21 Genodermatoses

Although this chapter is devoted to genodermatoses, many acquired disorders are also considered when they seem to fit into the general clinical picture. For example, acquired forms of porokeratosis are considered along with the less common inherited ones.

21.1 MIM Code

What is the MIM Code?

Victor A. McKusick, one of the giants of clinical human genetics, started using a numerical code when he began compiling his books entitled *Mendelian Inheritance in Man*. The books evolved into a website, OMIM (*Online Mendelian Inheritance in Man*), which today serves as the standard for clinical genetics and the most convenient way to acquire updated information on all genetic disorders.
The MIM code is given throughout this book whenever it is relevant. The first digit identifies the pattern of diagnosis: 1 = autosomal dominant inheritance; 2 = autosomal recessive inheritance; 3 = X-linked inheritance.

How to Use OMIM

1 Simply enter ONIM in Google or any search engine and you will land on OMIM—or enter www.ncbi.nlm.nih.gov/OMIM.
2 Search OMIM.
3 Enter the MIM code, or a key word or two if you are looking for a syndrome or set of findings.
4 You will see a list of disease descriptions likely to be relevant to your query; chose whichever ones seem most useful.
5 Now you can read an update about the disease, the gene, find extensive references, or be linked to Medline.

21.2 The Ichthyoses

Overview

The primary ichthyoses are a heterogenous group of inherited disorders featuring excessive scale. The alternate term *disorder of keratinization* is less offensive to patients who do not enjoy being told they resemble fish (ichthyosis is Greek for "fishlike condition"). Secondary or acquired ichthyosis describes similar scaly conditions appearing later in life.
The "brick and mortar" model of the epidermis helps one understand the genetic basis of the primary ichthyoses. The stratum corneum is made up of keratins and lipids. Mutations in keratins usually have autosomal dominant inheritance and can be viewed as "defective bricks." Mutations in the enzymes needed to produce and metabolize lipids are usually autosomal recessive, and represent "defective mortar."

Classification

- **Primary ichthyoses:**
  - *Common:*
    - Ichthyosis vulgaris (see below).
    - X-linked recessive ichthyosis.
  - *Rare:*
    - Congenital autosomal recessive ichthyoses:
    - Nonbullous congenital ichthyosiform erythroderma.
    - Lamellar ichthyosis.
    - Autosomal dominant lamellar ichthyosis.
    - Ichthyoses with epidermolytic hyperkeratosis:
    - Bullous congenital ichthyosiform erythroderma (Brocq).
    - Ichthyosis hystrix (Curth–Macklin).
    - Ichthyosis bullosa (Siemens).
    - Harlequin fetus.
    - Syndromes with ichthyosis:
    - Ichthyosis linearis circumflexa (Netherton syndrome).
    - X-linked dominant chondrodysplasia punctata (Conradi–Hünermann–Happle syndrome).
    - Refsum syndrome.
    - Sjögren–Larsson syndrome.
- **Secondary or acquired ichthyoses:**
  - Paraneoplastic marker for lymphoma and internal malignancies.

  Caution: Whenever ichthyosis appears in adult life for the first time, exclude an underlying malignancy.
  - *Infections:* Leprosy, tuberculosis, syphilis.
  - *Vitamin deficiency:* Vitamin A, vitamin B6, and nicotinic acid deficiency (pellagra, p. 302).
  - *Medications:* nicotinic acid (most common), triparanol, butyrophenone.

  Note: Any drug that alters lipids is potentially capable of inducing an ichthyosis-like condition.
  - **Miscellaneous:** Sarcoidosis, hypothyroidism, Down syndrome, long-term renal dialysis, severe xerosis in the elderly.

Ichthyosis Vulgaris

- **MIM code:** 146700.
- **Definition:** Most common form of ichthyosis and also the mildest.
- **Epidemiology:** Prevalence of 1:250.
- **Pathogenesis:** Abnormal formation of keratohyalin granules and delayed destruction of desmosomes because of defective or absent production of profilaggrin and filaggrin, producing a *retention hyperkeratosis*.
- **Clinical features:**
  - Usually starts in first year of life (months 3–12; not at birth), progressive until puberty, then usually improvement. Better in summer.
  - Clinically overlaps with xerosis, sometimes making definitive diagnosis difficult.
  - White fine scales of varying intensity on extensor surfaces (especially shins), trunk and lateral aspects of face. Flexures always spared (Fig. 21.**1**). No mucosal involvement.
  - Exaggerated palmoplantar markings (ichthyosis hand or foot).
  - Callus-like lesions on knees and elbows.

