practitioner may be unable to identify a primary cutaneous site of infection. In these children, non-cutaneous sources, which include lungs, bone, meninges, conjunctivae and ears, must be sought.

Small patches of impetigo respond well to topical antibiotic therapy (e.g. mupirocin, bacitracin, bacitracin-polymyxin B) and tepid tap-water compresses. Healthy infants with recalcitrant or widespread impetigo require oral antibiotics with broad-spectrum Gram-positive coverage (dicloxacillin, cefalexin and other cephalosporins, cotrimoxazole, amoxicillin-clavulanate). Neonates and young infants may not localize infection to the epidermis and superficial dermis. Any signs of progressive cellulitis or visceral dissemination require immediate hospitalization, parenteral anti-staphylococcal antibiotics, and supportive care. When infants develop infection in the first 2–3 weeks of life, even after discharge

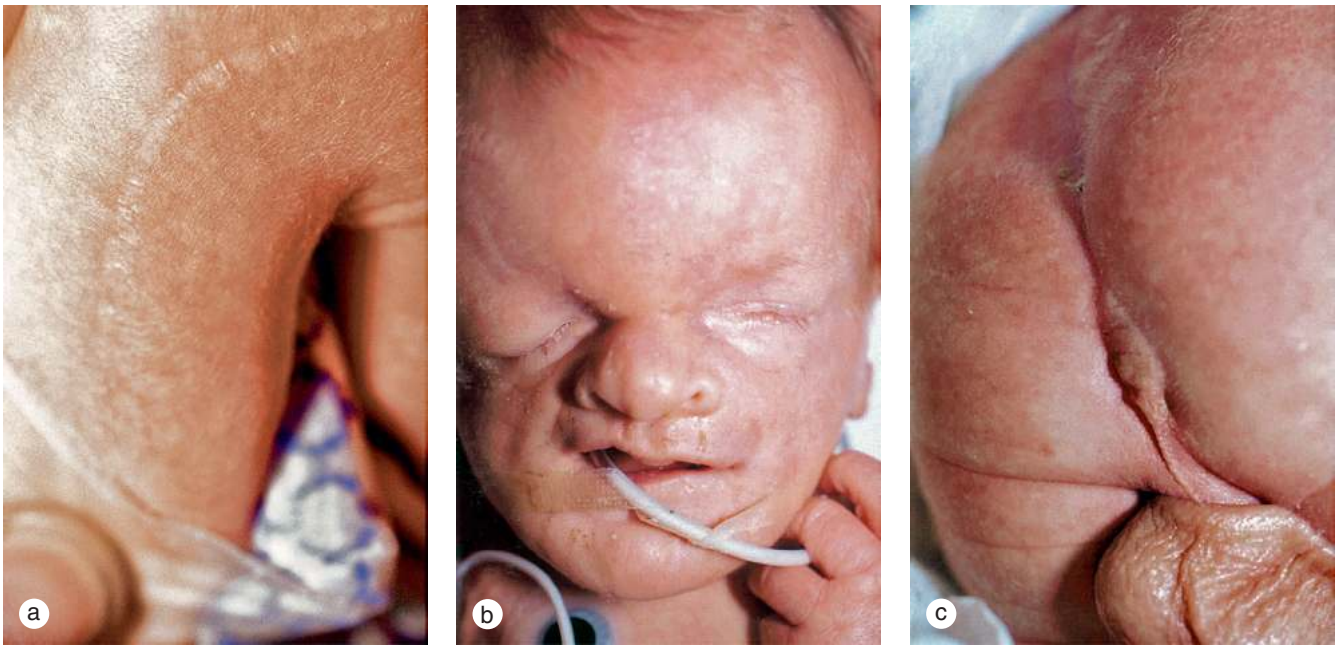


Fig 2.46 Varicella. **(a)** A linear scar was evident on the arm of this newborn whose mother developed chickenpox during the first trimester. **(b,c)** This child also had multiple central nervous system, ocular, genitourinary, and gastrointestinal anomalies. Note the dysmorphic facies **(b)** and imperforate anus **(c)**.



Fig 2.47 Staphylococcal scalded-skin syndrome developed in this neonate who was being treated for mastitis. Erosive patches were most marked on the **(a)** face and **(b)** diaper areas.

from the hospital, a nursery source should be suspected. Breeches in nursery hygiene and skin colonization of personnel must be investigated.

Disseminated candidiasis

Disseminated candidiasis in the newborn may be confused with bacterial infection. In congenital candidiasis, which develops during the first day of life, generalized erythematous papules, vesicles, and pustules may slough to leave large, denuded areas reminiscent of SSSS. The organism is acquired by ascending vaginal or cervical infection. The presence of oral thrush in some infants at birth and the identification of pseudohyphae and spores from pustules and scale are diagnostic. When infants acquire infection at delivery, the onset of lesions may be delayed by 7–10 days and erosive patches with satellite pustules are usually limited to intertriginous areas. Full-term infants often go on to heal with desquamation without treatment, although topical antifungals may help. Preterm infants are at high risk for dissemination, and early diagnosis and initiation of parenteral amphotericin may be lifesaving. As increasing numbers of tiny premature infants survive the first few weeks of life and undergo long-term systemic antibiotic therapy, infection with other opportunistic fungal organisms should be considered (Fig. 2.48).

Scabies

Scabies is a common, well-characterized infectious dermatosis produced by the *Sarcoptes scabiei* mite. The impregnated female burrows through the outer epidermis, where she deposits her eggs. The resultant diagnostic rash consists of pruritic, linear burrows on the finger webs, wrists, elbows, belt-line, areola, scrotum, and penis. In infants, burrows are widespread with involvement of the trunk, scalp, and extremities, including the palms and soles (Fig. 2.49). Although infants may be otherwise healthy and well grown, chronic infestation may result in poor feeding, fussiness, and failure to thrive. Chronic and recurrent infection, with pustules, crusting, and cellulitis, is a frequent complication.

The diagnosis is considered for any infant with a widespread dermatosis that involves the palms and soles, particularly if other family members are involved. The presence of burrows is pathognomonic, and an ectoparasite preparation is confirmatory. A drop of mineral oil is applied to a burrow, and the skin surface is stretched between the examiner's thumb and index finger. A #15 blade is used to scrape vigorously until the burrow is no longer palpable. This may leave a small bleeding point at the center of the burrow. The material is subsequently spread with the blade on a glass-slide and pressed under a coverslip. The female mite, eggs, and fecal material are readily visualized under a scanning 10× lens (see Fig. 1.7).

Until approximately 25 years ago, topical 1% lindane (γ-benzene hydrochloride) was the mainstay of treatment. Although the risk of toxicity with lindane is low when it is used appropriately in the medical setting, severe central nervous reactions have been reported in young infants, particularly wasted, chronically ill children. Even when used with proper dosing and skin care in healthy infants, significant blood levels have been detected. Alternative agents are either ineffective (crotamiton, benzyl benzoate), potentially toxic (sulfur ointment, benzyl benzoate), or cosmetically unacceptable (sulfur ointment). In 1989, permethrin 5% cream was introduced. Studies have shown that permethrin has a higher cure rate than lindane and that it may be used safely in children as young as 2 months.

At the start of therapy, parents are given careful instructions and limited quantities of the scabicide. The entire family and any others who have contact with the infant (such as baby-sitters) are treated simultaneously. Topical lubricants are necessary for several weeks after treatment to counteract drying and irritation produced by the scabicide and to resolve cutaneous lesions. Persistent pruritic nodules may arise from some burrows, particularly in intertriginous areas. Nodular scabies requires symptomatic treatment only. The appearance of new inflammatory lesions suggests reinfestation or inadequate therapy. Secondary infection responds to tap-water compresses and topical or oral antibiotics.

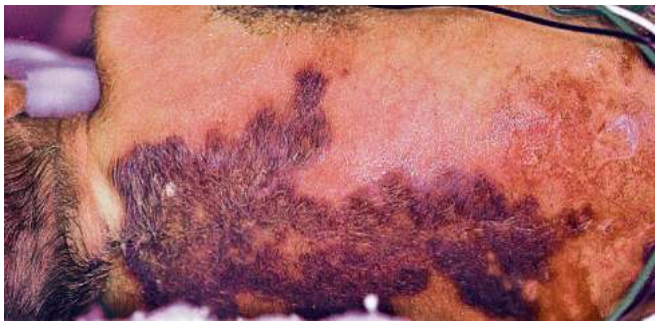


Fig 2.48 Primary cutaneous *Aspergillus* infection developed in this tiny premature infant who had extensive skin breakdown and was receiving parenteral antibiotics for pneumonia. The black eschars were loaded with hyphae.





Fig 2.49 Infants with widespread scabies. Burrows were present on **(a)** the trunk and **(b)** the feet. Nodules persisted on **(c)** the axillae and **(d)** the legs of these infants for 4 months. **(e)** This 10-week-old infant had been treated twice for scabies but continued to show evidence of burrows and papules until the entire family was treated. (Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure.)

Some investigators advocated the use of oral ivermectin for the treatment of scabies at a dose of 200 μg/kg, but it is not recommended for children under 5 years of age or <15 kg because of lack of safety data. In older children, its efficacy is probably comparable with permethrin, and it may be particularly useful in patients with acquired immunodeficiency syndrome or crusted scabies.

Mechanobullous diseases (epidermolysis bullosa)

Mechanobullous diseases (epidermolysis bullosa, EB) are a heterogeneous group of blistering dermatoses characterized by the development of lesions after trauma to the skin. Variants of EB are differentiated by their inheritance pattern, specific genetic mutations, clinical presentation, histopathology, and biochemical markers (Table 2.4). Although blisters may appear at birth or in the neonatal period, in mild, localized forms the onset of lesions is often delayed until later childhood or adult life.

Categorization of EB is into three major types based upon the cleavage plane of the blister. In EB simplex, blisters are intraepidermal, and the clinical course is usually mild (Fig. 2.50). In junctional EB, blisters form at the dermal–epidermal junction, usually



Fig 2.50 Epidermolysis bullosa simplex. Numerous blisters form primarily in pressure areas on the hands and feet.

Selected hereditary mechanobullous disorders						
Type	**Variant**	**Site of blister**	**Inheritance**	**Molecular defect**	**Onset**	**Clinical features**
Epidermolysis bullosa simplex (EBS)	EBS, localized	Basal layer for all EBS subtypes discussed here	Autosomal dominant	K5 (keratin 5), K14 (keratin 14)	Early childhood	Non-scarring blisters on hands and feet; hyperhidrosis
	EBS, Dowling–Meara		Autosomal dominant	K5 (keratin 5), K14 (keratin 14)	Birth	Grouped blisters, generalized denudation; nail dystrophy, milia, scarring may occur; keratoderma; improvement in adulthood
	EBS, other generalized		Autosomal dominant	K5 (keratin 5), K14 (keratin 14)	Birth	Non-scarring generalized blisters, worse on hands and feet
	EBS, muscular dystrophy		Autosomal recessive	PLEC1 (Plectin)	Birth (blisters); Muscular dystrophy (infant to adult)	Generalized blistering; muscular dystrophy; stenosis and granulation tissue in respiratory tract
	EBS, pyloric atresia		Possibly autosomal recessive	PLEC1(Plectin), ITGA6, ITGB4 ($\alpha6\beta4$-integrin)	Birth	Generalized blisters, aplasia cutis, pyloric atresia, deformities of pinnae and nasal alae, cryptorchidism
Junctional epidermolysis bullosa (JEB)	JEB–Herlitz	Lamina lucida for all JEB variants	Autosomal recessive for JEB all variants	LAMA3, LAMB3, LAMC2 (laminin-332)	Birth for all variants	Often lethal by 2 years; non-scarring widespread blisters; ≠ granulation tissue; nail dystrophy, loss; severe oral-dental involvement
	JEB–non-Herlitz			LAMA3, LAMB3, LAMC2 (laminin-332)		Localized blistering of hands, feet; nail dystrophy; enamel dysplasia
	JEB–pyloric atresia			ITGA6, ITGB4 ($\alpha6\beta4$-integrin)		Generalized blisters, widespread aplasia cutis possible, genitourinary malformations, pyloric atresia
Dystrophic epidermolysis bullosa (DEB)	DDEB, generalized	Sub-lamina densa for all DEB variants	Autosomal dominant	COL7A1 (type VII collagen) for DEB all variants	Birth for all DEB variants	Albopapuloid skin lesions in some; mild esophageal, oral involvement; normal lifespan
	RDEB, severe generalized					Marked skin fragility; widespread blisters, atrophy, scarring; nail dystrophy, loss; risk of squamous cell carcinoma; severe oral, dental, esophageal, intestinal, genitourinary involvement
	RDEB, generalized other					Mild widespread lesions; mild oral involvement; normal life span

Table 2.4 Selected hereditary mechanobullous disorders

through the lamina lucida in the basement membrane zone. Although patients may have mild disease comparable with EB simplex, in some children progressive blistering with involvement of the mucous membranes and gastrointestinal tract leads to inanition, sepsis, and death in the first 2 years of life (Fig. 2.51). Dystrophic EB is characterized by scarring blisters that form in the dermis beneath the basement membrane zone. Blisters may be localized to the hands and feet or widespread with involvement of the dentition, nails, airway, and esophagus (Fig. 2.52).

When infection has been excluded, EB should be considered in infants with recurrent blistering. Family history and examination of other family members aids in clinical diagnosis. A skin biopsy for immunomapping and/or electron microscopy provides precise identification of the cleavage plane in the skin (Fig. 2.53). Genetic counseling and prenatal diagnosis, particularly in severe variants, should be discussed with the family. Prenatal diagnosis is possible in some variants, using gene markers on amniocytes or electron microscopy on fetal skin biopsies.

In children with no family history of EB, it may be difficult to determine a prognosis in the newborn period. Infants with dystrophic EB may do very well, and children with junctional disease may develop a downhill course after a period of stabilization. In

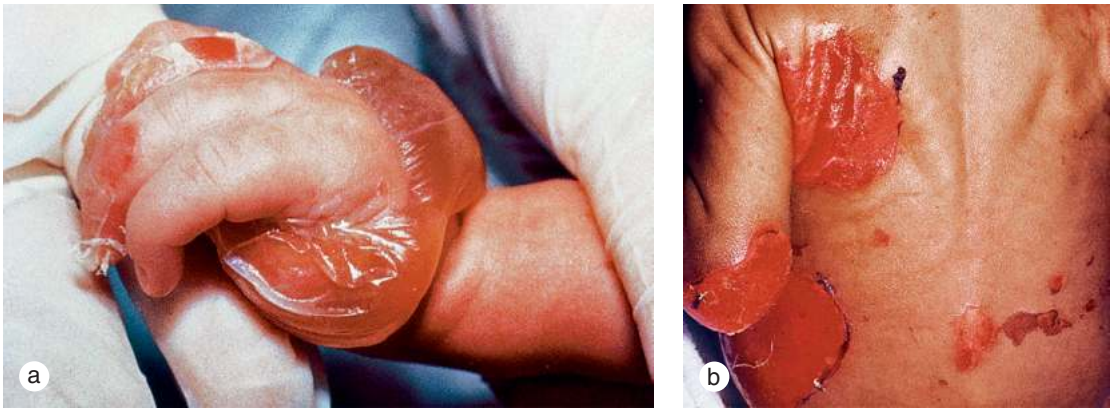


Fig 2.51 Junctional epidermolysis bullosa. Widespread involvement was seen in this infant at birth. **(a)** Note the erosions and the large, intact blister over the thumb and dorsum of the hand. **(b)** Large, denuded areas occur over the back and buttocks.

this setting, the practitioner should be reassuring and postpone discussion of prognosis until after a period of observation.

Treatment is dependent on the severity of EB. In mild variants, patients learn to avoid trauma that triggers bullae formation. Pain and progression of large blisters may be controlled by gently unroofing lesions or cutting a square skin window and covering with a topical antibiotic ointment and sterile gauze. Adhesives are applied from dressing to dressing and kept out of direct contact with the skin.

In severely affected children, the practitioner must orchestrate a multidisciplinary approach to management. The dermatologist, ophthalmologist, gastroenterologist, otolaryngologist, plastic surgeon, thoracic surgeon, dentist, and physical therapist, may be involved in care. Preventive care includes avoidance of trauma to the skin and mucous membranes, and early treatment of infection with topical and oral antibiotics. Iron may be required to replace chronic blood losses through the skin. Adaptic®, Vaseline® gauze, and Telfa® dressings help to retain moisture, reduce pain, and facilitate healing of erosions and ulcers. Topical dressings are gently held in place by clean wraps, such as gauze or Kling®, and soaked off without tearing at fresh granulation tissue. Semipermeable dressings (N-ter-face®, Ensure®, Vigilon®, Mepilex, Mepitel)



Fig 2.52 Dystrophic epidermolysis bullosa. **(a)** Blisters, erosions, and hundreds of milia are seen on the foot and ankle and **(b)** hand of this newborn. **(c)** In this child, severe scarring encased the fingers, resulting in syndactyly. **(d)** Recurrent blistering resulted in scarring and permanent nail loss in this adolescent.

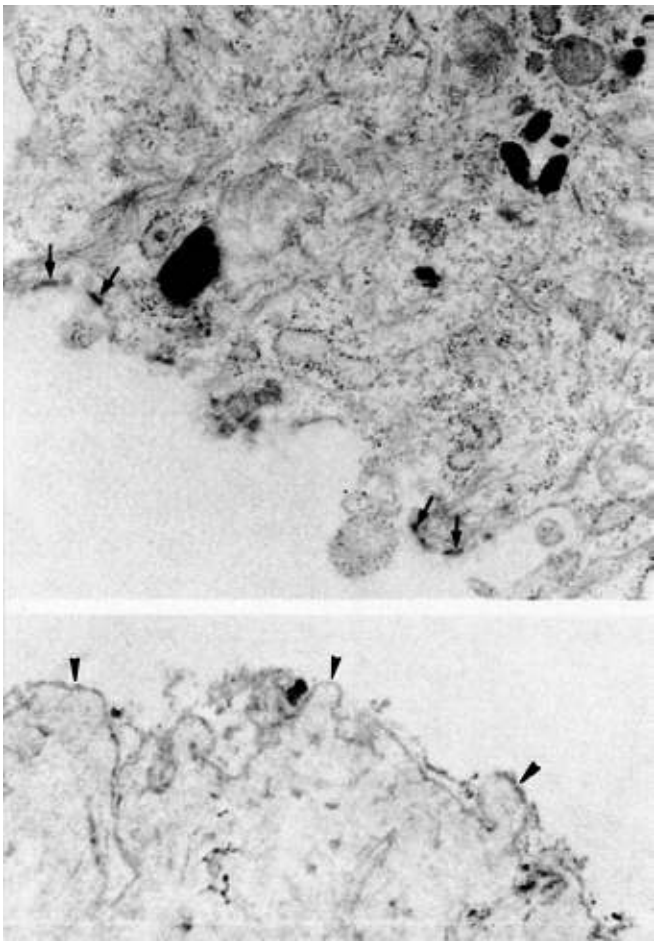


Fig 2.53 Electron microscopic examination of a skin biopsy from a newborn with junctional epidermolysis bullosa revealed hypoplastic hemidesmosomes (top, arrows) in the basal keratinocyte and lamina densa (bottom, arrowheads) on the dermal side due to separation within the lamina lucida.

and occlusive dressings (Duoderm®, Comfeel®) may be useful in the treatment of recalcitrant wounds. Good nutrition is mandatory for cutaneous healing and normal growth and development.

Aplasia cutis congenita

Aplasia cutis congenita is a heterogeneous group of disorders, the common feature of which is congenital absence of the skin. Although the cause is unknown, this entity has been recognized for over 250 years. In the classic form, one or several erosions or ulcerations covered with a crust or thin membrane involve the vertex of the scalp (Fig. 2.54). Healing with atrophic, hairless scars occurs over 2–6 months, depending on the size and depth of the ulceration (which may extend through the soft tissue into bone). This benign variant may be inherited as an autosomal dominant trait or occur sporadically. Less commonly, the trunk and extremities are involved and lesions may be associated with limb defects, EB, and chromosomal aberrations (Fig. 2.55). Lesions occurring on the scalp with a ring of surrounding long, dark hairs, known as the hair collar sign, are a forme fruste of a neural tube defect. MRI is warranted to evaluate for connection to the underlying brain and bone.

In uncomplicated aplasia cutis congenita, the defect is amenable to simple excision during later childhood or adult life. Large lesions may require staged excision and the use of tissue expanders (Fig. 2.56). In the newborn, care must be taken to evaluate the depth of the defect, prevent further tissue damage and infection, and search for associated anomalies. Gentle normal saline compresses, topical antibiotics, and sterile dressings are adequate for most patients. Large defects may respond to occlusive dressings (Duoderm®, Comfeel®). Occasionally, early surgical intervention is necessary.



Fig 2.54 Aplasia cutis congenita. This child, his mother, and his grandfather had similar hairless, atrophic plaques on the occiput. A thin, hemorrhagic membrane was noted at birth.

Perinatal trauma to the scalp may result in similar defects noted at birth or within the first month of life. Scalp blood sampling, monitor electrodes, and forceps may produce small ulcers that heal with scarring (Fig. 2.57). Halo scalp ring is another form of localized scalp injury rarely associated with caput succedaneum and cephalohematoma, which occasionally resolves with a scarring alopecia (Fig. 2.58). Other nevoid malformations, which commonly present as hairless patches on the scalp, resemble aplasia cutis congenita. However, these birthmarks do not appear crusted or atrophic and usually develop distinctive clinical features (Fig. 2.59) (see also Fig. 2.81; epidermal nevi and Fig. 2.82; sebaceous nevi). Some congenital pigmented nevi on the scalp that are lightly pigmented can also mimic aplasia cutis congenita.

Congenital erosive and vesicular dermatosis healing with supple reticulated scarring

Congenital erosive and vesicular dermatosis healing with supple reticulated scarring must be distinguished from EB and aplasia cutis congenita. Affected infants demonstrate widespread erythema, blistering, and erosions at birth involving >75% of body surface area, which heal within a few weeks to a few months with widespread reticulated scars (Fig. 2.60). Nails, scalp, and the tongue and oral mucosa may be involved. The majority of children are born prematurely and in many cases there is a history of maternal chorioamnionitis. Although most children grow and develop normally, abnormal neurodevelopment occurs in many cases.

Cases occur sporadically, and no inheritance pattern has been established. Extensive evaluations have excluded bacterial, fungal, and viral infections. Some infants have shown evidence of vascular insults in visceral sites and/or the placenta. However, the relationship between these findings and cutaneous lesions is unclear.

Unlike EB, new blisters do not occur except transiently in areas of old scarring. The pattern of blisters and erosions and subsequent



Fig 2.55 Aplasia cutis congenita. **(a)** An isolated cutaneous defect was evident on the arm of this newborn. **(b)** This premature infant with a small defect on the back of the neck had hemiatrophy of the right side of the body (Adams–Oliver syndrome).



Fig 2.56 Aplasia cutis congenita. **(a)** An extensive area of aplasia cutis was noted on the scalp of this newborn. **(b)** After 5 months the scalp was almost completely healed. When the child was 5 years old, the residual scar was repaired following tissue expansion.

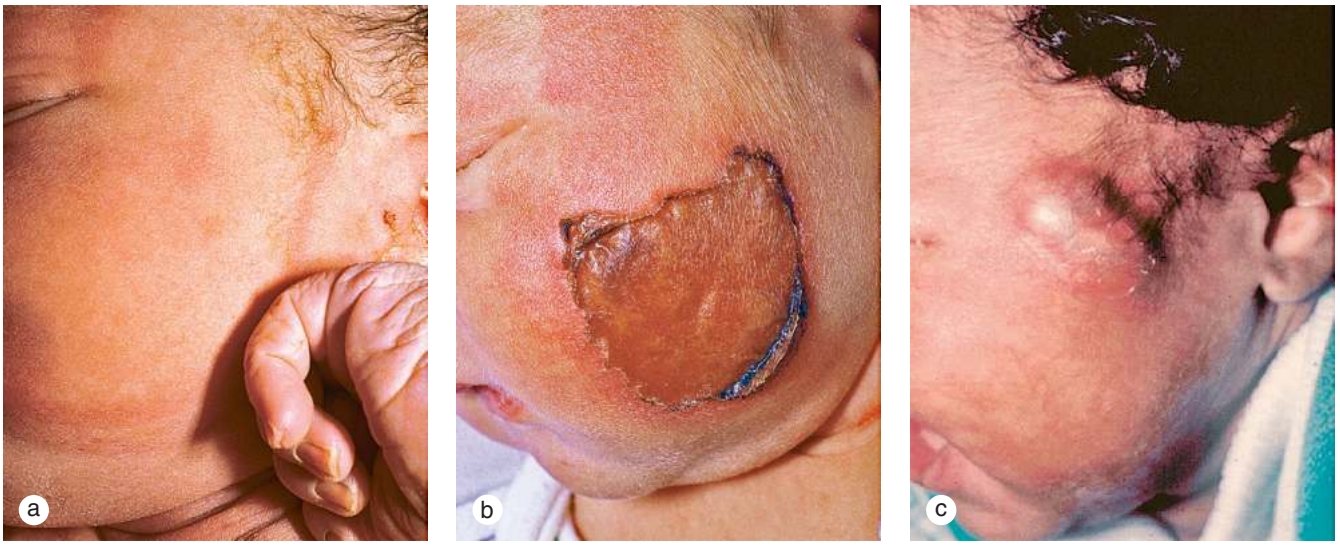


Fig 2.57 Similar defects to aplasia cutis congenita. **(a)** Forceps injuries are most commonly associated with bruising. However, **(b)** superficial necrosis and **(c)** fat necrosis occur rarely.



Fig 2.58 Perinatal trauma. **(a)** Cephalohematoma, a subperiosteal bleed which usually resolves uneventfully. **(b,c)** Rarely, perinatal trauma to the scalp results in a 'halo scalp ring' with scarring and permanent hair loss.

scarring differs markedly from aplasia cutis congenita and incontinentia pigmenti.

Mastocytosis

Mastocytosis may first come to clinical attention when cutaneous lesions blister. The disorder typically presents at birth or in the first few months of life as a solitary mastocytoma or multiple lesions of urticaria pigmentosa, otherwise known as cutaneous mastocytosis (Fig. 2.61). Most patients present as sporadic cases, but rare families with multiple affected individuals have been reported. C-kit autoactivating mutations that allow for persistent mast cell development are thought to play a role in adult mastocytosis and some cases of childhood disease.

Although the trunk is most commonly involved, these benign macules, papules, and plaques that contain aggregates of mast cells may involve any cutaneous site, as well as the gastrointestinal tract, bone marrow, lungs, kidneys, and nervous system. Skin lesions range from under 1 cm in diameter to large, infiltrated confluent plaques that cover the entire chest or back (Fig. 2.61d). Although the overlying epidermis may appear normal at birth, increasing age is associated with progressive localized hyperpigmentation and a leathery texture.

Nonspecific triggers of mast-cell degranulation, such as rubbing, hot water, vigorous physical activity, and certain medications (e.g. aspirin, anesthetic agents, radiography contrast material), may produce urtication of cutaneous lesions. Darier sign is a reliable physical finding in mastocytosis and refers to the hive that forms after stroking affected skin. If a Darier sign can be demonstrated, a skin biopsy to confirm the diagnosis is usually unnecessary. Infants are particularly prone to blister formation, and widespread blistering can be associated with fluid and electrolyte losses and increased risk of infection. Rarely, the release of histamine and other vasoactive mediators from mast cells triggers acute or chronic symptoms, including chronic diarrhea, gastric ulceration, uncontrolled pruritus, bleeding, and hypotension.

Pruritus and systemic symptoms are usually controlled with antihistamines. In infants with bullous mastocytosis and/or systemic disease, oral cromolyn sodium 20–40 mg/kg per day may be life-saving. In severe cases, topical corticosteroids under occlusion, systemic corticosteroids, or photochemotherapy (psoralen-ultraviolet A light, PUVA) may be useful. In many children, the number of papules and plaques increases for 1–2 years. During childhood, mastocytomas usually become less reactive and tan or brown overlying pigmentation fades slowly. Hyperpigmentation, urtication, and systemic symptoms may persist, however, in some individuals.

Incontinentia pigmenti

Incontinentia pigmenti is a neurocutaneous syndrome named for the peculiar marble-cake swirls of brown pigment that appear on the trunk and occasionally the extremities in later infancy and early childhood. In the newborn, patches of erythema and blisters are scattered on the trunk, scalp, and extremities. Blisters are typically oriented in reticulated lines and swirls that follow the lines of Blaschko, special embryonic cleavage planes (Fig. 2.62a,b). Although inflammatory lesions may recur for months, they usually give way to hyperkeratotic, warty plaques by several weeks to several months of age (Fig. 2.62c). The hyperkeratotic stage is typically followed by increasing pigmentation at 2–6 months of age (Fig. 2.62d). During later childhood, brown streaks often fade to leave atrophic hypopigmented patches. Although these subtle scars may be the only manifestation of cutaneous disease in older children and adults (Fig. 2.62e), missing teeth, dental malformations, and rarely nail dystrophy associated with recurrent or persistent subungual warty nodules may provide additional clues (Fig. 2.62f).

Histopathology of blisters in the newborn demonstrates characteristic intraepidermal edema and vesicles loaded with eosinophils. When incontinentia pigmenti is suspected, the child must be

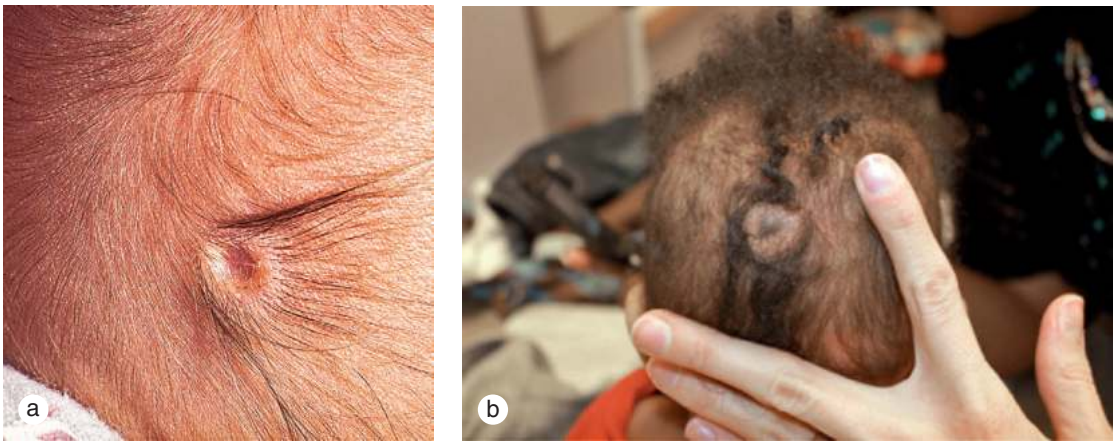


Fig 2.59 (a) Hair collar sign on the scalp of a newborn. **(b)** This healthy 4-month-old infant presented with a hair collar sign. MRI showed no underlying abnormality. (b, Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure.)

evaluated for associated defects, which may involve the central nervous system, heart, eye, skeletal system, and dentition. Incontinentia pigmenti is inherited as an X-linked dominant disorder that is lethal in males; 97% of affected infants are female. A careful examination of mothers often reveals subtle cutaneous findings. Mutations in the NEMO gene have been identified in 85% of patients tested.

NEVI/BIRTHMARKS

Nevus is a term used to describe a group of skin lesions that appear at birth or in the first months of life. Nevi are composed of mature or nearly mature cutaneous elements organized in an abnormal fashion. These hamartomas may comprise virtually any epidermal or dermal structure.

Vascular anomalies

For therapeutic and prognostic reasons, clinicians must distinguish between vascular malformations and hemangiomas and other less common vascular tumors of infancy. This categorization of vascular birthmarks, which is now widely accepted, was first proposed by Mulliken in 1982 and modified by the International Society for the Study of Vascular Anomalies in 1996. Accordingly, molecular and ultrastructural markers, histological findings, and biological behavior help to distinguish vascular malformations, which are composed of dysplastic vessels, from proliferative, hyperplastic vascular tumors (Table 2.5).

Vascular malformations are further divided based upon flow characteristics and the predominant type of vascular anomaly into slow-flow capillary, venous, and lymphatic malformations and fast-flow arterial or arteriovenous malformations (Table 2.6). Complex malformations may include components of several

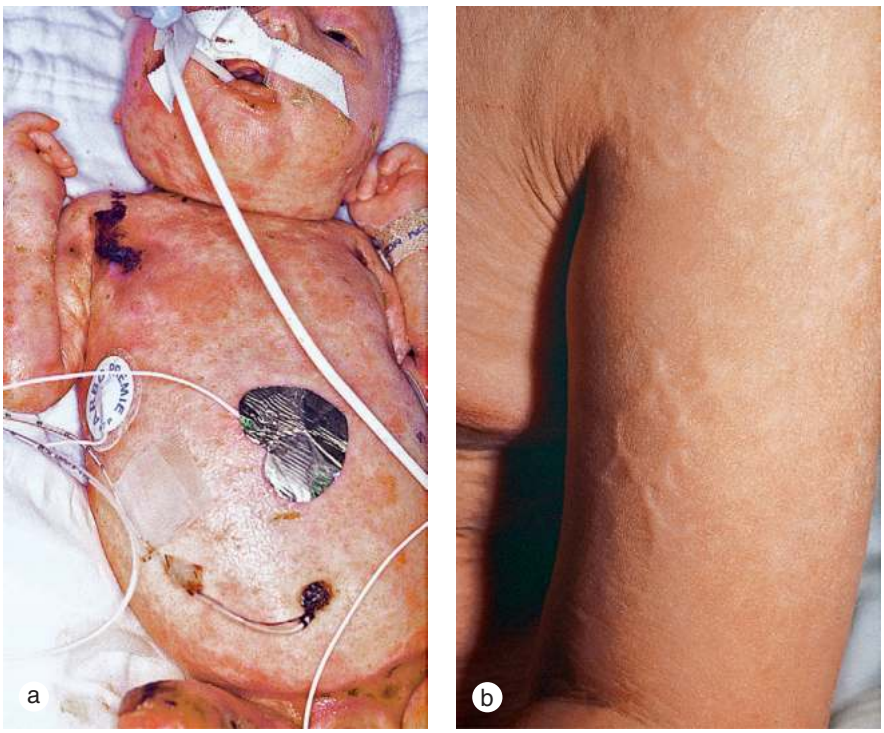


Fig 2.60 Congenital erosive and vesicular dermatosis. **(a)** Extensive vesicles and erosions were noted on the skin of this child in the delivery room. **(b)** Erosions and crusts healed with widespread reticulated, supple scarring.









Fig 2.61 Mastocytosis. **(a)** A Darier sign became evident in a single lesion on the back after rubbing (a, Courtesy Katherine B. Püttgen. Katherine B. Püttgen retains copyright of this figure). Brown macules and plaques typical of urticaria pigmentosa were scattered on the trunk of this infant. **(b)** Hyperpigmentation is prominent in this healthy black infant with urticaria pigmentosa. Note the blisters on her forehead. **(c)** Vesicles and crusted papules on a red urticarial base were present at birth in this asymptomatic newborn. After the crusts healed, no blisters recurred. **(d)** This infant with diffuse infiltrative lesions had widespread blistering and bleeding into lesions.

Distinguishing features of hemangioma versus vascular malformation

	Hemangioma	Vascular malformation
Clinical features	Subtle at birth Early rapid growth Slow spontaneous regression	Usually visible at birth Proportionate growth
Sex ratio	3 : 1 female predominance	1 : 1
Pathology	Proliferative neoplasm Hyperplastic endothelial cells	Flat endothelial cells Mature vascular structures
Bone changes	Rarely mass effect	Variable distortion, thinning, invasion, rare destruction
Immunohistochemical markers	Markers of proliferative vascular tumors	Lack of expression of markers
Coagulopathy	None (usually associated with other vascular tumors, e.g. tufted angioma)	Slow-flow venous, lymphatic and combined lymphatic-venous malformations May develop coagulopathy

Table 2.5 Distinguishing features of hemangioma versus vascular malformation



Fig 2.62 Incontinentia pigmenti. Vesicles on an erythematous base extended in a linear pattern down the **(a)** legs and **(b)** trunk of an 8-day-old girl. **(c)** Warty papules developed on the fingers of this 4-month-old girl in the site of earlier vesicles. **(d)** Progressive 'marble cake' hyperpigmentation was first noted on the trunk of this patient at 4 months of age. **(e)** Subtle scarring on the legs was the only sign of incontinentia pigmenti in the mother of the child. Note the absence of hair follicles in the linear scars. **(f)** This 60-year-old woman with incontinentia pigmenti has had recurrent warty subungual nodules and nail dystrophy since adolescence. A biopsy showed eosinophilic dermal inflammation and dyskeratosis.

Vascular malformations	
Vascular anomaly	**Flow characteristics**
Infantile hemangioma	Fast
Capillary malformation	Slow
Venous malformation	Slow
Lymphatic malformation	Slow
Arteriovenous malformation	Fast

Table 2.6 Vascular malformations

different vascular structures. Although simple uncomplicated lesions tend to be localized and well circumscribed, large segmental or widely disseminated lesions are often complex and associated with extracutaneous anomalies.

Hemangiomas are the most common vascular neoplasm of infancy and occur in nearly 10% of Caucasian newborns by 12 months of age. They must be distinguished from the rare kaposiform hemangioendothelioma and tufted angioma which may be associated with the development of disseminated coagulopathy known as Kasabach–Merritt syndrome. A number of other tumors of infancy may present as bluish-purple lesions that may be confused with hemangiomas. Clinical features, course, and histopathologic findings help to differentiate these lesions.

Vascular malformations

Capillary malformations

Salmon patches are common innocent capillary malformations which occur in 60–70% of newborns (Fig. 2.63). Lesions are usually located on the nape of the neck (stork bite), glabella, forehead (angel kiss), upper eyelids, and sacrum. Although salmon patches on the face usually fade during the first year of life and tend to be camouflaged by normal pigmentation, they may persist indefinitely when located on the neck and sacrum. The pink patches also darken with crying, breath holding, and physical exertion. These lesions are not associated with extracutaneous findings and do not usually require further evaluation.

At birth, 0.2–0.3% of newborns have port-wine stains (PWS). Unlike salmon patches, PWS represents a capillary malformation that tends to persist unchanged during childhood and to darken and thicken in adolescence and adulthood (Figs 2.64–2.66). Progressive angiomatous papules and nodules and underlying soft tissue hypertrophy develop gradually over years (Fig. 2.66). Although unilateral lesions on the head and neck are most common, any part of the body surface and mucous membranes may be involved.

Occasionally, PWS provide a clue to extracutaneous defects. More than 35 named syndromes have been described in association with cutaneous vascular malformations.

Children with involvement of the first division of the trigeminal nerve may have a vascular malformation of the ipsilateral meninges, cerebral cortex, and eye (Sturge–Weber syndrome; Fig. 2.64). Seizures, mental retardation, hemiplegia, and glaucoma may develop during the first several years of life. Superficial vascular lesions associated with limb or segmental trunk hypertrophy are typical of Klippel–Trénaunay syndrome, which is the eponymous term for a capillary venous or capillary lymphatic venous malformation (Fig. 2.65). Up to 50% of these patients may have underlying malformations of the deep venous system as well.

Phakomatosis pigmentovascularis is a malformation syndrome in which a capillary malformation is associated with either an



Fig 2.63 Salmon patches. **(a)** Typical, light-red, splotchy patch at the nape of the neck in a healthy newborn. **(b)** Similar patches were present on this child's eyelids, nose, upper lip, and chin.

epidermal nevus (Type I), dermal melanocytosis (i.e. Mongolian spot) with or without nevus anemicus (Type II), nevus spilus with or without nevus anemicus (Type III), or dermal melanocytosis and nevus spilus with or without nevus anemicus (Type IV). In Maffucci syndrome superficial venous malformations are associated with deep complex venous and lymphatic malformations and multiple enchondromas of bone, particularly the long bones (Fig. 2.67). There is a risk of malignant degeneration to chondrosarcomas, particularly affecting the skull.

Cutis marmorata telangiectatica congenita (CMTC), also know as congenital phlebectasia, presents with distinctive localized, segmental, or widespread reticulated blanching patches (Fig. 2.68). Although CMTC can involve any site, there is a preponderance of lesions on the extremities. Cases are usually sporadic, more common in girls, and more commonly reported in association with extracutaneous anomalies (musculoskeletal anomalies, coarctation of the aorta and other arterial and venous anomalies, cardiac defects, aplastic cutis congenita) than typical capillary malformations. However, this may represent a reporting bias; most lesions are probably restricted to the skin and contiguous soft tissue. Diffuse atrophy of the involved limb or reticulated atrophy following the course of vascular changes may develop, and erosions or ulcerations may follow with minor trauma.

Infants with PWS deserve a thorough physical examination for signs of systemic disease. Children with forehead and periorbital



Fig 2.64 Port-wine stains. **(a)** A port-wine stain involved the ophthalmic distribution of the trigeminal nerve on the face of this infant with Sturge–Weber syndrome. **(b)** After four treatments with the yellow-pulsed dye laser the lesion had almost completely resolved.

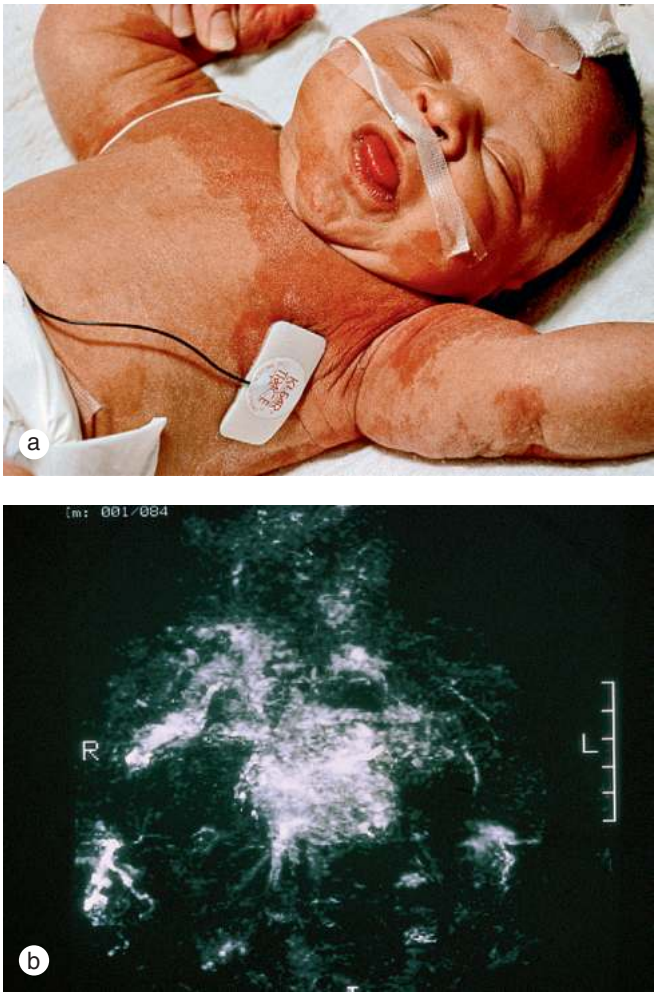


Fig 2.65 Port-wine stains. **(a)** At birth this newborn had a port-wine stain that involved his upper chest, neck, and portions of both arms and was associated with soft-tissue hypertrophy (Klippel–Trénaunay–Weber syndrome) and high-output cardiac failure. **(b)** This composite magnetic resonance image of his body demonstrates increased blood flow to the right side of his neck and both upper extremities, with the greatest flow to the right shoulder and arm.

involvement require careful neurodevelopmental follow-up, regular eye examinations to exclude glaucoma, and further neurologic studies as indicated.

Rehabilitative cosmetics (e.g. Dermablend®, Covermark®) provide reasonable, safe, but temporary camouflage of PWSs (Fig. 2.69). Definitive treatment eluded practitioners until approval of the pulsed dye laser in the early 1980s (Fig. 2.64b); while refinements in laser technology continue to occur the original physics of the pulsed dye laser remain relatively unchanged from original models. Unlike previous modalities, including the argon and carbon dioxide lasers, the pulsed-dye laser has an extremely low risk of scarring. By selective photothermolysis the yellow beam damages vascular structures while leaving the surrounding skin virtually unscathed. This device is safe, relatively painless, and effective in infants and children, as well as in adults. Maximal improvement of PWS requires multiple treatments separated by a 6–10-week healing period. Because the laser penetrates only 1.5–2 mm deep into the skin it results in little improvement in those malformations with a deep component. Consequently, early



Fig 2.66 Port-wine stain. Purple papules and nodules began to appear in this congenital port-wine stain on the neck of a 48-year-old man. The nodules disappeared with pulsed dye laser therapy.





Fig 2.67 (a,b) Maffucci syndrome. This 50-year-old woman had extensive port-wine stains and venous malformations on her trunk and extremities. She subsequently developed multiple firm nodules on her hands and feet.





Fig 2.68 Cutis marmorata telangiectatica congenital. Localized reticulated vascular malformations were present in these healthy infants with lesions on **(a)** the right knee and **(b)** the left leg. A complete medical evaluation failed to reveal other abnormalities.

treatment in childhood produces the best outcome with the fewest number of treatments and the least cost. With increased use of lasers, recurrence of PWS has been documented and patients should be counseled that further treatment may be required in the years following completion of laser therapy.

Venous malformations

Venous malformations are slow-flow congenital anomalies comprised of large dilated vascular channels lined by flat endothelium. The walls of these vessels are generally thin and fibrous. Although they may be found at any level in the skin or mucous membranes, they tend to occur in the mid to deep dermis and fat.



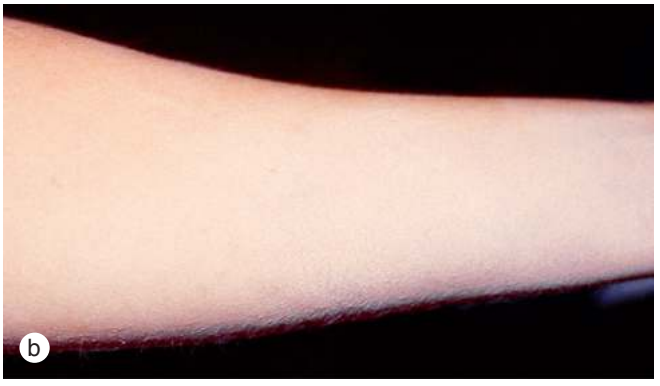


Fig 2.69 Port-wine stains. **(a)** An extensive port-wine stain on the arm of this teenager. **(b)** It was readily camouflaged with a corrective cosmetic.



Fig 2.70 Blue rubber bleb nevus syndrome. A 16-year-old girl was evaluated for multiple 3 mm–1 cm blue nodules on the skin. She had a history of similar lesions in the gastrointestinal tract which were discovered during surgery for small bowel obstruction from intussusception.



Fig 2.72 Lymphangioma circumscriptum. A small cluster of grayish-purple vesicles on the knee of an adolescent demonstrates the typical 'frog spawn' appearance.

Superficial venous malformations present as scattered or grouped blue or purple papules and nodules (Fig. 2.70). Deeper lesions may demonstrate a subtle blue hue at the surface and are defined by the partially compressible ropy texture (Fig. 2.71). Small localized lesions usually occur as isolated malformations, but large or disseminated lesions should raise the possibility of a more complex malformation syndrome such as blue rubber bleb nevus syndrome or Maffucci syndrome.

Over time, venous malformations can produce distortion in underlying bone and significant disfigurement, while lesions located near joints may be associated with increasing swelling, pain and functional impairment. Although many lesions can be managed with conservative measures such as compression garments, high-risk or symptomatic lesions may be ablated with a combination of percutaneous sclerotherapy and surgical excision.



Fig 2.71 Venous malformation. A small subcutaneous congenital venous malformation on the right 2nd finger was associated with aching pain particularly following intense physical activity in this 6-year-old boy.

Lymphatic malformations

Microcystic lymphatic malformations, referred to in older literature as lymphangioma circumscriptum, are a group of localized congenital malformations of the lymphatic system, most of which become clinically evident at birth or during infancy. These lesions may represent lymphatic structures that failed to link with the rest of the lymphatic or venous system. Clinically similar lesions may result from lymphedema secondary to tumor infiltration, surgical or accidental injury to normal lymphatics. Larger deeper lesions characterized by larger lymph-filled cystic spaces are known as macrocystic lymphatic malformations; these have a predilection for the head and neck (see Fig 9.13a) and may surround and compress vital structures in the anterior neck. Their presence may be marked by overlying superficial lymphatic malformations or capillary vascular malformations such as a port-wine stain. Combined microcystic and macrocystic lesions can occur. Some 90% of lymphatic malformations involve skin and soft tissue and the remaining 10% involve viscera or bone.

Superficial lymphatic malformations consist of one or several patches of thick-walled skin-colored to gray vesicles that resemble fish eggs or frog spawn (Fig. 2.72). Thrombosis or bleeding into vesicles after trauma may result in purple or black discoloration. Lesions may be associated with an underlying soft-tissue fullness or extensive swelling of the involved area. Although there is a predilection for involvement of the proximal extremities and limb girdle regions, lesions may occur at any cutaneous or mucous membrane site.

Lymphatic malformations may be associated with complex congenital vascular malformations (Fig. 2.73). In Proteus syndrome, extensive dermal and subcutaneous lymphatic and venous malformations are associated with cutaneous PWS, soft-tissue tumors, and epidermal nevi. Vascular malformations may extend into the mediastinum, peritoneum, retroperitoneal space, and viscera. Organ dysfunction, recurrent soft-tissue infection, and musculoskeletal involvement may be debilitating and life-threatening.

Surgical management of lymphangiomas is difficult, because they often extend around vital structures, and recurrence rates are high.



Fig 2.73 Proteus syndrome. Massive hypertrophy of the leg was associated with an extensive cutaneous port-wine stain, soft-tissue tumors, and a deep lymphangiohemangioma that involved the thigh, peritoneal cavity, and retroperitoneal space in this 1-month-old boy.

Superficial lesions may be ablated with the carbon dioxide laser, and deeper malformations may improve with sclerotherapy.

Arteriovenous malformations

Arteriovenous malformations are uncommon fast-flow anomalies that arise most commonly on the head and neck; they represent the most dangerous of all vascular anomalies and are associated with significant potential morbidity. About half of the lesions are present at birth when they may be mistaken for capillary or venous malformations. In some patients a tense vascular mass, palpable thrill, bruit, and infiltration of the overlying skin provide clues. Ultrasound and magnetic resonance imaging studies will demonstrate the true character of these lesions. Arteriovenous malformations are potentially life-threatening anomalies that may suddenly expand after accidental trauma or partial surgical excision. Enlargement may also occur during puberty, pregnancy, or after trauma.

Vascular tumors

Hemangiomas

Although a recognizable lesion is only rarely present at birth, hemangiomas occur in up to 10% of Caucasian infants by 1 year of age (Fig. 2.74). Infantile hemangiomas (IH) are two to three times more common in girls. Prematurity has recently been shown to be the most significant risk factor for the development of IH. Lesions typically begin with a nascent phase as barely visible telangiectasias or red macules that rapidly grow into bright red partially compressible tumors. The early telangiectasias with surrounding pallor are often present at birth or within the first few days of life and may be mistaken for capillary malformations or minor birth trauma. Many IH have a deep dermal or subcutaneous component (Fig. 2.75). Occasionally, lesions lack a superficial component altogether and can only be differentiated from vascular malformations by the growth pattern (Fig. 2.76). Histologically, early rapidly growing lesions are highly cellular and demonstrate small slit-like vascular lumina. As lesions mature the vascular lumina become better defined, and the endothelium lining of vessels becomes flatter. Healing is mediated by apoptosis and a subsequent reduction in cell proliferation. Regression is associated with fibrosis and replacement of the vascular tissue with fat.

Infantile hemangiomas generally double in size in the first 2 months of life and reach 80% of their maximum size by 3–5 months of age (the early proliferative phase.) Proliferation may continue at a slower rate in some lesions until 6–12 months of age. Signs of early involution, such as graying of the surface and flattening of the deeper component, subsequently develop. Regression occurs in roughly 25% by age 2 years, 40–50% by age 4 years, 60–75% by age 6 years, and 95% by adolescence. Involution is independent of sex, location, and number of hemangiomas.

Unfortunately, scarring, loose skin, or telangiectasias remain in up to 50% of children. Both deep and segmental IH have a longer growth phase and subsequently take longer to regress. Another small group of hemangiomas is fully formed at birth and referred to as congenital hemangiomas or rapidly involuting congenital hemangiomas (RICH). The majority of reported lesions began to regress shortly after birth, and many disappeared in 12–18 months.

Although hemangiomas are benign tumors and regression is the rule, these lesions may rarely compromise vital functions when they are located near the anus, urethra, airway, or eye. Hemangiomas around the eye or extending into the orbit may be associated with obstruction amblyopia or direct damage to orbital contents (Fig. 2.77). Multiple hemangiomas or single, large, rapidly growing lesions in young infants may be associated with high-output cardiac failure or disseminated intravascular coagulation (Kasabach–Merritt syndrome; see Fig. 2.80b). In children with more than five cutaneous IH, lesions may involve internal organs, including the liver, gastrointestinal tract, lungs, kidneys, and central nervous system (Fig. 2.78).

In children in whom IH pose a threat to function of an organ or where they present with disfigurement severe enough to likely result in the need for future surgery, medical treatment is warranted. The traditional therapy for over 40 years has been high-dose corticosteroids (prednisolone at 2–3 (and sometimes up to 5) mg/kg per day). Since the introduction of propranolol in 2008, as an additional therapeutic option in the treatment of IH, its use has become widespread. While randomized placebo-controlled trials are lacking, propranolol does appear to have eclipsed use of oral corticosteroids by the majority of practitioners due to its apparent improved safety and efficacy in retrospective comparisons. As a non-selective beta-blocker, propranolol's greatest risks in this population include hypoglycemia, hypotension, and bradycardia. Combined therapy with propranolol and oral corticosteroids is occasionally necessary for severe lesions. Since the discovery in the mid-1990s of the up to 20% risk of spastic diplegia in infants under 1 year of age when treated with interferon-α, this therapy has fallen out of favor. Other interferon-α side-effects include fever, neutropenia, elevated liver function tests, flu-like symptoms, and increased fussiness. Vincristine is a third-line option in the setting of life-threatening IH. In selected lesions, there may be a role for intralesional steroids and/or early surgical excision during the proliferative phase of growth. However, in the majority of cases, surgery should be deferred until partial or complete involution has occurred.

Hemangiomas in the diaper area and other skin creases are prone to ulceration and infection (Fig. 2.79). Careful hygiene, topical and systemic antibiotics, occlusive dressings, barrier pastes, and pulsed dye laser may be required to prevent cellulitis and scarring. Failure of these conservative interventions should prompt discussion of systemic therapy in ulcerated IH associated with persistent pain, infection, and/or bleeding.

In general, IH are not associated with extracutaneous syndromes, but there are some notable exceptions. Midline hemangiomas, particularly in the lumbosacral area, with segmental morphology or large size may be associated with underlying vertebral and spinal

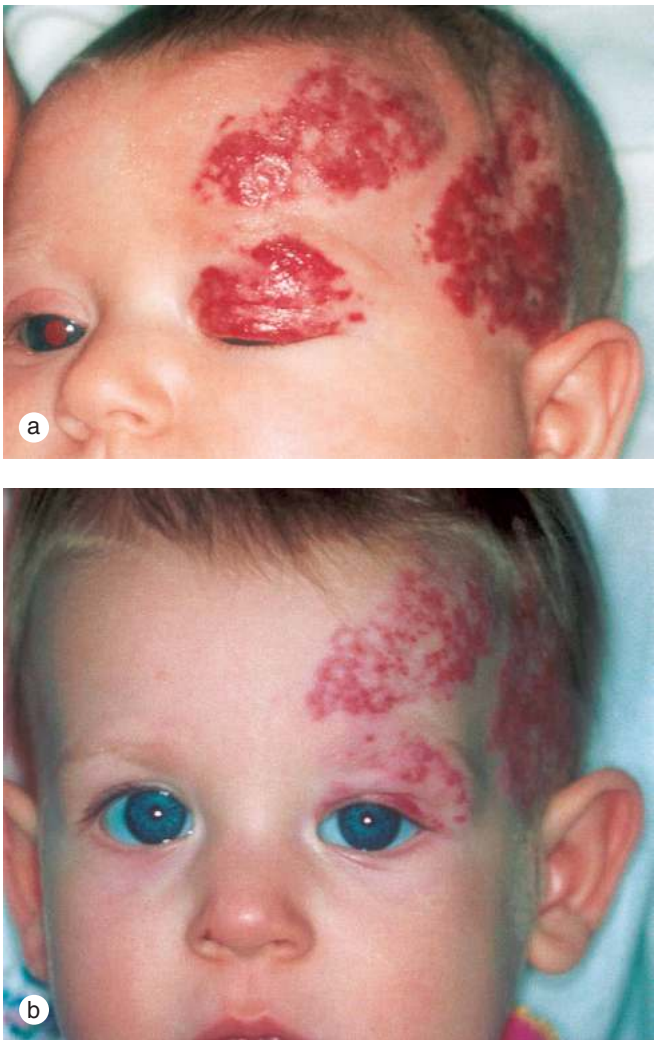




Fig 2.74 Regressing hemangioma. **(a)** This large segmental hemangioma which appeared at 2 weeks of age was treated with high-dose oral steroids for 4 months because of obstruction of the left eye. **(b)** At 2 years later the lesion had decreased dramatically, and **(c)** by age 7, there were only subtle residual changes.



Fig 2.75 The segmental infantile hemangioma on this child's forehead had both a superficial and a deep dermal component. The hemangioma involuted over 3 years without leaving a scar.

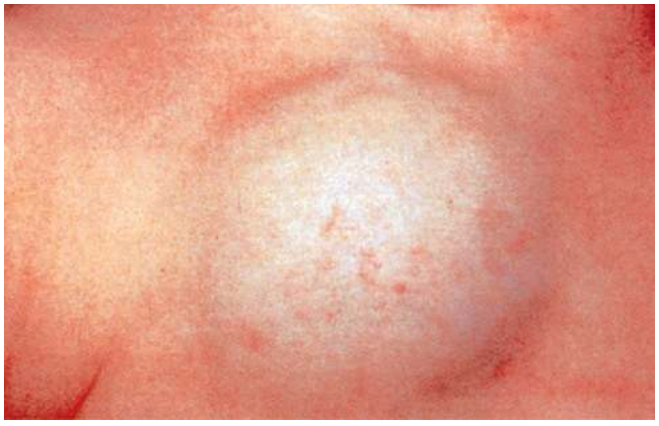


Fig 2.76 Deep infantile hemangioma. The vessels that make up this large, partially compressible lesion are deep beneath the skin surface, but still impart a bluish hue to the overlying skin. Note the indistinctness of the margins.



Fig 2.77 This regressing segmental infantile hemangioma extended into the orbit and produced a large refractive difference between the two sides. The tumor also produced destruction of the nasal septum and obstructed the airway, which resulted in the need for tracheostomy.



Fig 2.78 Hemangiomatosis. Multiple hemangiomas dotted the back and extremities of this 3-month-old girl.



Fig 2.79 A large hemangioma on the back of a 10-month-old girl developed an area of central necrosis that was associated with secondary bacterial infection and sepsis.

cord anomalies (Fig. 2.80a). The association of lumbosacral IH and underlying genitourinary, spinal and renal anomalies have been reported by various authors under the acronyms of LUMBAR, SACRAL and PELVIS syndromes. Ultrasound within the first 8–12 weeks can be used to exclude these anomalies; after this window of time, MRI is necessary. Massive hemangiomas on the face and scalp have been associated with PHACE syndrome or **P**osterior fossa brain malformations, **H**emangiomas, **A**rterial anomalies, **C**ardiac defects, and **E**ye defects. Magnetic resonance imaging (MRI) has proved particularly useful for delineating the extent of these defects.

Although the yellow pulsed-dye laser was originally approved for treating PWS, it appears to be useful in treating early, thin hemangiomas and residual telangiectasias later in childhood. The superficial component of rapidly growing hemangiomas can be shut off with the pulsed-dye laser, and overlying ulcerations, which have failed to respond to topical measures, heal quickly after laser therapy. However, the pulsed-dye laser is not effective for preventing or eradicating the deeper component of hemangiomas.

Hemangiomas must be distinguished from other vascular tumors of infancy. Pyogenic granuloma is a common vascular tumor, composed of granulation-like tissue that usually arises after the newborn period typically in older infants and toddlers. The lesion presents as a bloody, crusted nodule usually under 1 cm in diameter. Pyogenic granulomas are common on the face and are treated by destruction with electrocautery or laser. Tufted angiomas appear at birth or within the first few years of life as infiltrated red to purple plaques or large firm exophytic nodules. Although many have a protracted course, some involute without treatment within the first 2 years of life or respond to oral steroids. A skin biopsy may be necessary to distinguish tufted angiomas from rare sarcomas of early infancy. Kasabach–Merritt syndrome is usually associated with tufted angioma, kaposiform hemangioendothelioma, or occasionally hemangiopericytoma, all of which share clinical features with hemangiomas (Fig. 2.80b).

Hamartomatous nevi

Hamartomatous nevi include a number of birthmarks that contain various epidermal, dermal, and subcutaneous structures.

Epidermal nevi

Epidermal nevi occur in 0.1–1% of children and consist of proliferating epidermal keratinocytes. Most epidermal nevi appear at birth or during early infancy as localized, linear, warty, subtly to markedly hyperpigmented plaques (Fig. 2.81). Lesions may involve any cutaneous site and extend onto mucous membranes. Epidermal nevi range in size from a few millimeters to extensive lesions that involve a large portion of the trunk and extremities. Infants with large lesions must be evaluated for associated defects, which include seizures, mental retardation, and skeletal and ocular defects (epidermal nevus syndrome). Occasionally, children with small epidermal nevi also demonstrate extracutaneous anomalies. Skin lesions may respond to the application of topical retinoids or keratolytics such as lactic acid, salicylic acid, and urea. Small lesions can be excised or ablated by carbon dioxide laser.

Sebaceous nevi

Nevus sebaceus of Jadassohn is characterized by a linear, crescent-shaped, or round, hairless, yellow, cobblestone-like plaque on the scalp (Fig. 2.82a). Although lesions usually involve the head and neck, nevi occasionally appear on the trunk and extremities. Rarely, lesions extend over a large portion of the body surface and are associated with multiple neuroectodermal and mesodermal defects (nevus sebaceous syndrome). Histology demonstrates

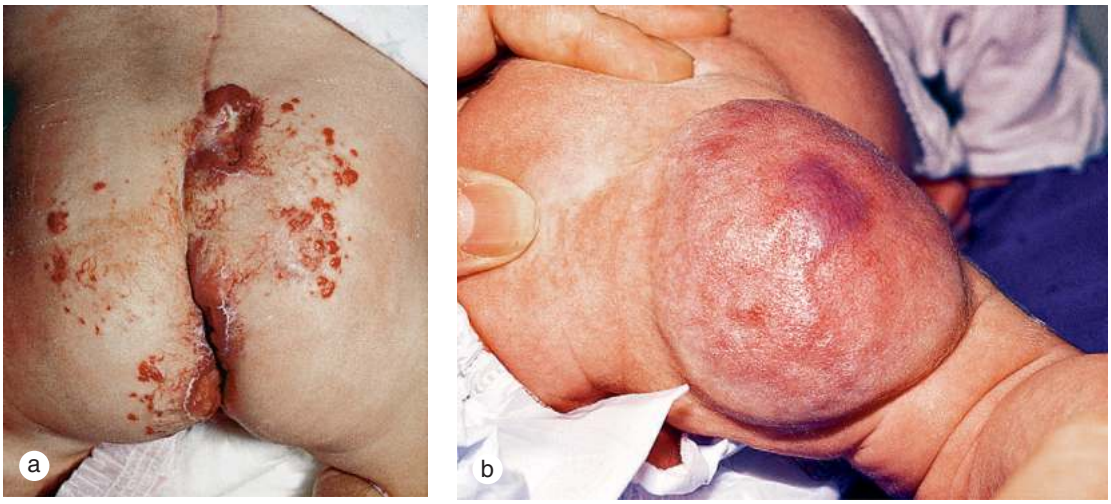


Fig 2.80 Complicated hemangiomas. **(a)** This extensive sacral hemangioma was associated with a tethered cord. Note the scar from correction of the spinal defect. Ulceration of the hemangioma from irritation in the diaper area was a recurrent problem. **(b)** A violaceous patch on the back of the left thigh in a 3-week-old infant suddenly became firm and elevated. A complete blood count revealed a platelet count of 5000, and a biopsy showed a kaposiform hemangioendothelioma. The lesion did not improve with systemic steroids or interferon, but several months later it suddenly flattened and the platelet count jumped to over 1 000 000.

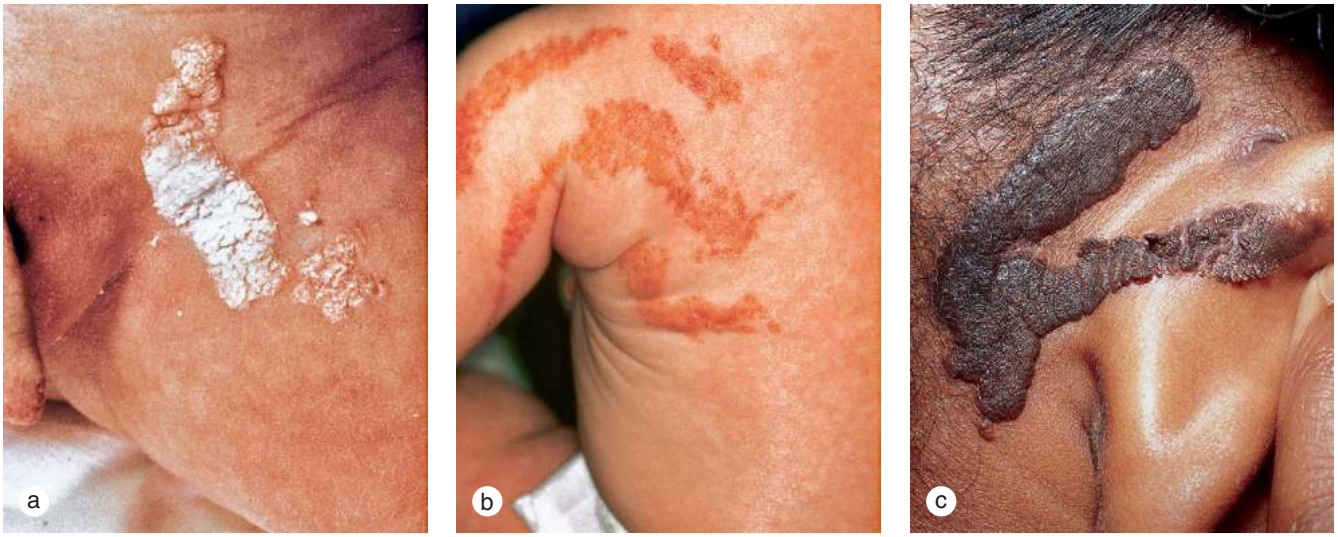


Fig 2.81 Epidermal nevi. **(a)** An epidermal nevus on the upper thigh of a newborn still covered with vernix caseosa. **(b)** Three linear, warty plaques extend across the upper chest and down the arm of a healthy toddler. **(c)** A 10-year-old girl complained of itching from a congenital, V-shaped, warty plaque behind her ear.

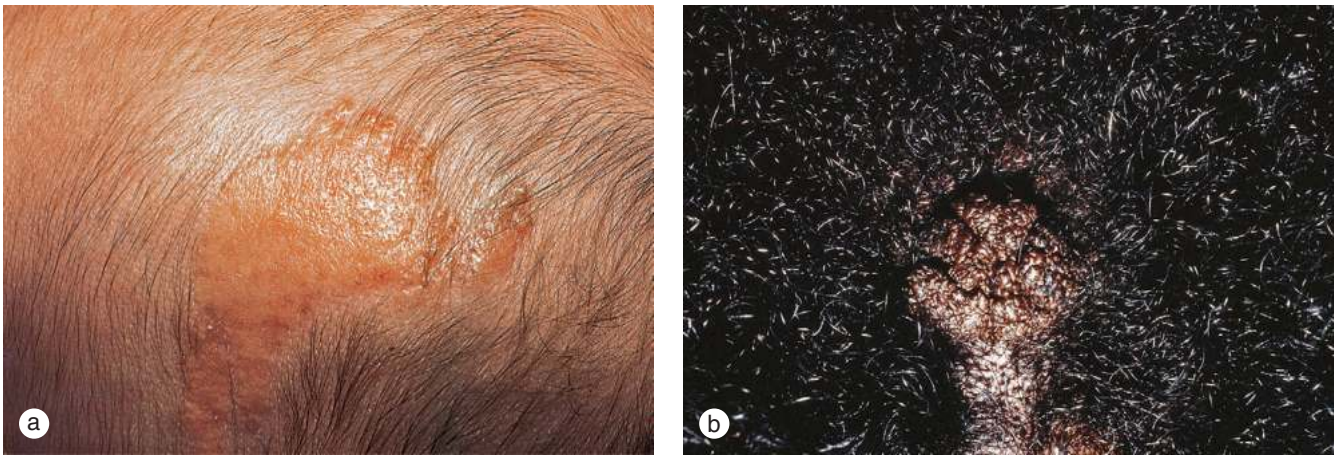


Fig 2.82 Sebaceous nevi. **(a)** Sebaceous nevus of Jadassohn. A yellow, cobblestone-like, hairless patch present since birth. **(b)** Syringocystadenoma papilliferum arose in this sebaceous nevus on the scalp of a teenage boy. Local excision gave an excellent cosmetic result.



Fig 2.83 Congenital smooth muscle hamartoma. This slightly hairy plaque on the left buttock of a 3-year-old girl demonstrates a pseudo-Darier's sign.



Fig 2.84 Connective tissue nevus. This reticulated fibrotic plaque on the arm of a 10-year-old boy remained unchanged since birth. A medical evaluation for associated disorders was unrevealing.

multiple sebaceous glands, ectopic apocrine glands, and incompletely differentiated hair structures.

In the past, basal cell carcinomas were thought to be the most common neoplasm arising within sebaceous nevi with an incidence in adults ranging from 10% to 20%. However, current evidence suggests that most basaloid neoplasms are actually benign trichoblastomas with basal cell carcinomas accounting for <1%. A number of other benign lesions have also been reported primarily in adults (Fig. 2.82b). Benign hypertrophy of the sebaceous and apocrine components associated with the development of warty nodules and plaques can occur transiently at birth, but is often progressive at puberty. Elective excision of problematic lesions can be delayed until puberty in most patients.

Smooth muscle and pilar hamartomas

Smooth muscle and pilar hamartomas contain smooth muscle bundles and may be associated with prominent hair follicles (Fig. 2.83). Clinically, these innocent nevi are characterized by minimally hyperpigmented, supple 1.0–5.0 cm diameter plaques on the trunk. A pseudo-Darier sign or rippling of the skin occurs with rubbing. Hyperpigmentation and hair may become prominent. These lesions do not contain nevocellular nevus cells and pose no risk of malignancy. They may mimic the histologic and clinical features of Becker nevus, also known as hairy epidermal nevus.

Connective tissue nevus

Connective tissue nevus defines a group of hamartomas with increased quantities of dermal collagen and variable changes in elastic tissue (Fig. 2.84). Lesions appear in the newborn as 1.0–10 cm diameter plaques composed of fibrotic papules and nodules, which often give a *peau d'orange* texture to the skin. Although typically located on the trunk, lesions may be widely disseminated and any cutaneous site may be involved.

Connective tissue nevi may occur as isolated skin findings or in association with asymptomatic osteopoikilosis or radiographic densities in the long bones and the bones of the hands and feet (Buschke–Ollendorff syndrome). The shagreen patch of tuberous sclerosis cannot be differentiated clinically and histologically from an innocent connective tissue nevus. Consequently, a careful search for other stigmata of tuberous sclerosis must be performed in all children with these hamartomas.

Congenital pigmented nevi

Congenital pigmented nevi are pigmented macules or plaques, often with dense hair growth noted at birth or during the first few months of life (Fig. 2.85). Pigmented nevi contain nevomelanocytic nevus cells, cells derived from neural crest and that share with normal skin melanocytes the ability to produce melanin. At birth, the lesions may be light tan with lightly pigmented vellus hairs. During infancy the nevus darkens and hair may become prominent. Occasionally, darkly pigmented lesions lighten during the first 1–2 years of life. Small dark macules or nodules may also appear within the borders of the nevus (Fig. 2.85b).

Giant, congenital pigmented nevi may reach over 20 cm in diameter and are associated with a 2–6% lifetime risk of melanoma (Fig. 2.85c,d). The highest risk of malignant change occurs in the first 10 years of life, prior to puberty. Other tumors of neural-crest origin rarely arise within large lesions (Fig. 2.85c). Multistage procedures with tissue expansion may be feasible in selected patients. Unfortunately, large areas of the nevus may not be amenable to surgical management, and close observation with photographs is required. Trials with dermabrasion and laser surgery in infancy have been disappointing. Regular examinations include careful palpation of the entire lesion, because melanomas may arise deep within the nevus. Some practitioners recommend periodic MRI or CT scans to follow large nevi. Radioimaging studies can also be used to document leptomeningeal involvement, which is commonly associated with giant pigmented nevi that cover the scalp, neck, and/or back. The presence of inaccessible central nervous system lesions is important when assessing the risk of malignancy and planning surgical intervention.

Medium-size (1.5–19.9 cm diameter) and small (under 1.5 cm diameter) congenital pigmented nevi may also be associated with a higher risk of malignant change than acquired moles. However, the incidence is unknown, and there are no uniformly accepted guidelines for their management. Small size and high parental anxiety may dictate early surgical excision, but removal of these nevi is usually safely left until later childhood when local anesthetic and outpatient surgery is possible. The vast majority of small congenital nevi follow a benign course and observation throughout life is reasonable.

TUMORS

In addition to nevi, a number of other disorders present as lumps and bumps in the newborn. Many of these lesions are self-limited (fat necrosis, juvenile xanthogranuloma, hematoma) or innocent (dermoid cyst, lipoma), but some tumors herald the onset of serious systemic disease (leukemia, neuroblastoma, rhabdomyosarcoma).



Fig 2.85 Congenital pigmented nevi. **(a)** This small congenital pigmented nevus was associated with a tuft of dark hair on the scalp of an infant. **(b)** An innocent medium-size 5 cm by 3 cm nevus uniformly studded with dark brown papules on the back of a 3-year-old boy was unchanged since birth. **(c)** A giant pigmented nevus contained numerous darkly pigmented nodules. This child had leptomeningeal involvement and developed a malignant melanoma in the central nervous system. **(d)** A large tumor developed within a giant pigmented nevus which involved the diaper area of this newborn. The tumor contained structures that arose from various neuroectodermal elements. The tumor was excised in several stages.

Juvenile xanthogranulomas

Juvenile xanthogranulomas (JXGs) commonly present at birth or within the first year of life (Fig. 2.86). Enlarging, 0.5–4.0 cm diameter, pink to yellow papules, plaques, and nodules with overlying telangiectasias involve the head, neck, trunk, and occasionally the extremities. Nearly half of the lesions are solitary, but multiple nodules may be scattered over the skin surface.

A confirmatory skin biopsy demonstrates characteristic lipid-laden histiocytes. Generally, JXGs are asymptomatic, and laboratory studies, which include a serum lipid profile, are normal. However, the presence of multiple cutaneous lesions, especially in a child presented at <2 years of age, should prompt referral to a pediatric ophthalmologist for eye exam. JXGs are the most common cause of spontaneous anterior chamber hemorrhage (hyphema) in children. Further extracutaneous work-up should be based on symptoms.

In most children, no therapy is required. Surgical excision can lead to unnecessary scarring, and in early infancy to recurrent lesions at the operative site; also, new lesions may continue to erupt for several months. After a period of growth in infancy, JXGs slowly flatten, and involution is often complete by mid-childhood (Fig. 2.86b).

Dermoid cysts

Dermoid cysts appear as 1.0–4.0 cm diameter compressible or rubbery subcutaneous nodules at the site of closure of embryonic clefts. Although the lesions are usually noted in the newborn, subtle cysts may escape detection until they become inflamed in later infancy or early childhood. The forehead and periorbital area (Fig. 2.87a) are the most common sites of involvement, but dermoids occasionally present on the mid chest, sacrum, perineum, and scrotum (Fig. 2.87b).

Dermoid cysts are lined by an epidermis that contains mature adnexal structures, which include sebaceous glands, eccrine glands, and apocrine glands. Although there is no risk of malignancy, lesions on the head may extend to the periosteum and cause erosion of the underlying bone. Cysts may be surgically excised during infancy or childhood.

Lesions on the head must be differentiated from hematomas, encephaloceles, and malignant tumors. A CT scan and MRI of the head demonstrate the cystic nature of the dermoid cyst and exclude the possibility of communication with the central nervous system or infiltrative tumor.

Dermoids that overlie the sacrum may be associated with occult defects of the vertebral column and spinal cord. The tumor and associated anomalies can be visualized with ultrasound and MRI.

Recurrent infantile digital fibroma

In recurrent infantile digital fibroma, single or multiple fibrous nodules appear on the fingers and toes (Fig. 2.88). Although these







Fig 2.86 Juvenile xanthogranuloma. **(a)** This tumor developed abruptly on the chin of a 3-month-old boy. Numerous tiny papules developed around the primary lesion. **(b)** After 1 year the tumor and satellites had almost completely resolved without treatment. **(c)** A solitary xanthogranuloma on the leg of an infant shows the typical yellow plaque with surrounding telangiectasias.



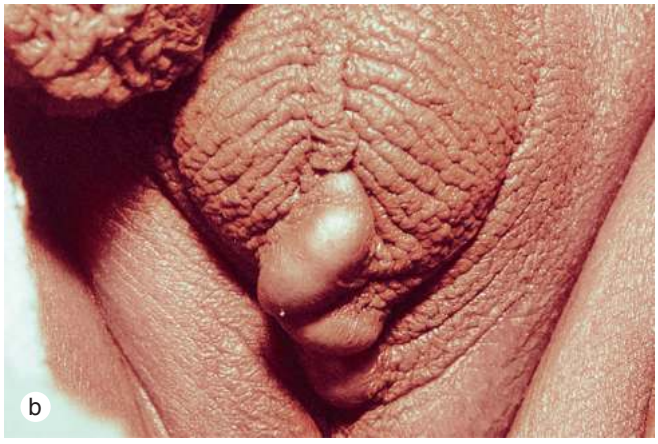


Fig 2.87 Dermoid cyst. **(a)** This partially compressible mass was present on the nose at birth. A computed tomography scan of the head (to exclude a communication with the underlying central nervous system) was normal. **(b)** This cyst on the median raphe of the scrotum of a 4-month-old remained unchanged from birth.



Fig 2.88 Recurrent infantile digital fibroma. This tumor on the finger of a 7-month-old boy recurred after local excision. However, after an initial growth phase, it began to involute without further therapy.



Fig 2.89 Myofibromatosis. An infiltrating subcutaneous tumor on the thigh of a 1-month-old infant demonstrated histologic features of myofibromatosis. Other benign and malignant tumors, which include neuroblastoma, leukemia, and lymphoma, should be considered in the differential diagnosis.



Fig 2.90 Blueberry muffin rash. This infant with congenital rubella demonstrated the typical cutaneous lesions of extramedullary hematopoiesis. (Reprinted with permission from Bernard A. Cohen© DermAtlas, Johns Hopkins University; 2000–2012)

tumors may occur in older children, 85% are diagnosed before 1 year of age and many are noted at birth or in the 1st month of life. Lesions rarely exceed 2.0 cm in diameter. Skin biopsy demonstrates numerous fibroblasts and interlacing collagen bundles. The presence of perinuclear intracytoplasmic inclusion bodies was considered to suggest a viral etiology, but this has been refuted by electron-microscopy studies. Although excision is followed by recurrence in 75% of cases, most digital fibromas involute spontaneously within several years.

Infantile myofibromatosis

Infantile myofibromatosis, also referred to as congenital fibromatosis, usually presents as a solitary, firm, red or blue, mobile, subcutaneous tumor (Fig. 2.89). However, multiple tumors may involve muscle and bone, and visceral lesions may produce organ dysfunction, particularly in the lungs. Histologically, these well-circumscribed tumors contain fibroblasts and smooth muscle cells with no cytologic atypia. Solitary lesions are usually excised without recurrence, but new tumors may erupt for the first several months of life. In the majority of infants who do not have severe visceral disease, spontaneous involution occurs in the 1st year of life.

Malignant tumors

Malignant tumors rarely present at birth or in the newborn period. Of patients with neuroblastoma, 50% are diagnosed in the first 2 years of life, and many develop clinical disease before 6 months of age. Although cutaneous metastases are seen in only about 3% of all patients with neuroblastoma, nearly one-third of affected newborns present with skin lesions as their initial manifestation. Metastases usually appear as 0.5–2.0 cm diameter, firm bluish-red papules and nodules on the trunk and extremities. Stroking results in blanching and a red halo, probably because of the release of catecholamines from tumor cells. These 'blueberry muffin' lesions must be differentiated from areas of extramedullary hematopoiesis seen in infants with congenital infections, such as rubella, cytomegalovirus, and toxoplasmosis (Fig. 2.90).

Cutaneous plaques and tumors may also be the earliest finding in newborns with leukemia (Fig. 2.91), rhabdomyosarcoma (Fig. 2.92), lymphoma, and a number of other carcinomas and sarcomas. Skin biopsy of rapidly growing or infiltrative lesions may lead to early diagnosis and therapy.

REACTIVE ERYTHEMAS

Reactive erythema refers to a group of disorders characterized by erythematous macules, plaques, and nodules, which vary in size, shape, and distribution. Unlike specific dermatoses, they represent reaction patterns in the skin triggered by a number of different endogenous and environmental factors. In infants, erythema multiforme, erythema nodosum, urticaria, and vasculitis occur



Fig 2.91 Congenital leukemia cutis. This newborn presented with a hemoglobin of 5.0 g/dL (3.1 mmol/L) and infiltrative, pale pink, annular plaques on the extremities.



Fig 2.92 Rhabdomyosarcoma. This rapidly growing congenital mass was part of an infiltrating rhabdomyosarcoma that involved the cheek, orbit, nose, and sinuses of this infant. This child was treated with surgical debulking of the mass and chemotherapy.

after exposure to various infections and drugs. Just as in older children and adults, management of affected infants involves identification and elimination of the offending agent and supportive care. Several reactive erythemas, however, are peculiar to infancy.

Neonatal lupus erythematosus

Neonatal lupus erythematosus is the most common cause of congenital heart block. Although cutaneous lesions may not appear until several months of age, they are frequently present at birth. Affected infants demonstrate annular erythematous plaques with a central scale, telangiectasias, atrophy, and pigmentary changes (Fig. 2.93). Lesions are typically in the range 0.5–3.0 cm in diameter and may spread from the scalp and face to the neck, upper trunk, and upper extremities. Although development of the cutaneous rash does not require sunlight, it may be triggered or exacerbated by sun exposure.

The cause of neonatal lupus is unknown. However, the presence of transplacentally acquired anti-ssA (Ro) and anti-ssB (La) antibodies is thought to play a primary role in the pathogenesis of the disorder. In adults, anti-ssA and anti-ssB antibodies are associated with Sjögren syndrome and a photosensitive variant of systemic lupus known as subacute cutaneous lupus erythematosus.

In addition to conduction defects and structural cardiac anomalies, affected infants may develop hepatosplenomegaly, anemia, leukopenia, thrombocytopenia, and lymphadenopathy. With the exception of cardiac involvement, neonatal lupus usually resolves spontaneously in 6–12 months, as transplacentally derived antibody wanes. The use of low- and medium-potency topical corticosteroids on intensely inflammatory cutaneous lesions for several weeks may reduce the risk of scarring. Subtle atrophy, telangiectasias, and pigmentary changes may persist indefinitely. Rarely, infants require systemic corticosteroids and supportive care. Parents are instructed to protect children with sunscreens

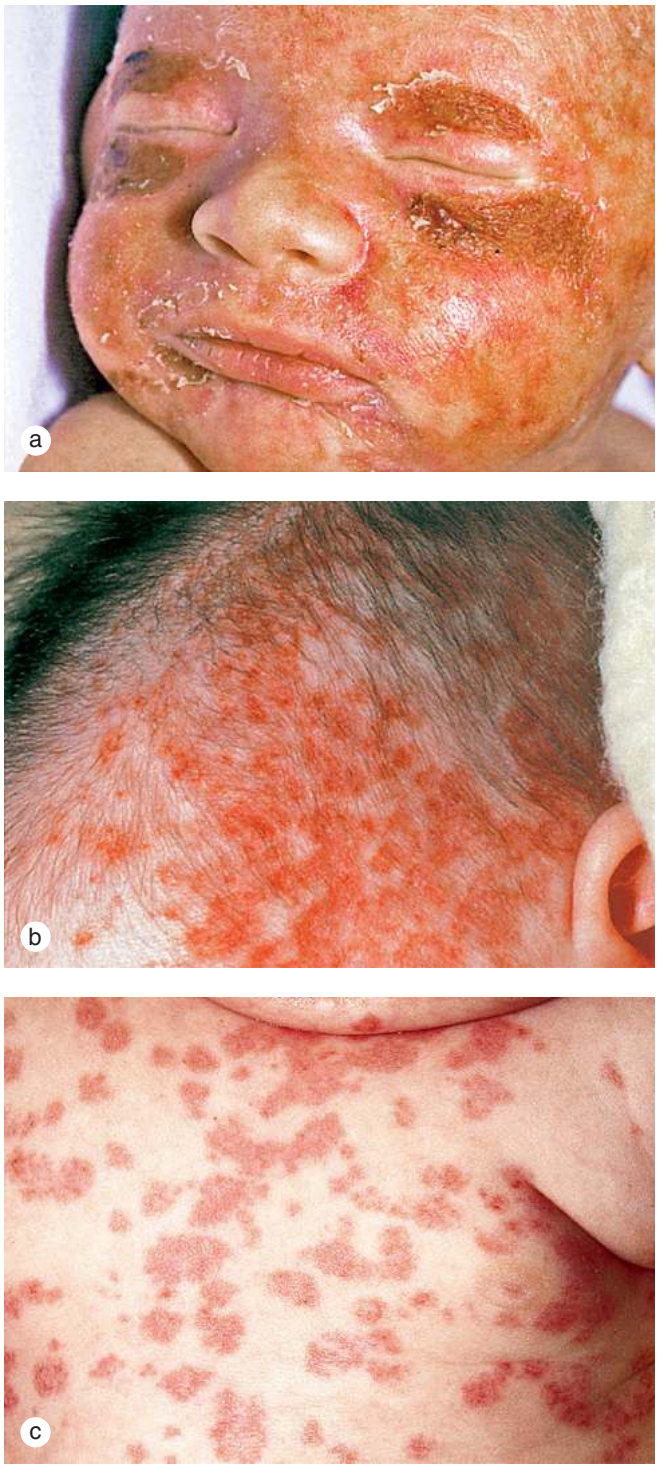


Fig 2.93 Neonatal lupus erythematosus. **(a)** This newborn presented with extensive cutaneous atrophy and telangiectasias of the face, hepatosplenomegaly, and thrombocytopenia. **(b,c)** At 1 month of age, this infant developed an extensive eruption of annular red plaques with central atrophy. **(b)** Lesions first appeared on the scalp and face, and **(c)** subsequently spread to the neck and trunk.

and to ensure that the infant avoids direct sun exposure for at least 4–6 months. Mothers who have no clinical signs of lupus also require careful follow-up, because they are at increased risk of developing overt disease.

Annular erythema of infancy

Annular erythema of infancy is an innocent gyrate erythema that presents during the first 6 months of life with red papules and plaques that enlarge in a centrifugal pattern (Fig. 2.94). Lesions may develop a dusky center and exceed 10 cm in diameter over 1–3 weeks. Plaques periodically fade, only to recur for months to years. Although this reaction may be triggered by infections, drugs, and malignancy, evaluation for an underlying disease is usually unrevealing. Fortunately, infants generally continue to thrive and most lesions eventually resolve without treatment. However, in a subset of infants with familial annular erythema, lesions may persist indefinitely.



Fig 2.94 Annular erythema of infancy. This eruption persisted for months on the trunk and extremities of an otherwise healthy infant.

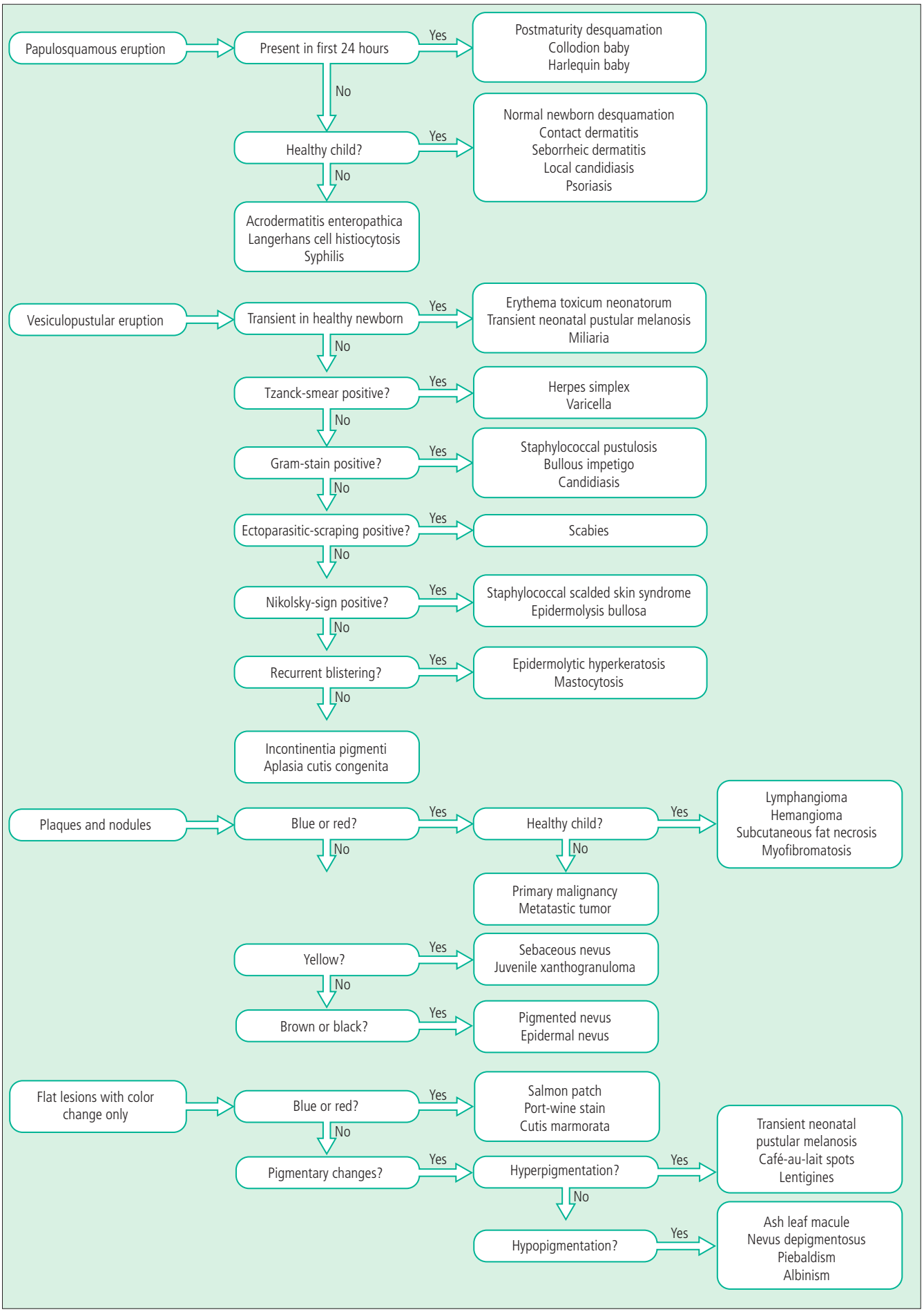


Fig 2.95 Algorithm for evaluation of neonatal rashes.

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Chapter 3

Papulosquamous Eruptions

Bernard A. Cohen

INTRODUCTION

Papulosquamous eruptions comprise a group of disorders characterized by the presence of superficial papules and scale. These conditions account for a large number of patients in both pediatric dermatology and pediatric primary-care practice. In disorders of keratinization (psoriasis, pityriasis rubra pilaris, keratosis follicularis, ichthyosis, hyperkeratosis of the palms and soles, and porokeratosis), cutaneous lesions develop as a result of genetically programmed retention or increased production of scale in the epidermis. In the inflammatory dermatoses (dermatitides, pityriasis rosea, pityriasis lichenoides, lichenoid dermatoses, and fungal infections), clinical findings result from epidermal response to dermal inflammation. An algorithmic approach to diagnosis for the papulosquamous disorders is summarized at the end of the chapter (see Fig. 3.55).

DISORDERS OF KERATINIZATION

Psoriasis

Psoriasis is a common disorder characterized by red, well-demarcated plaques with a dry, thick, silvery scale (Fig. 3.1). The



Fig 3.1 Psoriasis. **(a)** Typical erythematous plaques are topped by a silver scale on the trunk of an adolescent. **(b)** Thick tenacious scale extends from the forehead, neck, and ears onto the scalp of this 10-year-old girl. **(c)** Thick plaques on the palms, soles, elbows, and knees of this 8-year-old boy caused severe pain when he attempted to walk or use his hands. **(d)** Another boy with an impressive plantar keratoderma had difficulty walking. **(e)** Widespread guttate lesions erupted on the trunk and extremities of this child 1 week after a streptococcal pharyngitis.

condition affects 1–3% of Americans, of whom an estimated 40% develop the eruption before the age of 20 years. Psychosocial impairment in addition to physical symptoms make early diagnosis and intervention critical in children and adolescents.

Psoriasis is a multifactorial disorder with both hereditary and environmental components. In more than one-third of patients, other family members are affected. A number of human leukocyte antigen (e.g. HLA Cw6) types have been associated with psoriasis in different populations. Several genetic loci have been under investigation, and recent studies suggest a major susceptibility region for early-onset psoriasis on chromosome 6p21.3. Although the factors that initiate the rapid turnover in epidermal cells, which contributes to psoriatic plaques, are unknown, upper respiratory tract viral and streptococcal infections, urinary tract infections, and other infections are known to precipitate outbreaks in genetically predisposed individuals. Triggers of psoriasis also include drugs (interferon, lithium, carbamazepine, indometacin, beta-blockers, terfenadine, terbinafine, isotretinoin, antimalarials), climate, cigarette smoking, alcohol, psychologic stress, and malignancy. Once the process is initiated, keratinocytes within the epidermis, under the influence of cytokines and cells of the immune system, amplify the psoriatic cascade resulting in angiogenesis, hyperproliferation, and altered cell differentiation.

Cutaneous lesions tend to locate on the scalp, the sacrum, and the extensor surfaces of the extremities. About 50% of children present with large plaques over the knees and elbows. Thickening and fissuring of the skin of the palms and soles (keratoderma) may also be present (Fig. 3.1c,d). In one-third of children, many drop-like lesions (guttate psoriasis) are scattered over the body, including the face, trunk, and extremities (Fig. 3.1e). In infancy, psoriasis may present as a persistent diaper dermatitis. In older children, the eyelids, genitals, and periumbilical areas are commonly involved (Fig. 3.2). Scalp disease may develop as an isolated finding, but is often seen with other variants (Fig. 3.1b). Itchy red plaques with thick, tenacious scale are often evident at the frontal hair line and around the ears. Nail changes, which may also occur as the first manifestation of psoriasis, include onycholysis (separation of the nail plate from the nail bed to produce 'oil drop changes'), nail pitting, yellowing, increased friability, and subungual hyperkeratosis (see Fig. 8.58a,b).

Of psoriasis patients, 8% suffer from psoriatic arthritis, one of the seronegative spondyloarthropathies. In half of these individuals arthritis develops before the skin rash. Examination of the joints characteristically demonstrates heat, pain, and swelling of multiple joints of the hands and feet, particularly the distal interphalangeal joints. The arthritis tends to be progressive with the development of flexure deformities and contractures. In addition to the typical lesions of plaque psoriasis, patients often demonstrate severe psoriatic involvement of the hands, nails, and feet (Fig. 3.3). The HLA B-27 antigen is usually positive.

Rarely, children develop erythrodermic psoriasis with acute widespread erythema and scaling or pustular psoriasis with generalized erythema and pustule formation (Fig. 3.4). These variants are associated with high fevers, chills, arthralgias, myalgias, and severe cutaneous tenderness. Fluid and electrolyte losses and leukocytosis may be marked. Secondary bacterial infection and sepsis can occur.

Psoriatic lesions are often induced in areas of local injury, such as scratches, surgical scars, or sunburn, a response termed the Koebner or isomorphic phenomenon (Fig. 3.5). In areas of thick scale, tortuous capillary loops proliferate close to the surface. Gentle removal of the scale results in multiple, small bleeding points, referred to as the Auspitz sign (Fig. 3.6).



Fig 3.2 These lesions were present on the **(a)** eyelids, **(b)** penis and navel of this 8-year-old boy for 6 months before **(c)** he developed widespread papules and plaques on his arms and legs. **(d)** This 11-year-old girl had a persistent periumbilical plaque for over a year.



Fig 3.3 Psoriasis and psoriatic arthritis were debilitating in this adolescent girl.

The diagnosis is usually made by identifying the typical morphology and by the distribution of skin lesions. Confirmatory skin biopsy findings include regular thickening of the epidermal rete ridges, elongation and edema of the dermal papillae, thinning of the epidermis overlying tortuous dermal capillaries, absence of the granular layer, parakeratosis, spongiform pustules, and Munro microabscesses. In children skin biopsies may not always be diagnostic, particularly in early disease and certain anatomic sites such as the keratoderma of the palms and soles.

The course of psoriasis is chronic and unpredictable, marked by remissions and exacerbations. A number of different topical agents, which include lubricants, corticosteroids, tar, dithranol (anthralin), and keratolytics, are useful in managing cutaneous lesions. Topical calcipotriol (and other vitamin D3 analogs), tazarotene (a member of the acetylenic class of retinoids), and topical corticosteroids with ultra-high potency may also play a role in the treatment of thick, localized plaques in some children. Occlusive dressings and pulsed dye laser, which targets tortuous vessels at the base of psoriatic plaques, may be useful in localized disease. Disseminated, chronic or recalcitrant disease may require ultraviolet (UV) light therapy

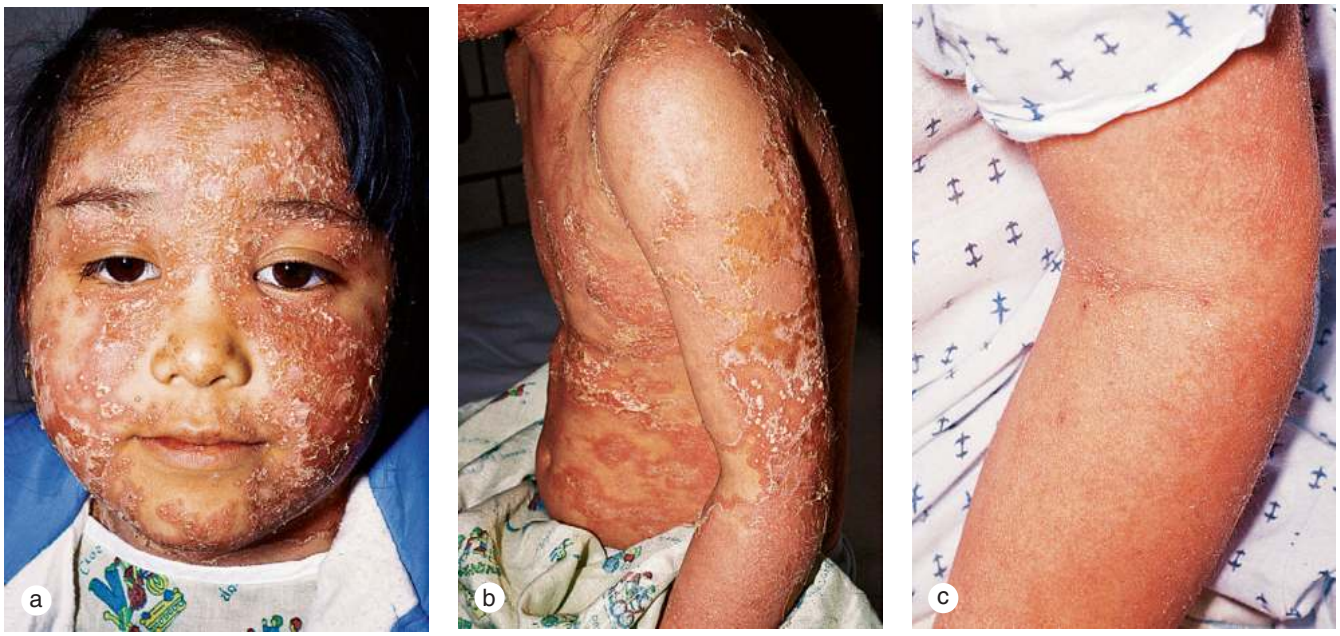


Fig 3.4 Pustular and erythrodermic psoriasis. **(a,b)** Generalized pustulation developed suddenly within psoriatic plaques on this 8-year-old child. Skin lesions were associated with fever, chills, and arthralgias. **(c)** Erythroderma appeared in another 8-year-old girl with psoriasis. She also complained of chills, pruritus, and fatigue.



Fig 3.5 Koebner phenomenon in psoriasis. Pruritus was severe in this child who developed linear plaques in excoriations.



Fig 3.6 Auspitz sign. Removal of the thick scale from a psoriatic plaque produces small points of bleeding from underlying tortuous capillaries.

(broadband UVB 290–320 nm, narrowband UVB 311–313 nm, PUVA = psoralen photosensitizer plus UVA 320–400 nm). Where available, narrowband UVB light therapy has replaced broadband UVB and PUVA in children because of improved safety and efficacy comparable with PUVA. Life-threatening erythrodermic and pustular psoriasis and psoriatic arthritis usually respond to oral retinoids (acitretin) and antimetabolites (methotrexate). Cyclosporin, an immunosuppressant that inhibits T-cell activation has been approved for use in adults with severe psoriasis and may be useful in children with severe, recalcitrant, disfiguring, incapacitating, or life-threatening disease. Recent studies with systemic tacrolimus and pimecrolimus have also shown these agents to be highly effective, but further data are needed on long-term safety. Both calcineurin inhibitors are also available in a topical formulation that may be effective for treating selective patients with facial and intertriginous (inverse) psoriasis. The use of systemic agents requires close laboratory and clinical monitoring.

A relatively new group of pathogenesis-based treatments capable of selective disruption of the psoriatic cascade show promise for management of severe disease in children. The anti-T-cell agent alefacept, anti-tumor necrosis factor agents etanercept, adalimumab, and infliximab, and the monoclonal antibodies directed against interleukin 12–23 pathway ustekinumab have been shown to be effective in adults. Several of these agents have already been approved for the treatment of pediatric arthritis and/or inflammatory disease. Although there were recent favorable recommendations for approval of etanercept for pediatric psoriasis in the United States and the European Commission approved marketing of this agent for children 8 years of age or older, etanercept was recently withdrawn for consideration by the Food and Drug Administration by the manufacturer.

Pityriasis rubra pilaris

Pityriasis rubra pilaris (PRP) is an uncommon disorder of keratinization characterized by small follicular papules, widespread orange-red scaly plaques surrounded by islands of spared skin, and marked thickening of the skin on the palms and soles (Figs 3.7, 3.8). Onset of disease occurs most commonly in prepubertal children and in adults over 50 years old, and has been associated with trauma and acute, self-limited illness. Most cases are sporadic and acquired, but a familial variant has been reported. Overall, 75% of cases resolve spontaneously within 3–4 years, but in familial disease persistence is the rule.

In childhood, the circumscribed variant, which accounts for a majority of the cases, begins with the development of coalescing hyperkeratotic papules on the elbows and knees and a palmoplantar keratoderma (Fig. 3.8). Superficial, red, scaly plaques occasionally appear on the face and trunk. Less commonly, children develop a pattern that mimics the classic adult variety. The eruption begins with follicular, hyperkeratotic patches on the back, chest, and abdomen, which expand to involve interfollicular skin. Lesions on the scalp and other sebaceous areas develop simultaneously or soon thereafter and may disseminate. Even in widespread disease, islands of spared skin of normal appearance are characteristic. Discrete, hyperkeratotic papules may also remain present over the knuckles, wrists, elbows, and knees. In erythrodermic PRP, facial edema and scale may result in ectropion formation. Nail dystrophy with subungual hyperkeratoses may also be present.

The clinical presentation, particularly with keratoderma of the hands and feet and follicular papules, helps to differentiate PRP from psoriasis, seborrheic dermatitis, atopic dermatitis, and pityriasis rosea. A skin biopsy that demonstrates interfollicular orthohyperkeratosis and perifollicular parakeratosis is typical, but not diagnostic.



Fig 3.7 Pityriasis rubra pilaris. **(a)** Discrete hyperkeratotic follicular papules on the trunk and extremities of this 10-year-old girl progressed over several weeks to give confluent plaques. **(b)** Note several discrete areas of sparing on the abdomen and arm flexures.