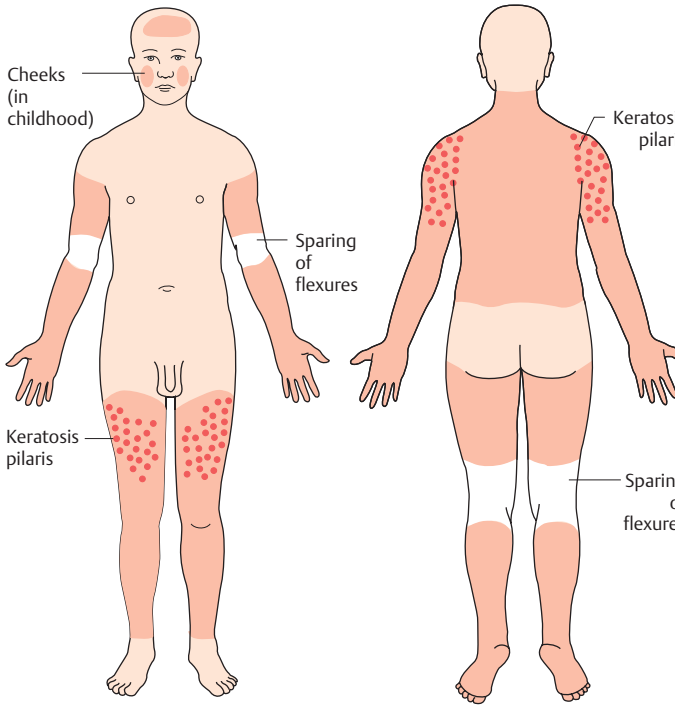


Fig. 21.1 · **Ichthyosis vulgaris. a** Localization. **b** Appearance.

- Follicular hyperkeratoses on shoulders (keratosis pilaris); sometimes also involves buttocks, thighs and upper arms.

  ▶ ***Note:*** When confronted with extensive keratosis pilaris, always think of ichthyosis vulgaris.
- *Associated disorder:* Atopic dermatitis (50%).

▶ **Histology:** Mild hyperkeratosis with an absent granular layer; normal dermis.

▶ **Diagnostic approach:** Clinical examination; biopsy may be helpful, but often equivocal. Best clues are family history, early onset, spared flexures, and hyperlinear palms.

- **Differential diagnosis:** Other forms of ichthyosis, acquired ichthyosis, extreme xerosis (particular problem in blacks).
- **Therapy:** Topical urea compounds most useful; watch concentration (irritating if too high) and chose a well-tolerated vehicle; alternatives include lactic acid and salicylic acid or combinations thereof. Lubrication of skin after bathing most crucial; defatting soaps should be avoided.
  Note: Topical corticosteroids absolutely useless—just a very expensive cream!

X-linked Recessive Ichthyosis

- **Synonym:** Steroid sulfatase deficiency.
- **MIM code:** 308100.
- **Definition:** Ichthyosis seen only in men as a result of steroid sulfatase deficiency.
- **Epidemiology:** Prevalence of 1:6000 among men.
- **Pathogenesis:** Mutation in steroid sulfatase gene *STS* at Xp22.32 means that the mortar (cholesterol sulfate) cannot be broken down, so once again a *retention hyperkeratosis* develops.
- **Clinical features:**
  - *Ichthyosis* (100%):
    - Starts in first 6 months, progressive until puberty, then stable; improves in summer.
    - Large brown polygonal scales divided by wide splits (Fig. 21.**2**).

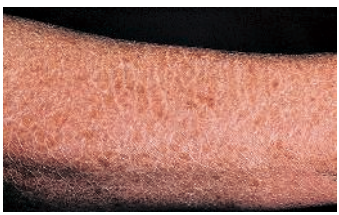


Fig. 21.**2** · X-linked recessive ichthyosis: coarse brown scales.

    - In younger patients, prominent involvement of scalp, ears, and neck (*dirty neck*).
    - On trunk and extremities, typically localized severally involved areas.
  - *Ocular involvement* (100%):
    - Asymptomatic corneal opacities.
    - May also be found in carrier females.
  - *Complications of pregnancy* (30–40%):
    - Deficiency of placental steroid sulfatase leads to low levels of estrogens.
    - Often delayed onset of labor or inadequate contractions.
  - *Hypogonadism* (25%):
    - Reduced androgen synthesis leads to hypergonadotropic hypogonadism.
    - Testes often undescended with increased risk of testicular carcinoma.
- **Histology:** Hyperkeratosis, normal to thickened granular layer.
- **Diagnostic approach:**
  - Clinical examination (dirty neck), history of abnormal delivery or affected uncles; elevated plasma cholesterol sulfate level or lipoprotein electrophoresis showing increasing motility of β- and pre-β-lipoproteins.
  - Also arrange for ophthalmologic and urologic consultation; consider testosterone replacement.

- **Differential diagnosis:** In contrast to ichthyosis vulgaris, no hyperlinear palms, no keratosis pilaris, flexural involvement and larger, darker scales.
- **Therapy:** Same as ichthyosis vulgaris; also worth trying 10% cholesterol ointments topically, especially in infants who do not tolerate urea or lactic acid.

Collodion Baby

A number of forms of ichthyosis present at birth with infant encased in a tight membrane of adherent keratinocytes, which has been compared to parchment or collodion. Kollodes is the Greek word for glutinous or glue-like. The membrane is then shed, leaving either normal skin (*lamellar exfoliation of newborn*) or, more often, one of the forms of nonbullous congenital ichthyosiform erythroderma or lamellar ichthyosis. Both disorders are heterogenous and also show overlaps. Our listing and description is deliberately simplified; when confronted with a case, consult OMIM or a specialized text.