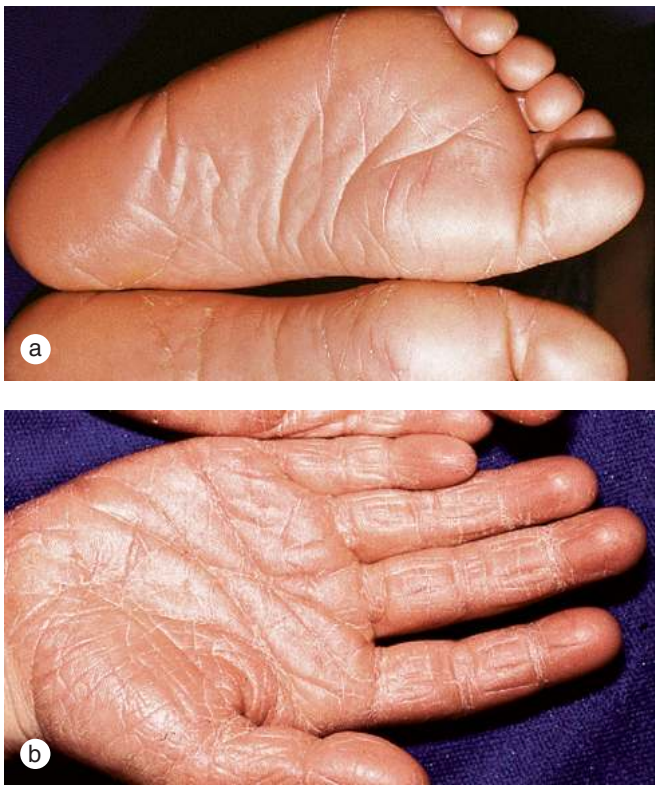


Fig 3.8 Pityriasis rubra pilaris. This child developed a salmon-colored keratoderma of the **(a)** soles and **(b)** palms.



Fig 3.9 Keratosis follicularis. Hyperkeratotic follicular papules erupted progressively on the trunk and face of this 9-year-old girl. **(a)** Some of the most prominent lesions are demonstrated on her shoulder. An adolescent demonstrates almost confluent papules on the **(b)** chest and an associated keratoderma on his **(c)** feet. **(d)** Asymptomatic confluent pebbly papules on the tongue of this 20-year-old man were noted with magnification.

Although PRP is usually self-limited in childhood, severe, disabling disease may require systemic therapy with retinoids or methotrexate. Variable response to therapy has been reported with topical vitamin D analogs, phototherapy, and systemic immunosuppressive agents including steroids, ciclosporin, and azathioprine. Recently, there has been increasing clinical experience with the systemic biologic agents in adults and children with this disorder (see psoriasis).

Keratosis follicularis (Darier disease)

Keratosis follicularis is an autosomal-dominant disorder that typically presents in children from 8 to 15 years old and is characterized by hyperkeratotic follicular papules on the face, scalp, neck, and seborrheic areas of the trunk (Fig. 3.9). Although the onset is usually insidious, a rapidly progressive course may follow an inciting event, such as intense sun exposure or a viral infection. Red, scaly papules coalesce to form widespread, thick, odoriferous, greasy plaques, particularly on the scalp, forehead, around the ears, shoulders, mid-chest, and mid-back. Flexures may also be involved, with moist vegetative plaques.

Other characteristic lesions include flat-topped, warty papules on the dorsum of the hands and tiny hyperkeratotic papules and pits on the palms and soles. Subtle pebbly papules on the oral mucosa may simulate leukoplakia. Nail dystrophy, with thickening or thinning of the nail plate, fracture of the distal nail plate, longitudinal white and red streaks, and subungual hyperkeratosis, may also be present.

The genetic defect in Darier disease has been mapped to chromosome 12q23–q24.1, which results in dysfunction of an endoplasmic reticulum Ca^{2+} ATPase (SERCA2) and subsequent disruption of intracellular Ca^{2+} signaling. Although the cause is unclear, there is also a predisposition to certain bacterial, viral, and fungal infections. The tendency of affected individuals to develop disseminated herpes simplex (Kaposi varicelliform eruption) and recurrent staphylococcal infections has been recognized for years.

The characteristic clinical picture permits easy differentiation of Darier disease from other papulosquamous disorders such as seborrheic dermatitis, PRP, and psoriasis. Classic histologic changes from skin biopsy, which include dyskeratosis (with the formation of corps ronds and corps grains), suprabasal acantholysis (leading to the formation of suprabasal clefts), and the formation of villi by upward proliferating dermal papillae, confirm the diagnosis.

Although Darier disease tends to persist throughout life, many patients experience episodic flares and remissions in disease activity. Topical vitamin A acid may be helpful in managing early lesions. However, its use is limited by a high risk of irritation. Experience with oral retinoids has been promising, but prolonged use may be associated with unacceptable complications, which include hyperostosis, epiphyseal plate changes, increased skin fragility, and teratogenicity. Aggressive protection from the sun and treatment of secondary bacterial and viral infections also control exacerbations.



Fig 3.10 Progressive hyperkeratosis began on the palms and soles of this father and toddler son by 3 months of age.



Fig 3.11 Olmsted syndrome. Severe scarring keratoderma of the palms and soles was associated with perioral and perigenital hyperkeratosis, hyperhidrosis, recurrent cutaneous infections, and poor growth in this 5-year-old girl. Treatment with oral retinoids resulted in some decrease in the palmar and plantar lesions.

Ichthyoses

The ichthyoses are a heterogeneous group of scaling disorders characterized by retention hyperkeratosis (ichthyosis vulgaris, X-linked ichthyosis) or increased proliferation of epidermal cells (lamellar ichthyosis, epidermolytic hyperkeratosis). These diseases may be differentiated by clinical findings, histopathology, biochemical markers, and specific genetic mutations, as outlined in Chapter 2.

Palmoplantar keratoderma

Keratoderma is a heterogeneous group of disorders of keratinization defined by the presence of focal or generalized thickening of the skin of the palms and/or soles. Although difficult to characterize, keratodermas can be classified based on whether they are acquired or inherited, isolated or associated with other cutaneous or systemic findings, and specific morphologic features and extent of involvement of lesions on the palms and soles (Table 3.1). Inherited keratodermas can be subdivided based on the mode of inheritance, presence of other ectodermal and non-ectodermal findings, and specific genetic and molecular markers. The astute clinician can often make a specific diagnosis by searching for key findings in the Online Mendelian Inheritance in Man database supported by the National Library of Medicine and the Johns Hopkins University School of Medicine.

Unna-Thost (non-epidermolytic type), the most common genetic variant, is inherited in an autosomal dominant pattern and is associated with a defect in type 1 and type 16 keratins. This keratoderma presents in the first year of life with diffuse hyperkeratosis restricted to the palmar and plantar surfaces (Fig. 3.10). Although lesions may be asymptomatic, hyperhidrosis may lead to maceration and the formation of painful fissuring, blisters, and bacterial superinfection. Unna-Thost must be differentiated from a number of unusual keratodermas associated with hyperkeratoses that extend to the dorsal surfaces of the hands and feet, elbows, knees, and develop at distant sites (Fig. 3.11).

Focal keratoderma with discrete papules and plaques on the palms and soles also appears as an isolated phenomenon or in association with other cutaneous findings and systemic disease. A mild autosomal-dominant variant with pits and hyperkeratotic papules in the hand and foot creases occurs in 2–5% of blacks (Fig. 3.12). Occasionally, this keratoderma is painful and requires surgical treatment.

Neurosensory deafness, carcinoma of the esophagus (Howel-Evans syndrome), and peripheral neuropathy (Charcot–Marie–Tooth disease) are rarely associated with palmoplantar keratoderma and may be excluded by auditory screening and a careful family history.

Hyperkeratosis of the palms and soles that presents as part of a diffuse disorder of keratinization, such as psoriasis or pityriasis rubra pilaris, is differentiated by a thorough examination of the integument for other diagnostic clinical findings. Unfortunately, it may be difficult to make a specific diagnosis until other features of the underlying disorder manifest.

Porokeratosis

Porokeratosis is a disorder of keratinization characterized by annular, sharply demarcated plaques with raised hyperkeratotic borders (Fig. 3.13). Although many rare subtypes have been described, four distinctive variants are recognized, based on morphology and distribution of the lesions, time of onset, triggering factors, mode of inheritance, and, in some instances, specific genetic mutations.

Porokeratosis of Mibelli

Subtle, reddish-brown, scaly papules that slowly enlarge to form irregularly shaped plaques with hypopigmented atrophic centers and raised, grooved (double-edged) borders are typical of this condition, which invariably develops in childhood (Fig. 3.13a–c). Plaques are usually unilateral, and vary in size from a few millimeters to several centimeters in diameter. One to three lesions are usually present. This rare, autosomal-dominant variant appears most commonly on the extremities, thighs, and perigenital skin, although any area that contains mucous membranes can be involved. Biopsies of the longitudinal furrow in the border demonstrate the diagnostic coronoid lamella, which consists of a parakeratotic column that fills a deep, epidermal invagination.

This variant has been associated with clonal chromosomal abnormalities in chromosome 3 in the region 3p14–p12. Chromosomal instability may rarely result in the development of squamous cell carcinoma within these slowly progressive lesions. Although excision or carbon dioxide laser surgery may be useful,

Variants of palmoplantar keratoderma						
Type	**Disorder**	**Genetics**	**Onset**	**Involvement**	**Hyperhidrosis**	**Associated findings**
Diffuse palmoplantar keratoderma	Unna–Thost syndrome	Autosomal dominant (1:200–1:40 000); varies with ethnic group KRT1 (keratin)1 chromosome 12q 13.13 KRT16 17q 21.2 chromosome	Infancy	Palms, soles	Severe	Occasional deafness, rarely total Anomalous pulmonary venous return
	Keratoma hereditarium mutilans (Vohwinkel syndrome)	Autosomal dominant (rare) Recessive variant with ectodermal dysplasia Mutation in connexin 26 and loricrin gene on chromosome 1q21.3	Infancy	Honeycomb keratoderma; star-shaped plaques on hands and feet, elbows, knees	±	Digital constriction band; deafness; alopecia May be associated with diffuse epidermolytic hyperkeratosis
	Mal de Meleda keratoderma	Autosomal recessive Mutation on chromosome 8q24.3 SLURP1 gene	Infancy	Palms, soles, elbows, knees, including dorsal surfaces (transgridiens)	±	Flexion contractures; constriction bands; koilonychia; diffuse ichthyosis
	Tylosis (Howel–Evans syndrome)	Autosomal dominant Linked to chromosome 17q25	Adolescence	Soles, sometimes palms	±	Esophageal carcinoma; epidermal cysts; thin lateral eyebrows, follicular papules
	Papillon–Lefèvre syndrome	Autosomal recessive Mutation on 11q14.2	Birth to 2–3 years	Soles more severe than palms, intense erythema, wrists, ankles, elbows, knees; follicular hyperkeratoses	±	Nail dystrophy; periodontitis; calcification of falx cerebri; mental retardation; arachnodactyly
	Olmsted syndrome	Autosomal dominant? X-linked recessive? Defect in keratins 5,14	Infancy	Progressive, diffuse involvement of hands, feet, leads to flexion contractures, digital amputation	(Anhidrosis)	Periorificial hyperkeratosis Oral leukokeratosis
Focal palmoplantar keratoderma	Punctate palmoplantar keratoderma	Autosomal dominant (2–5% African-Caribbeans)	Childhood, adolescence	Palms, soles	–	Variable
	Tyrosimia Type II (oculo-cutaneous tyrisonosis, Richner–Hanhart syndrome)	Autosomal recessive 16q22.2	Infancy through adulthood	Fingertips, palms		Corneal ulcerations; mental retardation
	Porokeratosis, palmar, plantar, and disseminated 1	Autosomal dominant (rare)	Childhood through adulthood	Extremities, trunk	–	Squamous cell carcinoma, increased with immuno-suppression

Table 3.1 Variants of palmoplantar keratoderma





Fig 3.12 Focal keratoderma. Asymptomatic hyperkeratotic papules and pits **(a)** developed on the hand creases of an Afro-American teenager. Painful punctuate papules and pits began in adolescence on the palms and **(b)** soles of this young man similar to lesions on his father, uncle, grandfather and several siblings.









Fig 3.13 Porokeratosis. Porokeratosis of Mibelli on **(a)** the thumb, **(b)** the right hip, and **(c)** the chin. **(d)** This adolescent with disseminated superficial actinic porokeratosis began to develop asymptomatic nummular patches on his legs after a sunburn when he was 16 years old. Note the hyperkeratotic borders in all of the patients, which demonstrated a coronoid lamella on skin biopsy. All lesions were slowly progressive.

recurrences have been reported, and it is not practical to treat extensive lesions.

Linear porokeratosis

This variant presents much like the Mibelli variant. However, plaques are linearly arranged on the distal extremities and trunk, where they demonstrate a zosteriform pattern. Onset is also in early childhood, but the mode of inheritance has not been established.

Disseminated superficial actinic porokeratosis

Disseminated superficial actinic porokeratosis (DSAP) is a common autosomal-dominant variant with delayed expression, found primarily in lightly pigmented individuals of Celtic extraction. Many small, 2–4 mm diameter, hyperkeratotic papules appear symmetrically on sun-exposed surfaces of the extremities during the 2nd and 3rd decades of life (Fig. 3.13d). These brown, red, or skin-colored lesions may coalesce to form irregular, circinate patterns. Progression of papules, which occurs particularly during the summer months, can be slowed by aggressive use of sun protection. A mutation in some families with DSAP has been identified at 12q23–24.1.

Punctate porokeratosis

Punctate porokeratosis affects the palms and soles and has been described as a distinct entity. However, it usually presents in association with the Mibelli or linear variant. Punctate porokeratosis may also occur as a widely disseminated form reminiscent of disseminated superficial actinic porokeratosis, but with involvement of both sun-exposed and sun-protected areas. It is included in the differential diagnosis of punctate keratoderma.

INFLAMMATORY DERMATITIDES

Many of these disorders demonstrate changes of both acute (erythema, edema, vesiculation, crusts) and chronic (scaling, lichenification, hypopigmentation, hyperpigmentation) inflammation. Microscopically, dermatitis is recognized by the presence of intercellular edema (spongiosis), variable epidermal thickening (acanthosis), and the presence of dermal inflammatory cells, usually lymphocytes. Research and development of a number of new medications designed to selectively inhibit the dermatitic inflammatory cascade have led to more specific understanding of the molecular basis of these disorders. Various dermatitides may be differentiated by clinical features and specific histologic patterns.

A reasonable way to think of these conditions is as exogenous ('outside job') versus endogenous ('inside job') phenomena. Exogenous disorders include irritant and allergic contact dermatitis and photodermatitis. Endogenous dermatitides include atopic dermatitis, dyshidrotic eczema, nummular dermatitis, and seborrheic dermatitis. Juvenile palmar and plantar dermatosis and perioral dermatitis are triggered by a combination of inside and outside factors. Pityriasis rosea and parapsoriasis present with distinctive dermatitic patterns, but their causes are unclear.

Contact dermatitis

Contact dermatitis refers to a group of conditions in which an inflammatory reaction in the skin is triggered by direct contact with environmental agents. In the most common form, irritant contact dermatitis, changes in the skin are induced by caustic agents such as acids, alkalis, hydrocarbons, and other primary irritants. Anyone exposed to these agents in a high enough concentration for a long enough period of time develops a reaction. The rash is usually acute (occurring within minutes), with itching or burning, well-demarcated erythema, edema, blister formation, and/or crust formation.

By contrast, allergic contact dermatitis is a T-cell-mediated immune reaction to an antigen that comes into contact with the skin. In the initial phase of the reaction, antigens are processed by Langerhans cells in the epidermis under the influence of keratinocyte-derived cytokines. T-cells subsequently migrate to regional lymph nodes where there is clonal expansion of the specifically sensitized lymphocytes. Elicitation of an allergic response occurs on subsequent exposure to the allergen with proliferation of T lymphocytes in the skin as well as regional lymph nodes.

Although contact dermatitis frequently presents with dramatic onset of erythema, vesiculation, and pruritus, the rash may become chronic with scaling, lichenification, and pigmentary changes (Fig. 3.14). At times the allergen is obvious, such as poison ivy or nickel-containing jewelry. Often, however, some detective work is required to elicit the inciting agent (Fig. 3.14f). The initial reaction occurs after a period of sensitization of 7–14 days in susceptible individuals. Once sensitization has occurred, re-exposure to the allergen provides a more rapid reaction, sometimes within hours. This is a classic example of a Type IV delayed-hypersensitivity response.

The most common allergic contact dermatitis in the USA is poison ivy or rhus dermatitis, which typically appears as linear streaks of erythematous papules and vesicles (Fig. 3.15). However, with heavy exposure or in exquisitely sensitive individuals, the rash may appear in large patches. When lesions involve the skin of the face or genitals, impressive swelling can occur and obscure the primary eruption. Direct contact with the sap of the plant (poison ivy, poison oak, or poison sumac), whether from leaves, stems, or roots, produces the dermatitis (Fig. 3.16). Indirect contact, such as with clothing or pets that have brushed against the plant, with logs or railroad ties on which the vine has been growing, or with smoke from a fire in which the plant is being burned, is another means of exposure. Areas of skin exposed to the highest concentration of rhus antigen develop the changes first. Other sites that have received lower doses react in succession, which gives the illusion of spreading. However, once on the skin, the allergen becomes fixed to epithelial cells within about 20 min and cannot be spread further. Thorough washing within minutes of exposure may prevent or reduce the eruption. Barrier creams (e.g. Ivy Guard®) applied before exposure may afford some protection.

Other common contact allergens include nickel, formaldehyde resin, wool alcohols, fragrance mix, and cobalt chloride. Several studies using standard patch-test techniques show that the prevalence of contact sensitivity to these allergens in children is similar to that of adults. Moreover, patch testing in children is safe and effective and clinically significant findings may exceed 70% in carefully selected patients.

Some allergens, known as photosensitizers, require sunlight to become activated. Photocontact dermatitis caused by drugs (e.g. tetracyclines, sulfonylureas, and thiazides) characteristically erupts in a symmetric distribution on the face, the 'V' of the neck, and the arms below the shirt sleeves. Topical photosensitizers (e.g. dyes, furocoumarins, halogenated salicylanilides, p-aminobenzoic acid) produce localized patches of dermatitis when applied to sun-exposed sites. These agents are found in cosmetics, sunscreens, dermatologic products, germicidal soaps, and woodland and house plants (see Chapter 7).

Occasionally, the local reaction in a contact dermatitis is so severe that the patient develops a widespread, immunologically mediated secondary eczematous dermatitis. When the dermatitis appears at sites that have not been in contact with the offending agent, the reaction is referred to as 'autoeczematization' or an 'id' reaction (Fig. 3.17).



Fig 3.14 Allergic contact dermatitis. Allergic contact dermatitis as a result of the application of benzocaine demonstrates sharply demarcated, hyperpigmented, lichenified patches on **(a)** the neck and **(b)** the top of the hands. **(c)** The location of the rash helps to determine the cause of a contact dermatitis, such as in this girl with a nickel allergy. **(d)** This child became sensitized to the elastic waistbands of his underwear. **(e)** An 11-year-old girl had a persistent itchy dermatitis for 6 months which resolved after she started using a paper toilet seat cover at school. **(f)** This boy developed a chronic contact dermatitis to nickel.



Fig 3.15 Poison ivy or rhus dermatitis. **(a)** Linear streaks of pruritic papules and vesicles are typical of contact dermatitis to a plant, as seen on the thigh of this 13-year-old boy. **(b)** A 10-year-old girl developed intense facial edema after brushing against poison ivy. **(c)** In highly sensitized children, large blisters can develop. This child was swinging from vines in the woods.





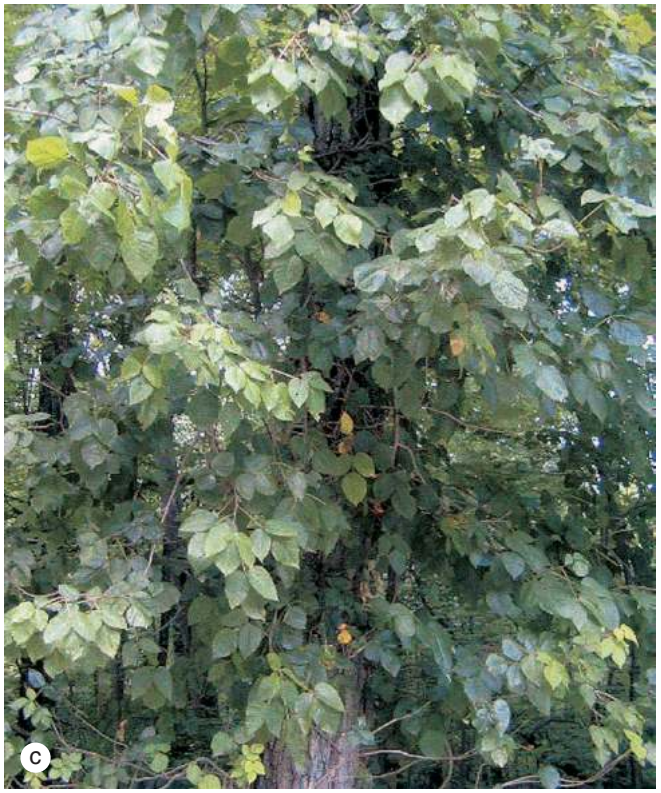


Fig 3.16 Plants that provoke dermatitis after direct contact with the sap. **(a)** Poison ivy has characteristic shiny leaves in groups of three; it may grow as a vine or low shrub or bush. **(b)** Poison oak (courtesy of Dr Mary Jelks) also has leaves in groups of three, although the edges tend to be more scalloped than those of poison ivy. **(c)** Poison ivy vine climbing up a tree.





Fig 3.17 (a) An adolescent boy developed severe poison ivy contact dermatitis on his arms the day after a hike in the woods. **(b)** The next day a widespread itchy eczematous papular eruption appeared on his trunk and extremities.

A careful history usually reveals the source of contact dermatitis. In some patients, patch testing with a standardized tray of common antigens or the suspected antigen and several controls is necessary to confirm the diagnosis.

Although small areas of contact dermatitis are best treated topically, widespread reactions require and respond within 48 h to a 2-to 3-week tapering course of systemic corticosteroid; these begin at 0.5–1.0 mg/kg per day. Patients may experience rebound of the rash when treated with a shorter course. Oral corticosteroids may also be indicated in severe local reactions that involve the eyelids, extensive parts of the face, the genitals, and/or the hands, where swelling and pruritus may become incapacitating.

Atopic dermatitis

Also known as eczema, this is a chronically recurrent, genetically influenced skin disorder of early infancy, childhood, and occasionally adult life. Although it was initially described in the nineteenth century, it was not until 1935 that Hill and Sultzberger first characterized the clinical entity. The term *atopy*, derived from the Greek word which means 'not confined to a single place,' was introduced in 1923 by Coca and Cooke to describe a cohort of patients with asthma and allergic rhinitis who demonstrated immediate wheal and flare reactions upon skin testing with a variety of environmental allergens. The sera of these patients contained skin-sensitizing antibodies that were subsequently characterized as IgE immunoglobulins. It was later recognized that these atopic individuals also frequently manifested the itchy, eczematous dermatitis which was labeled atopic dermatitis.

The term *eczema*, which means 'boil over,' is used by many physicians when referring to atopic dermatitis. However, most dermatologists use the word eczematous as a morphologic term to describe the clinical findings in various sorts of acute (erythema, scaling, vesicles, and crusts) and chronic (scaling, lichenification, and pigmentary changes) dermatitis. Both acute and chronic dermatitis may be present in atopic patients at different sites at the same time and the same site at different times during the course of the disease.

Although data are not precise, recent surveys reveal that atopic dermatitis is rather common, with an incidence of 7:1000 individuals in the USA. The prevalence is highest among children, affecting 15–20% of all children between 6 months and 10 years of age. Subtle findings may be present during the first few months of life, and nearly 60% of patients have an initial outbreak by their first birthday. Another third develop disease between 1 and 5 years. The onset of eczema in adolescence and adulthood is unusual and should alert the clinician to the possibility of other diagnoses.

In families with a history of allergic rhinitis or asthma, nearly one-third of the children are expected to develop skin lesions of atopic dermatitis. Inversely, in patients with atopic dermatitis, one-third are expected to have a personal history of allergic rhinitis or asthma, with two-thirds showing a family history of these disorders. Half of those who manifest the dermatologic condition in infancy or childhood ultimately develop allergic respiratory symptoms. Atopic dermatitis does not appear to be linked to the histocompatability locus antigen, as has been described in allergic rhinitis. Rather, it seems to be inherited as an autosomal trait with multifactorial influences.

Many external factors, which include dry skin, soaps, wool fabrics, foods, infectious agents, and environmental antigens, act in concert to produce pruritus in susceptible individuals. The resultant scratching leads to acute and chronic changes typical of atopic dermatitis.

The pathogenesis of inflammation is unclear, and no single factor has been implicated in the initiation of the inflammatory cascade. However, there is evidence that expansion of type 2 cytokine-secreting lymphocytes play a major role in the acute phase of atopic dermatitis (Fig. 3.18). This results in increased levels of pro-inflammatory cytokines such as interleukin-4, -10, and -13, and of IgE and a corresponding decrease in interferon-gamma. Inflammatory dendritic cells have also been shown to increase in atopic skin which further fuels inflammation and the itch–scratch cycle.

In a subset of atopics defects in barrier function may play an initiating role. Mutations in the filaggrin gene are associated with the development of ichthyosis vulgaris, barrier dysfunction, and an increased risk of developing atopic dermatitis. Predisposition to atopic dermatitis has also been associated with alteration in ceramide content of stratum corneum and disturbed maturation of lamellar bodies which serve as water-retaining molecules in the barrier.

Although there is no one specific laboratory study or clinical finding in atopic dermatitis, over the years clinicians and investigators have developed a series of major and minor diagnostic criteria (Table 3.2). In addition to a history of pruritus, the distribution, morphology, and evolution of skin lesions in atopic dermatitis follow a characteristic pattern (Fig. 3.19). The infantile phase begins between shortly after birth and 6 months of age and lasts about 2–3 years. Typically, the rash is composed of red, itchy papules and plaques, many of which ooze and crust. Lesions are symmetrically distributed over the cheeks, forehead, scalp, trunk, and the extensor surfaces of the extremities (Fig. 3.20). The diaper area is usually spared.

The childhood phase of atopic dermatitis occurs between 4 and 10 years of age. Circumscribed, erythematous, scaly, lichenified plaques are symmetrically distributed on the wrists, ankles, and flexural surfaces of the arms and legs (Fig. 3.21). The ear creases and back of the neck are also commonly involved. These areas develop frequent secondary infections, probably as a result of the introduction of organisms by intense scratching. Although the eruption may become chronic and rarely generalized, remissions may occur at any time. Most children experience improvement during the warm, humid summer months and exacerbations during the fall and winter.

Of children with atopic dermatitis, 75% improve by 10–14 years of age; the remaining individuals may go on to develop chronic adult disease. Major areas of involvement include the flexural

Diagnostic criteria for atopic dermatitis

Major criteria (all required for diagnosis)	Common findings (at least two)	Associated findings (at least four)
Pruritus Typical morphology and distribution of rash	Personal or family history of atopy Immediate skin-test reactivity White dermographism Anterior subcapsular cataracts	Ichthyosis, xerosis, hyperlinear palms Pityriasis alba Facial pallor, infraorbital darkening Dennie–Morgan folds Keratoconus Hand dermatitis Repeated cutaneous infections

Table 3.2 Diagnostic criteria for atopic dermatitis

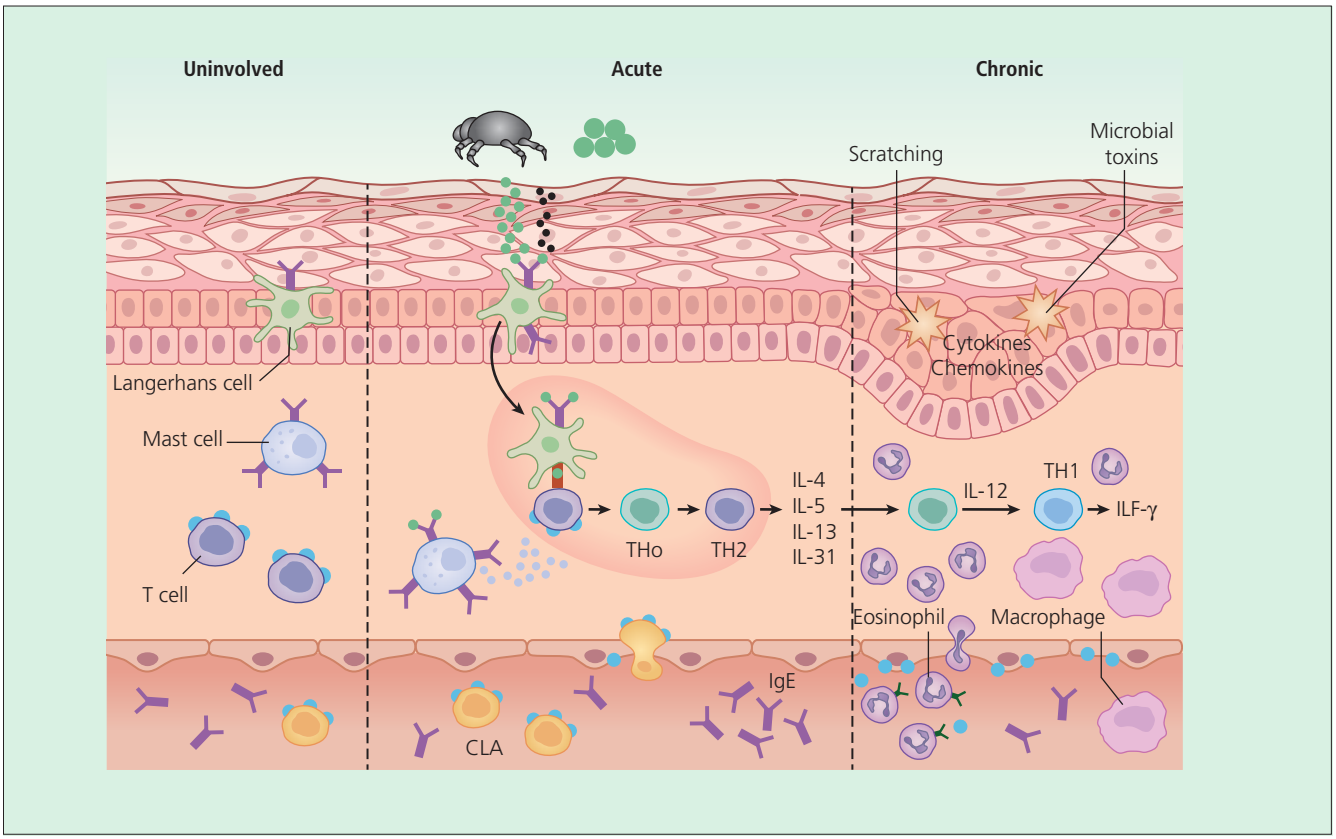


Fig 3.18 In genetically predisposed individuals, external factors including environmental irritants and allergens, bacteria, fungi, viruses, and foods trigger the differentiation of Th2 lymphocytes from Th0 lymphocytes and the release of acute inflammatory mediators (IL-4, 5, 13, 31). In chronic disease Th1 lymphocytes are activated and chronic inflammatory mediators are upregulated.

creases of the arms, neck, and legs. Chronic dermatitis may be restricted to the hands or feet, but some patients develop recurrent, widespread lesions.

Nummular eczematous dermatitis

Although nummular eczematous dermatitis was initially described as distinct from atopic dermatitis, clinicians frequently use this term to describe the discrete, coin-shaped, red patches seen on many patients with atopic dermatitis (Fig. 3.22). Lesions typically appear as tiny papules and vesicles, which form confluent patches on the arms and legs. Nummular lesions may be extremely pruritic, and they are difficult to treat, particularly during the winter months when the incidence seems to peak.

Prurigo nodularis

While chronic rubbing results in lichenification, and scratching in linear excoriations, individuals who pick and gouge at their itchy, irritated skin tend to produce markedly thickened papules known

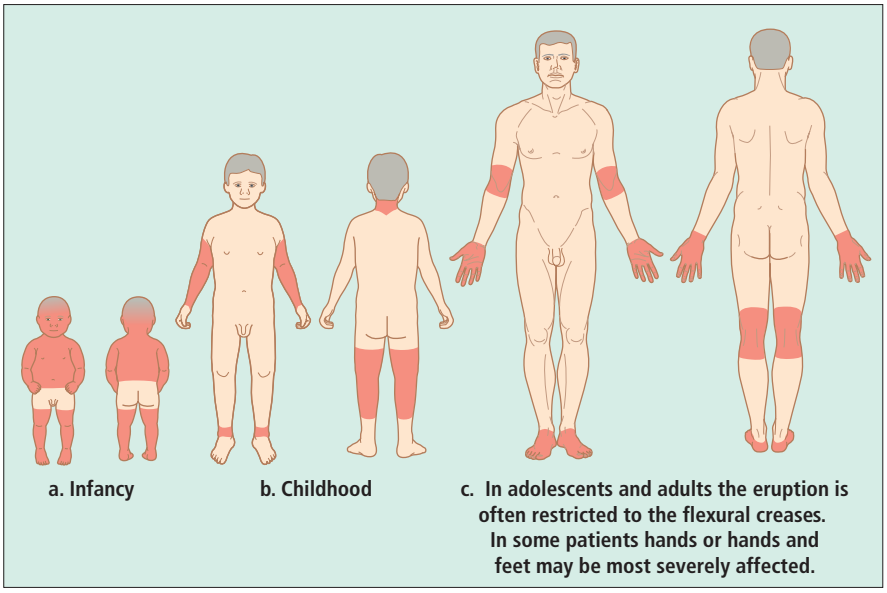


Fig 3.19 Characteristic distribution of lesions of atopic dermatitis in infancy, childhood, and adulthood. **(a)** In infancy, widespread lesions may be generalized, sparing only the diaper area. The head and neck, as well as the flexural and extensor surfaces of the distal extremities, are often severely involved. **(b)** In older childhood, lesions tend to involve the flexural surfaces of the upper and lower extremities, as well as the neck. With severe flares of disease activity, the rash may become more generalized. **(c)** In adolescents and adults the eruption is often restricted to the flexural creases. In some patients, hands, or hands and feet, may be most severely affected.



Fig 3.20 Infantile eczema. **(a)** This infant has an acute, weeping dermatitis on the cheeks and forehead. Involvement of **(b)** the trunk and **(c)** the extremities with erythema, scaling, and crusting is evident. Note the severe involvement of the extensor surfaces of the leg and sparing of the leg crease. **(d)** Usually the diaper area is the only portion of the skin surface that is spared.

as prurigo nodules (Fig. 3.23). Although prurigo nodularis is not specific to atopic dermatitis, many patients with these nodules also have an atopic diathesis, which manifests as allergic rhinitis, asthma, or food allergy. Frequently, other stigmata of atopic dermatitis are present as well. Prurigo lesions tend to localize to the extremities, although widespread cutaneous involvement is observed in some cases.

Follicular eczema

Although a few atopic patients present initially with a predominance of follicular papules, virtually all patients develop these 2–4 mm diameter follicular lesions sometime during their clinical course (Fig. 3.24). Lesions are usually widespread on the trunk, but careful observation also reveals their presence on the extremities, particularly early in flares of disease activity. In children with chronic disease, discrete papules may be obscured by excoriations and lichenification, particularly in the flexural creases.

Ichthyosis vulgaris

Although ichthyosis vulgaris (IV) is inherited independently of atopic dermatitis, hyperlinearity of the palms and soles typical of IV is a frequent finding in patients with atopic dermatitis. Moreover, recent discoveries of the mutations causing IV and the prevalence of these defects in atopics have highlighted the potentiation of atopic dermatitis in IV-affected individuals. (Fig. 3.25). Retained polygonal scales are usually evident on the distal lower extremities (see Fig 2.34), but they may also show a generalized distribution. Xerosis associated with ichthyosis may contribute to the pruritus present in atopic dermatitis.

IV, which is inherited in an autosomal dominant pattern with an incidence of 1:250, is associated with a defect in profilaggrin which is converted into filaggrin, the major protein comprising keratohyalin. The severity of IV increases with decreasing levels of functioning filaggrin.

Keratosis pilaris

Although keratosis pilaris is often an isolated finding, it is commonly associated with atopic dermatitis and/or ichthyosis vulgaris. Keratosis pilaris results from retention of scales in the follicular infundibulum, which clinically is characterized by horny follicular papules and erythema on the upper arms, medial thighs, and cheeks (Fig. 3.26). Occasionally, more widespread papules appear on the back, buttocks, and legs.

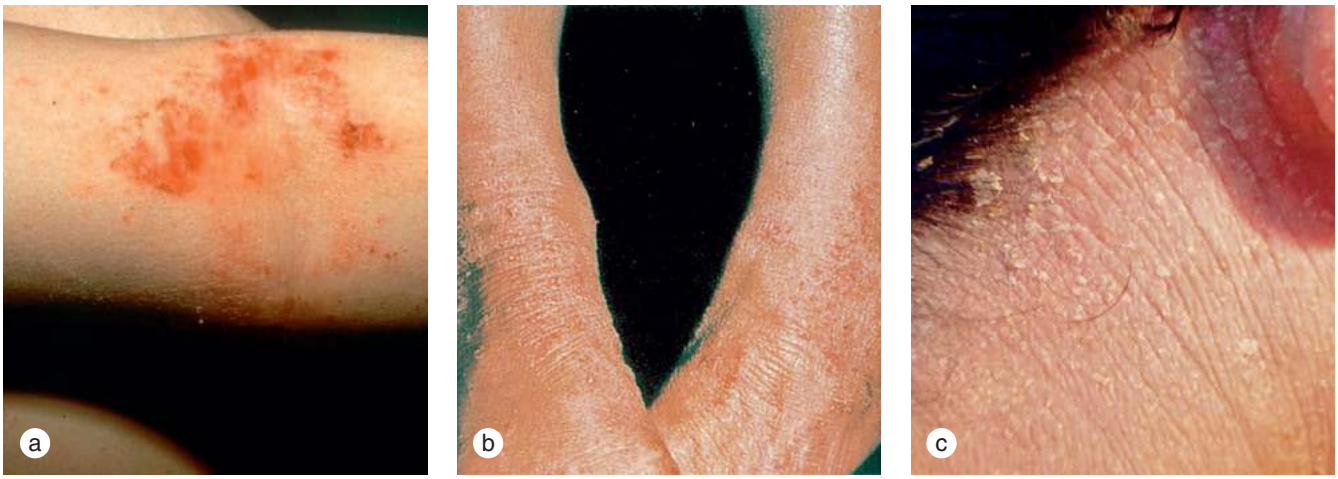


Fig 3.21 Childhood eczema with lesions on **(a)** the arm, **(b)** the ankles, **(c)** neck and **(d)** the buttock creases.

Infraorbital folds

Often referred to as Dennie sign or Morgan lines, extra infraorbital folds are suggestive of atopy (Fig. 3.27). In many patients, these represent current or past local inflammation produced by persistent scratching and rubbing of the tissues. Although not specific for atopic dermatitis, it may be a useful finding when seen in association with other typical physical signs.

Pigmentary changes

Postinflammatory hypopigmentation and hyperpigmentation occur commonly in atopic patients, especially in the setting of chronic disease (Fig. 3.28). Although pigmentary changes may be quite prominent, this is not always the case; subtle and poorly demarcated areas of hypopigmentation in atopic subjects are referred to as pityriasis alba (Fig. 3.29). Changes are most marked in darkly pigmented individuals or lighter-skinned patients after tanning. The extremities and face are the areas most commonly involved. Although some postinflammatory pigmentary changes persist indefinitely, fading of hyperpigmentation and repigmentation of lightened areas usually occur during prolonged remissions.

Hand (and foot) dermatitis

Involvement of the hands and feet is common at all ages and may be the only manifestation of atopic dermatitis in adolescents and



Fig 3.22 Nummular eczema. **(a)** An adolescent demonstrated the acute exudative round patches of nummular eczema. **(b)** The term nummular eczema is also used to describe the chronic circular patches on the extremities and trunks of atopic patients, exemplified by the patches on another adolescent.



Fig 3.23 Prurigo nodularis. Widespread lichenified nodules involve the trunk and extremities of an adolescent boy with severe atopic dermatitis. Nodules may be particularly resistant to therapy.





Fig 3.24 Follicular eczema. In some patients, follicular papules may be the only manifestation of atopic dermatitis. These lesions also occur in many atopic patients during the course of their disease, as in **(a)** this adolescent with follicular papules on his thighs and legs and **(b)** a 10-year-old boy with lesions involving his hands and forearms.

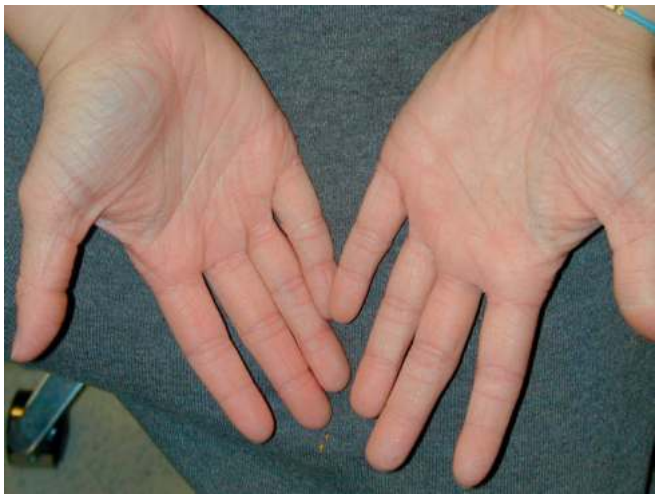


Fig 3.25 This 13-year-old boy had a history of atopic dermatitis and ichthyosis vulgaris associated with hyperlinearity of her palms and soles and coarse non-inflammatory scale on her legs.





Fig 3.26 Two adolescent boys demonstrate the typical features of keratosis pilaris with dramatic horny follicular papules on **(a)** the extensor surfaces of the thigh and **(b)** the lateral aspect of the cheek.



Fig 3.27 Dennie's sign or Morgan line. Eyelid edema and lichenification from chronic rubbing resulted in the development of a double infraorbital fold. Although not specific to atopic dermatitis, this feature suggests such a diagnosis when seen in association with other, more pathognomonic findings.

adults. The rash is commonly triggered by contact irritants. However, in children with recalcitrant dermatitis, a contact allergen should be excluded. Clinical findings include dry, scaly patches on the palms and soles and frequent fissuring of the palms, soles, and digits. The term 'dyshidrotic eczema' is reserved for patients with atopic dermatitis who develop intensely pruritic, deep-seated, inflammatory vesicles on the sides of the palms, soles, and/or digits



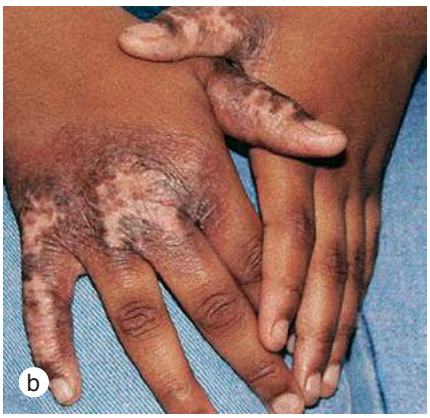


Fig 3.28 Postinflammatory hypopigmentation and hyperpigmentation associated with lichenification are marked on the **(a)** ankles and **(b)** hands of this 9-year-old girl with severe, chronic atopic dermatitis.



Fig 3.29 Pityriasis alba. In some atopic patients, subtle inflammation may result in poorly demarcated areas of hypopigmentation, known as pityriasis alba. Lesions are most prominent in darkly pigmented individuals.

(Fig. 3.30). This is actually an inaccurate name, because histopathology of these lesions demonstrates spongiotic vesicles, typical of an acute dermatitis, and normal sweat glands. Involvement of the paronychial skin may result in separation of the nail from the underlying nail bed (onycholysis) as well as in yellowing and pitting of the nail plate (Fig. 3.31).

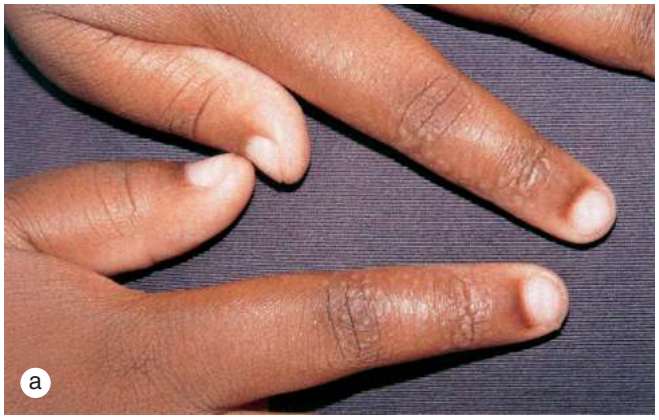




Fig 3.30 Dyshidrosis. Chronic pruritic deep-seated papules and vesicles recurred on the fingers **(a, b)** of this atopic 12-year-old boy. He had typical flexural lesions on his arms and legs.



Fig 3.31 Nail dystrophy. Nail changes, including onycholysis and pitting, can occur when chronic dermatitis affects the fingertips, as in this adolescent.

Secondary bacterial infection is the most frequent complication of atopic dermatitis. Since it may also trigger an acute exacerbation of clinical disease, early recognition and treatment are mandatory. Crusted, exudative patches suggest superinfection (Fig. 3.32). Although Group A β-hemolytic streptococci are occasionally found in these infected areas, investigators now report a predominance of *Staphylococcus aureus*.

Complications of atopic dermatitis

Primary herpes simplex may produce widespread cutaneous and, on rare occasions, disseminated visceral disease in patients with atopic dermatitis. The acute development of multiple, grouped, 2–3 mm diameter vesicles or crusts associated with high fever and worsening pruritus suggests the diagnosis of eczema herpeticum (Fig. 3.33). Tzanck smear, viral culture, double fluorescent antibody, and/or herpes-simplex-specific polymerase chain reaction confirm the diagnosis and aciclovir is started immediately.

A number of other organisms, which include human papillomaviruses (warts), the virus that causes molluscum contagiosum, and dermatophytes, such as *Trichophyton rubrum*, may produce chronic, recalcitrant infections in atopic patients.

Differential diagnosis

Although the histopathology of affected skin is characteristic (hyperkeratosis, acanthosis, spongiosis, lymphocytic dermal



Fig 3.32 Secondary bacterial infection in atopic dermatitis. **(a)** Bullous impetigo developed in the flexural creases of an 8-year-old child with severe atopic dermatitis. **(b)** This toddler with atopic dermatitis required multiple courses of oral antibiotics for recurrent impetigo of the face.

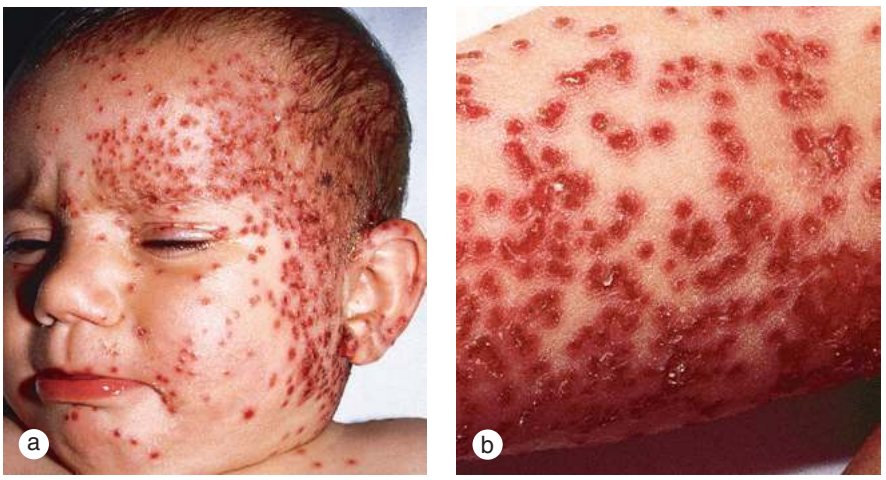


Fig 3.33 Herpes simplex. Eczema herpeticum, the primary cutaneous manifestation of herpes simplex virus infection in atopic patients, spread rapidly over **(a)** the trunk and face, and **(b)** the extremities of this 10-month-old girl. Note the uniform, clustered 2–3 mm diameter vesicles and punched-out vesicles and erosions. A Tzanck smear at the bedside showed multinucleated giant cells, and a positive viral culture confirmed the diagnosis 12 h later.



Fig 3.34 Scabies. This 10-year-old girl was diagnosed with infected eczema. Although she did improve with oral antibiotics, the burrows were readily visible on her palms and wrists, and scrapings from several elongated papulopustules yielded female mites.

inflammation), skin biopsies are not diagnostic. Atopic dermatitis is a clinical diagnosis. Characteristic pruritic cutaneous findings in a patient with a family history of atopy suggest the disorder.

A number of conditions may mimic the clinical findings of atopic dermatitis. It can be differentiated from infantile seborrheic dermatitis by the distribution of lesions, since atopic dermatitis spares moist, intertriginous areas such as the axilla and perineum, where seborrhea is prominent. Exposure history and distribution help differentiate contact dermatitis, as do the discreteness of lesions, pattern, and lack of symptoms in pityriasis rosea. Thick, silvery scale and the Koebner phenomenon help differentiate psoriasis, and central clearing with an active, scaly, vesiculopustular border helps to differentiate tinea corporis. The eruption in Langerhans cell histiocytosis is usually hemorrhagic and accompanied by chronic draining ears, hepatosplenomegaly, and other systemic findings. An acral distribution of lesions, lack of pruritus, and associated viral symptoms suggest Gianotti–Crosti syndrome. Many patients infested with scabies develop a widespread immunologically mediated autoeczematization which may obscure the burrows. A careful search for the primary lesions on the genitals, wrists, finger web spaces, breasts, and axillae will aid in distinction of this easily treated sometimes chronic pruritic eruption from atopic dermatitis (Fig. 3.34 and Table 3.2).

Treatment of atopic dermatitis

Therapeutic measures are individualized according to the morphology of the skin lesions, distribution of the rash, and age of the patient. Infants, for instance, may benefit from aggressive efforts to protect their skin from environmental irritants and scratching. Loose-fitting cotton clothing with long sleeves and foot coverings may be optimal.

Although bathing and the use of soaps was once believed to exacerbate atopic dermatitis, increasing evidence contradicts this view. Daily swimming or baths in the summer and on alternating days in winter, followed by liberal application of lubricants, help to cleanse and hydrate the skin. Emollients are tailored to the patient to increase compliance. In general, greasy, occlusive preparations are safest and most effective. However, some patients may prefer less occlusive agents. Mild cleansers may help to reduce bacterial colonization and the risk of secondary infection. Their use should be restricted to areas in which bacteria are most likely to thrive, such as the groin, axilla, and umbilicus.

Low- and medium-potency topical corticosteroids are particularly useful during periods of increased disease activity. Twice-daily applications are restricted to the worst areas and tapered as soon as possible. The skin is monitored for signs of corticosteroid overuse, which include atrophy, loss of pigment, and telangiectasias. High-potency products are reserved for special instances in which severe disease is limited to small patches of thick skin, such as on the hands and feet or for brief courses over large areas as an alternative to oral corticosteroids.

The topical non-steroidal calcineurin inhibitors tacrolimus and pimecrolimus may be highly effective in many atopics. These agents can be used safely on the face, genital area, breasts, and axillae without risk of atrophy or pigmentary alteration. They are also compatible with emollients and topical steroids and are approved for daily short-term use (3 months) as well as long-term, intermittent use (for 1 year or longer). These agents are not approved for use in children under 2 years of age, but pharmacologic studies in patients down to 3 months of age show these medications to be comparable in safety and efficacy in younger children. Data from two long-term safety studies sponsored by manufacturers with the sanction of the Food and Drug Administration should be available within the next 5 years.

When eczema is severe, antihistamines may relieve pruritus. They are particularly useful at bedtime, when itching is the most severe, and their sedative effects may help. However, antihistamines must be used with caution in infants and toddlers, who may develop paradoxic excitation. Tachyphylaxis to a given agent may develop after prolonged therapy, and it may be necessary to change the class of antihistamine prescribed. Moreover, there is no evidence that long-active non-sedating antihistamines are effective in suppressing pruritus.

Secondary bacterial infections are frequently associated with exacerbation, and may cause an acute flare of atopic dermatitis. This complication requires prompt intervention. Oral antibiotics, such as cephalosporins and semisynthetic penicillins, or alternatively clindamycin and erythromycin, are indicated when infection is evident. If the infection is widespread, parenteral antibiotics may be necessary. Localized patches of impetiginization may be managed with topical antibiotics, such as bacitracin and mupirocin. In severe disseminated infections, appropriate cultures are obtained prior to initiating antibiotic therapy.

Infection unresponsive to antibacterials raises the specter of eczema herpeticum. Patients with disseminated primary cutaneous herpes simplex infection also present with acute worsening of their dermatitis and, frequently, fever, adenopathy, irritability, and decreased appetite. These children require aggressive, symptomatic treatment and immediate parenteral antiviral therapy (aciclovir 15 mg/kg per day in three divided doses). Unfortunately, oral acyclovir is not well absorbed in children. However, several newer antiviral medications, famciclovir and valaciclovir hydrochloride, are readily bioavailable when taken orally. Although these medications are not likely to be reformulated for children, a special syrup formulation of valacyclovir is circulating on the internet and is available at many pharmacies:

Valacyclovir oral suspension (50 mg/ml)
Ingredients: Valacyclovir caplets 500 mg #9, Ora-Plus 45 ml, Ora-Sweet qs 90 ml *Directions*: (1) Crush caplets in a mortar and add 5 ml sterile water. (2) Mix together into smooth paste. (3) Add Ora-Plus in small increments. (4) QS to 90 ml with Ora-Sweet. (5) Shake well and refrigerate (expiration 21 days).

During acute flares with vesicle and crust formation, application of tepid tap-water compresses three times a day for 15–20 min, topical lubricants such as petrolatum, Eucerin® cream,

Aquaphor®, and Acid Mantle® cream, and oral antibiotics should result in rapid improvement. In chronic disease, liberal use of emollients, judicious use of low- and medium-potency topical corticosteroid ointments twice daily, antihistamines, and avoidance of environmental irritants may bring symptomatic relief.

The soak and smear technique with bathing or compressing followed by he application of emollients, plastic wrap occlusion, and long underwear or other occlusive garments to strategic areas, particularly at bedtime may also help to shut down flares and heal chronic skin changes. In selected children with severe recalcitrant longstanding disease there may be a role for phototherapy (e.g. UVB, PUVA) and oral immunosuppressive anti-inflammatory medications (e.g. cyclosporine, methotrexate).

Most patients with chronic atopic dermatitis are troubled by the effect of the rash on their physical appearance. Therefore, emotional support and psychologic counseling may be helpful adjuncts in the care of these patients. Behavioral feedback and counseling can also be used to help parents and patients manage chronic pruritus.

Seborrheic dermatitis

Seborrheic dermatitis is characterized by a symmetric, red, scaling eruption, which occurs predominantly on hair-bearing and intertriginous areas, which include the scalp, eyebrows, eyelashes, perinasal, presternal, and post-auricular areas, and the neck, axilla, and groin. In affected infants, scalp lesions consist of a greasy, salmon-colored, scaly dermatitis called cradle cap (see Fig. 2.38d). A severe type may be more generalized. In adolescents, the dermatitis may manifest as dandruff or flaking of the eyebrows, post-auricular areas, nasolabial folds, and/or flexural areas (Fig. 3.35). When the patches on the face are well defined, they may form a petaloid pattern (Fig. 3.35a). Occasionally non-inflammatory scale reminiscent of infantile cradle cap develops in the scalp of older children and adolescents. Tinea (pityriasis) amiantacea probably represents a variant of scalp seborrheic dermatitis in older children, consisting of thick tenacious localized plaques of sticky scale which bind down tufts of hair (Fig. 3.35b).

Although the pathogenesis of seborrheic dermatitis is unknown, *Malassezia (Pityrosporum)* and *Candida* species have been implicated as causative agents. A role for neurologic dysfunction is suggested by the increased incidence and severity in neurologically impaired individuals. Immunodeficiency states, particularly acquired immunodeficiency syndrome in which 20–80% of individuals are affected, may also be associated with severe atypical clinical manifestations.

The dermatitis of seborrhea is usually subtle and non-pruritic. Most cases respond to low-potency topical corticosteroids and may clear spontaneously. Antiseborrheic shampoos that contain pyrithione zinc, selenium, or salicylic acid may help. Ketoconazole and ciclopiroxolamine shampoo and cream have also been approved for the treatment of seborrhea. Secondary bacterial infection with Group A beta-hemolytic streptococcus and/or *Staphylococcus aureus* occurs commonly in the neck, axillary, and groin creases in infants and should be cultured and treated with appropriate oral antibiotics.

In infants and young children, atopic dermatitis may be confused with seborrheic dermatitis. However, atopic dermatitis in infants invariably spares moist sites, such as the diaper area and axilla, and produces intense pruritus. The distribution of rash in Langerhans cell histiocytosis may resemble seborrheic dermatitis. However, the presence of purpura, poor growth, diarrhea, and other systemic complaints would be unusual for uncomplicated seborrheic dermatitis. Erosive patches in a seborrheic distribution associated with poor growth, diarrhea, irritability, and hair loss suggest the diagnosis of acrodermatitis enteropathica or other nutritional deficiencies. Finally, persistent diaper dermatitis and cradle cap may be difficult to differentiate from psoriasis even with a skin biopsy because of overlapping histologic features.

Juvenile palmar-plantar dermatosis

Also known as sweaty sock syndrome, juvenile palmar-plantar dermatosis is seen commonly in toddlers and children of school age. Chronic pink, scaly patches with cracking and fissuring begin in the fall or winter on the anterior plantar surfaces of the feet and great toes (Fig. 3.36). Occasionally, patches spread to the other toes and hands. Although the cause is unknown, excessive sweating and/or the repeated cycle of wetting of the skin during the day while shoes are worn and drying of the skin at night, may trigger the condition. Consequently, treatment consists of lubrication and covering the feet at night. Topical corticosteroids may be necessary in severe cases. The eruption tends to subside in the summer, and

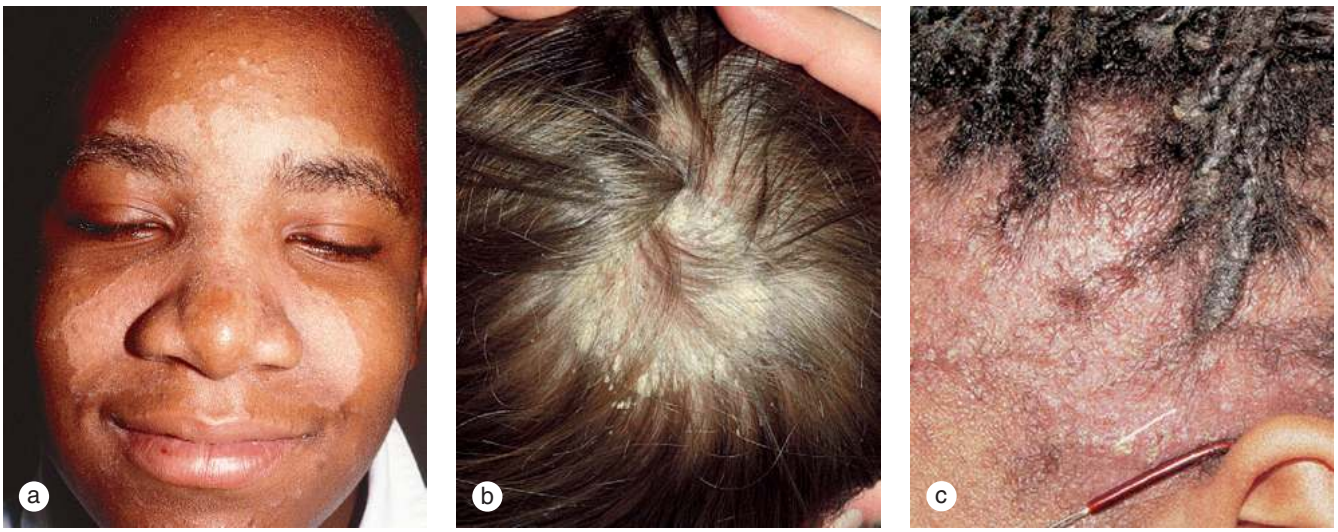


Fig 3.35 Seborrheic dermatitis. **(a)** A 12-year-old boy developed scaly, pink, hypopigmented patches on the face in a petaloid pattern while **(b)** a 10-year-old boy demonstrates the thick adherent scale typical of tinea amiantacea. **(c)** Note the confluent red scaly patches on the scalp and forehead of this 15-year-old girl.



Fig 3.36 Sweaty sock syndrome (juvenile palmar-plantar dermatosis) was evident on the weight-bearing surfaces of the toes and soles of this healthy 8-year-old boy. The rash resolved with aggressive use of lubricants alone.

resolution in adolescence is common. Children with atopic dermatitis may be particularly prone to develop this dermatosis.

Allergic contact dermatitis differs from sweaty sock syndrome by the tendency for involvement of the dorsum of the hands and feet. Tinea pedis usually presents on the instep and interdigital web spaces. Chronic atopic dermatitis may be difficult to differentiate from sweaty sock syndrome unless other stigmata of atopy are present.



Fig 3.37 Lip-licker's contact dermatitis recurred every winter in this teenage boy. Involvement was always restricted to the lips and contiguous skin.

Perioral/periorificial dermatitis

In the simplest form, perioral dermatitis represents a contact dermatitis from repeated wetting and drying of the skin associated with persistent lip-licking or thumb-sucking, especially during the winter months. Elements of both acute and chronic dermatitis closely encircle the mouth and may involve the vermilion border (Fig. 3.37).

Some children develop asymptomatic red papules, pustules, and nodules on either a normal-appearing or red, scaly base on the chin and nasolabial folds (Fig. 3.38a,b). Lesions may extend to the





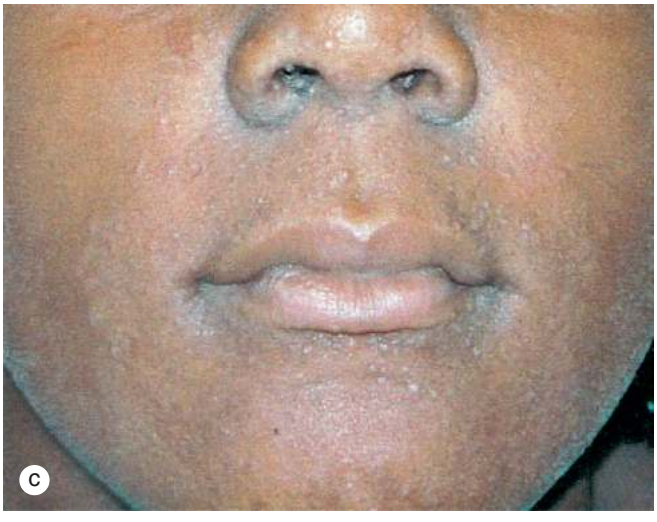


Fig 3.38 Perioral dermatitis with bright-red papules, pustules, and scale **(a)** erupted on the cheeks, chin, and upper lip, and nose of this 4-year-old boy. **(b)** Note the perioral sparing in this 10-year-old girl. The rash vanished after 4 weeks of treatment with oral erythromycin and non-comedogenic moisturizers. **(c)** The perioral dermatitis in this adolescent failed to respond to topical and oral agents, but resolved after 6 weeks of oral tetracycline.

cheeks, eyelids, and forehead. Although initially reported in association with the use of fluorinated topical corticosteroids on the face, this type of perioral dermatitis occurs more frequently in children with no history of topical agents. It has also been described most commonly in black school-age boys (Fig. 3.38c). Some immunocompromised patients may develop a rosacea-like facial eruption indistinguishable from periorificial dermatitis and attributed to a hypersensitivity reaction to *Demodex* mites on the face.

Interestingly, histopathology demonstrates features of dermatitis, folliculitis, and occasionally granulomatous inflammation consistent with rosacea or sarcoidosis. However, affected children are usually otherwise healthy, and the rash improves with oral antibiotics such as erythromycin and tetracycline (for children over 12 years old). Topical antibiotics, benzoyl peroxide, vitamin A acid, and other keratolytics may also be useful. Topical corticosteroids are used with extreme caution because of the risk of precipitating a superimposed folliculitis, telangiectasias, and atrophy, particularly with long-term exposure.

Pityriasis rosea

Pityriasis rosea (PR) is an innocent, self-limited disorder that can occur at any age, but is more common in school-age children and young adults. A prodrome of malaise, headache, and mild constitutional symptoms occasionally precedes the rash. In about half of the cases, the eruption begins with the appearance of a 'herald patch' (Fig. 3.39a). This 3–5 cm diameter, isolated, oval, scaly, pink patch, may appear anywhere on the body surface, although it occurs most commonly on the trunk and thighs. Central clearing produces a lesion that commonly simulates tinea corporis. Within 1–2 weeks, numerous smaller lesions appear on the body, usually concentrated on the trunk and proximal extremities (Fig. 3.39b–d). These begin as small, round papules, which enlarge to form 1–2 cm diameter oval patches with dusky centers and scaly borders. The long axes of the patches often run parallel to the skin lines over the thorax and back, to create a 'Christmas-tree' pattern. Occasionally, pityriasis rosea spreads to involve much of the skin surface, including the face and distal extremities. Inflammation may be so intense that some blistering and hemorrhage become clinically apparent. The rash reaches a peak in several weeks and slowly fades over 6–12 weeks.

Although the cause of pityriasis rosea has not been established the frequent reporting of a viral-like prodrome, clustering of cases, occasional occurrence among close contacts, and peak incidence in winter and early spring suggest a viral etiology. Several investigators have detected DNA sequences for human herpesvirus 6 and human herpesvirus 7 in patients with pityriasis rosea. PR-like eruptions have also been reported in association with acute infection with *Mycoplasma pneumoniae* and enteroviruses. However, in most case studies no infectious agents have been identified.

Ultraviolet light and oral erythromycin may hasten the disappearance of the eruption. However, postinflammatory hyperpigmentation, particularly in dark-complected individuals, may persist

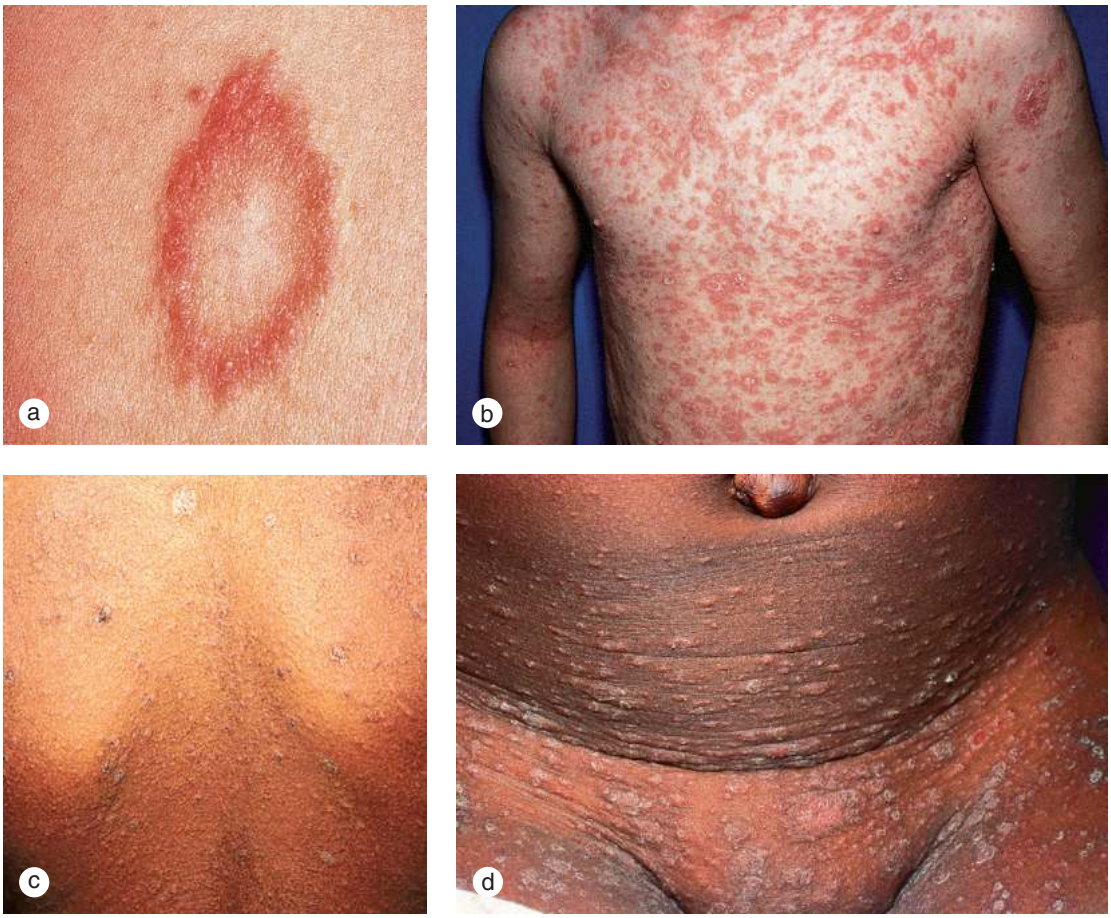


Fig 3.39 Pityriasis rosea. **(a)** The large herald patch on the chest of this 10-year-old girl shows central clearing, which mimics tinea corporis. **(b)** Numerous oval lesions on the chest of a white teenager. **(c)** Note the Christmas-tree pattern on the back of a black adolescent. **(d)** Small, papular lesions, as well as larger scaly patches, were most prominent on the abdomen and thighs of this 5-year-old girl.



Fig 3.40 The eruption of secondary syphilis may mimic pityriasis rosea. **(a)** A truncal rash in a Christmas-tree pattern on this adolescent resolved after treatment with intramuscular penicillin. Her Venereal Disease Research Laboratories titer was 1:2056. Hyperkeratotic 'copper penny' papules, which are distinctive for syphilis, are seen on **(b)** the palms and **(c)** the tops of the feet of adolescents. These also resolved quickly with antibiotics. **(d)** A painless chancre developed on the penile shaft of a teenage boy with primary syphilis.

for months. Phototherapy can also be used to camouflage these distressing pigmentary changes.

Other eruptions that can resemble pityriasis rosea include guttate psoriasis, viral exanthems (particularly some cases of Gianotti–Crosti syndrome), secondary syphilis (Fig. 3.40), and drug reactions (gold salts, bismuth, clonidine, penicillamine, isotretinoin, metronidazole, ACE inhibitors). The herald patch may suggest tinea, but fungus can be excluded by a negative potassium hydroxide (KOH) preparation and fungal culture.

Pityriasis lichenoides

Pityriasis lichenoides includes a group of self-limiting disorders with a spectrum of clinical presentations from the acute, papulonecrotic eruption of pityriasis lichenoides et varioliformis acuta (PLEVA, Mucha–Habermann disease) to the chronic dermatitic papules of pityriasis lichenoides chronica (PLC). Although most common in older children and young adults, pityriasis lichenoides may occasionally occur in infants and young children, with a slight predominance in boys.

Acute forms usually begin with the sudden onset of 2–4 mm diameter red macules and papules, which evolve over several days into vesicular, necrotic, and eroded lesions (Fig. 3.41). Healing occurs within several weeks with postinflammatory pigmentary changes and occasionally chickenpox-like scars. Although the rash is usually asymptomatic and has a predilection for the trunk, pruritus may be intense and lesions may spread to involve the neck, face, and extremities, which include the palms and soles. Fever and other mild constitutional symptoms may precede or accompany the acute phase. The eruption appears in successive crops, which settle down over weeks to months. Relapses and remissions occur episodically, but after several months most patients develop the more subtle lesions of PLC.

In PLC, which may also appear *de novo*, the typical rash consists of round 2 mm–1 cm diameter reddish-brown papules which develop a shiny brown scale adherent at the center (Fig. 3.42). Episodic crops of papules heal over several weeks, with pigmentary changes but no evidence of scarring. In fact, postinflammatory pigmentary changes may be the first findings to bring attention to the rash (Fig. 3.43). Although the eruption is self-limiting and usually heals without scarring, it may evolve for 5–10 years.

Although the cause is unknown the detection of monoclonal T-cell populations in the inflammatory infiltrate in some cases of acute and chronic pityriasis lichenoides suggests a benign self-limited lymphoproliferative process.

The histopathology of skin biopsies is distinctive, but not diagnostic. In the mild form, minimal dermatitic changes are seen, with spongiosis and parakeratosis. A mild, chronic, perivascular infiltrate is found in the dermis associated with some hemorrhage and pigment incontinence. In acute disease the inflammation may be intense and extend down into the deep dermis and up into the

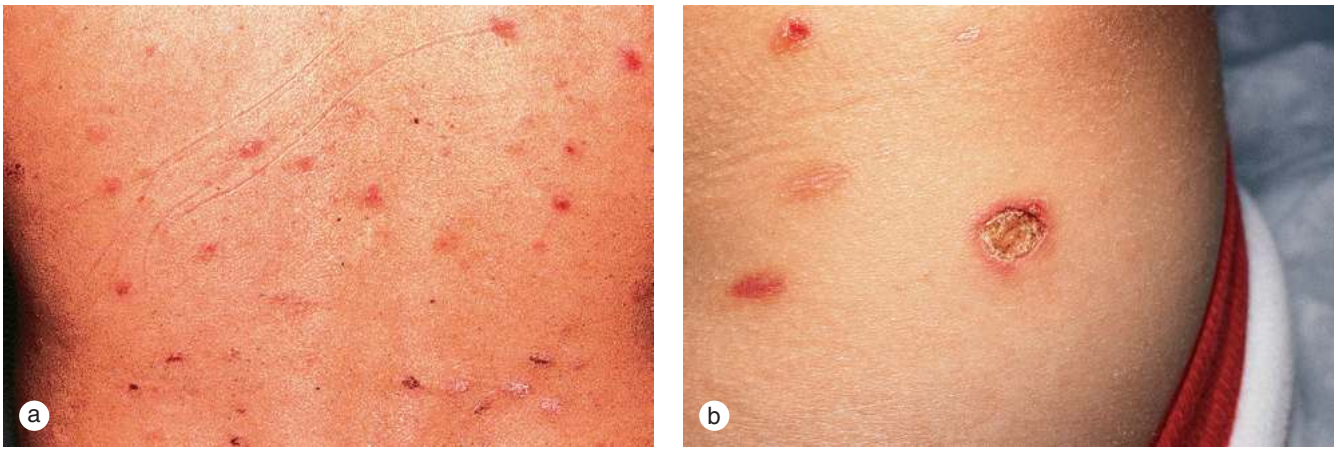


Fig 3.41 Pityriasis lichenoides et varioliformis acuta. **(a)** Asymptomatic hemorrhagic papules erupted in a pityriasis rosea-like pattern on the trunk and proximal extremities of this 15-year-old boy. **(b)** Recurrent papulonecrotic lesions continued to evolve on the trunk of this 5-year-old for over a year.

epidermis. Dyskeratosis is usually marked and necrosis of the epidermis may occur, with the formation of erosions. Endothelial cell swelling is marked, and vascular necrosis may occur. Hemorrhage is seen in the dermis and epidermis.

Although most children do well without treatment, phototherapy with UVB, PUVA, or natural sunlight may be useful in persistently symptomatic individuals. There may also be a role for oral antibiotics, such as erythromycin or tetracycline, in difficult patients. However, the use of systemic corticosteroids and methotrexate does not seem warranted except in rare patients with destructive painful or scarring disease.

At the onset, PLEVA may be mistaken for varicella. However, the lack of symptoms or mucous membrane lesions and the subsequent chronic course help to exclude chicken pox. Lymphomatoid papulosis is a chronic, benign, self-limiting disorder that is often clinically indistinguishable from PLEVA. However, the histopathology is characterized by an atypical lymphohistiocytic infiltrate, suggestive of lymphoma. In some children and adults a lymphomatoid papulosis-like eruption rarely occurs as a presenting picture for systemic lymphoma. Cutaneous vasculitis, impetigo, insect bites, and scabies are also considered during the acute phase.

The only differentiation between PLC and pityriasis rosea is the extremely protracted course. In pityriasis alba, the borders of the patches are indistinct and other stigmata of atopy are usually present. Patch-stage mycosis fungoides, a cutaneous T-cell lymphoma, may begin with subtle, scaly, hypopigmented or hyperpigmented patches that mimic PLC (Fig. 3.44). Consequently, any child with a long-standing rash suggestive of PLC must have a skin biopsy to exclude lymphoma. Parents are counseled regarding the chronic but innocent course of this disorder.

LICHENOID DERMATOSES

Lichen planus

Lichen planus (LP) is a distinctive dermatosis, characterized by pruritic, purple, polygonal papules (the '4-p sign') which involve the flexures of the arms and legs, mucous membranes, genitals, nails, and scalp (Fig. 3.45). The eruption in LP typically



Fig 3.42 Pityriasis lichenoides chronica. A few diffusely scattered, shiny, hyperpigmented papules continued to appear for years in this 11-year-old boy. Note the central adherent scale.



Fig 3.43 Postinflammatory hyperpigmentation was severe in this child with generalized pityriasis lichenoides et varioliformis acuta. Fortunately, the pigmentary changes healed over several months as his disease evolved into the more indolent pityriasis lichenoides chronica.

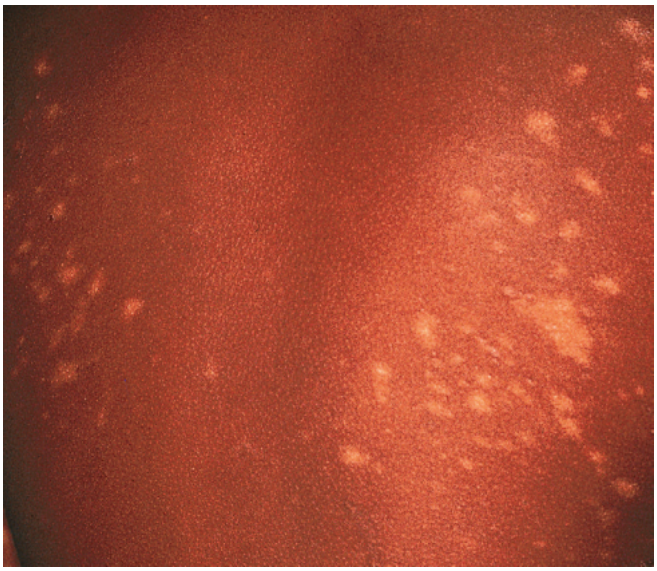


Fig 3.44 A 10-year-old child had asymptomatic, hypopigmented, minimally scaly oval patches on his trunk for several years. A skin biopsy demonstrated atypical, dermal, lymphocytic inflammation with extension into the epidermis characteristic of cutaneous T-cell lymphoma.

demonstrates the Koebner or isomorphic phenomenon, in which cutaneous lesions appear or extend in areas of trauma (scratches, excoriations, burns, scars). Only 2% of cases present before 20 years of age; however, patients with the familial variant develop LP in childhood. Some investigators have found an increased prevalence in African-American children compared with Caucasians. Although the cause of LP is unknown, complement and immunoglobulin depositions along the basement membrane zone suggest an immunologic mechanism.

Typically, itchy, violaceous 3–6 mm diameter papules appear abruptly on the wrists, ankles, and/or genitals (4-p sign: pruritic, polygonal, purple papules). Lesions may spread over the forearms, shins, and lower back. Rarely, widespread rash covers much of the body surface. In areas of involvement contiguous, shiny-topped papules may form a white, lacy, reticulated network known as Wickham striae. Their visibility may be enhanced by the application of a small quantity of mineral oil and examination with side lighting and a hand lens. Confluent lesions may form annular or linear plaques. Intense, dermal inflammation may be associated with the development of vesiculobullous lesions, and hypertrophic, verrucous plaques may evolve, particularly on the shins, in chronic disease (Fig. 3.46). In some reported series the incidence of thick hypertrophic pruritic plaques on the legs, particularly the shins, may approach 25%.

Wickham striae may also be present on the buccal mucosa, gingivae, lips, and tongue. Mucous membrane findings, which are present in two-thirds of patients with LP, also include erythema,



Fig 3.45 Lichen planus. **(a)** Violaceous, polygonal papules almost to confluence appeared over several weeks on the dorsum of the hands and feet, ankles, and wrists of this 16-year-old boy. **(b)** Lesions are somewhat hyperpigmented on the forearm of this black adolescent. **(c, d)** White papules formed Wickham's striae on the lips of this child, who also had typical papules on the penis.

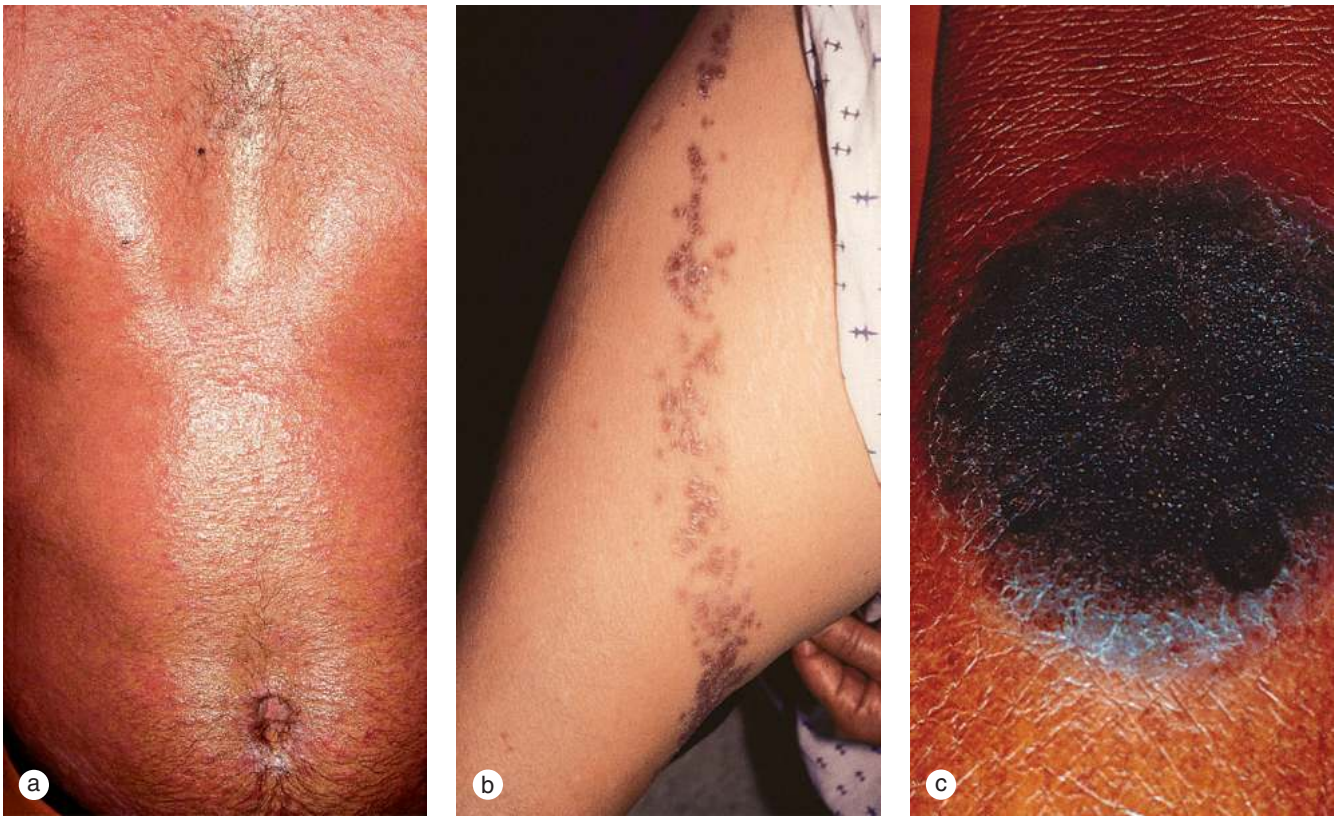


Fig 3.46 Lichen planus variants. **(a)** Diffuse, eruptive lichen planus responded to treatment with psoralen-ultraviolet A. Over 90% of this boy's body was involved with confluent papules on the trunk and extremities. **(b)** This asymptomatic, linear plaque progressed slowly for over a year. **(c)** Extremely pruritic, hypertrophic plaques were present on the shins of this 18-year-old girl.

white papules that resemble leukoplakia, vesicles, erosions, and deep, painful ulcerations.

Also, LP may present with follicular papules, particularly in the scalp where cicatricial alopecia may be progressive. Nail involvement, seen in about 10% of patients, includes brittleness, thinning, fragmentation, longitudinal ridging or striations, and partial or complete shedding of the nail. Pterygium formation, atrophy, subungual hyperkeratosis, and lifting of the distal nail plate may also occur (see Fig. 8.60). Rarely, nail disease appears without cutaneous involvement.

Skin biopsies characteristically demonstrate hyperkeratosis, focal thickening of the granular layer, irregular acanthosis, and a band-like or interface infiltrate of lymphocytes and histiocytes in the dermis, close to the epidermis and associated with damage to the basal cell layer.

Although the cause is unknown, cell-mediated immunologic reactions are probably important in the pathogenesis of disease. This is supported by a predominance of CD4+ and CD8+ T-cells in the inflammatory infiltrate. Moreover, some patients with graft-vs-host disease and drug reactions associated with T-cell dysregulation have developed eruptions clinically indistinguishable from lichen planus.

The presence of eosinophils in the dermal infiltrate suggests the possibility of a drug reaction. Prurigo nodules in eczema may be associated with other stigmata of atopic dermatitis, and the lesions of discoid lupus erythematosus usually demonstrate atrophy. Nail disease must be differentiated from other causes of nail dystrophy, and oral LP may mimic viral infection, primary blistering dermatoses, erythema multiforme, and leukoplakia.

Although many cases resolve within 1–2 years, some eruptions persist for 10–20 years. Localized lesions often respond well to topical corticosteroids. Oral LP may be resistant to treatment, and some success has been achieved with topical retinoic acid, topical tacrolimus ointment, intralesional corticosteroids, oral retinoids, oral corticosteroids, and swish-and-spit cyclosporine. Although quite painful, intralesional corticosteroids are also useful in the treatment of nail disease. Patients with generalized LP have been treated with systemic corticosteroids and retinoids. However, therapeutic benefits must be weighed against the long-term consequences of these medications. In fact, PUVA may provide a relatively safe alternative for disseminated disease.

Lichen nitidus

Lichen nitidus, an uncommon, chronic, asymptomatic eruption, is characterized by flat-topped, flesh-colored 2–3 mm diameter papules that demonstrate the isomorphic phenomenon (Fig. 3.47). Although many practitioners consider lichen nitidus to be a variant of LP, the peak incidence in children between 7 and 13 years, the uniformly tiny lesions (which do not have a tendency to coalesce), and the lack of pruritus establish this disorder as a distinct entity. The rash progresses slowly over months to years, with a predilection for the arms, abdomen, and genitals. The majority of patients are male.

Skin biopsies demonstrate findings reminiscent of LP, but are restricted to only one or a few papillae. The overlying horny layer exhibits parakeratosis, and at the lateral margin of the lesion the rete ridges extend downward to form a claw around the underlying infiltrate.



Fig 3.47 Lichen nitidus. **(a)** Asymptomatic, uniform, 2–3 mm diameter, shiny papules began on the face and spread to the trunk and extremities of this 6-year-old boy. **(b)** Note Koebner's phenomenon on the arm, where papules developed in an incidental excoriation. **(c)** Koebner's phenomenon is also evident in this lightly pigmented girl with minimally inflammatory papules on her arms.

Papular or follicular eczema may be differentiated from lichen nitidus by the presence of pruritus and other markers of atopy. Keratosis pilaris appears in characteristic locations and is inherited as an autosomal-dominant trait. Examination of flat warts with side lighting and magnification usually reveals a rough surface, unlike the smooth, shiny surface of papules in lichen nitidus. However, both lichen nitidus and flat warts can develop a Koebner phenomenon, and a skin biopsy may be necessary to differentiate them.

Lichen striatus

Lichen striatus is a linear, lichenoid eruption that appears most commonly in children of school age. Flat-topped papules arise suddenly in unilateral streaks and swirls conforming to the lines of Blaschko, usually on the extremities, upper back, or neck. However, any area, including the palms, soles, nails, genitals, and face, may become involved (Fig. 3.48). Lesions usually develop some overlying dusty scale and mild erythema. Hypopigmentation may bring attention to the eruption, especially in dark-skinned children.

Lichen striatus usually fades without treatment in 1–2 years. Lubricants and topical corticosteroids may be useful to decrease scale and inflammation in cosmetically important areas. There are also anecdotal reports of successful treatment with topical tacrolimus ointment.

Although the cause is unclear, the development of lesions along the lines of Blaschko suggests that the cutaneous defect may result from a somatic mutation that arises embryologically. Expression of the aberrant clone may be triggered by an environmental insult such as a viral infection or trauma. The ensuing inflammation results in clinical lesions with a predominance of CD8+ T-cells, and resolution occurs with elimination of the abnormal keratinocyte clone. A similar process may explain linear lichen planus and linear graft-versus-host disease.

This condition can also be mistaken for linear epidermal nevi, linear porokeratosis, flat warts, linear psoriasis, and linear ichthyotic eruptions. When the clinical course is confusing, a skin biopsy helps to differentiate these disorders. Lichen striatus usually demonstrates dermatitic changes in the epidermis, with a lymphocytic perivascular infiltrate in the superficial and mid-dermis that frequently extends into the deep dermis.

FUNGAL INFECTIONS

Tinea

Two types of fungal organisms, dermatophytes and yeasts, produce clinical cutaneous disease. Dermatophytes include tinea or ringworm fungi, which infect skin, nails, and hair (see Chapter 8). Although *Candida* and *Pityrosporum* yeast infections usually involve the skin, *Candida* can infect mucous membranes and rarely disseminates to viscera, particularly in immunocompromised patients.

Tinea corporis

This is a superficial fungal infection of non-hairy or glabrous skin. It has been called *tinea* (Latin for intestinal worm) or 'ringworm' because of its characteristic configuration, which consists of



Fig 3.48 Lichen striatus. Asymptomatic, linear, scaly papules appeared on the **(a)** leg, **(b)** abdomen, **(c)** abdomen and scrotum, and **(d)** face of young children. In each case, histology demonstrated findings typical of lichen striatus. After a variable period of progression (6–24 months) these lesions resolved without treatment.

pruritic annular plaques with central clearing or scale and an active, indurated, and/or vesiculopustular, worm-like border (Fig. 3.49). Lesions, which may be single or multiple, typically begin as red papules or pustules that expand over days to weeks to form 1–5 cm diameter plaques. Tinea corporis can be found in any age group and is usually acquired from an infected domestic animal (*Microsporum canis*) or through direct human contact (*Trichophyton*, *Microsporum*, and *Epidermophyton* species).

Clinically, tinea may be differentiated from atopic dermatitis by its propensity for autoinoculation from the primary patches to other sites on the patient's skin, by spread to close contacts, and by the central clearing noted in many lesions. Moreover, the rash of atopic dermatitis tends to be symmetric, chronic, and recurrent in a flexural distribution. Unlike tinea, patches of nummular eczema are self-limited and do not clear centrally. The herald patch of pityriasis rosea is often mistaken for tinea. However, scrapings obtained for KOH preparation are negative, and subsequent development of the generalized rash with its characteristic truncal distribution is distinctive. The clinical patterns, associated findings, and chronicity help differentiate psoriasis and seborrhea from tinea. Granuloma annulare produces a characteristic ringed plaque. However, on palpation, the lesions are firm and do not have epidermal changes (scales, vesicles, pustules). Granuloma annulare is also asymptomatic.

The diagnosis of tinea is confirmed by KOH examination of the skin (see Fig. 1.6). The first step is to obtain material by scraping the loose scales, vesicles, and pustules at the margin of a lesion. These are mounted on the center of a glass slide and 1 or 2 drops of 20% KOH are added. Next, a glass coverslip is applied and gently pressed down with a finger tip or the eraser end of a pencil to crush the scales. The slide can then be heated gently, taking care not to boil the KOH solution and, again, the coverslip is pressed down. The slide is placed under a microscope, with the condenser and light at low levels to maximize contrast, and with the objective at low power. On focusing up and down, true hyphae are seen as long, greenish, hyaline, branching, often septate rods of uniform width that cross the borders of epidermal cells. Cotton fibers, cell borders, or other artifacts may be falsely interpreted as positive findings.

Tinea infections on glabrous skin respond readily to topical antifungal creams or lotions (imidazoles such as clotrimazole, econazole, miconazole, ketoconazole, sulconazole, oxiconazole; the allylamines naftifine and terbinafine; ciclopirox olamine; tolnaftate). Some topical agents such as ciclopirox also demonstrate antibacterial activity. When lesions are multiple and widespread, oral therapy with griseofulvin, itraconazole, terbinafine, or Diflucan is indicated.

Although topical steroids may be used in combination with topical or oral antifungal agents for short periods of time to suppress severe inflammation and resultant pruritus, prolonged use of steroids may delay proper diagnosis or result in premature discontinuation of antifungal therapy. Ringworm skin lesions suppressed by steroids are referred to as tinea incognito (Fig. 3.50).

Tinea pedis

Commonly referred to as athlete's foot, tinea pedis is a fungal infection of the feet with a predilection for web space involvement (Fig. 3.51). It is common in adolescence, but somewhat less so in prepubertal children. The infecting organisms are probably acquired from contaminated showers, bathrooms, and locker room and gym floors, and their growth is fostered by the warm, moist environment of shoes.



Fig 3.49 Tinea corporis. The characteristic annular lesions show many variations in appearance. **(a)** This lesion has a raised active border and shows some central clearing and scale. **(b)** Sharply circumscribed tinea faciei demonstrates erythema, scale, and pustule formation throughout the expanding patch. **(c)** An inflammatory tinea or kerion on the arm has marked edema and vesiculation. **(d)** Multiple expanding lesions spread quickly in a toddler who acquired infection from the family kitten. **(e)** This child had an isolated itchy expanding annular plaque on the ear. **(f)** An annular cluster of follicular papules and pustules on the leg of this adolescent girl for 4 months did not improve with oral antibiotics. A skin biopsy showed granulomatous inflammation around hair follicles and a culture grew *Trichophyton tonsurans* typical of Majocchi granuloma, a variant of tinea corporis.



Fig 3.50 This 9-year-old girl with tinea corporis was treated repeatedly for 6 months with topical steroids. Each time she improved, but the rash flared as soon as the treatment was discontinued. Note the multiple concentric annular and serpiginous plaques typical of tinea corporis within the larger well-demarcated border.

In some cases, scaling and fissuring predominate; in others, vesiculopustular lesions, erythema, and maceration are found. The infection starts and may remain between and along the sides of the toes. However, lesions can extend over the dorsum of the foot and can involve the plantar surface as well, particularly the instep and the ball of the foot. Patients complain of burning and itching, which are frequently intense. Although the rash occasionally involves both feet and the hands, asymmetric involvement with sparing of one hand or foot is typical of tinea.

Diagnosis is suspected on clinical grounds and confirmed by KOH preparation and/or fungal cultures of skin scrapings. The mainstays of treatment include topical antifungal creams or powders and measures to reduce foot moisture. Oral antifungal agents may be necessary for persistent of widespread tinea pedis. Onychomycosis or tinea unguium occurs when tinea pedis spreads to nails. Although onychomycosis is unusual in young children, the prevalence increases with increasing age and should be considered in any child with asymmetric nail dystrophy and contiguous skin involvement. Three months of daily oral therapy with oral terbinafine and itraconazole may be curative in up to 50% of affected individuals but is not approved by the FDA for children. Many individuals do better during the summer months, while wearing sandals. For those with severe inflammatory lesions, oral antifungal agents may be required, and secondary bacterial infections, particularly with Gram-negative organisms, may be a problem.

Tinea pedis is differentiated from contact dermatitis of the feet by the tendency of the latter to involve the dorsum of the feet and to spare the interdigital web spaces. In dyshidrotic eczema, KOH preparations and fungal cultures are negative. Psoriasis and PRP are differentiated from tinea by their symmetric moccasin-glove distribution and other characteristic stigmata. Cutaneous larva migrans, most commonly caused by a hookworm of dogs and cats, *Ancylostoma braziliense*, creates a narrow serpiginous erythematous plaque which may become vesicular, bullous, and crusted on the sole of the foot (Fig. 3.51c). The tunnel-like lesion should be distinguished from the asymmetric dermatitic lesions of tinea pedis as well as the symmetric lesions of dyshidrotic eczema.

Yeast

Candida and *Pityrosporum* account for the majority of yeast-related cutaneous disease.



Fig 3.51 Tinea pedis. **(a)** Macerated, eroded, and crusted patches extend from the toe web spaces to the plantar surfaces of the toes and foot in this 5-year-old boy. **(b)** Dry, scaly, red patches extend from the web spaces to the top of the toes and foot in a 4-year-old boy. **(c)** This 6-week-old girl had a 10-day history of an expanding annular plaque on the plantar surface of the right foot. All of these children had at least one parent with chronic or recurrent tinea pedis.

Candidiasis

Candida colonizes the gastrointestinal tract and skin shortly after birth and may produce localized infection (thrush and diaper dermatitis), as well as disseminated cutaneous and systemic infection in the newborn. Recurrent and persistent infection in infancy may be associated with the use of antibiotics. However, it should also raise the suspicion of heritable or acquired immunodeficiency (Fig. 3.52a,b). Candidal paronychia is also a common problem in otherwise healthy toddlers who suck on fingers and toes (Fig. 3.52c). Yellowing, pitting, and other signs of nail dystrophy associated with *Candida* in this setting usually resolve without therapy; however, they may benefit from the application of topical

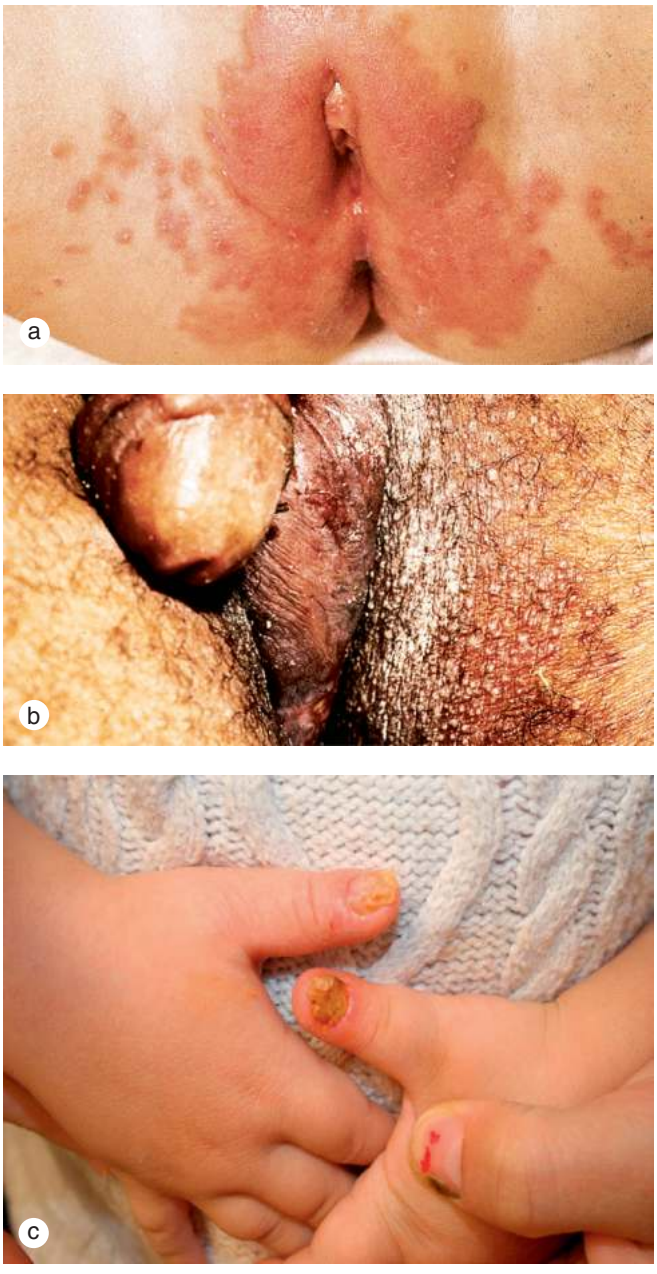


Fig 3.52 Candidiasis. **(a)** A red, papular rash with pustules at the periphery erupted on the anogenital area of this child who was on chronic antibiotics for recurrent ear infections. **(b)** A teenage diabetic on antibiotics developed a painful, red, macerated eruption dotted with pustules on the scrotum, penis, and groin. **(c)** A chronic paronychia with erythema at the base of the nail, loss of the cuticle, and dystrophic changes of the nail developed in a 2-year-old thumb-sucker. Scrapings from all three patients grew *Candida* species.

antifungal creams. Perlèche, manifested as erythema, maceration, and fissuring of the corners of the mouth, occurs commonly in diabetics and lip lickers, and may become secondarily infected by *Candida*. Topical antifungals, as well as aggressive use of lubricants, may be necessary to eradicate the condition.

Candidiasis resulting from the use of oral antibiotics in older children and adolescents or persistent infection in compromised hosts will respond quickly to oral Diflucan when topical measures are difficult or ineffective. In some patients, intermittent oral antifungal prophylaxis may be necessary.

Tinea versicolor

Tinea versicolor is a common dermatosis characterized by multiple, small, oval, scaly patches that measure 1–3 cm in diameter, usually located in a guttate or raindrop pattern on the upper chest, back, and proximal portions of the upper extremities of adolescents and young adults (Fig. 3.53a,b). However, all ages may be affected, including infants (Fig. 3.53c). Facial lesions are seen occasionally and may be the only area of involvement in breast-feeding babies, who acquire the organism from their mothers.

The rash is usually asymptomatic, although some patients complain of mild pruritus. Typically, the cosmetic appearance is more bothersome. Lesions may be light tan, reddish, or white in color, giving rise to the term versicolor. Patches tend to appear hyperpigmented in light-pigmented patients and hypopigmented in dark-pigmented patients. In some individuals, a folliculitis characterized by 2–3 mm diameter red papules and pustules develops on the chest, back, and occasionally, the face.

Tinea versicolor is caused by a dimorphous form of *Pityrosporum* (*Malassezia*), which commonly colonizes the skin by 4–6 months of age. Warm, moist climates, pregnancy, immunodeficiency states, and genetic factors predispose to the development of clinical lesions.

The diagnosis of tinea versicolor can generally be made on the basis of the clinical appearance of lesions and their distribution. It can be confirmed by a KOH preparation of the surface scale, which demonstrates short pseudohyphae and yeast forms that resemble spaghetti and meatballs. Although the pathogenesis of the color change is not fully understood, the fungus is known to produce azelaic acid, a substance that interferes with tyrosinase activity and subsequent melanin synthesis.

The differential diagnosis of tinea versicolor includes postinflammatory hypopigmentation and vitiligo. The history, distribution, and distinct borders help to differentiate tinea versicolor from postinflammatory hypopigmentation, and the presence of fine, superficial scaling and some residual pigmentation helps to exclude vitiligo.

Topical desquamating agents, such as selenium sulfide and propylene glycol, produce rapid clearing of tinea versicolor. Localized lesions may be treated effectively with topical antifungal creams, while recalcitrant cases may respond to oral ketoconazole, itraconazole, or fluconazole. Patients must be counseled about the high risk of recurrence and reminded that pigmentary changes may take months to clear, even after eradication of the fungus.

Confluent and reticulated papillomatosis of Gougerot and Carteaud

Gougerot–Carteaud syndrome is an uncommon eruption that comprises brown or slate-gray papules, which often become confluent on the seborrheic areas of the chest and back, particularly in black adolescents and young adults (Fig. 3.54). Although this eruption may be noted in healthy adolescents with a normal body mass index, the prevalence is increased in obesity. Reticulated patches may extend over much of the back, shoulders, chest, and abdomen. Although the cause is not known, many investigators attribute the rash to *Pityrosporum* infection, while others consider it to be a variant of acanthosis nigricans.

Unfortunately, the rash is usually refractory to topical antifungal treatment. However, over a period of months to years, most patients improve without treatment, and others respond to traditional therapy for tinea versicolor. Several investigators have also demonstrated a response to oral minocycline, oral isotretinoin, and topical calcipotriol. In fact, the standard of care has shifted to oral tetracyclines and other oral antibiotics, when tetracyclines are contraindicated, for widespread and/or recalcitrant cases.

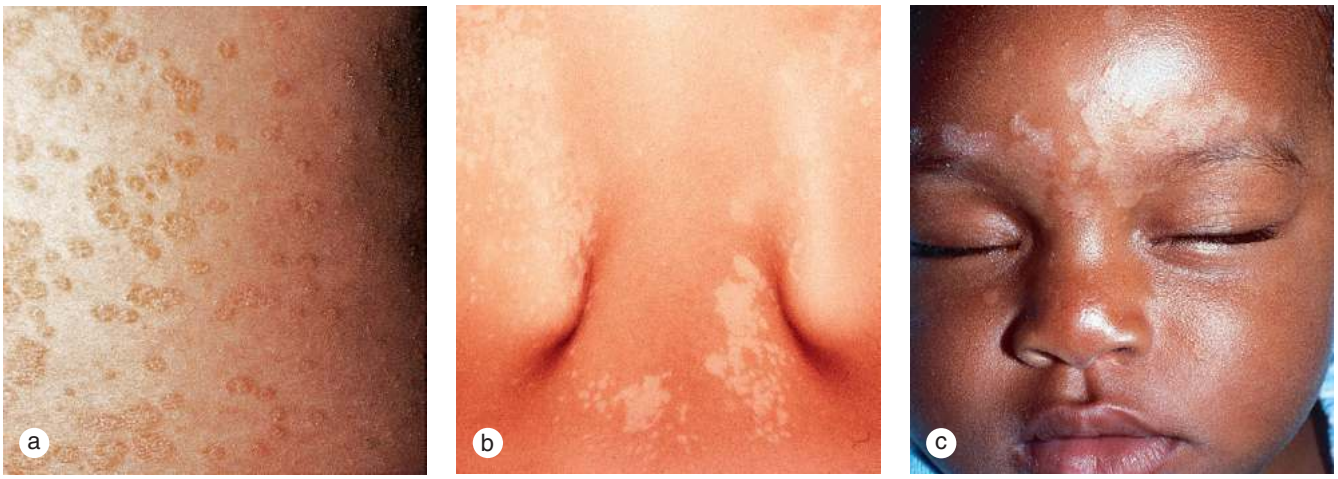


Fig 3.53 Tinea versicolor. **(a)** The well-demarcated, scaly papules appear darker than surrounding skin on the back of a white adolescent. **(b)** Sun-exposed papules on the back of this child failed to tan, resulting in a hypopigmented rash. **(c)** A 4-month-old black girl developed hypopigmented, scaly papules on her face. Her mother had widespread lesions on the chest and back.

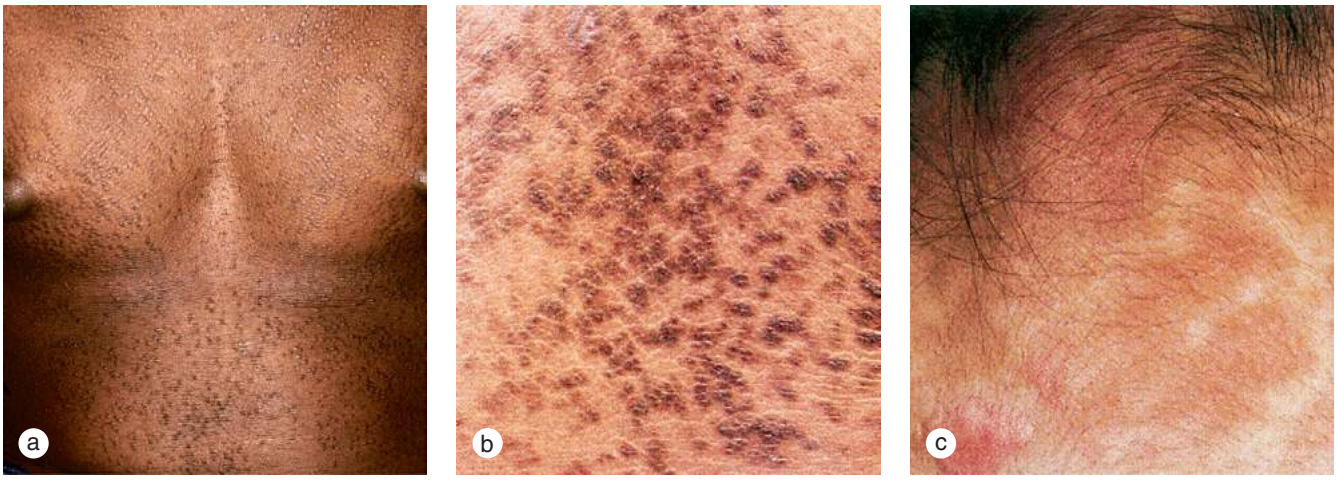


Fig 3.54 Confluent and reticulated papillomatosis. **(a)** Asymptomatic, hyperpigmented papules disseminated over the trunk of this healthy Afro-American adolescent. Multiple scrapings for tinea versicolor were negative, and he failed therapy with topical keratolytics. **(b)** At a visit several months later the papules on his upper trunk were confluent and reticulated. The rash disappeared 2 years later without treatment. **(c)** A similar eruption developed on the neck of this healthy light-pigmented adolescent before disseminating over the back and chest.

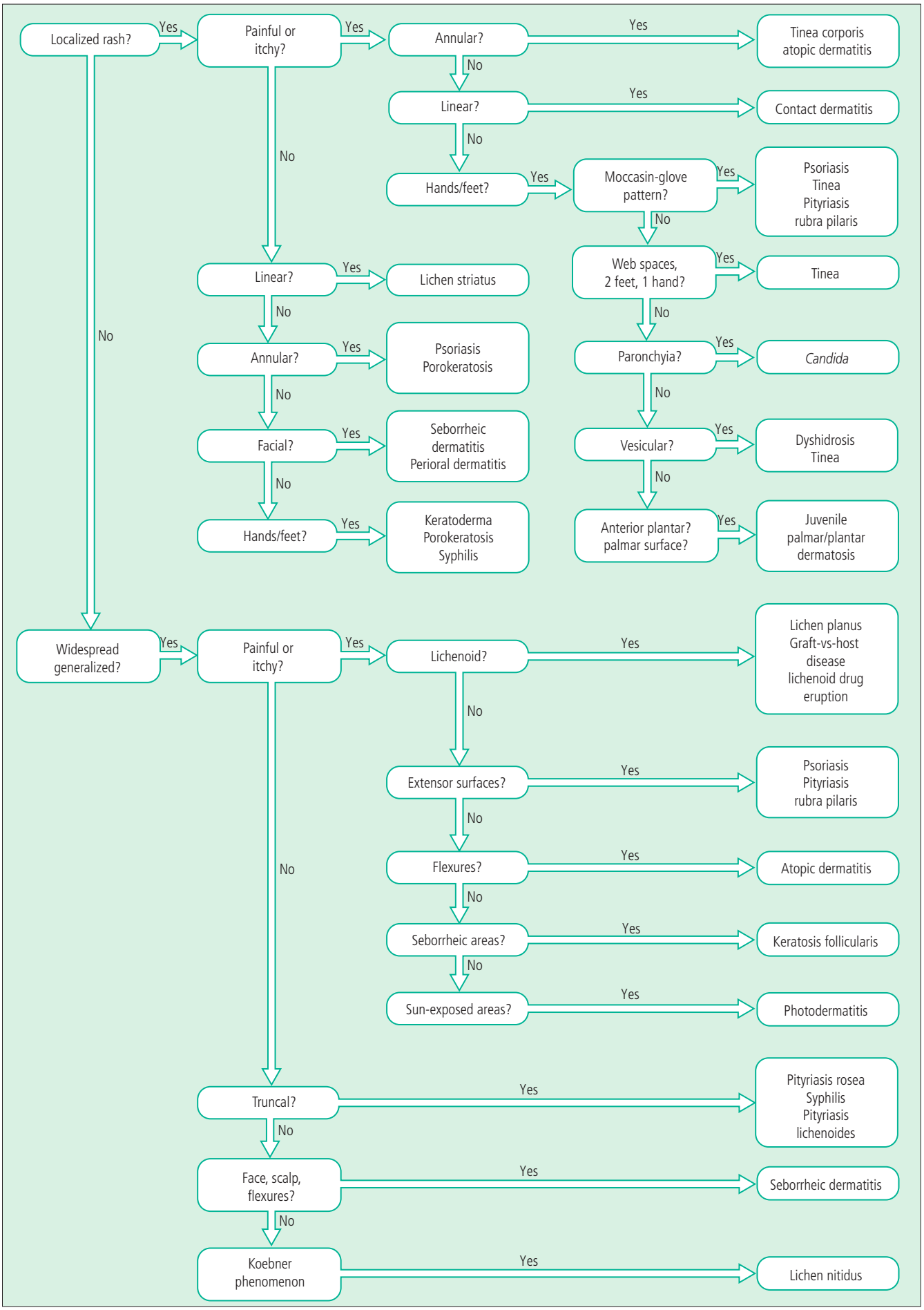


Fig 3.55 Algorithm for evaluation of papulosquamous disorders.

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Chapter 4

Vesiculopustular Eruptions

Bernard A. Cohen

INTRODUCTION

Vesiculopustular eruptions range from benign, self-limited conditions to life-threatening diseases. Early diagnosis, especially in the young or immunocompromised child, is mandatory. An algorithmic approach to diagnosis for vesiculopustular dermatoses is summarized at the end of the chapter (see Fig. 4.29).

An understanding of the structures that account for normal epidermal and basement membrane zone adhesion provides clues to the clinical diagnosis and pathogenesis of blistering diseases (Fig. 4.1). Epidermal cells are held together by desmosome–tonofilament complexes. Electron-dense tonofilaments insert into desmosomes in the keratinocyte plasma membrane and project toward the nucleus. Intercellular bridges extend between keratinocytes and are associated with a sticky, glycoprotein-rich, intercellular, cement substance. In the basement membrane zone tonofilaments insert into hemidesmosomes, which are attached to the lamina densa by anchoring filaments that traverse an electron-lucent layer known as the lamina lucida. The electron-dense lamina densa is, in turn, affixed to the dermis by anchoring fibrils. Elastic microfibril bundles, which arise in the upper dermis, also insert into the lamina densa.

A number of proteins that play a role in the structural integrity of the skin have been identified in the basement membrane zone, and hereditary or autoantibody-induced defects in these proteins may lead to clinical disease. Bullous pemphigoid (BP) antigen appears on the bottom of the basal cell plasma membrane and within the lamina lucida. Laminin is present within the lamina lucida, and type IV collagen has been isolated to the lamina densa. In epidermolysis bullosa acquisita (EBA) antibodies against type VII collagen have been identified in the dermis, just beneath the lamina densa. Fluorescein-tagged antibodies directed against these proteins may be used to identify the site of blister formation in disorders that involve the dermal–epidermal junction. Salt-split skin can be used as a substrate to more specifically localize antibodies above or below the basal lamina region.

In general, flaccid bullae arise within the epidermis, and tense lesions involve the dermis. Specific diagnoses, however, rely on identification of clinical patterns, histopathology, and immunofluorescent findings. A few rapid diagnostic techniques also aid in developing a working diagnosis.

VIRAL INFECTIONS

Herpes simplex virus

Herpes simplex virus (HSV) is a common cause of oral lesions in toddlers and children of school age. Primary herpetic gingivostomatitis begins with extensive perioral vesicles and pustules, and intraoral vesicles and erosions (Fig. 4.2). The gingivae become edematous, red, friable, and bleed easily. Epithelial debris and exudates may form a membrane on the mucosal surfaces. The eruption is usually accompanied by fever, irritability, and cervical adenopathy. Lesions may also be scattered on the face and upper trunk. In infants and toddlers, lesions are frequently autoinoculated onto the hands. Patients are observed for dehydration as symptoms abate over 7–10 days.

Herpetic gingivostomatitis can be differentiated from enteroviral infections, which usually produce vesicles, ulcerations, and petechiae on the hard palate and spare the gingivae. Although aphthae may be very painful, they are usually isolated lesions that lack the diffuse inflammation associated with herpes.

Primary herpes simplex infections may involve any cutaneous or mucous membrane surface and generally result from direct inoculation of previously injured sites. Lesions consist of herpetiform or clustered red papules, which evolve into vesicles and, not infrequently, pustules in 24–48 h (Figs 4.2, 4.3, 4.4, 4.5). During the following 5–7 days vesicles rupture and crust over. Desquamation and healing are complete in 10–14 days. Primary herpes infection on the distal finger is called herpetic whitlow (Fig. 4.3b,c). Just as in herpetic gingivostomatitis, primary infections at other sites may be associated with painful local adenopathy and flu-like symptoms.

In children, most infections are caused by HSV Type 1, whereas HSV Type 2 is most commonly found in genital infections in adolescents and adults (Fig. 4.4). However, HSV Type 2 can also be found in non-genital areas, and Type 1 virus may be spread from mouth to hand to genital sites. Although sexual contact must be considered in any child who develops genital herpes, non-venereal sources are probably most common. Vesicles are usually restricted to the perineum and genital skin, and quickly ulcerate. Erythema and edema may result in severe dysuria and urinary retention.

In immunocompromised children or patients with certain skin conditions, such as atopic dermatitis, seborrheic dermatitis, and immunologic blistering disorders, herpes simplex may disseminate over the entire skin surface (eczema herpeticum or Kaposi varicelliform eruption; see Fig. 3.33) and to the lungs, viscera, and central nervous system. HSV may also produce sepsis and/or meningitis with neurologically disabling or life-threatening disease in the nursery. Early diagnosis and antiviral therapy can reduce morbidity and mortality in these clinical settings.

Following the initial episode, HSV enters a dormant state. A number of endogenous and environmental factors may trigger reactivation of the virus, such as a *Streptococcus* infection of the throat, an upper respiratory infection, sunburn, and surgery (Fig. 4.5). Lesions usually occur near the site of the primary eruption, mucous

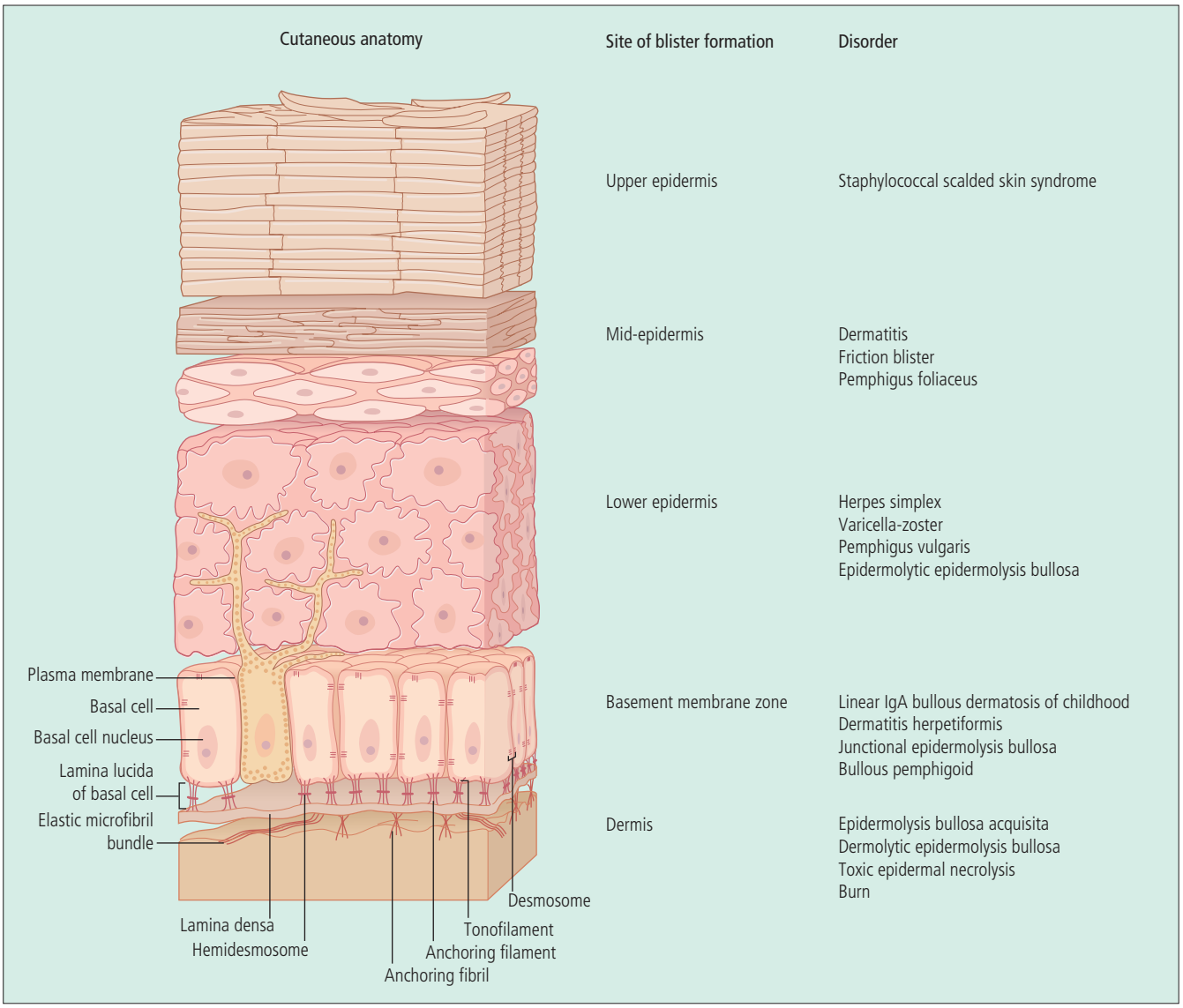


Fig 4.1 Anatomy of vesiculopustular dermatoses.

membranes are not usually involved, systemic symptoms are absent, and the rash heals in less than a week. Although recurrences are unpredictable, disease-free periods tend to increase with time, even in individuals who initially experience frequent recurrences.

A clinical suspicion of herpes simplex can be confirmed quickly by performing a Tzanck smear in the emergency room or at the bedside. Viral cultures in reliable laboratories turn positive in 12–36 h. In some centers, polymerase chain reaction studies or immunofluorescent staining of blister fluid debris on glass-slides, is used for rapid and reliable confirmation. The Tzanck smear is obtained by removing the roof of a blister with a scalpel or scissors and scraping its base to obtain the moist, cloudy debris (see Fig. 1.9). This is spread onto a glass-slide with the scalpel blade, desiccated with 95% ethanol, and stained with Giemsa or Wright stain. The diagnostic finding in viral blisters is the multinucleated giant cell, which is a syncytium of epidermal cells with multiple, overlapping nuclei; hence, it is much larger than other inflammatory cells. Unfortunately, a positive Tzanck smear cannot be used to differentiate between HSV and varicella, and a viral culture should be obtained when the clinical situation dictates. When the risk of viral infection is high or a delay in initiating therapy could be disastrous for the patient, particularly the compromised host, antiviral treatment should be started even when the Tzanck smear is negative until infection can be confirmed by more sensitive and specific studies.

In general, management of herpes infections is symptomatic with cool compresses, lubricants, and oral analgesics. Topical antiviral agents are of little use in the treatment of uncomplicated infections in normal hosts. Immunocompromised children with primary or recurrent herpes simplex infections and patients with severe primary herpetic gingivostomatitis or genital herpes usually improve quickly with parenteral aciclovir (5 mg/kg every 8 h). In some children, especially older patients without oral involvement, oral aciclovir may be administered. Several orally administered drugs, which include valaciclovir hydrochloride and famciclovir, achieve consistent blood levels. Although they are not yet approved for use in children, check recommendations as these medications should provide a safe, effective alternative to parenteral aciclovir for children with serious herpetic infections. In recurrent disease, initiation of oral aciclovir with the prodromal tingling in the skin before the appearance of blisters may abort the episode. In selected children with frequent, multiple, widespread recurrent eruptions,

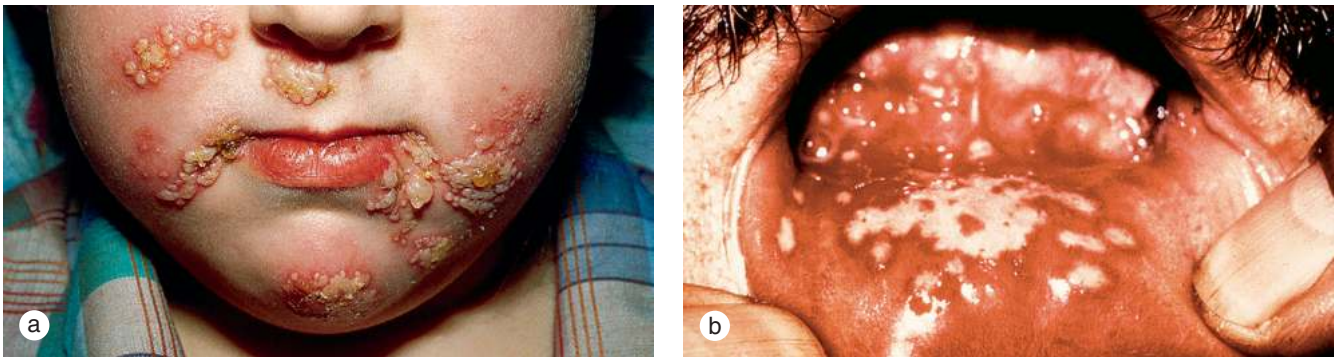


Fig 4.2 Herpetic gingivostomatitis. **(a)** This 6-year-old boy developed extensive perioral vesicles and mucous membrane erosions with his first bout of herpes simplex. **(b)** A 19-year-old experienced severe pain from widespread gingival and buccal mucosal vesicles and erosions during the peak of his primary herpes infection.

long-term, suppressive therapy may be necessary. Recent investigations have demonstrated that extended prophylactic therapy for infants following neonatal HSV infection can reduce the risk of late neurologic sequelae.

Herpes simplex infections are usually differentiated from other blistering eruptions by the typical clustering of lesions, the clinical course, a positive Tzanck smear and viral culture, and characteristic skin-biopsy findings. Impetigo may mimic herpes. However, bullae tend to be relatively large, with a central crust and peripheral extension, and a Gram stain demonstrates Gram-positive cocci. Blistering distal dactylitis, which is caused by Group A β-hemolytic streptococci or *Staphylococcus aureus*, may be mistaken for a herpetic whitlow (Fig. 4.6). In staphylococcal or streptococcal infection, the lesions on the finger tips usually coalesce to

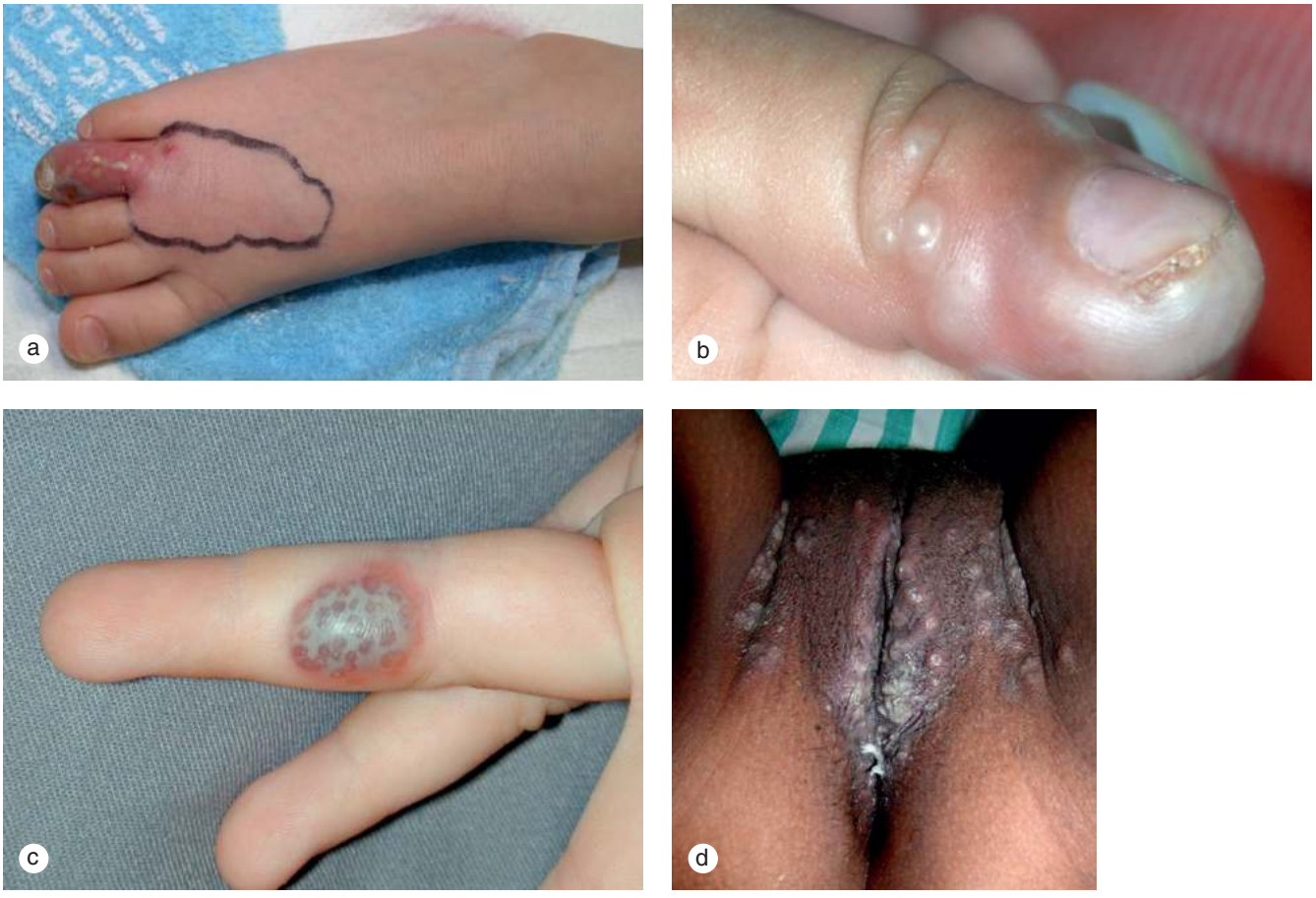


Fig 4.3 Primary herpes simplex infection. **(a)** A healthy 3-year-old girl developed clustered uniform vesicles and pustules on her right 4th toe associated with painful erythema, edema and a sterile lymphangitis on the top of her foot. **(b)** Herpetic whitlow developed by autoinoculation from oral lesions in this 4-year-old boy. Oral and finger lesions resolved without treatment in 2 weeks. **(c)** A multiloculated bulla was also noted on the finger of this child with herpetic whitlow. **(d)** A 16-year-old sexually active girl developed painful vesicles on the genital area, which cleared following 10 days of oral acyclovir.



Fig 4.4 Clustered pustules appeared on the posterior thigh of a teenager with recurrent herpes simplex Type 2 infection.



Fig 4.5 Recurrent herpes simplex erupted around the eye of this 11-year-old boy. The cornea was not involved, and vesicles crusted over in less than a week.



Fig 4.6 Blistering distal dactylitis developed on the right thumb and index finger of a 5-year-old girl. Cultures from her throat and thumb grew Group A β-hemolytic streptococci. The infection responded quickly to oral amoxicillin.

form one or several 5–10 mm diameter blisters, and Gram stains and cultures demonstrate the causative bacterium. Unlike impetigo at other sites, blisters on the fingers tend to be tense because the stratum corneum or outer layer of the epidermis is thick on acral surfaces. Occasionally, the eruption of herpes simplex may form a dermatomal pattern. In this situation, a viral culture is required to exclude herpes zoster.

Varicella (chickenpox)

Varicella is a mild, self-limited infection in most children. However, disseminated disease is a problem in the neonate and immunosuppressed child. Early administration of varicella-zoster immune globulin to immunocompromised children exposed to varicella may be preventive, and antiviral therapy in patients with disseminated lesions may be life-saving. The introduction of varicella vaccine into the primary immunization series has reduced the incidence of varicella and the risk of complications.

After exposure to varicella, the incubation period varies from 7 to 21 days. Fever, sore throat, decreased appetite, and malaise precede the skin lesions by several days. Early cutaneous findings vary from a few scattered, pruritic, red papules to generalized papules that evolve in 24 h to vesicles on a bright red base (dew drops on a rose petal, Fig. 4.7). Central umbilication of blisters follows rapidly, and crusting and desquamation occur within 10 days. New papules and vesicles continue to appear for 3–4 days. Vesicles may also be identified on mucous membranes, particularly the buccal mucosa and gingivae. Although the blisters are intraepidermal and usually heal without scarring, some develop deep inflammation or become secondarily infected and heal with pitted or hypertrophic scars (Fig. 4.8a,b).

Oral or parenteral acyclovir is indicated for treatment of varicella in immunocompromised patients and normal hosts with severe disease. However, famciclovir and valaciclovir provide better bioavailability and more convenient dosing. Unfortunately, the newer antiviral agents are not routinely available in liquid preparations. However, special formulating pharmacies may be able to prepare valacyclovir syrup for children who cannot swallow capsules. Pruritus may be intense and responds to cool compresses, calamine lotion, and oral antihistamines. Topical products containing antihistamines should be avoided because of the risk of significant percutaneous absorption and systemic toxicity. Secondary infection is usually caused by staphylococci, and is treated with oral antibiotics such as dicloxacillin, cefalexin, or erythromycin (Fig. 4.8c). When cellulitis or other deep, soft-tissue infection complicates chickenpox, hospitalization and parenteral therapy may be required. An increase in Group A β-hemolytic streptococcal fasciitis has been reported in association with recent varicella epidemics (Fig. 4.8d). Rarely, progressive purpura and necrosis of large areas of skin herald the onset of disseminated intravascular coagulation (Fig. 4.8e). This phenomenon, referred to as purpura fulminans, occurs in fewer than 1 in 20 000 cases of varicella.

Administration of systemic corticosteroids, even in normal children, is contraindicated during varicella infection and may result in severe blistering, disseminated viral infection, and increased risk of complications. As a consequence, it is important to differentiate chickenpox from contact dermatitis, insect bites, and mononucleosis or other viral infections. The Tzanck smear may be particularly useful early in the course of disease, when only a few skin lesions are present. Polymerase chain reaction studies should be used for rapid diagnosis of blistering eruptions in immunocompromised hosts and for practitioners caring for these patients when varicella is suspected.

Although the world was declared officially free of smallpox (variola) in 1980, this virus has resurfaced recently as a potential



Fig 4.7 Chickenpox. **(a)** A dew drop on a rose petal is the characteristic primary lesion in chickenpox. **(b)** Lesions in various stages of development, including red papules, vesicles, umbilicated vesicles, and crusts developed in close proximity on the forehead of a toddler with varicella. **(c)** Severe varicella with blisters almost to confluence erupted within 24 h over much of the skin surface of this 6-year-old boy who was on high-dose systemic corticosteroids for inflammatory bowel disease.

biological warfare agent. Chickenpox can be distinguished from smallpox in which lesions develop on the face and distal extremities and spread centrally. Early red macules and papules become vesicular and pustular over several days, and adjacent lesions tend to be in the same stage of development. New lesions, which are firm and deep-seated, may appear for 1–2 weeks, become confluent, and often heal with scarring. Patients are usually ill-appearing, and the rapid diagnostic Tzanck smear is negative for multinucleated giant cells. Many medical centers have developed protocols for isolating and evaluating patients with suspected smallpox infection.

Herpes zoster

Herpes zoster or shingles represents a reactivation of the dormant varicella virus from the sensory root ganglia. The most commonly involved sites include the head and neck and the thoracic sensory nerves (Fig. 4.9). After a variable prodrome, which may include mild constitutional symptoms and localized itching and burning, linear, clustered, red papulovesicles appear in a unilateral linear pattern in one or several dermatomes. In some children, the eruption may be completely asymptomatic. Over 3–5 days, the rash reaches its full extent, and during the ensuing 1–2 weeks vesicles and erosions develop umbilicated crusts and desquamate, much like in chickenpox.

Although 6–10 lesions may appear outside the primary dermatomes in normal individuals, the development of widespread cutaneous lesions suggests the possibility of an immunodeficiency state and an increased risk of visceral involvement. Children with lymphoreticular malignancies are over 100 times as likely to develop zoster as healthy children. However, most cases of childhood zoster occur in normal hosts.

Normal children who develop chickenpox during the first 2 months of life may also be prone to zoster. In these patients, protective antibody titers tend to be low and skin-test reactions are diminished, which suggests a blunted, immunologic response to varicella in early infancy. This phenomenon may result from transient, maternal antibody protection, which wanes during the first 4 months of life.

The presence of a dermatomal bullous eruption is virtually diagnostic for herpes zoster. However, herpes simplex occasionally presents in a dermatomal pattern. Moreover, zoster may be confused with herpes simplex early in the course, when only a few clustered vesicles are present and the dermatomal organization is not yet apparent.

Management of shingles is usually limited to supportive measures similar to those for chickenpox. In disseminated disease, administration of parenteral aciclovir may be life-saving. Oral aciclovir, valacyclovir, or famciclovir can also be used in immunocompromised hosts and normal patients with symptomatic disease. Normal individuals who develop eye involvement also benefit from antiviral therapy and are followed closely by an ophthalmologist. The high risk of zoster in patients undergoing bone marrow transplantation or other elective immunosuppression may require antiviral prophylaxis in these children. Although there is no approved herpes zoster vaccine for children and the risk of infection is generally low, zoster vaccine (ZOSTAVAX®, Merck & Co., Inc.) was licensed in the USA in 2008 for prophylaxis against zoster in adults over age 50.

Although systemic corticosteroids may be administered to reduce the risk of postherpetic neuralgia in adults over 60 years of age, this treatment has not been shown to be beneficial in young adults or children. Moreover, the incidence of this problem in childhood is extremely low. Children with shingles must be isolated from individuals who are susceptible to chickenpox because of the risk of acquiring infection from direct contact with skin lesions.

Hand-foot-and-mouth disease

Hand-foot-and-mouth disease is a distinctive, self-limited viral eruption caused most frequently by Coxsackie virus A16. The disease is highly infectious and, like other enteroviruses, peak incidence occurs in the late summer and fall. After exposure, the incubation period is 4–6 days. A 1–2-day prodrome of fever, anorexia, and sore throat is followed by the development of 3–6 mm diameter elongated, gray, thin-walled vesicles on a red or noninflamed base. As the name suggests, lesions appear most commonly on the palms, soles, and sides of the hands and feet, but red papules and vesicles may also erupt on the buttocks, trunk, face, arms, and legs (Fig. 4.10a,b). The enanthem is characterized by



Fig 4.8 Complications of varicella. **(a)** Multiple hypopigmented scars developed on the trunk of this 10-year-old boy several weeks after chickenpox. **(b)** Dome-shaped hypertrophic scars developed on the preauricular skin of this toddler. Note the small congenital pit at the anterior end of the superior helix. **(c,d)** Bullous impetigo spread quickly by scratching in a 4-year-old boy with chickenpox. Note the pus at the bottom of the large bulla **(c)** and infected lesions on the abdomen **(d)**. **(e)** While this child was recovering from varicella, several lesions on the top of her foot became infected with group A β-hemolytic streptococci. The rapidly spreading area of erythema responded quickly to high-dose parenteral penicillin. **(f)** A 7-year-old girl with healing chickenpox developed purpura fulminans, with expanding bruises on her legs. Laboratory studies were consistent with disseminated intravascular coagulation, which resolved on heparin therapy. Note the resolving chickenpox vesicles on her leg.

vesicles that rapidly ulcerate to leave sharply marginated erosions on a red base on the tongue, buccal mucosa, and posterior pharynx (Fig. 4.10c). Although cutaneous and mucosal lesions may be completely asymptomatic, pruritus and burning can be severe. Systemic symptoms, which include fever, diarrhea, sore throat, and cervical adenopathy, may be absent or mild, and treatment is supportive. The eruption usually clears in less than a week.

In late 2011 and spring 2012, a new clinical variant caused by Coxsackie A6 virus, previously reported in Asia and Africa, spread to North America. Although symptoms and the rash were also self-limited, high fever and more widespread skin lesions are characteristic. The skin eruption is reminiscent of disseminated herpes simplex infection but identification of the typical lancet-shaped enteroviral vesicles on the hands and feet provides a clue to the diagnosis (Fig. 4.11).

BACTERIAL INFECTIONS

Impetigo

Expanding, honey-colored, crusted patches or bullae with a central crust suggest the diagnosis of impetigo (Fig. 4.12, also see Fig. 3.32a,b). In older children in temperate climates, lesions appear

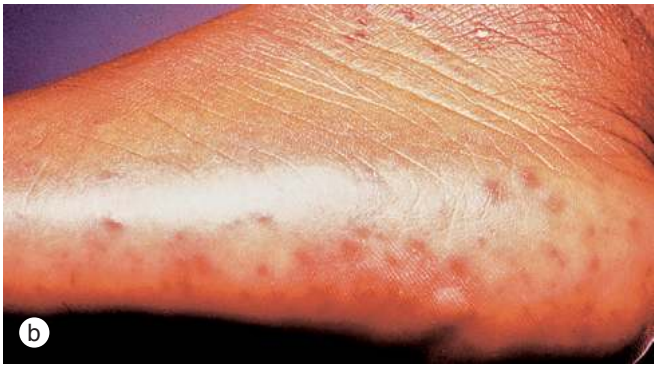






Fig 4.9 Herpes zoster infection. **(a)** Herpes zoster involved the right, mid-thoracic dermatomes in an otherwise healthy 10-year-old girl with a history of chickenpox when 2 years old. **(b)** Periorbital cellulitis was initially considered in this toddler with impressive edema and erythema of the right eye. The diagnosis of shingles became apparent 1 day later, when the characteristic dermatomal vesiculopustular rash appeared. Both children had uneventful recoveries without treatment. **(c)** This 9-year-old boy complained of painful swelling for several days before dermatomal clustered vesicles erupted on his right arm and hand. He improved quickly with oral valaciclovir.





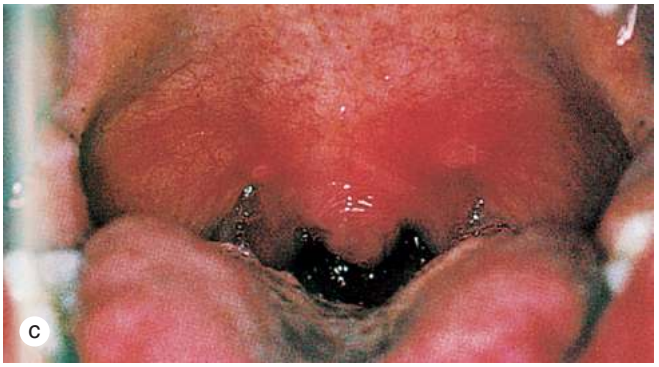


Fig 4.10 Hand-foot-and-mouth disease. Characteristic elongated vesicles on a red base are shown on **(a)** the palmar surface of the fingers and **(b)** the plantar surface of the foot of children with Coxsackie hand-foot-and-mouth disease. **(c)** The enanthema, consisting of shallow yellow ulcers surrounded by red halos, may be found on the labial or buccal mucosa, the tongue, soft palate, uvula, and anterior tonsillar pillars. When the enanthema occurs in the absence of a rash, the disorder is known as herpangina.

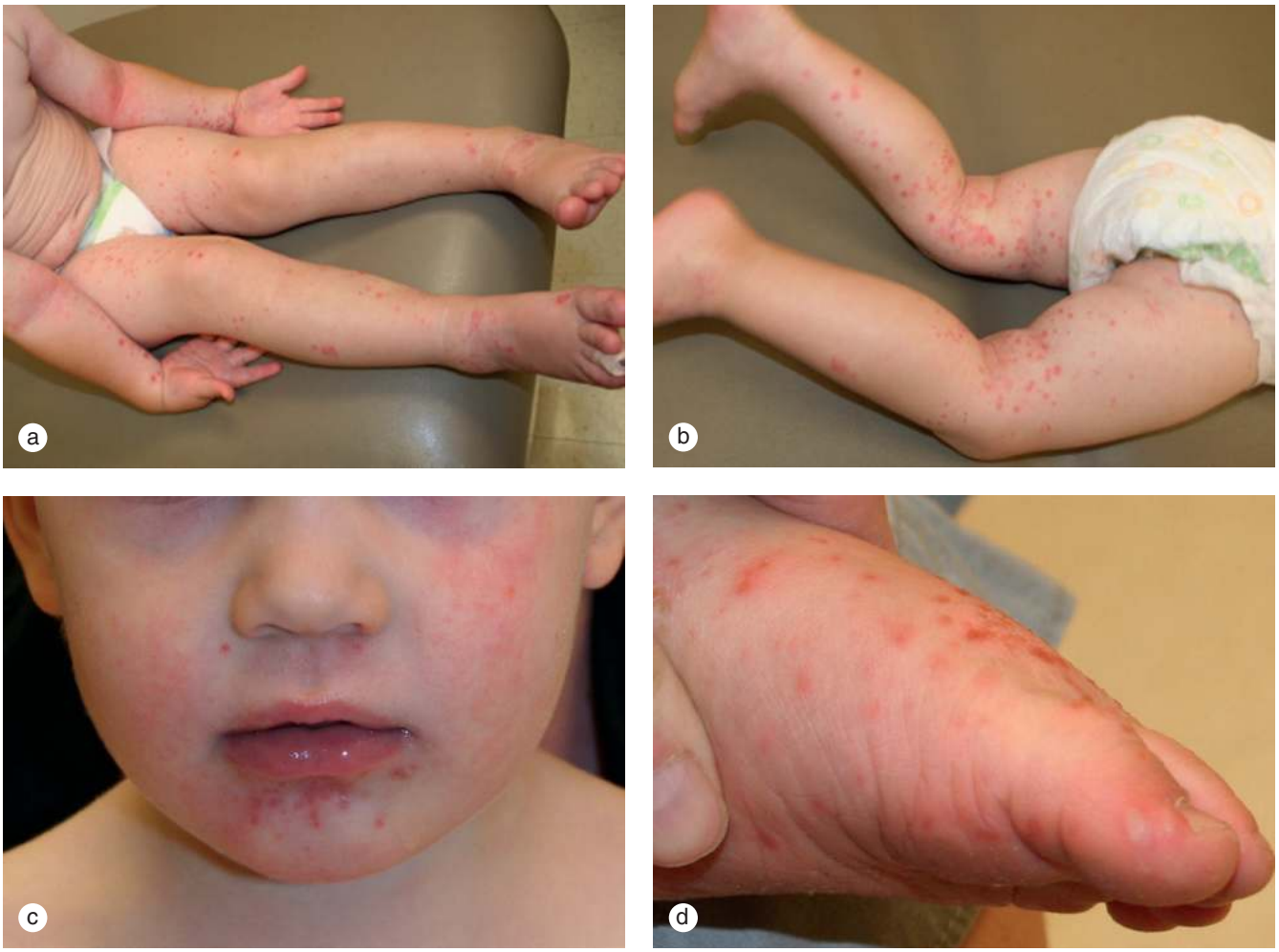


Fig 4.11 Coxsackie A6 virus infection. A 2-year-old boy developed high fever and widely disseminated vesicles and crusts concentrated on the **(a)** arms, **(a,b)** legs, and around the **(c)** mouth. He had erosions on his palate and on careful observation lancet-shaped vesicles on a red base on his hands and **(d)** feet. The blisters began to dry in 2 days and resolved within 5 days without treatment.

most commonly on exposed skin during the summer months. Although Group A β-hemolytic streptococci were the predominant organisms 25–30 years ago, *Staphylococcus aureus* alone or in combination with streptococci is recovered from a majority of cultures. As a consequence, anti-staphylococcal antibiotics are now the drugs of choice for treatment.

Impetigo is often a self-limiting process. However, complications, which include cellulitis and disseminated infection, as well as spread to family members and classmates, can be limited by antibiotic therapy. Topical antibiotics such as bacitracin, polymyxin B, neomycin, may be used in localized disease, but increasing resistance to traditional topical antibiotics probably makes mupirocin and retapamulin a better first-line choice. Widespread lesions have been treated with oral agents such as cefalexin, amoxicillin-clavulanate, and erythromycin. Unfortunately, over 50% of staphylococcal isolates are reported to be resistant to erythromycin in the USA. Recently, community-acquired meticillin resistance has become a major problem with a prevalence of 70% in many areas. Consequently, the practitioner must select antibiotic coverage based on the resistance patterns in their respective communities (e.g. clindamycin, trimethoprim-sulfamethoxazole, tetracyclines) and consider resistance when patients fail to respond to appropriate doses of anti-staphylococcal antibiotics.

Staphylococcal scalded-skin syndrome

Staphylococcal scalded-skin syndrome (SSSS) occurs almost exclusively in infants and toddlers (Fig. 4.13, also see Fig. 2.47). It has, however, been reported with increasing frequency in older children and adults, particularly in debilitated patients with decreased renal function. This process is considered in any child who develops a generalized, tender erythema associated with a Nikolsky sign. When a Nikolsky sign is present, a minimal shearing force produced by finger pressure induces a skin slough or blister formation.

SSSS occurs when exfoliative toxin produced by certain staphylococci binds to a desmosomal adhesion molecule desmoglein-1 in the subgranular region of the epidermis resulting in cleavage at this site high in the epidermis. Interestingly, this is the same adhesion molecule that is targeted by autoantibodies in pemphigus foliaceus.

Although SSSS is usually self-limiting in healthy children who rapidly develop antibodies to the toxin, immunocompromised patients may develop complications related to their primary staphylococcal infection. Moreover, renal excretion of the toxin may be slowed in patients with impaired renal function (e.g. chronic renal failure) or renal clearance of the toxin (e.g. infants). Most SSSS is associated with a primary cutaneous infection. However, the soluble toxin that causes the rash may be produced by an occult



Fig 4.12 Bullous impetigo. **(a)** A large doughnut-shaped blister with a central crust and smaller satellite lesions suggests the diagnosis of bullous impetigo. **(b)** Widespread blisters in this toddler responded quickly to oral cefalexin. **(c)** Painful impetiginized pustules obscured the primary diagnosis of scabies in this teenager. A careful examination, however, revealed burrows on her palms and soles, and she was treated with oral cefalexin and topical 5% permethrin cream. **(d)** A healthy adolescent with an irritant dermatitis from shaving developed expanding confluent crusted papules typical of secondary impetiginization from *Staphylococcus aureus*. **(e)** A 5-year-old girl who was recovering from varicella developed several confluent erosions with an expanding bulla at the periphery and central crusting.



Fig 4.13 Staphylococcal scalded-skin syndrome. **(a)** A healthy 3-year-old boy developed fever, periorificial periarticular crusting, and generalized, tender red skin. Nikolsky sign was present, and *Staphylococcus aureus* was cultured from the crust around the eyes. **(b)** Note the Nikolsky sign in the axilla as evidenced by superficial sloughing of the skin from movement of the arm.

infection, such as osteomyelitis, septic arthritis, pneumonia, or meningitis. Healthy children respond to oral anti-staphylococcal antibiotics, which eradicate the infection and subsequent toxin production. Infants, severely ill older children, and patients with occult infection require appropriate culturing and parenteral therapy. Parents are also counseled about the generalized desquamation that develops 10–14 days after the acute infection.

Staphylococcal folliculitis

Staphylococcal folliculitis is a common problem in older children and adults. Red papules and pustules on an inflamed base erupt in a follicular pattern, most frequently on the buttocks, thighs, back, and upper arms (Fig. 4.14). Occasionally, superficial follicular pustules evolve into painful, deep-seated furuncles or spread to neighboring follicles and soft tissue to create an abscess or carbuncle. Abscesses and resultant cellulitis may be associated with fever, malaise, and sepsis. The incidence of furunculosis and abscess formation has increased dramatically with the spread of meticillin-resistant *Staphylococcus aureus* and should not be mistaken for insect or spider bites.

Localized folliculitis may improve with topical antibiotics. However, widespread lesions respond best to topical benzoyl peroxide wash or systemic antibiotics. Additionally, abscesses are incised and drained, and cellulitis may require parenteral antibiotics.





Fig 4.14 (a) Staphylococcal folliculitis recurred chronically on the extremities of a healthy adolescent. He cleared with anti-staphylococcal antibiotics, and preventative antibiotics helped somewhat. **(b)** A 4-year-old boy developed recurrent pustules and deep-seated boils on his extremities. A bacterial culture revealed meticillin-resistant *Staphylococcus aureus* sensitive to clindamycin.

Children with chronic folliculitis often have predisposing dermatoses such as keratosis pilaris. Children with Down syndrome are particularly prone to folliculitis on the trunk and proximal extremities. Long-term use of antiseptic soaps, topical antibiotics (e.g. clindamycin, tetracycline, erythromycin), dilute bleach baths, and peeling agents (e.g. benzoyl peroxide, retinoic acid, salicylic acid) may reduce the risk of recurrent infection. Persistent or difficult-to-treat folliculitis, especially when associated with furunculosis, should prompt culturing for meticillin-resistant *Staphylococcus aureus* infection.

Certain hydrating lotions and creams that are also designed to remove scale (e.g. Carmol® and Ureacin® with urea, LactiCare®, AmLactin and Lac-Hydrin® with lactic acid) may be beneficial. Patients are also instructed to avoid tight clothing, and occlusive moisturizers. In toddlers, folliculitis may improve after toilet training. Older children with enuresis should also be encouraged to remove wet clothing as soon as possible.

IMMUNOBULLOUS DERMATOSES

Although there is clinical overlap among the various immunologically mediated vesiculobullous dermatoses, they can be differentiated on the basis of specific clinical patterns, histopathology, immunopathology, and response to therapy (Table 4.1). In pemphigus, blisters form within the epidermis. Chronic bullous dermatosis of childhood (CBDC), bullous pemphigoid (BP), dermatitis herpetiformis (DH), and epidermolysis bullosa acquisita (EBA) are characterized by subepidermal blisters.

Intraepidermal disorders

Childhood pemphigus refers to a group of rare, chronic, potentially life-threatening immunobullous disorders characterized by flaccid intraepidermal bullae that erupt on normal-appearing or erythematous skin. Clinically and histologically, pemphigus can be divided into two types: pemphigus vulgaris and pemphigus foliaceus.

Pemphigus vulgaris

In pemphigus vulgaris (PV), intraoral erosions or scalp blisters precede more widespread lesions in half the patients for months. Eventually, vesicles and bullae develop on the trunk, scalp, face, and extremities in a seborrheic distribution (Fig. 4.15). By progressive extension, large areas of the body surface may become involved. Blisters heal insidiously without scarring, unless they become secondarily infected. Of these patients, 95% have intraoral involvement that may extend into the posterior pharynx and larynx. Pruritus, pain, and burning of the skin and mucous membranes may be severe, which results in decreased oral intake and marked weight loss. Nikolsky sign is usually present, and downward pressure on previously formed blisters may cause extension at the periphery (Asbaugh–Hansen sign). Pemphigus may also occur transiently in the newborn as a result of transplacental passage of the pemphigus IgG antibody from the mother to the baby.

Although the pathogenesis of pemphigus is still not completely understood, an IgG antibody directed against a transmembrane glycoprotein on the cell surface of keratinocytes has been identified in the skin, serum, and blister fluid of these patients. When the purified IgG obtained from blister fluid is injected into the peritoneal cavity of neonatal nude mice, it produces widespread blistering, which demonstrates acantholysis. Complement, IgA, and IgM have also been identified in blister fluid, but their roles in the development of bullae are not clear.

In pemphigus, the target antigen was identified as a desmoglein, one of several cadherin-type adhesion molecules that comprises desmosomes. Desmosomes are disk-shaped intercellular adhesive

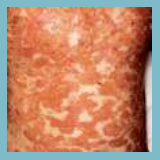
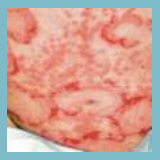
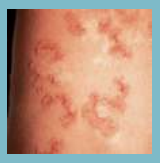
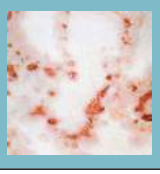
Immunobullous dermatoses					
	Immunoglobulin	**Location in skin**	**Target antigen**	**Clinical findings**	
Intraepidermal					
Pemphigus foliaceus	IgG	Intercellular, upper epidermis	Desmoglein-1	Seborrheic distribution	
Pemphigus vulgaris	IgG	Intercellular Lower half or full-thickness epidermis	Desmoglein-3 Desmoglein-3, 1	Intraoral lesions Intraoral lesions, widespread skin-deep erosions	
Subepidermal					
Linear IgA bullous dermatosis (CBDC)	IgA	Linear pattern in lamina lucida	97 kDa cleaved ectodimer of BP180 antigen	Vesicles, bullae, lower trunk, thighs, occasionally disseminated	
Bullous pemphigoid (BP)	IgA C3	Epidermal side of lamina lucida	BP230 (BPA1) BP180 (BPA2)	Bullae tend to be >2.0 cm but can mimic CBDC	
Dermatitis herpetiformis	IgA	Granular deposits in basement membrane zone at dermal papillary tips		Extremely pruritic papules, crusted vesicles on extensor surfaces of extremities, buttocks	
Epidermolysis bullosa acquisita (EBA)	IgG IgA	Sub-basement zone in lamina lucida	Collagen VII	May mimic dystrophic EB or CBDC, mucous membranes often involved	

Table 4.1 Immunobullous dermatoses

junctions that maintain the structural integrity of the epidermis. Disruption of desmosomes results in cleavage of the epidermis and blister formation. Desmoglein-1 is found throughout the epidermis and only minimally in the oral mucosa, whereas desmoglein-3 occurs primarily in the oral mucosa and the lower half of the epidermis. As a consequence, patients with autoantibodies directed against desmoglein-1 develop superficial lesions within the epidermis resulting in pemphigus foliaceus. The integrity of the lower half of the epidermis and the oral mucosa is maintained by normal desmoglein-3. Patients with autoantibodies directed against desmoglein-3 develop PV of the oral mucosa and limited or no lesions in the skin, because of normally functioning desmoglein-1 in the upper half of the epidermis. Finally, individuals with autoantibodies directed against both desmoglein-3 and -1 develop deep epidermal skin blisters as well as oral mucous membrane involvement.

Biopsies of fresh, intact vesicles with perilesional skin demonstrate intercellular edema and disappearance of intercellular bridges in the lower portion of the epidermis at the periphery. Separation of epidermal cells from one another leads to the formation of suprabasilar clefts and then frank blister formation, with the basal cells left hanging onto the basement membrane. Rounded up acantholytic keratinocytes may be found within the bullae and are easily demonstrated on Tzanck smears.

In virtually 100% of patients, fluorescein-labeled IgG can be demonstrated to bind to the epidermal intercellular space in the patient's normal-appearing and perilesional skin (Fig. 4.15c). This finding is referred to as positive direct immunofluorescence (DIF). Deposits of C3, IgA, or IgM are also identified in nearly half of the patients. For study of indirect immunofluorescence (IIF), unfixed frozen sections of various epithelium, such as monkey esophagus or normal human skin, are used. The patient's serum is applied to the specimen followed by fluorescein-labeled antihuman IgG at various dilutions. When the study is positive, fluorescence is seen in the intercellular spaces of the test specimen. The antibody titer refers to the highest dilution at which fluorescence is still noted. Although DIF is very sensitive, even early in the course of disease, IIF is less useful, particularly before lesions become widespread.





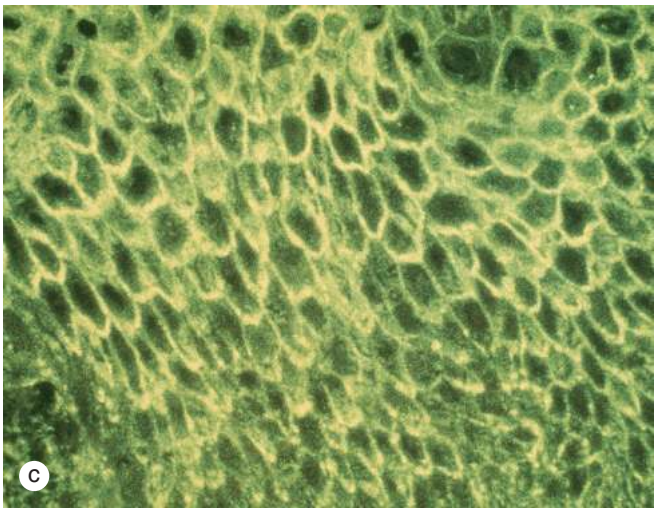


Fig 4.15 Pemphigus vulgaris. **(a)** A 7-year-old boy developed widespread superficial vesicles, bullae, and erosions on his trunk, extremities, and scalp. **(b)** He also had mucosal involvement with erosions on the lips, buccal mucosa, and larynx as well as the urethra and anus. **(c)** Anti-IgG antibody marks the epidermal intercellular cement substance on direct immunofluorescence.

Early PV restricted to the mouth must be differentiated histologically from other disorders that involve the oral mucosa, such as erosive lichen planus and aphthosis. Once cutaneous lesions appear, the typical clinical pattern, histology, and immunofluorescence differentiate PV from other immunobullous disorders.

Before the introduction of corticosteroids, patients often succumbed to sepsis. Management of fluid and electrolyte losses and supportive skin care may require admission to a burn unit. High-dose prednisone (2–5 mg/kg per day) may be life-saving. Recently, an anti-CD20 antibody directed against plasma cells has been used to achieve long-term remission off systemic corticosteroids. Some patients may require other corticosteroid-sparing immunosuppressive agents such as cyclophosphamide, azathioprine, or mycophenolate depending on their response to the corticosteroid taper and rituximab. Adjunctive therapy might also include intravenous immunoglobulin and immunoablative therapy with cyclophosphamide and plasmapheresis.

Pemphigus foliaceus

Pemphigus foliaceus (PF) is a more superficial and less aggressive immunobullous disorder. Although it occurs most commonly in middle age, in children this variant is more common than PV. Although PF tends to be sporadic and most cases have been reported in North America and Europe, an endemic variant known as fogo selvagem occurs primarily in children and adolescents in Brazil. Clinically and histologically, PF is indistinguishable from Brazilian pemphigus. Some medications, such as penicillamine have also been reported to trigger a PF-like eruption.

Much like PV, PF begins with crops of vesicles, flaccid bullae, and erosions on an erythematous base in a seborrheic distribution. However, the blisters, which result from autoantibodies directed against desmoglein-1, arise high in the epidermis and quickly crust over. The Nikolsky sign is usually positive, but mucous membranes, which contain little desmoglein-1, are invariably spared. When lesions become generalized, vesicles may be obscured by crust and scale, which gives the patient the appearance of an exfoliative erythroderma (Fig. 4.16). Even with widespread rash, patients tend to appear clinically well, and the course is often self-limiting.

Histopathology demonstrates acantholysis and bullae formation, much like in PV. However, the action occurs in the upper half of the epidermis, sometimes restricted to the area immediately beneath the stratum corneum. The intercellular space in the upper half of the epidermis shows IgG staining with direct immunofluorescence, and the indirect immunofluorescence is also usually positive. Chronic lesions typically show acanthosis, eosinophilic spongiosis, and eosinophilic dermal inflammation.

Patients with mild disease may respond to moderate- or high-potency topical corticosteroids. In many cases, systemic corticosteroids may be required for a while, and some investigators have reported success with antimalarials (hydroxychloroquine and chloroquine) and sulfonamides (sulfapyridine and dapsone). In severe cases rituximab has also been used to achieve long-term remission off corticosteroids.

Subepidermal disorders

Chronic bullous dermatosis of childhood

Chronic bullous dermatosis of childhood (CBDC) is a term used to describe a subepidermal immunobullous disorder with



Fig 4.16 Pemphigus foliaceus. A 10-year-old girl with generalized, slightly itchy, scaly, and crusted patches was referred for evaluation of possible pemphigus foliaceus. Although a skin biopsy was suggestive of pemphigus, a skin culture grew *Staphylococcus aureus*, and the rash resolved after 7 days of oral dicloxacillin. The recent understanding of the desmoglein story in pemphigus and SSSS explains the clinical and histological similarity of these two blistering disorders.

characteristic clinical features and linear IgA deposition at the basement membrane zone noted on direct immunofluorescent examination of perilesional skin. However, recent data suggest that CBDC may represent a number of different disorders with similar and overlapping clinical findings but varying and specific immunofluorescent markers.

Although tense 1.0–2.0 cm diameter bullae typically appear in CBDC in preschool children on the lower trunk, buttocks, legs, and top of the feet, children of any age may be affected (Fig. 4.17). Widespread lesions may involve any site on the body surface including the face, scalp, upper trunk, hands, and arms. Lesions erupt on red as well as normal-appearing skin, and often form rings composed of sausage-shaped bullae around a central crust or healing blister. Linear or annular vesicles on an inflamed base may suggest a 'string of pearls' (Figs 4.18, 4.19). Mucous membranes are not usually involved in linear IgA disease, a Nikolsky sign is not present, and burning and pruritus are variable. Some children are completely asymptomatic.

Histopathology of CBDC is indistinguishable from that of adult BP, which demonstrates a subepidermal blister with a dermal infiltrate of neutrophils and eosinophils. Occasionally, eosinophils form microabscesses at the tips of the dermal papillae reminiscent of DH. However, direct immunofluorescence shows linear deposits of IgA at the dermal–epidermal junction and is diagnostic (Fig. 4.20). Investigators have also shown that the site of deposition is within the lamina lucida, with accentuation near the basal cell membrane around hemidesmosomes. Circulating IgA antibodies are present in 50–75% of patients.

Although CBDC is often self-limiting with spontaneous resolution over 3–5 years, occasional cases persist after adolescence. Many children are exquisitely sensitive to small doses of dapsone (0.5–1.0 mg/kg per day). Blisters often respond within 1–3 days of initiating therapy, and medication may be tapered to low maintenance doses (12.5–25 mg/day or less). Resistant cases may require systemic corticosteroids, at least until the eruption comes under control. All patients on dapsone must be monitored for clinical and laboratory signs of hemolysis, methemoglobinemia, and neurologic complications.

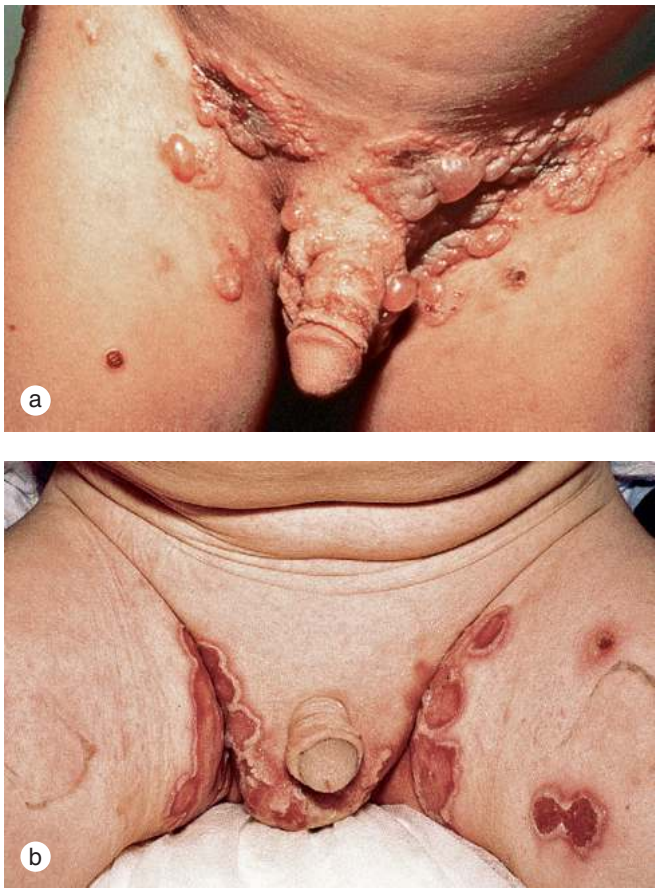


Fig 4.17 Linear IgA bullous dermatosis. Two 3-year-old boys presented with chronic, recurrent blisters in the diaper area. **(a)** Fresh, tense bullae spread along the inguinal creases onto the thighs and penis. **(b)** Ruptured bullae left annular and scalloped erosions.

Bullous pemphigoid

In bullous pemphigoid (BP) bullae tend to be large (>2 cm), but vesiculobullous lesions and distribution may be indistinguishable from linear IgA dermatosis (Fig. 4.21). Skin biopsies in BP also demonstrate subepidermal bullae with an eosinophilic dermal infiltrate. However, linear depositions of IgG and C3 at the dermal–epidermal junction in the lamina lucida are diagnostic for BP. When salt-split skin is used as a substrate for immunofluorescent studies, staining occurs on the epidermal side of the cleavage where one would expect to find BP230 and BP180 antigens. An unusual cicatricial variant of BP involves primarily the mucous membranes and occurs only rarely in childhood.

Dermatitis herpetiformis

Symmetric, extremely pruritic, clustered, 3–4 mm diameter vesicles on extensor surfaces of the extremities, lower trunk, and buttocks may suggest dermatitis herpetiformis (DH) (Fig. 4.22). In DH, the lesions arise on both red and normal-appearing skin and may occasionally exceed 1.0 cm in diameter. The skin biopsy of perilesional skin reveals characteristic, granular IgA deposits in the basement membrane zone and prominent neurophilic microabscesses at the dermal papillary tips. The high incidence of human leukocyte antigen (HLA) B8 antigens also defines DH, as does a gluten-sensitive enteropathy and a rapid response to dapsone.

Epidermolysis bullosa acquisita

Although initially thought to be rare in childhood, the use of salt-split skin as a substrate for immunofluorescent studies has often





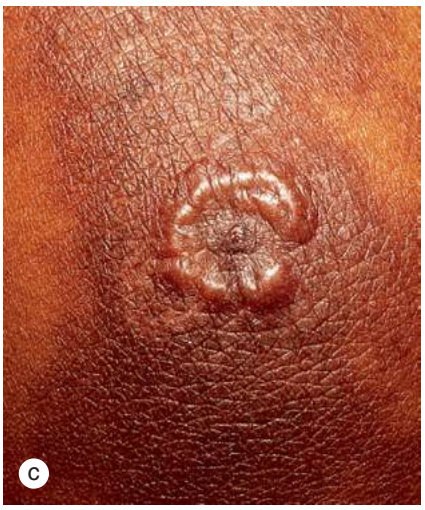


Fig 4.18 Widespread vesicles erupted over several days on the face, trunk, and extremities of two toddlers with linear IgA dermatosis **(a,b)**. Blisters were densest on the face and trunk **(a)** of the 12-month-old boy and the lower extremities **(b)** of the 14-month-old girl. **(c)** Annular blisters spread over the trunk and extremities in this 4-year-old boy. The eruption in all three children improved quickly with 12.5 mg/day of dapsone.

resulted in a diagnosis of epidermolysis bullosa acquisita (EBA) in children who would have previously been grouped with CBDC or BP (Fig. 4.23). EBA shares some clinical features with hereditary dystrophic (dermolytic) epidermolysis acquisita, and in both disorders blisters result from disruption of type VII collagen. Clinically patients with EBA may be indistinguishable from CBDC or BP.



Fig 4.19 This adolescent girl with a 9-month history of genital blisters and erosions failed to improve with topical antibiotics, antifungal creams, lubricants, or oral aciclovir. Sexual abuse was suspected until a skin biopsy, which demonstrated the classic findings of linear IgA bullous dermatosis, was performed.

However, they have a higher incidence of mucous membrane involvement and may be more resistant to therapy. Although EBA probably occurs most commonly as an isolated autoimmune disorder, until recently it has been reported primarily in association with other immunologically mediated conditions such as systemic lupus erythematosus and inflammatory bowel disease.

Histology reveals a subepidermal blister with a neutrophil-rich infiltrate, but eosinophils may also be present. Direct immunofluorescence typically shows deposition of linear IgG at the basement membrane zone. Indirect immunofluorescence with salt-split skin demonstrates IgG on the dermal side of the split. Recently, a group of patients with IgA EBA have been reported. Clinicians should consider the addition of prednisone-sparing medications early in the management of these patients, particularly if mucous membrane involvement is widespread and severe.

The indirect immunofluorescence findings in cicatricial pemphigoid are similar to EBA. However, cutaneous lesions are usually limited. In some cases, these disorders can only be distinguished with immunofluorescent electron microscopy, in which type VII collagen is identified as the autoantibody target on an ultrastructural level.

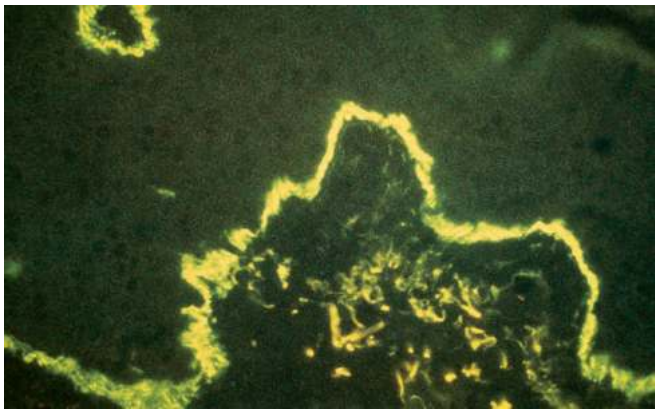


Fig 4.20 Direct immunofluorescence shows diagnostic linear IgA deposition along the dermal–epidermal junction.









Fig 4.21 (a,b) Tense blisters on an urticarial base developed insidiously on the extremities and trunk of an adolescent with bullous pemphigoid.



Fig 4.22 This adolescent boy developed an intensely pruritic widespread blistering eruption most densely distributed on the extensor surfaces of his arms and legs, back, and buttocks. Histologic and immunofluorescent findings were typical of dermatitis herpetiformis.



Fig 4.23 Epidermolysis bullosa acquisita. **(a)** An adolescent with poorly controlled systemic lupus erythematosus developed a diffuse painful blistering eruption composed of large bullae which on biopsy and immunofluorescent studies showed changes typical of (IgG) epidermolysis bullosa acquisita. This disorder is indistinguishable from bullous lupus erythematosus. **(b,c)** A 9-year-old boy without underlying connective tissue disease developed annular urticarial plaques with vesicles and bullae on his face **(b)**, neck **(c)**, and upper trunk. Laboratory findings were diagnostic for IgA epidermolysis bullosa acquisita.

The target lesions of classic erythema multiforme (EM), particularly when blistering is present, may be confused with those of CBDC. However, the acute clinical course, histopathology, and negative immunofluorescence readily differentiate EM. Early in its course, CBDC is often misdiagnosed as bullous impetigo. Moreover, bullae of CBDC that are secondarily infected respond to antibiotic therapy. However, the persistence of blistering despite antibiotic therapy, the widespread distribution of the eruption, and negative Gram-stains and cultures suggest a non-infectious etiology.

Recurrent herpes simplex virus infection and the possibility of sexual abuse can also be excluded by the characteristic skin biopsy findings (Fig. 4.23).

MECHANOBULLOUS DISORDERS

Friction blisters

Friction blisters occur frequently on the soles, palms, and palmar surfaces of the fingers after vigorous exercise or other repetitive activities which cause shearing of thick areas of epidermis that are firmly attached to underlying tissue (Fig. 4.24a). In patients with chronic localized or generalized edema, particularly in the setting of malnutrition, minor trauma may result in blister formation. Similar blisters can result from rubbing and sucking (Fig. 4.24b). Histologically, these lesions may be identified as non-inflammatory, intraepidermal blisters, which are usually located just beneath the granular layer. Although blisters heal quickly in healthy individuals, impetiginization and cellulitis are frequent complications in compromised hosts.



Fig 4.24 (a) Friction blisters. Large, hemorrhagic blisters developed in areas of minor trauma on the trunk and extremities of a cachectic, chronically ill child during an episode of acute renal failure. Blistering healed as renal function returned to normal and cutaneous edema resolved. A skin biopsy demonstrated intraepidermal blisters without inflammation. **(b)** Sucking blisters. Recurrent hemorrhagic blisters appeared on the thumb of a 10-year-old thumb-sucker. These blisters can arise within the epidermis or basement membrane zone.

Epidermolysis bullosa

Hereditary epidermolysis bullosa is a heterogeneous group of mechanobullous disorders differentiated by clinical findings, depth of blister formation, biochemical markers, inheritance patterns, and specific genetic mutations (see Table 2.4). In most of these conditions, vesiculobullous lesions appear at birth or in early infancy. Several variants, however, do not present until adolescence or adult life.

In recurrent epidermolysis bullosa of the hands and feet, or Weber–Cockayne syndrome (an autosomal-dominant epidermolytic variant), blisters may first appear on the soles during rigorous physical activity such as track-and-field sports and military boot camp. Vesicles and bullae are usually restricted to the distal extremities, and particularly the palms and soles. Healing occurs without scar formation, and the nails and mucous membranes are not affected. Histopathology demonstrates a suprabasilar split in the epidermis, and electron microscopy shows cytolysis within the basal cell layer. Although these findings are also typical of friction blisters in normal individuals, clumping of tonofilaments in basal cell keratinocytes is specific for Weber–Cockayne syndrome.

Recurrent blistering of the palms and soles, particularly during warm weather when blistering is more common, suggests the disorder. A positive family history clinches the diagnosis. Blistering may be reduced by using extra cushioning in shoes and avoiding unnecessary trauma to the hands and feet, particularly during warm weather. Cool tap-water compresses may help symptomatically, and topical antibiotics reduce the risk of secondary infection. The use of topical antiperspirants, such as 10–20% aluminum hydroxide, 10% formaldehyde, or 10% glutaraldehyde, may decrease the blistering as well as associated hyperhidrosis of the palms and soles. Some patients have also benefited from applications of tincture of benzoin or Mastisol.

DERMATITIS

In acute dermatitides, inflammation and associated edema may be so intense that vesiculation occurs (see Fig. 3.15c). Blisters erupt frequently in acute contact irritant and allergic dermatitis, as well as in atopic dermatitis, seborrhea, and insect-bite reactions (Fig. 4.25). Whenever blistering develops in this setting, secondary infection with *Staphylococcus* or herpes simplex virus is also considered.

A Tzanck smear and Gram-stain exclude bacterial and viral infection. Skin biopsies demonstrate variable acanthosis or thickening of the epidermis, exocytosis or an influx of lymphocytes into the epidermis, and spongiosis or intercellular edema. It is the intense edema that eventually breaks apart desmosomal attachments and results in spongiotic blister formation. Immunofluorescence studies should be negative.

Blistering from dermatitic reactions can usually be differentiated clinically from thermal burns, cold injury, and ischemic insults to the skin that result in subepidermal blisters.

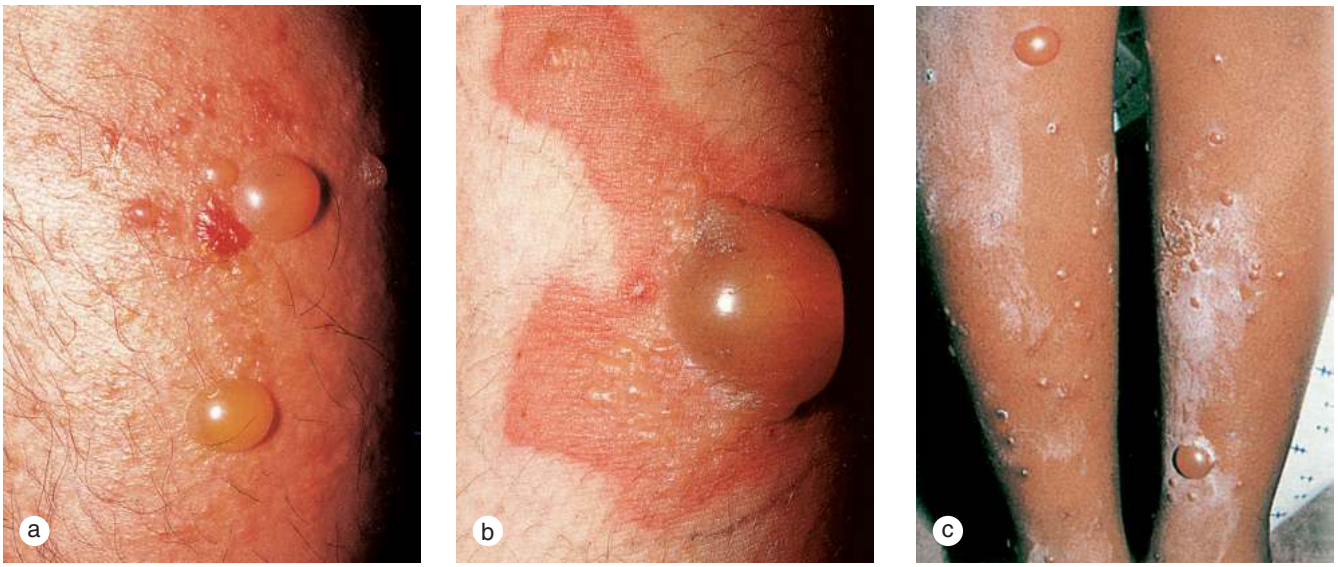


Fig 4.25 Dermatitic blisters. **(a)** Acute poison ivy dermatitis resulted in blisters on the arm of a 9-year-old boy. Note the surrounding erythema, edema, and papules typical of an allergic contact dermatitis. **(b)** Vesicles and a large bulla erupted on an extremely well-demarcated red base on the arm of a teenager who admitted to applying acid to create the lesions. **(c)** This child's lower legs are studded with numerous, thick-walled vesicles and bullae, which formed in response to flea bites.

ERYTHEMA MULTIFORME, STEVENS–JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS

In the past, clinicians have considered erythema multiforme (EM), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) as related disorders with clinical and histologic overlap. Although they may share some clinical and histologic features, erythema multiforme should be viewed separately, as a usually benign self-limiting disorder with rare complications, while SJS and TEN represent the variable expression of a distinct syndrome with a significant risk of morbidity and mortality. SJS and TEN are most commonly triggered by medications, while erythema multiforme usually follows an infection.

Erythema multiforme

In the classic eruption, originally described by Ferdinand von Hebra in 1860, the rash is symmetric and may occur on any part of the body, although it usually appears on the dorsum of the hands and feet and the extensor surfaces of the arms and legs (Fig. 4.26). Involvement of the palms and soles is common. The initial lesions are dusky, red macules or edematous papules that evolve into target lesions with multiple, concentric rings of color change. The annular configuration occurs as the central inflammatory process spreads peripherally and leaves behind a depressed, damaged epidermis. When epidermal injury is severe, full-thickness necrosis results in central bulla formation. The eruption continues in crops that last 1–3 weeks. In most children with this so-called minor variant, mucous membrane involvement is minimal and restricted to the mouth, the disease is self-limiting, and systemic manifestations are limited to low-grade fever, malaise, and myalgia. Rarely oral involvement is severe enough to interfere with oral intake and require parenteral rehydration. Recurrent EM occurs in association with recurrent herpes simplex virus infection and may respond to suppressive oral antiviral therapy. Unfortunately, some patients with recurrent outbreaks improve only with oral steroids, and recurrences may be frequent enough to result in steroid-induced complications.

Stevens–Johnson syndrome and toxic epidermal necrolysis

Stevens–Johnson syndrome (SJS) is a severe mucocutaneous syndrome with epidermal involvement and large areas of mucous membrane necrosis and sloughing. Toxic epidermal necrolysis (TEN) represents the most severe end of the spectrum with widespread cutaneous and mucous membrane involvement. In SJS, constitutional symptoms are severe and include high fever, cough, sore throat, vomiting, diarrhea, chest pain, and arthralgias. After a prodrome lasting 1–14 days, but usually 1–3 days, abrupt onset of symmetric erythematous macules occurs on the head and neck, and spreads to the trunk and extremities (Fig. 4.27). Blister formation occurs within hours and is often hemorrhagic, extensive, and confluent. Mucous membrane involvement, particularly of the eyes, nose, and mouth, is widespread and severe. It consists of the formation of fragile, thin-walled bullae that rupture with minimal trauma, to leave ulcerations that are rapidly covered by exudate. Keratitis may result in ocular infection and synechiae formation. The urogenital and perirectal areas may also become involved. Loss of the epidermal barrier results in fluid and electrolyte imbalances and a high risk of secondary bacterial infection. Mortality ranges between 5% and 25%.

Toxic epidermal necrolysis

With TEN, patients usually begin with fever, sore throat, malaise, and a generalized, sunburn-like erythema, followed by sloughing of large areas of skin (Fig. 4.28). The entire skin surface, as well as conjunctivae, urethra, rectum, oral and nasal mucosa, larynx, and tracheobronchial mucosa, may become involved. Although a Nikolsky sign is present and the erythema is reminiscent of SSSS, the site of cleavage in TEN as in SJS is at the dermal–epidermal junction, which results in full epidermal necrosis.

Frozen sections of sloughed epidermis can be used for rapid differentiation of TEN from SSSS while the practitioner awaits the definitive results of a skin biopsy. However, clinical distinction of these disorders is usually possible, because erosions and sloughing of the mucous membranes do not develop in SSSS. Intensive



Fig 4.26 Erythema multiforme. **(a)** Typical target lesions erupted on the arms and legs of this 9-year-old boy with recurrent erythema multiforme associated with herpes simplex infection. He had only minimal mucous membrane involvement. **(b)** An adolescent with erythema multiforme minor developed painful erosions around the urethra. **(c,d)** A healthy 5-year-old girl developed widespread bullous erythema multiforme with sparing of the mucous membranes. She cleared with 10 days of tapering oral prednisolone.



Fig 4.27 Stevens–Johnson syndrome. **(a)** Widespread blistering and erosions developed on the skin and mucous membranes of this 3-year-old girl with Stevens–Johnson syndrome. **(b)** Widespread areas of necrotic blisters and ulcerations can heal







Fig 4.27, Continued (c) with marked permanent hyperpigmentation in dark-pigmented individuals. **(d,e)** Hemorrhagic crusts on the lips are characteristic of Stevens–Johnson syndrome.







Fig 4.28 Toxic epidermal necrolysis. **(a)** After 7 days of a course of oral co-trimoxazole for otitis media, this 8-year-old girl developed high fever, and generalized erythema and edema followed by sloughing of large sheets of skin. Mucous membranes were severely involved. Note Nikolsky sign on her upper cheek, induced by accidental minor trauma. **(b)** At 3 weeks after starting an anticonvulsant this 10-year-old boy developed generalized erythema followed by diffuse blistering and sloughing of the skin and mucous membranes. **(c)** At 10 days of age this tiny premature infant developed toxic epidermal necrolysis while on multiple antibiotics. Denuded areas of skin occurred over bony prominences and around tape and monitor sites. Stevens–Johnson syndrome.

supportive measures are required to avoid fluid and electrolyte losses and secondary bacterial infection. Respiratory distress syndrome has been reported in severe cases.

Morbidity and mortality risks may be higher than those in patients with SJS. In uncomplicated cases, re-epithelialization of the skin occurs within several weeks and full recovery in 4–6 weeks. Scarring may develop in areas of secondary infection. As in SJS careful ongoing ophthalmologic evaluation is necessary to reduce the complications of severe conjunctival and corneal involvement.

Skin biopsy findings in EM, SJS, and TEN show a perivascular mononuclear cell infiltrate with some eosinophils in the papillary dermis. Variable hydropic degeneration of the basal cell layer is associated with the formation of colloid bodies and subepidermal blister formation. In SJS and certainly TEN widespread dyskeratosis and epidermal necrosis are present.

In the event of drug-induced SJS and TEN, it is imperative that the clinician identifies the inciting agent. Failure to do so may result in a persistent reaction, higher risk of complications and mortality, and severe recurrent disease on re-exposure to the medication. During acute episodes, careful cleaning and protection of bullous lesions is imperative to reduce the risk of infection. Patients with severe SJS and TEN may require intensive supportive care in a burn unit. Although a number of systemic medications have been reported in case reports and small trials including oral steroids, intravenous immunoglobulin, cyclosporin, tumor necrosis factor-α antagonists, and thalidomide, there are no satisfactory controlled trials demonstrating efficacy of these agents. Moreover, there is some evidence to show that systemic corticosteroids may actually increase the risk of complications and prolong hospitalization.

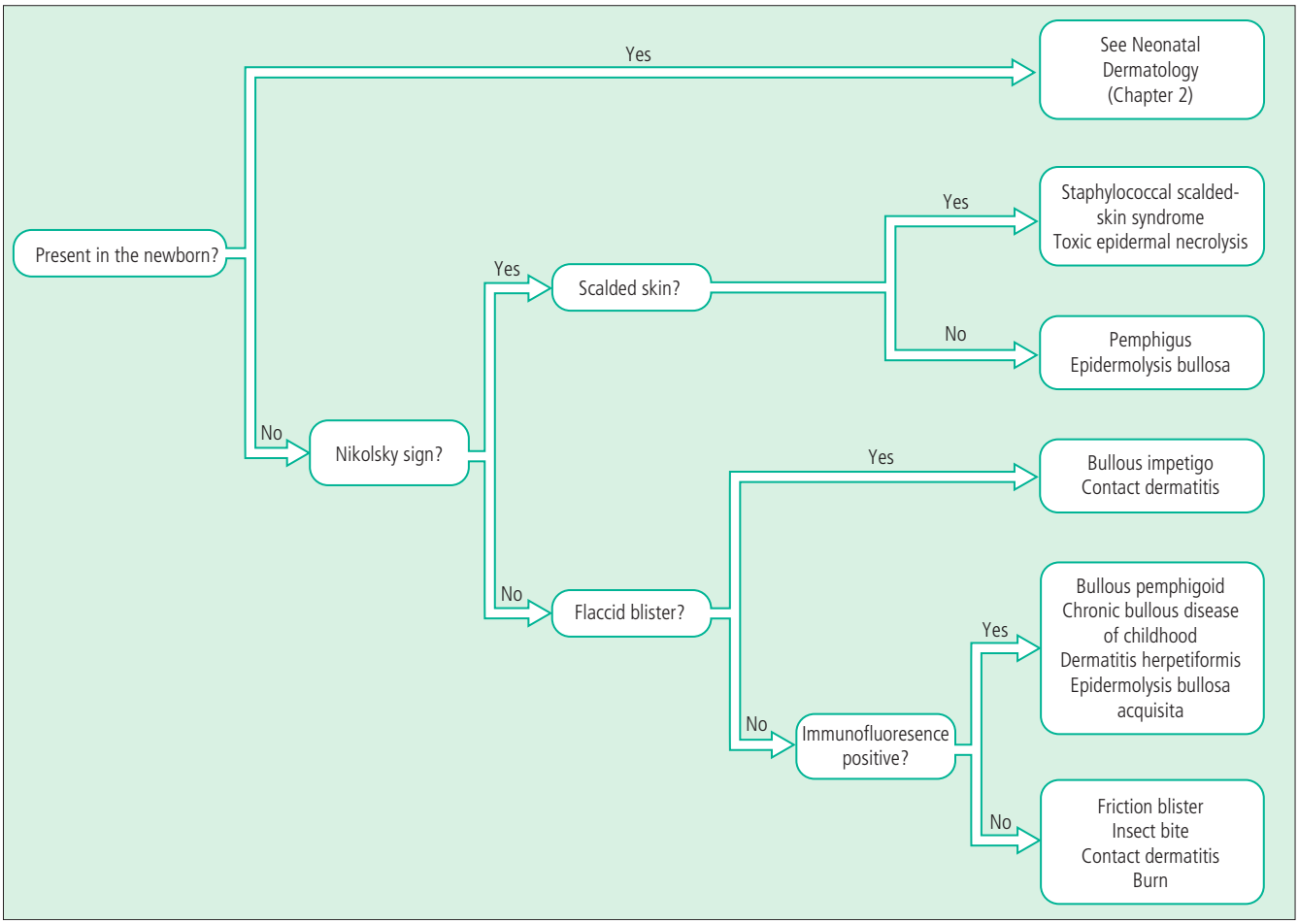


Fig 4.29 Algorithm for evaluation of vesiculopustular dermatoses.

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Chapter 5

Nodules and Tumors

Bernard A. Cohen

INTRODUCTION

Nodules and tumors in the skin often raise fears of skin cancer. Fortunately, primary skin cancer is extremely rare in childhood, and most infiltrated plaques and tumors are benign (Table 5.1). Hemangiomas, congenital nevi, and tumors of the newborn are reviewed in Chapter 2, while pigmented nevi and melanomas are discussed in Chapter 6. The focus in this chapter is disorders of childhood and adolescence.

Several clinical clues, including the depth and color of lesions, aid in developing a differential diagnosis. Superficial growths are readily moved back and forth over the underlying dermis, whereas the overlying epidermis and superficial dermis may slide over deep-seated tumors. Some dermal and subcutaneous lesions characteristically produce tethering of the overlying skin. Epidermal tumors include warts, molluscum, and seborrheic keratoses. Milia, neurofibromas, granuloma annulare, mastocytomas, scars, keloids, xanthomas, xanthogranulomas, nevocellular nevi, and adnexal tumors involve the superficial and mid dermis. Leukemia, lymphoma, melanoma, lipomas, and metastatic solid tumors involve the dermis and/or fat and may extend deep into subcutaneous structures.

Histologic diagnosis of 775 superficial lumps excised in children

Type	*n*	(%)
Epidermal inclusion cysts	459	59
Congenital malformations (pilomatrixoma, lymphangioma, brachial cleft cyst)	117	15
Benign neoplasms (neural tumors, lipoma, adnexal tumors)	56	7
Benign lesions of undetermined origin (xanthomas, xanthogranulomas, fibromatosis, fibroma)	50	6
Self-limited processes (granuloma annulare, urticaria pigmentosa, insect bite reaction)	47	6
Malignant tumors	11	1.4
Miscellaneous	35	4

Modified from Knight PJ, Reiner CB, Pediatrics 1983, 72:147.

Table 5.1 Histologic diagnosis of 775 superficial lumps excised in children

Color may suggest the specific cell types that comprise various cutaneous nodules and tumors. For instance, yellow tumors might include large quantities of fat in a lipoma or lipid-laden histiocytes in xanthomas or xanthogranulomas. Nevocellular nevi, epidermal nevi, mastocytomas, and seborrheic keratosis contain varying amounts of the brown pigment melanin in nevus cells or keratinocytes. Vascular tumors are usually red or blue, and primary or metastatic nodules may appear in various shades of red, purple, and blue, depending on their depth and degree of vascularity.

Finally, the diagnosis of certain genodermatoses associated with cutaneous and/or internal malignancies allows the clinician to develop strategies for close monitoring. Early recognition of malignancy in this setting may be lifesaving (Table 5.2). An algorithmic approach to diagnosis for nodules and tumors is summarized at the end of the chapter (see Fig. 5.39).

SUPERFICIAL NODULES AND TUMORS

Warts

Warts are benign epidermal tumors produced by human papillomavirus (HPV) infection of the skin and mucous membranes. In children they are seen most commonly on the fingers, hands, and feet. However, they can infect any area on the skin or mucous membranes (Figs 5.1–5.8). The incubation period for warts varies from 1 to 3 months and possibly up to several years, and the majority of lesions disappear within 3–5 years. Local trauma promotes inoculation of the virus. Thus, periungual warts are common in children who bite their nails or pick at hangnails (Fig. 5.3).

Investigators have identified over 100 HPV types capable of producing warts, and many of these organisms produce characteristic lesions in specific locations. For instance, the discrete, round, skin-colored papillomatous papules typical of verruca vulgaris (common warts) are produced by HPV-2 and HPV-4 (Figs 5.1, 5.4). The subtle, minimally hyperpigmented flat warts (verruca plana), which are caused by HPV-3, are frequently spread by deliberate or accidental scratching, shaving, or picking and may become widespread on the face, arms, and legs (Fig. 5.5).

Plantar warts are most commonly caused by HPV-1 (Fig. 5.2). Although not proved, the transmission of these warts probably occurs by contact with contaminated, desquamated skin in showers, pool decks, and bathrooms. Although often subtle on the surface, their large size may be hidden by a collarette of skin of normal appearance, and the overlying or surrounding calluses often cause pain when the patient walks. While plantar warts may be confused with corns, calluses, or scars, they can be differentiated by their disruption of the normal dermatoglyphics. Characteristic black dots in the warts are thrombosed capillaries.

Cancer-associated genodermatoses			
Disease	**Associated cancer**	**Clinical manifestations**	**Genetics**
Basal cell nevus syndrome (Gorlin syndrome)	Many basal cell carcinomas (mean age of onset 15 years) on sun-exposed and non-sun-exposed areas; medulloblastoma; astrocytoma	Many basal cell nevi, palmar and plantar pits, jaw cysts, calcification of the falx cerebri, ovarian fibromas, fused ribs	Autosomal dominant; PTCH1 gene on chromosome 9q22.32
Hidrotic ectodermal dysplasia (Clouston syndrome)	Squamous cell carcinoma of palms, soles, nail bed	Normal sweating, total alopecia, severe nail dystrophy, palmar and plantar hyperkeratosis	Autosomal dominant GJB6 gene
Acrokeratosis paraneoplastica (Basex syndrome)	Basal cell carcinomas of the face (second to third decade)	Follicular atrophoderma, localized anhidrosis and/or generalized hypohidrosis	Autosomal dominant Xq24–q27
Dysplastic nevus syndrome (familial, atypical, multiple-mole syndrome)	Cutaneous and intraocular melanoma, lymphoreticular malignancy, sarcomas	Multiple, large reddish-brown moles with irregular borders and non-uniform colors, usually on trunk and arms; familial occurrence of melanoma	Autosomal dominant genetic heterogeneity
Multiple hamartoma syndrome (Cowden disease)	Carcinoma of the breast, colon, thyroid	Coexistence of multiple, ectodermal, mesodermal, and endodermal nevoid neoplasms; punctate keratoderma of the palms; multiple angiomas, lipomas	Autosomal dominant; PTEN gene on chromosome 10q23.31
Neurofibromatosis Type 1 (von Recklinghausen disease)	Optic pathway gliomas Malignant peripheral nerve sheath tumors Fibrosarcomas Squamous cell carcinomas Non-lymphocytic leukemia Pheochromocytoma Carcinoid meningiomas	Café-au-lait spots Skeletal anomalies Neurofibromas Lisch nodules Axillary freckling Xanthogranulomas	Autosomal dominant NF1 gene Sporadic mutations in 50% of cases
Neurofibromatosis Type 2	Acoustic neuromas Schwannomas Meningiomas Astrocytomas	Neurofibromas ± Café-au-lait macules Cataracts	Autosomal dominant NF2 gene SCH gene on 22q11–13.1 Sporadic mutations in 50% of cases
Multiple mucosal neuroma syndrome (multiple endocrine neoplasia Type IIB)	Pheochromocytoma, medullary thyroid carcinoma	Pedunculated nodules on eyelid margins, lip; tongue with true neuromas	Autosomal dominant; gene locus 10q11.2; sporadic mutation in 50% RET gene
Intestinal polyposis II (Peutz–Jeghers syndrome)	Adenocarcinoma of the colon, duodenum; granulosa cell ovarian tumors	Pigmented macules on oral mucosa, lips, conjunctivae, digits; intestinal polyps	Autosomal dominant; STK11/LKB1 gene on chromosome 19p13.3; sporadic mutation in 40%
Intestinal polyposis III (Gardner syndrome)	Malignant degeneration of colon, adenomatous polyps; sarcomas, thyroid carcinoma	Polyps of the colon, small intestine; globoid osteoma of mandible with overlying fibromas; epidermoid cysts; desmoids	5q21–q22 APC gene
Tuberous sclerosis	Rhabdomyoma of myocardium, gliomas, mixed tumor of kidney	Triad of angiofibromas, epilepsy, mental retardation; ash-leaf macules; shagreen patches; subungual fibromas; intracranial calcification in 50%	Spontaneous mutation in 75%; autosomal dominant in 25%; heterogeneous loci, 9q34 (TSC1), 16p13 (TSC2)
Epidermolysis bullosa dystrophica dominant	Squamous cell carcinoma in chronic lesions	Lifelong history of bullae; phenotype not as severe as in recessive forms	Autosomal recessive, chromosome 3p21 (collagen type VII gene)

Table 5.2 Cancer-associated genodermatoses

Cancer-associated genodermatoses			
Disease	**Associated cancer**	**Clinical manifestations**	**Genetics**
Epidermolysis bullosa dystrophica recessive	Basal, squamous cell carcinoma in skin, mucous membranes (especially esophagus)	Bullae develop at sites of trauma; present at birth or early infancy; may involve mucous membranes, esophagus, conjunctivae, cornea	Autosomal recessive, chromosome 3p (collagen type VII gene)
Albinism	Increased incidence of cutaneous malignancies	Lack skin pigment, incomplete hypopigmentation of ocular fundi, horizontal congenital nystagmus, myopia	Tyrosinase positive: autosomal recessive, gene locus 15q11.2–q12 Tyrosinase negative: autosomal recessive, gene locus 11q14q21
Congenital telangiectasia erythema (Bloom syndrome)	High incidence of leukemia, lymphoma; squamous cell cancers of esophagus; adenocarcinoma of colon, often by 20 years of age	Small stature; cutaneous photosensitivity presenting as telangietic, facial (malar) erythema	Autosomal recessive; gene locus 15q26.1 RECQL3 gene
Chédiak–Higashi syndrome	Malignant lymphoma	Decreased pigmentation of hair, eyes; photophobia; nystagmus; abnormal susceptibility to infection	Autosomal recessive CHS1 gene
Poikiloderma congenitale (Rothmund–Thomson syndrome)	Cutaneous malignancies Osteosarcoma	Poikiloderma, short stature, cataracts, photosensitivity, nail defects, alopecia, bony defects	Autosomal recessive; gene locus 8q24.3 RECQL4 gene
Xeroderma pigmentosum	Basal and squamous cell carcinoma of skin, malignant melanoma	Marked photosensitivity, early freckling, telangiectasia, keratoses, papillomas, photophobia, keratitis, corneal opacities	Autosomal recessive; gene loci – complementation group A – 9q22.33 XPA gene group B – 2q14.3 ERCC3 gene group D – 19q13.32 ERCC2 gene group F – 13p13.12 ERCC4 gene
Wiskott–Aldrich syndrome (Eczema thrombocytopenia-immunodeficiency syndrome)	Lymphoreticular malignancies, malignant lymphoma, myelogenous leukemia, astrocytoma	Eczema, thrombocytopenia, bleeding problems (i.e. melena, purpura, epistaxis), increased susceptibility to skin infections, otitis, pneumonia, meningitis	X-linked recessive; gene locus Xp11.2–11.3 WAS gene
Dyskeratosis congenita	Squamous cell carcinoma of oral cavity, esophagus, nasopharynx, skin, anus	Reticulated hypo- and hyperpigmentation of skin, nail dystrophy, leukoplakia of oral mucosa, thrombocytopenia, testicular atrophy	X-linked recessive (most common); gene locus Xq28 DKCI gene

Table 5.2 Continued

Warts can also be found on the trunk, oral mucosa, and conjunctivae. Condyloma acuminatum and flat warts in the anogenital area are usually caused by non-carcinogenic HPV-6 and HPV-11 (Fig. 5.6). However, a number of HPV including types 16, 18, 42–45 have been associated with cervical carcinoma in women and more recently nasopharyngeal carcinomas in men and women. With this in mind the Food and Drug Administration approved the administration of quadrivalent (Gardisil) and bivalent (Cervarix) HPV vaccine for girls from age 11–26 in 2006 and for boys from age 9 in 2011.

Although sexual abuse must be considered in any child with anogenital warts, most are transmitted in a non-venereal fashion. However, in adolescents and young adults genital warts emerged in the 1980s as the most common sexually transmitted disease. Unfortunately, HPV in this setting can be transmitted to newborns at delivery with a subsequent latency period of up to 2–3 years.

Warts are self-limited in most children, but persistent, widespread lesions suggest the possibility of congenital or acquired immunodeficiency (Fig. 5.7). In fact, warts may become a serious management problem in oncology and transplant patients who are chronically immunosuppressed.

Topical irritants, including salicylic acid and lactic acid in occlusive vehicles such as collodion or under tape occlusion, are safe, effective, and relatively painless preparations with which to treat warts that are not in sensitive areas such as the eyelids and perineum.

Recalcitrant lesions may respond to destructive measures, which include liquid nitrogen, electrocautery, and carbon dioxide laser surgery. However, patients and parents must be cautioned about the risk of recurrence and scarring (Figs 5.8, 5.9). Moreover, there is no evidence-based literature to show that painful destructive measures are any better than placebo. Immunotherapy with

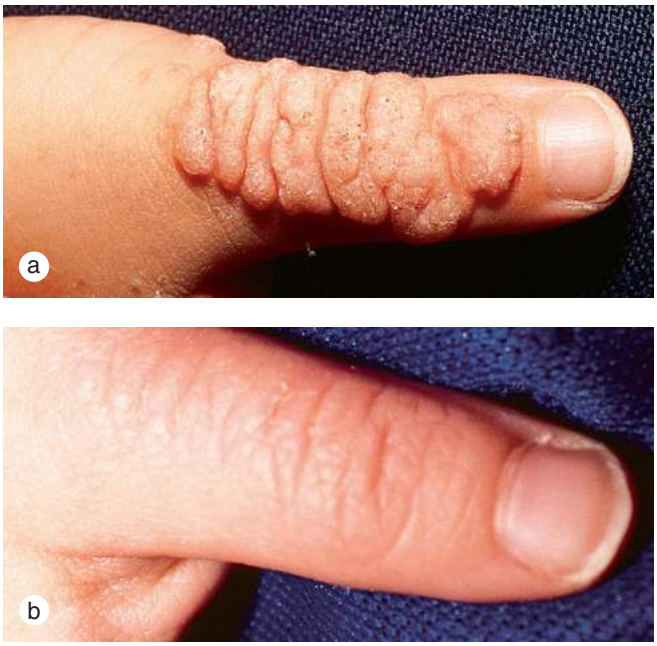


Fig 5.1 Warts. **(a)** Multiple common warts grew to confluence on the thumb of a 4-year-old boy. **(b)** Shortly before surgery was scheduled, the warts began to regress without treatment.



Fig 5.2 Plantar warts. Two painful papules are seen over the ball of the foot. Note how they interrupt the normal skin lines.



Fig 5.3 Subungual common wart. This wart persisted despite repeated painful treatments with liquid nitrogen. A year later it resolved after therapy was discontinued.

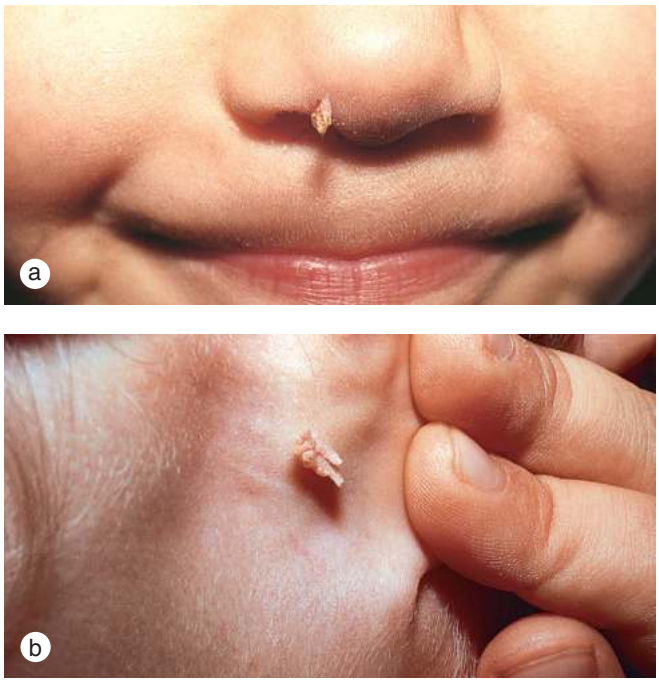


Fig 5.4 Verruca vulgaris. Filiform warts developed on **(a)** the nose and **(b)** the ear of these children of school age.

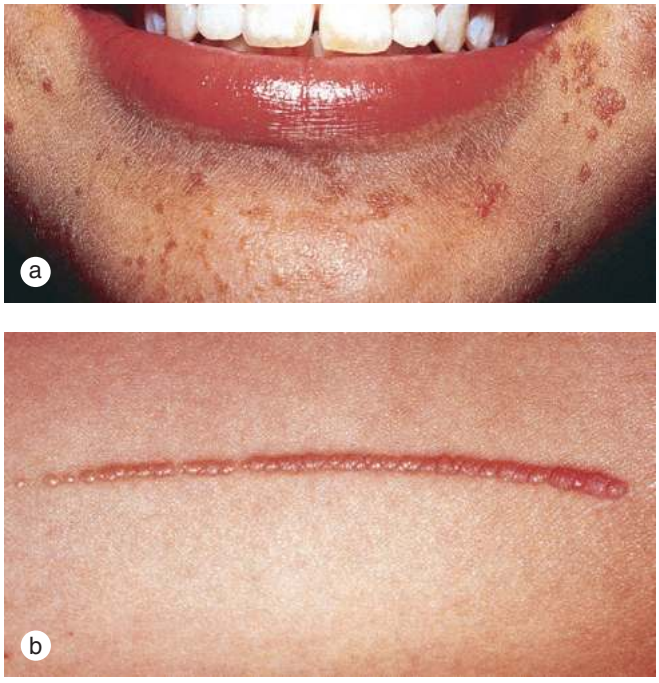


Fig 5.5 Verruca plana. **(a)** The tiny, light-brown warts on the chin of a 12-year-old girl were spread by scratching. These asymptomatic warts were initially diagnosed as acne. **(b)** Flat warts were inoculated in a line on the flank of a 5-year-old girl.

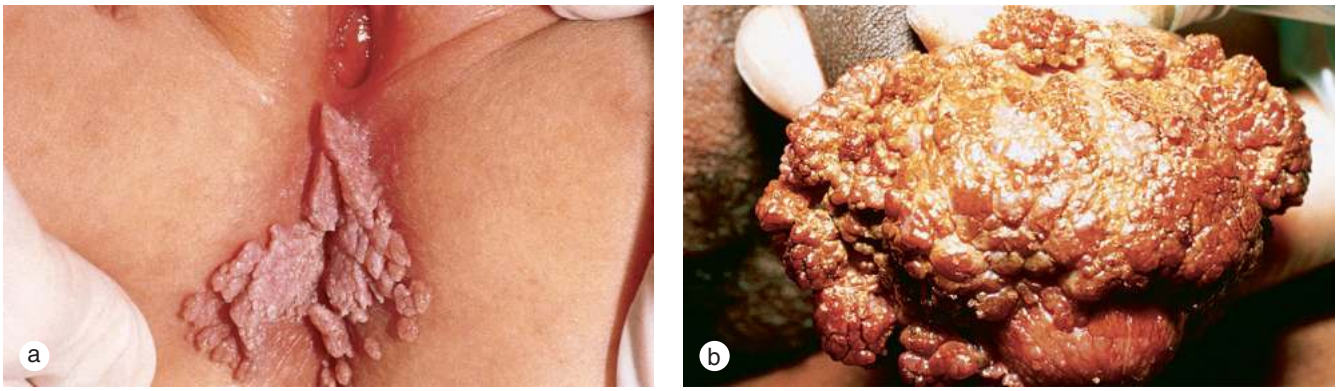


Fig 5.6 Anogenital warts and condyloma. **(a)** The warts developed at 8 months of age in this infant whose mother had extensive vaginal and cervical papillomavirus infection at delivery. These lesions resolved after treatment with podophyllotoxin. **(b)** Large condyloma enveloped the glans penis of this adolescent boy.

topical contact sensitizers, such as squaric acid, diphenylcyclopropenone, and rhus extract is still considered experimental, and parents are counseled accordingly. Although intralesional *Candida* antigen has been used to treat warts since 1978 and topical 5-fuorouracil more recently, neither has been approved by the Food and Drug Administration and use should be considered off-label. Remember, most warts resolve without treatment in 3–5 years, and children should play a role in deciding on therapy for these benign lesions.

Large warts in the diaper area may cause itching, burning, bleeding, and secondary bacterial infection. Although not approved for use in children, judicious home application of topical imiquimod cream and podophyllotoxin gel or solution are safe and effective in symptomatic cases. Scissors excision with electrocautery and carbon dioxide laser ablation may be effective in recalcitrant cases. However, painful destructive measures can only be performed with deep sedation or general anesthetic. As with common warts, most anogenital warts in normal hosts will regress without treatment over 3–5 years.