Nonbullous Congenital Ichthyosiform Erythroderma

- **MIM code:** 242100.
- **Definition:** Rare severe ichthyosis presenting at birth.
- **Pathogenesis:** One of the first examples of proven genetic heterogeneity, as several different mutations cause the same clinical syndrome. All three involve lipid metabolism and have autosomal recessive inheritance:
  - Tranglutaminase-1 (*TGM1*) at 14q11.2; also involved in lamellar ichthyosis.
  - Two lipoxygenases at 17p13.1 (*ALOX12B* and *ALOXE3*).
- **Clinical features:**
  - Frequently born as collodion baby.
  - Fine white scales and erythroderma (usually severe but variable). Also ectropion and scarring alopecia (Fig. 21.**3**).
  - Nail dystrophy, hypotrichosis, short stature, cardiac malformations.

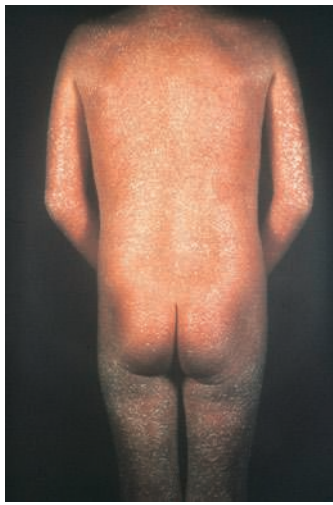


Fig. 21.**3** · Nonbullous congenital ichthyosiform erythroderma.

- **Histology:** Hyperkeratosis with focal parakeratosis, hypergranulosis and acanthosis; keratinocyte membranes periodic acid–Schiff (PAS) positive.
- **Therapy:** Systemic retinoids may be helpful, but long-term use problematic; otherwise, as for ichthyosis vulgaris.

Chanarin–Dorfman syndrome

- MIM code 275630; *CG158* gene at 3p21; similar to nonbullous congenital ichthyosiform erythroderma but with lipid inclusions in epidermal cells, cataracts, deafness, and often mental retardation.

Autosomal Recessive Lamellar Ichthyosis

- **MIM code:** 242300.
- **Definition:** Severe uncommon (1:100 000) ichthyosis.
- **Pathogenesis:** Several genes identified; most common is transglutaminase-1 (*TGM1*) at 14q11.2, but several other loci known. Unique problem in that one mutation can produce two clinical patterns: fine scale and erythroderma or thick scales and prominent ectropion.
- **Clinical features:**
  - Frequently born as collodion baby.
  - Thick dark scales, marked facial involvement, often ectropion, sometimes persistent erythroderma, temperature intolerance (sweat ducts clogged or defective) (Fig. 21.**4**).
- **Histology:** The transglutaminase-1 can be stained in frozen sections of skin; if absent, suggests diagnosis.
- **Diagnostic approach:** Very confusing; both autosomal dominant lamellar ichthyosis and lamellar ichthyosis/nonbullous congenital ichthyosiform erythroderma overlap. Both are much more rare than lamellar ichthyosis.
- **Therapy:** Patients often require systemic retinoids; otherwise, same treatment as ichthyosis vulgaris.

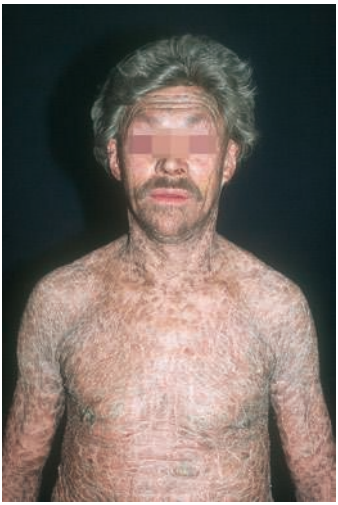


Fig. 21.**4** · Autosomal recessive lamellar ichthyosis.

Autosomal Dominant Lamellar Ichthyosis

- **MIM code:** 146750.
- Rare form of ichthyosis; autosomal dominant inheritance with gene undetermined. Can mimic either lamellar ichthyosis or less often nonbullous congenital ichthyosiform erythroderma. *TGM1* not involved. Treatment difficult but identical to other forms of lamellar ichthyosis.

Ichthyoses with Epidermolytic Hyperkeratosis

- Epidermolytic hyperkeratosis is a specific histologic finding with clumped keratohyaline granules and vacuolization of stratum spinosum and granulosum. It is found in several types of ichthyoses, as well as in palmoplantar keratoderma (Vörner type), epidermal nevi, sporadic papules (epidermolytic acanthoma), and as a chance focal finding in normal skin.

Bullous Congenital Ichthyosiform Erythroderma (Brocq)

- **Synonym:** Epidermolytic hyperkeratosis.
- **MIM code:** 113800.
- **Definition:** Uncommon (1:100000) severe generalized disorder with blisters and hyperkeratotic lesions.
- **Pathogenesis:** Mutations in keratin 1 and 10 genes; this keratin pair is expressed above the basal layer. Structural mutation with autosomal dominant inheritance; about 50% of cases familial and 50% new mutations.
- **Clinical features:**
  - At birth, widespread blisters and erosions; child looks as if burned.
  - During infancy, flaccid blisters at sites of pressure or friction.
  - Then development of distinctive dirty, spiny, hyperkeratotic lesions, often scattered on an erythematosus background; most often in flexures.
  - Palmoplantar keratoderma common, especially with keratin 1 mutation.
- **Histology:** Microscopic picture so distinctive that skin biopsies were used for prenatal diagnosis; intracellular vacuolization in stratum spinosum and granulosum, clumped keratohyaline granules, compact hyperkeratosis.
- **Diagnostic approach:** Clinical examination, biopsy.
- **Differential diagnosis:** At birth, confused with epidermolysis bullosa and staphylococcal scalded skin syndrome. Later, clinically distinctive.
- **Therapy:** Systemic retinoids help with keratoses but may increase tendency to blister; watch for infections; otherwise, same as ichthyosis vulgaris.