Several innocent epidermal growths are often confused with warts. Dermatosis papulosa nigra (DPN) describes a variant of seborrheic keratosis which appears in about a third of black individuals (Fig. 5.10). Although seborrheic keratoses usually do not erupt until middle age, small, brown, warty DPN typically begins to develop during adolescence in a symmetric, malar distribution on the face. The neck and upper trunk may also be involved. Although DPN is of no medical consequence, irritated or unsightly lesions may be snipped, frozen, cauterized, or gently lasered following the application of a topical anesthetic. Patients must be warned about the risk of postinflammatory pigmentary changes after treatment. Another type of innocent epidermal lesion, pearly penile papule, is often diagnosed as warts. Uniform, 1–3 mm



Fig 5.7 Extensive, recalcitrant warts spread over **(a)** the top and **(b)** the bottom of the feet of a teenager with severe combined immunodeficiency.

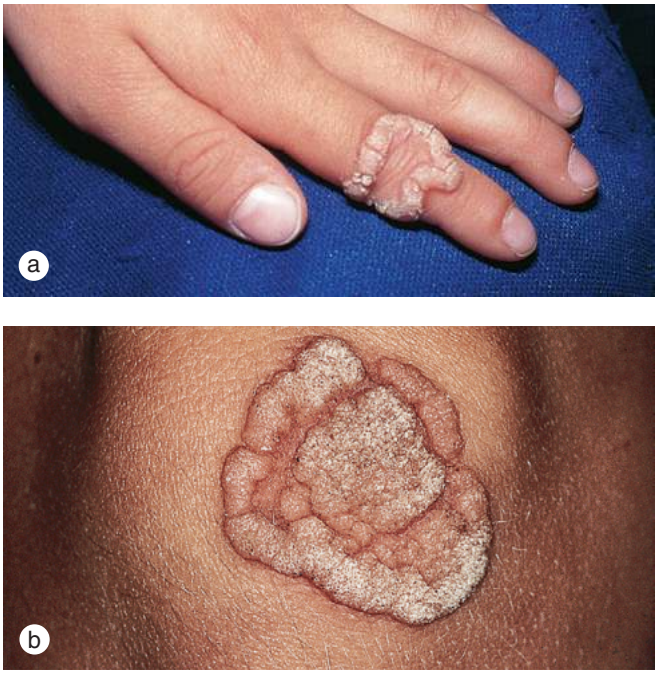


Fig 5.8 Recurrence of warts. **(a)** A 10-year-old boy developed a recurrent ring wart after liquid nitrogen treatment of a large common wart on the index finger. **(b)** A 10-year-old girl had a similar complication after treatment of a wart on her knee.



Fig 5.9 A 10-year-old boy developed multiple scars after liquid nitrogen therapy of warts on his knee.

diameter papules ring the corona at the base of the glans penis. Pearly penile papules, which appear in up to one-third of men by adolescence, are asymptomatic and probably represent a normal variant. No treatment is required.

Molluscum contagiosum

Molluscum contagiosum, caused by a large DNA poxvirus, is characterized by sharply circumscribed single or multiple, superficial, pearly, dome-shaped papules (Fig. 5.11). They usually start as grouped, pinpoint papules and increase in size to 3–5 mm in diameter. Many lesions have umbilicated centers, which are best seen with a hand lens (dermatoscope, otoscope). Molluscum is endemic in young children, in whom involvement of the trunk, axillae, face, and diaper area is common. Lesions are spread by scratching and frequently appear in a linear arrangement (Fig. 5.11c). In teenagers and adults, molluscum occurs frequently in the genital area as a sexually transmitted disease (Fig. 5.12) and diffusely in immunocompromised hosts.

A white, cheesy core can be expressed from the center of the papule for microscopic examination, which reveals the typical molluscum bodies. Destruction of lesions by curetting their cores or by application of a blistering agent (cantharidin) and plastic tape, peeled off in 1–3 days, is curative of individual lesions. Curettage probably is the least traumatic approach to therapy and associated with the lowest risk of scarring. However, recurrences and the development of new papules are common, and most cases in normal hosts undergo spontaneous remission within 6 months to 2 years of diagnosis. Consequently, treatment is usually directed against symptomatic lesions only. Moreover, there is no evidence-based literature to show that any treatment is superior to placebo.

Bacterial superinfection may be treated with appropriate topical or oral antibiotics. The development of scaly, red eczematous rings around old papules may herald the onset of a delayed hypersensitivity or 'id' reaction and resolution of the infection (Fig. 5.11e). As in children with warts, patients with widespread, recalcitrant molluscum should be screened for congenital and acquired immunodeficiency.



Fig 5.10 Small, brown papules typical of dermatosis papulosa nigra slowly increased in number and size on the face of this black adolescent. Her parents had similar lesions, which began to appear in late childhood.

Basal cell carcinoma

Basal cell carcinoma (BCC) presents as a non-healing, pearly, reddish-gray to brown papule or plaque with a central dell or crust and peripheral telangiectasias (Fig. 5.13). Although BCC occurs primarily in middle age and the elderly, the tumor is being recognized with increasing frequency in adolescents and young adults, particularly in fair-skinned individuals in sunny climates. The risk of developing BCC has been clearly linked to ultraviolet light exposure, and most lesions appear on sun-exposed sites, such as the face, ears, neck, and upper trunk. An indolent, superficial malignancy, uncomplicated BCC responds readily to electrodesiccation and curettage or simple excision. However, neglected lesions may become locally destructive and invade deep soft tissues, bone, and dura. Protection from excessive sun exposure, aggressive use of sunscreens, and careful skin surveillance should reduce the risk from BCC.

When BCC is diagnosed in sun-protected areas or in children, the practitioner must search for predisposing factors, such as radiation or arsenic exposure, a pre-existing nevus sebaceus or scar, or a hereditary condition such as xeroderma pigmentosum and basal cell nevus syndrome. In basal cell nevus syndrome, an autosomal-dominant disorder, numerous basal cell nevi are noted on the trunk, scalp, face, and extremities during the first decade (Fig. 5.14). In time, many of these lesions begin to enlarge and develop into progressive BCCs. Other stigmata include palmar and plantar pits, jaw cysts, calcification of the falx cerebri, ovarian fibromas, and fused ribs. Early diagnosis and removal of enlarging BCCs reduces the need for more extensive and disfiguring surgery.

In children, BCC may be confused with warts, molluscum contagiosum, seborrheic keratoses, pigmented nevi, and other epidermal and superficial dermal growths. It should be considered in any slowly progressive, crusted, or ulcerated plaque, particularly if risk factors are present.

DERMAL NODULES AND TUMORS

Granuloma annulare

When fully evolved, granuloma annulare is an annular eruption histologically characterized by dermal infiltration of lymphocytes and histiocytes around altered collagen (Fig. 5.15a–d). The lesion begins as a papule or nodule which gradually expands peripherally to form a ring 1–4 cm in diameter. Multiple rings may overlap to form large, annular plaques. In some cases the rings are broken up into segments. The overlying epidermis is usually intact and has the same color as adjacent skin. However, it may be slightly red or hyperpigmented. Most lesions are asymptomatic, although a few are reported to be mildly pruritic. Granuloma annulare most commonly erupts on the extensor surfaces of the lower legs, feet, fingers, and hands, but other areas may be involved.

Over months to years, old plaques and papules regress while new lesions appear. Eventually, granuloma annulare resolves without treatment. The origin is unclear, but some lesions may be associated



Fig 5.11 Molluscum contagiosum. **(a)** Multiple, pearly papules dot the arm of this 8-year-old girl with widespread molluscum. **(b)** A close-up view demonstrates the central umbilication present on mature molluscum lesions. **(c)** Note the linear spread of papules on the neck of this child, which followed scratching. **(d)** Molluscum on the eyelid margin and conjunctivae are particularly irritating and difficult to treat. **(e)** Red, scaly, dermatitic patches encircled this toddler's molluscum shortly before their resolution.

with insect-bite reactions or other antecedent trauma. The presence of aberrant immune regulation has been suggested by the recent observation of an increased incidence of granuloma annulare in patients infected with human immunodeficiency virus. In adults, granuloma annulare, especially multiple eruptive lesions, have appeared in association with diabetes mellitus (Fig. 5.15e). This is not the case in children.

Granuloma annulare is most commonly confused with tinea corporis or ringworm. However, the thickened, indurated character of the ring and lack of epidermal changes, such as scale, vesicles, or pustules, enable clinical distinction. A deep dermal or subcutaneous variant of granuloma annulare may be mistaken for rheumatoid nodules seen in rheumatic fever and other connective tissue disorders (Fig. 5.16). These lesions are referred to as subcutaneous granuloma annulare and pseudorheumatoid nodules. Practitioners should avoid the latter term, because the subcutaneous variant is not associated with local symptoms or systemic disease. Subcutaneous nodules occur most commonly on the extremities and scalp, where they are often fixed to the underlying periosteum. The diagnosis is often suggested by the presence of typical annular dermal plaques. When necessary, skin biopsies reveal changes similar to the more superficial lesions.

Adnexal tumors

Neoplasms may arise from any structure in the skin. Although many tumors of the adnexal structures can only be differentiated by specific histopathology, some demonstrate distinctive clinical patterns.

Epidermoid cysts

Epidermoid cysts (ECs) are slow-growing dermal or subcutaneous tumors that usually reach a size of 1–3 cm diameter and occur most commonly on the face, scalp, neck, and trunk (Fig. 5.17). They also occasionally develop on the palms and soles. These cysts account for a majority of cutaneous nodules found in children and may be present at birth or appear anytime in childhood. Although they are usually associated with hair follicles, ECs may arise from the epithelium of any adnexal structure. Primary lesions probably represent a keratinizing type of benign tumor. Other cysts occur as



Fig 5.12 Anogenital molluscum. **(a)** Molluscum developed on the penile shaft of this sexually active adolescent. **(b)** A healthy 6-year-old girl with molluscum on the chest and right arm accidentally inoculated lesions onto the anogenital skin.



Fig 5.13 A slowly enlarging, reddish-tan plaque on the upper chest of an 18-year-old boy developed a nodular component with overlying telangiectasias. A skin biopsy demonstrated basaloid budding typical of basal cell carcinoma. The child had red hair, blue eyes, light complexion, and a history of frequent sunburns since early childhood.



Fig 5.14 Basal cell nevus syndrome. Numerous 1–3 mm diameter papules composed of proliferating basaloid cells and two larger nodules, which demonstrated changes typical of basal cell carcinoma, are on the shoulder and neck of a 15-year-old girl with basal cell nevus syndrome. In addition to the widespread cutaneous tumors, she had subtle palmar and plantar pits and a history of jaw cysts. Her father, uncle, and grandmother had similar cutaneous lesions.

a response to trauma or inflammation such as in nodulocystic acne (see Fig. 8.23c).

Histologically, ECs consist of epidermal-lined sacs, which arise most commonly from the infundibular portion of the hair follicle. Rupture of the cyst and spillage of the epithelial debris contained within results in acute and chronic dermal inflammation. These lesions may become red and painful. Non-inflamed cysts can be readily excised. However, inflamed lesions may be settled down first with intralesional injections of corticosteroids and oral antibiotics before surgery is attempted.

Most ECs are solitary. When multiple lesions are present, the preceding injury or inflammatory process is usually apparent. In other cases, the development of multiple cysts suggests the diagnosis of Gardner syndrome or intestinal polyposis Type III. In this autosomal-dominant syndrome, increasing numbers of cysts, especially on the face and scalp, are associated with large-bowel polyposis and a 50% risk of malignant degeneration, osteomatosis that involves the bones of the head, and desmoid tumors, particularly of the abdominal wall. Members of affected families may now be screened for the genetic marker.

Milia represent miniature ECs that range from 1 to 3 mm in diameter. Although they occur commonly in the newborn (see Fig. 2.18a,b), they may be acquired after acute and chronic cutaneous injury, such as abrasions, surgery, and recurrent blistering in epidermolysis bullosa (see Fig. 2.52). Although milia often resolve without treatment, some remain indefinitely. Curettage or gentle puncture and expression with a comedone extractor or 22-gauge needle is usually curative.

A number of other cystic tumors in the skin, including trichilemmal cysts, pilomatrixomas, vellus hair cysts, steatocystoma, and dermoid cysts, may be confused clinically with ECs.

Trichilemmal cysts

Trichilemmal cysts are clinically indistinguishable from ECs. However, they are less common than ECs, occur almost exclusively on the scalp, and appear as multiple lesions in a majority of patients. Trichilemmal cysts tend to be inherited in an autosomal-dominant pattern. Histologically, these lesions can be differentiated from epidermal cysts by the absence of a granular layer and the presence of a palisading arrangement of the peripheral cells in the cyst wall. The cyst cavity contains homogeneous, keratinous material, unlike the laminated, horny material seen in ECs.



Fig 5.15 Granuloma annulare. Characteristic, doughnut-shaped, dermal plaques on **(a)** the foot of a light-pigmented boy and **(b)** the thigh of a dark-pigmented girl. In both children the epidermal markings are preserved. **(c)** A large, confluent plaque is developing from merging papules on the arm of a 9-year-old boy. **(d)** Multiple, asymptomatic 2–4 mm diameter papules erupted on the hand of a teenager. **(e)** Disseminated granuloma annulare developed in a 20-year-old individual with insulin-dependent diabetes mellitus.

Pilomatrixoma

Pilomatrixoma, or calcifying epithelioma of Malherbe, presents as a sharply demarcated, firm, deep-seated nodule covered by normal or tethered overlying skin (Fig. 5.18). Superficial tumors develop a bluish-gray hue, and occasionally protuberant, red nodules are present. Lesions range in size from under 1 cm to over 3 cm diameter. Although pilomatrixomas may arise at any age, 40% appear before 10 years of age, and over 50% by adolescence. These tumors often come to the attention of anxious patients or parents when rapid enlargement follows hematoma formation after trauma.

Pilomatrixomas occur most commonly on the face, scalp, and upper trunk. They are usually solitary, but multiple lesions develop occasionally. Although most pilomatrixomas do not appear to be inherited, there are several reports of familial cases in an autosomal dominant pattern.

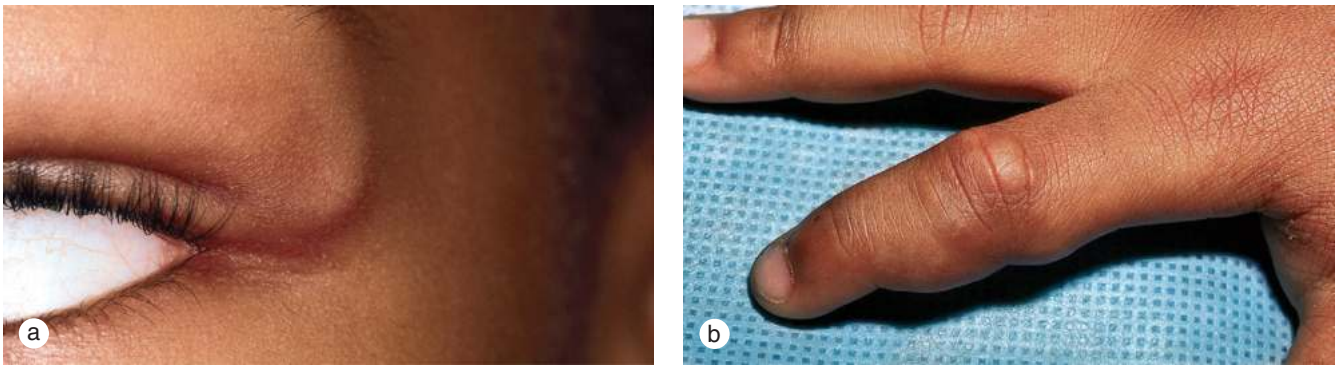


Fig 5.16 Subcutaneous granuloma annulare. Asymptomatic subcutaneous nodules persisted for over a year **(a)** on the upper eyelid of a 7-year-old boy and **(b)** on several fingers of a 10-year-old girl.



Fig 5.17 A small epidermal cyst (6 mm) developed on the cheek of a 5-year-old boy after an insect bite.

Histologically, this well-demarcated, encapsulated tumor demonstrates a distinctive pattern with islands of basophilic and shadow epithelial cells. Eosinophilic foci of keratinization and basophilic deposits of calcification are scattered throughout.

Although pilomatrixomas are usually asymptomatic, rapid enlargement, ulceration, or gradual progression to a large size may prompt surgical removal. They can usually be excised easily with local anesthetic.

Vellus hair cysts

Vellus hair cysts erupt as multiple, 1–2 mm diameter, follicular papules on the axillae, neck, chest, abdomen, and arm flexures of children and young adults (Fig. 5.19). Some of the papules have an umbilicated center, suggestive of molluscum contagiosum, and impacted, lightly pigmented vellus hairs may poke out of the center. These asymptomatic lesions resolve over months to years without treatment. Familial cases with autosomal-dominant inheritance have been described. Topical retinoids may hasten the resolution of these innocent cysts, but irritation may limit therapy.

Steatocystoma

Steatocystoma may appear sporadically as a solitary tumor or in an autosomal-dominant pattern with numerous, non-tender, 1–3 cm diameter, firm, rounded, cystic nodules tethered to the overlying skin (Fig. 5.20). Cysts usually begin to develop on the chest, arms, and face in childhood or adolescence. When ruptured, cysts exude an oily or milky fluid, and in some cases small hairs. The walls of the cyst characteristically contain flattened, sebaceous gland lobules or abortive hair follicles. Electron microscopy findings suggest that steatocystoma arises either from sebaceous ductal epithelium or from the hair outer-root sheath. A few bothersome cysts may be removed by simple excision. In some patients with hundreds of lesions, 13-cis-retinoid acid (isotretinoin) has been shown to shrink existing tumors and shut off the development of new ones at least temporarily.





Fig 5.19 Multiple asymptomatic 1–3 mm vellus hair cysts on the **(a)** axillae of a 7-year-old boy and **(b)** the chest of an 11-year-old boy.

Dermoid cysts

Dermoid cysts are congenital, subcutaneous cysts 1–4 cm in diameter, and are found most commonly around the eyes and on the





Fig 5.18 Pilomatrixoma. **(a)** A pilomatrixoma was removed from the forehead of a 7-year-old boy. Note the characteristic bluish-gray dermal papule. **(b)** This rock-hard nodule on the upper arm of a 5-year-old girl developed a central ulceration.





Fig 5.20 (a) Numerous steatocystomas began to appear on the chest, neck, and face of this adolescent when he was 8 years old. His father and brother had similar nodulocystic lesions. **(b)** This 21-year-old woman has also had progressive nodules on her chest and axillae since adolescence, similar to her father and brother.



Fig 5.21 Syringomas dot the eyelids of this adolescent. The papules responded quickly to gentle vaporization with carbon dioxide laser.

head and neck (see Fig. 2.22). On the head, most dermoids are non-mobile, because they are often fixed to the periosteum. Dermoid cysts grow slowly and may cause thinning of the underlying bone. Unlike epidermal cysts, the epithelial lining of dermoid cysts contains multiple adnexal structures, which include hair follicles, eccrine glands, sebaceous glands, and apocrine glands.

Multiple facial papules and nodules

Multiple facial papules and nodules suggest the diagnosis of syringomas, angiofibromas (see Fibrous tumors, below), or trichoepitheliomas. Differentiation is made on the basis of clinical and histologic findings.

Syringomas

Syringomas appear as multiple, 1–2 mm diameter, skin-colored to yellow-brown papules on the lower eyelids and cheeks (Fig. 5.21). Occasionally, they occur as isolated lesions or in a widely disseminated, eruptive form with hundreds of papules on the face, axillae, chest, abdomen, and genitals (Fig. 5.22). Although they develop most commonly in adolescent girls and young women, they may appear at any age in males and females. They also develop more commonly in children with Down syndrome.

Histologic findings demonstrate characteristic, multiple, small ducts lined by two rows of flattened epithelial cells in the superficial dermis. The lumina of the ducts contains amorphous debris, and some ducts possess comma-like tails which give the appearance of tadpoles.

Although occasionally disfiguring, lesions are usually asymptomatic. Syringomas may be effectively removed by a number of methods, including carbon dioxide laser, electrocautery, cryosurgery, and surgical excision.

Trichoepitheliomas

Trichoepitheliomas occur most commonly as solitary, skin-colored tumors <2 cm in diameter on the face of children or young adults. Multiple lesions are inherited as an autosomal-dominant trait (Fig. 5.23). In this setting, trichoepitheliomas appear first in childhood, and increase slowly in number and size. Numerous papules and nodules between 2 and 8 mm in diameter occur on the cheeks, nasolabial folds, nose, and upper lip. Histopathology shows a typical dermal tumor that consists of horn cysts of varying sizes and formations, resembling BCCs. Histologic differentiation from basal cell tumors is occasionally difficult.

Unfortunately, tumors may increase indefinitely and cause severe disfigurement. Surgical excision, electrocautery, and laser ablation have been used to deal with the most problematic lesions.



Fig 5.22 Syringomas. Multiple 2–3 mm glistening whitish-yellow papules gradually increased in number on the genitals of a healthy 12-year-old boy.



Fig 5.23 Trichoepitheliomas slowly increased in size and number on **(a)** the face and **(b)** the back of this 17-year-old boy. Note the involvement of the nasolabial folds and the upper lip. At least five individuals in three generations of his family were affected.

Xanthomas

Xanthomas are yellow dermal tumors that consist of lipid-laden histiocytes. They are usually associated with an abnormality of lipid metabolism, and their presence may provide a clue to an underlying systemic disease.

Poorly soluble lipids are transported in serum by lipoproteins. Abnormalities in lipid transport and metabolism may result in elevations of serum triglycerides and/or cholesterol. The deposition of these lipids in skin and soft tissue results in the development of xanthomas.

Although conditions such as fulminant hepatic necrosis from serum hepatitis and poorly controlled diabetes mellitus may trigger hyperlipidemia, a number of primary inherited dyslipoproteinemias have been defined (Table 5.3). Medications such as antiretroviral agents used in the management of human immunodeficiency virus infection can also elevate lipids and trigger the formation of xanthomas.

The recognition of a number of clinical variants may help to define a particular systemic disorder (Fig. 5.24). Planar xanthomas present as soft, slightly infiltrated, yellow plaques at any site, but with a predilection for previously injured skin such as old lacerations and acne scars. Xanthelasma, an example of planar lesions on the eyelids, is associated with hypercholesteremia in about half of the cases. Diffuse lesions may involve the extremities, trunk, face, and neck. In childhood, planar xanthomas occur in diabetes mellitus, liver disease, and histiocytosis syndromes.

Tuberous xanthomas arise as reddish-yellow nodules on the extensor surfaces of the extremities and buttocks. Although they may coalesce to cover a large area, tuberous lesions do not become adherent to the underlying soft-tissue structures, as do tendinous xanthomas. They may occur with elevations of cholesterol or triglycerides.

Tendinous xanthomas present as smooth, asymptomatic nodules on ligaments, tendons, and other deep, soft-tissue structures. They are usually several centimeters in size and occur most commonly on the ankles, knees, and elbows.

Eruptive xanthomas develop suddenly as 1–4 mm diameter, yellowish-red papules over the extensor surfaces of the extremities,



Fig 5.24 Xanthomas erupted in two children **(a, b)** with congenital biliary atresia and chronic liver failure. **(b)** Note the involvement of the hand and finger creases. The infiltrated nodules and plaques resolved after liver transplantation. **(c)** Widespread xanthomas erupted in this 19-year-old woman with primary biliary cirrhosis.

Hyperlipidemias and electrophoretic patterns									
Type (prevalence)		**Pattern**	**Chol**	**TG**	**Inheritance**	**Defect**	**Clinical presentation**	**Age of detection**	**Secondary diseases**
Type I	a. Buerger–Gruetz syndrome or Familial hyperchylomicronemia	Chyl	+	+++	AR	Decreased lipoprotein lipase (LPL)	Eruptive xanthomata Abdominal colic Steatosis and organomegaly Lipemia retinalis	Early childhood	Pancreatitis, diabetes
	b. Familial apoprotein CII deficiency					Altered ApoC2	Retinal vein occlusion Acute pancreatitis		
	c.					LPL inhibitor in blood			
Type II	a. Familial hypercholesterolemia	LDL	+++	+ or NI	AD	LDL receptor non-functional or deficient	Xanthelasma Tendinous xanthomas Corneal arcus Tuberous xanthomas Atherosclerosis	Early childhood in homozygote	Hypothyroidism nephrotic syndrome
	b. Familial combined hyperlipidemia (common)					Decreased LDL receptor and increased ApoB results in increase VLDL	Same, abnormal GTT		Hepatic disease
Type III	Familial combined hyperlipidemia (relatively common)	IDL	++ (variable)	+ (variable)	AR	Homozygous apolipoprotein E2, decreased remnant clearance, overproduction of VLDL	Xanthomas tuberous, palmar, tendinous, eruptive, abnormal GTT, hyperuricemia, atherosclerosis, obesity	Adult	Hepatic disease dysglobulinemia uncontrolled diabetes
Type IV	Familial hypertriglyceridemia (most common)	VLDL and Chyl	+	++	AD	Increased VLDL production and Decreased LPL	Atherosclerosis, abnormal GTT, eruptive or tuberous xanthomas High TG levels can cause pancreatitis	Adult	Hypothyroidism, diabetes, pancreatitis glycogen storage disease, nephrotic syndrome, multiple myeloma
Type V	(uncommon)	Chyl, VLDL	+	++	AR	Overproduction of VLDL, defect in catabolism of VLDL	Abnormal pain, obesity, xanthomas (eruptive), hepato-splenomegaly	Early adult	Diabetes, insulin dependent, pancreatitis, alcoholism

Chol, cholesterol; TG, triglycerides; Chyl, chylomicrons; LDL, low density lipoproteins; VLDL, very low density lipoproteins; IDL, intermediate density lipoproteins; AR, autosomal recessive; AD, autosomal dominant; GTT, glucose tolerance test; NI, normal.

Table 5.3 Hyperlipidemias and electrophoretic patterns

buttocks, and bony prominences (Fig. 5.24c). Their appearance is usually associated with marked elevation in triglycerides, especially in poorly controlled diabetics or in patients with Types I, III, IV, and V hyperlipidemias.

Xanthomas must be differentiated from xanthogranulomas, which are not usually associated with systemic disease or elevated serum lipids (see Fig. 2.86). Xanthogranulomas rarely appear in large numbers; they are single in about 50% of the cases, and fewer than five nodules are present in most of the rest.

Fibrous tumors

Keloids

A number of benign dermal tumors result from the proliferation of fibroblasts in the dermis. During the healing process that follows an injury to the skin, loss of normal structures and the laying down of collagen by fibroblasts may result in the formation of a scar. In certain predisposed individuals the collagen may become particularly thick, which results in a hypertrophic scar. Over the ensuing 6–9 months many of these scars flatten. However, some may persist or develop into keloids that continue to thicken and extend beyond the margins of the initial injury (Fig. 5.25). These rubbery nodules or plaques can be pruritic or tender, especially during the active growing phase. Keloids may arise sporadically or occur in a familial form. They are most common in dark-pigmented individuals, and have a predilection for the ear lobes, upper trunk, and shoulders. Fortunately, they are not seen on the mid-face. If treated early, hypertrophic scars and keloids may regress with intralesional corticosteroid injections alone or in combination with surgery. However, recurrences are common.

Dermatofibromas

Dermatofibromas present as firm, indolent, 0.3–1.0 cm diameter, reddish-brown dermal nodules (Fig. 5.26). Although dermatofibromas are most common in adults, about 20% occur before 20 years of age, and they account for 2% of all cutaneous nodules found in children. Tumors may arise as single or multiple lesions (usually fewer than five) on any site, including the palms and soles. However, they appear most commonly on the arms and legs. Although the cause is unknown, many lesions are thought to follow minor trauma, such as insect bites or folliculitis.

On examination, dermatofibromas often demonstrate dimpling with lateral pressure because of attachment of the dermal nodule to an overlying, thickened, and hyperpigmented epidermis.



Fig 5.25 A 10-year-old girl developed a progressive keloid in **(a)** a thoracotomy scar. **(b)** A large nodule grew on the ear lobe of this adolescent after ear piercing. **(c)** Acne keloidalis nuchae erupted on the back of the scalp of this 11-year-old boy. The appearance of the multiple small keloids was preceded by pseudofolliculitis.

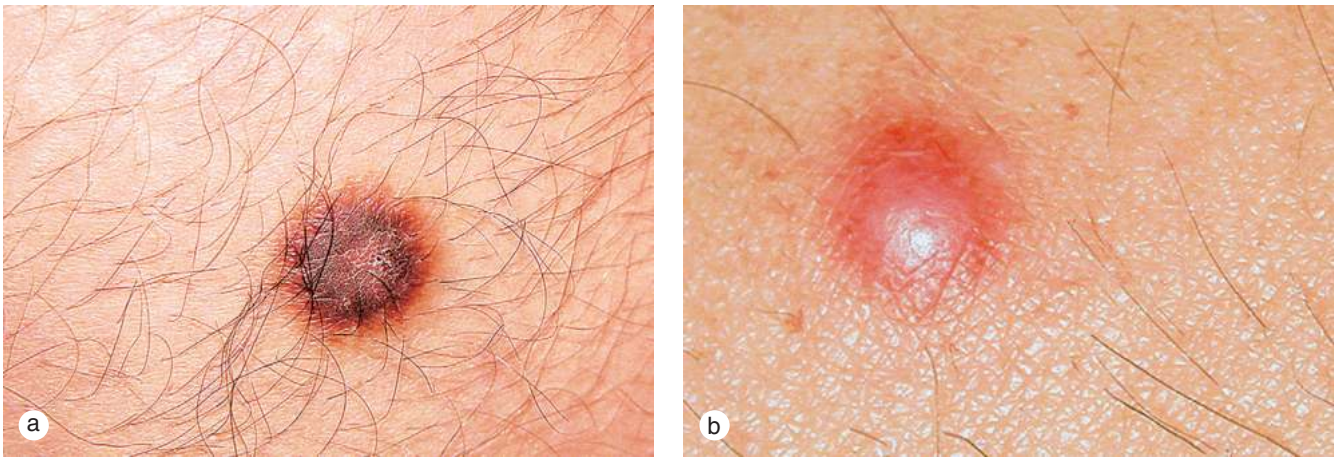


Fig 5.26 Dermatofibroma. **(a)** An indolent, 1 cm diameter, firm, brown nodule appeared 2 years previously on the leg of this 17-year-old boy. The overlying epidermis was thickened and hyperpigmented. **(b)** A pink smooth-topped 1 cm papule with slight hyperpigmentation developed on the leg of a healthy adolescent girl. The asymptomatic nodule had changed little since it appeared 6 months earlier.

Dermatofibromas may come to the attention of the patient after sudden enlargement following trauma and resultant hemorrhage. Histology, which reveals proliferating fibroblasts and histiocytes, permits easy differentiation from melanocytic tumors such as nevi and melanomas.

The early papules and nodules of dermatofibroma sarcoma protuberans (DFSP) may be mistaken for dermatofibroma (Fig. 5.27). However, the persistent slow or occasional accelerated growth of DFSP and predilection for the trunk and proximal extremities should suggest the diagnosis. Although these locally aggressive tumors are rare in children, congenital and early childhood cases have been reported.

Angiofibromas

Although angiofibromas may develop as solitary papules in healthy individuals, their presence alerts the clinician to the diagnosis of tuberous sclerosis (Figs 5.28, 5.29). In children with tuberous sclerosis, these dermal tumors gradually increase in size and number during childhood, involve the scalp, cheeks, and nasolabial folds, and spare the upper lip. Subtle angiofibromas may be mistaken for flat warts, comedones, or seborrheic keratoses. Histopathology demonstrates a fibrous tumor with an increase in numbers of fibroblasts and amount of collagen, and capillary dilatation. The presence of acne-like papules beginning well before puberty suggests the diagnosis, even in otherwise healthy children of normal intelligence.

In children without evidence of tuberous sclerosis, the presence of progressive angiofibromas should prompt a search for multiple endocrine neoplasia type 1 which is also associated with angiofibromas. Multiple angiofibromas may occasionally be found in patients without other markers of systemic disease and may represent examples of mosaicism for tuberous sclerosis or MEN1.



Fig 5.27 A young adult had a large tumor excised from his left shoulder a year ago. He subsequently developed a new tumor on the left chest and recurrent nodules in the scar of the original lesion.

Vascular tumor

Pyogenic granuloma

Pyogenic granulomas, also known as lobular capillary hemangiomas, are common in children (especially toddlers) (Fig. 5.30). These benign, soft, bright red, usually solitary vascular neoplasms range in size from 2 mm to 2 cm and are often preceded by trauma to the involved area. Pyogenic granulomas typically exhibit rapid growth and bleed readily with minor trauma. In children, 77% occur on the face or neck. They often develop a positive Band-Aid sign, or contact irritant dermatitis in the shape of the dressing and surrounding adhesive needed to keep pressure on the hemorrhagic papule. Mean age of presentation is around 6 years of age and 14% occur in the first year of life. It rarely occurs before 4 months of age. There is a slight male predisposition of 1.5 : 1 and Caucasian patients make up 84% of cases.

Pyogenic granulomas also tend to erupt on the buccal mucosa and gingivae of up to 2% of pregnant women during the first 5 months of pregnancy perhaps due to hormonal influences. In this setting they are referred to as granuloma gravidarum or pregnancy tumor. Pyogenic granulomas may also occur with increased frequency over vascular malformations such as port wine stains, particularly after treatment with pulse dye laser or during pregnancy.

Historically, the name 'granuloma pyogenicum' was used because the lesion was presumed infectious and granulomatous but is actually neither. Although most clinicians still refer to these lesions as







Fig 5.28 Angiofibromas. **(a)** Small, reddish-brown facial papules were initially dismissed as acne. **(b)** Subtle, brown papules were diagnosed as moles. Both children were of normal intelligence and had no history of seizures. Skin biopsies demonstrated findings typical of angiofibromas. **(c)** This profoundly mentally retarded boy with tuberous sclerosis developed progressive angiofibromas over much of his face. Note the involvement of the nasolabial folds and sparing of the upper lip.

pyogenic granulomas, in 1980, the name lobular capillary hemangioma was introduced to reflect the pathophysiology of the benign vascular tumor.

Biopsy of the lesions shows a loose fibrous tissue matrix with proliferating capillaries similar to that of granulation tissue.

In children pyogenic granulomas are most commonly confused with infantile hemangiomas. However, hemangiomas usually



Fig 5.29 A teenager with tuberous sclerosis demonstrated multiple discrete and confluent connective tissue nevi on his back in addition to facial angiofibromas and scattered truncal hypopigmented macules.

appear within the first few weeks of life, grow for 3–4 months, and then go on to regress. Fortunately, bleeding and ulceration do not occur in most lesions. This is in contrast to pyogenic granulomas which are only rarely present in the first few months of life and typically present with bleeding after minor trauma. The differential diagnosis for non-vascular solid red tumors includes spindle and epithelial cell nevi, amelanotic melanoma, and angiolymphoid hyperplasia with eosinophilia. These tumors have distinctive clinical findings, natural histories, and histologic findings.

Shave excision and electrocautery can be completed safely and effectively with minimal risk of scarring in less than a minute without sedation in most children. However, it is important to wait 5–7 min after anesthetic infiltration to allow the epinephrine to take effect and lower the risk of bleeding at the time of removal. Topical treatment with silver nitrate is often associated with rapid recurrence of lesions. Although pulsed dye laser ablation may be used, it often requires repeated treatments over a period of weeks. Large lesions (>10 mm) may be treated with carbon dioxide laser or surgical excision.

Neural tumors

Neurofibromas

Neurofibromas are the most common tumors of neural origin for which a patient might seek dermatologic consultation (Fig. 5.31). These soft, compressible, skin-colored, 0.5–3 cm diameter tumors arise in the dermis and occasionally in the subcutaneous fat. Neurofibromas occur sporadically as solitary lesions or progressively in large numbers in patients with neurofibromatosis (see Fig. 6.1).

Neuromas

Neuromas arise in three settings. Traumatic neuromas are solitary, painful nodules that develop in scars after surgery or trauma. Pain resolves quickly after surgical excision. Traumatic neuromas also include amputation neuromas and congenital, rudimentary, supernumerary digits, which occur most commonly on the ulnar side of the base of the 5th finger (see Fig. 2.23). Idiopathic neuromas are rare lesions that develop in early childhood through adult life as solitary or multiple 0.2–1 cm diameter dermal nodules on the skin and oral mucosa (Fig. 5.32). They are not associated with multiple

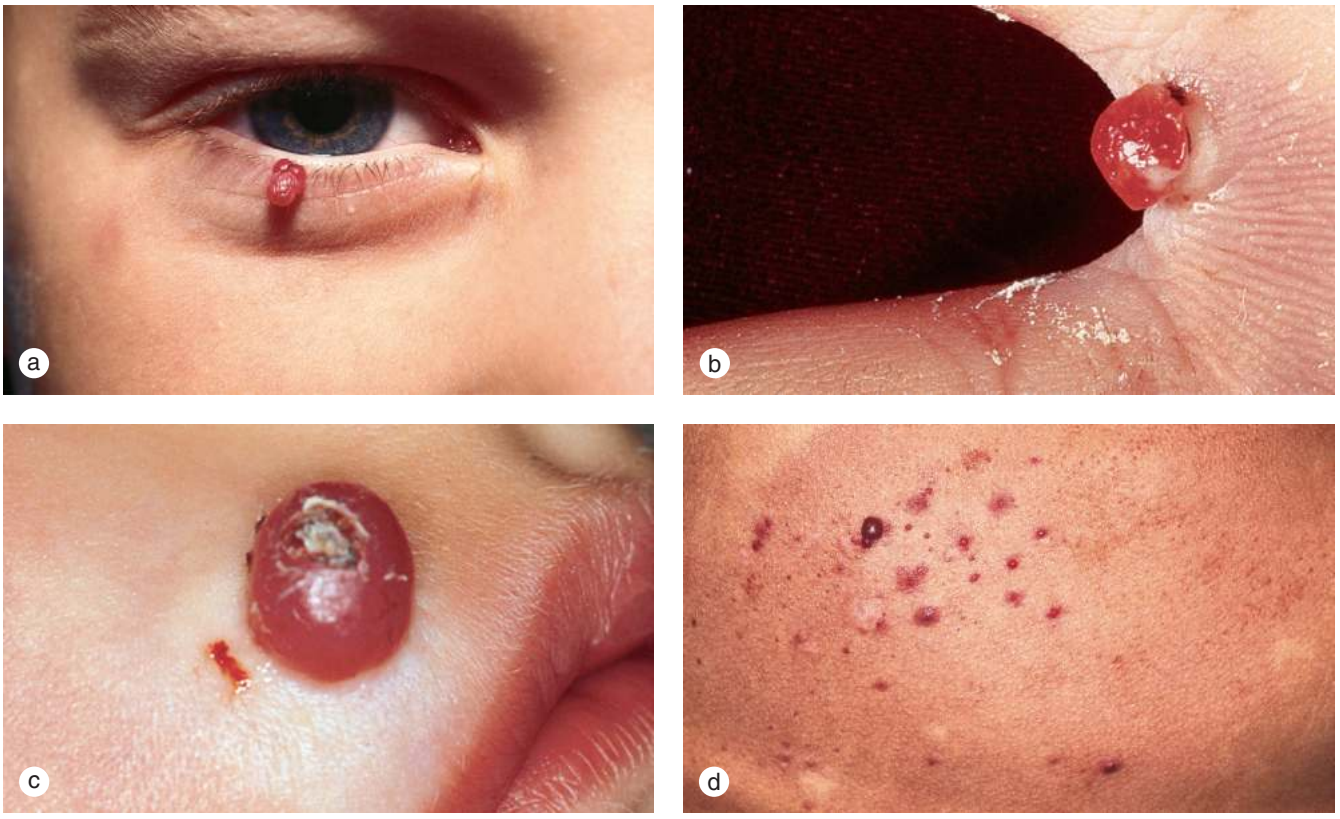


Fig 5.30 Pyogenic granuloma. **(a)** A hemorrhagic papule developed on the lower eyelid of this 8-year-old boy. **(b)** Another rapidly growing, friable lesion is present between the fingers of a 5-year-old boy. **(c)** This 8 mm diameter nodule with a central crust bled profusely several times before surgical removal. **(d)** Multiple satellite lesions erupted on the back of a 10-year-old boy several months after the appearance of a single pyogenic granuloma.

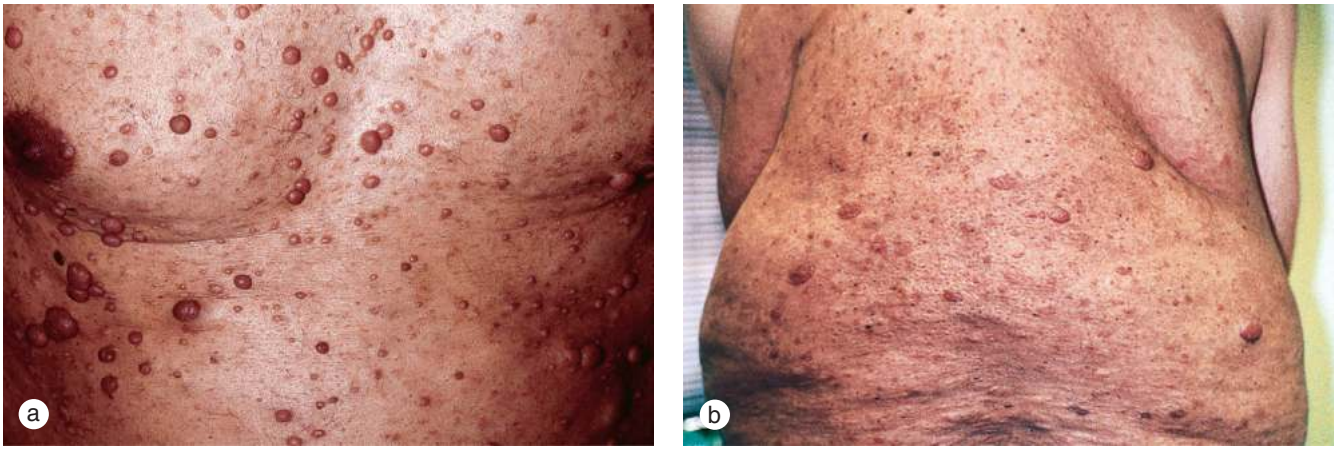


Fig 5.31 Neurofibromas. **(a)** Widespread, compressible tumors developed over much of the body surface of this young man with neurofibromatosis Type I. The neurofibromas began to appear when he was 10 years old. His 4-year-old son had multiple café-au-lait spots, but no cutaneous tumors. **(b)** A giant, plexiform neurofibroma slowly grew to involve most of this teenager's back. Note the multiple, overlying, cutaneous neurofibromas and café-au-lait spots.



Fig 5.32 Neuromas. Over 50 small, yellow, dermal nodules erupted on the face, neck, trunk, and extremities of a 3-year-old girl. She has no signs of multiple endocrine neoplasia, and the family history is negative.



Fig 5.34 Lymphoma. An indolent nodule on the thigh of a 7-year-old boy was initially diagnosed as a persistent insect-bite reaction. During the following year several new nodules appeared on his legs and buttocks and regressed without treatment. Biopsy of the initial lesion shown here, which persisted throughout the period, demonstrated a lymphoma positive to Ki-1 marker.

endocrine neoplasia. Finally, multiple, mucosal neuromas are part of an autosomal-dominant syndrome (multiple endocrine neoplasia Type IIB) in which numerous small tumors begin to appear on the lips, oral mucosa, and face in early childhood. Recognition of this syndrome is important because of the associations with medullary thyroid carcinoma, which can develop in young children and adults, and pheochromocytoma in adolescents and adults.

In multiple mucosal neuroma syndrome, facial lesions may be confused with angiofibromas, trichoepitheliomas, multiple trichilemmomas in Cowden disease, and extensive papillomavirus infection. However, the large numbers of nerve bundles seen on skin biopsy are distinctive. Nodules on the trunk and extremities cannot be differentiated from other dermal tumors without a biopsy.



Fig 5.33 Lymphocytoma cutis. A 1 cm diameter, painless nodule persisted for over a year on the forehead of a teenage boy. A skin biopsy from the center of the lesion demonstrated a lymphocytic infiltrate in the dermis that formed lymphoid, follicle-like structures. Intralesional corticosteroids resulted in some improvement.

Lymphocytoma cutis

Lymphocytoma cutis presents as asymptomatic nodules and plaques most commonly on the face, but any site may be involved. Although multiple lesions may erupt, solitary nodules ranging from less than 1 cm to several centimeters in diameter are the rule (Fig. 5.33). Most tumors develop in adolescents and young adults.

The differentiation from a non-Hodgkin lymphoma, which also presents as a single nodule, may be impossible. Histologic findings demonstrate a mixed dermal infiltrate of large and small lymphocytes separated from the epidermis by a small band of normal collagen. The infiltrate may become organized into structures that resemble lymph follicles. The frequent presence of an admixture of plasma cells and/or eosinophils indicates no malignancy. Unfortunately, the histology is not specific, and the usual innocent nature of the eruption in children is defined by the clinical course. Nodules heal without treatment over months to years. Some patients may benefit from intralesional corticosteroids.

Clinically, lymphocytoma cutis is indistinguishable from cutaneous nodules found in lymphoma and leukemia, and all children deserve a careful history and complete physical examination to exclude signs and symptoms of systemic disease (Figs 5.34, 5.35). Other infiltrative processes, such as Langerhans cell histiocytosis, non-Langerhans cell histiocytosis, follicular mucinosis (Fig. 5.36), and mastocytomas, as well as insect-bite reactions, sarcoidosis, deep fungal infections (Fig. 5.37), mycobacterial infections (Fig. 5.38), and dermatofibromas may resemble lymphocytoma cutis. The clinical course, histologic findings, and culture results help to define these entities. Rarely, other malignancies, such as leukemia, rhabdomyosarcoma, neuroblastoma, and renal carcinoma, present initially with cutaneous nodules. Their rapid growth and histologic pattern differentiate these malignancies from benign lymphocytoma cutis.

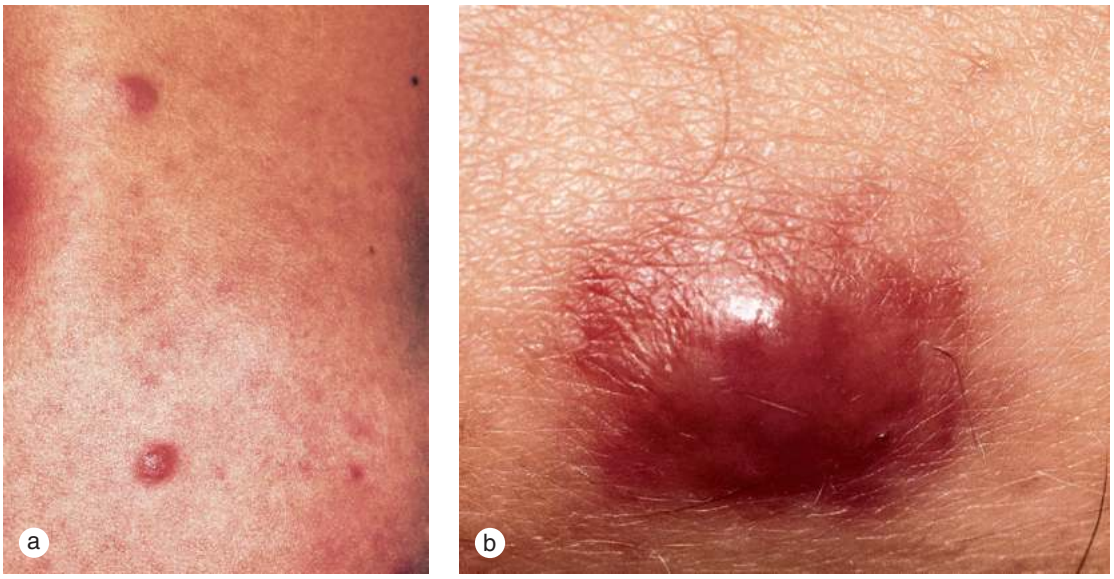


Fig 5.35 Leukemia cutis. An adolescent with myelogenous leukemia developed **(a)** small, cutaneous nodules on his scalp and **(b)** several larger tumors on his trunk and extremities, associated with a recurrence of disease in his bone marrow.



Fig 5.36 A 13-year-old girl had a firm red plaque on her chin for over 6 months. A skin biopsy showed changes typical of alopecia mucinosa. Her mother applied a topical steroid, and the lesion resolved in several months.



Fig 5.37 Sporotrichosis. A teenage boy developed a slowly expanding, painless, violaceous, indurated plaque on his left 5th finger. Sporotrichosis was diagnosed on a skin biopsy and confirmed by fungal culture. The lesion healed in 3 months with oral administration of a saturated solution of potassium iodide.



Fig 5.38 Cutaneous tuberculosis. This infection began as a small nodule on the nose and grew into a large, infiltrative tumor that involved the center of her face. The diagnosis was confirmed by skin biopsy and mycobacterial culture. She responded to antibiotics with almost complete clearing of the tumor in 4 months.

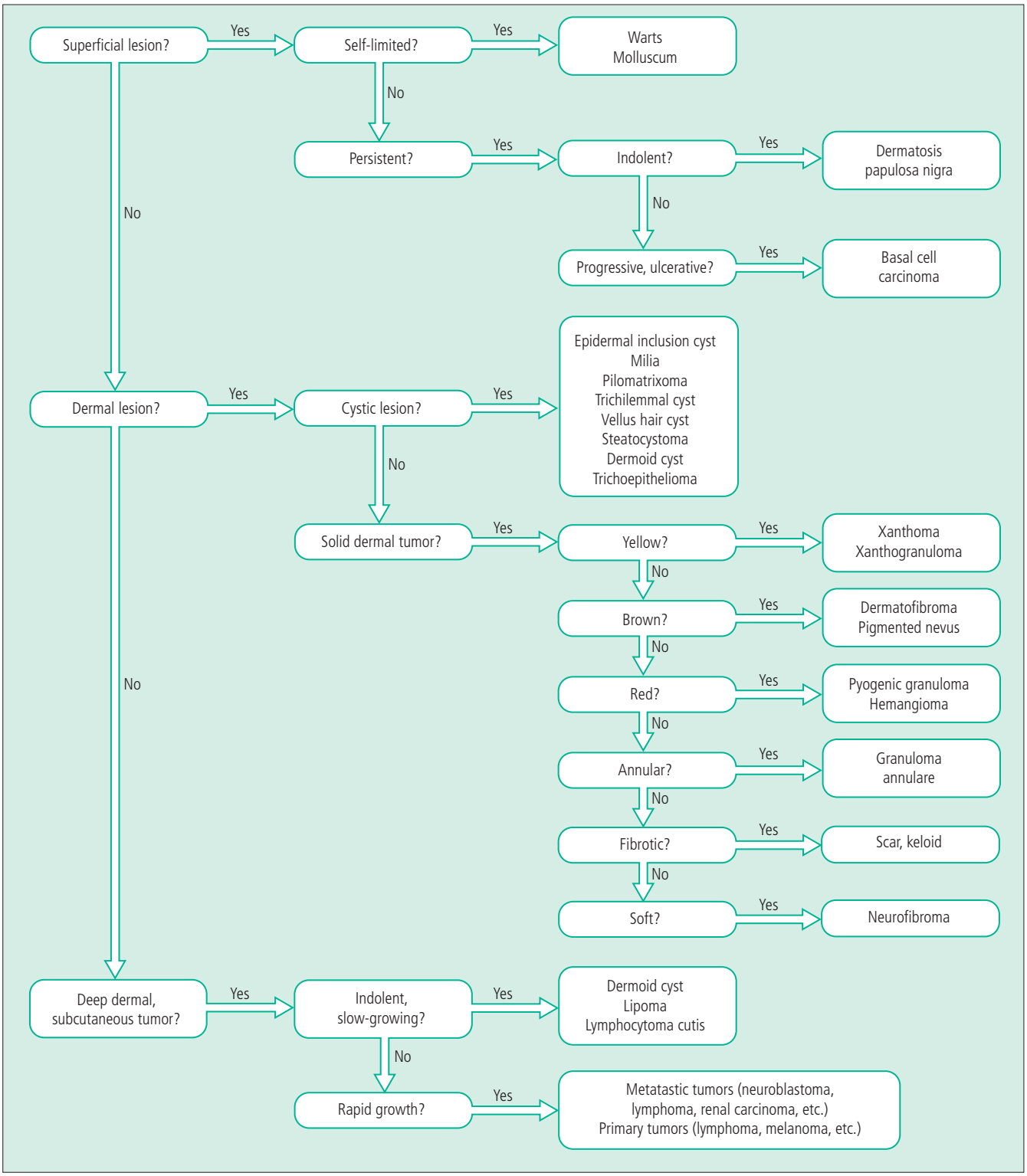


Fig 5.39 Algorithm for evaluation of nodules and tumors.

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Chapter 6

Disorders of Pigmentation

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INTRODUCTION

Although most disorders of pigmentation in infancy and childhood are of cosmetic concern only, some provide clues to an underlying multisystem disease. Disorders of pigmentation may be differentiated clinically by the presence of either increased or decreased pigmentation (and sometimes both in the same patient!) occurring in a localized or diffuse distribution. An algorithmic approach to diagnosis for disorders of pigmentation is summarized at the end of the chapter (see Fig. 6.28).

HYPERPIGMENTATION

Pigmented lesions are localized areas of hyperpigmentation that are frequently due to developmental or hereditary factors, and often appear early in childhood. Pigmented lesions may also be acquired during childhood following inflammatory rashes or exposure to actinic, traumatic, chemical, or thermal injury. A useful way to classify pigmented lesions is by identifying whether they occur in the epidermis or dermis. Epidermal melanosis occurs when increased numbers of epidermal melanocytes are present in the basal cell layer or when increased quantities of melanin are present in epidermal keratinocytes. Dermal melanosis results from increased melanin in dermal melanocytes or melanophages. Although epidermal melanosis may result in dark-brown or black lesions, most appear tan or light-brown. In contrast, dermal melanosis usually produces slate-gray, dark-brown, and bluish-green lesions.

Epidermal melanosis

Café-au-lait spots

Café-au-lait spots are discrete, tan macules that appear at birth or during childhood in 10–20% of normal individuals. Lesion sizes vary from freckles to patches greater than 20 cm in diameter and may involve any site on the skin (Fig. 6.1a,d–f).

Although most children with café-au-lait spots are healthy, the presence of six or more lesions, each >5 mm in diameter in someone <15 years old (and lesions >1.5 cm in diameter for older individuals) is a diagnostic marker for classic neurofibromatosis (i.e. von Recklinghausen disease or National Institutes of Health classification NF-1). Conversely, 90% of individuals with neurofibromatosis have at least one café-au-lait spot. Often present at birth, café-au-lait spots usually increase in size and number throughout childhood, particularly during the first few years of life in children with neurofibromatosis. Other lesions in neurofibromatosis such as axillary freckling (Crowe's sign) (Fig. 6.1a), neurofibromas (Fig. 6.1b,c), and iris hamartomas (i.e. Lisch nodules), may not appear until later childhood or adolescence.

Histologic findings include increased numbers of melanocytes and increased melanin in melanocytes and keratinocytes. Giant pigment granules have been identified in café-au-lait spots of neurofibromatosis, but they may also be seen in sporadic café-au-lait spots, nevi, freckles, and lentigines.

Pigmented-lesion lasers (Q-switched ruby, neodymium:yttrium-aluminum-garnet, and alexandrite lasers) provide a safe, effective, and relatively painless therapeutic alternative for removing café-au-lait spots.

Café-au-lait spots are not specific for neurofibromatosis and have also been associated with other disorders including tuberous sclerosis, McCune–Albright syndrome, LEOPARD syndrome, epidermal nevus syndrome, Bloom syndrome, ataxia-telangiectasia, and Silver–Russell syndrome (Table 6.1).

Freckles (ephelides)

Freckles or ephelides are usually 2–3 mm in diameter, reddish-tan and brown macules that appear on sun-exposed surfaces, particularly the face, neck, upper chest, and forearms (Fig. 6.2). They typically arise in early childhood on lightly pigmented individuals. Lesions tend to fade in the winter and increase in number and pigmentation during spring and summer months. Photoprotection with clothing, sunblocks, and sunscreens may decrease the summer recurrence of freckles, which are generally of cosmetic importance only. The development of progressive, widespread freckling in sun-exposed sites may suggest an underlying disorder of photosensitivity such as xeroderma pigmentosum (Fig. 6.3) (see pp. 193–196, Chapter 7). Additionally, a large number of freckles in healthy children is an independent risk factor for development of melanoma in adulthood.

Histologically, freckles demonstrate excess pigment at the basal cell layer of the epidermis. The number of melanocytes may be decreased, but those that remain are larger and show increased and more prominent dendritic processes.

Lentigo simplex

In contrast to a freckle, a lentigo is a darker macule with more uniform color that does not demonstrate seasonal variation. A lentigo may be 2–5 mm in diameter and arise on any site on the skin or mucous membranes. Because it is rare to observe the presence of merely one lentigo, the plural term 'lentigines' is often used in clinical practice (see Figs 6.2, 6.4, 6.6).

Lentigo simplex commonly occurs during childhood and does not show a predilection for sun-exposed surfaces. The lentigines of lentigo simplex range from brown to black and may be indistinguishable clinically from junctional pigmented nevi.

Microscopically, lentigo simplex shows elongation of the rete ridges, an increase in concentration of melanocytes in the basal



Fig 6.1 Café-au-lait spots. **(a–c)** This 16-year-old girl with neurofibromatosis had multiple café-au-lait spots since early childhood. **(a)** Her axilla demonstrates a 4 cm diameter café-au-lait spot and diffuse freckling. **(b)** At puberty she began to develop widespread neurofibromas. Note the variable size of the dermal tumors on her abdomen. **(c)** Cutaneous neurofibromas also erupted on her nipples. Note the extensive freckling on her breasts. **(d)** In the center of a large café-au-lait spot, which was present at birth, this 6-year-old girl developed a spongy tumor. Skin biopsy of the mass demonstrated a neurofibroma. Note the dark-brown, pigmented nevus within the café-au-lait spot. **(e)** A large, unilateral café-au-lait spot was noted at birth on this infant's abdomen. She subsequently developed other findings typical of Albright syndrome. **(f)** This healthy 8-year-old boy had a large segmental café-au-lait macule which was unchanged from birth.

layer, an increase in melanin in both melanocytes and basal keratinocytes, and melanophages in the upper dermis.

Several special variants of lentigo simplex are recognized, which include lentiginosis profusa, LEOPARD syndrome (multiple lentigines syndrome), and speckled lentiginous nevus.

Lentiginosis profusa

Lentiginosis profusa is characterized by the presence of diffuse, multiple, small, darkly pigmented macules from birth or infancy. Occurrence is usually sporadic, and children are otherwise healthy and develop normally. This entity must be differentiated from LEOPARD syndrome, in which diffuse lentigines are associated with multisystem disease.

LEOPARD syndrome

In LEOPARD syndrome, the lentigines (L) are tan or brown, first appear in early infancy, and increase in number throughout childhood (Fig. 6.4). Axillary freckling and café-au-lait spots appear frequently. Other anomalies, which are suggested by the LEOPARD mnemonic and occur to a variable degree, include electrocardiographic conduction abnormalities (E); ocular hypertelorism (O); pulmonic stenosis (P); abnormal genitalia (A); growth retardation (R); and neural deafness (D). This disorder is inherited as an autosomal-dominant trait. LEOPARD syndrome is caused by a mutation in the *PTPN1* gene which encodes for SHP-2, a protein tyrosinase phosphatase. In both lentiginosis profusa and LEOPARD syndrome the mucous membranes are spared. In a related disorder called LAMB syndrome, multiple lentigines are associated with atrial myxoma (A), cutaneous papular myxomas (M), and blue nevi (B).

Speckled lentiginous nevus

Speckled lentiginous nevus, or nevus spilus, presents at birth as a discrete tan or brown macule, which becomes dotted with darker, pigmented macules during childhood (Fig. 6.5). The light-brown patch demonstrates histologic changes typical of lentigo simplex, while the dark, pigmented macules show nests of nevus cells at

Café-au-lait spots		
Disorder	**Other skin findings**	**Systemic involvement**
Neurofibromatosis	Axillary freckling, Lisch nodules (iris), neurofibromas	Skeletal abnormalities, neurologic involvement
Albright syndrome	Few large café-au-lait spots	Precocious puberty in girls, polyostotic fibrous dysplasia
Watson syndrome	Axillary freckling	Pulmonary stenosis, mental retardation
Silver–Russell dwarfism	Hypohidrosis in infancy	Small stature, skeletal asymmetry, clinodactyly of 5th finger
Ataxia-telangiectasia	Telangiectasia in bulbar conjunctivae and on face, sclerodermatous changes	Growth retardation, ataxia, mental retardation, lymphopenia, IgA, IgE, lymphoid tissue, respiratory infections
Tuberous sclerosis	Hypopigmented macules, shagreen patch, adenoma sebaceum, subungual fibromas	Central nervous system, kidneys, heart, lungs
Turner syndrome	Loose skin, especially around the neck, lymphedema in infancy, hemangiomas	Small stature, gonadal dysgenesis, skeletal anomalies, renal anomalies, cardiac defects
Bloom syndrome	Telangiectatic erythema of cheeks, photosensitivity, ichthyosis	Short stature, malar hypoplasia, risk of malignancy
Multiple lentigines (LEOPARD syndrome)	Lentigines, axillary freckling	Electrocardiogram abnormalities, ocular hypertelorism, pulmonic stenosis, genital abnormalities, growth retardation, sensorineural deafness
Westerhof syndrome	Hypopigmented macules	Growth and mental retardation

Table 6.1 Café-au-lait spots

the dermal–epidermal junction. The risk of malignant change is unknown, but may be increased, as in small congenital pigmented nevi.

Peutz–Jeghers syndrome

Peutz–Jeghers syndrome is an autosomal dominant disorder characterized by diffuse, small, slate-gray to black macules on the skin and mucous membranes at birth or during early childhood. Lesions increase in number throughout childhood. The face is most commonly involved, in particular the vermilion border of the lips and buccal mucosa, but macules may appear on the hands, arms, trunk, and perianal and genital skin (Fig. 6.6). Axillary freckling may also occur. Cutaneous lesions may either occur alone or be associated with intestinal polyposis usually of the small bowel. Although the risk of malignant change in the gastrointestinal tract is low, polyps may act as a lead point for intussusception and consequently result in bleeding or obstruction.

Although the pigmented lesions in Peutz–Jeghers syndrome are clinically indistinguishable from lentigines, the histology reveals increased pigmentation only in the basal cell layer. Some



Fig 6.2 Freckles and lentigines. **(a)** This fair adolescent girl with a history of extensive sun exposure developed widespread freckles in sun-exposed areas of her face, upper trunk, and extremities. Note the darker macules on her lower vermillion border and right upper lip which persisted in the winter and were typical of solar lentigines. She also had a few small acquired pigmented nevi scattered in sun-exposed areas. **(b)** A 13-year-old boy had similar lesions on his shoulders.







Fig 6.3 Xeroderma pigmentosum. **(a)** This adolescent was exquisitely sensitive to sunlight and developed widespread solar lentigines in sun-exposed areas. Note the actinic cheilitis on her lower lip. **(b)** An 8-year-old boy with developed almost confluent solar lentigines, actinic keratoses, and squamous cell carcinomas such as the crusted plaques on his upper back and **(c)** face. He also had a persistent keratitis with scarring.



Fig 6.4 Lentigo. Multiple lentigines persisted all year round on the face, upper trunk, and extremities of this 13-year-old boy with LEOPARD syndrome. The mucous membranes were spared, but he had lip involvement, axillary freckling, and multiple café-au-lait spots. His sister, father, and grandfather had similar cutaneous findings.

investigators have found increased numbers of melanocytes, which suggests that this disorder may represent a distinct form of epidermal melanosis. Some cases of Peutz–Jeghers syndrome have been associated with mutations in the *STK11/LKB1* gene on chromosome 19p13.3, which encodes a serine-threonine protein kinase.

Cutaneous macules may become disfiguring and typically respond well to destructive measures, such as gentle liquid nitrogen freezing or carbon dioxide laser ablation. Pigmented-lesion lasers are a safe, effective, and relatively painless therapeutic alternative.

Solar lentigines

Solar lentigines usually do not become apparent until the 4th and 5th decades of life, although they may appear in later childhood or adolescence, particularly in lightly pigmented individuals who spend extensive time outdoors. These irregularly shaped, darkly pigmented macules range from a few millimeters to a few centimeters in diameter and appear on sun-exposed skin. Although the risk of malignant degeneration is minimal, they provide a marker of significant sun exposure. Children and parents should be counseled regarding the cumulative risk of actinic damage and use of protective clothing and sunscreens.

Becker nevus

Becker nevus (hairy epidermal nevus) typically develops as a unilateral patch of hyperpigmentation on the shoulder, chest or back although any skin site may be involved. This common lesion is usually followed by overlying hypertrichosis within 2 years and occurs most frequently in boys (Fig. 6.7). Pigmentation is usually uniform and well demarcated, but reticulated patches may be present. The coarse, long hairs may extend beyond the area of hyperpigmentation.

Histologically, the epidermis demonstrates acanthosis and rete ridge elongation in association with increased pigment in the basal cell layer and melanophages in the upper dermis. Smooth muscle bundles in the dermis may be increased in some cases, reminiscent of changes observed in congenital smooth muscle hamartomas.

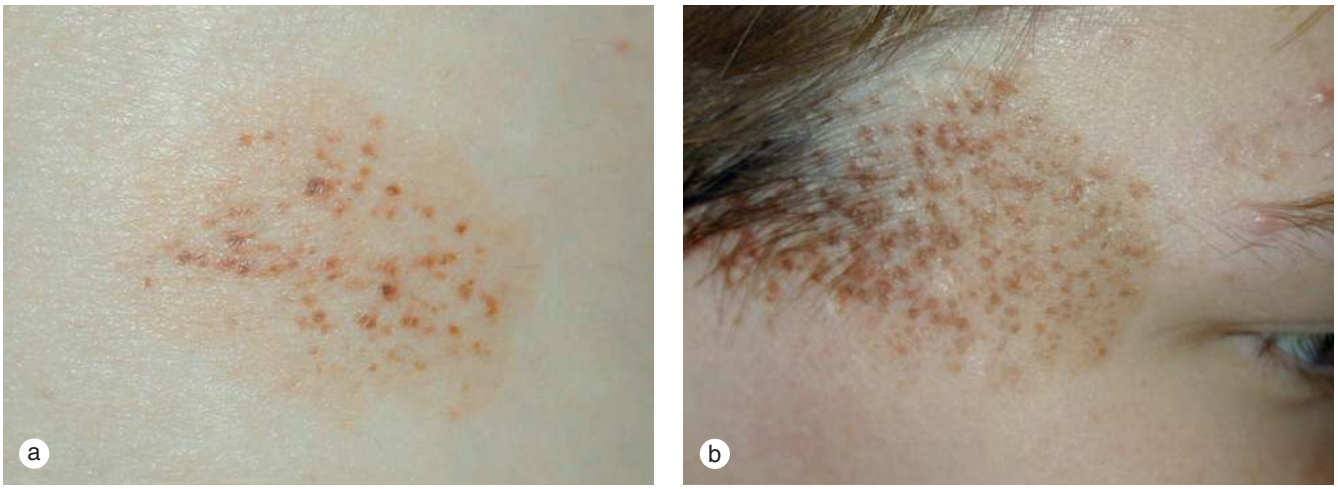


Fig 6.5 Nevus spilus. These speckled nevi were unchanged since they were noted at birth. Note the subtle tan background studded with dark macules on the **(a)** leg and **(b)** temple of these school-age children.

As in other epidermal melanoses, gentle destructive measures may result in improvement of hyperpigmentation. Use of photoprotection decreases darkening from sun exposure during the summer months. Bleaching agents containing hydroquinone (e.g. Solaquin Forte®, Eldoquin, Glyquin, Melanex®), or azelaic acid may also be effective.

However, patients should be made aware that inadvertent contact of these drugs with normal contiguous skin may result in hypopigmentation. Pigmented-lesion lasers are also effective for eradicating excess pigment in Becker nevus but recurrence may occur within 1–2 years. Shaving, depilatories, and electrolysis may be helpful for nevi with prominent hair.

Acanthosis nigricans

Acanthosis nigricans is marked by brown-to-black hyperpigmentation within distinctive velvety or warty skin in intertriginous areas. A number of clinical variants are recognized. An inherited variant usually erupts during infancy or childhood, but may also occur at puberty (Fig. 6.8a). Lesions tend to intensify in adolescence and may fade somewhat during adulthood. Inheritance is usually autosomal dominant and cutaneous findings may be associated with insulin resistance. An endocrine variant is usually associated with a pituitary tumor or polycystic ovary syndrome and insulin resistance. Obesity is a variable feature. A malignant variant can often be differentiated from other variants of acanthosis nigricans by its extensive and more florid lesions, rapid progression, and onset usually in middle age and rarely in childhood. Associated tumors include gastric carcinoma, lymphoma, Hodgkin disease, and osteogenic sarcoma. Idiopathic acanthosis nigricans is the most common variant (Fig. 6.8b–e). While not associated with a specific endocrine disorder, this variant often occurs in obese individuals with insulin resistance who are at significant risk for type II diabetes. Pigmentation may decrease after puberty, particularly in patients who undergo weight reduction. Drug-induced acanthosis nigricans may occur with nicotinic acid, diethylstilbestrol, oral contraceptives, and exogenous glucocorticoids. Recently acanthosis nigricans has also been reported in a subset of patients with Crouzon craniosynostosis due to a mutation in the *FGFR3* gene encoding for fibroblastic growth factor receptor 3 protein.



Fig 6.6 Peutz–Jeghers syndrome. This smiling, 12-year-old girl developed progressive lentigines on her face, particularly her lips, in early childhood. She also has involvement of the extremities, trunk, and mucous membranes.



Fig 6.7 Becker nevus. Progressive, mottled hyperpigmentation began at 13 years of age and was followed by the development of dark, coarse hair on the back of this 17-year-old boy.



Fig 6.8 Acanthosis nigricans. **(a)** Progressive, leathery thickening of the skin and hyperpigmentation developed on the face, neck, chest, back, and flexures of this healthy 9-year-old boy with familial acanthosis nigricans. Note the symmetric patches on his chin and cheeks. **(b)** This healthy toddler also with benign familial acanthosis nigricans developed progressive generalized thickening of the skin noted here on the abdomen, arms, and legs. **(c–e)** Symmetric, velvety patches appeared over the bony prominences and flexures of this obese, dark-pigmented adolescent with 'benign' acanthosis nigricans. Lesions were most prominent over **(c)** the knuckles, **(d)** axilla, and **(e)** neck. A light-pigmented obese adolescent developed similar lesions most prominent on her **(f)** neck.

Although acanthosis nigricans is most intense in skin creases of the neck, axilla, and groin, it may also be present on skin over bony prominences, including the knuckles, elbows, knees, and ankles. In cases of malignant acanthosis nigricans, mucous membranes may be involved.

Histopathology demonstrates hyperkeratosis, minimal acanthosis, and marked papillomatosis. Although there may be a slight increase in melanin in the basal cell layer, hyperpigmentation is likely due to compact hyperkeratosis.

Melasma

Melasma occurs as brown to brown-gray patches typically on the face but may also occur on the forearms and chest. The distribution is often symmetric and occurs primarily in pubertal girls and women (Fig. 6.9) although adolescent boys may also be affected. While melasma is usually idiopathic, it can be associated with pregnancy or the ingestion of oral contraceptives. Lesions tend to increase in size and degree of hyperpigmentation after sun exposure.

Histologically, epidermal and dermal melanization may occur, with many patients demonstrating pigment in both sites. An increased number of epidermal melanocytes is observed and increased pigment is found in epidermal keratinocytes and dermal melanophages.

Clinically, melasma must be differentiated from postinflammatory hyperpigmentation and phytophoto contact (berloque) dermatitis. Berloque dermatitis frequently appears after sun exposure of skin with inadvertent application of a photosensitizer such as musk ambrette, a common component of perfumes.

Pigmentation often wanes after pregnancy or discontinuation of oral contraceptives. However, treatment with potent topical sunscreens, bleaching agents (hydroquinone) or pigmented-lesion lasers may be helpful.



Fig 6.9 Melasma. Diffuse, mottled, tan pigmentation developed on the forehead and cheeks of this young woman shortly after she began taking oral birth-control pills. Note the wrinkling related to extensive sun exposure that undoubtedly exacerbated the melasma.

Dermal melanosis

Mongolian spots

Mongolian spots are poorly circumscribed, slate-gray to blue-green congenital macules or patches (Fig. 6.10a,b). Lesions range from a few millimeters to over 20 cm in diameter and are typically found on the trunk and proximal extremities of 80–90% of black infants, 75% of Asians, and 10% of white infants. Nearly 75% of all mongolian spots appear on the lumbosacral region. Mongolian spots do not require therapy and usually fade or are camouflaged by normal pigment by 3–5 years of age. When lesions are clinically confused with a pigmented nevus, skin biopsy reveals characteristic melanocytes in the dermis of a mongolian spot.

Special variants of the mongolian spot include the nevus of Ota and nevus of Ito which tend to persist into adult life.

Nevus of Ota

Nevus of Ota (nevus fuscoceruleus ophthalmomaxillaris) represents a unilateral, patchy, dermal melanosis of the face in the distribution of the trigeminal nerve (Fig. 6.10c,d). Although most cases are sporadic, rare family clusters have been reported. Lesions tend to be slate-gray to brown in color with a 'powder-blast burn' appearance. The forehead, temple, periorbital area, cheek, and nose are commonly involved. Rarely, pigmentation is bilateral and large areas of the face and oral mucous membranes are affected. Melanin pigment involves the eye in about half the cases. About 50% of lesions are present at birth, and the remainder appear during puberty. Although lesions are most common on Asians and blacks, all races are affected, and the majority of patients are female.

Nevus of Ito

Nevus of Ito (nevus fuscoceruleus acromiodeltoideus) is a similar pathologic process to nevus of Ota in which unilateral pigmentation is located over the supraclavicular, deltoid, and scapular regions. Although a nevus of Ito usually occurs as an isolated lesion, it may be accompanied by a nevus of Ota.

Although nevus of Ito and nevus of Ota are benign dermal melanoses rare cases of malignant degeneration have been reported. Extensive lesions are amenable to corrective therapy, usually by cosmetic camouflage. Treatment with Q-switched ruby and other Q-switched pigmented lesion lasers results in safe, effective destruction of abnormal pigment with little risk of scarring or recurrence.

Incontinentia pigmenti

Incontinentia pigmenti is an inherited, multisystem disorder defined by reticulated hyperpigmentation in a 'splashy' pattern (see Fig. 2.62). An inflammatory phase in the newborn precedes the pigmentary change in over 90% of affected children.

Nevoid hyperpigmentation (hypopigmentation)

Nevoid hyperpigmentation (and hypopigmentation) should be distinguished from incontinentia pigmenti and presents with localized or diffuse whorled hyperpigmentation *without* antecedent inflammation (Fig. 6.11). These children may demonstrate variable genetic mosaicism in the skin and occasional involvement of multiple organ systems. Localized lesions are quite common and only rarely associated with systemic disease or genetic transmission. These skin lesions may be segmental or follow the lines of Blaschko and likely represent somatic mutations which occur late in embryologic development. Widespread nevoid pigmentation probably occurs early in development and is more likely to be associated with systemic involvement and genetic transmission. Consequently, affected children, particularly those with disseminated cutaneous lesions, require a careful evaluation for neurocutaneous, skeletal, dental, cardiac, and other anomalies.

Postinflammatory hyperpigmentation

The most common cause of increased pigmentation is postinflammatory hyperpigmentation. This alteration in normal pigmentation follows many inflammatory processes in the skin, such as a diaper dermatitis, insect bites, drug reactions, and traumatic injury. Lesions are usually localized and typically follow the distribution of the resolving disorder (Fig. 6.12). Although epidermal melanocytes appear normal, aberrant delivery of melanin to the surrounding keratinocytes results in deposition of pigment in dermal melanophages. Areas of hyperpigmentation are more marked in darkly pigmented children. No therapy is necessary, and lesions usually fade over several months.

Fixed drug eruption

A special subset of drug reactions known as a fixed drug eruption produces unusual persistent hyperpigmentation, particularly on the face, genitals, and scattered lesions on the trunk and extremities (see Fig. 7.4). After exposure to certain medications, such as minocycline, ibuprofen (and other non-steroidal anti-inflammatory drugs), phenobarbital, and phenolphthalein (in laxatives), patients develop acutely inflamed, dusky-red, edematous, round to oval, 1–3 cm diameter plaques, which may become frankly bullous centrally. These target lesions are clinically and histologically indistinguishable from target lesions found in erythema multiforme minor (von Hebra). When the drug is discontinued the reaction subsides to leave residual postinflammatory pigmentation. On re-exposure to the inciting agent, new lesions may appear, but the old lesions recur in the same 'fixed' spots. The reactivity of the skin seems to reside in the dermis. This notion is based upon the observation that normal epidermis grafted over affected dermis becomes reactive, whereas involved epidermis loses its sensitivity once grafted onto normal dermis. Although the pathogenesis is not understood, investigators have proposed that the inciting drug triggers keratinocytes to release cytokines that ultimately activate epidermal T-lymphocytes.

Acquired nevomelanocytic nevi

Acquired nevomelanocytic nevi, also referred to as pigmented nevi and pigmented moles, begin to develop in early childhood as small, pigmented macules 1–2 mm in diameter. In early, flat lesions, nevus cells are located at the dermal–epidermal junction and are called junctional nevi (Fig. 6.13a). As nevi slowly enlarge and become papular, nevus cells migrate into the dermis to become compound nevi (Fig. 6.13b). Many nevi become fleshy or pedunculated over a period of years, particularly those on the upper trunk, head, and neck. Histopathology of these nevi



Fig 6.10 Mongolian spot. **(a)** Widespread and confluent Mongolian spots were noted at birth on this premature black infant. The pigment was slate-gray in color. **(b)** Note the large Mongolian spot on the left hip and abdomen of this light-pigmented infant. **(c)** A nevus of Ota involved the forehead, cheek, and contiguous scalp of an otherwise healthy black infant. The lids and conjunctivae were spared. **(d)** Note the mottling on this nevus of Ota 2 months after the first treatment with the Q-switched ruby laser. **(e)** This healthy toddler shows a nevus of Ito on the back.

demonstrates nevus cells restricted to the dermis, hence the so-called intradermal nevus.

During puberty, nevi increase in darkness, size, and number. However, most normal acquired nevomelanocytic nevi do not exceed 5 mm in diameter, and retain their regularity in color, contour, texture, and symmetry. The majority of nevi appear on sun-exposed areas, but lesions may involve the palms, soles, buttocks, genitals, scalp, mucous membranes, and eyes. Generally, nevi change slowly over months to years and warrant observation only.

Sudden enlargement of a nevus, with redness and tenderness, may occur because of an irritant reaction or folliculitis. Trauma from clothing or scratching may produce hemorrhage or crust formation that heals uneventfully. Another more gradual change



Fig 6.11 Nevoid hyperpigmentation. A healthy 3-year-old boy was noted to have congenital hyperpigmented patches with segmental and Blaschkoid feature.



Fig 6.12 Postinflammatory hyperpigmentation. Marked hyperpigmentation developed in this 5-year-old boy from recurrent insect bites. Although the pigment faded somewhat, it was still noticeable 2 years later.

that causes concern in patients and parents is the appearance of a hypopigmented ring and mild local pruritus around a benign nevus (Fig. 6.14). This so-called halo nevus is caused by a cytotoxic T-lymphocyte reaction against both nevus cells and contiguous melanocytes. As a result, the nevus tends first to lighten and then disappear completely, and the halo eventually re-pigments. Occasionally, halo nevi are associated with vitiligo or the loss of pigmentation in areas of normal skin that have no nevi.

As long as the clinical appearance of a nevus is unremarkable, excision is unnecessary. However, a number of changes in pigmented lesions may portend the development of melanoma, including:

- Change in size, shape, or contours with scalloped, irregular borders
- Change in the surface characteristics, such as flaking, scaling, ulceration, bleeding or the development of a small, dark, elevated papule or nodule within an otherwise flat plaque
- Change in color, with the appearance of black, brown, or an admixture of red, white, or blue
- Burning, itching, or tenderness, which may be an indication of an immunologic reaction to malignancy.







Fig 6.13 Acquired nevomelanocytic nevus. **(a)** This brown macule on the labia of a 3-year-old girl was flat on palpation. Darkening and increase in size of the macule prompted a biopsy, which revealed a benign junctional nevus. **(b)** A shave excision of this facial nodule showed a compound nevomelanocytic nevus. **(c)** This young adult had a brown papule in adolescence which became fleshy and lost most of the pigment. Biopsy showed an intradermal nevus.



Fig 6.14 Halo nevus. Large, depigmented halos surround innocent-looking nevi on the back of a 9-year-old boy.



Fig 6.16 Atypical pigmented nevi. This adolescent with a family history of malignant melanoma and multiple individuals with atypical moles demonstrates numerous nevi with variable size, shape, and pigmentation in sun-exposed areas.

Melanomas

Fortunately, melanomas are rare in children. However, the incidence is increasing, and curative treatment is contingent on early diagnosis and prompt excision. A keen awareness of diagnostic features is important.

Melanomas in children may occur *de novo* or within acquired or congenital nevi (Fig. 6.15a,b; see Fig. 2.85 and discussion in Chapter 2 for melanoma in congenital nevi). Family history of malignant melanoma and the presence of multiple, unusually large, and irregularly pigmented, bordered, and textured nevi carries a high lifetime risk of melanoma, which may approach 100%. Malignant melanoma in this hereditary setting is referred to as familial atypical mole syndrome (familial dysplastic nevus syndrome; Fig. 6.16). During early life, children in such families may develop only innocent-looking nevi. However, the predisposition for the development of malignant melanoma is autosomal dominant, which imparts a 50% risk to children of affected parents. The presence of a large number of nevi, particularly on the scalp and sun-protected sites in prepubertal children, may be an early marker for atypical mole syndrome. Children in these high-risk families must be observed carefully for the development of atypical nevi, especially throughout adolescent years. Changing nevi of unusual appearance must be biopsied to exclude malignant degeneration. As many as 5% of light-pigmented individuals with a negative family history of melanoma may develop at least one atypical mole in a lifetime. Patients with sporadic atypical mole syndrome (i.e. without a family history of melanoma) should also be observed for malignant changes although the risk of melanoma is probably lower than in patients with a positive family history of melanoma.

A rare cause of melanoma in the pediatric age group is transplacental spread of maternal melanoma. Neonates born to mothers with a history of melanoma must be examined and followed carefully. Conversely, mothers of infants born with melanoma must be examined thoroughly for signs of malignancy.

Differential diagnosis of childhood melanoma includes congenital and acquired nevomelanocytic nevi, the blue nevus (a small,





Fig 6.15 Melanoma. **(a)** This lesion shows the irregularity of outline, color, and thickness typical of a melanoma. **(b)** A black papule developed in the border of a 3.5 × 1.5 cm congenital pigmented nevus. Biopsy showed a thin melanoma, and the lesion was excised with a 1 cm margin.

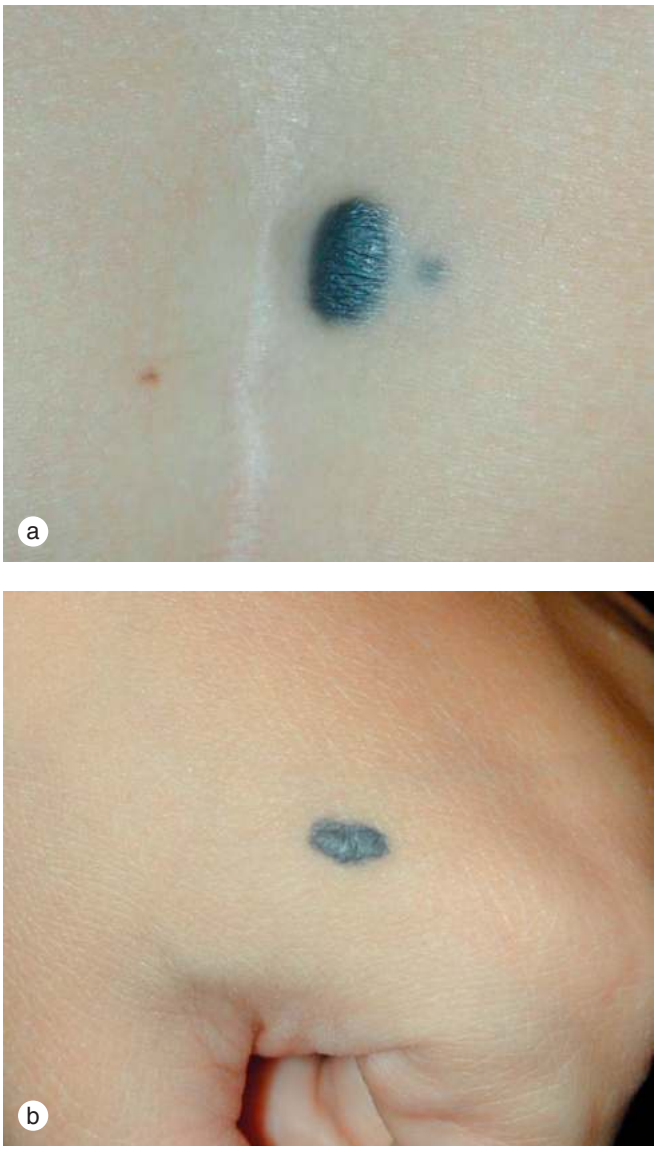


Fig 6.17 Blue nevus. The blue papules are made up of deep nevus cells. **(a)** This 3-year-old girl had a blue nevus appear at 1 year of age above the gluteal cleft followed by a new smaller nevus 6 months later. She had a small sinus tract just below the nevus which was removed shortly after birth. **(b)** An adolescent boy had a blue papule on the left hand for a year. After a few months of growth the nevus stabilized.

firm, blue papule that consists of deep nevus cells; Fig. 6.17a,b), traumatic hemorrhage (especially under nails, on heels, or on mucous membranes), and a number of innocent vascular lesions such as pyogenic granuloma or hemangioma.

Spindle and epithelial cell nevus

Spindle and epithelial cell nevus is an innocent nevomelanocytic nevus that may be clinically and histologically confused with malignant melanoma (Fig. 6.18a–e). This type of nevus is more commonly known as a Spitz nevus named after Dr Sophie Spitz, who first described this nevus histologically in 1948, Initially, Spitz nevus was also referred to as 'benign juvenile melanoma.' However, this term should be discarded, because 'melanoma' is misleading and these lesions have also been described in adults. Spitz nevi frequently appear as rapidly growing, dome-shaped, red papules or nodules on the face or extremities. Occasionally they contain large quantities of melanin and may appear brown or black. If the lesion has clinical features of an innocent acquired nevus, it can be observed. However, early rapid growth may prompt the clinician to obtain a biopsy. In most histopathologic specimens, malignant melanoma can readily be excluded. Consequently, simple excision is usually adequate.

Diffuse hyperpigmentation

Diffuse hyperpigmentation has rarely been reported as progressive familial hyperpigmentation. Affected infants are born with splotches of macular hyperpigmentation that slowly increase in size and number to involve much of the skin surface. This can usually be differentiated from the normal pigmentary darkening that occurs during the first year of life in many infants, particularly dark-skinned infants. Generalized bronze pigmentation may develop after phototherapy for hyperbilirubinemia, particularly in infants with a high conjugated bilirubin component. Most cases have resolved uneventfully after discontinuation of phototherapy, but occasional hepatic abnormalities and deaths have been reported.

Generalized hyperpigmentation may also occur after exposure to certain drugs (e.g. heavy metals, phenothiazines, antimalarials) and in association with a number of systemic endocrine and inflammatory disorders. In adrenocortical insufficiency, Cushing syndrome, and acromegaly, melanotropin-stimulating hormone or other hormones capable of stimulating pigment production may cause generalized hyperpigmentation. Pigmentation may be particularly marked in skin creases on the palms and soles, as well as mucous membranes. Increased epidermal and dermal melanin also occurs in hemochromatosis, chronic renal and hepatic disease, and extensive cutaneous fibrosis associated with dermatomyositis and scleroderma.

HYPOPIGMENTATION AND DEPIGMENTATION

Partial or complete pigmentary loss may be congenital or acquired and may occur in a localized or diffuse pattern. Localized disorders of pigmentation include hypopigmented macules of the newborn, nevoid hypopigmentation (incontinentia pigmenti achromians), piebaldism, postinflammatory hypopigmentation, and vitiligo. Generalized pigmentary disturbances occur in albinism and progressive vitiligo.

Localized hypopigmentation

Hypopigmented macules

Localized hypopigmentation is characteristic of several nevoid phenomena, which include hypopigmented macules, nevoid hypopigmented anomaly (incontinentia pigmenti achromians), and piebaldism.

Although as few as 0.1% of normal newborns have a single hypopigmented macule or nevus depigmentosus (see below), these findings may be a marker for tuberous sclerosis (Fig. 6.19a,b). These macules typically appear at birth as 0.2–3 cm diameter lesions on the trunk of 70–90% of individuals with tuberous sclerosis. Only a small minority of lesions are actually lancet- or ash-leaf-shaped. They may be round, oval, dermatomal, segmental, or irregularly shaped and vary from pinpoint confetti spots to large patches over 10 cm in diameter. Although any site can be involved, truncal involvement is most common.

The identification of hypopigmented macules may be enhanced in lightly pigmented children by the use of a Wood lamp. The visible purple light that passes through the Wood filter is absorbed by melanin. In a darkened room, subtle areas of depigmentation or hypopigmentation appear bright violet, whereas normally



Fig 6.18 Spindle and epithelial cell nevus. **(a)** This red multilobulated nodule stabilized at 1 cm in diameter a month after it first appeared. **(b)** This rapidly growing brown papule on the knee of a 5-year-old girl showed histologic findings typical of a pigmented Spitz nevus. Stable lesions in healthy children were biopsy proven Spitz nevi on the **(c)** left cheek, **(d)** left ear, and **(e)** right ear. **(f)** Multiple aggregated Spitz nevi erupted on the left arm of this healthy 6-year-old girl.

pigmented skin absorbs most of the light and appears dull purple or black.

Although the majority of children with hypopigmented macules are normal, there is no reliable study to exclude systemic disease. Tuberous sclerosis is transmitted as an autosomal-dominant trait, but 25–50% of affected children represent sporadic cases with new mutations in tuberous sclerosis complex genes, *TSC1* and *TSC2*. As mutational analysis of these genes is expensive and labor-intensive affected children usually require close observation for the onset of other cutaneous findings (adenoma sebaceum, angiofibromas, or subungual fibromas) and systemic symptoms (seizures, intracranial tumors) which may be delayed for years (see Figs 5.28, 5.29). A careful family history and cutaneous examination of other family members may demonstrate subtle findings of tuberous sclerosis. The presence of asymptomatic rhabdomyomas, calcified intracranial tubers, renal angiolipomas, and cystic lesions in the kidneys and lungs also support the diagnosis in otherwise healthy-appearing individuals.

Nevus depigmentosus

The term nevus depigmentosus (achromic nevus) should probably be used to describe the majority of children with one or two hypopigmented macules and no other signs of neurocutaneous disease (Fig. 6.20). However, nevus depigmentosus has been

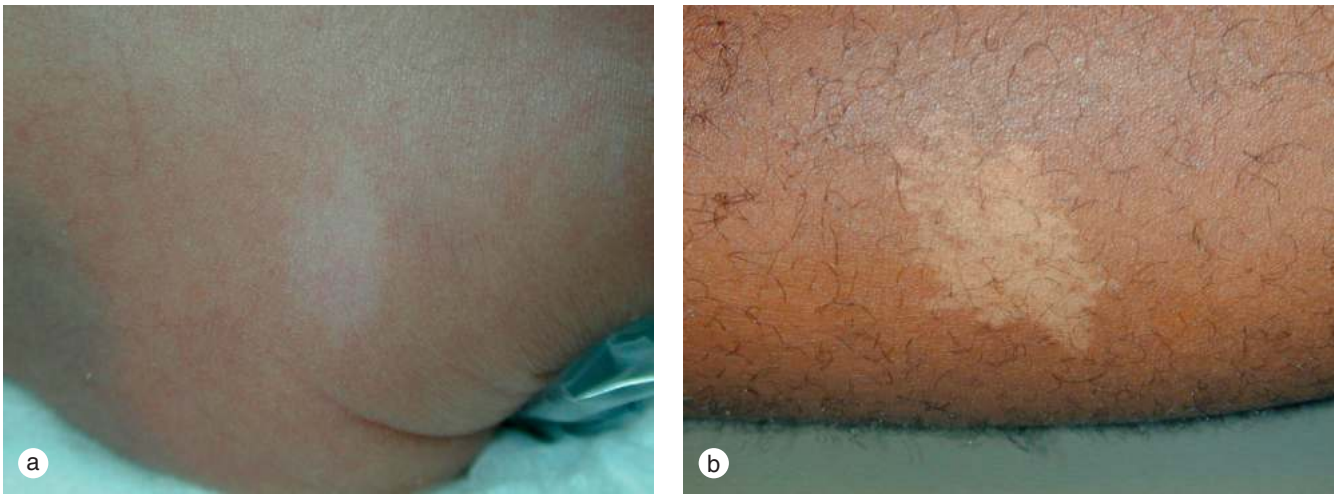


Fig 6.19 Ash leaf macules. **(a)** A subtle hypopigmented macule was discovered on the right buttock of this newborn with persistent seizures. **(b)** A congenital hypopigmented macule was present on the thigh of an 18-year-old boy with tuberous sclerosis.

reported in rare cases in association with hemi-hypertrophy and mental retardation without findings of tuberous sclerosis. Hypopigmented macules on cosmetically important areas are readily camouflaged by rehabilitative cosmetics such as Dermablend® and Covermark®.

Nevus anemicus

Nevus anemicus is often misdiagnosed as an ash leaf macule. This congenital patch, usually located on the trunk, appears pale compared to surrounding normal skin (Fig. 6.21). However, a Wood lamp examination demonstrates the presence of normal pigment. Rubbing the area results in erythema from vasodilatation in surrounding normal skin, while the lesion remains unchanged. A persistent increase in vascular tone, which results in maximal vasoconstriction in the nevus, seems to account for this phenomenon.

Nevoid hypopigmentation (incontinentia pigmenti achromians)

Nevoid hypopigmentation (incontinentia pigmenti achromians, also known as hypomelanosis of Ito, named after Dr Minor Ito who first described the disorder in 1952) is characterized by congenital hypopigmentation with a marble-cake pattern. This dyspigmentation, which follows embryonic cleavage lines known as the lines of Blaschko, resembles the pattern of hyperpigmentation found in incontinentia pigmenti (Fig. 6.22).

Genetic mosaicism has been demonstrated in some patients when gene markers from hypopigmented skin are compared with those of normal skin and peripheral lymphocytes. The genetic mutations are quite varied and unrelated to incontinentia pigmenti. As a consequence, nevoid hypopigmentation is probably a better term for these skin lesions.

Although most children with nevoid hypopigmentation are healthy and develop normally, some patients manifest associated neurologic, developmental, dental, skeletal, and ophthalmologic anomalies. Affected children require a careful medical, neurologic, and ocular examination, as well as close neurodevelopmental observation with further in-depth studies tailored to clinical findings. As with nevoid hyperpigmentation, the extent of cutaneous lesions may correlate with the onset of mutations during embryologic development; more extensive cutaneous lesions may be a marker for earlier embryologic defects and a higher risk of systemic involvement and genetic transmission.



Fig 6.20 Nevus depigmentosus. At birth an otherwise healthy infant was noted to have a hypopigmented patch on the suprapubic area.



Fig 6.21 Nevus anemicus. This adolescent had a congenital pale patch on his back which was initially diagnosed as nevus depigmentosus. Note that the patch becomes better defined after scratching the surrounding skin. This patch tans normally in the summer and does not enhance with Wood light.



Fig 6.22 Nevoid hypopigmentation. This healthy 6-month-old boy had congenital hypopigmented patches on the right arm, chest, and both sides of the abdomen which followed the lines of Blaschko.



Fig 6.24 At birth a patch of mottled hypopigmentation was discovered on this infant's forearm. Also note the white forelock characteristic of piebaldism. There was a family history of similar skin lesions associated with hearing loss and eye findings characteristic of Waardenburg syndrome.

Piebaldism

Piebaldism (partial albinism) is a rare, autosomal-dominant disorder characterized by a white forelock and circumscribed congenital leukoderma (Fig. 6.23a–c).

The typical lesions include a triangular patch of depigmentation and white hair on the frontal scalp, with the apex of the patch pointing toward the nasal bridge as well as hypopigmented or depigmented macules on the face, neck, ventral trunk, and/or flanks. However, depigmented patches may involve any part of the skin surface. Within areas of decreased pigmentation, scattered patches of normal pigment or hyperpigmentation may occur. The lesions are stable throughout life, although some variability in pigmentation may occur with sun exposure. Special variants of piebaldism include Waardenburg syndrome (Fig. 6.24), an autosomal-dominant disease in which leukoderma is associated with lateral displacement of the inner canthi and inferior lacrimal ducts, a flattened nasal bridge, and sensorineural deafness, and Wolf syndrome, an autosomal-recessive disorder associated with multiple neurologic defects.

Piebaldism is caused by a mutation in the *KIT* proto-oncogene which is required for the proliferation and migration of melanoblasts from the neural crest in murine embryogenesis. Waardenburg syndrome has been divided into two variants based on mutations in different but related genes, *PAX 3* and *MITF*.

Postinflammatory hypopigmentation

Postinflammatory hypopigmentation may appear after any inflammatory skin condition. Patches are usually variable in size and irregularly shaped, although they may be remarkably symmetric in disorders such as seborrheic and atopic dermatitis (see Figs 3.27, 3.28, 3.29). Areas of pigmentary alteration are usually seen in

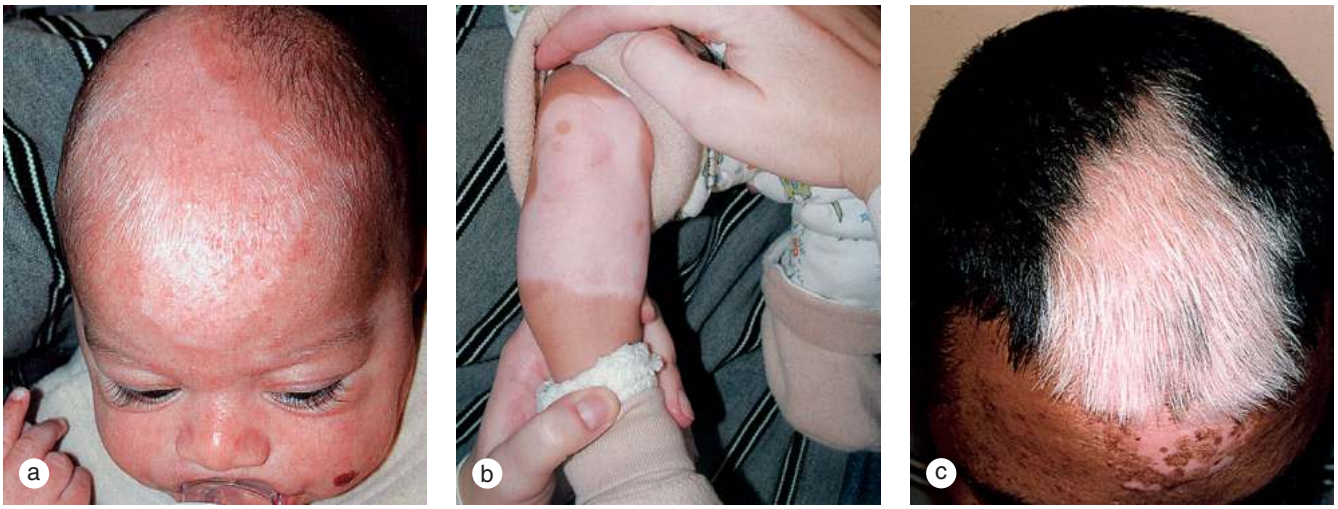


Fig 6.23 (a) This healthy infant had a large patch of white skin and hair on the mid scalp extending to the forehead. **(b)** He also had a depigmented patch on his right leg which was studded with normally pigmented and hyperpigmented macules. **(c)** His father, grandfather, and uncle had similar lesions on the scalp and scattered lesions on the trunk and extremities.

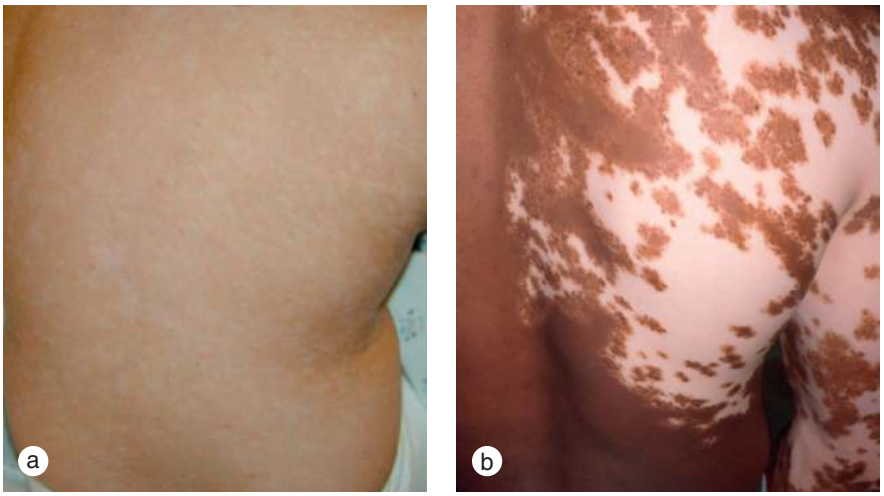


Fig 6.25 (a) This 10-year-old girl had pityriasis lichenoides with chronic inflammatory papules resulting in post-inflammatory hypopigmentation. Note the indistinct borders and red scaly inflammatory papules **(b)** This adolescent boy with vitiligo had sharply demarcated depigmented macules without signs of inflammation.

association with the primary lesions of the underlying disorder. Concomitant hyperpigmentation is also a frequent finding.

Postinflammatory hypopigmentation may be differentiated from vitiligo (Fig. 6.25a), which demonstrates well-demarcated depigmentation, and nevus depigmentosus, which appears at birth. In addition postinflammatory hypopigmentation may be differentiated from tinea versicolor (see Fig. 3.51) which typically forms lesions that are uniform in size and shape, minimally scaly, and prominent in seborrheic areas on the trunk.

Vitiligo

Vitiligo is an acquired disorder of pigmentation in which there is complete loss of pigment in involved areas. Lesions are macular and usually appear progressively in a characteristic distribution around the eyes, mouth, genitals, elbows, hands, and feet (Figs 6.25b, 6.26a–e). Spontaneous but slow repigmentation, particularly after exposure to the summer sun, may occur from the edges of active lesions and within hair follicles, which results in a speckled appearance. Transient hyperpigmentation of the contiguous normal skin or hypopigmentation at the advancing edge may produce a trichrome, with depigmentation centrally and normal pigmentation around an area of hyper- or hypopigmentation. Histologically, melanocytes are absent in areas of vitiligo, and evidence suggests that these are destroyed by an autoimmune mechanism. Rarely, the pigment in the eye may become involved. Consequently, a thorough eye examination is performed for all patients with vitiligo.

Early in the course of vitiligo, some children respond to twice-daily applications of medium- to high-potency topical corticosteroids or the topical non-steroidal immunomodulator tacrolimus. Topical therapy may stabilize lesions in the winter until sunlight is readily available in the spring and summer. Some adolescents are pleased with the temporary camouflage provided by rehabilitative cosmetics (e.g. Dermablend®, Covermark®) and topical dyes (e.g. Chromelin®, Dy-O-Derm®, Vitadye®). Most patients with progressive vitiligo that fails to respond to sunlight or topical corticosteroids will re-pigment at least partially with phototherapy. Light therapy may be administered with an oral or topical psoralens photosensitizer and sunlight (PUVA-sol) or artificial long-wavelength ultraviolet light (PUVA). Systemic light therapy is rarely associated with cataract formation and requires diligent use of protective goggles and regular ophthalmologic follow-up. Alternatively, narrow-band UVB light therapy may achieve comparable results without the use of a photosensitizer and recent investigations have demonstrated beneficial results by combining topical therapies with light therapies. A novel and evolving approach to treating vitiligo involves epidermal cellular grafting although results can vary widely on a case-to-case basis. Although some investigators recommend autoimmune screening (antithyroid, antiadrenal, antigastrin antibodies, etc.) in patients with vitiligo, the results of studies comparing children with vitiligo with age-matched controls have been equivocal.

Vitiligo can be readily differentiated from nevoid pigmentary disorders, which are stable and usually congenital. Vitiligo is rare in infancy, but appears before 20 years of age in about 50% of affected individuals. In postinflammatory hypopigmentation, the edges are not usually crisp and careful observation reveals residual pigmentation. Tinea versicolor can also be differentiated from vitiligo by the presence of pigment and fine scale, which reveals spores and pseudohyphae on potassium hydroxide preparation (see Fig. 1.6).

Diffuse hypopigmentation

Albinism

Albinism is a heterogeneous group of inherited disorders manifested by generalized hypopigmentation or depigmentation of the skin, eyes, and hair (Fig. 6.27a–c). It occurs as an autosomal-recessive, oculocutaneous form and as an X-linked ocular variant form (Table 6.2).