Ichthyosis Hystrix (Curth–Macklin)

- **MIM code:** 146590.
- Rare ichthyosis showing autosomal dominant inheritance with characteristic spines (hystrix means porcupine, referring to spikes or spines), palmoplantar keratoderma, and epidermolytic hyperkeratosis. One family had keratin 1 mutation, but probably heterogenous. Peculiar binucleated keratinocytes. Treatment with systemic retinoids. There are other even rarer forms of ichthyosis and epidermal nevus with a hystrix appearance and with varying histologic pictures.

Ichthyosis Bullosa (Siemens)

- **MIM code:** 146800.
- Mild form of congenital ichthyosis resembling congenital ichthyosiform erythroderma but without erythroderma. Mutation in keratin 2e gene, which is ex-

pressed even higher in epidermis. Patients described in German as "molting," as frequently sheets of skin are shed in irregular pattern. Histology shows epidermolytic hyperkeratosis. Treatment same as bullous congenital ichthyosiform erythroderma.

Harlequin Fetus

- **Synonym:** Ichthyosis congenita gravis.
- **MIM code:** 242500.
- Rare devastating disorder, barely compatible with life. Children born with extremely thick scales separated by erythematous fissures, fancifully compared to a harlequin's costume. Massive ectropion, eclabium; respiratory problems from construction by scales. Exact defect in keratin not known. Few survivors, with lifelong systemic retinoids.

Syndromes with Ichthyosis

Netherton Syndrome

- **Synonym:** Ichthyosis linearis circumflexa, Comèl–Netherton syndrome.
- **MIM code:** 256500.
- **Definition:** Distinctive syndrome with ichthyosiform skin changes, trichorrhexis invaginata, and atopic dermatitis.
- **Pathogenesis:** Mutation in *SPINK5* gene at 5q32, which codes for serine protease inhibitor; autosomal recessive inheritance.
- **Clinical features:**
  - Skin changes include:
    - Generalized erythroderma, especially severe on face; about 20% of childhood erythroderma are Netherton syndrome.
    - Circinate slightly raised erythematous bands on trunk (*ichthyosis linearis circumflexa*) with distinctive *double-edged scale*.
    - Complicated by overlapping features of atopic dermatitis including flexural and facial dermatitis; more difficult to treat than ordinary atopic dermatitis.
  - Hair shaft shows trichorrhexis invaginata (bamboo hairs) (p. 510).
  - Increased frequency of food allergies, urticaria, and infections.
  - Sometimes failure to thrive, rarely mental retardation.
- **Diagnostic approach:** Clinical examination, examination of hairs; often elevated IgE levels. Occasionally aminoaciduria.
- **Therapy:** Difficult to manage; keratolytics for ichthyotic lesions; in testing of topical tacrolimus, only patients to absorb significant amounts were those with Netherton syndrome who experienced considerable toxicity. Sometimes systemic retinoids help.

Conradi–Hünermann–Happle Syndrome

- **Synonym:** X-linked dominant chondrodysplasia punctata.
- **MIM code:** 302960.
- **Definition:** Rare complex of cutaneous, ocular, and bony disorders.
- **Pathogenesis:** Mutation in *EBP* gene, a sterol isomerase located at Xp11.22–11.23. Lethal in males; presents in mosaic pattern in female infants.
- **Clinical features:**
  - Skin at birth shows ichthyosiform erythroderma; later hyperkeratotic areas as well as pigmentary changes following Blaschko lines. Also scarring alopecia and unruly hair.
  - Radiograph of epiphyses shows stippling (chondrodysplasia punctata); resolves with time, so not reliable for diagnosis later in life.
  - Scoliosis, nasal hypoplasia, cataracts.

- **Diagnostic approach:** Clinical examination, radiography, genetic analysis.
- **Differential diagnosis:** Several other disorders diagnosed as chondrodysplasia punctata, with different patterns of inheritance and varying degrees of skeletal change. Consult OMIM or geneticist.
- **Therapy:** Interdisciplinary management; skin tends to be major problem only early in life.

Sjögren–Larsson Syndrome

- **MIM code:** 272200.
- Rare ichthyosis; autosomal recessive inheritance with defect in *FALDH* at 17p11.2 coding for fatty aldehyde dehydrogenase. Common only in northern Sweden. Fine scaling of neck and abdomen, coupled with ophthalmologic and CNS abnormalities, as well as mental retardation.

Refsum Syndrome

- **MIM code:** 266500.
- Rare ichthyosis; autosomal recessive inheritance, with defect in *PAHX* at 10pter-p11.2 coding for a phytanic acid hydroxylase. Fine white scale resembling ichthyosis vulgaris but coupled with peripheral and cranial nerve dysfunction and cardiomyopathy. Increased plasma phytanic acid.

CHILD Nevus or Syndrome

- Peculiar type of ichthyosiform epidermal nevus (p. 414), often listed with ichthyosis.

21.3 Other Keratinization Disorders

Follicular Keratoses

Just as the stratum corneum sheds scales, the hair follicle epithelium must shed its outermost keratotic material. Normally the combination of lipid secretion and hair growth cleanses the follicle, but sometimes a plug of keratin is retained. After a follicle has been plugged, it may become gaping or patulous, producing *follicular atrophoderma*. A comedo in acne sounds similar, but it is an intrafollicular plug without an elevated component.

Conditions with plugged follicles include:

- **Keratosis pilaris:**
  - Most common; seen in almost everyone at some time in life.
  - Plugs accompanied by mild follicular erythema.
  - Usually over triceps area, but may also involve shoulders, buttocks, and thighs.
  - Associated with atopic dermatitis, ichthyosis vulgaris, and vitamin A deficiency.
  - Treatment consists of soaking, aggressive scrubbing, and using keratolytic lotions (such as urea or lactic acid lotions). Although topical retinoids sound as if they should work, they are surprisingly ineffective.
- **Keratosis pilaris atrophicans:** Also known as ulerythema ophryogenes, features plugged follicles on cheeks and eyebrows, leading to alopecia and follicular atrophoderma.
- **Keratosis spinulosa:** Also known as lichen spinulosus, consists of localized grouped white plugs usually on trunk of children.
- **Keratosis follicularis spinulosa decalvans:** MIM code 308800; uncommon disorder with X-linked recessive inheritance; features follicular keratoses on exposed areas along with scarring alopecia, palmoplantar keratoderma, photophobia, corneal dystrophy, and often atopic dermatitis.

- **Other disorders:** Both Darier disease (see below) and pityriasis rubra pilaris (p. 278) can start with follicular keratosis.

Darier Disease

- **MIM code:** 124200.
- **Definition:** Common genodermatosis with primarily follicular keratoses, distinctive histology, and autosomal dominant inheritance.
- **Epidemiology:** One of the most common genodermatoses; prevalence 1:30 000; little interference with fertility, so larger pedigrees common.
- **Pathogenesis:** Darier disease provided one of the first surprises in the search for genes causing dermatoses. The defect is in a calcium-channel regulating gene *ATP-2A2* at 12q24.1 which codes for SERCA2, an ATPase isoform. The disturbance in calcium homeostasis is thought to interfere with desmosome stability.
- **Clinical features:**
  - Onset of skin disease usually around puberty. Multiple tiny (2–4 mm) rough brown papules; most common in seborrheic areas (midchest, face, retroauricular) (Fig. 21.**5**). Sometimes provoked by light.
  - Also abnormal digital hieroglyphics, tiny palmoplantar pits, and longitudinal white or red nail stripes.
  - Occasionally painful palmoplantar keratoderma with bullae.
  - Cobblestone papules seen on palate, but also on pharyngeal, genital, and rectal mucosa.
  - *Acrokeratosis verruciformis Hopf:* Flat papules on the sides and backs of hands; genetic studies have shown same mutation, indicating that this is simply one manifestation of Darier disease and not a separate entity, although it often appears without other stigmata.
  - Increased likelihood of generalized infections with herpes and vaccinia viruses.
- **Histology:** Distinctive combination of acantholysis and individual cell keratinization, producing *corps ronds* (cells with peculiar keratin inclusions) and *grains* (parakeratotic material).
- **Diagnostic approach:** Clinical examination, biopsy; family history often positive.
- **Differential diagnosis:** Well-developed cases distinctive; early lesions confused with other follicular keratoses. Same histologic picture can be seen in Grover disease (see below) as well as epidermal nevi and acquired acanthomas, so clinicopathologic correlation required.
- **Therapy:** Acitretin 25–50 mg daily is probably the best treatment; should be used until disease under control and then stopped because of side effects. Tendency to secondary infections; some patients improve dramatically with antibiotics. Drastic approach is excision of severely affected area, such as soles, with skin grafting; donor dominance persists for months to years. Topical retinoids and keratolytics disappointing at best.

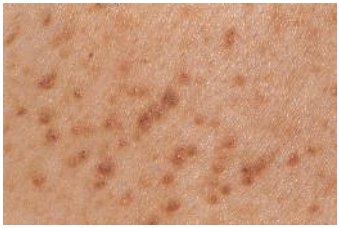


Fig. 21.**5** · Darier disease: keratotic brown papules.

Hailey–Hailey Disease

- **Synonym:** Familial benign chronic pemphigus.
- **MIM code:** 169600.
- **Definition:** Genodermatosis with frequent weeping dermatitis flexural patches; autosomal dominant inheritance.
- **Pathogenesis:** Mutation in *ATP2C1*, another calcium pump gene, at 3q21-q24; analogous to pathophysiology of Darier disease.
- **Clinical features:** Intertriginous areas are involved. Highly typical superficial erosions with fissures and splits; described as resembling "dusty road drying out after a rainstorm" (Fig. 21.**6**). Often foul-smelling. Occasionally nail streaks. Also predisposed to herpes and vaccinia infections, but less so than Darier disease.