In oculocutaneous albinism (OCA), both sexes and all races are equally involved. On the basis of clinical findings and biochemical markers, OCA may be divided into a number of variants. Tyrosinase-negative and tyrosinase-positive forms have been established based on the ability of plucked hairs to produce pigment when incubated in tyrosine-containing media. In tyrosinase-negative albinism, the tyrosinase enzyme is either absent or non-functional whereas tyrosinase-positive albinism is caused by a number of different defects in pigment synthesis and transport. The discovery of gene markers in some variants of albinism has allowed for specific DNA diagnosis in patients and carriers. In classic tyrosinase-negative OCA, children are born without any trace of pigment. Affected individuals have snow-white hair, pinkish-white skin, and blue eyes. Nystagmus is common, as is moderate-to-severe strabismus and poor visual acuity. Although tyrosinase-positive OCA may be clinically indistinguishable from tyrosinase-negative OCA during infancy, children with tyrosinase-positive OCA usually develop variable amounts of pigment with increasing age. Eye color may vary



Fig 6.26 Vitiligo. **(a)** Extensive depigmented patches developed on the backs of the hands of a 10-year-old girl. These patches were difficult to detect in the winter when her tan faded. **(b)** A progressive, disfiguring patch of vitiligo on the forehead of a 9-year-old girl was **(c)** well camouflaged with a corrective cosmetic. **(d)** A light-pigmented child with vitiligo developed white eyebrow hairs. **(e)** A light-pigmented 10-year-old girl with vitiligo developed white eye lashes. Note the vitiligo on her face manifested as lack of freckling on the left side of her nose and cheek.



Fig 6.27 Albinism. **(a)** This 19-year-old black man with oculocutaneous albinism already has extensive actinic damage. He works outdoors by the waterfront and has not used sunscreens. **(b)** Numerous actinic keratoses were removed from his face, upper back, and hands. The crusted plaque on the middle of his hand was a squamous cell carcinoma. **(c)** This 18-month-old boy had no detectable pigment. He had white hair, pale skin, nystagmus, and poor visual acuity.

Oculocutaneous albinism					
Disorder	**Incidence**	**Genetics**	**Pathogenesis**	**Clinical findings**	**Comments**
Tyrosinase-negative (OCA Type 1A)	1:28 000 African-Caribbeans 1:39 000 Caucasians Male = female	Autosomal recessive; tyrosinase gene on chromosome 11q14–q21	No tyrosinase activity	White hair and skin; blue-gray irides; no retinal pigment; nystagmus; poor visual acuity	Hair bulb test negative; DNA analysis available for prenatal diagnosis; no improvement with age
Yellow mutant (OCA Type 1B)	Rare, initially described in Amish, now in numerous races	Autosomal recessive; slicing of tyrosinase gene 11q14–q21	Melanocytes produce pigment, but hair-bulb test negative Hairs produce pheomelanin when incubated with L-tyrosine and cysteine	White-to-light tan skin darkens somewhat with sun and age; white hair at birth turns yellow with age; blue eyes at birth may darken with age; some retinal pigment; poor visual acuity may improve with age	
Tyrosinase-negative (OCA Type 2)	1:15 000 African-Caribbeans 1:37 000 Caucasians Male = female	Autosomal recessive; gene locus 15q11.2–q12	Some due to mutations in transport gene p with locus on chromosome 15q	White-to-cream color skin, light hair at birth darkening with age; blue, tan, hazel irides; minimal retinal pigment; nystagmus; photophobia; poor-to-fair visual acuity	Hair bulb test positive; DNA linkage analysis and mutation detection available for prenatal diagnosis; pigment may improve with age
Albinoidism	Unknown	Autosomal dominant		Marked pigment dilution of the skin may mimic tyrosinase-positive albinism, but only minimal involvement of the eyes; normal visual acuity	
Hermansky–Pudlak syndrome	Over 200 cases reported Male = female	Autosomal recessive; HPS2 gene on chromosome 10q23	Tyrosinase-positive Bleeding secondary to platelet storage pool defect Lysosomal membrane defect results in accumulation of ceroid lipofuscin in macrophages in lung and gastrointestinal tract	Creamy white to almost normal skin varying with race; cream-to-red-brown hair; blue-to-brown irides; reduced retinal pigment; nystagmus; photophobia; poor visual acuity Increased bleeding with dental procedures, surgery, childbirth; epistaxis, menorrhagia, gingival bleeding Pulmonary fibrosis, granulomatous colitis, cardiomyopathy from ceroid deposition in viscera	
Chédiak–Higashi syndrome	Rare, fewer than 100 cases reported Male = female	Autosomal recessive, high consanguinity; LYST gene on chromosome 1q42–1q43	Lysosomal storage disease involving neutrophils, melanocytes, neurons, platelets, lymphocytes	White skin; blond-to-silver hair; blue-to-brown eyes with variable retinal pigment; photophobia; strabismus Recurrent sinusitis, pneumonia Progressive neurologic dysfunction with ataxia, muscle weakness, sensory loss, seizures Pancytopenia resulting in bleeding diathesis, anemia, sepsis	Fetoscopy at 18–21 weeks reveals fetal blood cells with characteristic neutrophilic granules

Table 6.2 Oculocutaneous albinism

Oculocutaneous albinism					
Disorder	**Incidence**	**Genetics**	**Pathogenesis**	**Clinical findings**	**Comments**
Cross syndrome	Rare	Autosomal recessive		White skin; white-to-blond hair; blue-to-gray irides; poor visual acuity; microphthalmia; cataracts Spastic diplegia, mental retardation	
Griscelli syndrome	Rare	Autosomal recessive; gene maps to 15q21		Silver color hair; severe combined immunodeficiency	Microscopic examination of hairs shows clumping of pigment in hair shafts, normal melanosomes, but reduced melanocyte dendritic processes
Prader–Willi syndrome	Unknown	Sporadic	Chromosomal and molecular changes of chromosome 15 at q11–q13 region	Light skin compared with relatives; normal-to-light hair; blue-to-brown irides; variable retinal pigment, normal to slightly reduced visual acuity Neonatal hypotonic hyperphagia; obesity; developmental delay, mental retardation	
Angelman syndrome	Unknown	Sporadic autosomal recessive?	Chromosomal and molecular changes of the proximal region of chromosome 15 similar to those of Prader–Willi syndrome	Light skin compared with relatives; normal-to-light hair; blue-to-brown eyes; variable retinal pigment; normal to slightly reduced visual acuity Growth retardation, developmental delay, mental retardation, ataxia, jerky gait, seizures Dysmorphic facies (microcephaly, flat occiput, protuberant tongue)	

Table 6.2 Continued

from gray to light brown, and hair may change to blond or light brown. Most black patients acquire as much pigment as light-skinned white patients.

In both tyrosinase-positive and -negative variants of albinism, 'clear cells' are noted in the basal cell layer of the epidermis, which may represent depigmented melanocytes. Electron microscopy demonstrates the presence of small amounts of melanin and mature melanosomes in tyrosinase-positive cases, but no melanin and only early stages of melanosome development in tyrosinase-negative patients.

Patients with OCA require aggressive sun protection to prevent actinic damage and early development of basal cell and squamous cell skin cancers. Strabismus and macular degeneration may also be associated with a progressive decrease in visual acuity. Consequently, regular eye exams are important.

Although the skin and hair appear clinically normal in ocular albinism, characteristic macromelanosomes have been demonstrated by electron microscopy. This finding is a reliable marker and may be used to confirm the diagnosis and identify asymptomatic female carriers. When available, DNA analysis can also establish a specific diagnosis.

Other disorders associated with diffuse hypopigmentation

Diffuse hypopigmentation may suggest a number of systemic disorders associated with defects in melanin synthesis in the skin, hair, and eyes. Children with inborn errors of amino acid metabolism (e.g. phenylketonuria, histidinemia, and homocystinuria) often demonstrate widespread pigment dilution. Hypopigmentation of skin and hair in Menke syndrome (also known as Kinky Hair disease) results from a defect in copper metabolism that interferes with the normal activity of copper-dependent tyrosinase (see Fig. 8.10). Hypohidrotic ectodermal dysplasia and deletion of the short arm of chromosome 18 are also associated with diffuse hypopigmentation and light hair color. Finally, children with malnutrition, particularly kwashiorkor, may develop hypopigmentation, which resolves when adequate calorie and protein intake resume.

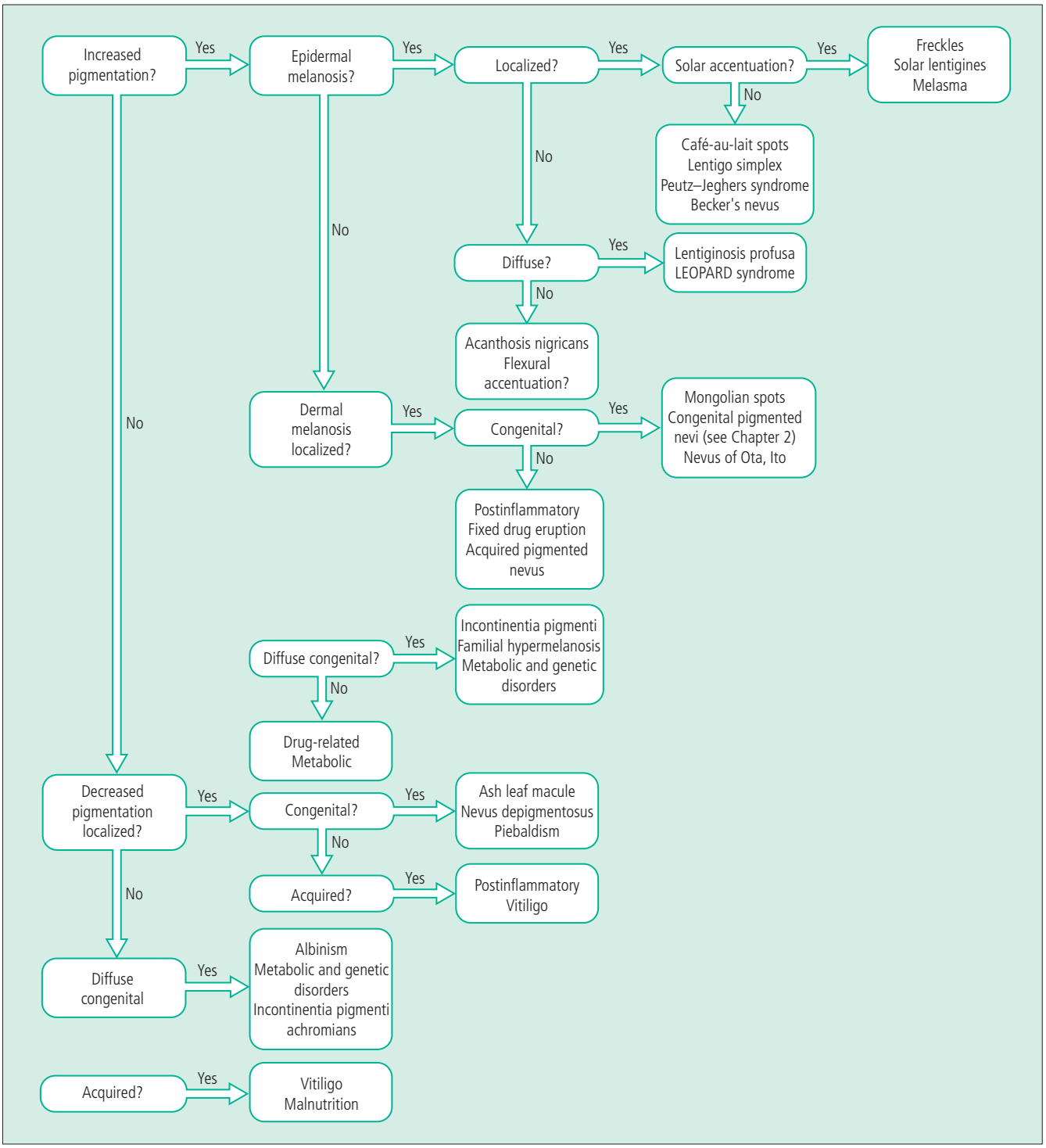


Fig 6.28 Algorithm for evaluation of disorders of pigmentation.

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Café-au-lait spot

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Chapter 7

Reactive Erythema

Bernard A. Cohen

INTRODUCTION

The term reactive erythema refers to a group of disorders characterized by erythematous patches, plaques, and nodules that vary in size, shape, and distribution. Unlike other specific dermatoses, they represent cutaneous reaction patterns triggered by a variety of endogenous and environmental agents. In children, the most common reactive erythemas include drug eruptions, urticaria, viral exanthems, erythema multiforme (EM), erythema nodosum, vasculitis, photosensitive eruptions, and collagen vascular disorders. An algorithmic approach to diagnosis for reactive erythema is summarized at the end of the chapter (see Fig. 7.58).

DRUG ERUPTIONS

Of all patients admitted to hospital, 2–3% experience an adverse drug reaction, and about half of these develop a rash. Of inpatient drug reactions, 0.1–0.3% result in death. Drug-induced rashes are also a frequent diagnostic problem in the outpatient setting. Although the skin rash often occurs alone, it may be accompanied by fever, arthritis, and other systemic findings. The incidence of drug reactions increases with increasing age and the number of medications used. Paradoxically, patients with hereditary or acquired immunodeficiency appear to be particularly prone to developing reactions from medications. For example, nearly 75% of human-immunodeficiency-virus-infected patients develop morbilliform eruptions from sulfonamides during their illness.

Over 50% of the rashes are morbilliform, followed by urticaria in 25%, fixed drug reactions in 10%, and exfoliative erythroderma, Stevens–Johnson (SJS)/toxic epidermal necrolysis (TEN), vasculitic, lichenoid, and acneiform eruptions in less than 5% each. Early recognition of drug-related rashes and discontinuation of the inciting agent may prevent progressive, life-threatening complications and certainly reassure patients, parents, and practitioners.

Morbilliform drug eruptions (including DRESS)

Morbilliform (measles-like, maculopapular, exanthematous) rashes account for the majority of drug-induced rashes. Typically, after 5–10 days of drug therapy, red macules and papules erupt on the extremities and spread centrally to involve the trunk. Not infrequently, however, the trunk is the first area to be involved and the rash spreads centripetally (Fig. 7.1). Lesions may become confluent, but the perioral and perinasal areas are often spared. Conjunctival and oral mucosal erythema may be prominent. Although the rash is often asymptomatic, pruritus may be severe. The skin may be the only organ system involved, but fever, arthralgias, and general malaise may follow. Occasionally, the rash resolves despite continuation of the medication, and rarely eruptions evolve into SJS/TEN with widespread necrosis of the epidermis.

Almost any drug can trigger a morbilliform rash. Common categories include antibiotics, anticonvulsants, and antihypertensives. Prompt diagnosis and discontinuation of the drug usually result in improvement in 1–2 days and resolution within 1 week. Occasionally, the rash does not appear until several days after the drug course has been completed.

DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) usually begins with a morbilliform eruption 2–6 weeks after initiation of the inciting medication. Lesions first appear on the face, upper trunk, and proximal extremities often with follicular accentuation and disseminate quickly. Edema may be intense resulting in the formation of vesicles, bullae, and pustules. High fever and multisystem involvement defines this disorder which is most often triggered by aromatic anticonvulsants phenytoin, carbamazepine, and phenobarbital (known in the past as anticonvulsant hypersensitivity syndrome), as well as lamotrigine, sulfonamides, and minocycline. Hepatitis, which may rarely be fulminant, generalized lymphadenopathy, myocarditis, pneumonitis, nephritis, thyroiditis, and meningoencephalitis, may develop.

Although the pathogenesis of DRESS is not fully understood, the reaction is thought to occur in genetically predisposed individuals who have a reduced capacity to metabolize arene oxide metabolites. Toxic metabolites accumulate and activate T-lymphocytes which drive the immunologic process including eosinophilic infiltration of the skin and viscera. Interestingly, reactivation of viruses including HHV6 and HHV7 in patients with DRESS also supports an immunologic mechanism and perhaps a drug–viral interaction. Immediate discontinuation of the inciting medication is critical, and systemic steroids may be required to shut off the disorder which may last for weeks to months (Fig. 7.2).

Unfortunately, morbilliform rashes often appear in febrile children who are placed on antibiotics for treatment of presumed bacterial infections such as sinusitis and otitis media. The differentiation of a viral infection with associated exanthem from a drug rash is usually impossible, and many of these children are labeled antibiotic allergic. In some patients, recognition of specific viral exanthems and serologic confirmation support an infectious etiology. Moreover, some drugs may interact with certain viruses to produce an exanthem such as the rash seen in up to 90% of children with mononucleosis who are treated with ampicillin (Fig. 7.3). The differential diagnosis also includes graft-vs-host disease and



Fig 7.1 A morbilliform reaction to phenobarbital developed in a toddler after 2 weeks of treatment for febrile seizures. Lesions were most prominent on **(a)** the face, and **(b)** the upper trunk and extremities. Note the perioral and perinasal sparing.

Kawasaki syndrome, but the medical history and associated findings help to exclude these disorders. Histologic findings in morbilliform drug reactions overlaps with viral exanthems and graft-vs-host disease, so skin biopsies usually do not help to distinguish these disorders.

Stevens–Johnson syndrome/toxoid epidermal necrolysis

Although SJS and TEN were initially thought to represent severe variants of erythema multiforme, recent pathogenetic investigations support the clinical separation of erythema multiforme and SJS/TEN. Although SJS/TEN may be triggered by drugs and a number of other infectious and biological agents, erythema multiforme has been most commonly associated with infectious agents, particularly herpes simplex virus, in children and adults. SJS/TEN are defined by a severe mucositis of multiple mucous membranes and variable cutaneous involvement (10–30% in SJS to over 30% in TEN) which may be life-threatening. Erythema multiforme presents with characteristic target lesions on the distal extremities. Although oral mucous membranes may be involved in half of affected individuals, the oral involvement is usually mild and self-limited. Although SJS/TEN are rare, the clinician must recognize these clinical patterns early to avoid or effectively deal with potentially serious complications. Classic erythema multiforme, SJS, and TEN are described in Chapter 4.

Fixed drug eruption

Fixed drug eruption is a distinctive reaction pattern characterized by the sudden onset of one or several erythema-multiforme-like annular, erythematous, edematous plaques from 1 cm to over 5 cm in diameter. Lesions occur after exposure to a number of medications (Fig. 7.4). Intense edema may result in bulla formation. When the drug is withdrawn, lesions flatten, erythema fades, and prominent postinflammatory hyperpigmentation persists for weeks to months. On re-exposure to the allergen, old lesions reappear and new plaques may develop and slowly progress. Widespread



Fig 7.2 DRESS. This adolescent developed high fever, hepatitis, generalized edema and a progressive diffuse erythema with follicular prominence on her extremities following treatment of acne with oral trimethoprim-sulfamethoxazole tablets.

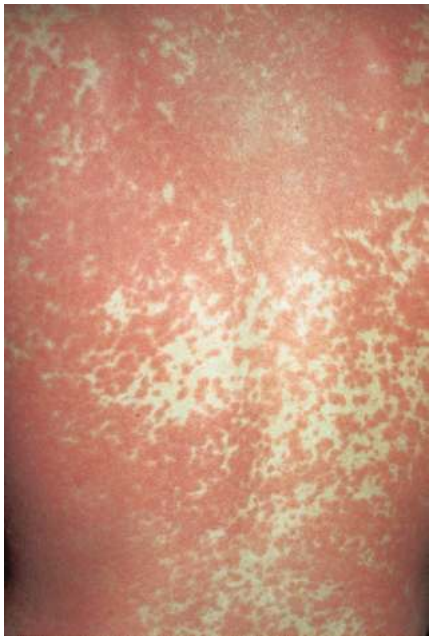


Fig 7.3 A teenager who was initially diagnosed with streptococcal pharyngitis was started on ampicillin. After 4 days, a morbilliform rash erupted on the trunk and spread to the face and extremities. A monospot test was positive in the office, and the antibiotic was discontinued.

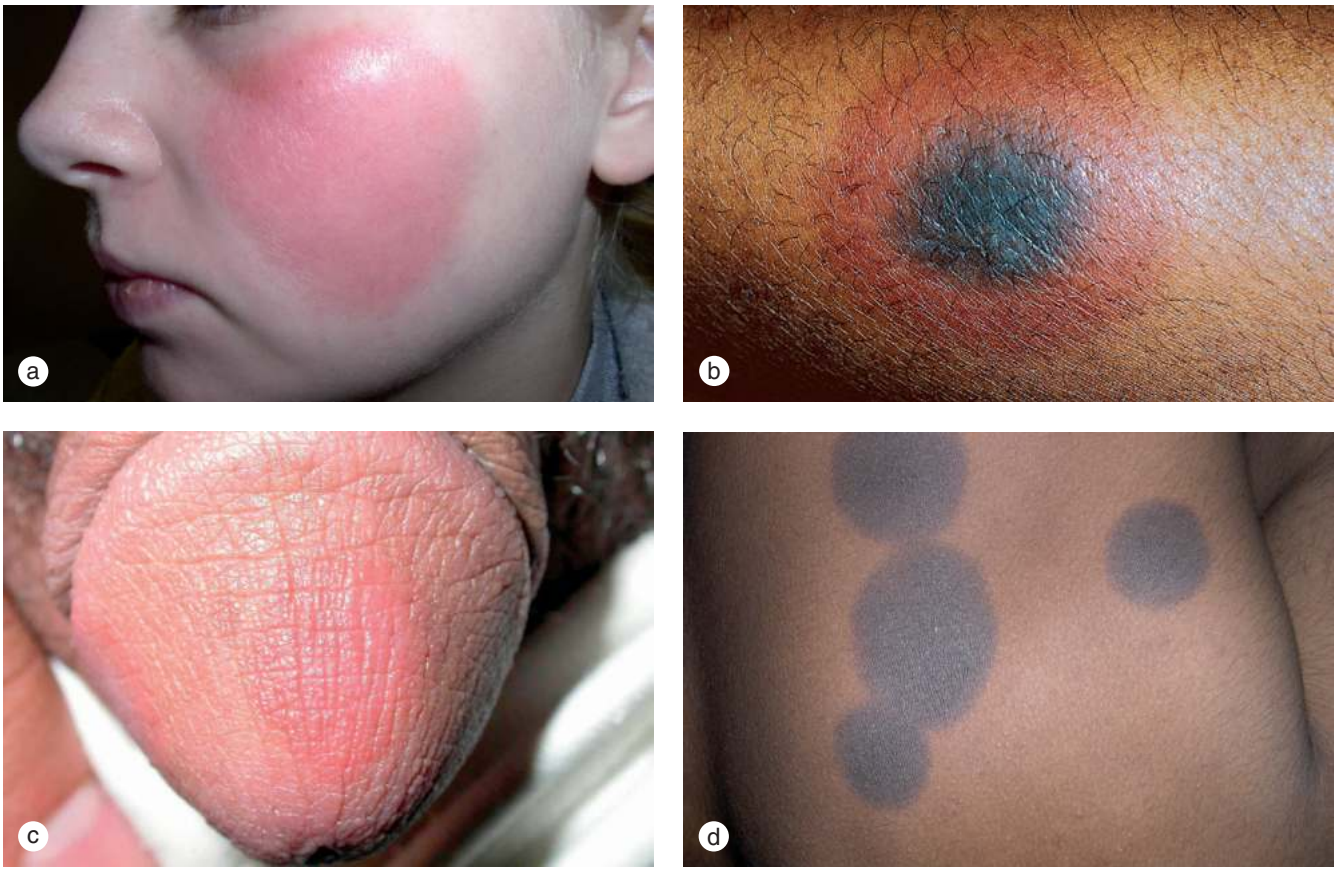


Fig 7.4 Fixed drug eruption. **(a)** This adolescent girl developed a recurrent fixed drug reaction whenever she took a non-steroidal anti-inflammatory drug for menstrual cramps. **(b)** This 10-year-old, darkly pigmented boy developed a recurrent target lesion in the same spot on his arm after exposure to a cold remedy. Note the dusky center with marked hyperpigmentation. **(c)** Typical itchy violaceous plaques developed on the glans penis of this adolescent boy when he was started on doxycycline for treatment of acne. **(d)** Dramatic hyperpigmented macules persisted after a fixed drug eruption to an oral antibiotic resolved.

bullous eruptions rarely occur with recurrent exposure to the offending agent.

Although the rash may develop on any site, the face, lips, genitals, and buttocks are the most commonly involved. The most frequent triggering agents include trimethoprim-sulfamethoxazole, aspirin, tetracycline, barbiturates, and non-steroidal anti-inflammatory drugs.

Although the mechanism is not known, T-lymphocytes that reside in the dermis and amplification by T-cells recruited from the circulation are thought to be responsible for the acute reaction as well as the cutaneous memory function of the fixed drug eruption. Suppressor/cytotoxic T-lymphocytes recognize drug-haptens which bind to proteins in basal keratinocytes and melanocytes to form a complete antigen which stimulates the immunologically mediated process. Histologic findings are similar to those of erythema multiforme, but pigment incontinence tends to be intense. This explains the impressive, discrete hyperpigmentation, which may be the only clinical finding between episodes. Once the diagnosis is considered, the allergen can be identified and avoided.

Urticaria

Urticaria, commonly known as hives, is characterized by the sudden appearance of transient, well-demarcated wheals that are usually intensely pruritic, especially when they arise as part of an acute, IgE-mediated hypersensitivity reaction (Fig. 7.5). Individual lesions usually last several minutes to several hours, but they may rarely persist for up to 24 h. Wheals may have a red center with an edematous white halo – or the reverse, an edematous white center with a red halo. Size can vary from a few millimeters to giant lesions over 20 cm in diameter. Central clearing with peripheral extension may lead to the formation of annular, polycyclic, and arcuate plaques that simulate erythema multiforme and erythema marginatum. The reaction may involve the mucous membranes and can spread to the subcutaneous tissue to produce woody edema known as angioedema (Fig. 7.6). Histopathology usually demonstrates a mild, lymphocytic, perivascular infiltrate with marked dermal edema.

Urticaria can be triggered by a variety of immunologic mechanisms, including IgE antibody response, complement activation, and abnormal response to vasoactive amines. Most cases of acute urticaria, which lasts less than 6 weeks, are caused by a hypersensitivity reaction to drugs, food, insect bites, contact antigens, inhaled substances, or acute infections. Physical agents, which include cold, heat, water, exercise, and mechanical pressure, may also trigger hives. Less than 5% of patients evolve into chronic urticaria, which lasts from 6 weeks to many years.

Specific drugs and foods known to cause hives should be avoided because of the risk of inducing anaphylaxis on subsequent exposure. Exhaustive laboratory studies in an otherwise healthy child are unlikely to be rewarding. Laboratory evaluation is guided by



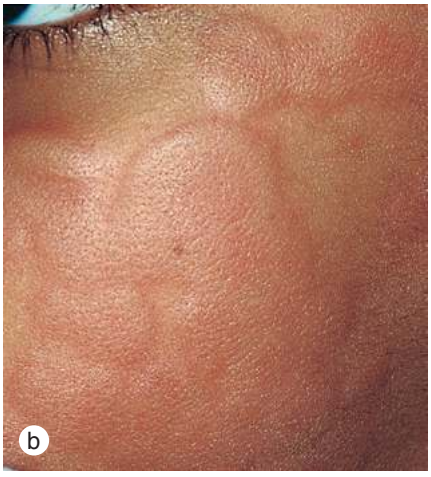




Fig 7.5 Urticaria. **(a)** Pruritic annular plaques recurred on the back of this healthy adolescent girl. **(b)** Wheals have become confluent on the face of this boy. **(c)** This infant developed recurrent urticaria and dermatographism demonstrated here by vertical linear red plaques with surrounding pallor.



Fig 7.6 This 12-year-old boy developed diffuse angioedema with some airway involvement shortly after receiving intramuscular penicillin following a dental procedure.

findings on history and physical examination. Patients with chronic disease require intermittent re-examination, particularly if other problems such as arthritis, diarrhea, or fever develop.

Extensive urticaria associated with pruritus may respond readily to H1 antihistamines such as diphenhydramine, hydroxyzine, or chlorpheniramine. Dosages should be increased to twice the recommended level or until unacceptable adverse reactions are noted. Most children accommodate quickly to sedation associated with these medications. In resistant cases, the addition of an H2 antihistamine, such as cimetidine or ranitidine, and/or β-adrenergic agonists, such as ephedrine and terbutaline, may be helpful. Several non-sedating antihistamines, which include cetirizine, loratadine, desloratadine, and fexofenadine, are particularly useful in some children with chronic urticaria. Adrenaline (epinephrine) may be lifesaving in urticaria and angioedema that involve the airway. Systemic corticosteroids are reserved for patients with life-threatening disease.

Urticarial eruptions may appear early in the course of serum sickness reactions triggered by infectious agents or drugs. Asymptomatic or painful, red papules and expanding annular plaques with hemorrhagic borders are associated with fever, arthralgias, periarticular swelling, and occasionally arthritis. Skin lesions differ from classic urticaria by the lack of pruritus and persistence beyond 24 h. Serum sickness reactions have been reported recently with cefaclor, but may also occur with a number of other antibiotics (Fig. 7.7a). Skin biopsies usually demonstrate a lymphohistiocytic, dermal, inflammatory infiltrate, but occasionally vasculitis may be present.





Fig 7.7 (a) A 10-month-old girl developed urticaria on the lower trunk and thighs while being treated with cefaclor for an ear infection. Although the drug was stopped, the annular plaques progressed and became purpuric centrally. The rash was accompanied by arthralgias, joint swelling, and fever consistent with a serum sickness picture. **(b)** Generalized migratory itchy papules and plaques (urticaria multiforme) developed in this 4-year-old girl with a viral gastroenteritis.

Urticaria may also occur during the prodrome of Henoch–Schönlein purpura, which is characterized by leukocytoclastic vasculitis with palpable purpura. Urticaria triggered by viral infections referred to as urticaria multiforme can be distinguished from serum sickness reactions and erythema multiforme by the presence of pruritus and a transient rapidly evolving course (Fig. 7.7b).

Erythema marginatum, one of the major criteria for rheumatic fever and which occurs in 20% of patients, may be confused with hives. This eruption is characterized by transient, asymptomatic, red papules that enlarge over several hours to form annular, scalloped, and serpiginous expanding plaques with narrow borders and central clearing (Fig. 7.8). Successive crops appear on the trunk and extremities as old plaques fade. New lesions typically flare with evening fever spikes, and involvement is restricted predominantly to the trunk and proximal extremities. The absence of pruritus helps to distinguish erythema marginatum from hives, and skin biopsies show predominantly a perivascular neutrophilic infiltrate. The diagnosis of rheumatic fever is dependent on the recognition of other well-defined criteria.

Urticaria must also be distinguished from the figurate erythemas and other reactive erythemas, discussed later in this chapter.

Exfoliative, lichenoid, and acneiform drug reactions

Drugs can also trigger reactions that mimic other cutaneous conditions. In an exfoliative erythroderma, widespread inflammation in the skin is associated with generalized erythema and scale. The entire surface is involved, including the scalp, palms, and soles. Although this reaction pattern usually evolves from a primary cutaneous disorder, such as atopic dermatitis, seborrheic dermatitis, psoriasis, or T-cell lymphoma, a number of medications, which include allopurinol, barbiturates, captopril, carbamazepine, cimetidine, diltiazem, griseofulvin, gold, thiazide diuretics, isoniazid, hydantoins, D-penicillamine, quinidine, and sulfonamides, have been implicated in some patients. A history of drug exposure, preceding rashes, and associated findings provides clues to the cause of the erythroderma. Histopathology usually reveals a chronic dermatitis. However, the presence of eosinophils may suggest a hypersensitivity reaction, while other distinct findings indicate an underlying skin disorder.



Fig 7.8 Erythema marginatum in a child with acute rheumatic fever. Note the scalloped margins and distribution on the trunk.

In lichenoid drug reactions, clinical findings are usually indistinguishable from those of lichen planus. However, the dermal infiltrate may contain eosinophils, which is unusual for classic lichen planus. Withdrawal of medications may result in improvement of the eruption over weeks to months. Drugs that have been reported to cause lichenoid reactions include thiazide diuretics, streptomycin, isoniazid, methyldopa, beta-blockers, naproxen, and captopril. Lichenoid drug reactions may be difficult to distinguish from graft-vs-host disease in transplant patients.

Acneiform drug reactions may be differentiated from typical acne vulgaris by the presence of uniform, inflammatory papules and pustules (rather than mixed comedones and inflammatory lesions in acne vulgaris), involvement of the usual acne areas (face, shoulders, upper trunk), as well as the lower trunk, arms, and legs, acute onset with introduction of the inciting drug, and resistance to standard therapy. Medications may also exacerbate pre-existing acne. Commonly identified drugs include corticosteroids, corticotropin, isoniazid, lithium, iodides, cyclosporine, and anticonvulsants. Although the eruption may improve with systemic and topical acne preparations, severe or recalcitrant cases may require a decrease or discontinuation of the medication if possible.

Acute generalized exanthematous eruptive pustulosis (AGEP) may also mimic an acute flare of acne. Disseminated pustules appear within 24 h of initiation of the inciting medication and may involve the palms and soles. Mild systemic complaints including fever, elevated liver enzymes, and rarely transient renal dysfunction have been reported. Lesions usually clear within 7–14 days of discontinuing the drug. The eruption has been associated with exposure to antibiotics (β-lactams, macrolides, cephalosporins), calcium channel blockers, carbamazepine, paracetamol, and a number of viral organisms (Fig. 7.9).



Fig 7.9 This patient developed a generalized red papular eruption with central pustules while on an antibiotic for pharyngitis.

Cytotoxic agents (e.g. cytosine arabinoside and more recently epidermal growth factor receptor inhibitors (e.g. cetuximab) have been implicated in the development of painful acneiform eruptions of the hands and feet with involvement of the palms and soles. Also know as neutrophilic eccrine hidradenitis, acral or palmoplantar dysesthesia syndrome, and hand foot syndrome, these lesions may present with edematous red papules, plaques, and pustules and may spread to seborrheic areas of the trunk and face (Fig. 7.10).

VIRAL EXANTHEMS

A number of viral infections have cutaneous manifestations that provide a clue to the diagnosis. In some, the skin rash is the major finding. Early recognition of distinct exanthems also helps to differentiate viral infections from drug reactions, bacterial and rickettsial rashes, and other reactive erythemas.

In the early twentieth century, clinicians commonly referred to childhood exanthems by number. Scarlet fever and measles were known as 'first' and 'second' disease, but the two rashes were frequently confused. Rubella was established as an entity distinct from measles and known as 'third' disease. In 1900, Duke described 'fourth' disease, which probably does not represent a distinct condition but a combination of rubella and scarlet fever. 'Fifth' disease is recognized today as erythema infectiosum, and roseola finishes off the numbered exanthems as 'sixth' disease. Many other viruses produce distinct reaction patterns in the skin. Infections from herpes- and poxviruses are readily diagnosed by their characteristic vesiculobullous eruptions, while infections from picornaviruses (which include the enteroviruses) are well recognized for their morbilliform exanthems.



Fig 7.10 This young adult developed painful indurated red confluent plaques on the palms and soles following infusion of bleomycin.

Viruses trigger exanthems by a number of mechanisms. Direct infection of the skin occurs in varicella, enteroviruses, and herpetic infections. Other rashes, such as measles and rubella, probably result from a combination of viral spread to the skin and host immunologic response. Some host–viral interactions are activated by exposure to certain drugs, exemplified by the generalized exanthem that occurs in over 95% of individuals with Epstein–Barr virus infection who receive ampicillin.

Measles and rubella

In the pre-vaccine era, measles and rubella were common and their exanthems became a paradigm for other 'morbilliform' rashes. Although the usual late winter to early spring epidemics have been interrupted by widespread vaccination in industrialized nations, failure to immunize significant numbers of children during the past decade has resulted in intermittent outbreaks in the USA.

Measles

Measles (rubeola, red measles, 10-day measles) is a highly contagious, potentially severe illness with a prodrome characterized by fever, malaise, dry cough, coryza, conjunctivitis, and severe photophobia (Fig. 7.11a). Several days into the course, diagnostic Koplik spots appear on the buccal and labial mucosae (Fig. 7.11b). Lesions consist of 1–3 mm diameter, bluish-white papules surrounded by red halos, which increase in number and fade over 2–3 days. Unfortunately, this characteristic enanthem is often transient and goes unnoticed.

On the 3rd or 4th day of illness, the exanthem first appears on the face as an eruption of blanching, red macules and papules, which spreads cephalocaudally over 3 days, and ultimately involves the palms and soles (Fig. 7.12). Once generalized, lesions become confluent on the face, trunk, and extremities in succession. Older lesions commonly develop a rusty hue from capillary leak and hemosiderin deposition. The rash begins to fade after 3 days and clearance is complete 3 days later, a total duration of 10 days for the illness. Widespread desquamation may appear 1–2 weeks after resolution of the rash.

Patients are contagious 4 days before the exanthem until 4 days after it appears. During the illness fever may be persistent and severe. Generalized adenopathy is common. Morbidity and mortality are highest in patients compromised by hereditary or acquired immunodeficiency and in developing countries in which malnutrition is rampant (supplementation with vitamins may reduce the risk of death and complications). Potential complications that result from primary viral infection or secondary bacterial infection include conjunctivitis, otitis media, pneumonitis, meningitis, acute encephalitis, and obstructive laryngotracheitis.

Atypical measles is an unusual syndrome that occurs in individuals who received killed measles vaccine, when it was available between 1963 and 1967, and are subsequently exposed to the measles virus. Unlike typical measles, the exanthem begins and remains primarily on the extremities and often develops a petechial component. Koplik spots are absent, fevers are high, and pneumonitis is usually severe. This disorder probably represents a hypersensitivity reaction to the virus and is most frequently confused with Rocky Mountain spotted fever and collagen vascular disease.





Fig 7.11 Rubeola/measles. **(a)** During and after the prodromal period, the conjunctivae are injected and produce a clear discharge. This is associated with marked photophobia. **(b)** Koplik spots, bluish-white dots surrounded by red halos, appear on the buccal and labial mucosae a day or two before the exanthem and begin to fade with the onset of the rash.

Rubella

Rubella (German measles) is known as 3-day measles, because the pink exanthem, which mimics a mild case of measles, usually evolves over 1–3 days. In fact, nearly 25% of patients may have only mild upper respiratory symptoms with little or no rash.

Rubella is typically associated with several days of low-grade fever, adenopathy, headache, sore throat, and coryza. In young children, fever may last for less than 24 h. Forchheimer spots consist of transient, small, red papules on the soft palate and are seen in some patients at the beginning of the rash. This exanthem helps to differentiate this otherwise non-specific eruption from other viral exanthems.

As with measles, peak incidence occurs in the late winter and early spring. Serologic testing may be useful to make a specific diagnosis, particularly if the patient is pregnant. Although complications are rare in children, the fetus is particularly vulnerable to intrauterine infection with complications that include spontaneous abortion, diffuse cataracts, microphthalmia, glaucoma, and congenital heart disease. Up to 25% of infected newborns develop severe, disseminated disease with jaundice, pneumonitis, meningoencephalitis, bony abnormalities, thrombocytopenia, blueberry muffin lesions, and a morbilliform exanthem. Babies with congenital infection may shed virus in urine, stools, and respiratory secretions for up to 1 year and should be isolated from other infants and pregnant women.

Erythema infectiosum (fifth disease)

In 1983, erythema infectiosum (or fifth disease) was linked to human parvovirus B19. Since then, investigators have defined the clinical features and epidemiology of infection in normal and compromised patients.

In its most commonly recognized clinical presentation, viral infection presents in children of school age with asymptomatic, slapped cheek erythema on the face and a lacy or reticulated, blanching erythema on the trunk and extremities (Fig. 7.13a–d). Although the exanthem usually fades over 2–3 weeks, lesions may recur for up to 3 months, especially when cutaneous blood flow is increased and after fever or vigorous physical activity.

The prevalence of B19 antibody is about 5–10% in children under 5 years of age and rises to over 50% in adults. Human volunteer studies suggest that the virus is spread in respiratory secretions. After an incubation period of 5–7 days, infectivity peaks during the viremia, which lasts 5–7 days. The end of viremia is marked by a rise in IgM and then IgG antibody, and followed 2–5





Fig 7.12 The measles exanthem. **(a)** A blotchy, erythematous, blanching eruption appears at the hairline and spreads cephalocaudally over 3 days. **(b)** Ultimately, the exanthem involves the palms and soles. With evolution, lesions become confluent on the face, neck, and upper trunk.

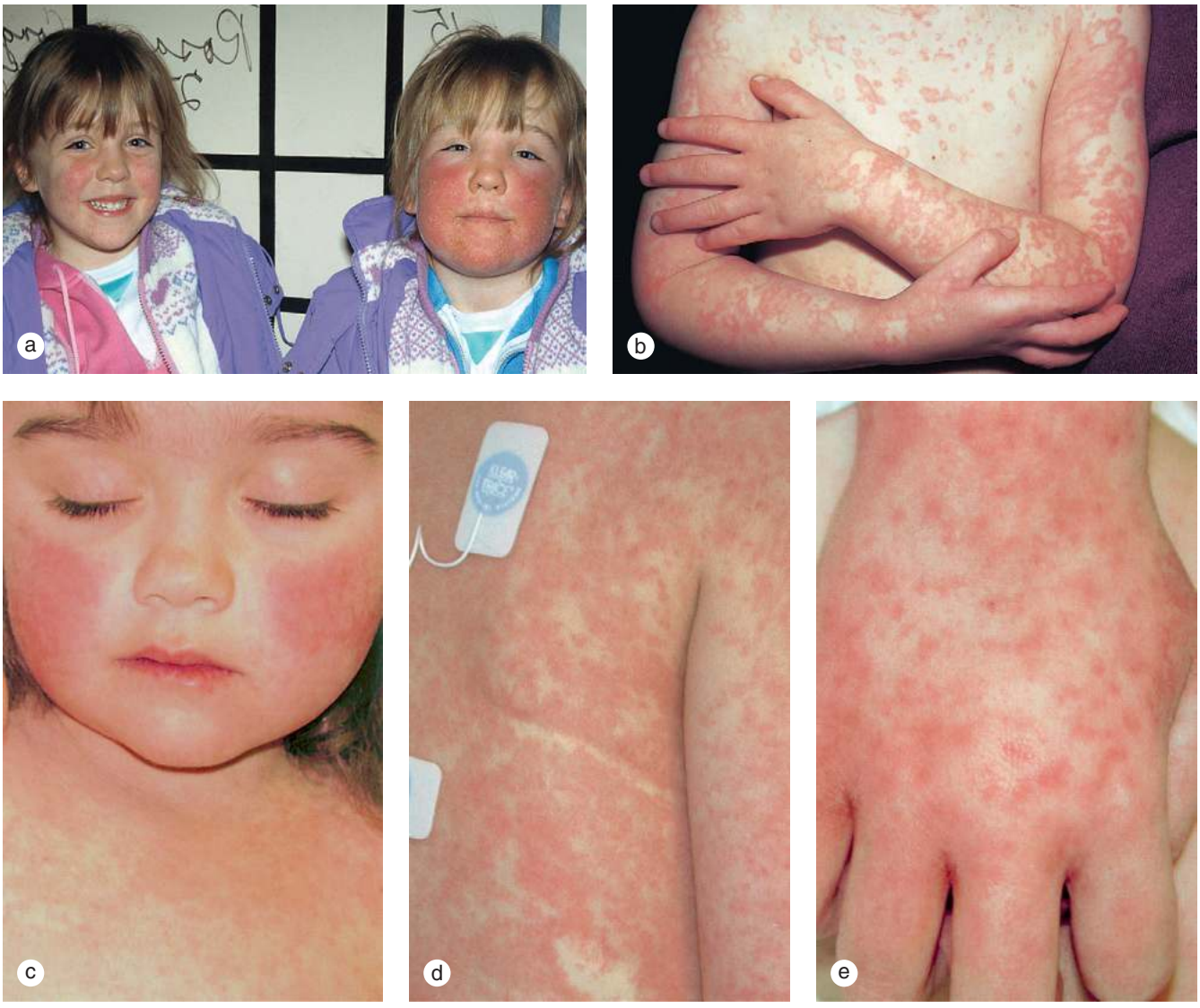


Fig 7.13 Fifth disease. **(a)** These sisters demonstrate the slapped cheek erythema typical of erythema infectiosum. Despite the edema in one girl, both were completely asymptomatic. **(b)** A diffuse, lacy, and confluent annular eruption appeared on this otherwise healthy 9-year-old boy during a recent fifth disease epidemic. The reticulated erythema on his arms flared intermittently for 6 weeks. **(c)** Slapped cheek erythema and **(d)** a diffuse, reticulated, morbilliform eruption developed in this 4-year-old girl with high fever, arthralgias, and myalgias. **(e)** Four days into her illness she developed discrete and eventually confluent purpuric macules and papules on her hands and feet. Serology for Parvovirus B19 was positive for acute infection.

days later by the appearance of the rash. Consequently, the risk of infection is low when the exanthem is diagnosed, and children can remain in school.

Associated symptoms, which include fever and arthralgias, are usually mild or absent in young children. However, arthralgias or frank arthritis may be severe in adolescents and adults. At least a quarter of patients with serologic evidence of disease do not develop the exanthem, and the arthropathy may develop before, after, or without the rash.

Early in the infection most patients experience a transient reticulocytopenia for 7–10 days and a clinically insignificant drop in hemoglobin level. This phenomenon, however, may trigger an aplastic crisis in patients with severe hemoglobinopathies. The virus has also been implicated as a cause of hydrops fetalis in pregnant women with no other evidence of clinical disease. However, recent reports suggest that parvovirus can rarely cause fetal malformations. In hereditary or acquired immunodeficiency syndromes, B19 may produce persistent infection and chronic, life-threatening anemia.

Human parvovirus B19 has also been isolated from children and adults with papular-purpuric gloves and socks syndrome (Fig. 7.13e). Although this painful itchy erythema, edema, and purpura of the palms and soles occurs most commonly in the spring at the peak of the HPVB19 season, it has also been associated with other viruses including Coxsackie virus B6 and human herpes virus 6. Red papules reminiscent of Koplik spots and erosions may also develop on the tongue, palate, and buccal mucosa, and fever and arthropathy are variable. Treatment is symptomatic, and the syndrome usually resolves in 1–2 weeks.

The reticulated exanthem of erythema infectiosum may be confused with livedo reticularis, a persistent, lacy, blanching, violaceous erythema that occurs in primary and secondary forms (Fig. 7.14). In the idiopathic variant, lesions are symmetric and widespread with poorly defined borders. Unlike cutis marmorata



Fig 7.14 Widespread livedo reticularis became particularly prominent on the extremities of this adolescent shortly after she started a neuroleptic medication for attention deficit hyperactivity disorder.



Fig 7.15 Roseola/exanthema subitum. A generalized, pink, maculopapular rash suddenly appeared on this infant after 3 days of high fever.

in neonates, the pattern does not resolve with warming. This occurs most commonly in young women who are otherwise healthy. The secondary variant is more common in men and has been reported in association with periarteritis nodosa, hepatitis, syphilis, and a number of other infections, connective tissue diseases, and malignancy.

Exanthema subitum (roseola)

Roseola, or exanthema subitum (the 'surprise' rash), has been recognized by pediatricians for over a century. The classic clinical course occurs in children between 6 months and 3 years old. After a 3–5-day illness marked by high-spiking fevers, which occasionally trigger febrile seizures, a sudden end to the fever is followed by the appearance of a widely disseminated, pink, papular rash (Fig. 7.15). As in fifth disease, the end of viremia is marked by the development of the rash and a rise in antibody to the causative agent: human herpesvirus 6 (HHV6). Consequently, the risk of infection is greatest during the febrile period and minimal after the appearance of the rash.

Serologic studies show an almost universal exposure of the population to HHV6. Although only one-third of infants develop clinical disease, prevalence of antibody increases from less than 10% in children under 6 months of age to 75–90% in adults. Consequently, a large number of children develop asymptomatic infection. Conversely, seroprevalence studies of febrile infants demonstrate that viral infection may commonly produce a febrile illness without a rash. A similar febrile disorder has been associated with HHV7 in some children.

Also, HHV6 has been linked to a mononucleosis-like illness in young adults, and its role as an immunomodulator is being investigated in the immunodeficient host.

Papular acrodermatitis (Gianotti–Crosti syndrome)

In 1955, Gianotti, while working in the Milan department of dermatology directed by Crosti, described a distinctive exanthem associated with anicteric hepatitis, lymphadenopathy, and hepatitis B surface antigenemia, subtype *ayw*. The skin rash consists of flat-topped, 3–10 mm diameter, skin-colored to red, edematous papules that involve the arms, legs, buttocks, and face (Fig. 7.16). Lesions on the calves and extensor surfaces of the arms may become so edematous as to appear vesicular, and occasionally frank vesicles are present.

During the past 15 years, it has become apparent that most cases in the USA are caused by various viruses, including enteroviruses, respiratory viruses, and Epstein–Barr virus. As most children are asymptomatic, no treatment is necessary. However, parents are counseled that the eruption may persist for up to several months.

Papular acrodermatitis can be differentiated from lichen planus, which is usually extremely pruritic. A negative history of recent drug exposure excludes a lichenoid drug eruption. Other viral eruptions also may be confused with papular acrodermatitis. Unfortunately, the histopathology is not specific and shows focal spongiosis and exocytosis in the epidermis overlying a perivascular, lymphocytic, dermal infiltrate.

Other viral exanthems

Exanthems associated with the enteroviruses are quite variable and usually follow a shorter incubation period than the classic viral exanthems. Although they occur all year round, the incidence peaks in the late summer and early fall. Morbilliform, vesicular, petechial, and urticarial eruptions are variably present, usually in association with fever (Fig. 7.17). Other symptoms may include meningitis, conjunctivitis, cough, coryza, pharyngitis, and pneumonia. Hand-foot-and-mouth disease is a distinctive entity associated with papulovesicular lesions on the palms, soles, palate, and (not infrequently) the trunk, particularly the buttocks. Coxsackie viruses A5, A10, and A16 and enterovirus 71 have been identified in patients with this syndrome.

Unilateral laterothoracic exanthem (asymmetric periflexural exanthem of childhood) (Fig. 7.17c) is another distinct clinical pattern that may be triggered by a number of organisms, including the enteroviruses. The asymptomatic or minimally pruritic morbilliform or scarlatiniform eruption usually begins near one axilla and, although it often remains predominant on the initial side, spreads over the trunk in infants and preschool children. The mean

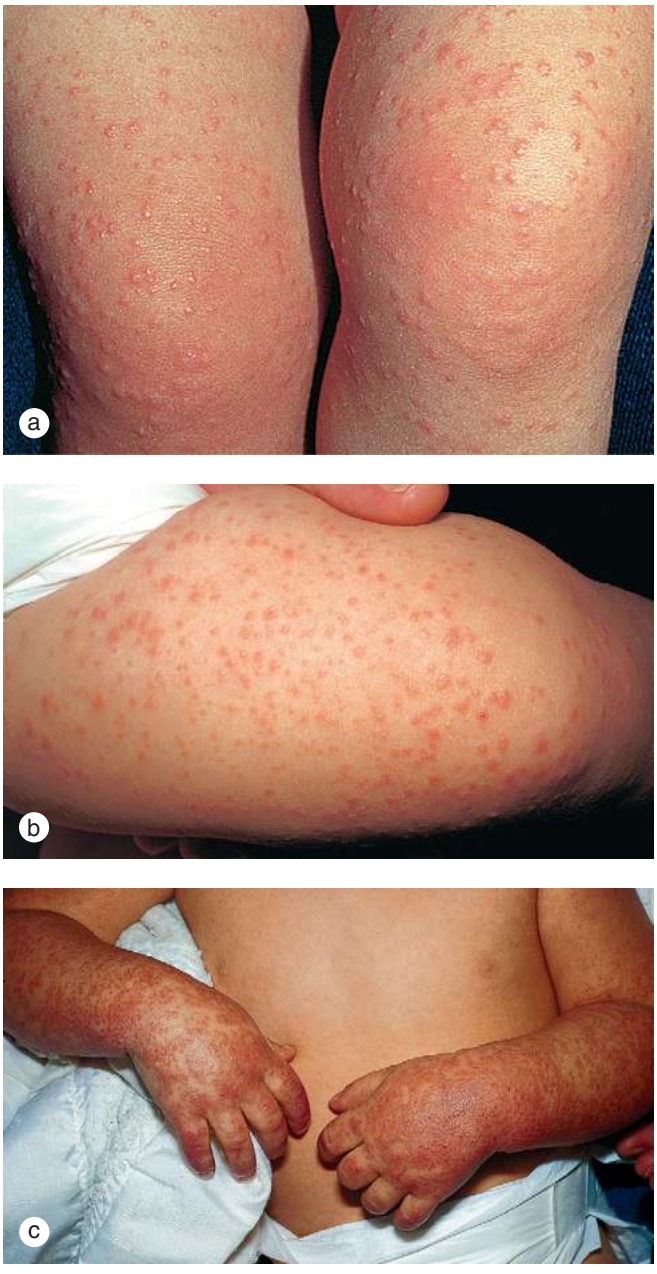


Fig 7.16 Papular acrodermatitis. A symmetric, acrally distributed, red, papular rash developed in this toddler with low-grade fever and loose stools. Note the discrete, edematous papules on the **(a)** knees and **(b)** thighs. **(c)** In some areas on his hands and forearms the lesions were confluent.

age of onset is 2 years, and girls are affected twice as often as boys. Lesions usually heal without scarring over 5 weeks. Although there is no diagnostic test, a unique eccrine lymphocytic infiltrate is identified in skin biopsies.

Papulovesicular rashes may be differentiated from varicella-zoster and herpes simplex infections by obtaining a Tzanck smear. The clinical course and, if necessary, cultures and serologic studies help to make a specific diagnosis. Although meningococcal infections tend to peak during the winter and spring, occasionally cases occur during the summer and fall enteroviral season. Consequently, the child with a petechial exanthem and presumed enteroviral meningitis must be evaluated carefully to exclude a bacterial infection.



Fig 7.17 (a) An urticarial viral exanthem spread from the trunk to the face and extremities in this infant. Lesions faded over several days. **(b)** A 6-year-old boy developed 1–2 mm red macules and petechiae on the distal extremities with involvement of the palms and soles. **(c)** This healthy 4-year-old boy developed a unilateral discrete and confluent papular eruption on his left chest which generalized over several days.

Infection with cytomegalovirus, Epstein–Barr virus, and respiratory viruses may be associated with macular, morbilliform, or urticarial exanthems, which are difficult to differentiate from drug rashes. Children who require medications and develop intercurrent viral infections may remain on their medications while under close observation. These minor viral exanthems usually fade in several days, while drug reactions tend to persist or intensify. However, drugs must be discontinued in any patients who develop urticaria, angioedema, Stevens–Johnson syndrome/TEN, or other signs of progressive allergic reactions.

SCARLATINIFORM RASHES

The rash of scarlet fever provides a model for a number of important disorders that must be differentiated by other signs and symptoms. Bacterial toxins, viral infections, drugs, and Kawasaki syndrome have all been associated with scarlatiniform eruptions.

Scarlet fever

Scarlet fever is characterized by a fine, red, papular, sandpaper-like rash that begins on the face and neck and generalizes to the trunk and extremities within 1–2 days (Fig. 7.18). The skin is warm and flushed, and some patients complain of mild pruritus. Circumoral pallor is typical, but not diagnostic. The rash ranges from a subtle pink to fiery red color and usually follows the onset of streptococcal pharyngitis by 24–48 h. Pastia lines are the accentuation of the rash from linear petechiae, which occurs in the flexural creases of the arms, legs, and trunk (Fig. 7.18b). Other associated symptoms include nausea, vomiting, fever, headache, general malaise, and abdominal pain. The palms, soles, and conjunctivae are usually spared. In classic cases, the pharynx is beefy red with palatal petechiae, purulent tonsillitis, and tender, cervical adenopathy. Early in the course the lingual papillae poke through a white membrane (white strawberry tongue; Fig. 7.19a). Shedding of the membrane by days 4–5 results in a bright red, strawberry tongue (Fig. 7.19b). In many patients, the throat infection is mild or completely asymptomatic. Scarlet fever may also be associated with streptococcal impetigo.

The rash is triggered by one of three antigenically distinct erythrotoxins, which are produced by most strains of Group A β-hemolytic streptococci. Development of antibodies against the streptococcal organism and erythrotoxin is protective and results in resolution of the symptoms and rash within 4–5 days. This is followed 1–2 weeks later by generalized desquamation, which is particularly marked on the finger tips and toes (Fig. 7.18c). While both oral and cutaneous infections with nephritogenic streptococci can trigger glomerulonephritis, only pharyngeal infections have been associated with subsequent development of rheumatic fever. Treatment of patients with amoxicillin or penicillin (erythromycin or other macrolides in penicillin-allergic patients) may shorten the course of fever and other symptoms. If antibiotics are initiated within 10 days of the onset of pharyngitis, the risk of rheumatic fever may be reduced from 3% to less than 1%. Unfortunately, early treatment of nephritogenic strains has not been shown to decrease the incidence of poststreptococcal renal disease. Moreover, asymptomatic pharyngeal infection may escape detection until after the development of late complications.

Several other toxin-mediated syndromes may be confused with scarlet fever. Children with staphylococcal scarlet fever develop a rash which may be indistinguishable from streptococcal disease. Nikolsky sign may be present, but pharyngeal signs are usually absent. Cultures from the typical purulent conjunctivitis or the oral or nasal pharynx invariably demonstrate *Staphylococcus aureus*. Unlike streptococcal scarlet fever, desquamation begins early in the course (by day 2) and is complete within a week. The clinical signs and course probably vary with the source of the infection, amount of staphylococcal exotoxin present, and host response. A similar eruption may accompany toxic shock syndrome. However, the eruption is usually accompanied by hyperemia of the conjunctivae, oral and vaginal mucosa, a strawberry tongue, and severe multisystem disease. The early findings in both staphylococcal scalded-skin syndrome and TEN may mimic scarlet fever. However, the presence of Nikolsky sign and progression to widespread sloughing of skin quickly differentiate these disorders. Scarlatiniform viral

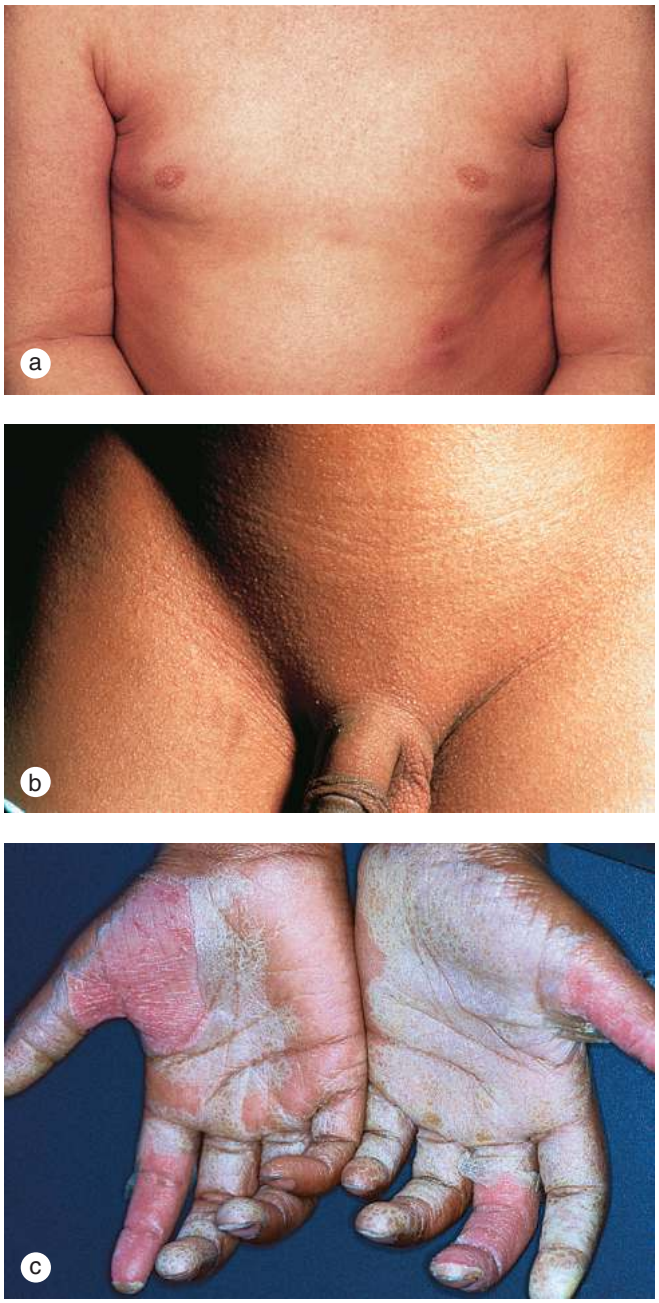


Fig 7.18 Scarlet fever. **(a)** A generalized, bright red, sandpaper-like papular rash developed in a 7-year-old boy with a streptococcal pharyngitis. Note the accentuation of the rash at the neck and axillary and antecubital creases. **(b)** A 5-year-old boy demonstrated a similar eruption with Pastia lines in the groin creases. **(c)** Widespread desquamation appeared in this 8-year-old girl 10 days after the onset of symptoms and rash, and was most prominent on the hands and feet.

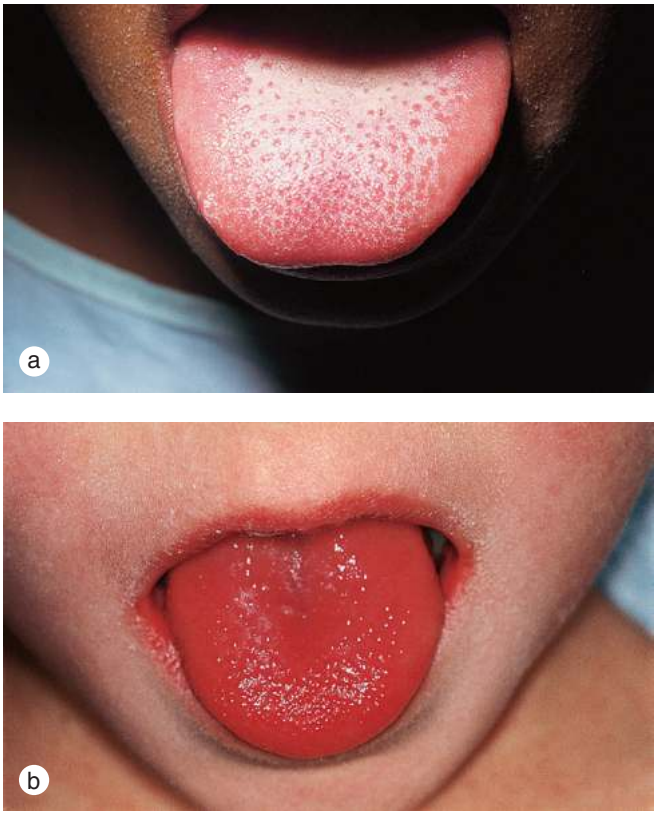


Fig 7.19 Scarlet fever. **(a)** A white strawberry tongue is usually followed by **(b)** a red strawberry tongue as the erythrotoxin-mediated enanthema evolves.

exanthems may occur with a number of different organisms. The course may be similar to that of scarlet fever and can only be differentiated by serologic studies and the absence of streptococci in throat or skin cultures.

Kawasaki syndrome

Although the exact etiology of Kawasaki syndrome is unknown, the epidemiology, clinical findings, and course suggest an as yet unidentified infectious agent. Early recognition is important to minimize the risk of coronary artery abnormalities. Intervention with intravenous gamma globulin, 2 g/kg, given over 10–12 h as a single infusion can reduce the incidence of coronary artery aneurysm formation from 20% to less than 4%. Over 75% of patients are under 4 years old and 50% less than 2 years of age. Cases occur all year round, with slight peaks in the late spring and late fall. Epidemics have also been reported. Although all races may be affected, the increased incidence among Japanese and intermediate risk of Japanese-Americans supports a genetic predisposition.

Kawasaki syndrome is defined clinically by the presence of five out of six major criteria, which are fever, usually unresponsive to antipyretics for at least 5 days, conjunctivitis, pharyngitis, erythema and edema of the hands and feet, rash, and adenopathy (Fig. 7.20). The acute phase, which lasts 10–14 days, begins with an abrupt onset of high fever and extreme irritability. A rash usually appears shortly after the fever and may take the form of a scarlatiniform, morbilliform, or urticarial exanthema or a combination of them. It is commonly accentuated in intertriginous areas, where maceration and scaling may be prominent, particularly on the perineum and inguinal creases (Fig. 7.20f). Facial swelling and pallor are commonly present. Other findings during the acute phase include non-purulent, conjunctival injection, erythema, edema, and cracking of the lips, palatal erythema and a strawberry tongue, painful erythema and edema of the hands and feet, and painful, unilateral, cervical adenopathy. Arthritis, diarrhea, abdominal pain, aseptic meningitis, hepatitis, urethritis, otitis, and hydrops of the gallbladder may also be present. The improvement in acute-phase mucocutaneous and systemic symptoms is often so dramatic that many practitioners look to this response to confirm their clinical diagnosis.

The subacute phase begins 10–14 days after the onset of symptoms, as the fever and rash improve. It is during this period that carditis associated with coronary angiitis becomes apparent particularly in untreated patients. By 3 weeks, most patients experience a thrombocytosis of over 1 million platelets/cm^3, which may further increase coronary morbidity. Widespread desquamation occurs 1–2 weeks after resolution of the rash, particularly over the fingers and toes where the skin is shed in large sheets. Although no specific laboratory tests are available for Kawasaki syndrome, leukocytosis is common and acute-phase reactants, which include C-reactive protein and erythrocyte sedimentation rate, are markedly elevated.

The convalescent phase begins in the 4th or 5th week and ends when the sedimentation rate returns to normal. Children require cardiac re-evaluation at least through this stage and for a year or more if aneurysms are detected.

The differential diagnosis includes viral exanthems, toxin-mediated bacterial disorders, connective tissue disease, and a number of other reactive erythemas.

Acral erythema and edema, one of the classic findings during the acute phase of Kawasaki syndrome, is also typical of papular acrodermatitis and other viral exanthems, Rocky Mountain spotted fever, erythromelalgia, pernio, and acrodynia (pink disease).

Papular acrodermatitis is easily differentiated from Kawasaki syndrome by the lack of fever and other systemic symptoms. The specific criteria and course of Kawasaki syndrome usually help to differentiate it from other viral infections that produce urticarial lesions and edema of the extremities. The findings in rickettsial diseases are also distinctive.

ACRAL ERYTHEMA

Erythromelalgia

Erythromelalgia is an unusual entity characterized by paroxysms of painful erythema of the hands and feet, which last for minutes to hours (Fig. 7.21). Patients often complain of warmth of the distal extremities followed by marked erythema and pain, which is initially improved by elevation and then only by increasing periods of immersion in cold water. Although the primary variant is usually familial and inherited in an autosomal dominant pattern, secondary erythromelalgia may be triggered by polycythemia vera, lymphoproliferative disorders, hypertension, and disorders associated with hyperviscosity. When the underlying condition is treated, symptoms improve. Unfortunately, primary disease is often recalcitrant and cold-water exposure results in an 'immersion foot,' with progressive vascular injury, recurrent ulcerations, and secondary bacterial infection. The inherited form of erythromelalgia has recently been linked to mutations in voltage-gated sodium channel Nav1.7, which is expressed in peripheral nociceptors.

Erythromelalgia and the following acral erythemas can usually be distinguished from chemotherapy-induced hand foot syndrome.



Fig 7.20 Kawasaki syndrome. Characteristic clinical findings demonstrated include **(a)** a generalized, morbilliform, erythema multiforme-like rash, **(b)** erythema and fissuring of the lips, **(c)** conjunctival injection, **(d)** lymphadenopathy, **(e)** palmar and plantar erythema with edema of the hands and feet, and **(f)** erythema and scaling in the groin creases.

Pernio

Pernio, also known as chilblains, results from cold exposure, usually just above freezing, and recurrent trauma. It is commonly reported in temperate climates, where women and children are most commonly affected. Typical lesions consist of painful nodules and plaques that overlie bony prominences on the hands and feet (Fig. 7.22). Histopathology demonstrates intense edema of the papillary dermis and endothelial swelling associated with a mononuclear, perivascular infiltrate. Inflammation may extend to vessels in the deep dermis and fat. Thin girls and young women, with a history of cold hands and feet, equestrians, scuba divers, and individuals who participate in fall and winter sports, are particularly prone to develop lesions. The risk of recurrences can be reduced by keeping the distal extremities warm and protected from trauma. Chilblains should be distinguished from child abuse in which cold exposure is not the primary trigger and chilblain lupus. Chilblain lupus may represent an overlap of pernio and lupus, but in time, many patients with chilblain lupus develop features both clinically and histologically of discoid lupus.

Acrodynia

Acrodynia, or pink disease, occurs in infants and toddlers as a result of chronic exposure to mercury. Painful, persistent erythema and swelling of the hands and feet are accompanied by other signs of sympathetic stimulation, which include tachycardia, hyperhidrosis, restlessness, and irritability. Treatment is directed toward removing the source of mercury exposure and chelation therapy.



Fig 7.21 Erythromelalgia. Necrotic blisters and ulcerations recurred chronically in this 11-year-old girl who received relief from throbbing, debilitating foot pain by dunking her feet in near-freezing water for up to 12 h a day. Her brother also had erythromelalgia, but his symptoms were mild and usually resolved with leg elevation alone.

PURPURAS

Bleeding into the skin may be an innocent finding in minor trauma or the first sign of a life-threatening disease. Early diagnosis and treatment, when necessary, requires that the practitioner recognizes and carefully evaluates any patient with purpura.

Cutaneous hemorrhage can be differentiated from hyperemia that results from increased blood flow through dilated vessels by failure of the hemorrhagic area to blanch when pressure is applied across the surface (diascopy). Diascopy can be demonstrated by pressing the skin apart between the thumb and index finger or by applying a glass or plastic slide. Pinpoint areas of hemorrhage are called petechiae; large, confluent patches are referred to as ecchymoses. Purpura results from extravascular, intravascular, and vascular phenomena.



Fig 7.22 Pernio. Painful, purple nodules developed on the sides of the feet and toes in this 13-year-old boy after walking with wet boots in a cold stream.

Extravascular purpura

Trauma is the most common cause of extravascular purpura in children. Non-blanching, purple patches caused by accidental trauma vary from a few millimeters to many centimeters in diameter and are usually located over bony prominences, such as the knees, elbows, the extensor surfaces of the lower legs, the forehead, nose, and chin. Petechiae are only occasionally present in otherwise healthy children, although they may occur on the face and chest after vigorous coughing or vomiting.

The presence of purpura on protected or non-exposed sites, such as the buttocks, spine, genitals, upper thighs, and upper arms, suggests the possibility of non-accidental trauma. In some cases, the shape of the bruise gives a clue as to the weapon used to inflict the injury.

Scars, sun damage, nutritional deficiency, inherited disorders of collagen and elastic tissue, and other factors that decrease the tensile strength of the skin may increase the risk of bruising caused by extravascular phenomena, even after minor trauma (Fig. 7.23).

Intravascular purpura

Intravascular purpura results from any disorder that interferes with normal coagulation. Petechiae and ecchymoses are present on the skin, mucosal bleeding may be seen, and in severe cases bleeding may occur in the kidneys, gastrointestinal tract, and central nervous system. Among the causes are autoimmune thrombocytopenic purpura (ATP), acute leukemia, aplastic anemia, sepsis, and clotting factor deficiencies.

Immune thrombocytopenic purpura (ITP)

In children, ITP is the most common cause of intravascular purpura. Patients typically present in the late winter and early spring, a few weeks to several months after a viral illness, with purpura of all sizes and no history of trauma. When injuries occur, ecchymoses may be impressive. Bleeding of the gums occurs regularly with brushing, and occult blood may be detected in the urine and stool. Fortunately, severe bleeding is unusual and most cases are self-limited, with improvement in platelet counts from less than 10 000/mm^3 to over 100 000/mm^3 within 1–2 months. The presence of ITP is associated with the development of an immunoglobulin G (IgG) that binds to platelets and results in increased destruction by the reticuloendothelial system. Antiplatelet antibodies have also been reported in patients with lupus erythematosus, leukemia, lymphoma, and drug reactions. Moderate-to-severe cases usually respond to treatment with intravenous immunoglobulin. Resistant patients may require systemic corticosteroids and/or splenectomy.

Patients with ITP may be clinically indistinguishable from those with leukemia and aplastic anemia (Fig. 7.24). Associated symptoms, which include fatigue, general malaise, fever, weight loss, and bone pain, suggest the diagnosis of leukemia. In leukemia, blasts may be discovered in the peripheral smear as well as the bone marrow. In ITP, the bone marrow demonstrates increased numbers of megakaryocytes, whereas they are usually decreased in leukemia. In aplastic anemia, purpura may be the first sign of marrow failure. All blood elements are decreased in the peripheral blood as well as in the bone marrow. Severe bacterial infection is a common complication. Children with inherited clotting-factor disorders bruise easily and may develop hemarthroses and bleeding into viscera. Petechiae are not usually seen in these patients.

Disseminated intravascular coagulation

Bacterial sepsis, disseminated viral infection, malignancy, and medications may rarely trigger disseminated intravascular coagulation,



Fig 7.23 Ehlers–Danlos syndrome. This child demonstrates a number of classic features of the disorder, which include **(a)** increased bruisability, **(b)** hyperelastic skin, and **(c)** hyperextensible joints. His father **(d)** had multiple, wide, atrophic purple scars over the shins, which accumulated over the years from trauma.

with widespread bleeding into the skin and viscera. Ecchymoses may progress rapidly to cover large areas of the body surface in minutes to hours (Fig. 7.25). Unfortunately, necrosis may develop in the center of some areas of purpura. In survivors, healing occurs with scarring and occasionally loss of digits or limbs.

Patients are usually critically ill and death may ensue quickly unless supportive measures, including urgent volume expansion, vasopressors, and parenteral antibiotic therapy, are begun immediately. Some intensivists recommend treatment with heparin, fresh frozen plasma, and systemic steroids. Laboratory studies demonstrate thrombocytopenia, decreased fibrinogen, prolonged bleeding time, and elevations in fibrin split products. In healthy children, meningococcemia, Rocky Mountain spotted fever, and streptococcal infections are the most common cause. In immunosuppressed patients opportunistic organisms should also be considered.



Fig 7.24 Intravascular purpura. A child with acute lymphocytic leukemia shows bruises of various sizes, which are typically found in individuals with low platelet counts.

Vascular purpura

Vascular purpura develops when an inflammatory process involves the vessel wall (vasculitis). In leukocytoclastic vasculitis, the inflammation is predominantly neutrophilic. In lymphocytic vasculitis and late stages of leukocytoclastic vasculitis, vascular damage is caused by infiltrating mononuclear cells. Sweet syndrome shows primarily leukocytoclastic changes, whereas pyoderma gangrenosum shares features of leukocytoclastic and lymphocytic vasculitis. Granulomatous vasculitis is uncommon in children, and usually presents in the setting of Wegener granulomatosis or allergic granulomatosis.

Leukocytoclastic vasculitis

Leukocytoclastic vasculitis results from immune complex deposition in dermal blood vessels and subsequent complement-activated leukocyte infiltration. Infections, medications, autoimmune disorders, and malignancy can trigger vasculitis.

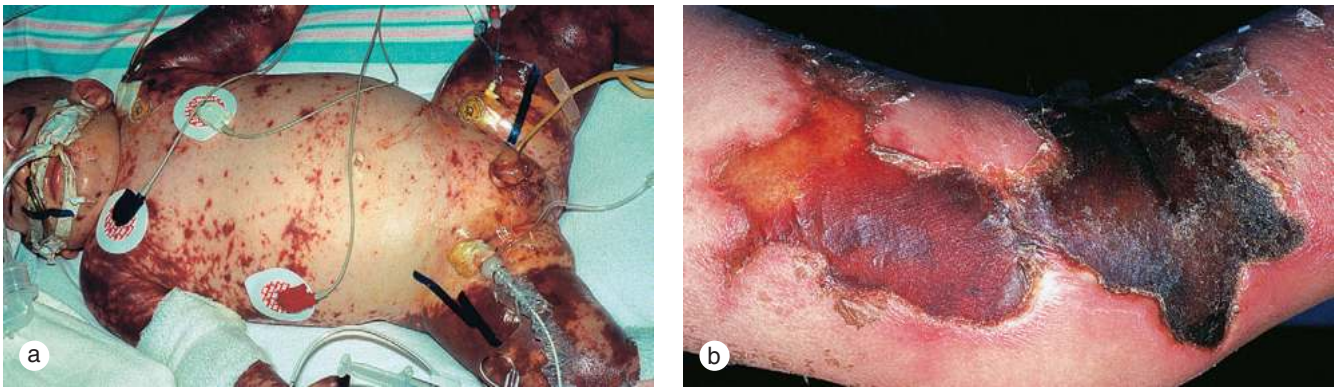


Fig 7.25 Disseminated intravascular coagulation. **(a)** Purpura fulminans developed in this infant with meningococcemia. Widespread bleeding into the skin was noted, particularly on the extremities. **(b)** A toddler with staphylococcal sepsis and DIC developed widespread cutaneous necrosis on the legs.

Henoch–Schönlein purpura

Henoch–Schönlein purpura (HSP), also known as anaphylactoid purpura or allergic vasculitis, is the most common form of leukocytoclastic vasculitis to occur in children, with peak incidence between 4 and 8 years old. However, HSP also has occasionally been reported in infants and adults.

Although the rash is characterized by palpable purpura, the typical 2–10 mm diameter, purpuric papules may be preceded by several days of urticaria. Lesions most commonly pepper the buttocks and the extensor surfaces of the arms and legs. However, any site may be involved including the face, ears, and trunk (Fig. 7.26). Crops erupt episodically for 2–4 weeks, and individual lesions usually fade over 3–5 days. Confluent ecchymoses occasionally evolve from confluent small lesions, and rarely necrosis and hemorrhagic bullae develop. Scalp edema and periarticular swelling (Schönlein purpura), and paroxysmal abdominal colic with melena or frankly bloody stools (Henoch purpura) may occur before, during, or after the rash. Vasculitis may also involve vessels in the kidneys, lungs, and central nervous system.

Recurrences occur in about half of patients for up to several months, but these episodes are usually mild. In most cases, the visceral disease is self-limiting. However, acute renal failure develops rarely and intussusception may complicate vasculitis in the bowel. More subtle renal disease may persist or develop over years and requires long-term monitoring.

Leukocytoclastic vasculitis involves small, dermal blood vessels, usually postcapillary venules. Classic histologic findings include endothelial swelling, fibrin deposition within and around the vessels, neutrophilic infiltrate within the vessel walls, and nuclear dust (scattered nuclear fragments from neutrophils). Vascular destruction with hemorrhage may be prominent. Fresh biopsies demonstrate IgA and C3 deposition around the dermal blood vessels.

Although most children with HSP may be observed at home, patients with progressive renal disease or severe abdominal pain require hospitalization.

A normal blood count, platelet count, and coagulation studies help to differentiate HSP from intravascular forms of purpura. Identification of typical clinical findings and course, histopathology, and other screening studies (e.g. antinuclear antibodies, ANA; rheumatoid factor, precipitin antibodies) exclude lupus erythematosus and other connective tissue disorders.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a leukocytoclastic vasculitis that involves small- and medium-sized arteries. A systemic form, which occurs extremely rarely in children, presents acutely with fever, weakness, abdominal pain, and cardiac failure. Despite treatment with high-dose corticosteroids and immunosuppressive agents, death may ensue quickly from renal failure, gastrointestinal bleeding, and bowel perforation. Cutaneous lesions, which include livedo reticularis, erythema, and purpura on the lower extremities, are not diagnostic.

Cutaneous PAN is more likely to come to the attention of the dermatologist. In this distinct variant, cutaneous findings predominate and the viscera are usually spared. Crops of painful nodules and annular plaques blossom on the arms and legs, particularly the hands and feet, and less commonly on the trunk, head, and neck (Fig. 7.27). Urticaria, livedo, and cutaneous ulcerations may also develop. Episodes last for several weeks and tend to recur for years. Although severe systemic disease does not usually occur, fever and arthralgias frequently accompany flares in disease activity.

The diagnosis of cutaneous PAN is made by establishing the clinical pattern and histopathology, which demonstrates a leukocytoclastic vasculitis of medium-sized arteries. Patients usually respond quickly to prednisone, but resistant cases require methotrexate or azathioprine. Nodules localized to the palms and soles melt away with intralesional corticosteroids. Long-term monitoring is required to detect those children who develop severe systemic involvement.

The painful nodules of cutaneous PAN may be difficult to differentiate from erythema nodosum, cold panniculitis, and lupus panniculitis, particularly early in the course. Associated clinical findings and histopathology, however, are distinctive in these disorders.

Infectious vasculitis

Although overwhelming infection with a number of bacterial organisms may trigger rapidly fatal disseminated intravascular coagulation with widespread bleeding into the skin, mucous membranes, and viscera, many patients develop discrete vasculitic lesions. In fact, the presence of 0.5–2 cm diameter, angulated, pink-to-red, hemorrhagic macules, papules, pustules, and plaques is associated with a relatively good prognosis (Fig. 7.28). Over several hours lesions become hemorrhagic and central necrosis with bulla formation or ulceration may develop. Prompt recognition of this condition and the initiation of antibiotics and supportive care may be lifesaving.

Although the rash may be caused by hematogenous dissemination of the organism to the skin, many lesions result from immune complex deposition in dermal vessels. For example, Osler nodes (tender nodules on the finger or toe pads) and Janeway lesions (small, painless nodules on the palms and soles) probably represent an immune-mediated phenomenon (Fig. 7.29). *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Haemophilus influenzae* type



Fig 7.26 Henoch–Schönlein purpura. Vasculitic lesions typically erupt on the extensor surfaces of the **(a)** arms, **(b)** legs, and **(c)** buttocks. Any area, including the **(d)** face and **(e)** genitals, may be involved. Non-pitting edema of the face, chest, and genitals may be prominent as in the child shown in **(e)**. **(f)** Necrosis of skin overlying the vasculitic papules may result in vesicles and bullae, particularly on the feet.

B, *Streptococcus pneumoniae*, other *Streptococcus* spp., and *Staphylococcus aureus* have been cultured from blood and skin in normal hosts with infectious vasculitis (Fig. 7.29d). Rocky Mountain spotted fever may produce a similar clinical picture, but the inflammation tends to be primarily lymphocytic. In immunosuppressed individuals these organisms, as well as opportunistic bacteria and fungi, must also be considered.

Ecthyma gangrenosum

Ecthyma gangrenosum, characterized by a punched-out ulceration with a central opalescent eschar and a hemorrhagic border, results from *Pseudomonas* septicemia (Fig. 7.30). Lesions typically appear on the lower abdominal wall, thighs, and groin in leukemics, burn patients, and other debilitated individuals who have been on antibiotics. Although most patients are severely ill with multiple lesions,

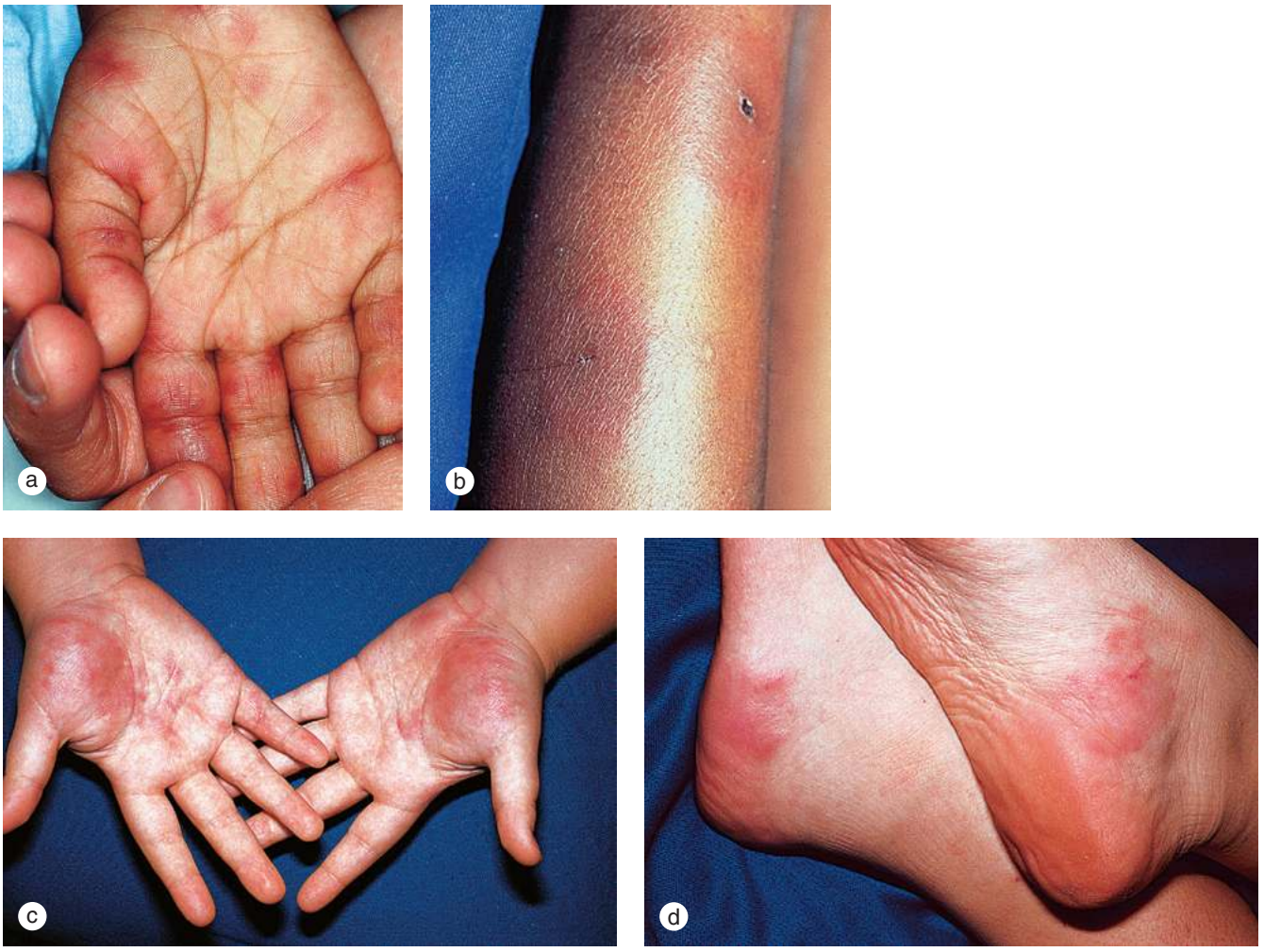


Fig 7.27 Polyarteritis nodosa. Over several days a 3-year-old girl developed painful nodules on the trunk, face, and extremities. **(a)** Lesions on the hands were associated with arthritis. **(b)** Some of the nodules on the legs developed central necrotic vesicles. A 13-year-old girl with chronic cutaneous polyarteritis nodosa complained of recurrent, painful, violaceous nodules on her **(c)** hands and **(d)** feet.

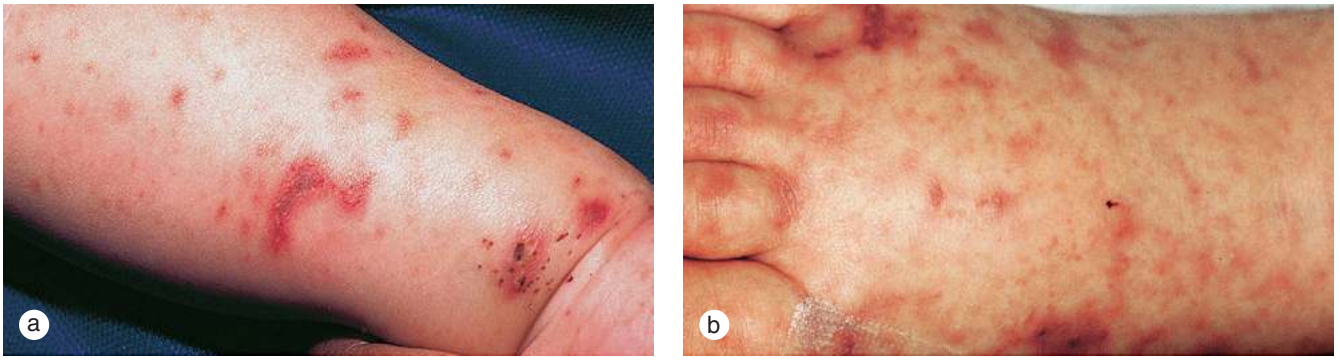


Fig 7.28 Infectious vasculitis. **(a)** Sharply angulated, purpuric, and necrotic papules developed on the extremities of a toddler with meningococcemia. He presented with meningitis and responded quickly to parenteral antibiotics. **(b)** A similar rash appeared on the extremities of a 6-year-old boy with Rocky Mountain spotted fever. In both children vasculitic papules spread to the palms, soles, and (to a lesser extent) the trunk.



Fig 7.29 Infectious vasculitis. **(a)** Osler nodes, splinter hemorrhages, and **(b)** Janeway lesions appeared on the hands and feet of this 10-year-old boy with acute bacterial endocarditis caused by *Staphylococcus aureus*. **(c)** Another child with subacute bacterial endocarditis developed vasculitis papules on his ears. **(d)** These exquisitely tender pustules on the right index finger and left ankle were the only cutaneous findings in a 16-year-old girl with gonococcal arthritis dermatitis syndrome. Blood cultures were negative, but cultures from the cervix grew *Neisseria gonorrhoeae*.

in some cases only one or several indolent ulcers are present. Other Gram-negative organisms, as well as fungi such as *Candida* and *Aspergillus* spp., may produce the same type of skin lesions.

The diagnosis can be made by searching for organisms in Gram-stains obtained from pustules and necrotic ulcers. Identification of specific organisms from blood and tissue cultures is required to select the appropriate antibiotics. Skin biopsies show a necrotizing vasculitis with neutrophils and a variable number of bacteria within vessels. Aplastic patients may show minimal inflammation with large numbers of organisms.

Lymphocytic vasculitis

Rather than being a distinct entity, lymphocytic vasculitis represents a reaction pattern in the skin found in a number of disorders in which lymphocytic inflammation predominates. Lymphocytic vasculitis has been described in cutaneous drug reactions, vasculitic lesions of Sjögren syndrome, and as a late phase of leukocytoclastic vasculitis. Pigmented purpuric dermatosis (PPD, Schamberg disease) is the only disorder in which lymphocytic vasculitis occurs consistently.

The development of asymptomatic localized patches of petechiae and larger patches of purpura, particularly on the lower extremities, characterizes PPD (Fig. 7.31a). Hemosiderin deposition and postinflammatory hyperpigmentation lead to shades of brown, gold, and bronze as lesions evolve. Confluent patches may form a reticulated pattern. Although lesions are usually flat and asymptomatic, fine scale and lichenoid papules may be associated with mild pruritus. In the lichen aureus variant rusty brown patches on the trunk, particularly the lower back, have been misdiagnosed as child abuse (Fig. 7.31b). Occasionally, disseminated lesions erupt over a few days to a few weeks and resolve over 2–3 months. This variant of PPD may overlap clinically and histologically with purpuric pityriasis rosea (Fig. 7.31c).

Skin biopsies from active areas demonstrate lymphocytes around and within the walls of superficial dermal capillaries. Mild hemorrhage and hemosiderin deposition are also present.

Clinically and histologically, it may be impossible to differentiate PPD from a drug reaction, and occasionally practitioners have reported children with large patches over the lower back or buttocks for suspected abuse. Unfortunately, no treatment has proved satisfactory, and lesions may persist for years. Systemic and topical corticosteroids and pulsed dye laser therapy may arrest progression temporarily.

Sweet syndrome

Sweet syndrome, also referred to as acute febrile neutrophilic dermatosis, is characterized by violaceous, 0.5–3 cm diameter nodules and plaques that erupt abruptly on the face and extremities (Fig. 7.32). Recurrent crops of nodules that appear over 1–8 months are heralded by high fever, arthralgias, and occasionally periarticular swelling and arthritis. Necrotic vesicles and bullae may also form. Although Sweet syndrome is self-limiting, symptoms may be debilitating. Skin lesions, arthralgias, and fever usually melt away with systemic corticosteroids; however, recurrences are common when the medication is tapered.

Although initially described in middle-aged women, a number of cases have been reported in infants and children. About 10% of adult cases are associated with myeloproliferative disorders,

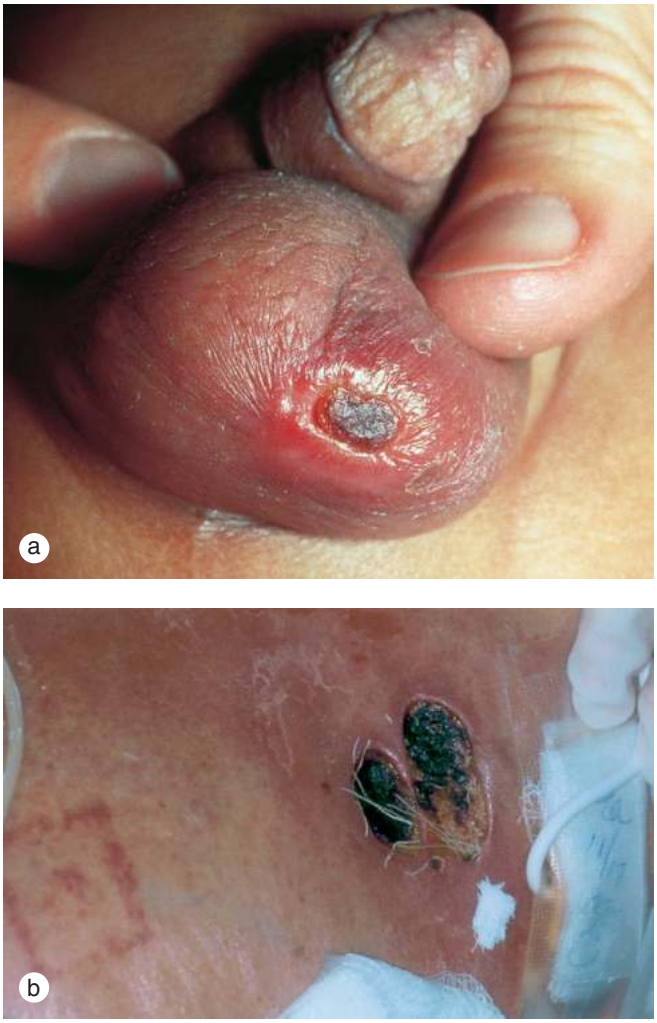


Fig 7.30 Ecthyma gangrenosum. **(a)** An infant with an inherited immunodeficiency experienced recurrent episodes of Gram-negative septicemia. *Pseudomonas* grew from cultures obtained from blood and the necrotic, crusted ulcer on the scrotum. **(b)** This 6-year-old liver transplant recipient developed a high fever and black necrotic bullae which ulcerated on his lower abdominal wall. A skin biopsy of the ulcer and blood cultures grew Gram-negative *Citrobacter*.

especially acute myelocytic or myelomonocytic leukemia. Children with this syndrome require a thorough physical examination and laboratory evaluation, including a blood count, peripheral smear, and bone marrow biopsy, to exclude any underlying disorder.

Sweet syndrome may be confused with erythema multiforme, erythema nodosum, viral exanthems, HSP, infectious vasculitis, and PAN. Although Sweet syndrome may be suspected because of the cutaneous lesions and clinical course, skin biopsy of a fresh lesion demonstrates diagnostic findings, which include a dense, perivascular, neutrophilic infiltrate and intense edema in the upper dermis, some leukocytoclasia without true vasculitis, and in some cases subepidermal bullae formation.

Pyoderma gangrenosum

In pyoderma gangrenosum, painful pustules or nodules develop central necrosis and an enlarging ulcer with a hemorrhagic, purple, undermined, advancing border (Fig. 7.33). Ulcers range in size from about 1 cm in diameter when they first appear to over 10 cm as they evolve. One or several lesions may occur, and any area, including the face, trunk, and extremities, may be involved. Lesions rarely develop in the upper airway and trachea. Pathergy, or the development of new lesions at sites of trauma, such as venipunctures, is a reliable diagnostic clue. An underlying systemic disease, such as inflammatory bowel disease, myelogenous leukemia, or rheumatoid arthritis, is associated with cutaneous lesions in half of the cases.



Fig 7.31 Progressive pigmented purpuric dermatosis. **(a)** Reticulated hyperpigmented patches had slowly advanced across the leg of a 15-year-old girl for years. **(b)** A golden brown eruption on this pre-schooler's left buttock was thought originally to represent physical abuse. **(c)** A diffuse asymptomatic eruption on this 9-year-old boy resolved without treatment 8 weeks after it appeared. Histologic findings were typical of pigmented purpura.

Skin biopsies show typical (but non-diagnostic) findings, which include a lymphocytic vasculitis at the advancing border and necrosis with abscess formation and reactive polymorphous inflammation that extends into the subcutaneous tissue.

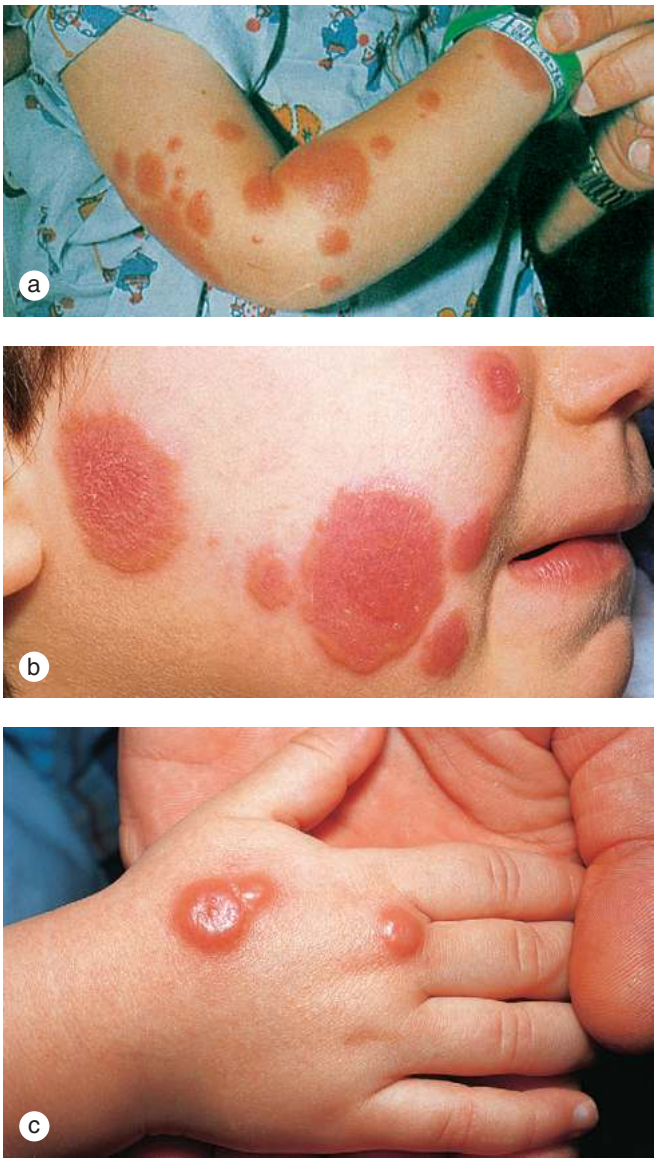


Fig 7.32 (a–c) Sweet syndrome. A 2-year-old girl developed fever, arthritis, leukocytosis, and widely disseminated, red-to-violaceous plaques and nodules, which demonstrated intense neutrophilic inflammation on skin biopsy. An extensive evaluation failed to reveal any underlying disease. Although she responded quickly to systemic corticosteroids, it took nearly a year to wean her because of frequent recurrences.

Pyoderma gangrenosum usually responds to treatment of the underlying condition. Idiopathic cases can be treated with antibiotics, systemic corticosteroids, dapsone, or tumor necrosis factor inhibitors. Resistant cases may require immunosuppressive agents such as azathioprine, methotrexate, or cyclosporine.

Granulomatous vasculitis

Granulomatous vasculitis is a term used to describe necrotizing granulomatous inflammation restricted to blood vessels. However, in Wegener granulomatosis and allergic granulomatosis (Churg–Strauss syndrome), which occasionally occur in children, granuloma formation typically occurs in extravascular sites.

In Wegener granulomatosis, necrotizing vasculitis and granulomas involve the upper and lower respiratory tracts and are accompanied by a focal necrotizing glomerulonephritis. Arteries and veins in multiple organs can be involved including the skin.



Fig 7.33 Pyoderma gangrenosum. **(a)** A 9-year-old boy developed a painful, expanding, crusted, necrotic plaque with an undermined border on his arm. An exhaustive medical evaluation was unrevealing until bone marrow biopsy demonstrated chronic myelogenous leukemia. **(b)** A similar plaque in a teenager with Crohn disease shows cribriform scarring as inflammation abates. Lesions in both children healed after aggressive treatment of the underlying disorders.

Cutaneous lesions (Fig. 7.34) including painful papules, nodules, necrotic vesicles, and large ulcers resembling pyoderma gangrenosum may disseminate over the extensor surfaces of the extremities and buttocks. Although not diagnostic, 80% of patients demonstrate antineutrophil cytoplasmic antibodies usually of the cytoplasmic type (c-ANCA).



Fig 7.34 Wegener granulomatosis. This 17-year-old boy developed ulcerated nodules on his nose in association with renal and pulmonary disease. All lesions cleared with systemic steroids and cyclophosphamide.

The cutaneous features of allergic granulomatosis overlap Wegener granulomatosis. However, this disorder is distinguished by the presence of systemic vasculitis associated with hypereosinophilia in the setting of pre-existing asthma and allergic rhinitis. Tender nodules may arise on the scalp or more widely on the extremities and less commonly the trunk. Distinctive histologic findings include a necrotizing vasculitis, tissue infiltration by eosinophils, and extravascular granulomas.

FIGURATE ERYTHEMA

A number of disorders are characterized by the development of annular plaques with a well-defined, advancing, red border and central clearing. Typical, but non-diagnostic, histologic findings include a tight, perivascular, mononuclear cell infiltrate in the superficial dermis with occasional extension to the mid and deep dermis. The overlying epidermis is normal or shows mild spongiosis. Erythema annulare centrifugum (EAC) and erythema chronicum migrans now usually referred to as erythema migrans, are the most commonly recognized figurate erythemas in children.

Erythema annulare centrifugum

In erythema annulare centrifugum (EAC), one or multiple asymptomatic, expanding, annular or serpiginous, red plaques with well-defined raised borders and trailing scales on the inner aspect of the border occur (Fig. 7.35). As lesions progress from <1 cm to over 20 cm in diameter over several weeks, new plaques may arise within the borders to produce concentric rings. The eruption typically spreads from the central trunk to the proximal extremities (centrifugal), and lesions continue to evolve for months to years.

Although EAC probably represents a hypersensitivity reaction to the same sort of phenomena that trigger urticaria and other reactive erythemas, a number of reports suggest a common association with chronic dermatophyte infection (e.g. tinea pedis, tinea cruris). Cases of EAC may erupt throughout childhood, but it occurs most commonly in adults. Annular erythema of infancy is undoubtedly a clinical variant of this disorder (Fig. 7.35c).

The persistence of individual lesions and lack of pruritus differentiate EAC from urticaria. The chronic course and absence of viral symptoms help to exclude an urticarial viral exanthem. Granuloma annulare may be excluded by the finding of epidermal changes (erythema and scale) in EAC. Although there are no specific laboratory tests for EAC, skin biopsy typically shows a tight, lymphocytic, perivascular infiltrate (coat-sleeve pattern) in the mid- and deep dermis. Dermatitic changes may also be present in the epidermis.

When a fungal infection is identified, oral antifungal medications may result in clearing of the rash. Otherwise, no specific treatment is indicated.

Erythema migrans

In erythema migrans, which marks the onset of Lyme disease, a single papule begins 3–30 days after a tick bite and expands quickly to form an enlarging, annular, red plaque with central clearing (Fig. 7.36). New lesions resulting from hematogenous spread of the organism may continue to evolve successively or in crops over several months. Plaques over 4 cm in diameter are typical, and some may exceed 30 cm. Mild, influenza-like symptoms, which include headache, sore throat, arthralgias, and malaise, are commonly associated with the skin rash. If untreated, resolution of skin lesions is followed several months later by a pauciarticular arthritis that involves the knees, elbows, and/or wrists in 50% of patients. In 15% of cases, neurologic abnormalities, including meningoencephalitis, neuropathy, or facial palsy, occur 2 weeks to 8 months after the tick bite. Cardiac symptoms, which appear in 5% of patients, may mimic rheumatic fever.