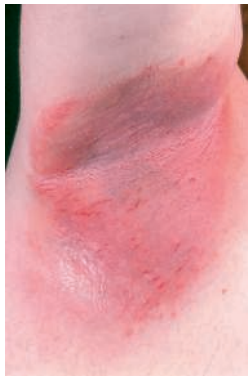


Fig. 21.**6** · Hailey–Hailey disease.

- **Histology:** Prominent acantholysis with little dyskeratosis ("collapsing brick wall") and frequent inflammation. Despite its alternative name, Hailey–Hailey disease has nothing to do with autoimmune pemphigus and immunofluorescence is negative.
- **Diagnostic approach:** Clinical examination, biopsy; family history often positive.
- **Differential diagnosis:** Usually misdiagnosed at first as candidiasis or intertrigo. In some instances, can appear very similar to Darier disease. Pemphigus vegetans also involves flexures but has thicker (vegetating) lesions.
- **Therapy:** Systemic acitretin is best choice but not as reliably effective as in Darier disease. Methotrexate 5–15 mg weekly can be tried. Both topical disinfectants and systemic antibiotics useful. Surgery just as in Darier disease, but easier to do, as worst areas are usually flexural areas which can be excised and covered with split-thickness graft.

Transient Acantholytic Dermatosis

- **Synonym:** Grover disease.
- **Definition:** Acquired intensely pruritic papular eruption with same histology as Darier disease.
- **Epidemiology:** Most patients are older men; often more severe in winter months with drier environment.

- **Pathogenesis:** Unknown.
- **Clinical features:** 1–2 mm pruritic red papules, sometimes juicy, occasionally with tiny vesicle; favor the trunk.
- **Histology:** Usually very similar to Darier disease; in other cases may have primarily acantholysis and resemble Hailey–Hailey disease or pemphigus foliaceus; immunofluorescence always negative.
- **Diagnostic approach:** Clinical examination, biopsy.
- **Differential diagnosis:** Folliculitis, dermatitis herpetiformis, prurigo simplex subacuta, scabies.
- **Therapy:** Phototherapy (PUVA or narrow band 311 nm) is most effective; also topical antipruritic agents. If drying seems to be a factor, then aggressive lubrication. Topical corticosteroids under occlusion briefly may help with itch..

Porokeratosis

- **Definition:** Group of probably unrelated disorders with same distinctive histologic appearance featuring cornoid lamellae.
- **Classification:**
  - *Porokeratosis Mibelli:*
    - Erythematous hyperkeratotic to atrophic plagues with distinctive border; usually one or few plaques.
    - More common in immunosuppressed patients, suggesting some may be viral.
    - Small risk of development of squamous cell carcinoma.
  - *Linear porokeratosis:* Probably variant of linear epidermal nevus with histology of porokeratosis, as grouped smaller lesions follow Blaschko lines.
  - *Disseminated superficial actinic porokeratosis (DSAP):* Multiple 1–2 cm atrophic patches with distinctive border on arms or legs in older individuals with sun damage; sometimes provokes by light (Fig. 21.**7**).

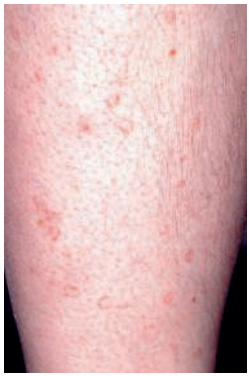


Fig. 21.**7** · Disseminated superficial actinic porokeratosis.

  - *Porokeratosis punctata palmoplantaris:* Multiple 1–2 mm papules on palms and soles; autosomal dominant inheritance. Columnar parakeratosis.
  - *Porokeratosis palmaris et plantaris disseminata:* Usually starts with multiple punctate lesions on palms and soles with onset in adolescence. Similar to porokeratosis punctata palmoplantaris but may also involve rest of body. Le-

sions fancifully compared to spines on a music box wheel. May have facial sebaceous hyperplasia as well.
- *Unilateral porokeratosis:* Lesions restricted to one side of body.

► **Histology:** The border should be biopsied, ideally with a small spindle-shaped piece of tissue with a long axis perpendicular to the prominent rim. This makes it easiest to identify the pathognomonic *cornoid lamella*—a focal area of disruption of the granular layer with a column of parakeratotic cells in the stratum corneum.
► **Diagnostic approach:** Clinical examination, biopsy.
► **Differential diagnosis:** Multiple lesions can be mistaken for psoriasis, lupus erythematosus, pityriasis rubra pilaris, or verrucous lichen planus. Solitary lesions often misinterpreted as tinea, warts, or actinic keratoses. The palmoplantar lesions are hard to diagnosis clinically; one can consider nevoid basal cell carcinoma syndrome, Cowden syndrome, punctate palmoplantar keratoderma, arsenical keratoses, and warts; only the biopsy provides the answer.
► **Therapy:** Cryotherapy or other destructive measures for limited lesions; otherwise, consider acitretin or PUVA (except for DSAP). Regular use of sunscreens; monitor for possible development of squamous cell carcinoma.