Lyme disease is caused by the spirochete *Borrelia burgdorferi*, which can be carried by *Ixodes dammini* and related ticks (Fig. 7.36e). These ticks are widely distributed throughout the USA and

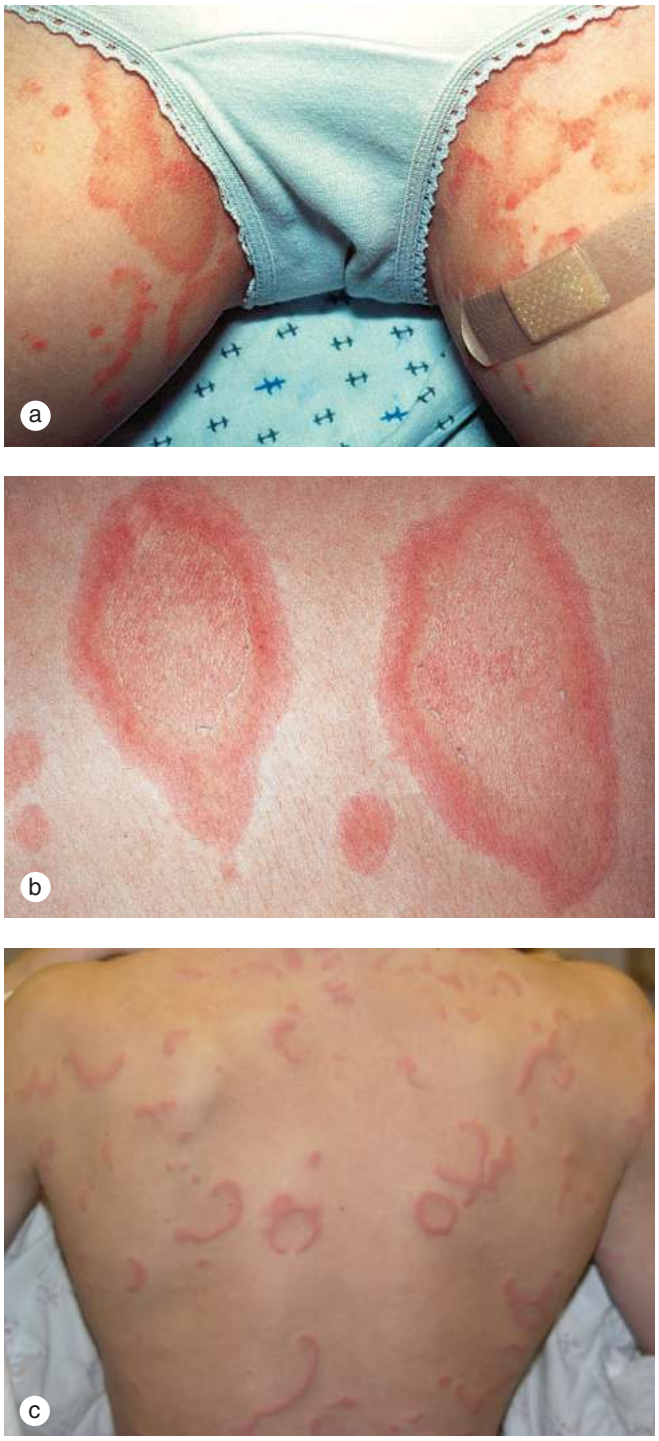


Fig 7.35 Erythema annulare centrifugum. **(a)** Symmetric, annular, red plaques slowly expanded on the anterior thighs of a 10-year-old girl. **(b)** Another child with large lesions on the trunk demonstrates the bright red border with fine trailing scale and central clearing. **(c)** Like his father, this adolescent boy has had a generalized evolving annular eruption since early infancy.



Fig 7.36 Erythema chronicum migrans. **(a)** A solitary, indurated, light-pink plaque with central clearing grew over several weeks from a small, red papule at the site of a tick bite. The lesion, as well as associated arthralgias and intermittent low-grade fever, resolved within 48 h of starting oral amoxicillin. **(b)** In many children multiple papules and plaques appear as the organism disseminates. **(c)** In this 12-year-old girl, two solid, dark-red patches were initially diagnosed and treated as cellulitis. **(d)** This adolescent boy developed several concentric expanding rings around the central tick bite. **(e)** The spirochete is transmitted from animals to humans by the tiny *Ixodes dammini* and related tick vectors.

Europe, and in many places such as coastal New England, the Great Lakes States, and the Mid-Atlantic Coast the infection has become endemic. The ticks are the size of a pinhead, and up to 50% of patients do not recall the bite.

The incidence of Lyme disease is highest in children, particularly boys, in whom multiple lesions are common, but all ages are affected. Although the diagnosis is usually made clinically, new, more reliable serologic tests may aid in differentiation of the annular plaques of erythema migrans from urticaria, viral exanthems, erythema marginatum, and EAC. Skin biopsy specimens obtained from the expanding border or the center of lesions may demonstrate spirochetes with the use of special silver stains in up to 50% of cases. When available, polymerase chain reaction studies and immunoperoxidase staining of monoclonal antibodies to the axial filaments of *Borrelia* are highly sensitive and specific. Otherwise, the histopathologic findings are not diagnostic and show changes typical of insect-bite reactions.

Any individual in an endemic area who develops an annular eruption, especially if it is associated with viral symptoms and a tick bite, should be treated to reduce the risk of arthritis and other late complications. Although treatment recommendations vary, a 14–21-day course of doxycycline 100 mg twice a day is the choice for older children and adults, and amoxicillin at a dose of 25–50 mg/kg per day, with a maximum of 2 g daily given in three divided doses, is recommended for children younger than 8 years old. Children allergic to penicillin may be treated with cefuroxime, 30 mg/kg per day in two divided doses (maximum 1000 mg/day or 1.0 g/day for 14–21 days).

Avoiding tick-infested areas or wearing protective clothing reduces the risk of exposure. Tick repellents containing

diethyltoluamide are also effective. However, excessive use of diethyltoluamide, particularly in infants and young children, has been associated with neurotoxic reactions. Low-concentration lotions (Skedaddle® 7.25% and OFF® 10%) are as effective as traditional repellents with concentrations over 50% and have a much better safety profile. The American Academy of Pediatrics currently recommends the use of products containing up to 30% DEET. Alternative repellents containing picaridin may also be effective. Tick inspections after hikes and camping trips and removal of ticks within 24–48 h of attachment also reduce transmission of the spirochete. Prophylactic treatment of tick bites before the development of erythema migrans has not been shown to be effective.

PANNICULITIS

Panniculitis refers to a group of disorders in which an inflammatory process involves the fat lobules, intervening fat septae, or both. Clinically, patients present with deep-seated, poorly defined, tender, violaceous nodules. The overlying epidermis is usually intact, although it may be taut and shiny. If necrosis develops, ulcerations may occur.

Erythema nodosum

Erythema nodosum (EN) is the most common panniculitis to appear in children, usually in adolescents. Typically, painful, red, subcutaneous nodules and plaques, 1–5 cm in diameter, erupt on the shins, but lesions may also involve the arms and thighs, and rarely the trunk and face (Fig. 7.37). Nodules usually fade over several weeks, but recurrences are frequent. In some cases, crops recur for months.

Over 100 years ago, the development of EN with tuberculosis was recognized. More recently, EN has been associated with a number of infections, including viral pharyngitis, streptococcal pharyngitis, histoplasmosis, coccidioidomycosis, and other deep fungi and atypical mycobacteria. Non-infectious inflammatory conditions, such as sarcoidosis, inflammatory bowel disease, and lupus erythematosus, may trigger the reaction.

The finding of a septal panniculitis without fat necrosis is characteristic of EN. Early in the course neutrophilic inflammation is common. Later, lymphocytes, histiocytes, and giant cells predominate. Vessels show endothelial cell swelling, inflammation in the vascular walls, and hemorrhage.

In most children, EN is self-limiting and treatment, when necessary, is tailored to the underlying disorder. Leg elevation and nonsteroidal anti-inflammatory agents may help to reduce the pain.

Cold panniculitis

In infants and young children, cold injury results in crystallization and rupture of fat cells and subsequent inflammation. Persistent, indurated, red nodules and plaques appear most commonly on the cheeks, but the trunk and extremities may also be involved (Fig. 7.38). Ulceration and atrophy do not usually develop, and nodules resolve without treatment in several weeks to several months.

Although the cause is not known, the increased saturation of fatty acids in the subcutaneous fat of infants compared with adults makes their fat more prone to solidification at low temperatures.

Subcutaneous fat necrosis of the newborn is a variant of cold panniculitis that occurs within the first month of life. Several circumscribed lesions appear on the trunk and proximal extremities in an otherwise healthy infant. Nodules heal without scarring, but transient depression of the skin surface occurs frequently and ulceration on occasion. Even after the skin lesions have resolved, affected infants should be monitored for up to 6 months of age for hypercalcemia and resultant renal calcinosis and failure to thrive.

Cold injury may also produce sclerema of the newborn. In this process, widespread, woody induration of the skin develops in a severely ill infant. This process probably results as a complication of multisystem failure and associated cooling of the skin and fat from decreased cutaneous perfusion. In skin biopsies from these

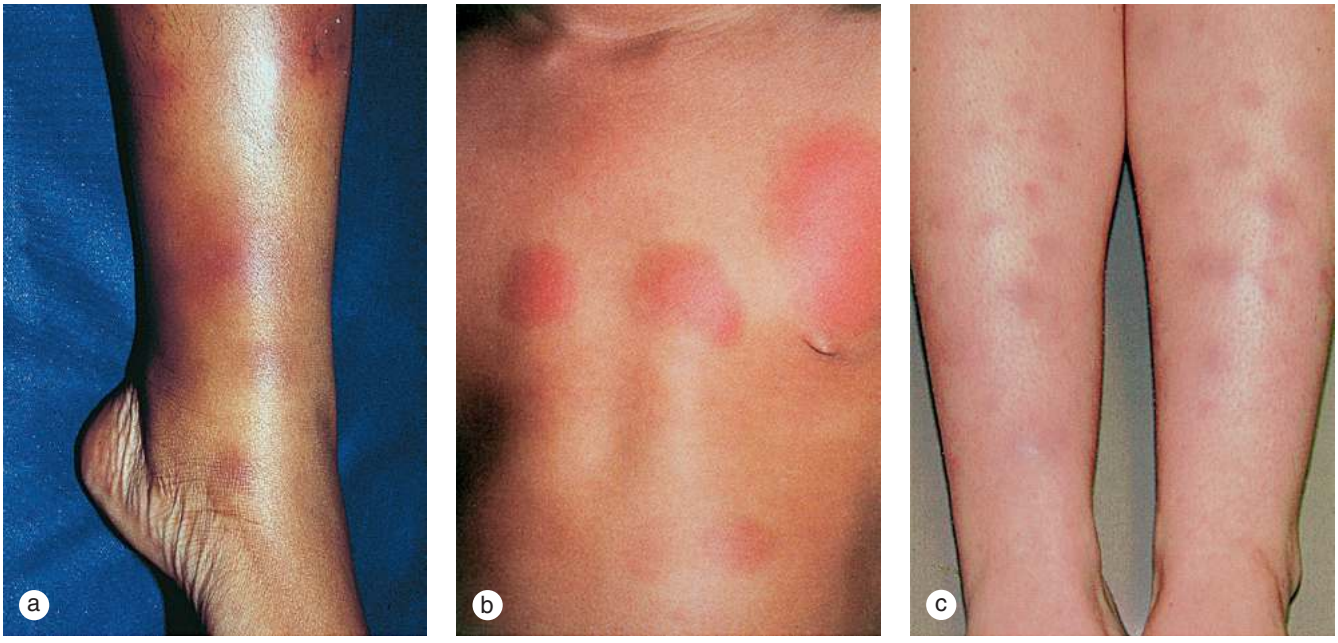


Fig 7.37 Erythema nodosum. **(a)** Tender, deep-seated nodules appeared on the shins of a 16-year-old girl 2 weeks after starting birth-control pills. The lesions resolved when the medication was discontinued. **(b)** An 18-month-old boy developed (biopsy proved) erythema nodosum on the chest and abdomen following a cold. The nodules resolved without therapy over several weeks. **(c)** This 15-year-old girl developed recurrent biopsy-proven erythema nodosum on her shins with flares of her systemic lupus erythematosus.



Fig 7.38 (a) Cold panniculitis appeared on the cheeks and chin of this 6-month-old infant 1 day after he was given an ice-filled teething ring. **(b)** This healthy newborn had tender subcutaneous confluent nodules on her back at birth. All lesions resolved by 2 months of age, and calcium studies were normal.

infants, edema of the fibrous septae is found with no necrosis of fat cells. Subcutaneous fat necrosis of the newborn and cold panniculitis in older infants and children are associated with necrosis of fat cells and granulomatous inflammation.

Morphologically, cold panniculitis may be confused with bacterial cellulitis (Fig. 7.39). However, in cellulitis the indurated plaques are warm, tender, and progressive, and the patients are febrile and of toxic appearance. Other nodular erythemas, such as polyarteritis nodosa and EN, are usually differentiated by the clinical course and skin biopsy findings when necessary.

Lupus panniculitis

In lupus panniculitis, persistent, purple, painless nodules, 1–5 cm in diameter develop on the face, extremities, and buttocks (Fig. 7.40). Although these lesions man occur in a child with other signs of systemic lupus erythematosus (SLE), they may be the first or only manifestation of the disease. Individual lesions may persist for months to years, and ulceration, scarring, and/or atrophy occur frequently. Unfortunately, lupus panniculitis is often resistant to treatment with antimalarial drugs, and the use of systemic corticosteroids and immunosuppressive agents should probably be guided by systemic symptoms.

Histopathology is non-specific and shows lymphohistiocytic inflammation within the fat lobules and hyalinization of fat cells. Inflammation and vasculitis may also occur in the fat septae.



Fig 7.39 Facial cellulitis/erysipelas. A painful, indurated, red plaque spread within several hours across the cheek of this 17-year-old girl. She also had a fever and tender cervical adenopathy, which resolved on parenteral penicillin.

PHOTOSENSITIVITY

Photosensitivity is a term used to describe a group of conditions marked by abnormal reactions to light. Sunburn is a phototoxic reaction that results from exposure to naturally occurring, short-wavelength, ultraviolet (UV) B light. Longer wavelength (UVA) light is only weakly phototoxic; however, all individuals deliberately or accidentally exposed to high-enough doses of topical or oral UVA-photosensitizing agents may also develop burns. In photoallergic reactions, susceptible patients, who are exposed to certain photosensitizing chemicals or drugs, develop an immunologically mediated rash which is activated by light. A number of genetic and metabolic disorders are associated with photosensitivity, and the recognition of cutaneous findings may be a clue to diagnosis. Photodermatoses include several specific conditions that have unusual reactions to light. In some of these dermatoses, the action spectrum, or the wavelengths that trigger the skin findings,



Fig 7.40 Lupus panniculitis. A 13-year-old boy presented with chronic, recurring, deep-seated nodules and plaques, which healed with punched-out scars.

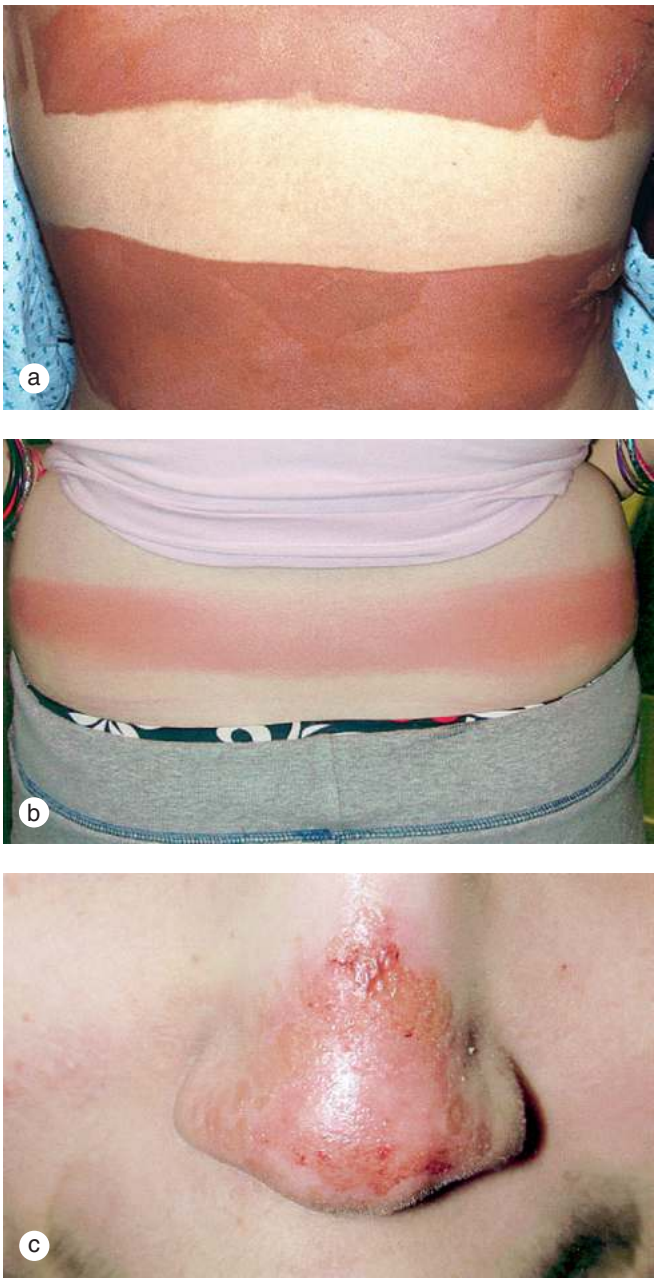


Fig 7.41 Phototoxic reaction. **(a)** A severe sunburn developed in sun-exposed areas after this teenager applied a topical photosensitizing cream to her skin and spent the day outdoors. Note the areas of sparing under her bathing suit. **(b)** This adolescent lacrosse player was burned in a narrow unprotected band above her waist. **(c)** A 16-year-old boy returned from a winter ski trip where he forgot to protect his nose with sun screen.

have been described. Finally, other diseases may be exacerbated by light. The recognition of this phenomenon may be important in managing these conditions.

Phototoxic and photoallergic reactions

Exposure of the skin to sunlight results in a number of biologic reactions. Small amounts of UVB activate the conversion of 7-dehydrocholesterol into vitamin D3. Large amounts of UV light produce erythema and swelling, known as sunburn (Fig. 7.41). Intense reactions may result in the development of blistering burns on sun-exposed surfaces. Healing is marked by desquamation, thickening, and hyperpigmentation of the skin.

Although UVB is 100 times more erythemogenic than UVA, the large quantity of UVA (1000× UVB) that reaches the ground contributes substantially to sunburn (10–15%). On overcast days, when 15–20% of UVB is absorbed and scattered by the cloud cover, the role of UVA is even greater. The minimum dose of light required to produce a discrete area of sunburn is referred to as the minimal erythema dose (MED). The MED tends to increase with increasing skin types. Individuals with skin type 1 always burn and never tan. These people have blonde or red hair, blue eyes, and often demonstrate freckling in sun-exposed sites. Skin type 2 denotes individuals who always burn at first, but sometimes tan after repeated sun exposure. Type 3 people occasionally burn, but tan readily. Olive-complected individuals who always tan fall into type 4. Types 5 and 6 include members of darkly pigmented races.

Factors that potentiate the development of sunburn include increasing elevation above sea level, wind, low humidity, and applications that result in thinning of the epidermis, such as peeling agents (topical retinoids, salicylic acid, lactic acid). Damage to DNA is the initiating event in the development of the erythema response. The subsequent production of inflammatory mediators (e.g. prostaglandins, histamine) triggers the clinical response. Factors that interfere with normal DNA repair mechanisms (hereditary defects in DNA repair enzymes or antimetabolites, such as methotrexate) result in an exaggerated, recurrent, or prolonged erythema response.

Wrinkling, elastosis, lentigines, and other 'age'-related changes in the skin result from long-term exposure to sunlight; the majority of most individual's lifetime exposure occurs during childhood and young adult life. It has been estimated that the incidence of non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) could be reduced by 75–80% if people used sun-protective clothing, sunscreens (chemicals that absorb UV light), and sunblocks (agents that reflect sunlight) from early childhood. Although most sunscreens (e.g. p-aminobenzoic acid, its esters, and cinnamates) provide good coverage against UVB, the number of UVA-protective agents is limited (see Chapter 1, Table 1.6). The sun-protective factor (SPF) of a product is determined by calculating the ratio of the MED of unprotected skin to the MED of sunscreen-protected skin. In infants, who should not be left in the sun, sunscreens are only rarely necessary. Parents of ambulatory children, particularly individuals with light pigmentation, should be given aggressive counseling about sun protection. People with skin types 1–2 must use sunscreens/sunblocks with an SPF of 15–30, whereas darker-pigmented individuals may be safe with lower SPFs, particularly after gradually increasing sun exposure has produced protective darkening of the skin. New sun protection guidelines were recently released by the FDA but more specific recommendations are still pending.

Unlike phototoxicity, photoallergic reactions involve an immunologic response in a small number of individuals who are sensitized to certain chemicals or drugs in the presence of sunlight. In many cases, a Type IV delayed hypersensitivity reaction results in the development of an eczematous dermatitis in a sun-exposed distribution, rather than a sunburn. A number of medications have been implicated in the production of both phototoxic and photoallergic reactions. Some of the most common photosensitizers are furocoumarins, nalidixic acid, dyes, salicylanilides, fragrances, p-aminobenzoic acid, phenothiazines, sulfonamides, tetracyclines, thiazides and related sulfonamide diuretics, and non-steroidal anti-inflammatory agents. Pseudoporphyria, cutaneous photosensitivity resulting in symptoms and skin findings mimicking porphyria in individuals without evidence of a defect in porphyrin metabolism, has been reported with exposure to a number of medications and most commonly non-steroidal anti-inflammatory drugs. Patients

on these drugs must be warned to protect themselves against the risk of photosensitivity.

Rarely, photoactivated, eczematous reactions persist for months or years. A persistent light reaction usually evolves from a previous photocontact allergic dermatitis, but oral medications have been implicated as well. In actinic reticuloid, the chronic dermatitis often spreads to involve covered sites, the lesions become lichenified and nodular, and skin biopsies may show lymphoma-like infiltrates in addition to a chronic dermatitis. In these patients, the dermatitis may be reproduced on normal patches of skin by exposure to UVA, UVB, and sometimes visible light, and MEDs at various wavelengths of UV light are markedly decreased. Some patients with atopic dermatitis note a flare of disease activity in sun-exposed sites. These individuals may be differentiated from patients with photoactivated eczematous reactions by the absence of exposure to photosensitizing drugs and topical agents, negative photopatch tests, and an abnormal MED to UVB only.

Photodermatoses

Polymorphous light eruption

Several photo-induced dermatoses may be identified by distinctive clinical and histologic findings. Polymorphous light eruption (PMLE) is the most common childhood photodermatosis, accounting for over 75% of photo-induced rashes. In PMLE, crops of red macules, papules, vesicles, or plaques typically erupt on exposed areas several hours to several days after intensive sun exposure in the early spring (Fig. 7.42). The morphology of lesions varies from patient to patient. However, the rash tends to be monomorphous in a given individual. PMLE appears most commonly in girls and women under 30 years old and may recur each spring for years. Although the rash usually progresses for several weeks, complete regression occurs within 3–4 weeks, despite continued light exposure. In fact, phototherapy (psoralen-UVA) has been used to trigger the reaction deliberately and treat or 'harden' the skin in a controlled setting to avoid inconvenient expression of the rash. PMLE is most common in temperate or northern climates, where the 'hardening' of the skin tends to wane during the winter months. In the sunbelt states and tropics, where sun exposure occurs all year round, the rash is less common and often spares the face and 'V' of the neck, which are most prominently exposed.

The histopathology of PMLE typically shows an intense, lymphocytic, perivascular infiltrate in the upper and mid dermis. Dermal edema may also be prominent. Differential diagnosis from lupus erythematosus may be difficult clinically and histologically. The histology of lupus usually demonstrates inflammation at the dermal–epidermal junction and the dermal infiltrate often surrounds both adnexal structures and vessels. However, early in the course of lupus the histology may be nonspecific, clinical findings may be confined to the skin, and serologic studies may be negative.

Solar urticaria

Although urticaria following sun exposure may be caused by medications or associated with systemic illness, such as lupus or porphyria, a rare group of otherwise healthy individuals develops hives within minutes of sun exposure. Although the lesions may become quite itchy and extensive, symptoms usually abate with continued light exposure. Various wavelengths of light, including UV and visible radiation, have been associated with hives.

In many cases, solar urticaria is caused by a Type I IgE-mediated reaction, and lesions result from the release of histamine and other vasoactive substances. In time, inflammatory mediators are depleted and lesions subside. Unfortunately, antihistamines only partially suppress solar urticaria. However, persistent light exposure can be maintained with phototherapy to keep the reaction under control.



Fig 7.42 Polymorphous light eruption. **(a)** Red papules and vesicles erupted on the face of a 14-year-old girl after a trip to the beach in the spring. She had experienced this phenomenon every spring for the previous 5 years. **(b)** An 8-year-old girl developed a mildly pruritic, papular rash on the tops of her hands and face after a spring picnic. In both girls the rashes peaked within several weeks and healed despite continuing sun exposure.

Genetic disorders

A number of inherited and metabolic disorders are associated with photosensitivity. In xeroderma pigmentosum, Bloom syndrome, Cockayne syndrome, and Rothmund–Thomson syndrome, light alone triggers an abnormal reaction in the skin and subsequent acute and chronic changes. Disorders that result in pigment dilution, such as albinism, phenylketonuria, and other aminoacidopathies, markedly increase sensitivity to phototoxic reactions. In congenital porphyrias, porphyria cutanea tarda, and Hartnup disease, endogenous metabolites function as potent photosensitizers (Fig. 7.43). In many of these disorders the clinical findings provide the key to diagnosis.

Photo-exacerbated disorders

Many disorders are triggered or aggravated by sunlight. For instance, although careful exposure to sun may result in improvement of psoriasis and repigmentation in vitiligo, sunburn often produces Koebner phenomenon and results in exacerbation of both disorders (Fig. 7.44). Sun exposure, particularly sunburn, is also known to exacerbate acne vulgaris, acne rosacea, erythema multiforme, viral exanthems, pemphigus and other bullous disorders, lichen planus, lupus erythematosus, pityriasis alba, and herpes labialis.

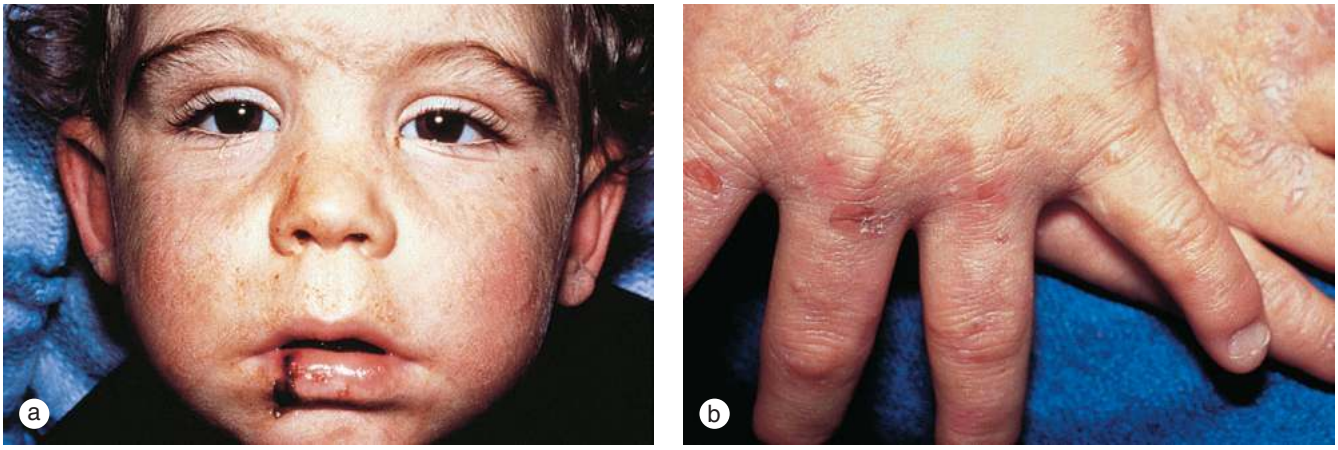


Fig 7.43 Congenital erythropoietic porphyria. Severe photosensitivity from accumulation of cutaneous porphyrins results in recurrent blistering and scarring in sun-exposed areas. **(a)** Note scarring, erosions, and hirsutism on his face and **(b)** scarring with milia formation on his hands.

COLLAGEN VASCULAR DISEASE

Collagen vascular disorders present with a myriad of confusing and overlapping cutaneous findings. Although the clinical picture and laboratory markers help to define a specific entity, often the practitioner is unable to make a definitive diagnosis. A number of autoantibody systems have been identified in these diseases. Antibodies target vascular endothelium and epithelial basement membrane zone structures, which results in cutaneous and visceral inflammation. In the skin, inflammation produces distinctive reaction patterns.

Lupus erythematosus

Lupus is a chronic multisystem disorder that can affect any organ system. Although systemic lupus erythematosus (SLE) was considered to be progressive, often with a fatal outcome, as recent as 25 years ago, the aggressive use of systemic corticosteroids and immunosuppressive agents has greatly improved the prognosis. Early intervention requires immediate recognition of variable and sometimes subtle signs and symptoms. Cutaneous findings may suggest the diagnosis.

The most common variant of lupus in childhood is SLE. Although the incidence is only 1:200 000 in childhood, nearly 25% of all

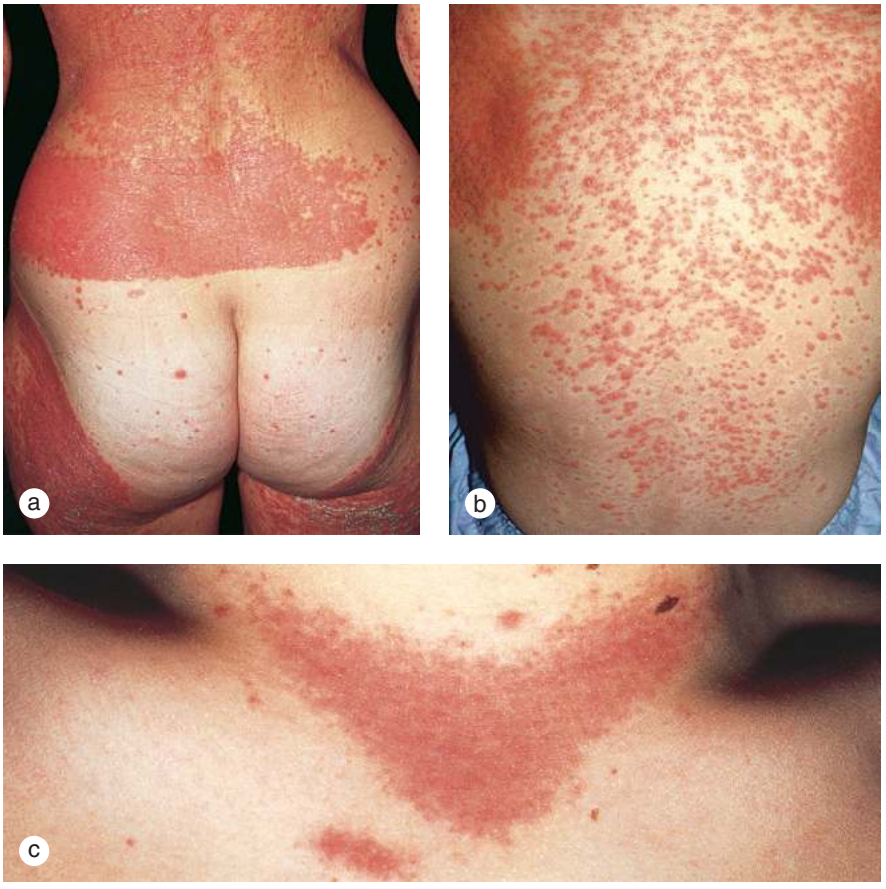


Fig 7.44 Photoexacerbated conditions. **(a)** This 18-year-old girl with psoriasis developed recurrent skin lesions in sun-exposed areas after a sunburn (Koebner phenomenon). **(b)** Photoexacerbation was evident in this child with varicella. The bathing trunk area was relatively spared. **(c)** For this girl, vasculitic plaques of Henoch–Schönlein purpura erupted in sun-exposed sites.



Fig 7.45 Discoid lupus erythematosus. **(a)** An atrophic, scaly, red plaque with a hyperpigmented border in the gluteal cleft showed histologic changes typical of lupus. **(b)** Atrophy, depigmentation, scarring alopecia, and telangiectasias persisted in an old lesion. **(c)** Follicular plugging, scale, atrophy and pigmentary changes were prominent on this adolescent's ears. **(d)** She also had lesions on the tops of her fingers.

cases begin before the age of 20 years. In young children, boys are affected almost as often as girls. However, in adolescence, when the incidence begins to rise, girls account for 80–90% of cases. Other forms of lupus, which are uncommon in childhood, include benign cutaneous or discoid lupus, lupus panniculitis, subacute cutaneous lupus, and neonatal lupus (see Fig. 2.93).

Discoid lupus lesions are the most common skin rash found in childhood SLE. This eruption is characterized by red, coin-shaped plaques 0.5–5 cm in diameter, with central atrophy and hypopigmentation, and peripheral hyperpigmentation (Fig. 7.45). Adherent scale, follicular plugging, and telangiectasias, especially in areas of atrophy, may be prominent. Although these plaques may develop on any area, sun-exposed sites, which include the face (in a malar distribution), scalp, ears, neck, upper trunk, and extensor surfaces of the arms are most commonly involved. Discoid lesions may be the sole cutaneous finding in SLE. However, when discoid lesions occur without systemic disease, the disorder is referred to as benign cutaneous or discoid lupus erythematosus (DLE). About 15–20% of patients with DLE eventually go on to develop SLE. These patients must be counseled and followed accordingly. Discoid plaques may progress and heal with extensive scarring. Topical corticosteroids, systemic corticosteroids, and antimalarial drugs are the mainstay of therapy, depending on the severity of the systemic disease. Topical retinoids have been used to remodel scars and treat hyperpigmentation when lesions go into remission.

Other cutaneous findings in SLE include red, edematous, malar rashes, diffuse, annular, psoriasis-like plaques in sun-exposed areas (subacute cutaneous lupus erythematosus), scarring and non-scarring scalp hair loss, rheumatoid nodules, nail fold telangiectasias, livedo reticularis, and palpable purpura that results from small vessel vasculitis (Fig. 7.46). Severe Raynaud phenomenon with digital infarcts may also develop. Mucous membranes can be involved, with nasal and oral ulcerations and painful erosions on the lip.

In addition to cutaneous features, the most common presenting complaints in SLE are fevers and arthralgias. Other common findings include pulmonary disease (pleuritis, pneumonitis – 66%), cardiac manifestations (pericarditis, myocarditis, endocarditis – 50%), lupus nephritis (60%), and central nervous system disease (50%).

Serologic findings may be very useful in establishing the diagnosis (Table 7.1). Almost 100% of patients with SLE have a positive antinuclear antibody (ANA). The rate of positivity varies, however, with the substrate used for the test. In the past, a subset of SLE patients were identified as ANA negative. Many of these patients have subsequently tested positive using Hep 2 cells, which are derived from a human tumor line, as a substrate. Although there is no direct correlation between ANA titers and disease activity, patients with high-titer ANAs tend to have active SLE. A number of other antibodies are also found in lupus patients and may



Fig 7.46 Lupus erythematosus. **(a)** A 13-year-old girl with systemic lupus erythematosus developed malar erythema, edema, and erosions associated with a flare of nephritis after spending a day in the sun at the beach. Other lesions typical of lupus include **(b)** annular, scaly patches and plaques, **(c)** psoriasis-like plaques, **(d)** erosions on the oral mucosa and vermilion border, and **(e)** Raynaud phenomenon with digital infarcts.

correlate with certain aspects of disease activity. One of these antibody systems, Ro (SSA) and La (SSB), which is directed against a small, cytoplasmic ribonuclear protein, is associated with photosensitivity, neonatal lupus, and subacute cutaneous lupus erythematosus. Ro and La are also found in Sjögren syndrome in the absence of SLE. Patients with photosensitivity should be counseled about sunscreens, protective clothing, and judicious sun exposure. Occasionally, systemic disease can be triggered by excessive sun exposure.

The symptoms of juvenile rheumatoid arthritis (JRA) may suggest the diagnosis of lupus (Fig. 7.47). However, the rash of JRA is urticarial and evanescent, peaking with fever spikes. Unlike the destructive arthritis of JRA, the arthritis in lupus is often transient and does not impair function. Many of the other reactive erythemas may share features with lupus. However, the diagnosis of lupus is dependent on clearly defined criteria.

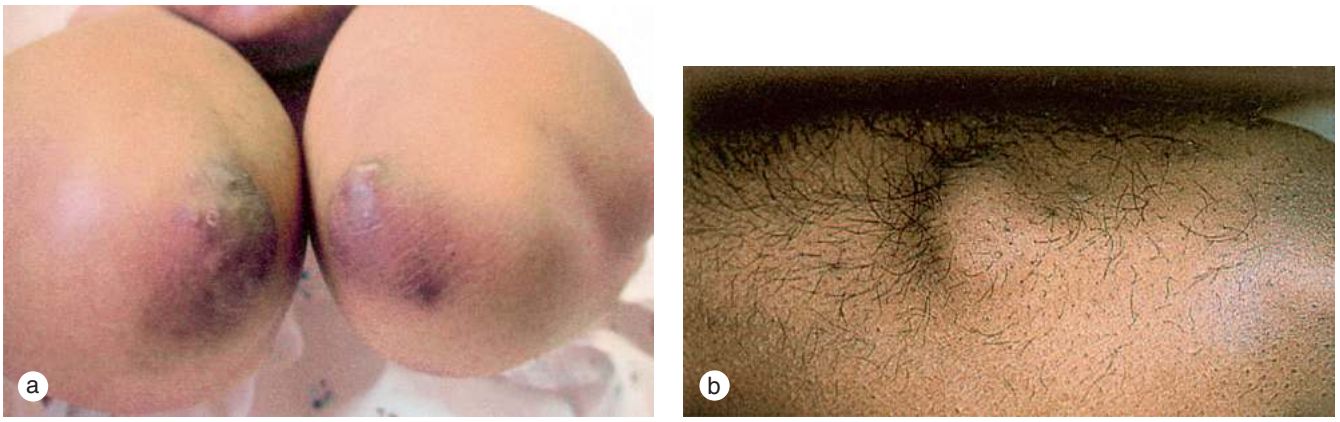


Fig 7.47 Rheumatoid nodule. This adolescent girl developed rheumatoid-factor-positive rheumatoid arthritis and systemic lupus erythematosus. The painless nodules appeared on her forearms. **(b)** Another adolescent girl with systemic lupus developed similar nodules on her forearms.

Autoantibodies in collagen vascular disorders				
	Designation	**Subtype**	**Antigen**	**Frequently associated disease states**
Antinuclear antibodies	dsDNA		Double-stranded DNA	Lupus erythematosus, nephritis (high specificity for SLE)
	ssDNA		Single-stranded DNA	Lupus erythematosus, other non-rheumatic diseases
	ENA		Extractable nuclear antigen	Subtypes as below
		Sm	RNAase-resistant glycoprotein (U1, U2, U4, U5, and U6 small ribonucleoprotein)	Lupus erythematosus, nephritis (high specificity for SLE)
		RNP	RNAase-sensitive ribonucleoprotein (U1 small ribonucleoprotein)	Lupus erythematosus, discoid lupus erythematosus; mixed connective tissue disease, Raynaud phenomenon
		Leukocyte specific		Rheumatoid arthritis, Felty syndrome
	SSC (RAP)		Trypsin-sensitive protein	Rheumatoid arthritis
	RANA			Rheumatoid arthritis
	NANA		Nucleolar ANA	Systemic sclerosis
	PM-1 (Mi)		Trypsin-sensitive protein	Polydermatomyositis
	DNP		DNA-histone	Drug-induced lupus erythematosus; rheumatoid arthritis; lupus erythematosus
	Centromere		Kinetochore	Calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia (CREST) syndrome
	Centriole		Centriole	Sclerosis–Raynaud phenomenon
	Scl-70		Non-histone nuclear protein	Systemic sclerosis, CREST syndrome
Anticytoplasmic antibodies	ssRNA		Single-stranded RNA	Systemic sclerosis
	Ro (SSA)		Acidic glycoprotein	Lupus erythematosus, photosensitivity, Sjögren syndrome, neonatal lupus
	Ribosomal		Ribosome	Lupus erythematosus
	La (SSB)		RNA-protein	Lupus erythematosus, neonatal lupus
Antineutrophilic cytoplasmic antibodies	c-ANCA			Wegener granulomatosis
Anticardiolipin, antiphospholipid antibodies			Platelet membrane phospholipid	Lupus anticoagulant syndrome

Table 7.1 Autoantibodies in collagen vascular disorders

Dermatomyositis

Dermatomyositis (DM) accounts for only 5% of pediatric collagen vascular disease. However, cutaneous lesions are distinctive and mark the onset of non-suppurative inflammation in the muscle. Unlike the adult variant, DM in childhood is self-limiting and not associated with underlying malignancy. Unfortunately, calcinosis cutis, which follows the disease, can be debilitating.

Most cases of childhood DM occur between 4 and 12 years of age. As in lupus, there is a 2:1 female predominance. There is no known inheritance pattern or racial predisposition.

Cutaneous findings may precede myositis for over a year, and the onset of signs and symptoms is usually insidious. Conversely, progressive, symmetric proximal muscle weakness may precede the rash by months. Patients often complain of easy fatigability with routine tasks such as brushing teeth, combing hair, and climbing steps. Muscle tenderness may be accompanied by anorexia, malaise, and fever. Dysphagia, dysphonia, and dyspnea occur in 10% of patients and signal palatal, esophageal, and thoracic involvement.

Nearly 75% of children with DM develop a diagnostic rash. Periorbital findings include a periorbital dermatitis, with or without edema, which gives a violaceous hue and is known as heliotrope (Fig. 7.48). A psoriasis-like rash involves the extensor surfaces of the elbows, knees, and knuckles (Fig. 7.49). When



Fig 7.48 Dermatomyositis. **(a)** Heliotrope. A young woman with dermatomyositis presented with violaceous erythema and edema of the upper eye lids. **(b)** A 10-year-old boy with a psoriasis-like dermatitis on the elbows and knees for 6 months developed rapidly progressive proximal muscle weakness. Erythema and scaling were prominent over the trunk **(c)** and scalp **(d)** of this 16-year-old girl who also developed diffuse alopecia.



Fig 7.49 Gottron papules **(a)** in a child with dermatomyositis are contrasted with **(b)** a psoriasis-like dermatitis on the hands of a patient with systemic lupus erythematosus. Note the sparing of the knuckles in lupus.



Fig 7.50 Dermatomyositis. **(a)** Despite resolution of cutaneous inflammation and myositis with systemic corticosteroids, telangiectasias progressed on the face of this 6-year-old girl. **(b)** Extensive cutis calcinosis, particularly over bony prominences, resulted in chronic, painful, draining ulcers and cellulitis in this 12-year-old boy with burned-out dermatomyositis. Note the white, chalk-like calcium deposits at the base of an ulcer on his knee.

over the distal interphalangeal joints these changes are referred to as Gottron papules. A malar rash reminiscent of lupus is variably present. Periungual and facial telangiectasias may become prominent. Diffuse erythema and scaling with alopecia may be prominent (Fig. 7.48d). Atrophy, fibrosis, hypopigmentation, and hyperpigmentation progress gradually, which results in telangiectasias (Fig. 7.50a) and poikiloderma with salt-and-pepper-like mottling.

Up to 50% of children with DM develop dystrophic calcification in skin and muscle, probably secondary to necrosis and scarring of the involved tissues (Fig. 7.50b). In some patients, painful, chronic ulceration of calcified nodules, recurrent cellulitis, and progressive contractures continue to limit recovery, even after active inflammation resolves. Complications may also occasionally result from gastrointestinal, cardiac, and pulmonary involvement. Treatment consists of aggressive use of systemic corticosteroids and physical therapy to preserve muscle function. In severe cases, methotrexate or other immunosuppressives may be required. Persistent, widespread telangiectasias and calcinosis cutis are resistant to therapy.

Clinical diagnosis is usually confirmed by detecting elevated muscle enzymes, typical electromyographic (EMG) findings, and muscle biopsy. In many centers magnetic resonance imaging has replaced muscle biopsy and EMG studies for diagnostic evaluation. In DM, as in lupus, the inflammatory process targets blood vessels in the involved tissues. Skin biopsies from the heliotrope rash, Gottron papules, and the psoriasiform dermatitis demonstrate perivascular and dermal–epidermal junction changes indistinguishable from those of lupus.

Scleroderma

Although scleroderma is uncommon, accounting for only 5% of collagen vascular disease in childhood, the most common variant, localized scleroderma or morphea, can be very subtle and is probably underdiagnosed.

Localized morphea can present in a plaque, linear, guttate, or generalized pattern (Fig. 7.51). Sclerotic plaques with an ivory-white center and an advancing lilac-colored border characterize scleroderma. During the course hyperpigmentation may also be marked. In the most common form one or several lesions from 1 to 10 cm in diameter appear on the trunk. In generalized morphea, similar widespread lesions develop on the trunk and extremities. Occasionally, multiple, small, oval lesions reminiscent of lichen sclerosis et atrophicus erupt on the upper trunk in the guttate variant. Morphea can also progress in a linear pattern, particularly on the scalp, face, and extremities. En coup de sabre describes a subset of linear morphea cases in which a furrow extends vertically from the scalp across the forehead and down the face. Involvement of the underlying soft tissue and bone may result in severe disfigurement. Central nervous system involvement in association with lesion on the face and scalp, is also probably more common than previously suspected. Intracranial lesions can result in significant morbidity and should be evaluated with brain magnetic resonance imaging. Progressive facial hemiatrophy (Perry–Romberg syndrome) probably represents a variant of en coup de sabre with minimal fibrosis but prominent atrophy and high risk of ocular, oral and central system involvement. Over months to years, lesions heal with softening of the involved areas and atrophy. In children, cutaneous disease with no systemic symptoms is not associated with progression to systemic sclerosis.

Laboratory findings in localized scleroderma are not specific or prognostic. Occasionally, eosinophilia is present on a complete blood count, and rheumatoid factor may be elevated. In 10–15% of cases, ANAs are present. Skin biopsies from new lesions or from the advancing borders of established lesions show lymphocytic inflammation between collagen bundles and around blood vessels in the deep dermis, which extends into the subcutis. Some areas of fat may be replaced by newly formed collagen. In late sclerotic plaques, thick, homogeneous collagen extends from the dermal–epidermal junction into the subcutaneous tissue. Adnexal structures appear to be enveloped in collagen, and little if any inflammatory infiltrate remains.

Unfortunately, therapy has been disappointing. The use of penicillamine, even in severe localized disease, has never been proven to be beneficial. Systemic antimalarials, vitamin D derivatives, and antimetabolites have been tried with variable response. Short courses of high-dose corticosteroids (1–2 mg/kg per day) may help to shut off rapidly progressive linear morphea when it endangers important structures. When central system lesions are present, tapering courses of oral corticosteroids over 2–3 months followed by 12–18 months of methotrexate has been advocated by some investigators. Recently, therapy with PUVA has been used with



Fig 7.51 Scleroderma. **(a)** Multiple, fibrotic plaques with central pigmentary changes and peripheral erythema slowly enlarged on the back of an adolescent girl. **(b)** An atrophic, fibrotic, hypopigmented plaque extended around the ankle of a 10-year-old girl for 2 years. Fortunately, she did not experience functional impairment. **(c)** A girl developed a similar plaque by her ear. **(d)** Linear morphea produced fibrosis and atrophy of the soft tissue of this young woman's right 4th finger, while **(e)** this adolescent developed lipoatrophy of the left hip and posterior thigh. **(f)** An unusual variant of morphea that affects the scalp, coup de sabre (stroke of the saber), extends from the mid-frontal scalp down the forehead to the nasal bridge.

some success for cutaneous lesions. Physical therapy may be necessary when lesions extend across joints.

Nephrogenic systemic fibrosis previously known as nephrogenic fibrosing dermopathy, a recently described disorder associated with renal failure and renal dialysis, may clinically overlap with morphea and other disorders characterized by localized cutaneous fibrosis, discussed at the end of the chapter. Patients typically develop progressive thickening of the skin of the extremities, flank, and/or back with sparing of the face and neck. Lesions are skin-colored or slightly red, painful, and often develop irregular ameboid borders. Contractures may be severe and incapacitating. During the last decade systemic involvement with fibrosis of eyes, lungs, bones, dura, and other organ systems has been described. Exposure to gadolinium-based contrast agents has been reported in many patients, and should be avoided in predisposed individuals. Histologic findings include a marked increase in fibroblast-like spindle cells and increased collagen and mucin deposition similar to scleromyxedema. Although lesions are usually restricted to the skin, rare cases with pulmonary involvement have been reported.

Progressive systemic sclerosis

Progressive systemic sclerosis (PSS) is rare in childhood, and clinically the course is similar to that of adult cases. Raynaud phenomenon is present in 90% of patients and may precede the onset of systemic disease by years. Classic findings in the skin include tightening of the skin associated with woody induration, edema, and pigmentary changes. Life-threatening disease in the gastrointestinal tract, musculoskeletal system, heart, lungs, and kidneys may result from PSS. Most patients with PSS develop ANAs, and nearly 50% have antinucleolar antibodies. A number of other antibody systems are also present in some cases of PSS and may have special prognostic value.

Lichen sclerosus et atrophicus

Lichen sclerosus (LS, lichen sclerosus et atrophicus) occurs most commonly in postmenopausal women. However, about 10% of cases appear in children under 7 years old. Although it has been reported more commonly in girls than boys, 14% of boys requiring circumcision for medical reasons had evidence of lichen sclerosus.

The anogenital area is the most common site of involvement. Typically, small, white, flat-topped papules arise on the cutaneous and mucous membrane surfaces of the labia, perineum, and perianal area. Confluent, white, atrophic patches may extend symmetrically in a figure-of-eight pattern around the vagina and rectum (Fig. 7.52). Scaling, vesiculation, and hemorrhage may be prominent, particularly after accidental trauma or rubbing and scratching from pruritus. A mild, watery discharge may be present. In some patients, extragenital patches on the trunk and extremities predominate (Fig. 7.53). In these lesions, follicular dimpling caused by hyperkeratosis with follicular plugging is characteristic. Truncal patches also share clinical and histologic features with morphea, and lesions typical of both entities have been described simultaneously in the same patients.



Fig 7.52 Lichen sclerosus et atrophicus. A pruritic, atrophic, eroded, hypopigmented patch involved the genital skin and mucous membranes in this 5-year-old girl. Note the bruising from scratching on the labia minora.

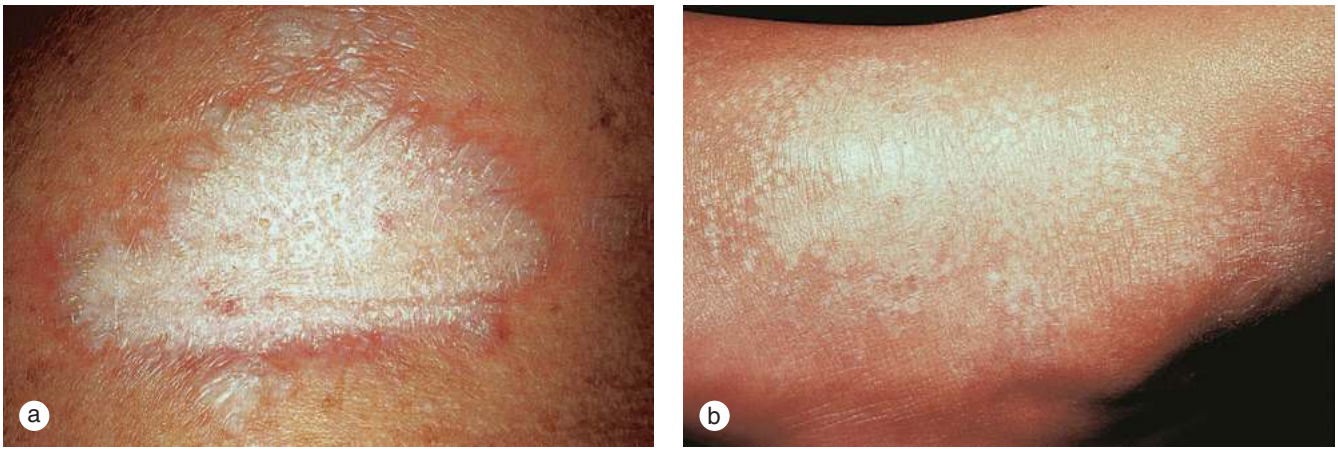


Fig 7.53 Lichen sclerosis et atrophicus. Atrophic, hypopigmented, scaly papules coalesced into confluent patches on **(a)** the trunk and **(b)** the extremities of a 10-year-old girl.

Girls with anogenital lesions typically complain of chronic pruritus, burning, erythema, scale, and erosions. However, the diagnosis should be considered in boys with recurrent erythema, balanitis, and tightening of the foreskin which can lead to phimosis. It was generally believed that lichen sclerosus resolves spontaneously at puberty, but recent series do not support this. Symptoms may abate, but atrophy and fibrosis tend to persist, and early intervention with high-potency topical steroid tapered over several months may induce remission. Although the cause is unknown, the association with morphea suggests an immunologic basis.

Histopathologic findings are often diagnostic. In addition to scale and follicular plugging, thinning of the mid-epidermis, hydropic degeneration of the basal layer, edema and homogenization of the upper dermis, and a band-like lymphohistiocytic infiltrate beneath the zone of homogenization are observed.

Clinically, LS must not be confused with child abuse, candidiasis, or streptococcal perianal or vaginal dermatitis. Cultures may be obtained to exclude bacterial and herpetic infections. The symmetric pattern and characteristic morphology of LS also help to eliminate child abuse as a serious consideration. In vitiligo, which may also present in a symmetric pattern in the anogenital area, the skin is completely normal except for depigmentation (Fig. 7.54). Inflammatory bowel disease may present with vaginal and perianal nodules, sinus tracts, and ulcers (Fig. 7.55). Other symptoms of gastrointestinal disease may be absent. Skin biopsies in these cases demonstrate granulomas typical of Crohn disease. Primary bullous dermatoses may also present a diagnostic dilemma. If the clinical presentation is not distinctive, a skin biopsy with direct immunofluorescence may be necessary to make the diagnosis.



Fig 7.54 Vitiligo developed around the vagina and anus of a 2-year-old girl, mimicking the pattern of lichen sclerosis et atrophicus.

Necrobiosis lipoidica

In necrobiosis lipoidica, reddish-yellow, indurated plaques typically appear on the shins in diabetics (Fig. 7.56). As the lesions expand from less than 1–4 cm in diameter or larger over months, the center of the plaque becomes shiny and atrophic. Telangiectasias extend from the center. Although lesions may remain stable and occasionally heal without treatment, most persist or slowly progress, and minor trauma may result in chronic, painful ulcerations. Some patients improve with topical or intralesional corticosteroids injected into the expanding red border.

About 75% of patients with necrobiosis lipoidica are female and over half have diabetes mellitus (necrobiosis lipoidica



Fig 7.55 Inflammatory bowel disease. **(a)** A 2-year-old girl was treated for chronic diaper dermatitis and candidiasis for months before the diagnosis of Crohn disease was considered. A biopsy of the perianal skin showed granulomas. **(b)** This 10-year-old boy had non-tender swelling of the penis for almost a year before the diagnosis of Crohn disease was made. Granulomas were noted on biopsy of his penis and colon.







Fig 7.56 Necrobiosis lipoidica. **(a)** A plaque on the shin of a 17-year-old diabetic demonstrates the typical red border and yellow, shiny, atrophic center with telangiectasias. **(b)** This patient developed a chronic, painful ulcer after repeated trauma. The ulcer healed after several months of treatment with occlusive dressings. **(c)** A healthy 20-year-old woman developed shiny atrophic fibrotic yellowish-pink plaques on her shins when she was 12. She had no personal or family history of diabetes and all glucose metabolism studies were normal.

diabeticorum). In some cases, necrobiosis lipoidica precedes the onset of clinical diabetes by years. Although the cause is unknown, investigators have suggested that some sort of vascular insult triggered by diabetes initiates the necrobiotic changes in collagen. Histologically, granulomatous inflammation is observed around altered and degenerating collagen, which extends in large bands into the deep reticular dermis. The overlying epidermis is atrophic and ulceration may be present. Thickening of vascular walls, endothelial cell proliferation, and occasionally vascular occlusion are seen throughout the dermis. The yellow color is imparted by deposition of lipid around necrobiotic collagen.

Necrobiosis lipoidica is usually differentiated from granuloma annulare, which does not develop epidermal changes. In some patients, fibrotic or atrophic plaques in scleroderma or LSA mimic necrobiosis. The clinical course and skin biopsy findings, however, are distinctive. One-third of juvenile diabetics develop diffuse, non-pitting, waxy edema of the hands during the first two decades of life (Fig. 7.57). Although this process may be associated with progressive joint contractures, distinctive cutaneous lesions, atrophy, and pigmentary changes do not occur. Histology demonstrates increased dermal collagen, which is thought to be caused by increased glycosylation of the proteins in the collagen matrix and by dermal fibroblast proliferation.



Fig 7.57 Prayer sign. This 16-year-old type I diabetic developed progressive, waxy, non-pitting edema of her hands, associated with joint contractures.

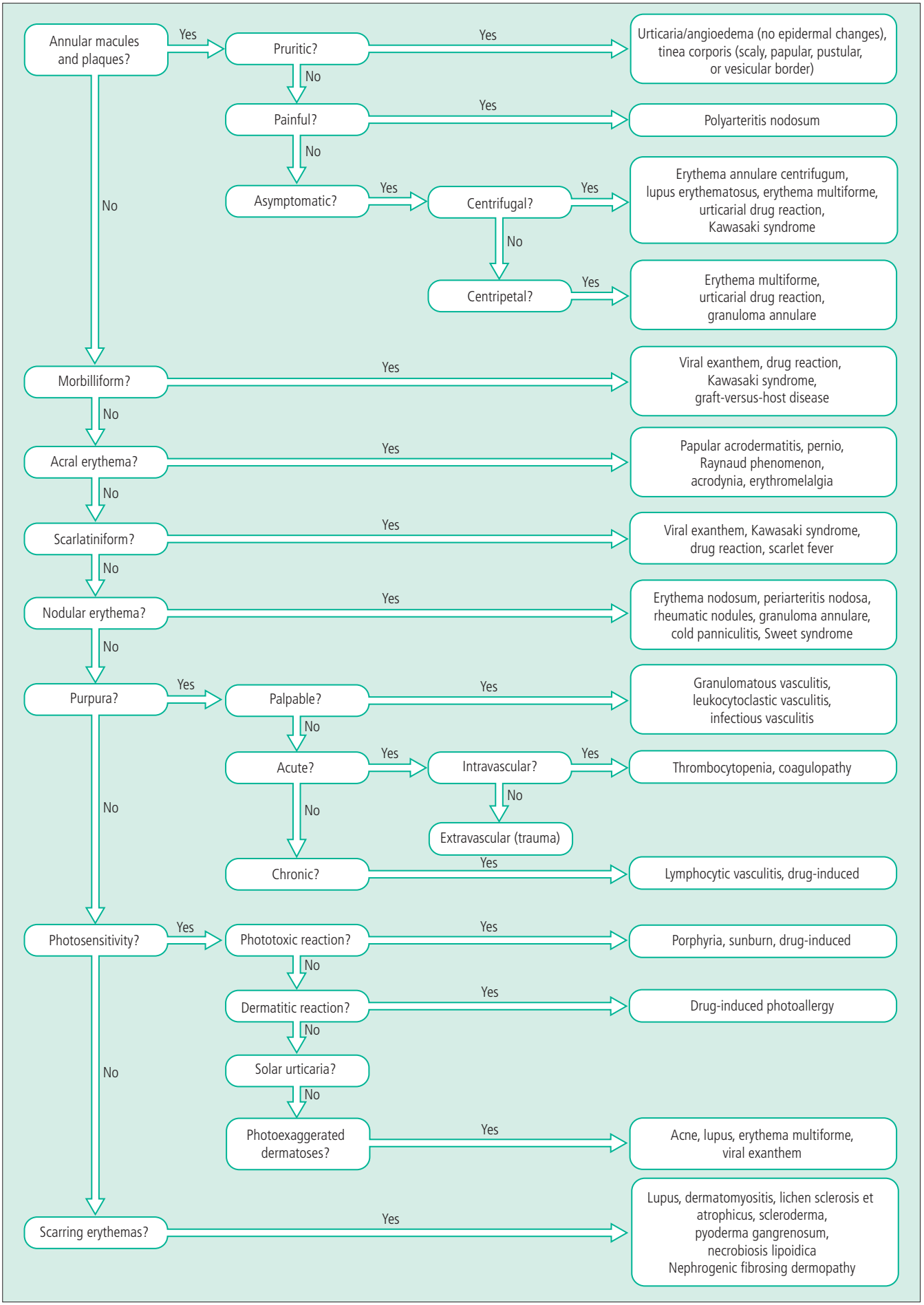


Fig 7.58 Algorithm for evaluation of reactive erythema.

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Chapter 8

Disorders of the Hair and Nails

Anna M. Bender and Bernard A. Cohen

INTRODUCTION

Diseases of the hair and nails are an important part of pediatric dermatology. Both hair and nails are composed of keratin, produced by the hair follicle and nail matrix. Some diseases are specific to these structures, while others affect the skin and other organ systems as well. In many cases, important diagnostic clues to skin and systemic disease can be found in related abnormalities of the hair and nails. Algorithmic approaches to diagnosis for disorders of the hair and nails are summarized at the end of the chapter (see Figs 8.69, 8.70).

HAIR DISORDERS

Embryology and anatomy

Hair follicles begin to form around 9–12 weeks' gestation on the face. They develop as a down-budding of the epidermis in association with proliferating mesenchyme, which eventually becomes the dermal papilla. The development of hair follicles continues in a cephalocaudal manner on the remainder of the body around 16–20 weeks' gestation. No new hair follicles develop after birth.

In the premature infant, the scalp, forehead, and trunk are covered by variable amounts of fine, soft, long, lightly pigmented lanugo hair (Fig. 8.1). Lanugo is usually shed *in utero* at 7–8 months' gestation. A second covering of subtle lanugo is shed shortly after birth and replaced by short, fine, non-pigmented vellus hair. Terminal hair is thicker and more darkly pigmented, and usually grows on the scalp, eyebrows, and eyelashes before puberty and the sites of sexual hair after puberty.

At term, most infants have full scalp coverage with normal terminal hair. However, shortly before birth or up to 4 months postnatally, infants undergo a period of brisk physiologic hair shedding when actively growing hairs convert to the resting phase and are then synchronously shed (Fig. 8.2). In blondes and redheads, the process is often complete before birth, and the hair is sparse at delivery. Shedding may be delayed in dark-haired individuals and may occur rapidly during early infancy. Parents should be reassured that this is a normal physiologic process.





Fig 8.1 Lanugo hair. A 31-week premature infant had extensive lanugo hair that covered most of the back. At term, this hair is usually shed before delivery.



Fig 8.2 Physiologic hair shedding. **(a,b)** These infants demonstrate the physiologic hair shedding that occurs in dark-haired babies at 3–5 months of age. In **(a)**, note the band of exaggerated alopecia, probably brought on by trauma, that girdles the occiput.

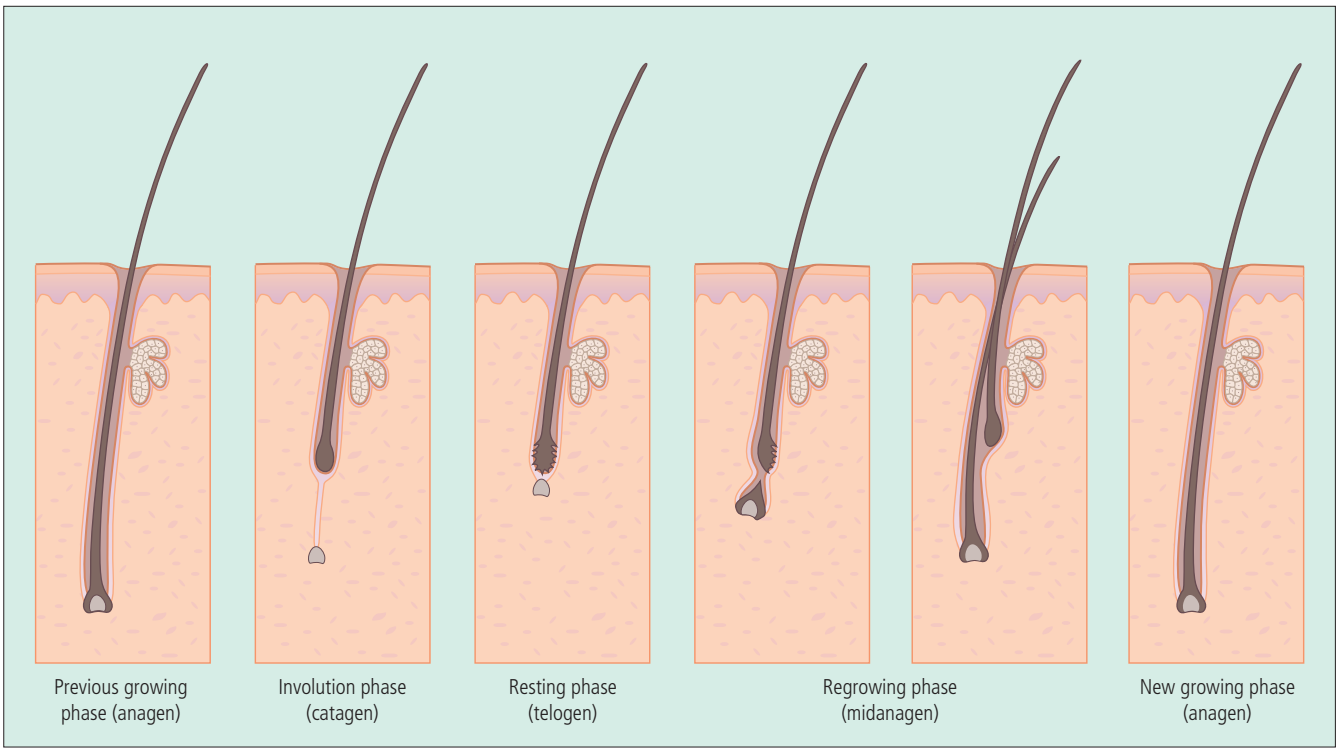


Fig 8.3 Normal hair cycle.

Throughout life, each hair follicle undergoes normal hair cycling, consisting of three phases (Fig. 8.3): anagen (growth phase), catagen (regression phase), and telogen (resting phase). The growth phase, anagen, typically lasts approximately 2–6 years. The length of anagen is genetically determined and varies by anatomic location. Following anagen, the regression phase occurs, catagen, and typically lasts 2–3 weeks. During this phase, the lower two-thirds of the hair follicle involutes. Finally, the resting phase, telogen, occurs and typically lasts 3 months. During the telogen phase, the proximal tip of the hair shaft forms a characteristic club shape (Fig. 8.4). After the telogen phase, the hair shaft is shed and anagen, the growth phase, occurs again. It is normal for a typical adult to shed approximately 100–200 scalp hairs per day.



Fig 8.4 Telogen effluvium. This 3-year-old boy developed rapid diffuse thinning of scalp hair 3 months after an acute febrile illness. This telogen hair loss was associated with a dramatic but transient increase in shedding of club hairs.

In the newborn, hair growth is synchronous, with all scalp hairs existing in the same phase of the hair cycle described above. Conversely, in the adult, hair growth is asynchronous, with individual scalp hairs existing in different phases of the hair cycle at any given time. At any given time, approximately 85–90% of adult scalp hairs exist in anagen; 10–15% exist in telogen; and less than 1% exist in catagen. The adult pattern of asynchronous hair growth generally becomes established anywhere between 4 months and 2 years of life. The normal ratio of hairs existing in anagen and telogen may be altered in certain hair disorders. For example, patients on chemotherapy with anagen effluvium may lose their hair in a process called anagen effluvium. Such patients may show a greatly increased ratio of telogen hairs on their scalp. An increased ratio of telogen hairs on the scalp also occurs in alopecia areata.

Congenital and hereditary disorders

The normal pattern of hair growth and shaft morphology may be disturbed in a number of hereditary disorders and congenital syndromes (Table 8.1).

Localized patches of alopecia may be associated with perinatal trauma or hamartomatous growths (Fig. 8.5a–e). In halo scalp ring, transient hair loss or permanent scarring results from local edema and vascular compromise produced by trauma to the scalp during labor. Scarring alopecia is a frequent complication of aplasia cutis congenita and incontinentia pigmenti, in which localized vasospasm, thrombosis, or vasculitis results in necrosis and ulceration of the skin. Aplasia cutis may present on the scalp with a ring of long, dark hair called the hair collar sign which may be an indication of an underlying neural tube defect (Fig. 8.6).

A number of nevi, such as hemangiomas, epidermal nevi, pigmented nevi, and connective tissue nevi, may also interrupt normal hair-growth patterns. Triangular alopecia is a distinctive non-scarring congenital developmental hair anomaly that may not

Selected hair anomalies

Alopecia (localized)
Non-scarring
- Hamartomatous nevi (e.g. epidermal, sebaceous)
- Pigmented nevi
- Hemangiomas
- Triangular alopecia

Scarring
- Incontinentia pigmenti
- Halo scalp ring
- Aplasia band

Hirsutism (localized)
Congenital pigmented nevus
Congenital smooth muscle and pilar hamartoma

Alopecia (generalized)
Hypohidrotic ectodermal dysplasia
Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome
Clouston syndrome
Cockayne syndrome
Dyskeratosis congenita
Hallermann–Streiff syndrome
Hay–Wells syndrome
Homocystinuria
Menkes syndrome
Progeria
Trichorhinophalangeal syndrome
Trichothiodystrophy
Cartilage–hair hypoplasia
Papillon–Lefèvre syndrome
Acrodermatitis enteropathica

Hirsutism (generalized)
Berardinelli lipodystrophy syndrome
Cerebro-oculo-facio-skeletal syndrome
Coffin–Siris syndrome
Fetal hydantoin syndrome
Frontometaphyseal dysplasia
Mucopolysaccharidoses
Leprechaunism
Marshall–Smith syndrome
Trisomy 18
Schinzel–Giedion syndrome
Fetal alcohol syndrome

Hair shaft anomalies
Monilethrix (beaded hair)
Pili torti (twisted hair)
- Menke Kinky Hair syndrome
- Wooly hair syndrome
- Wooly hair nevus
- Bazex syndrome
- Crandall syndrome
- Björnstad syndrome
- Scurvy

Pili trianguli et canaliculi
- Uncombable hair syndrome
- Ectodermal dysplasia

Trichorrhexis invaginata
- Netherton syndrome

Ribbon-like hair
- Trichothiodystrophy

Table 8.1 Selected hair anomalies

become evident until later childhood or adolescence (Fig. 8.5f). This condition presents with a stable patch of triangular, round or rectangular hair loss with the base of the lesion characteristically at the junctions of the frontal and temporal scalp. Lesions are usually unilateral but occasionally bilateral. Skin biopsy demonstrates normal vellus hairs.

Generalized sparse or abnormal hair growth suggests an inherited hair shaft anomaly or genodermatosis (Figs 8.7, 8.8). Monilethrix is a relatively common developmental hair defect that results in brittle, beaded hair (Fig. 8.9). The condition is autosomal dominant, and clinical manifestations usually appear after 2–3 months of age, when vellus hairs are replaced by abnormal, beaded hairs. Although the scalp is most severely affected, hair on any area of the body may be involved. The condition persists throughout life, but may improve in adolescence or adulthood.

Care must be taken not to confuse monilethrix with pili torti, another structural defect in which the hair shaft is twisted on its own axis (Fig. 8.10). Pili torti may be localized or generalized and also appears with the first terminal-hair growth of infancy. Pili torti may occur as an isolated hair defect or in association with a multisystem disorder, such as Menke syndrome (an inherited disease of copper metabolism which also affects the central nervous, cardiovascular, and skeletal systems). Similarly, trichorrhexis invaginata (bamboo hair) is associated with increased hair shaft fragility and easy breakage resulting in generalized sparse hair. This defect commonly occurs in the rare autosomal recessive genodermatosis Netherton syndrome characteristically manifested as trichorrhexis invaginata, ichthyosis linearis circumflexa, and severe atopic dermatitis (Fig. 8.11 and see Chapter 2).

In the ectodermal dysplasia syndromes, a heterogeneous group of genodermatoses, sparse hair is associated with dysmorphic facies and abnormalities of other structures, which include nails, sweat glands, and teeth (Fig. 8.12). In the hypohidrotic variants, early diagnosis may be lifesaving by preventing fatal hyperthermia, which may develop during otherwise self-limited childhood infections.

Trichothiodystrophy is a distinctive hair shaft defect of autosomal-recessive inheritance characterized by increased fragility, splitting of the hair, low sulfur content, and alternating light-and-dark transverse bands on polarizing microscopy (Fig. 8.13). Clinically, the hair is sparse, dull, and brittle. Multisystem features, including progeria-like appearance, mental retardation, growth retardation, hypogonadism, photosensitivity, cataracts, and other neurologic abnormalities, have been reported with trichothiodystrophy.

Children with congenital hair disorders require a careful medical and neurodevelopmental evaluation. Family history aids in establishing a pattern of inheritance. Hairs are examined microscopically to detect specific anomalies.

Acquired alopecia

Acquired alopecias may be differentiated by the presence or absence of clinical scarring. In non-scarring processes, inflammation may be clinically evident, subtle, or absent. Non-scarring disorders may be further subdivided by the presence of localized or diffuse involvement.

Scarring alopecia

Cicatricial alopecia presents with a scarring patch of alopecia with loss of follicular ostia. The most common inflammatory disorders resulting in scarring alopecia include discoid lupus erythematosus and lichen planopilaris, and folliculitis decalvans. A number of inflammatory disorders may involve the hair follicle primarily or by spread from contiguous skin. In lichen planus and discoid lupus

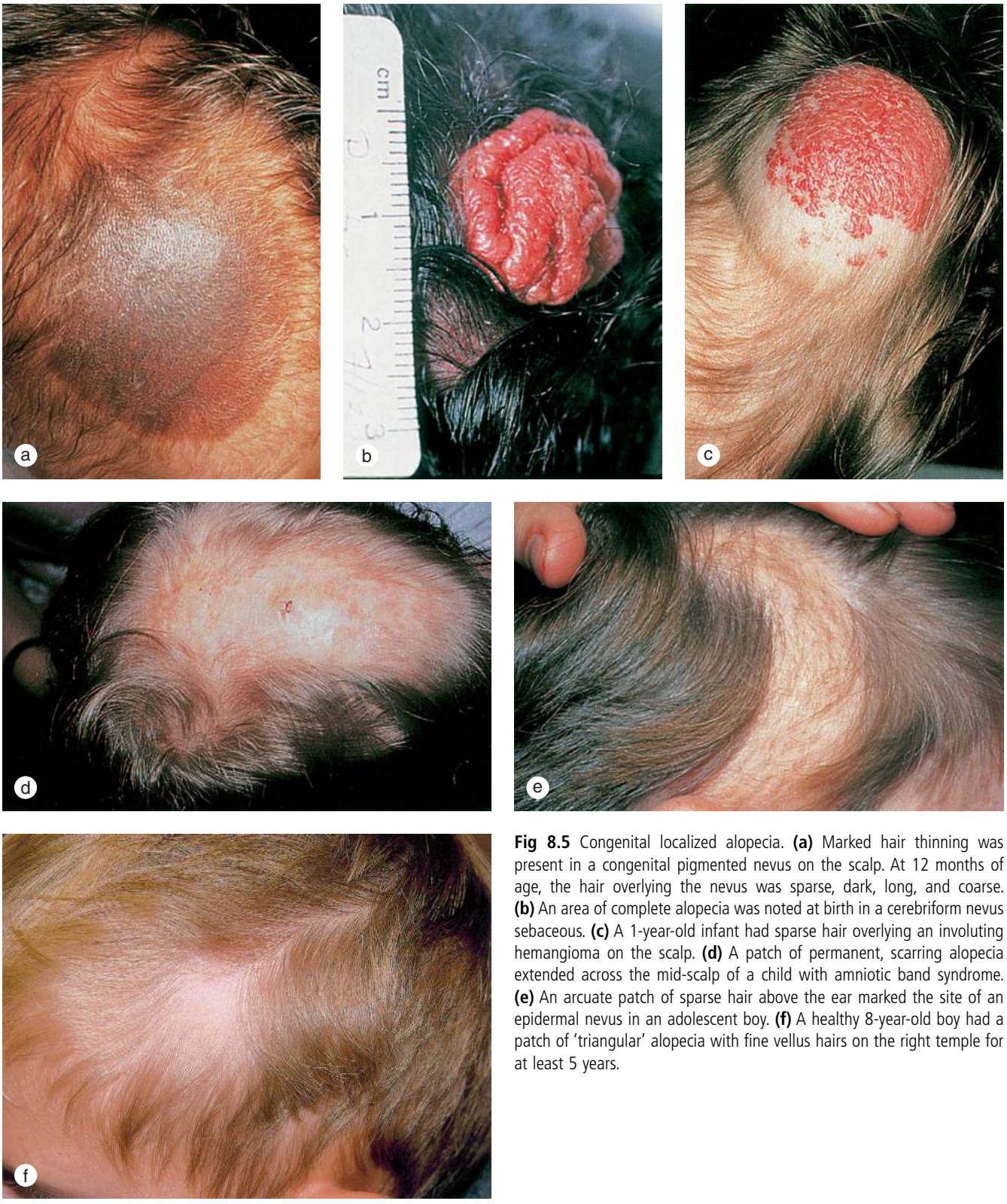


Fig 8.5 Congenital localized alopecia. **(a)** Marked hair thinning was present in a congenital pigmented nevus on the scalp. At 12 months of age, the hair overlying the nevus was sparse, dark, long, and coarse. **(b)** An area of complete alopecia was noted at birth in a cerebriform nevus sebaceous. **(c)** A 1-year-old infant had sparse hair overlying an involuting hemangioma on the scalp. **(d)** A patch of permanent, scarring alopecia extended across the mid-scalp of a child with amniotic band syndrome. **(e)** An arcuate patch of sparse hair above the ear marked the site of an epidermal nevus in an adolescent boy. **(f)** A healthy 8-year-old boy had a patch of 'triangular' alopecia with fine vellus hairs on the right temple for at least 5 years.

erythematosus of the scalp, inflammation around hair structures is usually seen early in the course of the disease and then later irreversible scarring occurs (Fig. 8.14). Acne keloidalis is a scarring folliculitis and perifolliculitis that often presents with fibrotic papules and pustules at the nape of the neck and occipital scalp in post-pubescent African-American men (Fig. 8.15). Folliculitis decalvans is a severe variant of non-infectious folliculitis that produces slowly but relentlessly, enlarging areas of cicatricial alopecia (Fig. 8.16). Dissecting cellulitis of the scalp may present with boggy suppurative nodules and abscesses of the scalp associated with alopecia (Fig. 8.17). Physical agents, which include allergens, irritants (acids and alkalis), thermal burns, and blunt trauma, may cause necrosis of the skin and non-specific scarring. Examples include alkali burns from hair-grooming products, surgical scars, and radiation-induced injuries. Scarring alopecia may also result from severe infection of the scalp. In addition, scarring alopecia



Fig 8.6 Aplasia cutis congenita with hair collar sign. This premature newborn was noted to have two contiguous round atrophic violaceous plaques on her scalp with surrounding dense hair.

may be associated with infiltrative disorders such as granulomatous infiltration in sarcoidosis or mucin infiltration in alopecia mucinosa (Fig. 8.18).

Patients with scarring alopecia deserve a careful examination of the skin, nails, and mucous membranes to identify clues for diagnosis. When the cause is not readily apparent, a skin biopsy is considered. A delay in diagnosis and treatment may result in widespread patches of disfiguring scarring alopecia.

Non-scarring alopecia

Most hair loss in children occurs without scarring. Clinically, the practitioner can differentiate between non-scarring alopecia associated with inflammation (erythema, scale, vesicles, pustules, etc.) and those disorders in which the scalp appears otherwise normal. The most common cause of inflammatory alopecia in children is



Fig 8.7 Ulerythema of the eyebrows and cheeks. In this variant of keratosis pilaris, inflammation of the pilosebaceous structures is associated with progressive alopecia and atrophy of the involved hair follicles. This may occur as an isolated disorder of keratinization or in association with other anomalies.



Fig 8.8 Uncombable hair syndrome is characterized by light blond, frizzy, unruly hair that does not lie flat on the scalp, which makes combing almost impossible. Diagnosis may be made by identifying the triangular-shaped hairs with longitudinal grooves along the hair shaft using light microscopy. Although some cases appear to be autosomal dominant, most are sporadic.



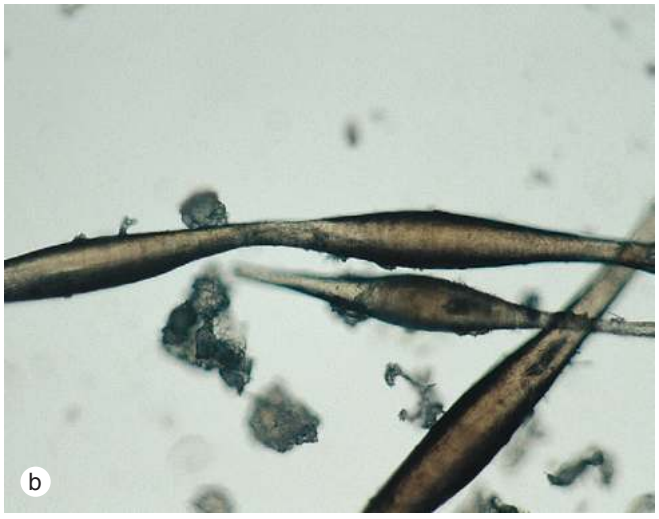


Fig 8.9 Monilethrix. **(a)** Short, broken hairs give the appearance of diffuse alopecia. **(b)** Microscopically, periodic narrowing of the hair shafts are seen. Hairs are brittle and break off at constricted points near the scalp.



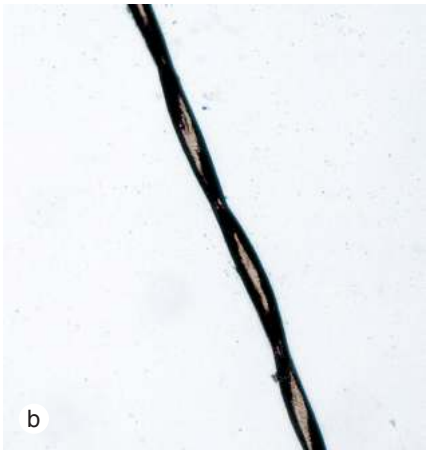


Fig 8.10 Menke syndrome. **(a)** This child presented with lightly pigmented skin, blue eyes, sparse hair that demonstrated pili torti, seizures, and loss of developmental landmarks. Copper and ceruloplasmin levels in the serum were low. **(b)** Twisting along the longitudinal axis is noted.



Fig 8.11 Trichorrhexis invaginata. Note the bamboo-like appearance of the hair shaft from a toddler with Netherton syndrome.



Fig 8.12 Hypohidrotic ectodermal dysplasia. This child demonstrates the typical findings of sparse hair, absent eyebrows and lashes, frontal bossing, supraorbital ridges, periorbital hyperpigmentation, and thick, everted lips.

tinea capitis. On the contrary, the scalp usually appears normal in telogen and anagen effluvium, alopecia areata, and traumatic hair loss.

Tinea capitis

Tinea capitis is the most common cause of hair loss in children between the ages of 2 and 10 years (Fig. 8.19). For unknown reasons, this form of ringworm is endemic among black school children, although it is occasionally found in whites.

A variety of clinical presentations of tinea capitis occur. In some children, mild redness and scaling of the scalp, reminiscent of seborrhea, are seen in areas of partial alopecia. In other cases, widespread hair breakage caused by endothrix, or invasion of the hair shaft by the fungus, creates the appearance of 'black dots' on the scalp with short, broken-off hairs poking up on the surface of the scalp. Occasionally, scalp lesions are annular, like patches of tinea corporis. In some children, sensitization to the infecting organism results in erythema, edema, and pustule formation. As

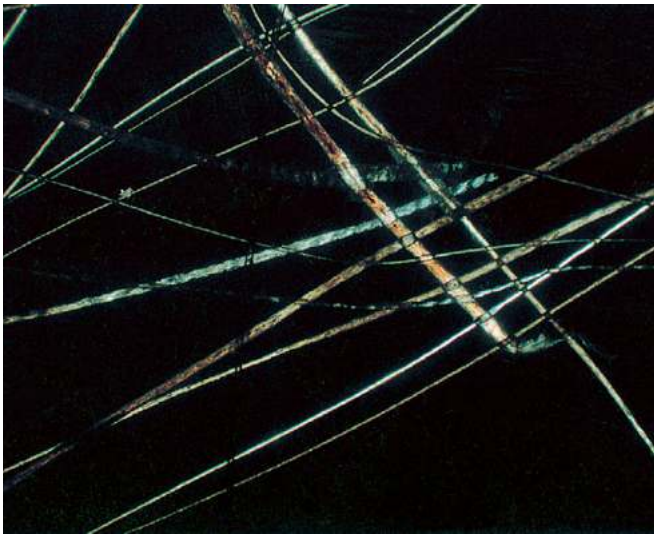


Fig 8.13 Polarized light microscopy demonstrates hairs with alternating dark and light bands referred to as tiger tails.

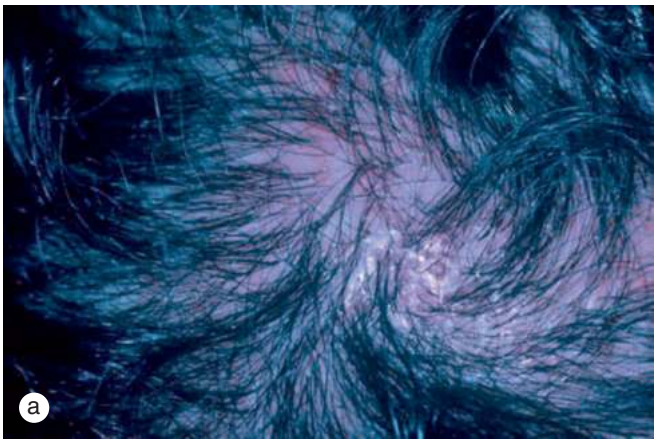




Fig 8.14 (a) Lichen planopilaris. Lichen planopilaris presents with follicular papules with collarets of scale leading to progressive scaring alopecia. **(b)** Discoid lupus. This woman had an 11-year history of slowly progressive pink scaly plaques on the sun-exposed areas of the face and scalp along with scarring alopecia. The well-demarcated pink scarring plaques presented with classical depigmentation centrally along with a peripheral rim of hyperpigmentation.



Fig 8.16 Folliculitis decalvans. This young man complained of recurrent pustules on the scalp leading to progressive patchy hair loss. His follicular papules and pustules improved with oral antibiotics and topical steroids, however the irregular bald patches remained. Note the areas of tufted folliculitis seen as multiple tufts of hair emanating from dilated follicular openings within the scarred patches.

the pustules rupture and the area weeps, thick, matted, yellow crusts form, which simulate impetigo. Less commonly, intense inflammation causes the formation of raised, tender, boggy, plaques studded with pustules, known as kerions. Large, and occasionally painful, occipital, postauricular, and preauricular adenopathy occurs with inflammatory tinea. Unless treated promptly and aggressively with oral antifungal agents and, in severe cases, oral corticosteroids, kerions may heal with scarring and permanent hair loss. Incision and drainage are not indicated, as loculations are small and septae thick.

Fungal infection of the scalp is readily confirmed by a potassium hydroxide (KOH) preparation of infected hairs. The best hairs for examination are those that are broken off at the surface. A good



Fig 8.15 Acne keloidalis nuchae. This healthy teenage boy developed follicular pustules on the back of his scalp which healed with itchy fibrotic papules.



Fig 8.17 Dissecting folliculitis. This man had a 10-year history of recurrent scarring hair loss associated with boggy fluctuant hairless plaques, suppuration, and a periphery of studded crusts and pustules.



Fig 8.18 Follicular mucinosis. This young woman developed slowly progressive asymptomatic violaceous hyperpigmented follicular papules and infiltrative plaques for 2 years. Lesions started on her scalp and face and spread to her neck and trunk. Skin biopsy showed changes typical of follicular mucinosis.

specimen may be obtained by scraping hairs and scale onto a glass slide with a #15 blade. A toothbrush may be used to brush hairs and scale from large areas of the scalp directly onto fungal medium for culture. Before 1970, most cases of tinea capitis in the USA were caused by *Microsporum* species, which fluoresce bright blue-green under Wood light. This screening tool is of little value today, because the endothrix infection produced by *Trichophyton tonsurans* does not fluoresce.

Oral griseofulvin administered over 2–4 months is effective. Although this usually eradicates infection, the risk of reinfection is high. Recurrent infection prompts a careful examination and possible culture of other family members to identify untreated cases. Concurrent use of selenium sulfide 2.5% shampoo may help minimize the risk of recurrence and of spread to siblings and classmates.

Ketoconazole is approved in the USA as an alternative for children with tinea capitis and a history of griseofulvin allergy. However, clinical studies show that it is less effective and, unlike griseofulvin, patients on ketoconazole require regular blood counts and liver profiles. Newer oral antifungals including fluconazole, terbinafine, and itraconazole, appear to be effective and safe in treating tinea capitis. Moreover, they tend to remain in hairs long after the drug is discontinued, which enables relatively short courses of therapy. Only fluconazole is available in a liquid. Although most children who present with scalp pustules have tinea capitis, bacterial folliculitis should also be considered, particularly if pustules are small, superficial, not associated with hair loss, and

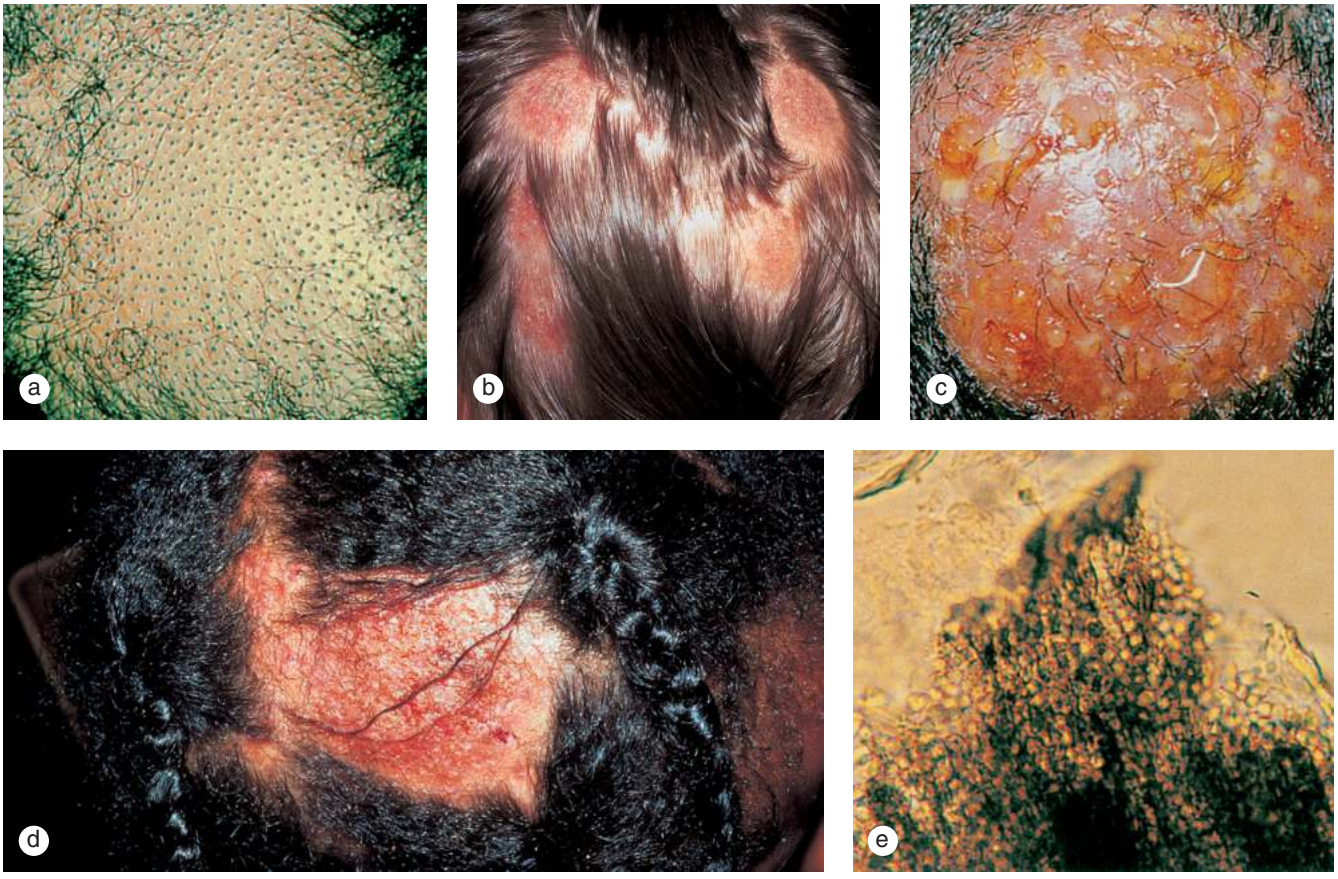


Fig 8.19 Tinea capitis. **(a)** Infiltration of the hair shafts has resulted in widespread breakage of the hair at the scalp, to produce a 'salt-and-pepper' appearance known as black dot ringworm. **(b)** Multiple, crusted patches developed in this child with tinea caused by *Microsporum canis*. **(c)** A boggy mass has formed as a result of an intense, inflammatory response known as a kerion. **(d)** A 10-year-old girl developed scarring alopecia after successful treatment of a large kerion with a 2-week course of prednisone and 4 months of griseofulvin. **(e)** Microscopic appearance of hair shafts infected with fungi. Note the tight packing of fungal arthrospores that cause hair shaft fragility and breakage (KOH mount for endothrix).



Fig 8.20 Impetigo of Bockhart. A toddler with tightly braided plaits developed follicular pustules in the area of greatest traction.

appear at the base of hairs under tension along parts in the hair. This disorder, termed impetigo of Bockhart, is easily treated by regular shampooing and loosening of the hair (Fig. 8.20). Occasionally, an oral antibiotic is required. Seborrhea may be difficult to differentiate from tinea. However, in seborrhea, scaly patches are usually symmetric and only mildly pruritic. A black schoolchild with patches of scalp 'seborrhea' warrants a KOH preparation and fungal culture to exclude tinea.

Alopecia areata

Alopecia areata is a form of asymptomatic, localized alopecia that presents with round patches of complete hair loss anywhere on the body, including the scalp, eyebrows, lashes, extremities, and trunk (Fig. 8.21). Occasionally, hair loss progresses to involve the entire scalp (alopecia totalis and body (alopecia universalis) (Fig. 8.22)). The insult that triggers alopecia areata is unknown, but probably immunologic in origin. Although clinical signs of inflammation are absent, skin biopsies from sites of active disease show perifollicular, lymphocytic inflammation as well as deposition of antibody and immune complexes.

Clues to diagnosis include the absence of inflammation and scaling in involved areas of the scalp and the presence of short (3–6 mm), easily epilated hairs at the margins of the patch. Under magnification, these hair stubs resemble exclamation points, as the hair shaft narrows just before its point of entry into the follicle. Another finding in many patients with alopecia areata is Scotch-plaid pitting of the nails, which consists of rows of pits that cross in a transverse and longitudinal pattern.

The course of alopecia areata is unpredictable. In adolescents and young adults, hair loss usually resolves without permanent alopecia over months to years. In infants and young children, particularly when alopecia is diffuse, the prognosis is more guarded. Treatment includes safe measures that do not carry risk of systemic toxicity. Topical corticosteroids, local irritants (e.g. tar preparations, dithranol), topical minoxidil, topical sensitizers (e.g. squaric acid dibutyl ester), and ultraviolet light therapy have been used with some success. Although oral corticosteroids may induce hair regrowth, no investigator has ever demonstrated that these medications change the prognosis of alopecia areata. Consequently, their use should be restricted to short courses in selected patients with widespread, rapidly progressive disease. Intralesional steroids should also be used with caution because of the risk of local as well as systemic toxicity.

Traumatic hair loss

A common form of benign hair loss in infants may be observed on the occipital scalp secondary to traumatic alopecia due to rubbing in infants who commonly sleep on their back. Parents should be reassured that this is a benign process and hair will grow back.

Traction alopecia

Traction alopecia is a form of traumatic alopecia common in young girls and women, whose hairstyles, such as ponytails, plaits, and braids, maintain a tight pull on the hair shafts (Fig. 8.23). This traction causes shaft fractures, as well as follicular damage. If prolonged, permanent scarring alopecia can result.

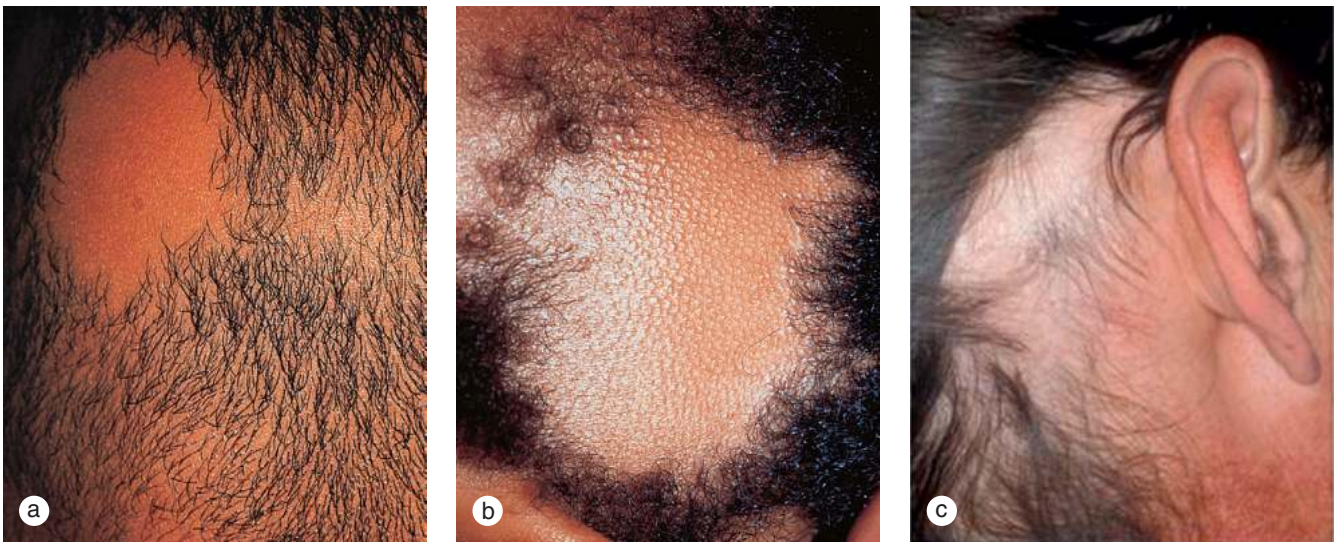


Fig 8.21 Alopecia areata. **(a)** Multiple, round patches of alopecia continued to progress despite treatment with griseofulvin for presumed tinea capitis. Cultures for fungus were negative, and the lesions of alopecia areata waxed and waned for years before resolving. **(b)** A round patch of alopecia, with no scale or inflammation, appeared on the scalp of this 10-year-old boy. The shiny, complete alopecia is typical of alopecia areata. **(c)** This woman developed patches of smooth non-scarring alopecia in a headband-like pattern extending from behind the ears around to her occipital scalp. The lack of inflammation or other changes in the skin was typical of alopecia areata.



Fig 8.22 Alopecia universalis. This healthy preschooler developed total body hair loss.

Hair pulling

Hair pulling, also referred to as 'trichotillomania', is a common disorder seen in toddlers, children of school age, and adolescents due to repetitive pulling and/or twisting of hair (Fig. 8.24). It often presents with oddly shaped patches of hair loss, often in broad, linear bands on the vertex or sides of the scalp, where the hair is easily twisted and pulled out. Rarely, the entire scalp, eyebrows, and eyelashes are involved. Hair pulling is most often confused with alopecia areata and can be distinguished based on the bizarre pattern of alopecia and presence of short, broken-off hairs of various lengths. Skin biopsy of the scalp from an area of recent hair pulling may demonstrate large numbers of catagen hairs, perifollicular hemorrhage, and trichomalacia.

Although hair pulling may occur in children with severe obsessive-compulsive psychiatric disease, many cases, particularly in preschool children, are associated with habitual behavior or situational stress (Fig. 8.25). In young, habitual hair twirlers, positive reinforcement or replacement of hair twirling with other socially acceptable alternative behaviors usually succeeds in extinguishing hair pulling. Adolescents and their parents often deny vigorously that the hair loss could be caused by the child, and thus the diagnosis rests on a high index of suspicion and recognition of the clinical findings.

Traumatic alopecia

Traumatic alopecia may also be caused by breakage of the hair shaft due to acquired structural defects of the hair occurring by traumatic hair-care practices. The most common defect is acquired trichorrhexis nodosa, which can develop at any age as brittle, short hairs that are easily broken. Microscopically, the distal ends of the hairs are frayed, resembling a broomstick (Fig. 8.26). Other hairs may have nodules that resemble two broomsticks stuck together on microscopy. Acquired trichorrhexis nodosa most commonly occurs in blacks arising from trauma of combing tightly curled hairs or from excessive usage of hot combs, hair-dryers, hair straighteners, or other chemicals. This disorder is self-limited, and normal hairs regrow when the source of damage is eliminated.

Other forms of deliberate and accidental physical, thermal, and chemical injury to the hair shaft and scalp can also cause alopecia. Examples include child abuse and pressure necrosis of the skin (Fig. 8.27).

Telogen and anagen effluvium

Telogen effluvium is the most common form of non-inflammatory, non-scarring, diffuse hair loss occurring in children (see Fig. 8.4). In this form of alopecia, some sort of systemic insult, such as severe illness, high fever, surgery, or certain drugs, triggers an abnormally high number of anagen hairs to switch over to telogen. This is followed 3–5 months later by diffuse, brisk, shedding of telogen hairs. Although quite distressing, telogen effluvium is temporary and rarely produces more than 50% hair loss. In fact, the hair loss marks the end of the process as new anagen hairs replace those being shed. In some children, telogen loss occurs repeatedly after recurrent ear infections and upper respiratory infections. Even in these cases, the prognosis for full recovery is excellent. Neither treatment nor laboratory studies are usually required. Early in the course, diagnosis may be confirmed by examination of hairs pulled from the scalp, which should demonstrate an increased percentage of telogen hairs. Parents are also reminded that hair grows only about 1 cm each month, so that the return to pre-telogen effluvium hair length may take many months.

In anagen effluvium, sudden loss of growing hairs is caused by abnormal cessation of the anagen phase. This occurs most commonly in cancer patients who are treated with radiation or systemic chemotherapy, especially cytotoxic agents. In this process, diffuse loss of up to 90% of scalp hairs occurs over several days to weeks. The extent of hair loss is determined by the toxicity of the agent

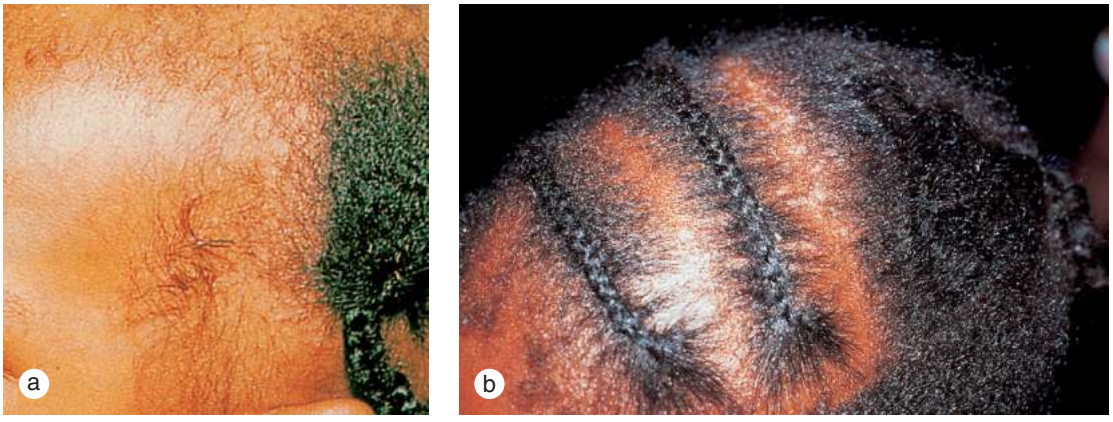


Fig 8.23 Traction alopecia. Alopecia is most prominent at **(a)** the periphery of the scalp and **(b)** along the parts in the hair. These areas are under the most traction.

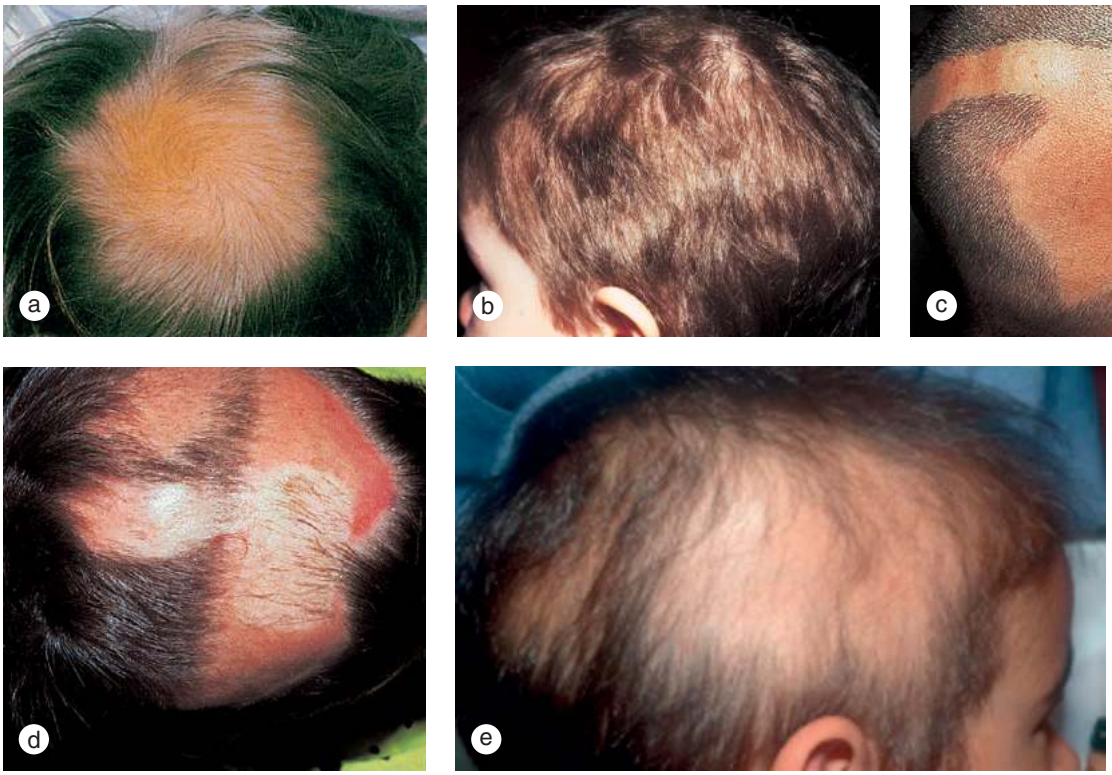


Fig 8.24 Hair pulling. **(a)** Alopecia from hair pulling is found most commonly on the occiput. **(b)** Hairs broken off and regrowing at various lengths may produce a moth-eaten appearance. **(c,d)** Bizarre patterns that defy anatomic landmarks are typical. In **(c)** a short haircut failed to camouflage the alopecia. In **(d)** note the rectangular area of regrowth in the mid scalp, which followed 1 month of covering with an occlusive dressing. **(e)** This healthy 4-year-old girl was observed twirling her hair at naptime and bedtime resulting in well-demarcated patches of hair thinning. She also had dry lusterless hairs of varying lengths giving a moth-eaten appearance. The hair loss disappeared a year later when she entered kindergarten.

and the dose and length of exposure. In anagen effluvium, the hair shaft tapers proximally like a pencil point and subsequently loses adhesion to the follicle.