Erythrokeratodermia

► **Definition:** Group of uncommon disorders with both erythroderma and keratotic lesions.
► **Erythrokeratodermia variabilis (Mendes da Costa):**
- MIM code: 133200.
- Autosomal dominant inheritance; involves mutation in either connexin 30.3 or 31, both located at 1p35.1. The connexins are involved in gap junctions between cells.
- Two distinct types of lesions:
  - Relatively stable psoriasiform with bizarre configurations, usually on extremities.
  - Rapidly changing erythematous macules and patches on trunk.
  - Relation between two types of lesions unexplained.
- No tendency to improvement.

► **Erythrokeratodermia symmetrica progressiva (Gottron):**
- MIM code: 602036.
- Autosomal dominant inheritance. Mutation in loricrin gene at 1q21; loricrin is major component of cornified cell envelope.
- Psoriasiform plaques on backs of hands and feet, spreading to shins; sometimes compared to stockings and gloves; quite stable but can involve other areas.

► **Histology:** Not diagnostic in either case; marked hyperkeratosis with acanthosis and parakeratosis in the case of the Gottron type.
► **Diagnostic approach:** Clinical examination, biopsy; family history often positive.
► **Differential diagnosis:** Confused with psoriasis or pityriasis rubra pilaris.
► **Therapy:** Systemic acitretin; otherwise keratolytics and other psoriatic regimens.

Hyperkeratosis Lenticularis Perstans

► **Synonym:** Flegel disease.
► **MIM code:** 144150.
► Rare disorder with flat keratotic papules on the extensor surfaces of the feet and hands. Histology shows focal hyperkeratosis with dermal lichenoid inflammatory infiltrate. Differential diagnostic considerations include acrokeratosis verruciformis and acrokeratoelastoidosis. Treatment difficult; try keratolytics or cryotherapy.

21.4 Palmoplantar Keratoderma

Overview

- **Definition:** Diffuse or localized hyperkeratotic lesions on palms and soles; either hereditary or acquired. Tylosis means callus, but is used as a synonym.
- **Diagnostic approach:** Clinical examination (diffuse, localized, punctate; transgrediens or not (extending away from palms and soles); history (congenital or acquired); biopsy (epidermolytic hyperkeratosis or not); associated findings.
- **Classification:**
  - *Hereditary palmoplantar keratoderma:*
    - Diffuse nontransgrediens palmoplantar keratoderma.
    - Diffuse transgrediens palmoplantar keratoderma.
    - Localized and punctate palmoplantar keratoderma.
  - *Hereditary palmoplantar keratoderma associated with other syndromes:*
    - Erythrokeratodermia.
    - Bullous congenital ichthyosiform erythroderma.
    - Some forms of epidermolysis bullosa (EB), especially EB simplex Dowling–Meara.
    - Hidrotic ectodermal dysplasia.
    - Darier disease.
  - *Acquired palmoplantar keratoderma:*
    - Paraneoplastic marker.
    - Pregnancy, menopause.
    - Many forms of dermatitis, secondary syphilis, tinea manuum, crusted scabies, psoriasis, hyperkeratotic lichen planus, Sézary syndrome.
    - Clavi, calluses.
    - Myxedema, lymphedema with reactive verrucous changes.
- **Therapy:** All keratodermas are treated the same. Mechanical debridement (pumice stone, sanding) following by keratolytic ointments; vitamin D analogues useful; retinoids not.

Diffuse Nontransgrediens Palmoplantar Keratoderma

- **Diffuse palmoplantar keratoderma (Vörner–Unna–Thost):**
  - *Synonym:* Epidermolytic palmoplantar keratoderma (EPPK).
  - *MIM code:* 144200.
  - *Pathogenesis:* Most common palmoplantar keratoderma; usually mutation in keratin 9 gene on 17q12–21; autosomal dominant inheritance.
  - *Clinical features:* Diffuse palmoplantar hyperkeratosis with sharp border; often fissures and rhagades (Fig. 21.**8a**).
  - *Histology*: Epidermis shows epidermolytic hyperkeratosis; the original idea that Unna–Thost keratoderma was separate and had no epidermolytic hyperkeratosis was mistaken. Often multiple biopsies needed.
- **Diffuse nonepidermolytic palmoplantar keratoderma:** Several rare syndromes exist that are clinically similar to Vörner but do not show epidermolytic hyperkeratosis. They likely represent other keratin mutations.
- **Tylosis with esophageal cancer:**
  - *Synonym:* Howel–Evans syndrome.
  - *MIM code:* 148500.
  - *Pathogenesis:* Rare disorder; autosomal dominant inheritance; gene defect located at 17q25 but gene product unknown.

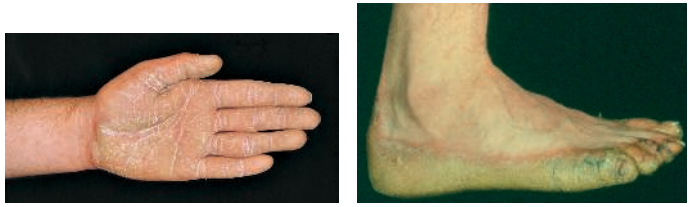


Fig. 21.**8** · Diffuse palmoplantar keratoderma. **a** Vörner–Unna–Thost type (nontransgrediens). **b** Mal de Meleda (transgrediens).