Full hair regrowth usually occurs when the toxic agent is discontinued. Anagen effluvium has also been reported with toxic levels of boric acid, thallium, arsenic, bismuth, warfarin, and lead as well as colchicine.

Anagen effluvium must not be confused with loose anagen syndrome, an autosomal-dominant disorder characterized by actively growing hairs that are loosely anchored to the follicle and easily and painlessly pulled from the scalp (Fig. 8.28). Although the typical patients described are blonde girls between 2 and 5 years old, children of both sexes and dark hair color may be affected. These children demonstrate short, variably sparse scalp hair and rarely require haircuts. A hair pull shows dystrophic anagen hairs with ruffled cuticles and darkly pigmented, misshapen hair bulbs with a 'baggy stocking' appearance. There is no known therapy, but many patients improve during adolescence. Although the



Fig 8.25 Hair pulling occurs frequently as a habitual behavior. At bedtime and naptime, this happy, healthy toddler pulls and twirls her hair and sucks her thumb.

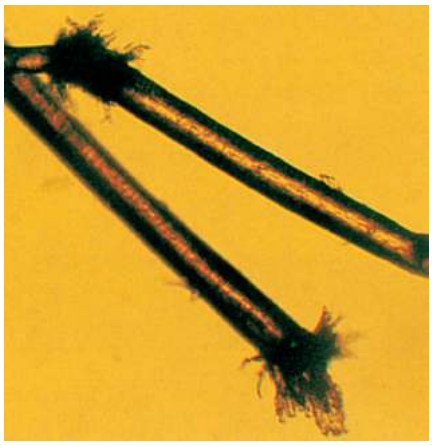


Fig 8.26 Trichorrhexis nodosa ('split ends') is a brittle hair shaft defect, usually caused by overmanipulation of the hair or chemical use. The frayed broom appearance is typical.



Fig 8.27 An 11-year-old boy developed pressure necrosis of the skin on the occiput and a linear patch of alopecia several days after liver transplant surgery. The area of injury conformed to the shape of a rubber doughnut, on which his head had been placed at the beginning of surgery.

relationship between loose anagen syndrome and alopecia areata is unknown, recently the disorders have been reported in the same patients.

Androgenetic alopecia may occur in both males and females and may be seen as early as late childhood or adolescence. Patients usually complain of thinning of scalp hair instead of shedding. In females, the frontal hairline is usually intact but there is decreased density of thinned hair in the frontal and vertex scalp compared with the occipital scalp. There is often a widened central part in the frontal scalp (Fig. 8.29). The male pattern androgenetic alopecia consists of bitemporal recession of the frontoparietal hairline and thinning of the vertex scalp hair (Fig. 8.30). Treatment may include topical minoxidil or oral finasteride which is only approved for males over the age of 18 years old. Spironolactone orally and oral contraceptive pills have been shown to be useful in adult female patients with androgenetic alopecia.

Generalized changes in the color and/or texture of the hair may also accompany a number of medical disorders (e.g. hypothyroidism, hyperthyroidism), the use of certain medications (e.g. antimalarials), and nutritional deficiencies (e.g. zinc, copper, protein; Fig. 8.31).

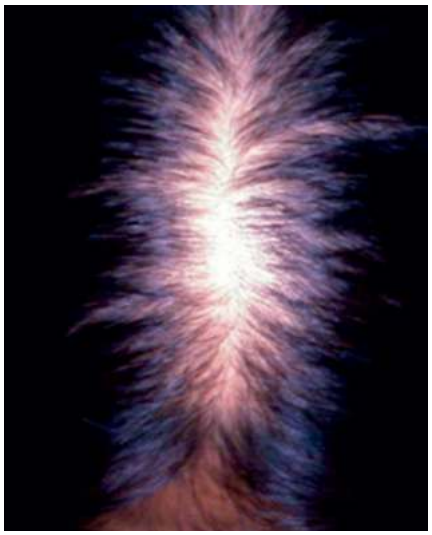


Fig 8.29 Androgenetic alopecia. This woman presented with widening of the central part on the top of her scalp in a Christmas-tree-like pattern. The density of scalp hair on her occipital scalp remained normal.



Fig 8.30 Androgenetic alopecia. This 30-year-old man developed gradual thinning of hair on the frontoparietal scalp and bitemporal recession over the last several years. His father had a similar pattern of hair loss.





Fig 8.28 Loose anagen syndrome. **(a)** This healthy toddler had diffusely sparse hair which was readily epilated. **(b)** The anagen hair bulb is misshapen, and the inner and outer root sheaths are missing. Note the wrinkling of the cuticle giving a 'baggy stocking' appearance.



Fig 8.31 Flag sign. A light pigmented band of hair appeared on the scalp of this 6-year-old girl with cystic fibrosis after several months of inadequate pancreatic enzyme replacement. When her medication was adjusted the hair pigment returned to normal, and the light band of hair continued to grow outward.

Hypertrichosis and hirsutism

Hypertrichosis refers to localized patches of increased hair growth, whereas hirsutism is a term used to describe excessive hair growth, usually in children and women, in an adult male pattern.

Congenital hypertrichosis has been noted in pigmented nevi and other cutaneous hamartomas. Generalized increase in hair at birth may occur as a normal physiologic variant. However, unusual patterns or persistence beyond early infancy prompt a careful evaluation for potentially serious hereditary aberrations (e.g. hypertrichosis lanuginosa, Cornelia de Lange syndrome) (Fig. 8.32).

Acquired, localized hypertrichosis occurs frequently in Becker's nevi, congenital melanocytic nevi, plexiform neurofibromas, and congenital smooth muscle hamartomas. The application of topical corticosteroids or androgens may also stimulate localized hair growth. Widespread hypertrichosis may appear in hypothyroidism, porphyria, and following the use of certain medications, such as phenytoin, cyclosporine, and minoxidil.

Hirsutism presents with excess hair growth in a male sexual distribution such as the upper lip, cheeks, chin, and lower abdomen (Fig. 8.33). Hirsutism may appear as a physiologic variant in an otherwise healthy child. However, an endogenous or exogenous source of androgens must be excluded especially if other signs of hyperandrogenism are present or if a patient has signs of premature puberty. Cushing syndrome, acromegaly, congenital adrenal hyperplasia, algon with ovarian, adrenal, or pituitary neoplasms may be associated with hirsutism. The most common cause of medically significant hirsutism is polycystic ovarian syndrome (PCOS). In PCOS, patients may present with evidence of hyperandrogenism, insulin resistance, oligomenorrhea, and cystic ovaries. Endocrinologic evaluation is guided by careful history and physical examination.

Acne

Acne vulgaris

Acne vulgaris, a disorder of the pilosebaceous apparatus, is the most common skin problem of adolescence (Fig. 8.34). Lesions may appear on the face as early as 8 years of age, but they usually begin to develop during the 2nd decade of life with the onset of puberty. Other areas with prominent sebaceous hair follicles, including the upper chest and back, may become involved.

The exact pathogenesis of acne is unknown. However, abnormalities in follicular keratinization are thought to produce the acne lesion that develops earliest, the microcomedone. In time, microcomedones may grow into clinically apparent, open comedones (blackheads; Fig. 8.34a) and closed comedones (whiteheads; Fig. 8.34b). The entire process is fueled by androgens, which stimulate sebaceous-gland differentiation and growth, and the production of sebum. The proliferation of *Propionibacterium acnes* in non-inflammatory comedones, and the rupture of comedone contents into the surrounding dermis, may trigger the development of inflammatory papules, pustules, and cysts (Fig. 8.34c–e). Cystic acne is characterized by nodules and cysts scattered over the face, chest, and back. This variant frequently leads to disfiguring scarring.

Although therapy must be individualized, patients with mild-to-moderate comedonal and/or inflammatory acne respond well to a combination of topical retinoids (tretinoin, adapalene, tazarotene), benzoyl peroxide, antibiotics, and azaleic acid. Moderate-to-severe papulopustular acne warrants the use of oral antibiotics in combination with topical agents. Oral 13-cis-retinoic acid (isotretinoin) is reserved for patients with severe, scarring, cystic acne recalcitrant to conservative measures.

Fortunately, acne is usually self-limited, and winds down in late adolescence and early adult life. However, some middle-aged adults continue to require aggressive treatment for stubborn disease.

Evaluation of a patient with acne includes a careful medical and family history and physical examination. Although no special laboratory studies are usually necessary, signs and symptoms of precocious puberty, hyperandrogenism, or ovarian dysfunction warrant further investigation. A history of severe acne in a 1st-degree relative also serves as a warning for potentially serious disease.

Acne fulminans is a form of severe cystic acne that occurs abruptly usually in young male adolescents with fever, leukocytosis, and osteolytic bone lesions (Fig. 8.35).

Acne may occur commonly in the first month of life and is referred to as neonatal acne. This usually manifests as small papules and pustules on the face and usually resolves without treatment (Fig. 8.36). Neonatal acne is thought to be related to exposure to maternal androgens and pityrosporum. Infantile acne occurs in older infants and young children and may present between 3 and 6 months of life with erythematous papules and pustules along with occasional deeper nodules that may be more persistent and difficult to treat (Fig. 8.37 and see also Fig. 8.34d).

Acneiform reactions differ from classic acne vulgaris by the presence of uniform lesions in a widespread distribution, which may extend to involve the arms, legs, and lower trunk (Fig. 8.38). Endogenous corticosteroids (e.g. Cushing syndrome), prednisone, anabolic steroids, isoniazid, anticonvulsants, and lithium may trigger acneiform eruptions. When the medication dose cannot be decreased or discontinued, traditional management with topical and oral acne preparations may help.

Acne vulgaris may be confused with bacterial or fungal folliculitis (Fig. 8.39). In folliculitis, pustules predominate and the distribution is often restricted to areas of occlusion. Gram stains, KOH preparations, and cultures also help to differentiate folliculitis from acne. Occasionally, an acne patient on long-standing antibiotics develops an acute worsening of acne in association with a Gram-negative folliculitis. This probably results from selection of a resistant Gram-negative organism. Pustules usually resolve with an alternative antibiotic or 13-cis-retinoic acid.

Acne rosacea is differentiated from acne vulgaris by the presence of red papules, pustules, cysts, and extensive telangiectasias, but the absence of comedones (Figs 8.40, 8.41). Rosacea occurs most



Fig 8.32 Hypertrichosis. **(a)** Becker's nevus with overlying hypertrichosis. At 12 years of age, this 17-year-old boy developed an irregularly shaped uniformly tan patch on the upper back and shoulder. Several years later, dark coarse hair began to appear over the patch. These changes are typical of a Becker nevus also known as a hairy epidermal nevus. **(b)** Congenital smooth muscle hamartoma. This healthy newborn had an asymptomatic flesh-colored plaque on his left wrist at birth associated with subtle coarse dark hair. Rubbing of the plaque led to 'pseudo-Darier's sign' mimicking urtication due to transient piloerection. A skin biopsy showed changes typical of a smooth muscle hamartoma. **(c)** Faun tail nevus. This 7-year-old girl had an abnormal tuft of hair present in the lumbosacral area since birth. Imaging studies of the underlying spine were normal. **(d)** Plexiform neurofibroma. This man presented with a pigmented plaque with terminal hairs with a 'bag of worms' consistency on palpation. He also had multiple neurofibromas and cafe au lait macules. **(e)** Cornelia de Lange syndrome. This 4-year-old boy had microcephaly, mental retardation, bushy eyebrows that met in the midline (synophrys), small upturned nose, and prominent eyelashes.

commonly in middle age, but some patients date the onset of lesions to adolescence or early adulthood.

Hidradenitis suppurativa

Hidradenitis suppurativa, also known as 'acne inversa' may develop in association with cystic acne or as a separate entity (Fig. 8.42). Hidradenitis is a severe, non-infectious inflammatory process that involves apocrine gland-bearing skin in the axilla, groin, suprapubic, and perianal areas. As with acne, hyperkeratosis of the follicular epithelium leading to follicular occlusion is probably the initiating event. In the acute form tender, red pustules and deep-seated nodules become fluctuant and discharge pus. Over time many patients develop chronic draining abscesses, sinus tracts, and severe scarring. Early in the course, hidradenitis improves with oral antibiotic therapy. Chronic disease responds only somewhat to antibiotics, 13-cis-retinoic acid, and systemic corticosteroids. Severe cases heal only after surgical excision of apocrine glands, scars, and sinus tracts in affected areas.

Fox–Fordyce disease also known as apocrine miliaria presents as pruritic dome-shaped skin-colored papules in areas of apocrine-bearing skin such as the axillae, areola, and perineal area (Fig. 8.43). It is thought to be due to apocrine sweat retention and is most commonly seen in post-pubescent females.

Miliaria

Miliaria crystallina is caused by eccrine duct obstruction superficially within or just beneath the stratum corneum resulting in clear, easily ruptured, asymptomatic vesicles that appear in crops (see



Fig 8.33 Hirsutism. **(a,b)** This adolescent girl developed slowly progressive generalized hirsutism when she was 14 years old. She showed coarse dark hairs in the male distribution of the upper lip, lower cheeks, and chin.

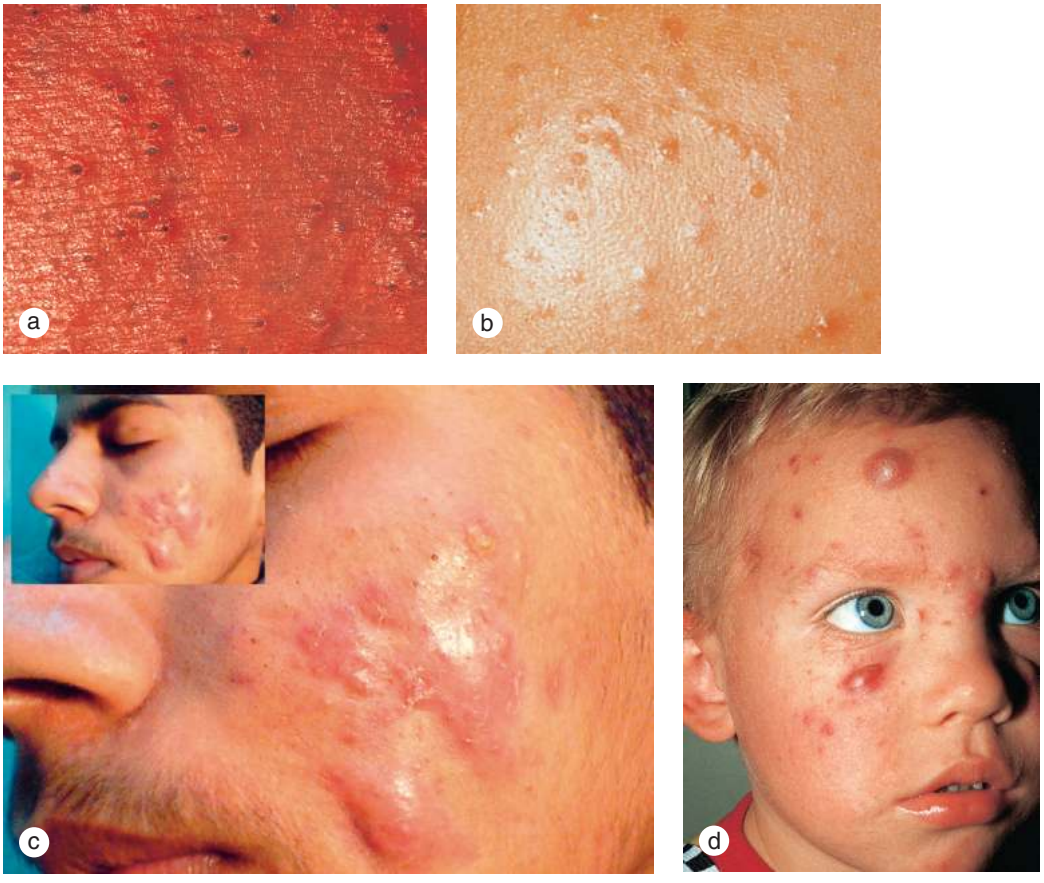


Fig 8.34 Acne. **(a)** Open comedones (blackheads) dot the forehead of this 16-year-old boy. **(b)** Closed comedones (whiteheads) cover the forehead of this 14-year-old girl. **(c)** Nodulocystic acne. This 18-year-old boy had a 3-year history of severe cystic acne consisting of deep tender nodules, violaceous cysts, pustules, and comedones. He improved dramatically with a 20-week course of oral 13-cis-retinoic acid (isotretinoin). **(d)** Papules, pustules, and cysts spread over the face, neck, and scalp of this toddler. He also responded well to 13-cis-retinoic acid. Both his parents had scars from previous cystic acne. **(e)** Pitted acne scarring. Multiple pitted scars remained after this patient's active acne was treated.



Fig 8.35 Acne fulminans. This healthy adolescent with severe nodulocystic acne developed widespread ulcerations and crusts shortly starting oral 13-cis-retinoic acid. Oral corticosteroids were added to his regimen and slowly tapered over 2 months.



Fig 8.36 Neonatal acne. This healthy newborn developed numerous scattered closed comedones and pustules on the face. The eruption resolved without therapy 1 month later.



Fig 8.37 Infantile acne. This healthy infant presented with several atrophic pink papules in various stages of healing on the bilateral cheeks.



Fig 8.38 Acneiform eruption. Uniform pustules on an inflamed base cover the trunk and proximal extremities of this 14-year-old boy who was placed on high-dose corticosteroids to manage inflammatory bowel disease. The eruption resolved when the corticosteroids were tapered.



Fig 8.39 Hot-tub folliculitis. Painful, red papules and pustules erupted (in a bathing suit distribution) on this teenage girl 24 h after lounging in a neighbor's hot tub. *Pseudomonas* grew from pus obtained from one of the lesions. Fortunately, she remained well, and the folliculitis resolved over 3 days without treatment.



Fig 8.40 Acne rosacea. This 19-year-old demonstrates the classic rash with red papules, pustules, cysts, and telangiectasias.



Fig 8.41 Perioral dermatitis. This 9-year-old girl developed asymptomatic red and confluent papules on the cheek, chin, and nose for over a month after using topical steroids on the face. Perioral dermatitis is considered a variant of rosacea and may be associated with topical steroid usage. A 6-week course of oral erythromycin resulted in complete and long-term clearing of the eruption.



Fig 8.43 Fox–Fordyce disease (apocrine miliaria). This young woman complained of persistent itchy skin-colored papules in her bilateral axillae that developed during adolescence.

Fig. 8.41). It more commonly occurs in the first few weeks of life due to eccrine duct immaturity. Miliaria ruba, also known as prickly heat, is another common disorder due to deeper obstruction of the eccrine duct. It occurs as 'heat rash' consisting of non-follicular pruritic papules in areas of occlusion (Fig. 8.44). It can be seen in children who are over-swaddled or bed-ridden or in older children and adults in hot climates or in occluded areas of the skin. The treatment is avoidance of excessive heat.

NAIL DISORDERS

As with hair disorders, abnormalities of the nails may provide a clue to the diagnosis of multisystem hereditary or acquired disease. Patients may also seek the advice of practitioners for nail problems because of pain or cosmetic concerns.



Fig 8.44 Miliaria rubra. This patient developed itchy non-follicular pink papules while in a hot and humid environment. The rash was more pronounced in areas of skin occluded by clothing.



Fig 8.42 Hidradenitis suppurativa. **(a)** This young man had recurrent inflammatory papules and nodulocystic lesions in the axillae and groin for 5 years. Although lesions initially improved with oral antibiotics, he subsequently developed draining sinus tracts. **(b)** This young woman had multiple indurated sinus tracts, nodules, and ulcers with purulent and necrotic drainage in her axillae.

Embryology and anatomy

Nails are first delineated as a fold in the skin of the developing fetus at 10–11 weeks. By the 15th week, the nail plate has already begun to keratinize, well before other epidermal structures. At birth, the nail is fully formed.

The major part of the nail comprises the hard nail plate, which arises from the matrix beneath the proximal nail fold (Fig. 8.45). The pink color of the nail bed is derived from the extensive plexus of vessels that lies beneath the normally transparent nail plate. A white, crescent-shaped lunula, which extends from under the proximal nail fold, represents the distal portion of the nail matrix. As the nail plate emerges from the matrix, its lateral borders are enveloped by the lateral nail folds. The skin that underlies the free end of the nail is referred to as the hyponychium, which connects the nail bed with the adjacent skin on the tips of the digits.

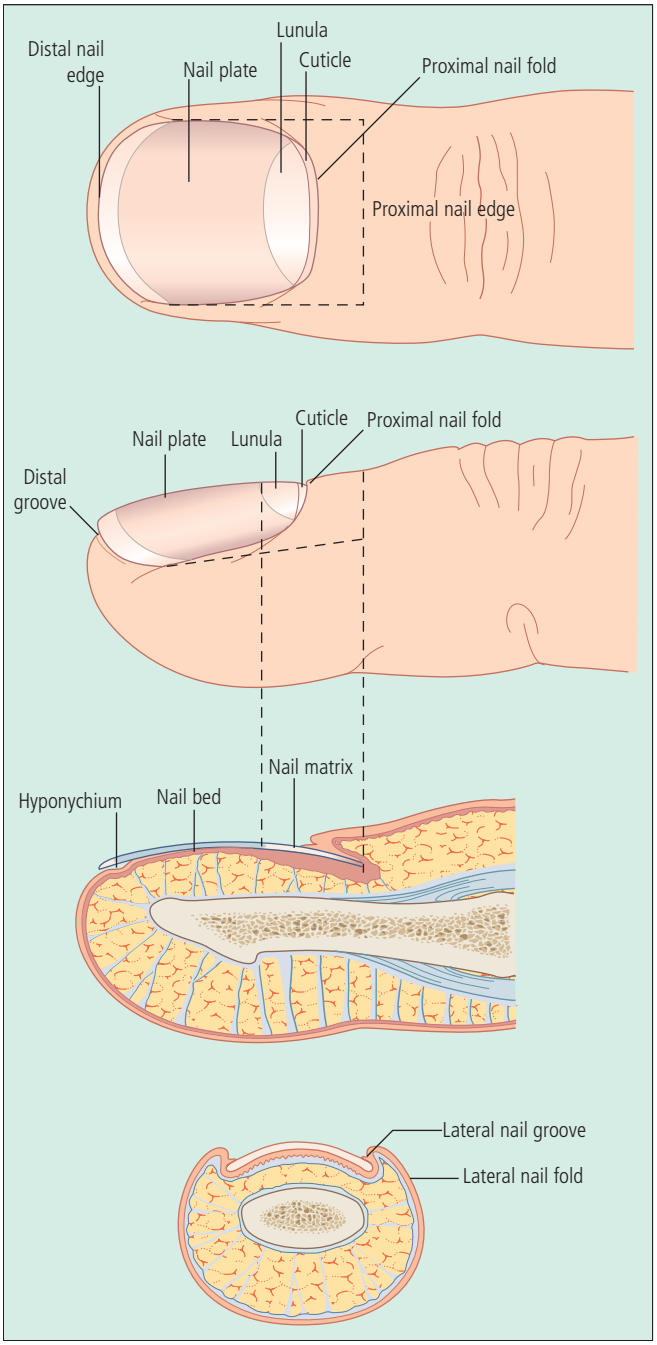


Fig 8.45 Anatomy of the nail.

Abnormalities in any part of the nail anatomy may result in characteristic clinical findings.

Congenital and hereditary disorders

Absence, hypoplasia, or dysplasia of the nails may occur as an isolated phenomenon or as part of an ectodermal dysplasia or other genodermatosis (Table 8.2).

Isolated malformations

Clubbing and spooning (koilonychia) of the nails may occur as autosomal-dominant abnormalities with no other anomalies

Selected nail anomalies

Anonychia
Deafness, onycho-osteodystrophy, mental retardation (DOOR) syndrome
Nail–patella syndrome
Hallermann–Streiff syndrome
Coffin–Siris syndrome
Klein syndrome

Hereditary ectodermal dysplasias
(Variable findings in which alopecia, dental defects, nail defects, or anhidrosis occur in combination with one sign affecting other structures of epidermal origin)

Chromosomal anomalies
Monosomies 4p, 9p
Trisomies 3q partial, 7q, 8, 8p, 9p, 13, 18, 21
Turner syndrome
Noonan syndrome
Group G-ring chromosome

Hyperplastic nails
Palmar–plantar keratodermas
Ichthyosis
Pachonychia congenita
Group G-ring chromosome

Koilonychia (spoon nails)
Mal de Meleda keratoderma
Monilethrix
Nail–patella syndrome
Incontinentia pigmenti
Trichothiodystrophy

Drug-induced malformations
Phenytoin, trimethadione, paramethadione
  Hyperpigmentation
  Hypoplasia
Warfarin
  Hypoplasia
Fetal alcohol syndrome
  Hypoplasia

Miscellaneous disorders with nail dystrophy
Epidermolysis bullosa
Acanthosis nigricans
Acrodermatitis enteropathica
Diabetes
Gingival fibromatosis
Hyper-IgE syndrome
Hyperuricemia
Lesch–Nyhan syndrome
Tuberous sclerosis

Table 8.2 Selected nail anomalies

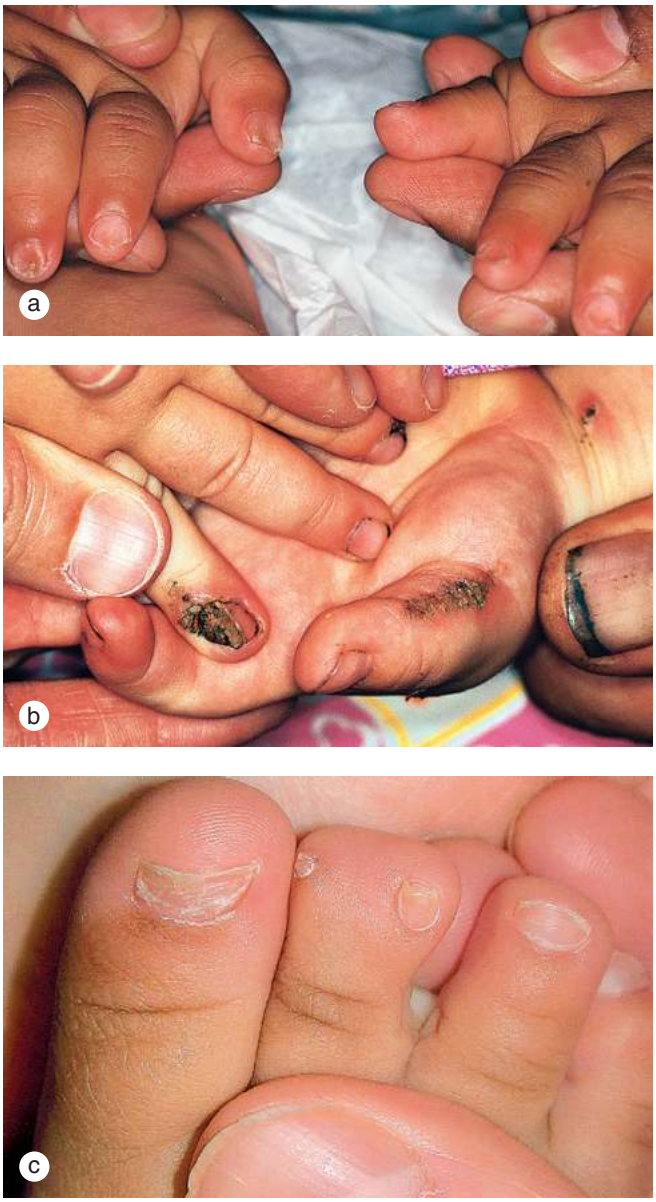


Fig 8.46 Congenital nail dystrophy. **(a)** Koilonychia was noted at birth in this infant whose mother had similar nails. **(b)** An extensive congenital epidermal nevus involved this infant's left thumb and right 5th fingernail. **(c)** Isolated congenital bifid nails were present in this infant and several other members of his father's family.

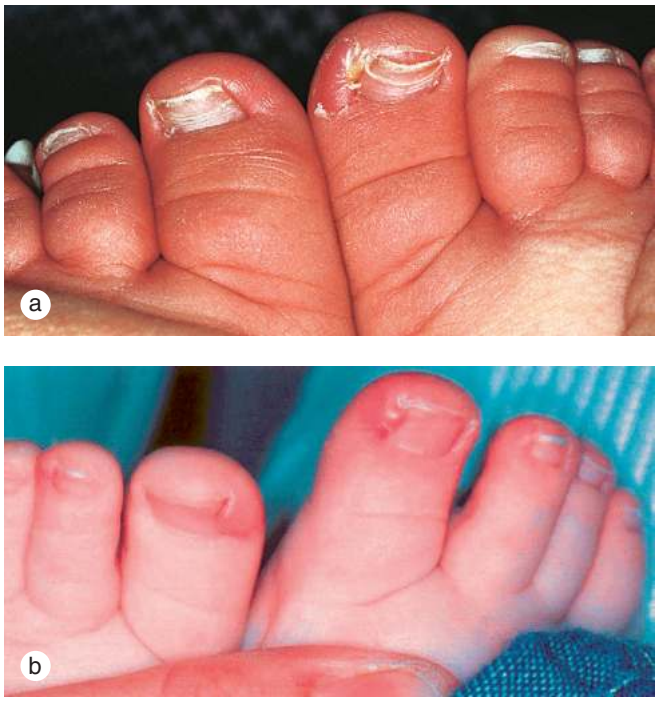


Fig 8.47 Congenital ingrown nails. **(a)** Congenital malalignment of the great toes resulted in recurrent ingrown toenails which were eventually repaired surgically. There was a family history of similar problems. **(b)** This infant had involvement of both great toenails, which improved without treatment by 12 months of age.

(Fig. 8.46). Although congenital ingrown toenails may result from congenital malalignment of the great toenails (and resolve only with surgical realignment), most cases are self-limiting and not related to an anatomic nail defect (Fig. 8.47). In the spontaneously regressing type, the ingrown nail may result from transient hypoplasia of the toenails, particularly the great toenails, which usually resolves within 12–18 months. Nail changes may be exacerbated by external trauma and recurrent/chronic paronychia.

Ectodermal dysplasias

Many of the ectodermal dysplasias are associated with nail abnormalities; some may be characteristic and diagnostic. In pachonychia congenita, an autosomal-dominant disorder with variable penetrance, hyperkeratosis of the nail bed, which develops in the first few months of life, is followed by vertical thickening and elevation of the nail plate with yellow-brown discoloration (Fig. 8.48). Minor trauma may induce painful separation of the nail plate from the nail bed and bleeding. Hyperhidrosis of the palms and soles, as well as callosities and blistering, is common. Other findings include leukokeratosis of the oral mucosae (not associated with malignant degeneration), thickening of the tympanic membranes that results in deafness, leukokeratosis of the cornea, and cataracts. Hyperkeratotic papules on the extensor surfaces of the extremities, dermoid cysts, and steatocystoma multiplex have also been reported.

Pachonychia congenita Jadassohn–Lewandowsky type, which is not associated with eye findings, is caused by a mutation in the keratin 16 gene (KRT16) or in the keratin 6A gene (KRT6A) located on chromosome 17q12–21, 12q13. Defects in the gene for keratin 17 (KRT17) and keratin 6B (KRT6B) are associated with the Jackson-Lawler type where corneal dystrophy is found without oral leukoplakia.

Dyskeratosis congenita may be confused with pachonychia congenita. However, in dyskeratosis congenita, which may be gender linked, autosomal dominant, or autosomal recessive, the nail plate is thinned with longitudinal ridging and pterygium formation (Fig. 8.49). In dyskeratosis congenita, poikiloderma with reticulated pigmentation, telangiectasias, and atrophy is most prominent on the neck and trunk. Leukoplakia of the oral mucosae may be associated with the development of squamous cell carcinoma and other malignancies of the gastrointestinal tract. Pancytopenia occurs in 50% of affected individuals during their second and third decades and resembles Fanconi anemia. Most cases are X-linked recessive and have been associated with mutations in the Xq28 gene encoding dyskerin (DKC1). Hypoplasia of the nails may also be a feature of hidrotic ectodermal dysplasia and Coffin–Siris syndrome (Fig. 8.50).

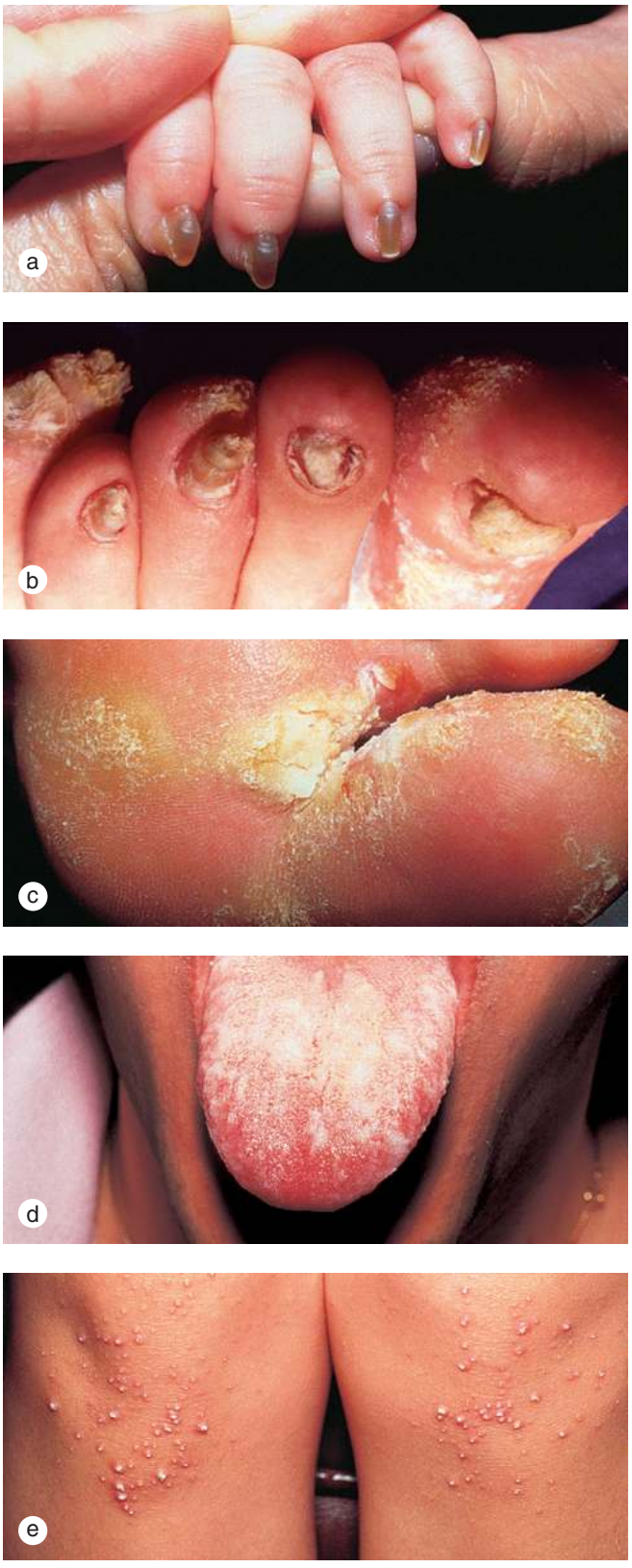


Fig 8.48 Pachonychia congenita. **(a)** At 3 months of age all 20 of this child's nails showed early changes of pachonychia with yellowing and pinched-up hyperplasia. **(b,c)** His father had marked involvement of all nails, as well as painful callosities on the dorsal and plantar aspects of the feet. **(d)** Leukokeratosis without a risk of malignant degeneration usually appears in infancy or early childhood and may involve the tongue, gingivae, and oral mucosae. **(e)** Hyperkeratotic papules on the extensor surfaces of the extremities are also common, particularly over the knees and elbows.



Fig 8.49 Dyskeratosis congenita. Unlike pachonychia congenita, the nails are usually thin, fragile, and hypoplastic.



Fig 8.50 Hypohidrotic ectodermal dysplasia. This child's **(a)** finger nails and **(b)** toenails were thin, somewhat hypoplastic, frequently dystrophic, and fractured by minor trauma.



Fig 8.51 Nail-patella syndrome. Both father and son had hypoplastic patellae and dystrophic, hypoplastic nails.



Fig 8.53 Fetal alcohol syndrome. This 3-year-old with developmental delay, dysmorphic facies, and other stigmata of fetal alcohol syndrome had multiple congenital hypoplastic and dysplastic nails.

Genodermatoses and systemic disease

Nail-patella syndrome is an autosomal-dominant disorder that presents with congenital absence or hypoplasia of the nails and patellae (Fig. 8.51). Glomerulonephritis occurs in a small percentage of cases and is rarely fatal. Heterochromia of the iris, keratoconus, and cataracts has also been reported.

Periungual fibromas, which arise from the proximal nail groove, are a common finding in patients with tuberous sclerosis. Although the fibromas do not appear until later childhood or adult life, they may provide the first clue to diagnosis in individuals who are otherwise mildly affected (Fig. 8.52).

Congenital hypoplasia of the nails in infants with intrauterine exposure to anticonvulsants, alcohol, warfarin, or other teratogens prompts a thorough evaluation for other drug-induced stigmata (Fig. 8.53).

Acquired nail disorders

Paronychia

Paronychia is a common childhood disorder. It presents as a red, tender swelling of the proximal or lateral nail fold. In the acute form, exquisite pain, sudden swelling, and abscess formation around one nail are caused by bacterial invasion after trauma to the cuticle (Fig. 8.54). Chronic paronychia may involve one or several nails. There is usually a history of frequent exposure to water (dishwasher's or thumb-sucker's paronychia). Tenderness is mild, and a small amount of pus may sometimes be expressed. In chronic cases, the nail may be discolored and dystrophic (Fig. 8.55). The causative organisms are *Candida* species, usually *C. albicans*.

Acute paronychia responds quickly to drainage of the abscess and warm tap-water soaks. Occasionally, oral antistaphylococcal antibiotics are required. Chronic lesions resolve with topical antifungal agents and avoidance of water. Parents of toddlers must be reassured that recurrent candidal paronychia eventually heals without scarring when thumb-sucking ends. Intermittent, chronic use of antifungal creams in young children is effective and safe.

Nail dystrophy

Nail dystrophy (distortion and discoloration of normal nail-plate structure), may result from any traumatic or inflammatory process that involves the nail matrix, nail bed, or surrounding tissues. Although onychomycosis, the result of dermatophyte fungal infection, is the most common cause of nail dystrophy in adults, it is unusual in children before puberty (Fig. 8.56). Dystrophic nails occur frequently as a complication of trauma (Fig. 8.57) or underlying dermatoses, such as psoriasis, atopic dermatitis, and lichen planus (Figs 8.58–8.61).

Trauma to the nail may cause a subungual hematoma, which results in a brown-black discoloration. This is particularly likely



Fig 8.52 Periungual fibromas, in the proximal nail groove. This is a common finding in patients with tuberous sclerosis.



Fig 8.54 Paronychia. An acute, staphylococcal paronychia developed after this child picked at a hangnail.





Fig 8.55 Chronic paronychia. **(a)** A chronic, candidal paronychia recurred for over a year on the finger of an otherwise healthy toddler. Note the erythema at the base of the nail and loss of the cuticle. **(b)** All 20 nails were discolored and hyperplastic in this 8-year-old boy with chronic mucocutaneous candidiasis. The chronic paronychia and nail dystrophy resolved on long-term treatment with oral ketoconazole.



Fig 8.56 Onychomycosis. This 4-year-old boy developed a single dystrophic toenail, which grew *Trichophyton rubrum* on fungal culture. His father had chronic athlete's foot.

following crush injuries. Usually, the diagnosis is simple, unless trauma is subtle. Although most hematomas resolve without treatment, large, painful collections of blood may be drained by drilling a small hole in the nail plate using a sterile, large-bore needle. This relieves pain and reduces the risk of infection. Dark pigmentation at the base of the great toenail, caused by jamming the toe into the end of the shoe at a sudden stop, is called 'turf toe' and also results from subungual hemorrhage (Fig. 8.62). This must be differentiated from melanoma and melanonychia (Fig. 8.63). Hemorrhage may be identified by the presence of purple-brown pigment in the distal nail and normal proximal outgrowth of the nail. In melanonychia, gray-brown streaks of pigment of varying width extend longitudinally from the proximal nail fold of one or several nails. Although this finding is common in darkly pigmented individuals, it may occur in individuals of any race at any age. Irregular or changing pigment streaks may require a nail biopsy to confirm their innocent nature and exclude melanoma.

Nail biting, grooming, and chronic manipulation of any sort may also result in nail dystrophy. Repeated trauma to the cuticle may



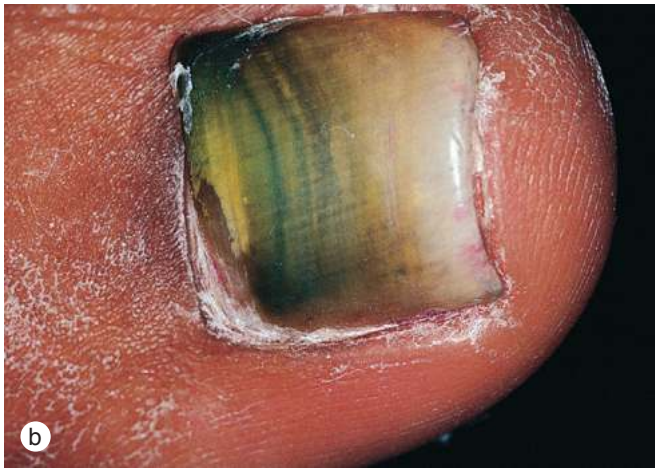


Fig 8.57 Traumatic nail dystrophy. **(a)** Onychoschizia (transverse splitting of the nail at the distal free edge) occurred in both great toenails as a result of recurrent trauma from basketball in this high-school athlete. **(b)** Another adolescent athlete developed chronic *Pseudomonas* infection in a dystrophic great toenail.



Fig 8.58 Nail psoriasis. **(a)** This 26-year-old male presented with pits on the fingernail surface, onycholysis, and mild subungual hyperkeratosis as well as generalized psoriatic plaques and **(b)** yellow, friable, flaking nails in another child with severe psoriatic arthritis.



Fig 8.59 Atopic nails. Multiple, transverse ridges and splitting of the nails developed in an atopic patient with generalized skin disease, which included severe hand involvement.

produce leukonychia (transverse white lines) and median nail dystrophy (central longitudinal ridging; Fig. 8.64).

Twenty-nail dystrophy (trachyonychia) is a disorder of otherwise healthy children of school age and is characterized by yellowing, pitting, increased friability, and other dystrophic changes that progresses over 6–18 months to involve most or all of the nails giving them a roughened texture (Fig. 8.65). Although the course is variable, in many cases the dystrophy resolves without scarring over a period of several years. This disorder probably includes a number of conditions that cannot be differentiated unless other cutaneous findings appear.

Nail dystrophy may accompany other skin disorders and help with their diagnosis. For example, alopecia areata is associated with characteristic Scotch-plaid pitting of the nails (Fig. 8.66). Psoriasis in the nail matrix results in scattered pits that are larger, deeper, and less numerous than those found in alopecia areata (see Fig. 8.58a). Psoriasis of the nail bed, especially under the distal



Fig 8.60 Lichen planus. An adolescent girl demonstrates the characteristic nail changes in lichen planus, which include onychorrhexis (longitudinal splitting) and pterygium formation (forward growth of the skin at the proximal nail fold, which results from scarring).



Fig 8.61 Lichen striatus. This healthy 7-year-old boy developed an asymmetric nail dystrophy as a linear lichenoid eruption extended down his left arm to the lateral aspect of his thumb. A biopsy of the skin showed changes typical of lichen striatus.

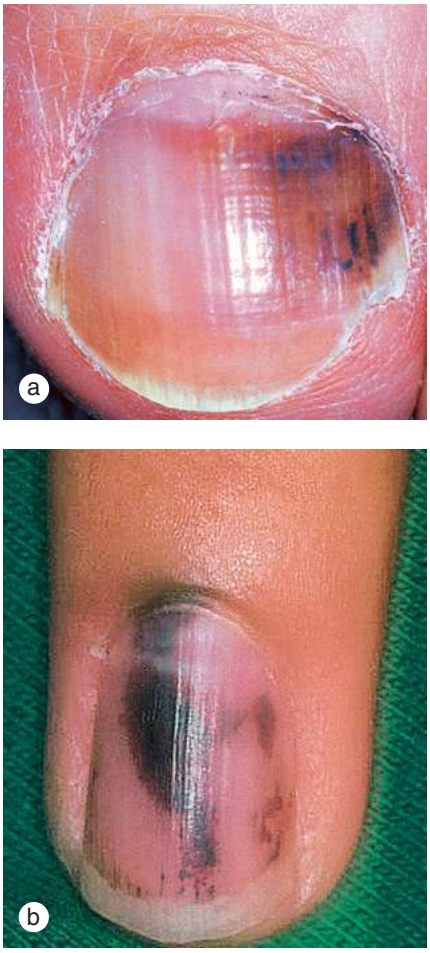


Fig 8.62 Traumatic subungual hematoma. **(a)** Discoloration as a result of traumatic hemorrhage under the toenail is common in children and athletic adults. It is a result of repeated jamming of the toe into the end of the shoe while running or stopping suddenly (turf toe). **(b)** This 10-year-old boy slammed his finger in a car door a week ago.

nail, causes separation of the nail plate from the underlying skin (onycholysis) and oil-drop discoloration with heaped-up scaling (see Fig. 8.58b). Onycholysis alone, without pits or discoloration, may be caused by trauma, infection, nail-polish hardeners, or phototoxic reactions to drugs such as tetracycline (Fig. 8.67).

Nail changes and systemic disease

Finally, nail findings may provide a clue to the diagnosis of underlying medical disorders (Fig. 8.68). For example, clubbing may be associated with chronic pulmonary disease or congenital heart disease with a right-to-left shunt. Splinter hemorrhages in the nail bed are a physical sign of bacterial endocarditis (see Fig. 7.26). Cyanosis of the nail beds in Raynaud phenomenon and periungual telangiectasias may support a diagnosis of collagen vascular disease. Thickened, yellow, slow-growing nails (yellow nail syndrome) occurs in chronic pulmonary disease and lymphedema. Koilonychia has been reported in hemochromatosis and iron deficiency. Half-and-half nails, in which the proximal nail appears white and the distal nail red, probably results from edema and changes in blood flow in the nail bed, and has been associated with uremia, heart failure, and cirrhosis. Leukonychia totalis may present at birth or develop in childhood. Although it may arise sporadically, it is most frequently inherited as an autosomal dominant trait and may be associated with other features such as epithelial cysts and renal calculi. The white color results from retention of nuclei within the nail plate rather than a disorder of the nail bed. Uniform, transverse, white lines and/or grooves in the nail that move distally with nail growth result from growth arrest because of systemic illness, medications, or toxins. These lesions, known as Beau lines, have been reported with acute childhood infections, surgery, chemotherapy, and flares of systemic disorders (Fig. 8.68).

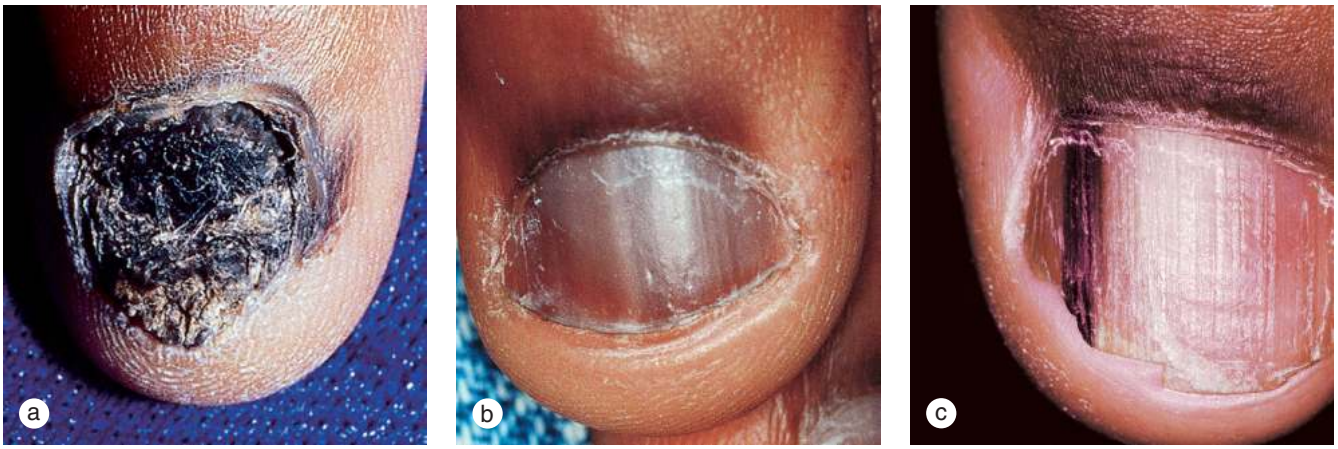


Fig 8.63 (a) In this patient with an acral melanoma, which arose in the nail matrix or nail bed, the nail has become dystrophic and the nail bed is infiltrated with pigmented, malignant cells. **(b,c)** In melanonychia, neat, hyperpigmented streaks extend vertically across the nail from the proximal nail fold. This can appear in **(b)** a diffuse pattern or **(c)** in narrow bands.







Fig 8.64 Traumatic nail changes. **(a)** Leukonychia consists of punctate lesions or transverse white lines that grow out along the nail plate and frequently result from trauma to the nail at the cuticle. **(b)** Median nail dystrophy developed in this teenage boy, who admitted to chronically picking at his nails. **(c)** This adolescent was an obsessive nail picker. In addition to median nail dystrophy he developed crusting and hemorrhage of multiple finger and toenails.



Fig 8.65 Trachyonychia. This otherwise-healthy 9-year-old boy developed an asymptomatic nail dystrophy which progressed to involve all 20 nails. Note the increased ridging, opalescence, and sandpaper-like roughness of all his nails. These nail changes can occur in association with lichen planus, psoriasis, atopic dermatitis, and alopecia areata.



Fig 8.66 Scotch-plaid pitting, transverse rows of regularly spaced pits, was associated with alopecia areata in this teenager.



Fig 8.67 Onycholysis. This young woman developed whitening of the distal nail plate with distal separation of the nail plate from the nail bed. It can be seen in inflammatory skin disorders such as psoriasis and secondary to chemical irritants, trauma, and medications. Onycholysis resulting from sunlight exposure is called photo-onycholysis and may occur in individuals taking oral doxycycline.



Fig 8.68 Nail changes and systemic disease. **(a)** Clubbing may occur as an isolated, inherited defect or a complication of chronic lung or heart disease. **(b)** Yellow nail syndrome with chronic yellowing and slow growth of all nails was noted in this patient with Hodgkin disease. **(c)** Half-and-half nails (proximal nail bed white and distal nail bed red) were a marker for uremia in this 14-year-old girl with chronic renal failure. **(d)** White nails developed in this healthy 9-year-old boy. There was no family history of leukonychia, and a complete physical examination failed to reveal other significant cutaneous or systemic findings. **(e)** Beau line. This patient developed a transverse groove several months after a serious systemic infection from which she recovered 6 months earlier. These growth arrest lines affected all 20 nails and slowly grew toward the distal edge of the nail plate. **(f)** Onychomadesis. This man presented with crusting and scaling at the base of the nail associated with nail shedding. Onychomadesis has been reported in patients with bullous dermatoses, febrile illnesses, psoriasis, and cutaneous drug eruptions, particularly Stevens–Johnson syndrome and toxic epidermal necrolysis.

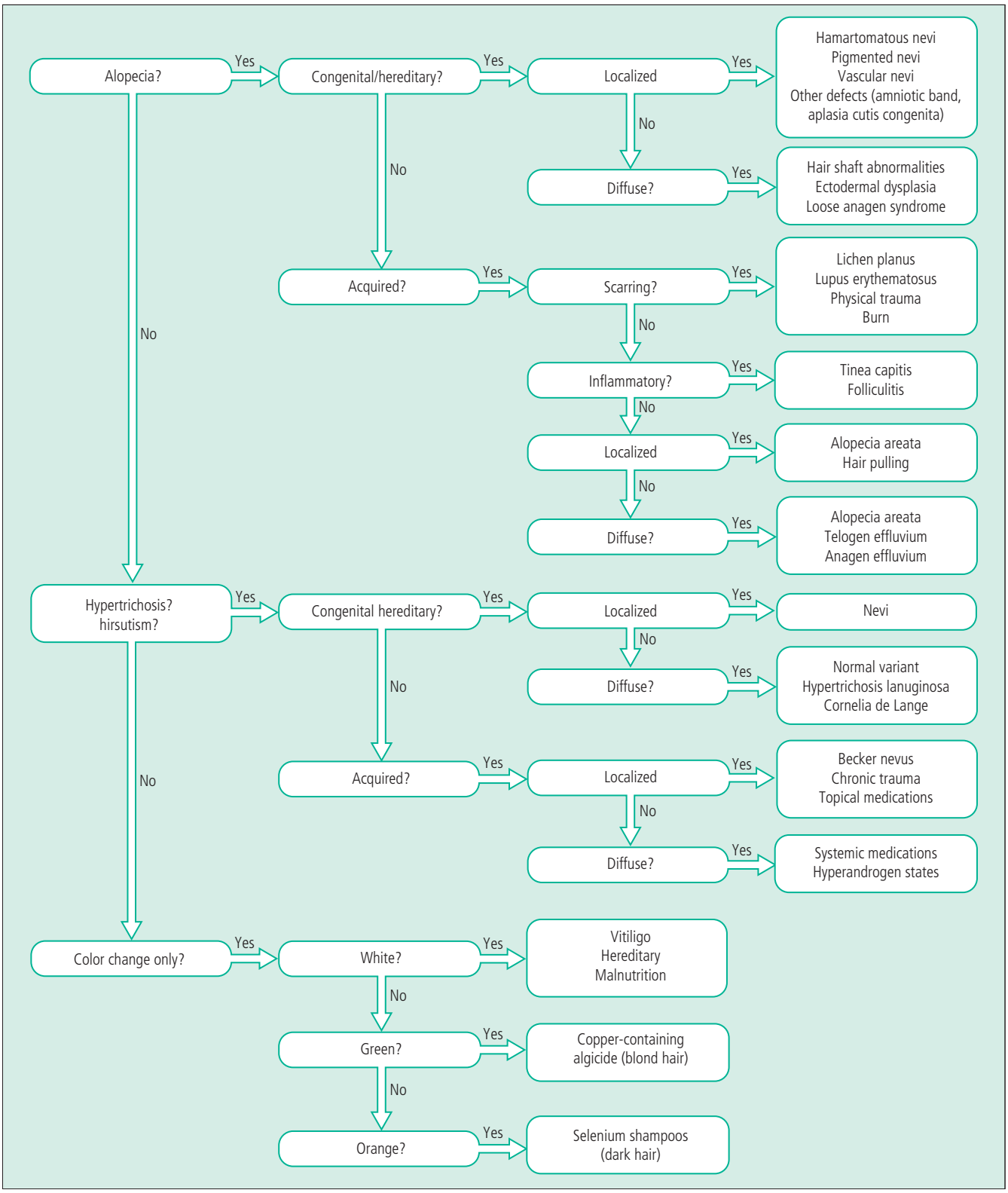


Fig 8.69 Algorithm for the evaluation of the hair.

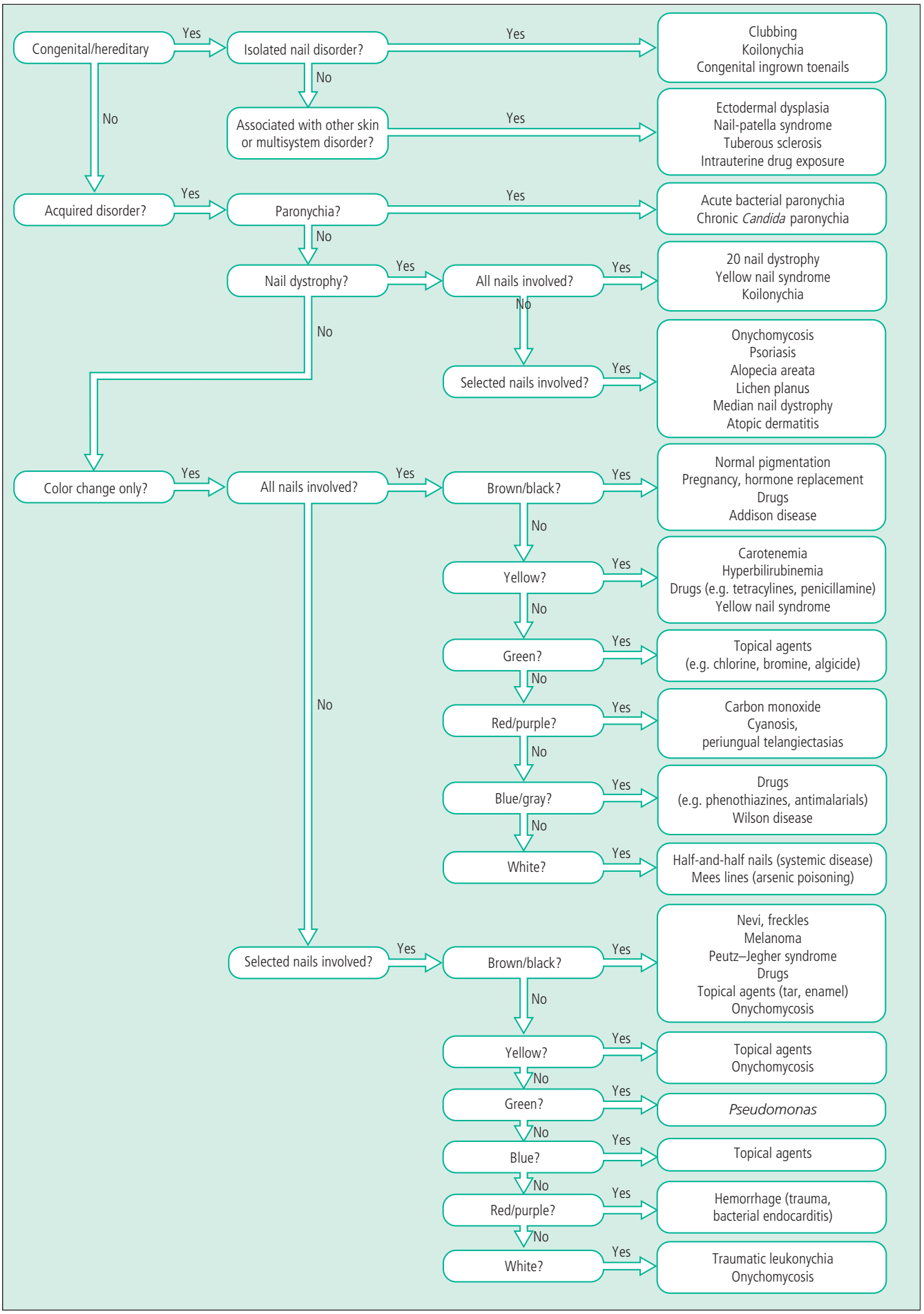


Fig 8.70 Algorithm for evaluation of disorders of the nails.

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Chapter 9

Oral Cavity

Bernard A. Cohen

INTRODUCTION

A full skin examination should always include close inspection of the mucous membranes, particularly the mouth. Clinical findings in the mouth may provide clues to the diagnosis of systemic disease (Fig. 9.1), and some cutaneous disorders are associated with specific oral findings (Fig. 9.2). Many lesions commonly identified in the skin occur in the mouth (Fig. 9.3a) or extend into the mouth from perioral skin (Fig. 9.3b). Some lesions evolve in the mouth before extending to or disseminating to the skin (Fig. 9.4).

A number of lesions arise from structures in the mouth and are usually confined to the mouth and contiguous structures. This chapter will focus on these disorders. An algorithmic approach to



Fig 9.1 Systemic lupus erythematosus. Erosions and scarring on the palate were early findings in this 14-year-old girl.



Fig 9.2 Graft-vs-host disease. White lichenoid patches and ulcerations on the vermillion border extending into the mouth were associated with widespread cutaneous findings in this adolescent who received a bone marrow transplant 3 weeks earlier.





Fig 9.3 (a) Hemangioma. Rapidly growing hemangioma on the inner aspect of the lower lip. **(b)** Herpetic gingivostomatitis. Vesicles and erosions on the lip and tongue.



Fig 9.4 Pemphigus vulgaris. Extensive intraoral and lip ulcerations were the first manifestation of pemphigus in this 8-year-old boy. He developed a pyogenic granuloma on the right buccal mucosa which was shaved and cauterized.

the evaluation of oral pathology is summarized at the end of the chapter (see Fig. 9.36).

ANATOMY OF THE ORAL CAVITY

The opening of the oral cavity (Fig. 9.5) is surrounded by the lips, two flexible muscular folds that extend from the corners of the mouth to the base of the nasal columella above and the mentolabial sulcus (fold above the chin) below (Fig. 9.5a). The lip is divided into three anatomic zones. The outer skin above and below the vermillion border is similar to skin at other sites and includes adnexal structures such as hair follicles, eccrine sweat glands, and sebaceous glands. The vermillion is a transitional zone with a thin stratum corneum and increased numbers of dermal blood vessels which impart a distinctive reddish-purple color. Although hair follicles and sweat glands are absent, ectopic sebaceous glands (Fordyce granules, see Fig. 9.26) may be present. The labial mucosa covers the inside of the lip and meets the alveolar mucosa. It contains large numbers of mucus-producing salivary glands.

The lips are anchored to the adjacent gingiva by the labial frenulum. The oral cavity is formed by the arch of the hard and soft palates above, the teeth and cheeks laterally, and the tongue on the floor of the mouth. The lips and teeth are separated by a shallow vestibule. The sides of the oral cavity are formed by the smooth pink to light-red buccal and labial mucosa. It merges with the alveolar mucosa which is loosely attached to the underlying periosteum. The opening of the parotid gland (Stensen's duct) is a triangular papilla located on the buccal mucosa of the vestibule opposite the second molars. The linea alba or occlusal line is a pale-white to pink streak along the line of dental occlusion.

The gingiva is divided into the fixed gingival, which is fixed to the alveolar process, and the free gingival, which is adjacent to the teeth and extends into the tissue that fills the space between the teeth, the interdental papillae. Although the free gingival is not usually pigmented, the attached gingiva appears stippled, and other parts of the buccal mucosa may appear highly pigmented in dark-skinned individuals.

The anterior two-thirds of the palate is know as the hard palate, which is formed from the medial and two lateral palatine processes. The overlying mucosa is fixed to the underlying bone and has a rough appearance and a median raphe. The soft palate continues the roof of the mouth posteriorly as a fold of mucosa and muscle that ends centrally in the uvula and laterally in the folds merging with the tonsillar pillars and the tongue. The palatine tonsils sit between the anterior and posterior pillars. Similar lymphoid tissue lies at the base of the tongue.

The tongue is a mass of intersecting muscles divided into the inner and outer tongue muscles (Fig. 9.5b). The anterior two-thirds of the tongue, which is derived from ectoderm, ends in a thin narrow tip or lingual apex, while the posterior third, which is derived from the end of the gut, is known as the lingual root. The junction of the root and the rest of the tongue forms a V-shaped groove known as the terminal sulcus that points toward the throat. The posterior end of the V marks the foramen caecum, the origin of the thyroid gland. The surface of the tongue is referred to as the dorsum that extends from the tip to the epiglottis, while the posterior portion is known as the base which merges with the loose mucosa on the floor of the mouth. The dorsum of the tongue, which is adapted for taste and mastication, is covered by specialized papillae. Filiform papillae appear as pointed spikes and are uniformly distributed over the surface giving the tongue a rough texture. They are primarily responsible for mechanical activities such as licking. Fungiform papillae are red mushroom-shaped structures that are interspersed among the filiform papillae but more concentrated on the anterior surface. They subserve the sense of sweet and salty taste. The circumvallate papillae are the largest and most prominent papillae. They are located along the terminal sulcus and are responsible for a bitter taste. The vestigial foliate papillae are located on the posterior lateral portion of the tongue and are usually associated with the lingual tonsils.

The floor of the mouth is formed by the lingual aspect of the mandible and posteriorly by the base of the tongue. It is divided in the center by the lingual frenulum which extends from the midline of the mandible to the ventral tip of the tongue. The plica sublingualis are symmetric mucosal folds with a fringed free edge on the ventral aspect of the tongue between the lingual frenulum and the lateral border of the tongue. Wharton's duct, the main excretory duct of the submandibular gland, exits at the sublingual caruncula adjacent to each side of the lingual frenulum.

Humans possess two sets of teeth: 20 primary teeth and 32 permanent teeth (Fig. 9.5c). Usually eruption of the primary teeth begins at 6 months of age and continues at a rate of one tooth a month until 2 or 2.5 years. The normal number of teeth for a given age can be estimated by subtracting 6 from the child's age in months up to 2 years of age. Eruption of the permanent teeth usually begins at age 6 years with appearance of the first molars. Calcification of the primary teeth begins at 3–4 months *in utero*, and calcification of the permanent teeth begins at birth and continues for 8–10 years. Dental enamel (thin outer protective barrier) is derived from ectoderm, while dentin (hard tissue that constitutes the bulk of teeth), cementin (cement-like substance that anchors dentin to the periodontal ligament), and pulp (loose connective tissue containing blood vessels and nerves).

BUCCAL MUCOSA

White sponge nevus

White sponge nevus is a rare genodermatosis first described by Cannon in 1935 (Fig. 9.6). This autosomal dominant disorder has a high degree of penetrance but variable expression, and results from mutations in genes coding for keratins 4 and 13 which are

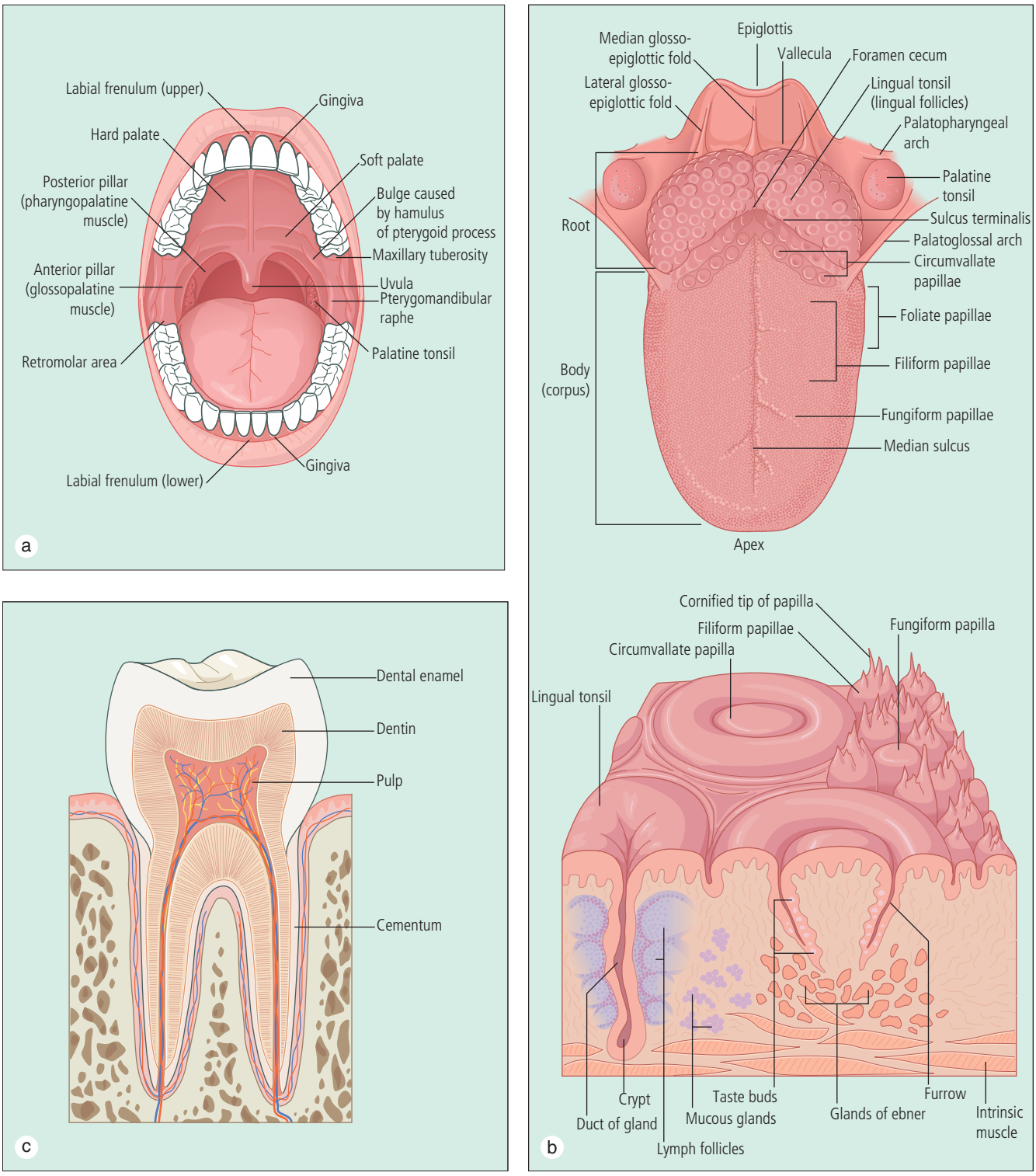


Fig 9.5 (a) Oral cavity. **(b)** Tongue. **(c)** Tooth.

found in the spinous layer of the oral mucosa. Defects in these keratin filaments result in thickening of the oral mucosa and formation of mucosal folding giving a spongy leathery texture. The mucosa appears swollen, and there may be areas where the upper layers are pulled away leaving fissures.

White sponge nevus may be present at birth, develop early in childhood, or be delayed until adolescence. Broad asymptomatic plaques usually involve the buccal mucosa bilaterally and may extend to the ventral surface of the tongue, labial mucosa, soft palate, alveolar mucosa, and the floor of the mouth. Rarely other mucosa including the vagina, rectum, nose, and esophagus may be involved.

Histologic findings include acanthosis and parakeratosis. The upper epithelial layers are vacuolated and contain pyknotic nuclei. Occasionally epidermolytic hyperkeratosis, characteristic of congenital ichthyosiform erythroderma, is seen.

These histologic and clinical features may overlap with the oral mucosal plaques found in patients with pachonychia congenita and



Fig 9.6 White sponge nevus. **(a)** This 9-year-old girl with pachyonychia congenita had asymptomatic plaques on her tongue and buccal mucosa noted shortly after birth. **(b,c)** Congenital asymptomatic plaques confined to the oral cavity in a healthy adolescent and left buccal mucosa in a healthy 6-year-old girl.

early dyskeratosis congenita. In type I pachonychia congenita, which is the most common variant, white sponge nevus of the oral mucosa is associated with massive nail plate thickening, follicular hyperkeratosis on the extensor surfaces of the arms and legs, palmar-plantar keratoderma, and hyperkeratosis. Patients with the type II variant demonstrate no mucous membrane findings, but may present with natal teeth. Early oral mucous membrane plaques in patients with dyskeratosis congenita are indistinguishable from pachonychia congenita, but oral leukoplakia does not usually appear until patients are in their early twenties. In early childhood, reticulated hyperpigmentation develops on the chest, neck, and arms, and generalized poikiloderma evolves by adolescence. Hypoplastic and dysplastic nail changes are a characteristic finding in dyskeratosis congenita in infancy or early childhood, and 50% of patients develop pancytopenia of the Fanconi type. Leukoplakia, which often involves multiple mucous membrane sites, is associated with a high risk of malignant degeneration.

Leukoedema may also be confused with white sponge nevus (Fig. 9.7). This asymptomatic process manifests as diffuse whitening of the buccal mucosa and may extend to the labial mucosa and tongue, but fixed mucosa is not affected. Although there may be shallow folds, the mucosa is not usually thickened, and unlike white sponge nevus, the whitening decreases or disappears with stretching. Leukoedema is common particularly in dark-pigmented individuals where it is often considered a normal variant.

White sponge nevus and leukoedema are asymptomatic and treatment is unnecessary.

Thrush (pseudomembranous candidiasis)

Thrush can be recognized by the characteristic white dots, patches, and plaques that develop most commonly on the buccal and labial mucosa and extend to the ventral tongue and palate as well (Fig. 9.8). Rubbing of the white lesions leaves a red patch and occasionally superficial bleeding erosions. In immunosuppressed individuals lesions can become widespread throughout the oral cavity. In both normal and immunocompromised hosts candidiasis can present with angular cheilitis as well.

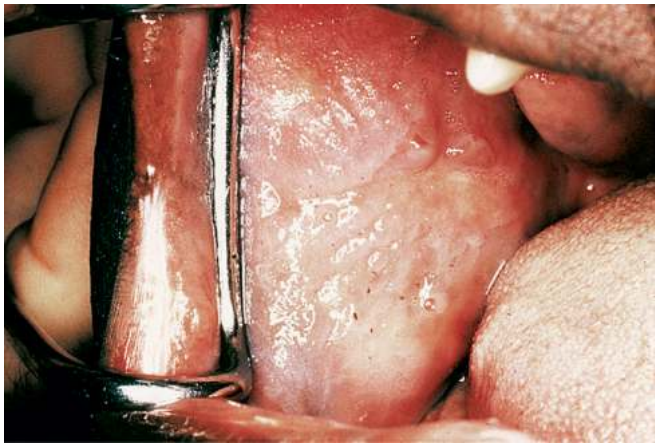


Fig 9.7 Leukoedema of buccal mucosa.

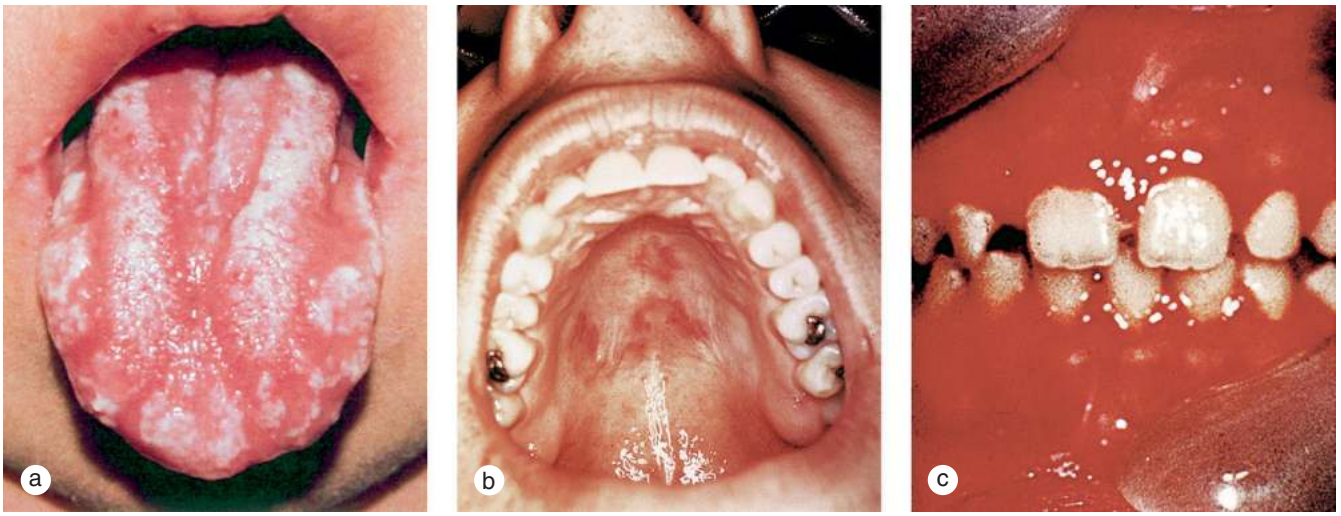


Fig 9.8 (a) Oral candidiasis with white plaques on the tongue. **(b)** White plaques and erosions on the palate and **(c)** confluent beefy red plaques on the gingiva. Note the angular cheilitis in the child in Figure 9.8a.

Of newborns, 10–15% present with thrush acquired most frequently from maternal vaginal candidiasis. Nursing mothers can also transmit infection to their offspring when their breasts are involved. In infants the buccal mucosa, tongue, and soft palate are most commonly involved, but lesions may appear on the posterior oral pharynx and lateral commissures of the mouth.

Persistent, widespread, or resistant candidiasis at any age should suggest the diagnosis of hereditary or acquired immunodeficiency. Thrush has also been reported in association with leukemia, lymphoma, inflammatory bowel disease, Addison disease, malnutrition, antibiotics, and oral corticosteroids.

The differential diagnosis includes leukoplakia, leukoedema, lichen planus, and white sponge nevus. These lesions can usually be distinguished by clinical findings, potassium hydroxide preparation of material from the white membrane, associated symptoms, and histologic evaluation if necessary.

Predisposing factors should be identified and treated if possible, and severe or persistent disease should prompt an evaluation for immunodeficiency. Topical imidazoles in cream, solution, or troche formulation may be effective, but resistant cases may require oral fluconazole or itraconazole. Fluconazole is available in convenient oral formulations for infants and young children of 10 mg/cc and 40 mg/cc.

TONGUE

Congenital malformations

Ankyloglossia is a usually minor developmental anomaly of the tongue resulting from a congenital short, thick lingual frenulum (Fig. 9.9). In the most severe variant the tongue may be fused with the floor of the mouth. Mild ankyloglossia occurs in 2–4% of newborns but is severe enough to require consultation in only 2–3/10 000 individuals.

Although limitation of movement of the tongue may be present, there is usually no interference with eating, swallowing, or speech development. However, there are rare reports of problems with breast-feeding.

The tongue normally tends to be short at birth, and lengthens with increasing age. As a consequence, most patients adapt to mild ankyloglossia which probably improves or resolves spontaneously. However, if functional problems persist, frenulectomy is usually curative.

Rarely, accessory frenula may be found in association with ankyloglossia and should prompt a search for other anomalies of the oral cavity including cleft lip, cleft palate, and, specifically, orofaciodigital syndrome type I.

Congenital vascular malformations, ranula, thyroglossal duct cysts, dermoid cysts, and ectopic thyroid will be discussed later with tumors at the base of the tongue and macroglossia.

Erythema migrans (geographic tongue)

Erythema migrans (geographic tongue, *stomatitis areata migrans*) is a common tongue lesion that is often detected on routine oral examination (Fig. 9.10). It affects 1–2% of adolescents and young adults, girls more often than boys, and typically begins in childhood. Lesions are usually asymptomatic but occasionally painful, especially when exposed to sour or spicy foods. Although the



Fig 9.9 Ankyloglossia. A 16-year-old girl was unable to fully extend her tongue.

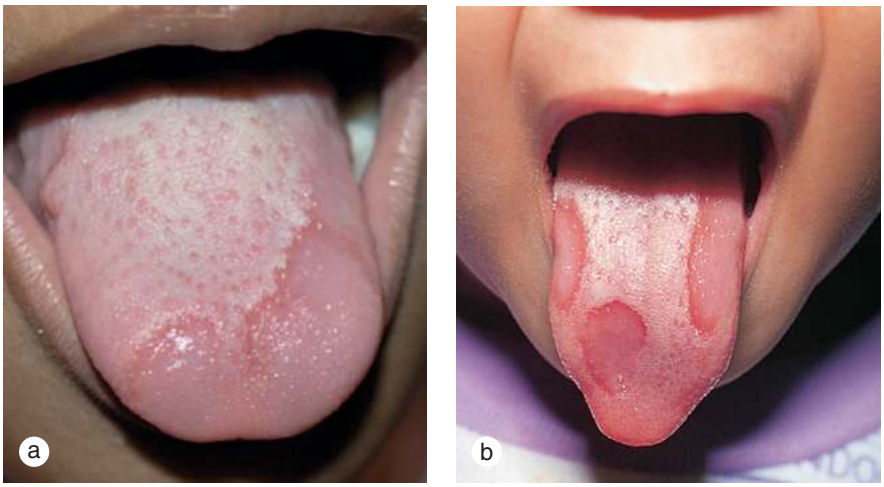


Fig 9.10 Geographic tongue. Atrophic patches in **(a)** 6-year-old girl and **(b)** a toddler.

tongue is most often affected, other mucosal sites may be affected including the buccal and labial mucosa and the soft palate.

Geographic tongue results from atrophy of the filiform papillae, while uninvolved fungiform papillae appear as red dots. The margin of lesions is slightly elevated, whitish, and thickened. Typically, a few 0.5–1cm patches begin on the edge or dorsum of the tongue and expand and increase in number over 3–5 days to form multiple serpiginous, annular, confluent patches giving a maplike appearance. Lesions persist for 10–14 days and recur periodically for years although the frequency of recurrences tends to decrease with increasing age.

Although patches usually occur as an isolated finding, geographic tongue may be associated with fissured tongue, psoriasis, and atopic dermatitis. Histologic features resemble psoriasis with acanthosis, hyperkeratosis, central atrophy, and a neutrophilic infiltrate in the lamina propria and epithelium. Geographic tongue may also be associated with balanitis circinata, a finding characteristic of Reiter syndrome.

No therapy is usually necessary, but some patients experience mild stinging with acidic or spicy foods. Rarely when symptoms are severe, temporary relief can be achieved with topical anesthetics.

Black hairy tongue (*lingua villosa nigra*)

Hairy tongue, which can range in color from yellow to brownish-black, results from benign hyperkeratosis and elongation of the filiform papillae on the dorsal lateral surfaces of the tongue and probably represents exaggeration of the normal coating of the tongue (Fig. 9.11). Asymptomatic scaling usually begins just anterior to the terminal sulcus and spreads anteriorly and laterally giving a triangular pattern.

Histopathology shows hyperkeratosis of the filiform papillae, overgrowth of bacteria and yeast, and non-specific inflammation.

Although the cause is unclear, hairy tongue may result from a microbial trigger that alters normal mouth flora. Oral and topical antibiotics, systemic and topical corticosteroids, methotrexate, antihypertensives, and tricyclic antidepressants have been associated with the development of hairy tongue. Chronic use of oral topical antiseptics containing hydrogen peroxide, chlorhexidine, and similar agents may also trigger the reaction.

Darkening of the hairy tongue probably results from chromogenic bacteria that colonize the scaly mass. The use of tobacco, certain food products, bismuth, and iron supplements may also contribute to the dark pigmentation.

Although hairy tongue may be resistant to treatment, elimination of triggers and routine brushing of the dorsum of the tongue with a toothbrush usually produces gradual improvement. Topical keratolytics such as urea and retinoic acid may also help.

Macroglossia

Enlargement of the tongue can be transient or persistent, unilateral or bilateral, and congenital or acquired (Table 9.1).

Transient swelling of the tongue results from anaphylaxis, C1-esterase deficiency (acquired or hereditary), insect bite reactions, and systemic disorders associated with generalized edema such as renal, hepatic, and cardiac failure. Accidental injuries (e.g. burns, blunt trauma) and abscesses can produce asymmetric painful enlargement of the tongue.

Persistent macroglossia can be associated with tumors, metabolic disease, and endocrinologic disorders. Deep hemangiomas can lead to dramatic tongue enlargement that may interfere with eating and swallowing and cause partial or complete airway obstruction



Fig 9.11 Black hairy tongue followed a course of oral antibiotics.

Causes of macroglossia
Congenital and hereditary
Vascular malformations
Lymphangioma
Venous malformation
Combined lymphatic-venous malformation
Hemangioma
Hemihyperplasia
Congenital hypothyroidism (cretinism)
Beckwith–Wiedemann syndrome
Trisomy 21
Mucopolysaccharidoses
Neurofibromatosis
Acquired
Infiltrative processes
Amyloidosis
Myxedema
Granulomatous inflammation
Acromegaly
Angioedema
Tumors

Modified from Oral and maxofacial pathology, WB Saunders, Philadelphia, 2002, p. 9.

Table 9.1 Causes of macroglossia

(Fig. 9.12). Surface changes from the superficial component of the hemangioma may provide a diagnostic clue. Early recognition and intervention may be life-saving with rapidly growing lesions.

Unlike hemangiomas, which slowly regress after 12 months of age, venous and lymphatic malformations persist indefinitely, and increasing ectasia may cause gradual progression of symptoms (Fig. 9.13).

The mouth is a common site for lymphangiomas which most commonly involve the tongue (Fig. 9.13b,c). Moreover, vascular malformations are the most common cause of macroglossia in childhood. Lymphatic malformations can also involve the lips, buccal mucosa, and palate. Deep or feeder lymphatics arise at the angle of the mandible and produce persistent unilateral facial swelling. Most lesions are solitary, poorly demarcated, and contain a deep component. Lymphangiomas less than 1 cm in diameter may occur in up to 4% of Afro-American infants along the alveolar ridge. They occur twice as frequently in girls compared with boys and are often bilateral. These small lymphangiomas usually resolve without treatment within several months.



Fig 9.12 Hemangioma with involvement of the tongue and partial airway obstruction.







Fig 9.13 Lymphangioma. **(a)** A massive lesion of the tongue was associated with a cystic hygroma in the neck of this infant. **(b)** This superficial lymphangioma of the posterior tongue was slowly enlarging in this 10-year-old boy. **(c)** This toddler demonstrates a subtle asymptomatic lymphangioma covering the dorsal surface of the tongue.

Vascular malformations tend to wax and wane in size particularly after accidental trauma. Asymptomatic lesions can be followed clinically and with magnetic resonance imaging studies. Progressive lesions may improve with laser, excisional, and/or sclerotherapy. However, recurrences are common.

Macroglossia can also occur with deposition disorders including scleredema, amyloidosis, lipoid proteinosis, and lysosomal storage disorders which rarely present in children. Congenital malformation syndromes associated with macroglossia include trisomy 21, Winchester syndrome, anhidrotic ectodermal dysplasia, Zellweger syndrome, and Beckwith–Wiedemann syndrome. Tongue enlargement has also been noted in endocrinologic disorders such as acromegaly and hypothyroidism and chronic inflammatory disorders such as cheilitis.

Median rhomboid glossitis (central papillary atrophy)

Median rhomboid glossitis refers to a frequent asymptomatic finding in the middle of the tongue that is associated with a decrease or absence of papillae and appears as a smooth-topped red to violaceous plaque (Fig. 9.14). The area first becomes apparent during adolescence, and is most frequently found by a dentist rather than the patient. The incidence in adults approaches 0.2%.

Although typically flat-topped, median rhomboid glossitis may be slightly elevated or markedly thickened and scaly. Lesions tend to form round plaques in the middle-third of the tongue and take on the characteristic oval or rhomboid configuration as they progress posteriorly.

Although initially thought to represent a developmental defect of the midline of the tongue and then a complication of candidiasis, it is now considered to result from loss of the filiform papillae in the area with or without *Candida*. Moreover, even when yeast is identified on cultures or biopsies, oral antifungal therapy may not result in clinical improvement.

When median rhomboid glossitis presents with a thick plaque or nodule, lesions must be distinguished from a lingual thyroid, thyroglossal duct cyst, and other tumors.

Granular cell tumor

Granular cell tumor was initially described by Abrikossoff in 1926 as granular cell myoblastoma, because the tumor cells were initially identified as immature muscle cells or myoblasts. Recent electron microscopic and immunohistochemical findings suggest a Schwann cell or neuroendocrine origin.

Although most common on the dorsal surface of the tongue, these tumors may appear throughout the oropharynx, and 40% of tumors occur on the skin in the subcutaneous tissue (Fig. 9.15). There are also reports of lesions in the esophagus, stomach, appendix, larynx, bronchus, pituitary gland, uvea, and skeletal muscle. Most tumors are solitary, but up to 64 have been described in a single patient.



Fig 9.14 Median rhomboid glossitis. An asymptomatic atrophic red patch on the posterior aspect of the dorsal tongue was noted on a routine dental examination.

Granular cell tumors typically present as 0.5–3.0 cm well-circumscribed, raised, firm nodules. Lesions are occasionally tender or itchy and may have a warty white surface. The histopathology of the surface often reveals pseudoepitheliomatous hyperplasia, but within the lamina propria the characteristic sheets of polygonal cells with multiple cytoplasmic granules can be found. Consequently, when granular tumors are suspected, superficial biopsies are inadequate and may be misinterpreted as invasive carcinoma.

Excision is usually curative as recurrences are rare.

Traumatic fibroma (irritation fibroma)

Traumatic fibroma is a benign nodule which commonly develops on the tongue, particularly on the tip of the tongue, buccal mucosa, and lips in areas prone to trauma (Fig. 9.16). This reactive process, which results from recurrent sucking, picking, and biting, usually presents as a solitary 0.05–1.0 cm nodule although multiple lesions may be present.

Fibromas may be sessile or pedunculated, and occasionally the surface may be eroded. Histologic findings include hyperplasia with dense collagen deposition and an overlying fibropurulent membrane. Inflammation is usually minimal unless ulceration is present.

Irritation fibroma responds well to surgical excision; recurrences are rare.

Tumors at the base of the tongue

Lingual thyroid

A lingual thyroid occurs when follicles of thyroid tissue are found in the substance of the tongue (Fig. 9.17). These lesions may arise from thyroid anlage that failed to migrate from the foramen cecum to the predestined site in the neck or from anlage remnants left behind in the tongue.

Lingual thyroid usually presents as a 2–3 cm dark vascular tumor with overlying vessels at the base of the tongue and may be associated with dysphagia, dysphonia, hemorrhage with pain, and a feeling of fullness in the throat.

Lesions usually develop in or slightly lateral to the midline between the anterior two-thirds and posterior third of the tongue near the foramen cecum. However, ectopic thyroid can be found anywhere from the foramen cecum to the perilaryngeal and rarely substernal areas. There is a 6:1 female predominance, and most cases become apparent early in life.

Interestingly 10% of tongues demonstrate a lingual thyroid at autopsy. Of individuals who develop symptomatic lesions, 70% lack normal cervical thyroid glands altogether. Moreover, 1% of patients with lingual thyroids reported in the literature developed thyroid carcinoma.

Before symptomatic lingual thyroid tissue can be surgically excised, patients should have a careful assessment of thyroid function, and the presence of normal thyroid tissue must be established. When the ectopic gland is the only thyroid present, it can often be moved to a safer more convenient site.

Thyroglossal duct cysts

As the thyroid anlage descends to the normal position below the thyroid cartilage by the 7th embryonic week an epithelial tract or duct, which remains attached to the base of the tongue, is formed. The thyroglossal duct epithelium usually undergoes atrophy, but

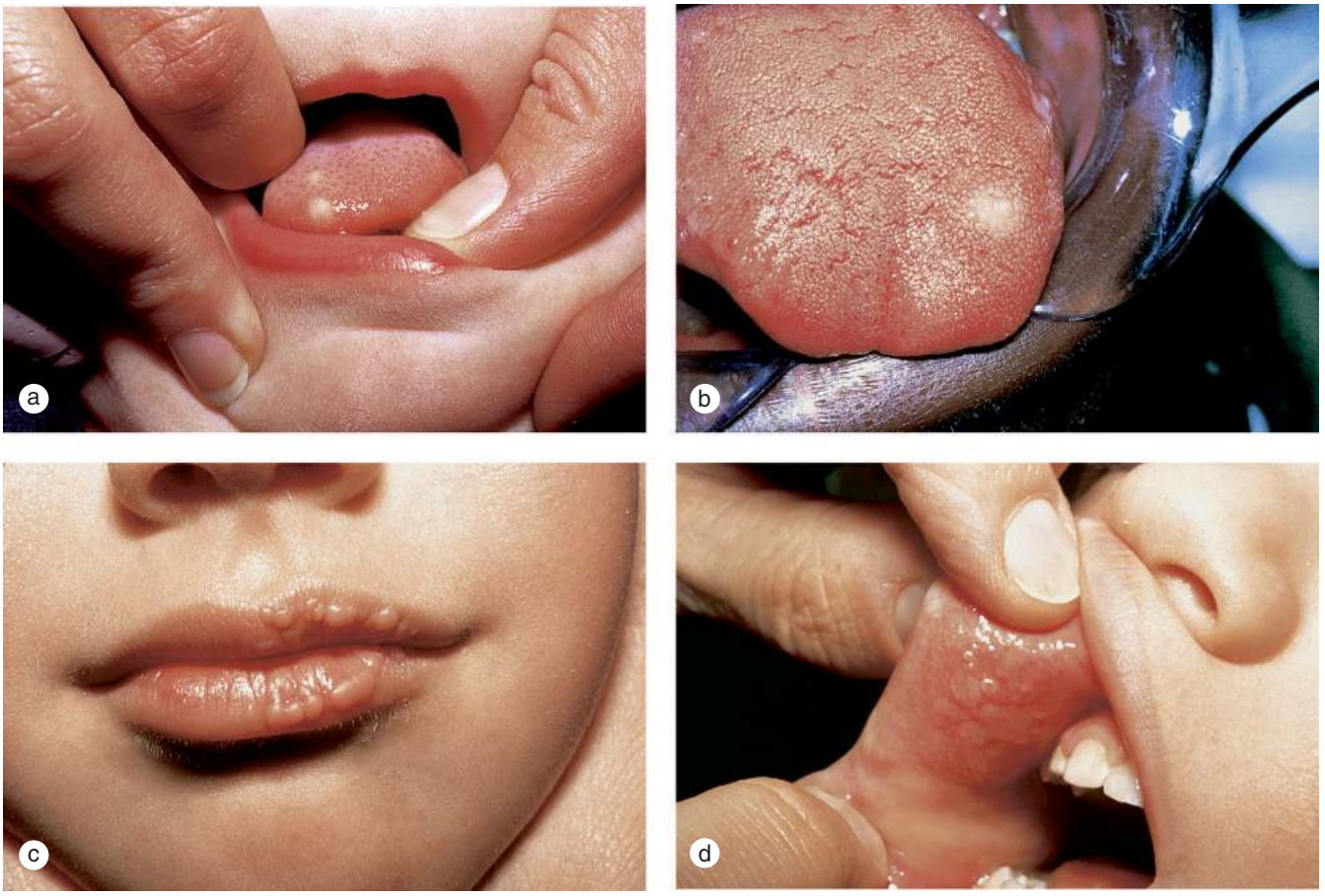


Fig 9.15 Granular cell tumor. **(a)** Asymptomatic papules and nodules developed on the tip of the tongue in a toddler and **(b)** the dorsolateral surface of the tongue in an adolescent. **(c)** Lesions were noted at birth on the lips and **(d)** buccal mucosa of a 4-year-old boy.

occasionally remnants may persist and give rise to cysts along the tract known as thyroglossal duct cysts (Fig. 9.18).

Thyroglossal duct cysts typically occur in the midline anywhere from the foramen cecum at the base of the tongue to the suprasternal notch. However, the majority develop below the hyoid bone. Cysts can appear at any age, but most are recognized within the first two decades. The majority of cysts are less than 3 cm in diameter and typically present as a painless, mobile, compressible mass unless they are infected. Lesions at the base of the tongue can lead to laryngeal obstruction. If they remain attached to the hyoid bone or tongue they tend to move vertically with extension of the tongue and swallowing.

Although there is at least a 10% risk of recurrence, cysts are most effectively treated with surgical excision. This risk can be reduced by removal of the midline section of the hyoid bone and muscular tissue along the entire thyroglossal duct tract.



Fig 9.16 Traumatic fibroma on the buccal mucosa.



Fig 9.17 Lingual thyroid. This large tumor at the base of the tongue was associated with intermittent dysphagia.



Fig 9.18 Thyroglossal duct cyst. Although this cyst was first noted in early childhood, it did not become symptomatic until the 3rd decade when it was surgically excised.

Lingual tonsils

Lingual tonsils are usually associated with the foliate papillae and are recognized as bilateral red, glistening papules and nodules on the posterolateral border of the tongue (Fig. 9.19). Although lymphoid tissue is part of the foliate papillae normally found in this area, papillae may become enlarged after trauma or with viral or bacterial pharyngitis. Hyperplasia of the foliate papillae may be mistaken for carcinoma.

Lymphoid tissue on the posterior third of the dorsum of the tongue, which is part of the oropharyngeal lymphoid tissue ring of Waldeyer, may also become intermittently or permanently enlarged with recurrent infections or chronic allergic sinusitis. Persistent hyperplasia is seen more commonly in atopic children and may be associated with dysphagia, dysphonia, a feeling of fullness in the throat, and obstructive sleep apnea. Symptomatic lesions can be ablated surgically.

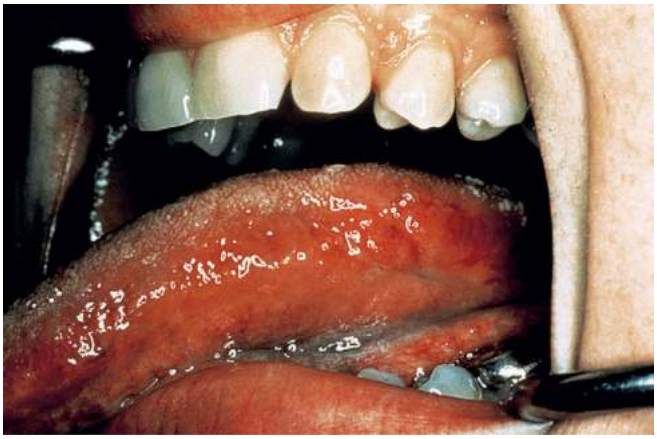


Fig 9.19 Lingual tonsil.



Fig 9.20 Ranula. A purple mass at the base of the tongue gradually increased in size after it first became apparent in early adolescence.

FLOOR OF THE ORAL CAVITY

Ranula

Ranula is a clinical term for a mucocele or mucous retention cyst located on the floor of the mouth and arises from trauma to the sublingual or submandibular salivary glands (Fig. 9.20). These lesions can be acquired or congenital, and most are unilateral, although they can rarely be bilateral. Ranula usually presents as a gray or bluish, glistening swelling that can reach a large size (over 5 cm in diameter) and can insinuate between the structures in the neck.

There are two types of ranula, the most common or simple variant which is usually confined to the oral cavity and the cervical ranula which can extend from the sublingual space around or through the mylohyoid muscle to the submandibular space. Ranula are usually treated by marsupialization.

Ranula should be distinguished from lymphangiomas that arise in a similar location in the floor of the mouth. Lymphangiomas also have a tendency to infiltrate and insinuate between structures in the neck and are difficult to remove surgically. Cystic hygromas in the neck can be confused with cervical ranula. Other tumors such as lipomas and dermoid cysts rarely develop in the floor of the mouth, and can only be excluded by biopsy.

Pigmentary changes of the oral mucosa

Physiologic pigmentation

Physiologic mucosal pigmentation, produced by mucosal melanocytes, is genetically acquired and tends to be more prominent in Afro-Americans and Asians and with increasing age (Fig. 9.21). Pigment may appear diffusely or in discrete linear or spotted patterns. Pigmentation is usually most prominent on the buccal mucosa along the bite line, but any oral structure may be involved.

Postinflammatory hyperpigmentation

Postinflammatory hyperpigmentation may develop after any injury to the oral mucosa. However, it is commonly seen in association with dermatologic disorders that produce full-thickness insults to the mucous membranes such as lichen planus and lupus erythematosus. Pigmentary changes also tend to be more prominent in darker-pigmented individuals.

Systemic and local hyperpigmentation

Mucous membrane pigmentation may also provide a clue to underlying systemic disease. Irregular or patchy mucosal hyperpigmentation commonly appears in Addison disease and occasionally in



Fig 9.21 Physiologic pigmentation of the tongue.

acromegaly. Oral café-au-lait macules can develop in neurofibromatosis and McCune–Albright syndrome. Other systemic triggers of pigmentation include heavy metal exposure, Wilson disease, hemochromatosis, Peutz–Jeghers syndrome (see Fig. 6.6), acquired immunodeficiency syndrome, and melanoma. A number of systemic medications including antimalarials, AZT, oral contraceptives, phenolphthalein, chlorpromazine, and quinidine may also increase mucosal melanin. Bluish-green pigment from minocycline may occasionally be deposited in the gingiva with or without concomitant involvement of cutaneous lesions.

The use of tobacco products and topical agents containing heavy metals can result in focal or diffuse hyperpigmentation of the oral mucosa. Silver-containing solutions such as silver nitrate can leave black or gray mottled staining. Mercury may leave blue-gray pigmentation, and tin- and bronze-containing agents can produce brown to black pigmentation.

Melanotic macules

Melanotic macules appear most commonly on the lower lip and usually measure less than 3 mm (Fig. 9.22). However, the buccal mucosa, gingival, or palate may also be involved (Fig. 9.22b). These innocent macules usually represent a freckle, lentigo, or junctional nevus, and in adults they must be distinguished from malignant melanoma.

The presence of multiple labial macules should raise the suspicion of a variety of syndromes and prompt a careful examination of the entire skin surface as well as oral and genital mucosa (see Fig. 6.4) (Table 9.2).

Hypopigmentation/depigmentation

Loss of pigmentation occurs most commonly from vitiligo, and the lips are most commonly involved (Fig. 9.23). Frequently vitiligo koebnerizes in a perioral distribution spreading from the corners of the mouth to the inner aspect of the lips, and occasionally over the entire vermillion border. Depigmentation can be subtle in light-complected patients but disfiguring in darker-pigmented individuals.

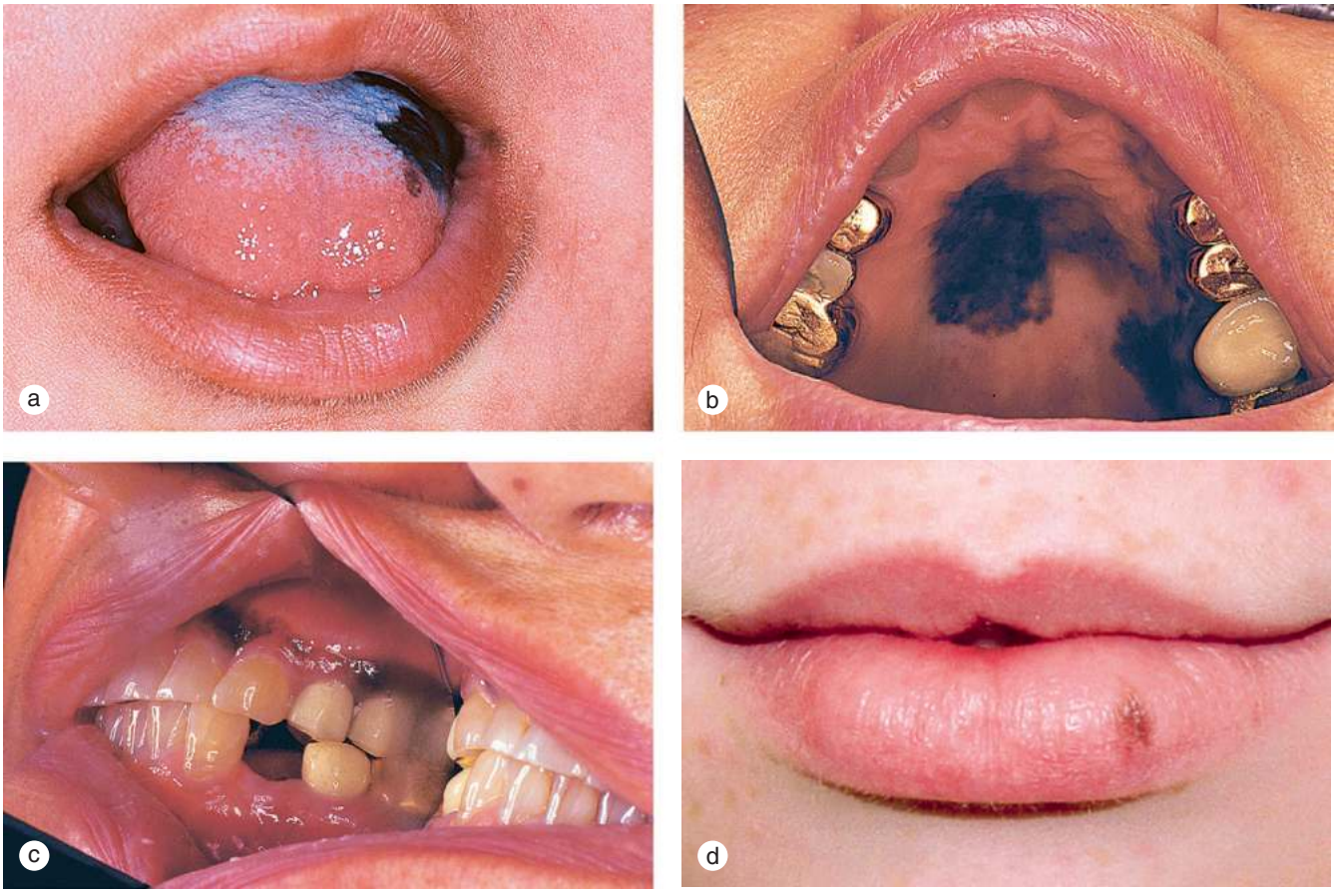


Fig 9.22 Melanotic macules. **(a)** A small pigmented nevus was noted at birth on the left side of this infant's tongue. **(b)** Lentigines developed on the palate, **(c)** gingiva, and **(d)** lower lip.

Disorders associated with pigmentary changes in the oral mucosa		
Disorder	**Oral/cutaneous findings**	**Associated findings**
Laugier–Hunziker syndrome	Oral, genital pigmented macules; longitudinal melanonychia	None
Peutz–Jeghers syndrome (see Fig. 6.6)	Labial, oral, genital, distal extremity pigmented macules; melanonychia; striata	Hamartomatous polyps; colonic carcinoma; pancreatic carcinoma; ovarian, testicular tumors
Carney complex (NAME/LAMB syndrome) (**N**evi, **A**trial myxomas, **M**yxoid neurofibroma, **E**phelides/**L**entigines, **A**trial myxoma, **M**ucocutaneous myxomas, **B**lue nevi)	Oral, cutaneous freckles, nevi, lentigines	Pigmented nodular adrenocortical disease; mammary fibroadenomas; testicular, thyroid, pituitary tumors
LEOPARD syndrome (Fig. 6.4) (**L**entigines, **E**KG abnormalities, **O**cular hypertelorism, **P**ulmonary stenosis, **A**bnormalities of genitals, **R**etardation of growth, **D**eafness)	Oral lentigines	Mental retardation; hypertrophic obstructive cardiomyopathy
Lentiginosis profusa	Pigmented macules on skin, oral mucosa	None

Table 9.2 Disorders associated with pigmentary changes in the oral mucosa

LIP

Congenital malformations

A complete discussion of lip (and palate) anomalies is beyond the scope of this chapter. However, it is important to recognize the significance of these findings. Although congenital lip pits and fistulas of the lower lip are rare, they may be associated with clefting of the upper lip and palate and a number of underlying genetic disorders (e.g. Van der Woude syndrome, popliteal pterygium syndrome, orofaciodigital syndrome). Anomalies of the eyes, ears, nails, feet, and some forms of ichthyosis have also been reported. Lesions may be single or multiple and range from subtle dimples to fistulas up to 25 mm.

Clefts of the lip, jaw, and/or palate occur more commonly with an incidence of 0.5–1.3:1000 births. In nearly one-third of patients, there is a family history of similar defects, and in 10% lesions are associated with specific syndromes (e.g. trisomy 13, orofaciodigital syndrome I, fetal hydantoin syndrome, Stickler syndrome, Pierre Robin syndrome, ectrodactyly–ectodermal dysplasia, ankyloblepharon–ectodermal dysplasia clefting).

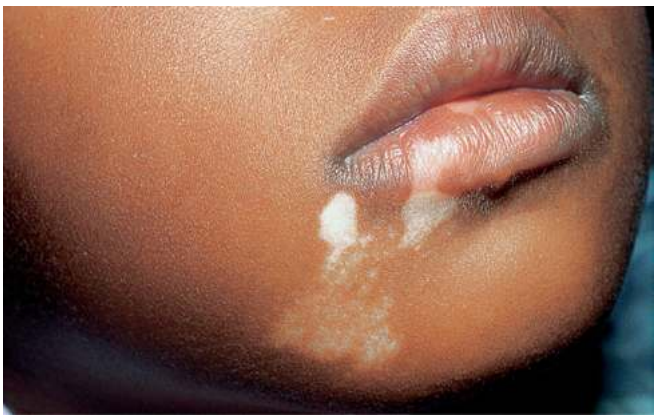


Fig 9.23 Vitiligo. A depigmented patch extended from the chin onto the lower vermillion border.

Cheilitis

Cheilitis results from a number of different disorders that produce inflammation of the lips and clinical findings that vary with the underlying trigger. The most common causes of cheilitis are irritant and allergic contact dermatitis, atopic dermatitis, and seborrheic dermatitis.

Cheilitis simplex

Cheilitis simplex or chapped lips refers to one of the most common forms of cheilitis that presents clinically with cracking, fissuring, and scaling of both lips but more commonly the lower lip. Chronic cases can progress to crusting, hemorrhage, and blister formation. Causes include acute and chronic sun exposure, atopic dermatitis, seborrheic dermatitis, and irritant and allergic contact dermatitis. However, repetitive biting, licking, and rubbing are probably the most common culprits.

Aggressive use of barrier lubricants such as petrolatum usually results in dramatic improvement. However, patients with obsessive-compulsive behavior may require psychiatric intervention, and in some patients this may be the first manifestation of primary psychiatric disease.

Contact dermatitis

Contact irritant and allergic dermatitis typically present with pruritic or burning scaling and fissuring of the lips with perioral extension. Occasionally angular cheilitis or perlèche is the only clinical sign.

Toothpaste and mouthwash, which spill over from the mouth where they only rarely cause symptoms, are the most common cause of contact irritant and allergic reactions on the lips. The components associated with contact reactions include clove oil, pimento oil, anise oil, menthol, and preservatives like parabens and ethylenediamine. Allergic contact cheilitis from tartar control toothpastes usually results from exposure to pyrophosphates. Topical medications such as antivirals, antibiotics, sunscreens, and disinfectants as well as food products such as apples and citrus fruits have also been reported to cause reactions. In patients sensitized to rhus allergen, mangoes, particularly the rinds, can cross react with poison ivy and produce an intense allergic contact cheilitis.

Successful treatment requires some detective work to identify the irritant or allergen, but patch testing may be necessary in some



Fig 9.24 Cheilitis. Dermatitis was restricted to the vermillion border and immediately contiguous skin in this chronic lip-licker.

patients. Other conservative measures such as cool compresses, emollients, topical steroids, and topical non-steroidal anti-inflammatory agents will help while the patient undergoes evaluation.

Lip-licker's dermatitis

Lip-licker's dermatitis is a variant of chronic irritant contact cheilitis that occurs more commonly in children than in adults (Fig. 9.24 and see Fig. 3.36). Although the vermillion border may be involved exclusively, red papules, scaling, and occasionally fissures and crusting may form a well-demarcated circumferential ring around the lips. The lesions extend as far as the tongue can reach and invariably spare the angle of the mouth.

Lip-licker's dermatitis results from repetitive wetting and drying of the perioral skin and tends to flare during the cold dry winter months. Aggressive application of bland emollients can improve lesions, but healing is not complete until the lip-licking ends.

Angular cheilitis

Cheilitis at the commissures of the mouth may present acutely or chronically with erythema, scales, crusts, fissures, and maceration (Fig. 9.8a). Lesions may spread to the adjacent skin and extend along the nasolabial folds. *Candida* and bacterial organisms, particularly *Staphylococcus aureus* and Group A β-hemolytic *Streptococcus*, may produce secondary infection.

Atopic dermatitis, seborrheic dermatitis, and contact irritant dermatitis from drooling may trigger angular cheilitis. In children associated systemic disorders include diabetes mellitus, anemia, conditions that increase or decrease saliva production (e.g. medications), immunosuppression (e.g. acquired immunodeficiency syndrome, immunosuppressive medications), and nutritional deficiencies. Irritation from malocclusion of the mouth due to abnormalities of the teeth, lips, or tongue and mechanical stretching of the corners of the mouth (e.g. dental procedures, intubation) can also predispose to the development of angular cheilitis.

Primary triggers should be identified and eliminated, and secondary infection should be treated. Prophylaxis with topical antibiotics, antifungals, and emollients may prevent recurrence of lesions in the setting of chronic systemic disease. Attention to good oral hygiene and dental care is also critical.

Cheilitis (orofacial) granulomatosa

Painless persistent swelling of the lip associated with fissured tongue and facial palsy should suggest the diagnosis of cheilitis granulomatosa or Melkersson–Rosenthal syndrome (Fig. 9.25). (In

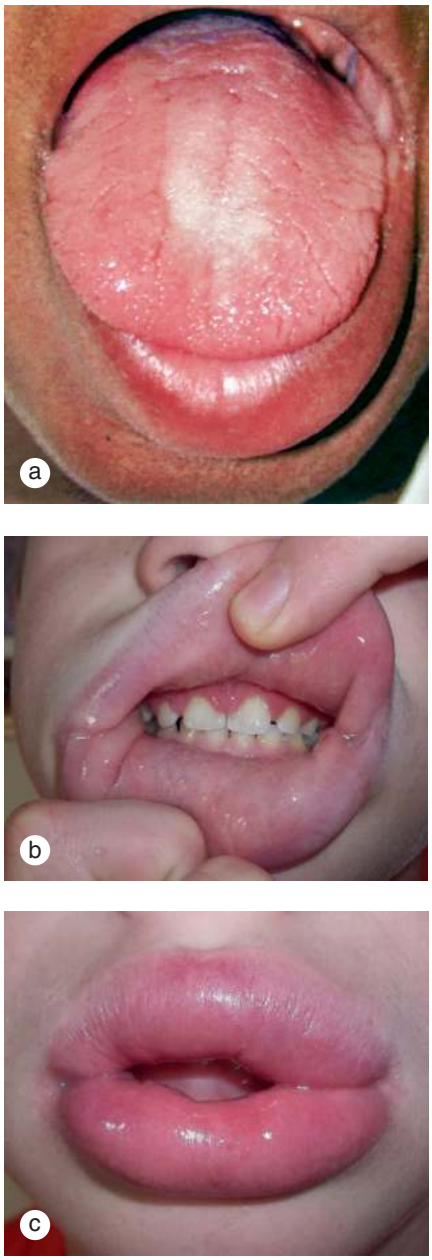


Fig 9.25 Cheilitis granulomatosa. **(a)** This 12-year-old boy had a 1-year history of persistent woody induration of the lower lip and an enlarged fissured tongue. Another 12-year-old boy complained of **(b)** persistent lip swelling for over 6 months and constipation for 2 years. Note **(c)** swelling of the inside of the lips and gingivae as well. Biopsy showed granulomatous inflammation and endoscopy showed ileitis consistent with Crohn disease.

1928, Melkersson described a patient with facial palsy and chronic lip swelling. Years later, Rosenthal added fissured tongue to the clinical syndrome.)

Cheilitis granulomatosa represents a subset of patients with orofacial granulomatosa, which encompasses a number of clinical presentations that reveal granulomatous inflammation on biopsy. Although the lips and tongue are most commonly involved, orofacial granulomatosa may include the cheeks and other parts of the face, palate, gingiva, and buccal mucosa. Lesions restricted to the lips alone are referred to as cheilitis granulomatosa of Miescher.

Of patients with orofacial granulomatosa 20–70% present with the full triad of lip swelling, fissured tongue, and facial palsy. The disorder peaks between ages 20 and 40 years, and occurs equally

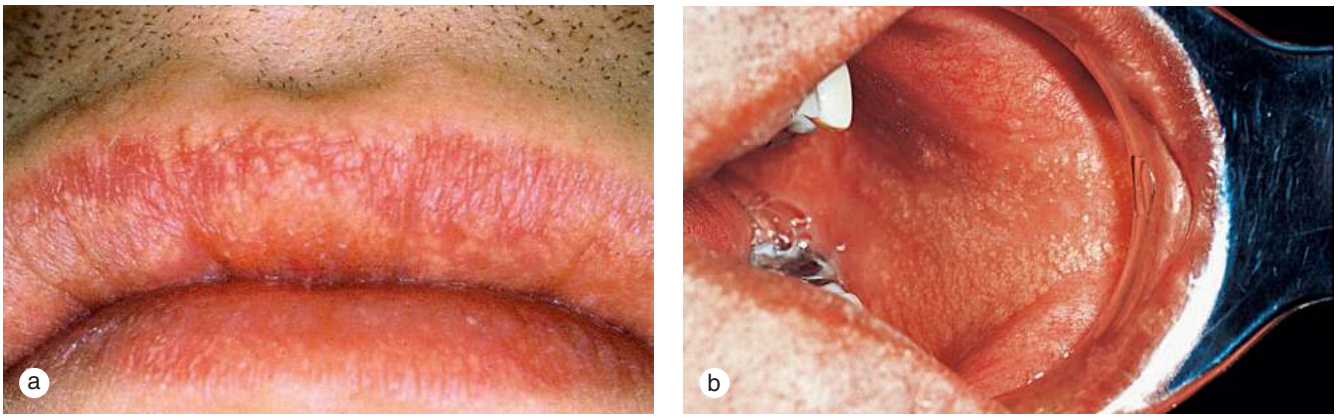


Fig 9.26 Fordyce granules. Asymptomatic papules developed on **(a)** the vermillion and **(b)** the buccal mucosa.

in men and women. Although most patients present sporadically, familial cases have been described.

Lip swelling, particularly of the upper lip, is usually the first symptom. Painless attacks, which can start with the lower lip or both lips, may last for days to weeks and clear completely between episodes. Eventually, many patients complain of persistent annoying swelling.

Facial palsy, typically unilateral, occurs in only 20–30% of patients, and rarely other cranial nerves can be involved. Fissured tongue, which occurs in 10–15% of normal individuals, is found in 50% of patients.

Histologic changes include non-caseating granulomatous inflammation with edema of the superficial lamina propria. Special stains for bacteria, fungi, and mycobacteria and a careful search for foreign material are negative. Chronic lesions demonstrate fibrosis.

Systemic granulomatous disorders including inflammatory bowel disease, sarcoidosis, and tuberculosis should be excluded by careful medical evaluation. Local causes of cheilitis such as oral infections, foreign body reactions, and contact dermatitis may also be discovered by careful history, review of systems, and other clues on physical examination.

Treatment is often unrewarding, although temporary relief of symptoms can be achieved with topical and intralesional steroids. Oral anti-inflammatory and immunosuppressive medications may help in chronic cases. Surgical reduction may be indicated in patients with persistent swelling associated with fibrosis.

Fordyce granules

Fordyce granules, or ectopic sebaceous glands, are the most common structural anomaly found in the mouth with a prevalence approaching 80% in adults. They were initially described by Kölliken in 1861 but were named after Fordyce who wrote about them in 1896.

Fordyce spots, which are most commonly present on the lips as tiny yellow papules, occasionally coalesce to form larger asymptomatic plaques (Fig. 9.26). The buccal mucosa is also commonly involved and occasionally the tongue, gingival, frenulum, and palate.

Lesions are probably present at birth but do not become clinically evident until during or following puberty. Fordyce granules are found in 20% of children, 30% of adolescents, and 70–80% of adults. They may actually become subtle or disappear altogether in the elderly.

Biopsies reveal normal sebaceous glands that are not associated with hair follicles. Although no treatment is necessary, superficial carbon dioxide laser can be used to ablate cosmetically disfiguring lesions.

Mucocele

Mucocele (mucous extravasation phenomenon) develops most commonly on the inner aspect of the lower lip and occasionally on the palate, upper lip, and buccal mucosa (Fig. 9.27). These mucous retention or extravasation cysts result from rupture of a salivary gland duct and spillage of mucin into the surrounding soft tissues. They are usually tense, small (<2 cm), non-tender, and fluid-filled and appear most commonly in children and young adults. The presence of mucin in the superficial soft tissue often gives a bluish translucent hue. They may rupture after trauma from teeth and tend to recur after spontaneous rupture or surgical intervention including cryosurgery, carbon dioxide laser ablation, and surgical excision.

Mucocele, which lacks an epithelial lining, differs from the salivary duct cyst that arises from salivary gland tissue and consists of an epithelial-lined cavity with mucoid secretions in the lumen.

Aphthae

Aphthae or canker sores, considered to be one of the most common oral lesions, present as painful mucosal erosions that start as red edematous papules which become necrotic and ulcerate (Fig. 9.28).



Fig 9.27 Mucocele. This boy admitted to picking and biting at his lower lip. This lesion was shaved and cauterized.

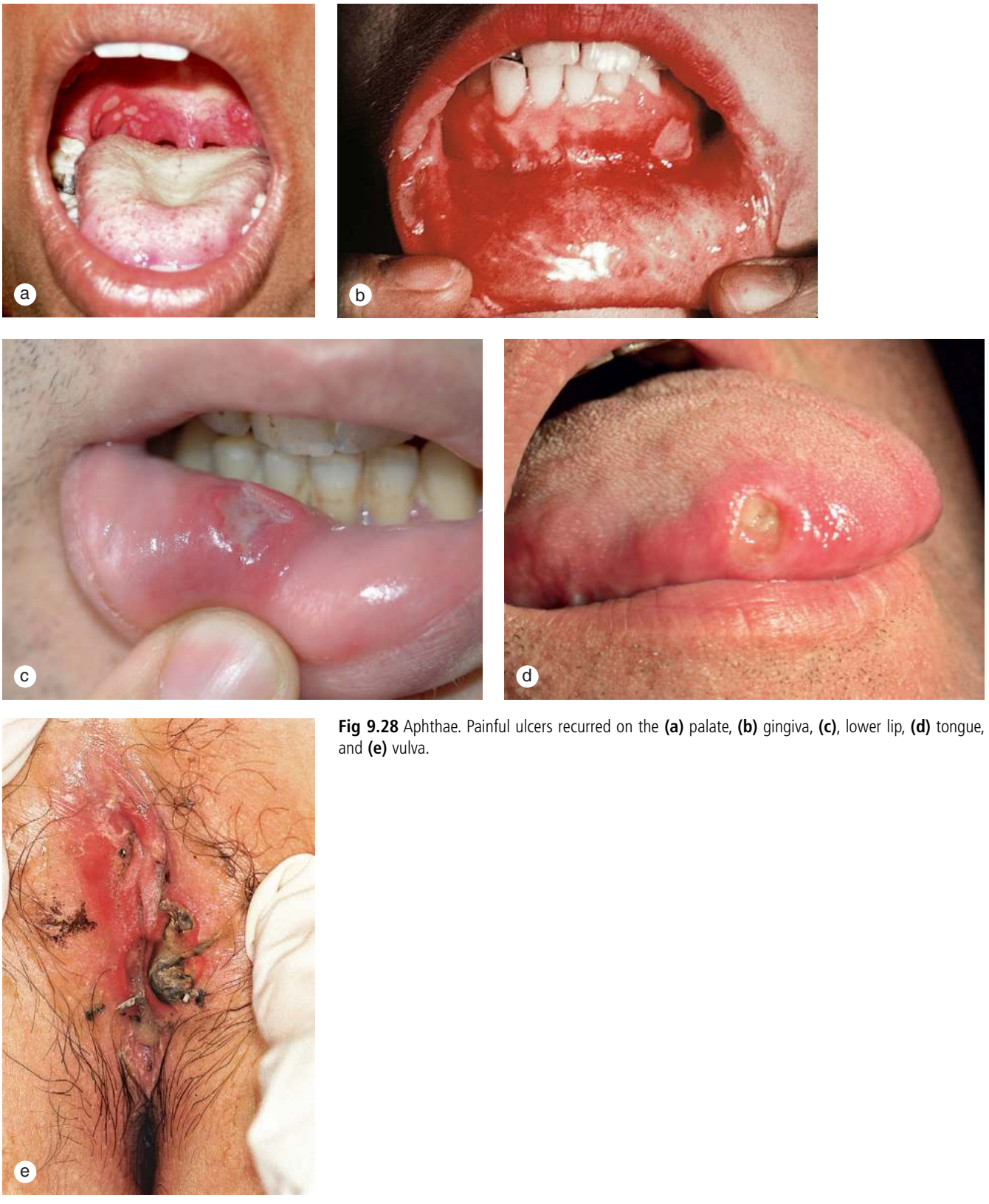


Fig 9.28 Aphthae. Painful ulcers recurred on the **(a)** palate, **(b)** gingiva, **(c)**, lower lip, **(d)** tongue, and **(e)** vulva.

They typically appear as small crateriform ulcers less than a centimeter in diameter with an overlying white-to-yellow fibrin membrane and a red halo. Minor aphthae heal within 1–2 weeks usually without scarring.

Recurrent aphthae occur in 10% of healthy individuals, often in a familial pattern, and more commonly in females than males. Although onset usually occurs between ages 10 and 30 years, they can begin at any time. Minor aphthae are characterized by 1–5 lesions at a time between 2 and 5 mm in size. Although any site on the oral mucosa can be involved, aphthae favor movable anterior oral mucosal surfaces, most commonly the labial mucosa, floor of the mouth, and lateral borders of the tongue. The frenulum and the uvula may also be involved. Rarely, the epiglottis, pharynx, and gastrointestinal tract are involved, but these locations should raise

the possibility of underlying inflammatory bowel disease and Behçet disease. Fixed mucosal surfaces, particularly the keratinized epithelium of the hard palate, and the vermillion are usually spared.

Involvement of the posterior oral mucosa, lesions over a centimeter in diameter, more than five lesions at a time, and persistence for weeks to months defines major aphthae. Ulcers are deep and exquisitely painful and may be associated with genital lesions that typically involve the labia or scrotum (Fig. 9.28e). Major aphthae may be associated with Crohn disease and ulcerative colitis as well as human immunodeficiency virus infection and acquired immunodeficiency syndrome. The oral lesions of Behçet disease may be indistinguishable from major aphthae, but arthritis, uveitis, cutaneous lesions, and central nervous system involvement should allow for distinction from isolated major aphthae. Recurrent, episodic aphthous stomatitis in association with fever should also raise the possibility of PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and adenitis). This rare self-limited periodic fever syndrome occurs most commonly in children under 5 years old.

Similar oral ulcers may be seen in gluten-sensitive enteropathy, malabsorption syndromes, drug reactions, trauma, herpangina, herpes gingivostomatitis, and herpes zoster (shingles).

Although the cause is unclear, some investigators have suggested a triggering role for trauma, psychosocial factors, food intolerance, and medications. Antiepithelial antibodies have been detected in many patients with major aphthae. However, they are also present in 10% of normal individuals and may represent an epiphenomenon in patients with disease.

Aphthae can be managed with topical and oral analgesics, topical (e.g. fluocinonide gel 0.05%) and intralesional corticosteroids, and topical tacrolimus ointment. Recent studies describe a role for oral thalidomide.

PALATE

Palatal cysts of the newborn

Palatal cysts, including Epstein pearls and Bohn nodules, appear in 75% of newborns and resolve within several weeks without treatment (Fig. 9.29). Epstein pearls were originally described as 1–3 mm whitish-yellow nodules occurring most commonly on the mid palatal raphe at the junction of the hard and soft palates. These cysts are thought to arise from remnants of epithelium trapped between the palatal shelves and the nasal process. Bohn nodules appear as similar nodules scattered over the hard palate often near the soft palate junction and are thought to be derived from the minor salivary glands. These terms are frequently used interchangeably and are also used to describe similar-appearing gingival cysts. The histology of palatal cysts shows a keratin-filled cyst identical to that of gingival cysts (see below).

GINGIVA

Gingival cysts of the newborn

Dental lamina cysts present as solitary or multiple 1–3 mm nodules on the alveolar processes in the newborn (Fig. 9.29). Similar to palatal cysts (Epstein pearls, Bohn nodules), these keratinized cysts also develop in 75% of newborns and resolve without treatment within several weeks to several months. They appear most commonly on the maxillary alveolus and are thought to arise from remnants of the dental lamina remaining after tooth formation.

Congenital epulis

Epulis is a general term used to describe a number of reactive gingival lesions with vascular, fibroblastic, and granulation tissue proliferation. Congenital epulis or congenital gingival granular cell tumor refers to an exophytic congenital tumor that arises from the alveolar ridge and has histologic features identical to those of granular cell tumor (Fig. 9.30).

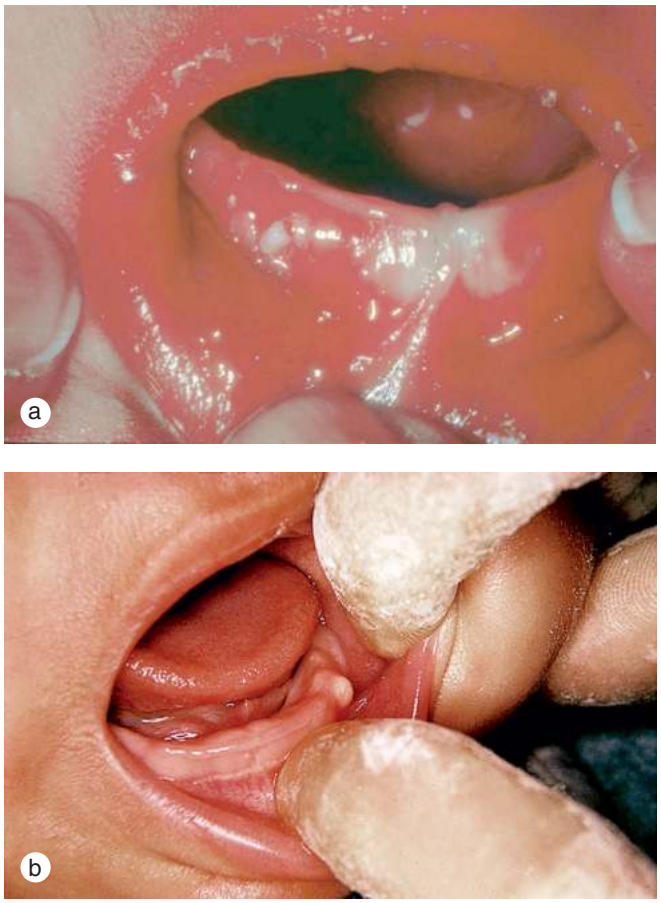


Fig 9.29 Palatal and gingival cysts. **(a)** Cysts were present on the right maxillary alveolus and palate and **(b)** left mandibular alveolus in these healthy newborns.

Congenital epulis typically presents as a mass protruding from the alveolar ridges of newborns. There is an 8–10 female to 1 male predominance of these 1–3 cm mucosal colored sessile or pedunculated tumors that arise from the maxillary or mandibular alveolar ridge. Rarely large tumors may interfere with feeding or obstruct the airway and require immediate surgical intervention. Some of these lesions have been diagnosed *in utero* by ultrasound and excised prenatally or shortly after delivery.

While the histologic findings in congenital epulis resemble those of granular cell tumors, immunohistochemical analysis shows that, unlike granular cell tumor, the tumor cells in congenital epulis are negative for S100 protein. Although radical surgery of complicated lesions may cause injury to the alveolar ridge and result in abnormal dental development, conservative excision usually results in cure without sequelae.

Melanotic neuroectodermal tumor of infancy

Melanotic neuroectodermal tumor of infancy is a rare pigmented neoplasm that usually occurs during the first 2 years of life (Fig. 9.31). Nearly 70% appear on the maxilla, but tumors have been reported to arise at other sites. The most frequent extramaxillary locations include the skull, mandible, brain, epididymis, and testis.

Although melanotic neuroectodermal tumors are benign, they may push on vital structures such as the airway and require early surgical intervention. Rare malignant variants may metastasize.

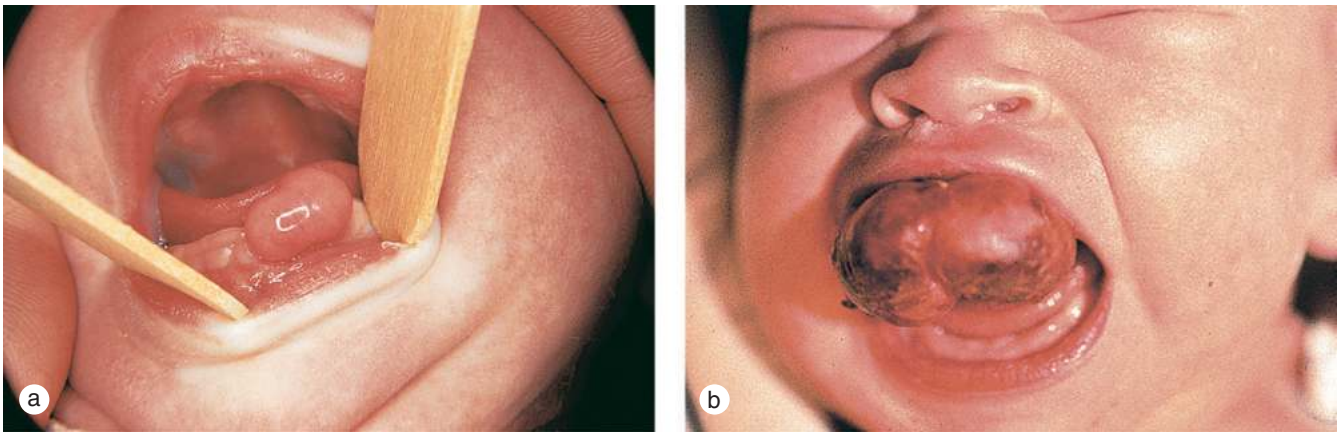


Fig 9.30 Congenital epulis. Lesions may arise from the **(a)** mandibular and **(b)** maxillary alveolar ridges.

Histologic features include nests of round cells separated by fibrous connective tissue. Large melanin-producing cells sit at the periphery of these nests.

Clinical findings overlap with congenital epulis, and the diagnosis should be confirmed with a biopsy. Excision is recommended, but recurrences may exceed 15%.

Pyogenic granuloma

Pyogenic granuloma is a benign neoplasm composed of granulation tissue that may represent a response to local irritation or trauma. Although most oral lesions arise on the gingiva, pyogenic granulomas may develop on the tongue, lips, and buccal mucosa (Figs 9.4, 9.32). Lesions are more common on the maxillary gingiva than the mandibular gingiva and are more often located anterior than posterior. Although they may develop at any age, they are more common in children and young adults. Lesions are particularly common in pregnancy when they are often referred to as granuloma gravidarum.

Although the cause is unclear, growth hormones such as estrogens and progesterone, which increase throughout pregnancy, may trigger the reaction. Growth hormone and other factors that promote growth and development in rapidly growing children may also play a role.

Granuloma gravidarum may regress spontaneously postpartum. However, irritated, bleeding, or symptomatic pyogenic granulomas can be excised and cauterized.

Gingival hyperplasia

Gingival hyperplasia (Table 9.3) may result from local inflammation or gingivitis and infiltrative processes that provide a clue to underlying systemic disease. In acute reactive gingival hyperplasia the gums are red, boggy, and bleed easily with minor trauma. In chronic fibrotic gingival hyperplasia chronic fibrosis which resembles scarring eventually covers the teeth. These two processes overlap and may be triggered by similar disorders (Fig. 9.33).

Acute gingivitis most commonly results from poor dental hygiene which may be a problem in chronically ill debilitated children (e.g. acquired immunodeficiency syndrome), poorly controlled diabetics, and pregnancy. Gingival hyperplasia can develop in scurvy and granulomatous disorders such as Crohn disease and Melkersson–Rosenthal syndrome. Although acute monocytic leukemia is most commonly associated with malignant infiltration of the gums, other leukemias can produce acute and chronic gingival hyperplasia. Drug-related gingival hyperplasia results from an increase in collagens but acute and chronic inflammatory changes may also be present. Although investigators have established a strong association with cyclosporine, phenytoin, and nifedipine, numerous other medications (e.g. anticonvulsants such as carbamazepine, ethosuximide, felbamate, phenobarbital, and sodium valproate; calcium channel blockers verapamil, felodipine, and diltiazem; erythromycin; oral contraceptives) and have been anecdotally reported to trigger gingival thickening. The prevalence peaks with phenytoin

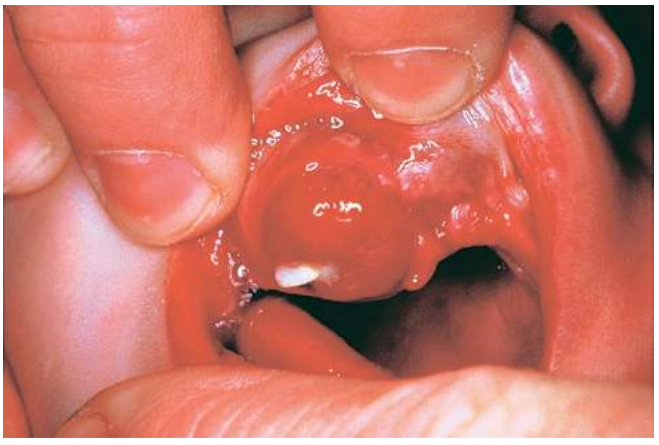


Fig 9.31 Melanocytic neuroectodermal tumor of infancy. This rapidly expanding tumor developed on the anterior maxilla in this toddler.



Fig 9.32 Pyogenic granuloma. This friable reddish-purple nodule developed on the gingiva of a pregnant adolescent.

Causes of gingival hyperplasia
Exogenous
Drugs (phenytoin, cyclosporine, oral contraceptives, nifedipine)
Hyperplastic gingivitis from mouth breathing
Nutritional deficiency (scurvy)
Poor dental hygiene/bacterial infection
Endogenous
Granulomatous disorders
Sarcoidosis
Wegner granulomatosis
Orofacial granulomatosis (Melkersson–Rosenthal syndrome)
Inflammatory bowel disease
Other infiltrative processes
Mucopolysaccharidoses
Mucolipidoses
Juvenile hyaline fibromatosis
Hereditary gingival fibromatosis
Amyloidosis
Leukemia

Table 9.3 Causes of gingival hyperplasia

at 50% of patients and occurs in 25% of individuals on cyclosporine and nifedipine.

Gingival fibromatosis which results in non-inflammatory fibrous change may follow any inflammatory gingivitis or develop in the setting of hereditary congenital gingival fibromatosis. Similar findings occur in a wide variety of fibromatoses and other syndromes (e.g. tuberous sclerosis).

Gingival hyperplasia can be minimized by careful attention to dental hygiene, but repeated surgery may be necessary in severe cases.

DENTAL DEVELOPMENT AND ANOMALIES

Dental anomalies may represent a local phenomenon or provide clues to underlying multisystem disease. As the teeth are derived from both ectoderm and mesoderm, occult malformations of other structures derived from these embryonic tissues may be reflected in dental defects. By 6–8 weeks of intrauterine development the dental buds, which arise from the oral epithelium, appear on the upper and lower jaws. Subsequently, the outer protective layer of enamel develops from the epithelium. The mesenchyme beneath the dental buds condenses to form the dental papillae. The mesenchyme in contact with the buds transforms into dentin, while the remaining mesenchyme forms the neurovascular core known as pulp.

The roots of the teeth are anchored to sockets in the mandible and maxilla by the periodontal membrane through which the neurovascular supply passes to the root apex. The bony processes

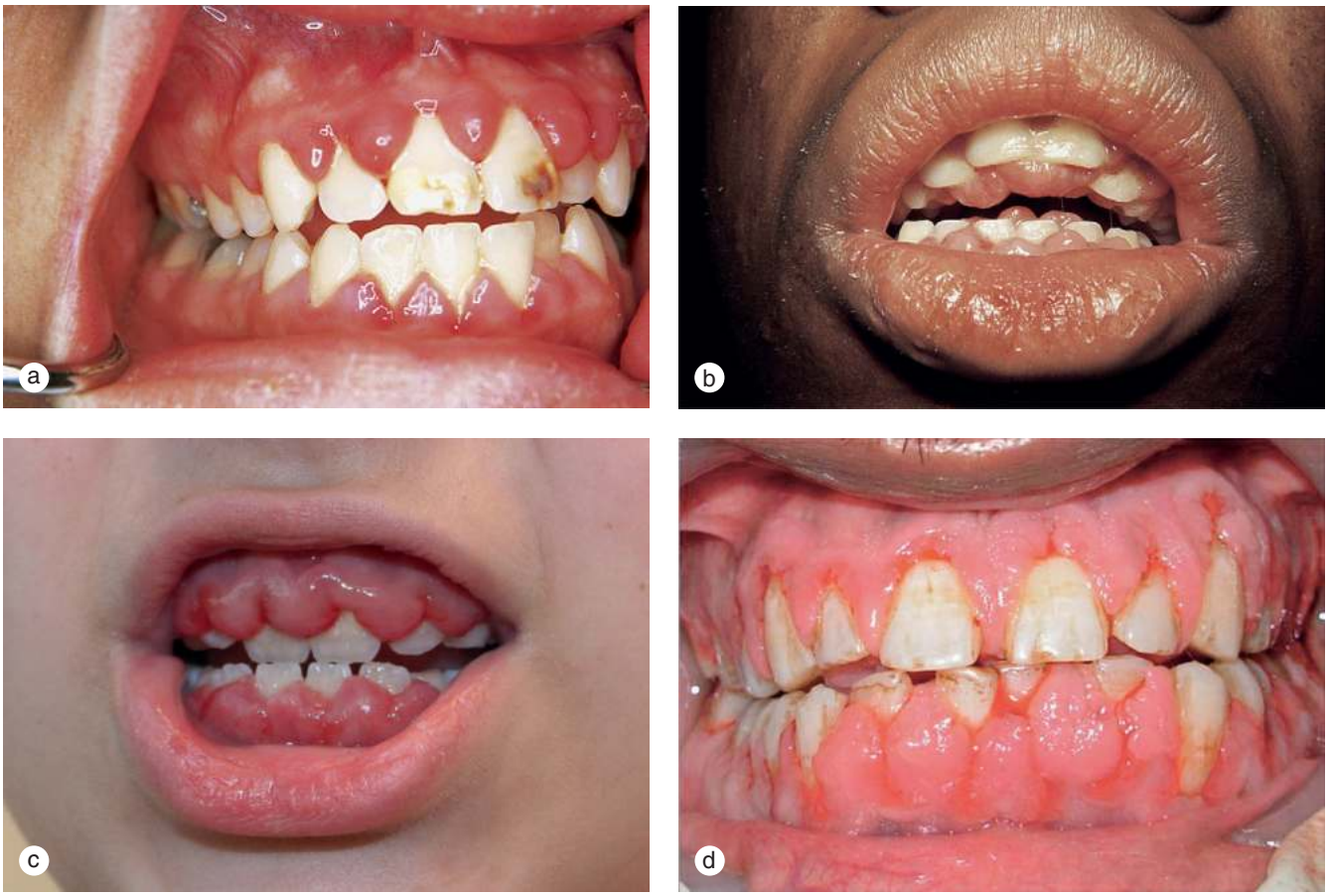


Fig 9.33 Gingival hyperplasia. **(a)** Diffuse hypertrophy of the gingiva developed in this chronic mouth breather and **(b)** seizure patient on phenytoin therapy. **(c)** Four-year-old girl with myelomonocytic leukemia and **(d)** adolescent on chronic cyclosporine therapy following liver transplantation.

between the teeth are referred to as the interdental septae. After the teeth erupt the visible portion is referred to as the crown, and the space between the crowns and the gingivae is called the gingival crevice. The interdental papillae refer to the gingivae located between the teeth.

Although there may be some variation in the chronology of dental development, marked delay in eruption or loss of teeth may also indicate underlying systemic disease (e.g. hyperimmunoglobulin E syndrome). At approximately 6 months of age, the mandibular central incisors erupt, followed shortly by the maxillary central incisors, and the maxillary and mandibular lateral incisors. At 2 years, all of the primary teeth have erupted except the second primary molars that appear by age 3. Until age 2 years, a rough estimate of the appropriate number of teeth for a given age can be calculated by subtracting 6 from the age in months. The eruption of permanent teeth begins with the first molars at age 6 and continues for approximately 6 years.

Occasionally, teeth are present in the newborn or erupt within the first month of life (Fig. 9.34). Although some investigators have suggested that these natal teeth represent predeciduous supernumerary teeth, most probably represent prematurely erupted deciduous teeth. If natal teeth are mobile and aspiration is a concern, removal is appropriate. However, stable teeth should be retained. Traumatic fibromas and ulceration of adjacent soft tissue known as Riga–Fede disease may occur during breast-feeding. However, protective measures may prevent local irritation.



Fig 9.34 Natal tooth. This loosely anchored natal tooth was extracted to eliminate the risk of aspiration.

Although environmental factors such as medications, syphilis, rubella, and irradiation may cause dental anomalies, most dental abnormalities are hereditary in nature. A number of gendermatoses (Fig. 9.35) may be associated with dental anomalies, and in some patients the dental findings may provide the first clues of a genodermatosis (Table 9.4).

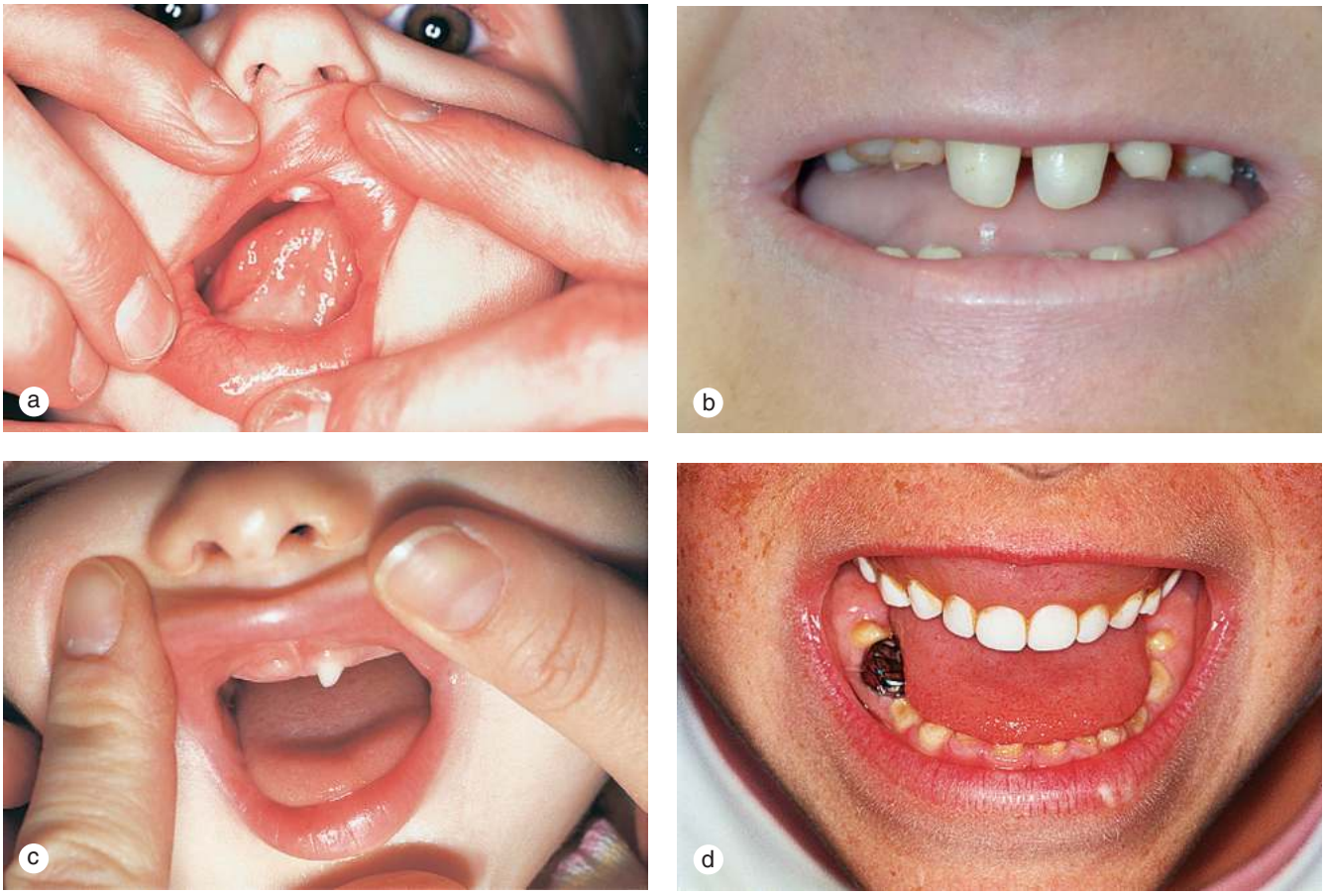


Fig 9.35 Dental anomalies. **(a)** Multiple teeth were hypoplastic and missing in this toddler with hypohidrotic ectodermal dysplasia. **(b)** This adolescent with hidrotic ectodermal dysplasia had multiple missing and malformed teeth. **(c)** Hypodontia and pegged teeth were the primary complication of incontinentia pigmenti in this 3-year-old girl. **(d)** This adolescent with epidermolysis bullosa developed chronic gingivitis and severe dental caries requiring extensive dental restoration.

Dental anomalies			
Disorder	**Inheritance**	**Dental anomalies**	**Associated anomalies**
Dentinogenesis imperfecta	Variable	Discolored, fragile teeth	Osteogenesis imperfecta
Ectodermal dysplasias			
Hypohidrotic	XLR	Absent or sparse abnormally formed teeth	Sparse hair; hypohidrosis; dysmorphic facies
Tooth and nail syndrome	AD	Hypodontia of permanent teeth	Sparse hair; small brittle nails
Trichodentoosseous syndrome	AD	Hypoplasia of dental enamel; taurodontia	Kinky hair; thin brittle nails
Rapp–Hodgkin syndrome	AD	Small, decreased number; conical teeth prone to caries	Coarse wiry hair; short, thick nails; hypohidrosis; midfacial hypoplasia; cleft palate
Ankyloblepharon, ectodermal, dysplasia, cleft lip/palate		Hypodontia, small discolored conical teeth	Cleft lip/palate; scalp erosions; absent/dystrophic nails; hypohidrosis

Table 9.4 Dental anomalies

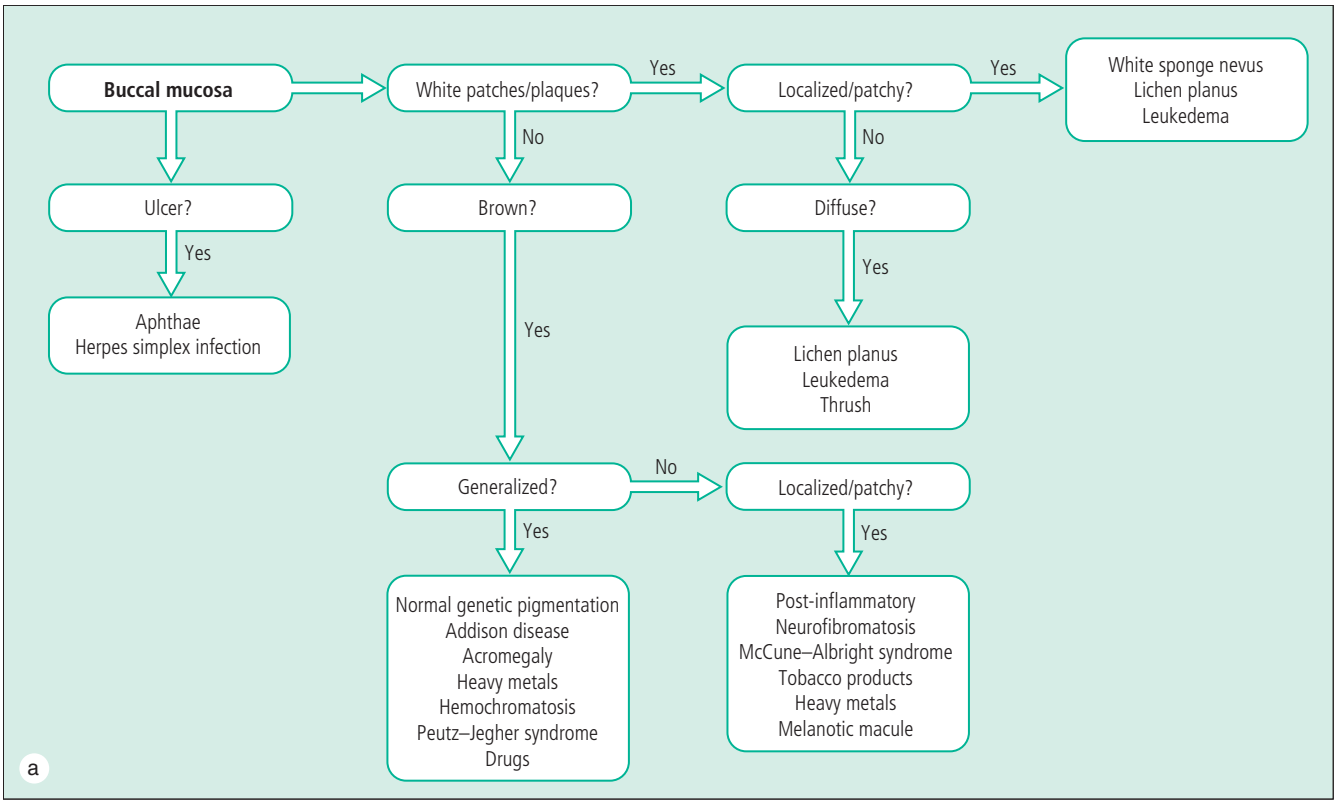
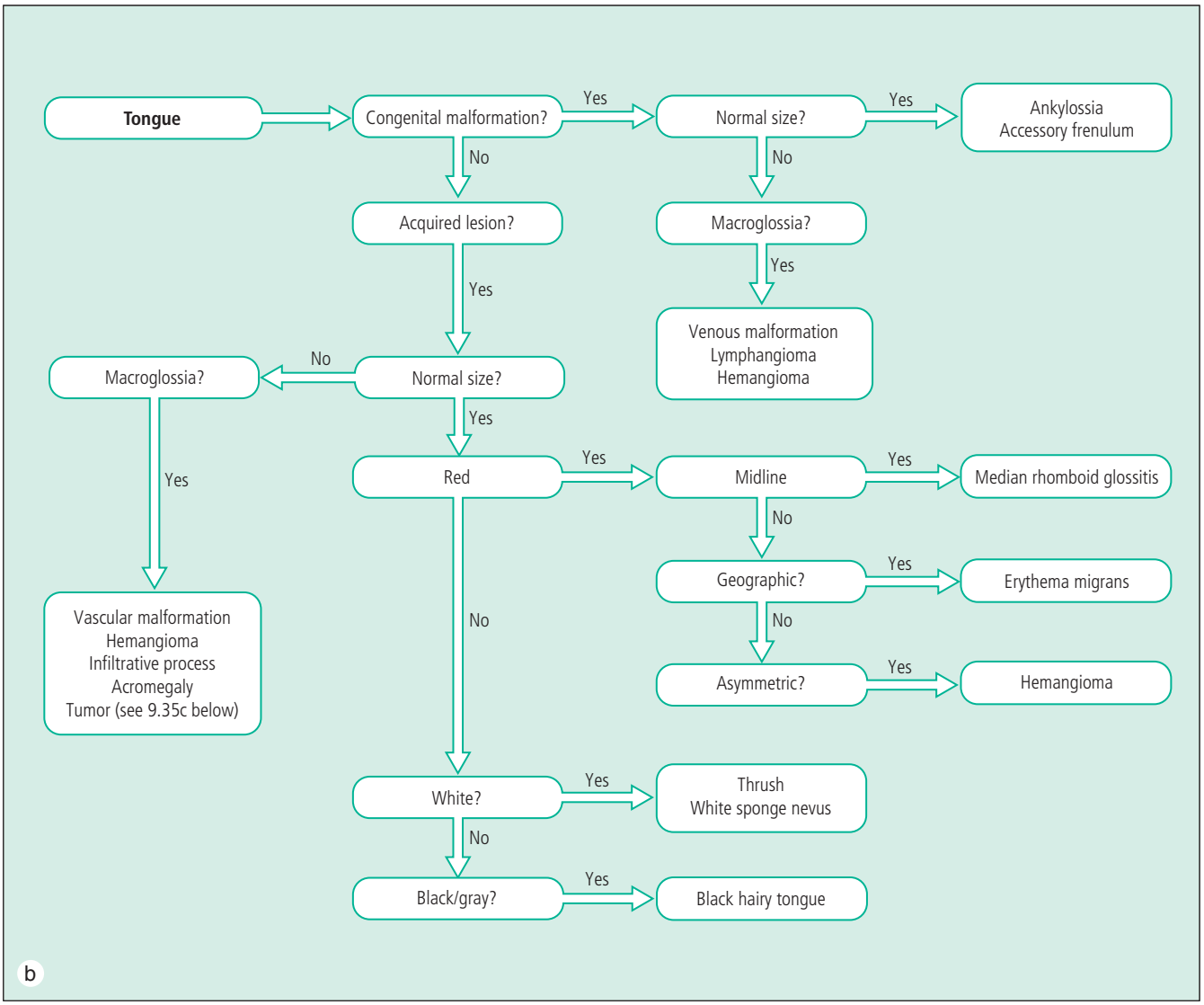


Fig 9.36 Algorithm for the evaluation of oral pathology.



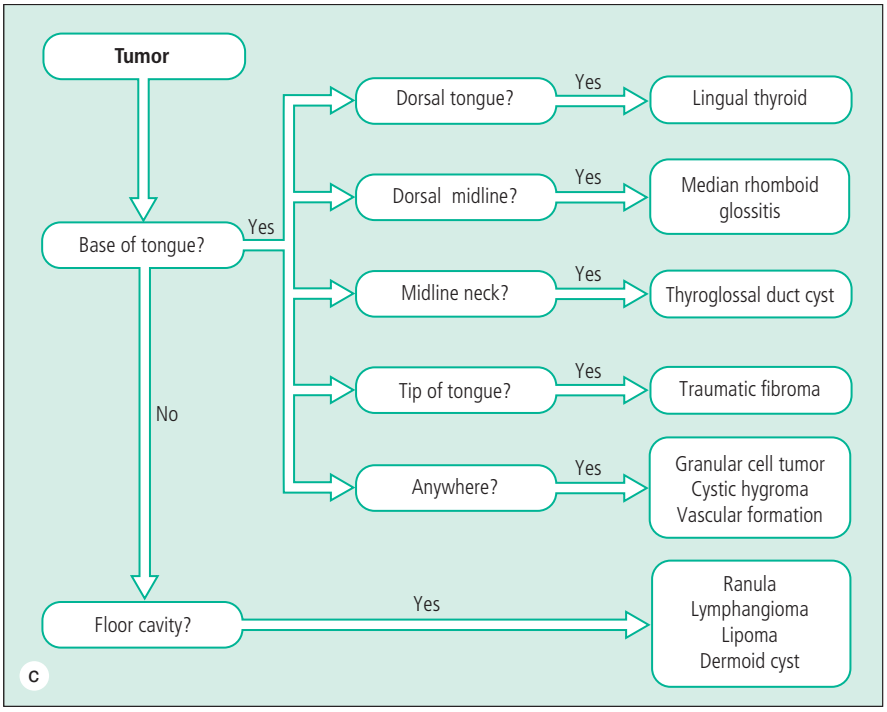
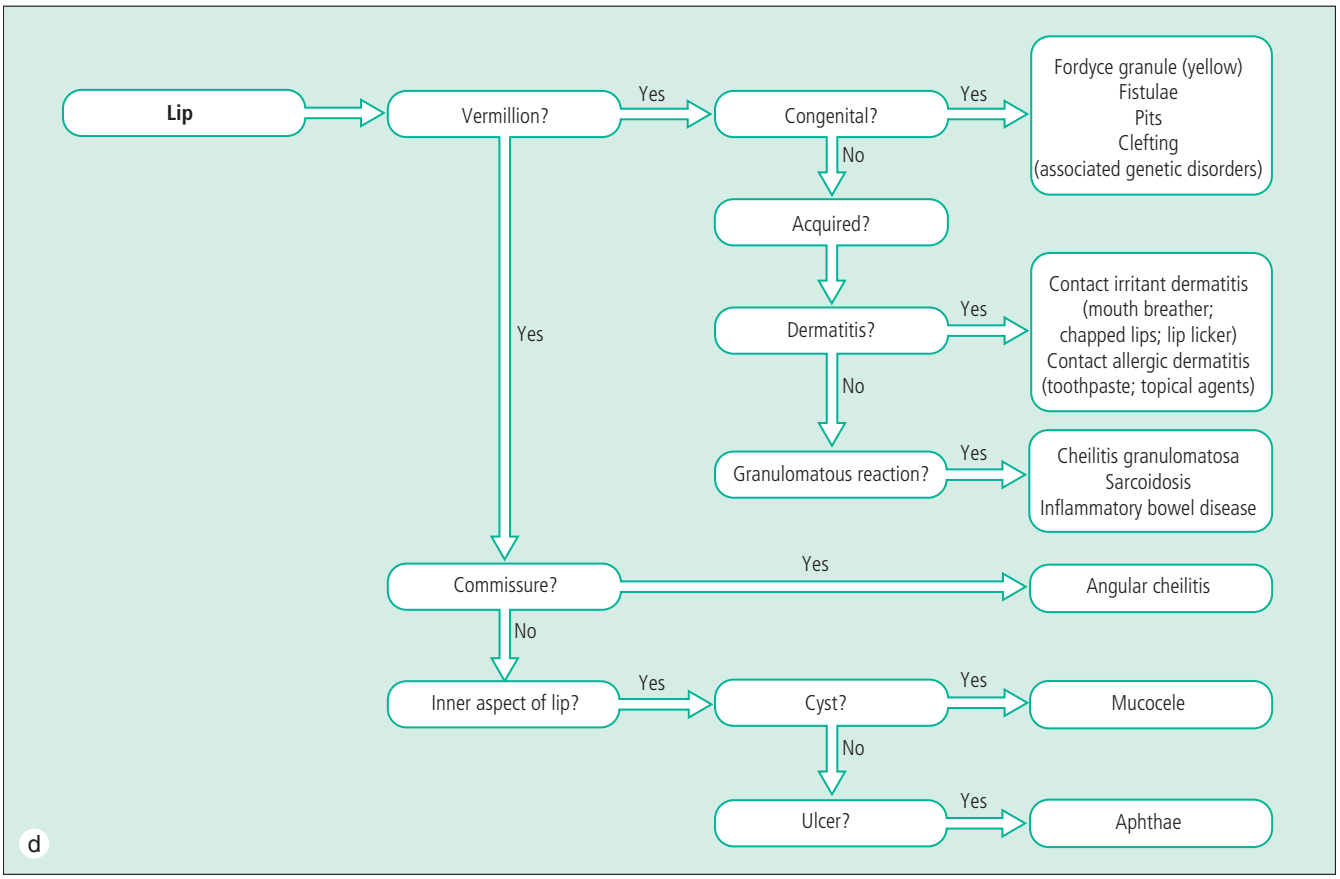


Fig 9.36 Continued



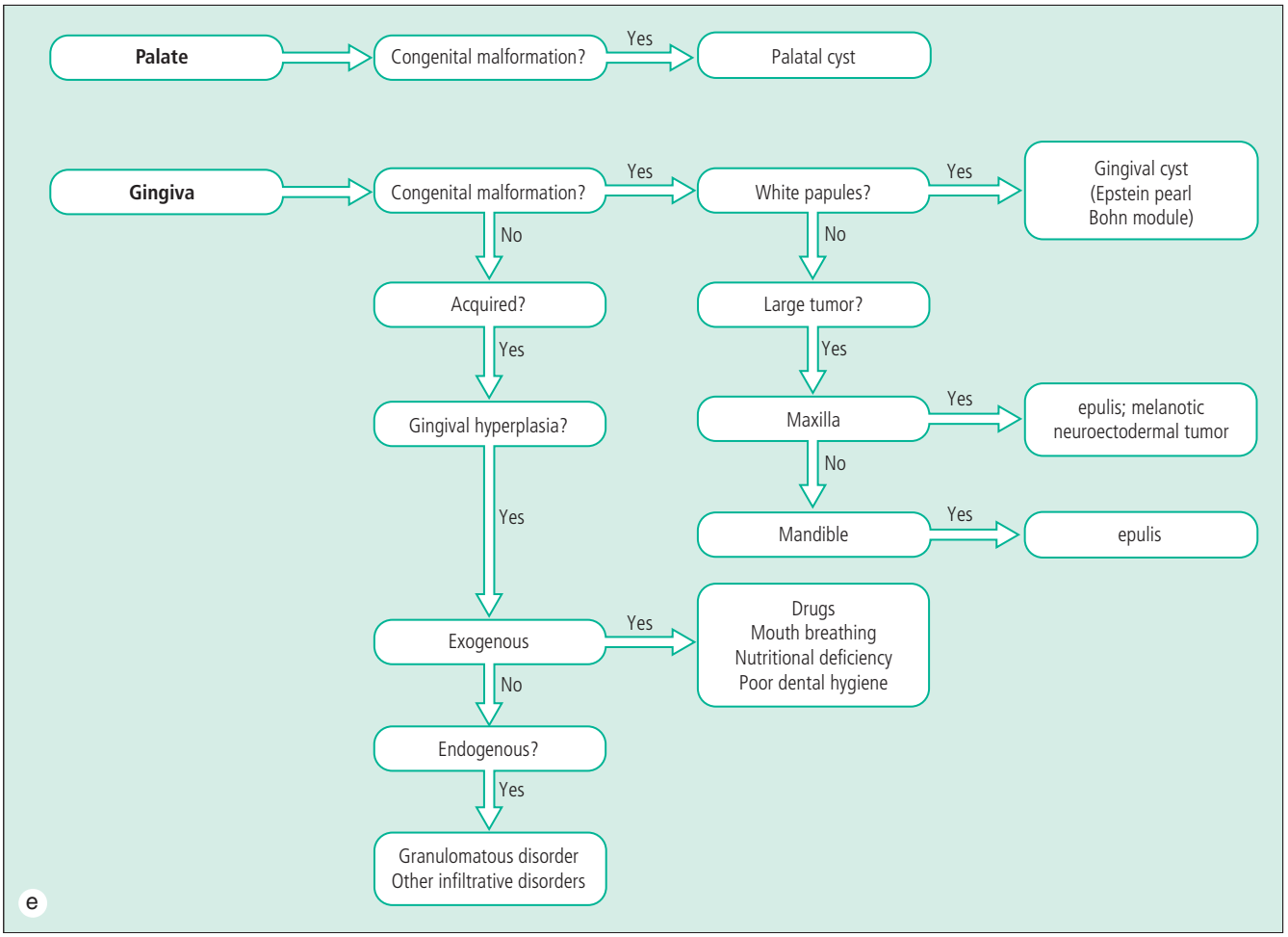


Fig 9.36 Continued

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Chapter 10

Factitial Dermatoses

Sherry Guralnick Cohen and Bernard A. Cohen

INTRODUCTION

Factitial is defined as 'artificial' or 'not natural'. In dermatology, factitial disease usually refers to a group of specific psychodermatoses. However, in this chapter, the definition is expanded to include a number of entities that do not fit neatly into other chapters. After a discussion of disorders with psychiatric implications, the cutaneous findings of child abuse are reviewed. The chapter concludes with sections on graft-vs-host reaction and acquired immunodeficiency syndrome (AIDS); diseases that have been, at least in part, created by human agency. An algorithmic approach to diagnosis for factitial dermatoses is summarized at the end of the chapter (see Fig. 10.22).

PSYCHODERMATOLOGY

Secondary psychiatric disorders, as well as psychophysiologic disorders, are common in pediatric practice. Fortunately, primary psychiatric disorders and neurologic and other organic disorders that mimic psychiatric disease (pseudopsychiatric disorders) are infrequent in children.

Secondary psychiatric disorders

Localized skin conditions, which involve cosmetically important areas such as the head and neck, or chronic, widespread rashes may be distressing enough to trigger secondary psychiatric disorders. In this group of diseases, disfigurement results in low self-esteem, social phobia, paranoia, and major depression. Common skin problems associated with secondary psychiatric disorders include psoriasis, cystic acne, alopecia areata, vitiligo, port-wine stains, and large, pigmented nevi.

Disfiguring lesions in infants and young children are a source of parental stress. However, if the lesions are treated before a critical period in psychologic development, long-term sequelae may be avoided. Although these critical periods are not well defined, many pediatricians agree that, if possible, treatment should be completed before patients begin school. For instance, facial pigmented nevi may be excised before kindergarten, and pulsed-dye laser treatment of port-wine stains may begin shortly after birth. Treatment of chronic, recurrent disorders, such as psoriasis and vitiligo, is scheduled to minimize school absence and is focused on eradicating the lesions that are most visible or symptomatic. In adolescents, even mild acne may trigger a great deal of anxiety, which can be controlled by physician counseling and appropriate medical management. Cystic acne is treated early and aggressively to avoid permanent scarring.

Periodic reassurance from the practitioner provides adequate support for many patients. Others may find participation in support-oriented groups, such as the National Vitiligo Foundation and the National Port-wine Stain Foundation, particularly helpful. However, when normal relationships with family and friends are disrupted, psychiatric consultation and counseling may be necessary.

Psychophysiologic disorders

Psychophysiologic disorders are also common in children. This term refers to a group of genuine dermatologic conditions that are triggered or exacerbated by emotional stress. Examples include atopic dermatitis, psoriasis, acne, hives, and hyperhidrosis.

Recognition of psychologic factors is key to successful treatment of these disorders. Some patients may require specific stress-reduction measures in addition to standard dermatologic therapy. Biofeedback training may help in disorders such as hyperhidrosis and atopic dermatitis, in which stress or anxiety can trigger a worsening of symptoms within minutes.

Primary psychiatric disorders

In this category of psychodermatoses, the skin becomes the focus of a primary psychosis. In most cases, either no true dermatologic disorder is present or minor findings are misinterpreted by the patient in accordance with his or her psychopathology. Although subtle symptoms may develop in childhood, most cases become manifest in adolescence or young adulthood.

Unlike innocent hair pulling which occurs commonly in toddlers and pre-schoolers, trichotillomania and acne excoriée are disorders in which patients demonstrate obsessive–compulsive symptoms. The DSM 5 describes trichotillomania as an impulse control disorder affecting 1.2% of the general population. The average age of onset is 9–10 years of age. Observational data show that one-third of these children had comorbid psychiatric conditions of generalized anxiety, social phobia, attention deficit hyperactive disorder, and oppositional defiant disorder. Studies show that cognitive behavioral therapy focussing on habit-reversal training is more effective than medications. Moreover, multiple case studies demonstrate that some of the newer antipsychotic medications can produce obsessive compulsive symptoms. Trichotillomania is not self-limiting and requires long-term psychiatric and medical therapy (see Fig. 8.24). In acne excoriée, a related obsessive–compulsive condition, patients pick and gouge trivial acne lesions on the face to produce erosions and ulcerations that may heal with scarring (Fig. 10.1). Acne excoriée usually occurs in young women.







Fig 10.1 Acne excoriée. A 17-year-old girl compulsively picked at subtle comedones, which created punched out ulcerations on **(a)** her forehead. Another adolescent girl **(b)** and boy **(c)** manipulated lesions on their cheeks and chin.





Fig 10.2 Factitial dermatitis. **(a)** An emotionally disturbed adolescent developed symmetric linear bruises on the arms. During counseling he admitted to producing the lesions with a coin. **(b)** Less well-defined areas of purpura developed acutely in another adolescent. These lesions cleared when the area was covered with a soft cast only to recur at other unprotected sites.

In monosymptomatic, hypochondriacal psychosis, patients develop a false fixation that there is a serious disturbance in their skin. The most common presentation is delusions of parasitosis, in which the individual is convinced that the skin is infested with imaginary mites, worms, or insects. Other examples include delusions of bromosis (foul odor) and dysmorphosis (abnormal or ugly appearance). These patients have little insight into their disease, and usually refuse consultation with psychiatrists. Unfortunately, the prognosis is guarded, and symptoms may persist indefinitely. Recent studies indicate that a large proportion of patients improve with pimozide, an antipsychotic drug of the diphenylbutylpiperidine group.

A subset of patients with self-induced skin disease, usually teenagers, develop lesions in association with situational stress (Figs 10.2–10.4). Disordered family dynamics, sexual abuse, school phobia, lost love, and other acute or chronic psychosocial problems may result in this form of attention-seeking behavior. When this diagnosis is suspected, lesions may be covered with occlusive dressings for several weeks to see if healing occurs. When confronted, the patients usually admit to the self-injurious behavior. Counseling and improvement in the situation often result in an end to the lesions.

Pseudopsychiatric disorders

When patients develop bizarre symptoms with few or confusing clinical findings, a psychiatric source is often considered. However, careful attention to the course of symptoms and development of skin lesions may give a clue to the true dermatologic diagnosis.

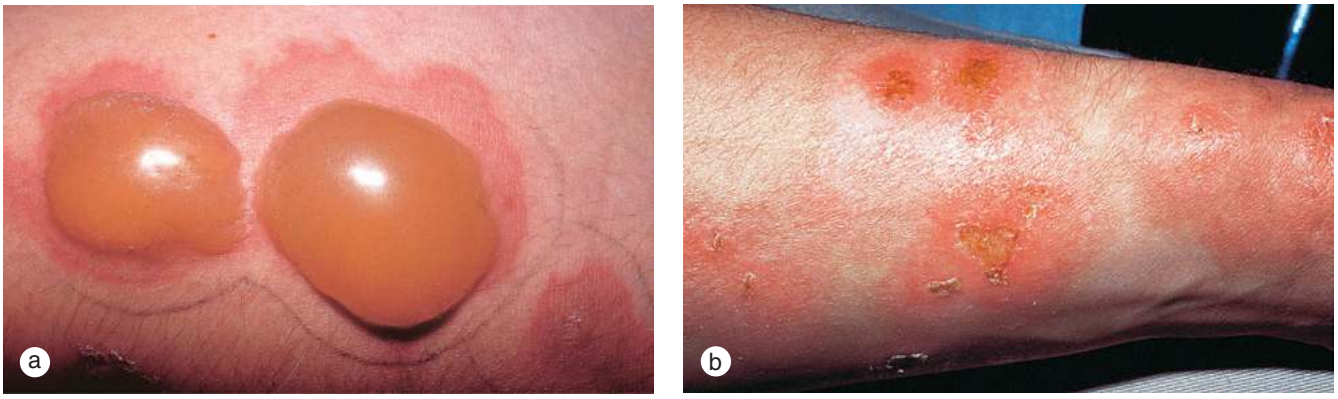


Fig 10.3 Factitial dermatitis. **(a)** A 15-year-old boy would periodically return from the woods behind his house with large, tense, bullous lesions on his arms. **(b)** Under close observation in the hospital, the lesions healed within several days. Later in therapy he admitted to applying a caustic liquid to the skin.

Dermatitis herpetiformis (DH) is a good example of a pseudopsychodermatosis. In DH, persistent, intense pruritus and subsequent excoriations, which obliterate the primary vesiculobullous lesions, make diagnosis difficult. Unless DH is considered and confirmed by skin biopsy and/or immunofluorescence studies, the patient may be mistakenly referred to psychiatry for evaluation of 'neurotic' excoriations. Scabies, folliculitis, urticaria, and other pruritic dermatoses may also be misdiagnosed as psychogenic pruritus.

Occasionally, children with temporal lobe seizures present with pseudo-delusions of parasitosis. Complaints of bizarre sensations in the skin also prompt a search for medication overdosage (e.g. diphenhydramine) or illicit drug exposure.

CHILD ABUSE AND NEGLECT

Although the true incidence of child abuse is unknown, over 2 000 000 children are estimated to be abused or neglected in the USA every year, which results in over 40 000 severely injured children and 4000 deaths. In many cases, affected children have been evaluated by practitioners who failed to recognize signs and symptoms that suggested the true diagnosis. Frequently, cutaneous findings provide clues to acute or chronic abuse.

Risk factors

Nearly two-thirds of children who suffer child abuse are under 3 years of age. Premature, disabled, and foster children are also more likely to be abused. About 75% suffer neglect; 15% suffer physical abuse and 10% of cases involve sexual abuse, of which girls are victims three times more often than boys. However, boys had a higher child fatality rate at almost 1.5 times higher than girls from abuse and neglect. Parental risk factors include a personal history of child abuse, poor socialization, and limited ability to deal with stress. Healthcare issues including cardiovascular disease, diabetes, and cancer have been linked to adverse childhood experiences. Although families living in poverty have increased exposure to stresses that may result in abuse and neglect, families of all socioeconomic levels may be affected. Alcoholism, addiction, and mental illness are often contributing factors. Families that move frequently and fail to develop support systems in the community are at particular risk.

Historical clues

When the history of how the injury occurred is vague or incompatible with the physical findings, abuse is included in the differential diagnosis. Inconsistencies in the history when parents are interviewed separately and changes in the history when it is taken by different health practitioners increase the index of suspicion.

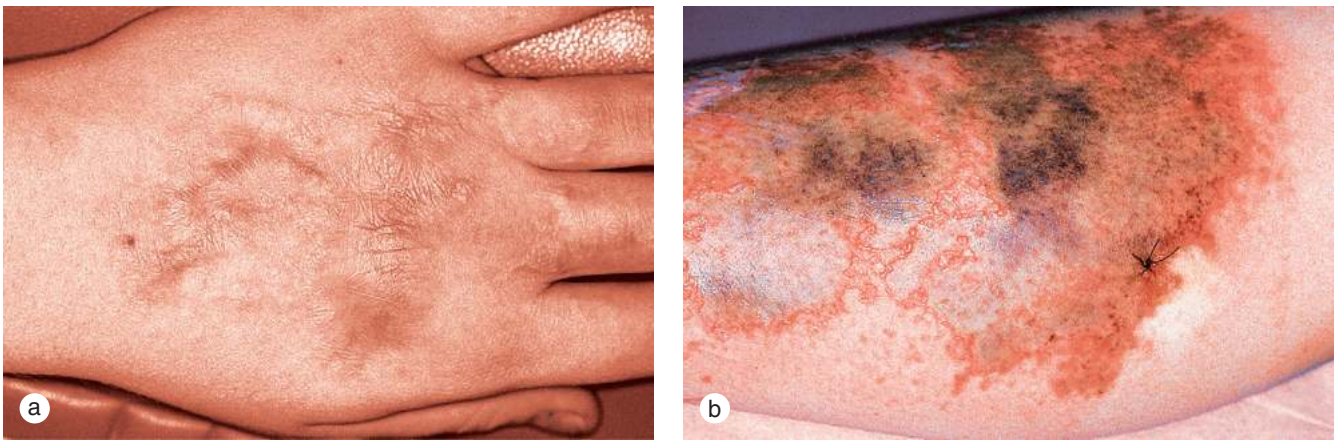


Fig 10.4 Factitial dermatitis. A 12-year-old girl has evidence of **(a)** old scarring and **(b)** new necrotic crusts on her leg from the application of a solvent to the skin. The fresh lesions healed under an occlusive dressing, which was left in place for 3 days.

Delay between the time of the injury and the visit to the clinician, inappropriate lack of concern for the injury, and abnormal interaction between the parent and child also raise suspicion.

A review of the primary care or emergency room medical records may reveal a large number of visits for accidental injuries, repeated fractures, and ingestions. Delayed immunizations and health maintenance visits may also serve as a warning. In infants and young children, poor growth or weight gain may be a sign of emotional abuse or neglect.

Clinical findings

Every child suspected of being abused deserves a thorough physical examination. Care must be taken to peruse the entire skin surface, including the anogenital area, mucous membranes, and scalp. All findings must be documented in the chart. Photographs of suspicious lesions are labeled and dated. The incident must be reported to the appropriate authorities, including Children's Protective Services or Social Services, and the police if necessary. Although the practitioner should play the role as an advocate for the family, the primary responsibility is the safety of the child.

Cutaneous lesions

The distribution and shape of skin lesions may provide a clue to diagnosis. Innocent, play-induced bruises usually appear over bony prominences. Bruises suggestive of abuse occur on the inner and outer thighs, ears, groin, genitals, cheeks, and torso (Fig. 10.5). Thumbprints on the chest and fingerprints on the back of a seizing or floppy infant point to the diagnosis of the so-called shaken-baby syndrome, in which shaking results in subdural hematoma with retinal hemorrhages.

Bruises appear purple and blue for the first 3–5 days and then change through greenish-yellow hues to faded brown at 10 days. Although it can be difficult to date bruises, multiple bruises of varying intensity and color may suggest an ongoing problem, and the parents' history may not be compatible with the evolution of lesions. Moreover, a complete skin examination with a Wood light may reveal old bruises that are no longer clinically visible.

In many cases, the configuration of bruises may conform to the imprint of the object used to induce injury. Linear lesions result from a wooden stick or metal wire. Circumferential bruises or erosions on the arms, legs, or neck may be caused by rope or wire ligatures (Fig. 10.6). Lamp cords (omega-shaped loops), belts ('U'-shaped cuts), belt buckles, and hands often inflict identifiable lesions (Fig. 10.7a,b). However, the clinician should always evaluate these lesions in the proper cultural context. Coining and cupping produce distinctive purpura in a non-abusive setting and should not be confused with potentially life-threatening non-accidental injury (Fig. 10.7c).

Human bites also have a characteristic appearance. Animal-induced injuries usually produce puncture wounds or tear the skin, while human bites cause crush injuries. Small bite marks may be inflicted by siblings. However, widths of greater than 4 cm occur with bites from adults.

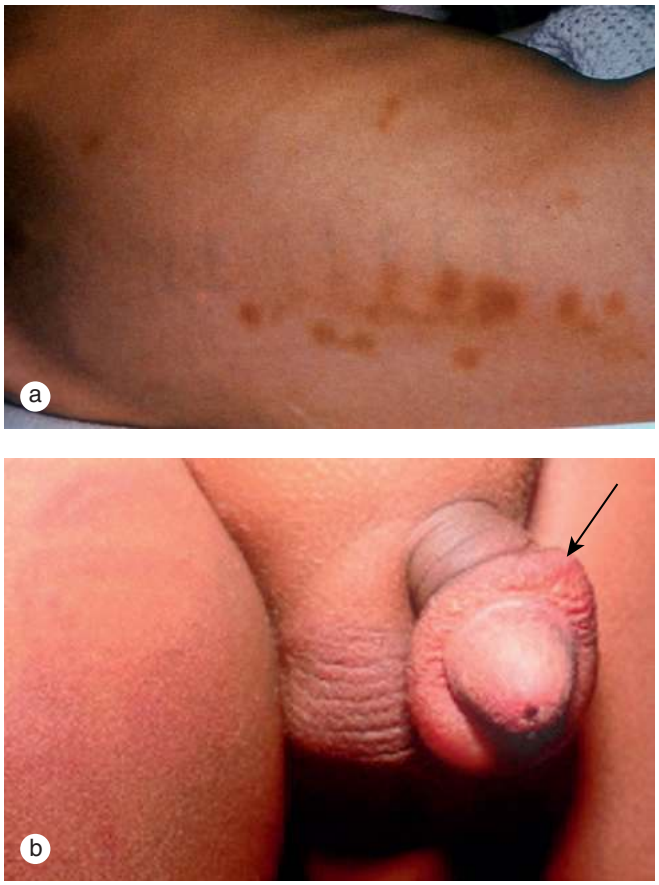


Fig 10.5 Physical abuse. **(a)** Multiple ecchymoses are evident over the back of this child who presented poorly nourished, but with normal coagulation studies. **(b)** This toddler developed edema of the foreskin after a beating with a belt. Note the belt-buckle mark on the right thigh.

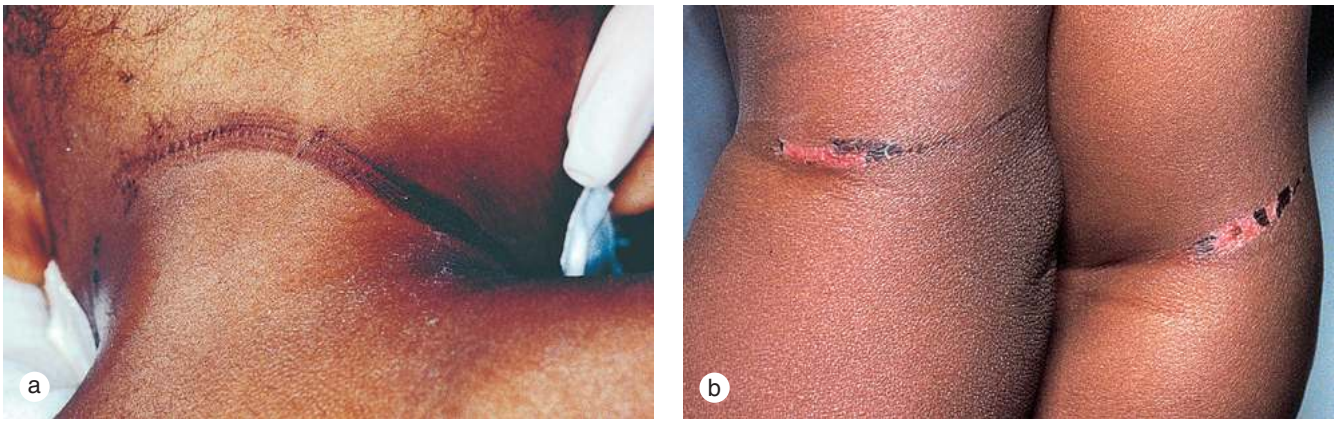


Fig 10.6 Physical abuse. These toddlers had rope tied around **(a)** the neck and **(b)** the legs, which produced circumferential bruising and erosions.







Fig 10.7 Physical abuse. The shape of lesions often gives a clue to the object used to inflict injury. **(a)** The end of a belt produced the 'U'-shaped cut on the leg of this 5-year-old boy. **(b)** Multiple scars produced by prior whipping with a looped cord are seen in this child. **(c)** Cupping purpura was induced deliberately in this adolescent to treat low back pain. Cupping and coining may be applied in a non-abusive setting and the shape of the lesions is virtually diagnostic.

Although burns are fairly common accidental injuries (Fig. 10.8), the shape and distribution of lesions, inconsistent history, and delay in seeking medical care may point to deliberate injuries. Burns from hot-water immersion are a common presentation for abuse. Symmetric lesions on the hands, feet, and diaper area are typical (Figs 10.9, 10.10). Frustration with toddlers during toilet training is a common complaint. The tops of the feet and hands may be more severely involved, because the skin on the palms and soles is thicker and may be relatively protected when the extremities are held against the bottom of the sink or tub. Burns from metal objects usually demonstrate the shape of the object (Fig. 10.11). A triangular-shaped injury may occur after branding from a hot iron. A child held against a hot, metal grate may show criss-crossing horizontal and vertical marks. Cigarette burns leave punched-out ulcers with dry, purple crusts (Fig. 10.12). They can be differentiated from impetigo by their uniform size and dry, non-expanding base. Repeated burns may result in lesions at various stages of healing. Some lesions may become impetiginized. Widespread, untreated impetigo and poor hygiene are also signs of child neglect.







Fig 10.8 Accidental scald. **(a)** A 2-year-old accidentally spilled a teacup filled with hot water onto her face, neck, and chest. Note the irregular, asymmetric, but well-demarcated borders of the burn. **(b)** The accidental splash-and-droplet pattern of blistering is typical of an accidental spill on this toddler, who grabbed a hot cup of tea from the table, while sitting on his grandmother's lap. **(c)** A 12-year-old girl with myelomeningocele and decreased sensation in the lower extremities accidentally dipped her feet into scalding water while preparing to take a bath.







Fig 10.9 Hot water immersion burns. **(a)** 1st- and 2nd-degree burns on the penis, thighs, and inguinal and suprapubic areas of a toddler who was held under a hot-water spigot. His sacrum and buttocks were spared. **(b)** Symmetric, healing, hot-water burns on the top of the foot of another toddler. Note the sharp line of demarcation at the ankle and sparing of the sole. **(c)** The partial thickness erosion on this toddler's buttocks resulted from a hot water dip injury.



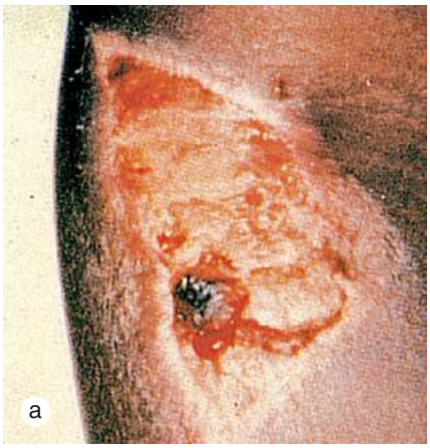
Fig 10.10 Caustic burn. A babysitter was applying a caustic liquid to patches in this child's diaper area. The morphology and course of lesions was not consistent with the history provided by the babysitter. Note the old scar on the abdomen.

Sexual abuse

Patients evaluated immediately after sexual assault often demonstrate evidence of physical and genital injury. Bruises on the head, neck, torso, and thighs are commonly present. Genital examination may show erythema, bruises, or lacerations (Fig. 10.13). In cases of molestation or incest, which usually occur chronically in a family setting, physical signs are subtle or absent. Patients may present with chronic vaginitis, healed scars in the anogenital area, a patulous introitus, or reflex relaxation of the anal sphincter on perineal stimulation. About 10–15% of these children show evidence of sexually transmitted diseases at the time of diagnosis. Consequently, evaluation includes culturing of the oral pharynx, rectum, and vagina for gonorrhea and chlamydiosis, and a serologic test for syphilis. Use of the urine nucleic acid amplification tests to confirm the diagnosis of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is less invasive.

Children who have been sexually assaulted require a thorough examination and collection of forensic data in a medical setting equipped for the special needs of this evaluation.

Occasionally, dermatologic disease can simulate the findings of sexual abuse (see Figs 4.19 and 7.55). Pyramidal protrusion refers to a firm pyramid-shaped congenital or acquired nodule that forms on the perineum following periods of constipation or diarrhea (Fig. 10.14). This smooth skin-colored to pink lesion should not be



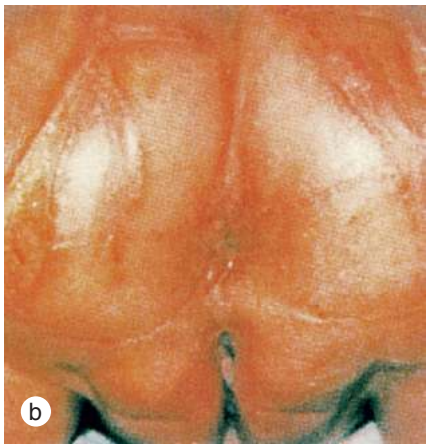


Fig 10.11 Hot-metal burns. **(a)** The pattern of this full-thickness burn to the arm reflects that a hot iron was used on this patient. **(b)** This infant received multiple, linear, full-thickness burns when she was forced to sit on the hot grill of a space heater.





Fig 10.12 Cigarette burns. **(a)** A fresh cigarette burn occurred when this 6-year-old allegedly walked into a lighted cigarette. Note the dry, yellow eschar in the center, with purplish peeled-back scale at the border. **(b)** Cigarette burns in various stages of healing are present on the hand and wrist of this abused 5-year-old child.

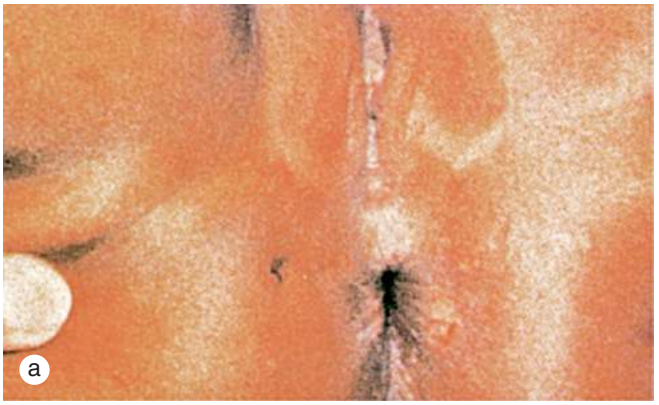




Fig 10.13 Sexual abuse. **(a)** Abrasions, contusions, and punctate tears of the perineum and perianal area can be observed in this prepubescent girl. **(b)** Severe, perianal lacerations, contusions, and abrasions are apparent in this prepubescent boy subjected to sodomy.



Fig 10.14 Pyramidal protrusion. This pink nodule appeared on the perineum following a 2-week episode of diarrhea in this 6-month-old girl. The lesion resolved without treatment over 4 months.



Fig 10.15 Ligature injury. This healthy infant developed edema of several digits after a hair accidentally became entangled around several toes. The hair was removed before the blood supply to the toes was interrupted.

Clinical staging and histologic grading of graft-vs-host disease

Stage	Cutaneous findings	Grade	Histologic finding
1	Erythematous macules, papules <25% BSA	1	Basal vacuolar change
2	Erythematous macules, papules 25–50% BSA	2	Dyskeratosis, dermal lymphocyte infiltrate
3	Erythematous macules, papules (>50% BSA) to erythroderma	3	Formation of dermal-epidermal clefts and microvesicles
4	Erythroderma with bulla formation and toxic epidermal necrosis	4	Separation of epidermis from dermis

Table 10.1 Clinical staging and histologic grading of graft-vs-host disease

confused with warts, molluscum, or scars. Bullous pemphigoid and linear IgA bullous dermatosis have been misdiagnosed as sexually transmitted herpetic infection. Candidiasis, lichen sclerosus et atrophicus, and inflammatory bowel disease with genital involvement may also mimic sexual abuse.

Other findings in abuse

Multiple, unexplained fractures of various ages that involve the long bones and ribs of an infant or young child are a sine-qua-non of child abuse. Often, the bony injuries are noted as an incidental finding when the child is brought to the practitioner for a single injury or some other, unrelated problem. When child abuse is suspected a complete skeletal survey is obtained to assess the full extent of the injuries. Blunt objects may cause intra-abdominal injuries, which include duodenal hematomas, small intestinal or mesenteric tears, and lacerations of the liver and spleen. These children may require hospital admission until their safety at home is assured. About 50% of children who are returned to the same environment are eventually killed by the abusive adult.

Innocent Mongolian spots and port-wine stains must not be mistaken for bruises. Past documentation in the child's medical record or observation over several days reveals the proper diagnosis. A bleeding diathesis, which may present with increased bruising, may be quickly excluded by a platelet count and coagulation studies. Insect bites may resemble cigarette burns and, in rare instances, osteogenesis imperfecta may simulate child abuse. Although ligature injuries from hair and cotton fibers around the genitals and digits may be accidental, abuse should always be excluded (Fig. 10.15).

GRAFT-VS-HOST DISEASE

Graft-vs-host disease (GVHD) is an immunologically mediated multisystem disorder caused by injury induced by immunocompetent, histoincompatible donor cells in a compromised recipient. Susceptible immunodeficiency states include the normal developing fetus, congenital immunodeficiency, and acquired immunodeficiency. Individuals who undergo bone marrow or solid organ transplantation may also be at risk.

When GVHD develops *in utero* in normal fetuses, viable maternal lymphocytes enter the fetal circulation by spontaneous maternal–fetal transfusion. Affected infants usually show signs of chronic disease at delivery. In infants with congenital immunodeficiencies, particularly T-cell deficiencies and severe combined immunodeficiency, the development of GVHD may be the first symptom of the immunodeficiency, which develops about 7–10 days after therapeutic blood transfusion (Fig. 10.16a). In many nurseries, sick infants receive irradiated blood that eliminates the risk of accidental infusion of viable lymphocytes. The most common group of children at risk for GVHD includes patients with acquired immunodeficiencies that result from chemotherapy, lymphoreticular malignancy, and bone marrow transplantation (Figs 10.16b–d, 10.17). Virtually every allogenic transplant patient experiences mild GVHD. Although less common, GVHD can also occur in some patients with autologous and syngeneic bone marrow transplantation.

Acute disease usually begins with a widespread, symmetric, pruritic, morbilliform rash within 2–6 weeks and up to 100 days after the introduction of donor cells (Fig. 10.16b–d). The face, neck, and the sides of the palms, soles, and digits are commonly involved. Less commonly follicular papules erupt, and rarely necrotic blisters and life-threatening toxic epidermal necrolysis follow (Table 10.1). Hepatic involvement is evident by the presence of elevated liver enzymes, and gastrointestinal symptoms include nausea and vomiting, and often progress to bloody diarrhea.

Chronic disease appears 100–400 days after the introduction of donor cells and may occur without antecedent acute symptoms. Chronic GVHD is a multisystem disease with autoimmune-like findings. Early in its course, the skin is involved with diffuse hypo- and hyperpigmentation, a lichenoid rash that resembles lichen planus, and scaly patches. Occasionally, patients develop a diffuse erythroderma. Untreated patients may eventually develop poikiloderma with atrophy, ulcerations, and progressive, widespread sclerodermatous changes (see Fig. 10.17a,b). Other findings include mucositis, cicatricial alopecia, vitiligo, dystrophic nails, Sjögren syndrome, and chronic pulmonary, cardiac, and gastrointestinal disease.

Fortunately, in transplant patients aggressive, immunosuppressive therapy with cyclosporine, tacrolimus, anti-thymocyte globulin, prednisone, cyclophosphamide, and other agents usually prevents the development of serious GVHD. Routine irradiation



Fig 10.16 Acute graft-vs-host disease. **(a)** A newborn with severe combined immunodeficiency developed graft-vs-host disease after a transfusion with non-irradiated, packed red blood cells. Note the diffuse erythema and scaling. **(b–d)** Severe skin disease developed 3 weeks after allogenic bone marrow transplantation in an adolescent with acute myelogenous leukemia. **(b)** A widespread morbilliform rash became confluent in the skin creases and over the thighs. Necrotic vesicles developed in the center of many red papules, reminiscent of erythema multiforme. Painful, violaceous nodules and plaques appeared on **(c)** the palms and soles, over the knuckles, and **(d)** around the nails. **(e,f)** This adolescent boy developed subtle reticulated erythema on his hands and feet 2 weeks after an autologous bone marrow transplant. The eruption persisted for 4–6 weeks and resolved without changes in his medications.

of blood products before transfusion also reduces the risk of GVHD in transplant patients and other immunodeficient individuals. In infants with congenital immunodeficiency, mortality is high despite intensive supportive care.

In most patients with GVHD, clinical findings can be used to direct medical therapy. In mild cases skin biopsies are of little value in distinguishing GVHD from drug reactions and viral exanthems. Although biopsy findings in severe disease may be diagnostic, it is prudent to treat aggressively and promptly, and pathology can be used to confirm the clinical diagnosis. Fortunately, with current prophylaxis for GVHD, most cases are mild and biopsies are usually unnecessary.











Fig 10.17 Chronic graft-vs-host disease. **(a)** Widespread atrophy, scaling, and fibrosis developed over a year after bone-marrow transplantation. This 14-year-old boy had experienced only minimal acute disease following his transplant. **(b)** Recurrent erosions, ulcers, and crusts formed on the arms, trunk, and legs in this 16-year-old boy with chronic disease. **(c,d)** A 6-year-old girl developed diffuse sclerodermatous changes and dyspigmentation typical of chronic graft-vs-host disease a year after bone marrow transplantation for acute lymphocytic leukemia. **(e)** She also developed lichenoid changes with some erosions in her mouth.

ACQUIRED IMMUNODEFICIENCY SYNDROME

Although the prevalence of AIDS is relatively low in children, the recent epidemic, which has spread to heterosexual women of childbearing age, has resulted in a rise in pediatric cases. In some areas, human immunodeficiency virus (HIV) seroprevalence among pregnant women exceeds 3%. The rate of transmission from untreated, asymptomatic mothers ranges from 15% to 35%. Other sources of infection in children include exposure to contaminated blood products, sexual transmission, and intravenous drug use.

Infected infants rarely develop overt disease during the first 3 months of life. However, before 1 year of age non-specific symptoms commonly include poor growth, generalized lymphadenopathy, hepatosplenomegaly, chronic oral thrush, and recurrent upper



Fig 10.18 Acquired immunodeficiency syndrome (AIDS). **(a)** Multiple, recalcitrant warts developed on the neck of a 2-year-old infant with AIDS. **(b)** This adolescent was plagued with disseminated, flat warts, demonstrated here by virtually confluent papules on the top of the hand. **(c)** Large, recalcitrant, genital warts were associated with bleeding and recurrent bacterial infections in this toddler. **(d)** Severe molluscum contagiosum became chronically irritated and secondarily infected in this 6-year-old girl with AIDS. When her lymphocyte count rebounded on antiviral therapy, the molluscum regressed.

respiratory, middle ear, and gastrointestinal infections. At least 50% of infected infants show central nervous system involvement, with neurodevelopmental delay or loss of milestones, acquired microcephaly, spastic diplegia, and quadriplegia. Pulmonary disease is the most common manifestation of pediatric AIDS, and affects over 75% of children during the first several years of life. Interstitial pneumonitis caused by *Pneumocystis carinii* is reported in 60% of patients. Lymphoid interstitial pneumonitis associated with Epstein–Barr virus infection occurs in about half of patients who survive the first year. Other important opportunistic pathogens include cytomegalovirus, *Candida*, *Mycobacterium avium-intracellulare* complex, and *Cryptococcus neoformans*. Patients are also susceptible to bacteremia, severe soft-tissue infection, pneumonitis, and meningitis from encapsulated bacterial organisms, such as *Streptococcus pneumoniae* or *Haemophilus influenzae*.

Skin lesions

Cutaneous findings may provide an early clue to diagnosis. Persistent diaper candidiasis and oral thrush, recalcitrant to topical therapy, occur commonly and prompt a search for HIV infection, especially in a child with growth failure or maternal risk factors. Many children are unable to localize common, usually self-limiting, viral infections. Widespread, recurrent herpetic gingivostomatitis and disseminated cutaneous herpes simplex, as well as chronic herpes infections, are a frequent problem. Recurrent, localized herpes zoster and disseminated zoster have also been reported. Widespread, recalcitrant warts or molluscum contagiosum may be the first sign of AIDS in an otherwise asymptomatic child (Fig. 10.18). Persistent and widespread dermatophyte infections that involve the skin, nails, and hair may occur. Disseminated, deep, fungal infections with cutaneous involvement, including cryptococcosis (Fig. 10.19) and histoplasmosis, have been described. Skin lesions produced by these fungi may simulate an indolent, bacterial folliculitis or molluscum.

Crusted scabies infestations, with thick, widespread, scaly papules and patches, require rapid identification to prevent spread to parents, teachers, and healthcare workers (Fig. 10.20). As in adults, the prevalence of seborrheic dermatitis, particularly widespread, erosive lesions, appears to be high in children with AIDS. Psoriasis, lichen planus, and other dermatoses may also be more common and more resistant to therapy in children and adolescents with HIV infection and AIDS (Fig. 10.21). Cutaneous manifestations of nutritional deficiencies, which include zinc-deficiency dermatitis, pellagra, and scurvy, have been noted, particularly in children with chronic gastrointestinal disease.

An increased frequency of drug eruptions has been reported in adults and children with AIDS. This is a serious problem in patients who require chronic prophylaxis against *Pneumocystis* with trimethoprim-sulfamethoxazole. The incidence of morbilliform drug rashes in adults on this regimen approaches 75%.

Other cutaneous findings in children with AIDS include ecchymoses from idiopathic thrombocytopenic purpura and chronic leukocytoclastic vasculitis. Although cutaneous Kaposi sarcoma is reported frequently in adults, in whom it is an AIDS-defining illness, it occurs only rarely in children.

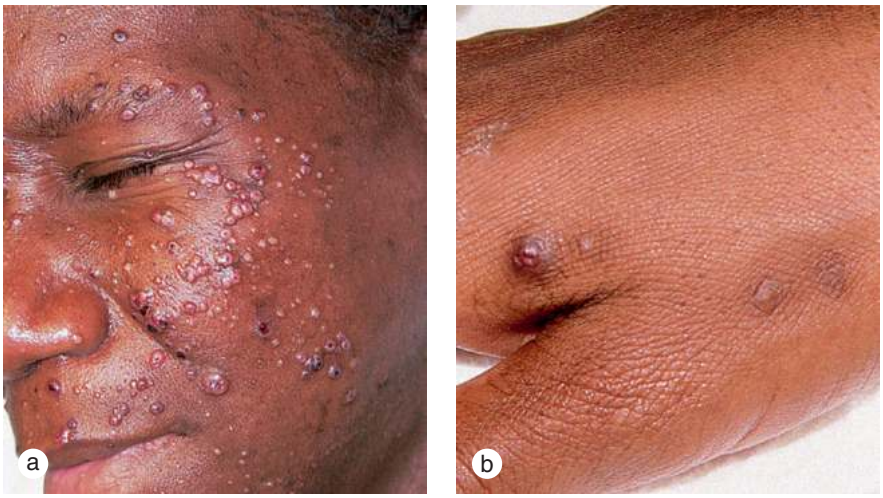


Fig 10.19 *Cryptococcus*. This young woman **(a,b)** with AIDS was initially diagnosed with widespread molluscum. However, a skin biopsy showed *Cryptococcus*, and she died several weeks later of disseminated infection.



Fig 10.20 Crusted scabies. A widespread, thick, scaly, crusted eruption shown on **(a)** the right hand and **(b)** the legs developed in an adolescent with severe neurologic involvement from AIDS. Scrapings demonstrated multiple scabies mites.



Fig 10.21 Adolescents with AIDS developed recalcitrant disseminated **(a)** psoriasis and **(b)** lichen planus.

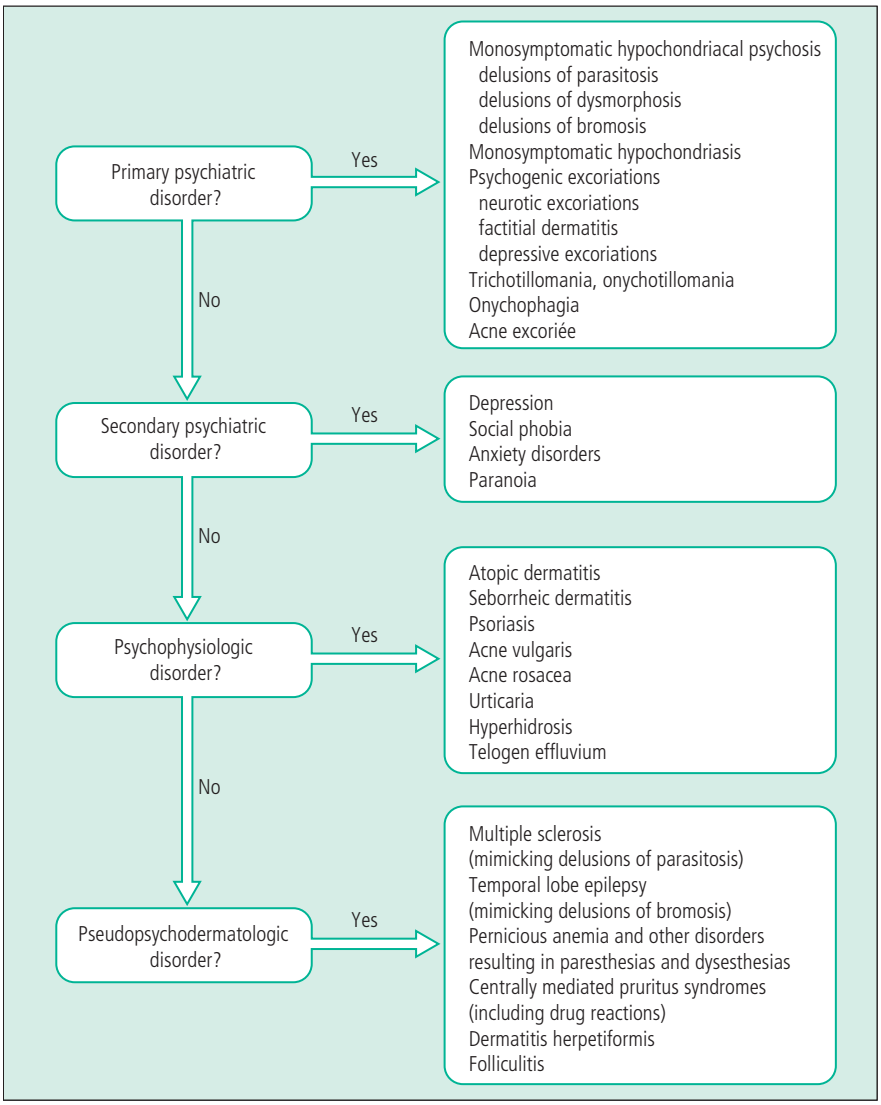


Fig 10.22 Algorithm for the evaluation of psychodermatologic disorders. (Modified from Koo JY, Do JH, Lee CS. Psychodermatology. J Am Acad Dermatol 2000; 43(5 Pt 1):848–853.)

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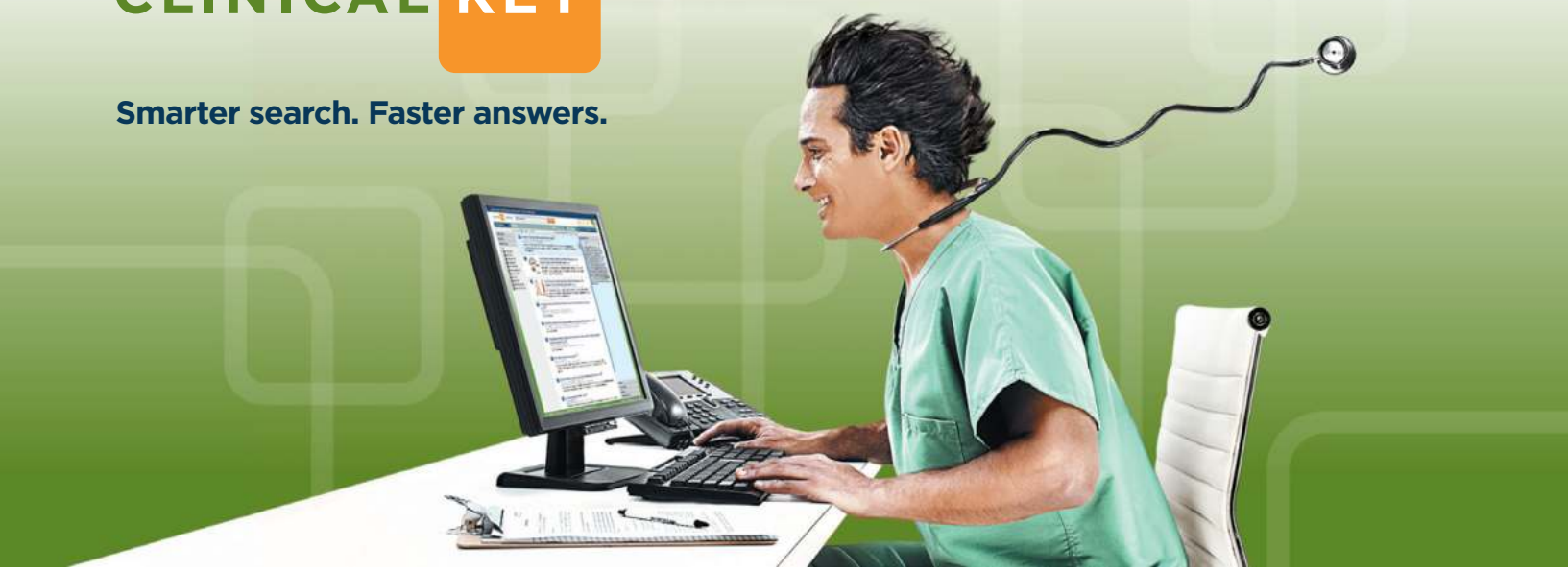
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