- *Clinical features:* Diffuse palmoplantar keratoderma appears in childhood along with benign leukokeratosis; affected patients have almost 100% risk of squamous cell carcinoma of the esophagus as adults (sometimes five decades after developing keratoderma).
- *Differential diagnosis:* Acquired palmoplantar keratoderma may accompany a variety of carcinomas; it appears in temporal connection with the tumor.

► **Naxos syndrome:**
- *MIM code:* 601214.
- Located at 17q21; gene for plakoglobin.
- Combination of cardiac myopathy with arhythmia, palmoplantar keratoderma, and woolly hair.
- Autosomal recessive inheritance; reported on Greek island of Naxos.

► **Schöpf–Schulz–Passarge syndrome:**
- *MIM code:* 224750.
- Genetic basis unclear; autosomal recessive inheritance.
- Palmoplantar keratoderma, apocrine hidrocystomas of the eyelids, hypodontia, hypotrichosis.

► **Olmsted syndrome:**
- Rare syndrome; genetic basis not understood.
- Combination of severe mutilating palmoplantar keratoderma and periorificial plaques (perioral, then later genital).

Diffuse Transgrediens Palmoplantar Keratoderma

► **Mal de Meleda:**
- *MIM code:* 248300.
- *Pathogenesis:* Autosomal dominant inheritance. Initially described among residents of the Adriatic island of Meleda. Mutation in *SLURP1* gene at 8qter, a transmembrane signaling protein.
- *Clinical features:*
  - Keratoderma with peripheral erythema that frequently extends onto dorsal aspects of hands and feet (Fig. 21.**8 b**).
  - Associated subungual hyperkeratosis, hyperhidrosis, nail dystrophy, and shortened digits.

► **Papillon–Lefèvre syndrome:**
- *Synonym:* Palmoplantar keratoderma with periodontitis.
- *MIM code:* 245000.
- *Pathogenesis:* Inherited in autosomal recessive fashion; mutation in cathepsin C gene (*CTSC*) at 11q14.1-q14.3; essential for neutrophil function.

- *Clinical features:* Severe periodontal disease, palmoplantar keratoderma and psoriasiform plaques on knees and elbows.
- *Haim–Munk syndrome* (MIM code 245010) is mutation in same gene but with a leukocyte adhesion defect in addition to the mucocutaneous findings.
- *Therapy:* Acitretin helps on occasion.

► **Vohwinkel syndrome:**
- *Synonym:* Mutilating palmoplantar keratoderma.
- *Pathogenesis:* Two different mutations produce similar clinical picture:
  - MIM code 124500; 13q11-q12 ; mutation in *GJB2* gene coding for connexin 26; autosomal dominant inheritance.
  - MIM code 604117; 1q21; mutation in loricrin (part of cornified envelope); autosomal dominant inheritance (also known as Camisa syndrome).
- *Clinical features:* Diffuse palmoplantar keratoderma plus pseudoainhum (constricting bands of digits) and peculiar starfish-pattern hyperkeratoses over flexures; those with loricrin mutation have ichthyosis; those with connexin mutation, deafness.

► **Sclerotylosis:**
- *Synonym:* Huriez syndrome.
- *MIM code:* 181600.
- *Pathogenesis:* Gene defect located at 4q23 but not further characterized; autosomal dominant inheritance.
- *Clinical features:* Diffuse palmoplantar keratoderma with atrophy, nail dystrophy, and increased incidence of cutaneous squamous cell carcinomas.

Localized and Punctate Palmoplantar Keratoderma

► **Punctate palmoplantar keratoderma:**
- *Synonym:* Buschke–Fischer–Brauer palmoplantar syndrome.
- *MIM code:* 148600.
- *Pathogenesis:* Etiology unclear; autosomal dominant inheritance.
- *Clinical features:* Many small (2–8 mm) keratotic lesions; coalesce over pressure points; onset in adolescence.
- *Differential diagnosis:*
  - Punctate lesions of the palmoplantar creases are common in blacks; probably not related to the diffuse form.
  - Often misdiagnosed as warts and incorrectly treated.

► **Porokeratosis punctata palmaris et plantaris** (p. 343).

► **Richner–Hanhart syndrome:**
- *Synonyms:* Tyrosine transaminase deficiency, tyrosinemia type II.
- *MIM code:* 276660.
- *Pathogenesis:* Gene located at 16q22.1-q22.3; codes for tyrosine transaminase.
- *Clinical features:* Painful punctate palmoplantar keratoderma, as well as corneal ulcers.
- *Therapy:* Low phenylalanine-low tyrosine diet.

► **Striate palmoplantar keratoderma:**
- *Synonym:* Brunauer–Fohs–Siemens syndrome.
- *Pathogenesis:* Three mutations identified, all with autosomal dominant inheritance:
  - MIM code 148700; 18 q12.1-q12.2; desmoglein 1.
  - MIM code 125647; 6p21; desmoplakin (also associated with woolly hair and cardiac myopathy as autosomal recessive variant).
  - MIM code 139350; 12q11-q12; keratin 1.

- *Clinical features:* Linear hyperkeratotic plaques run the length of the fingers and onto the palm; can be very disabling.

► **Hereditary painful callosities:**
- *MIM code:* 114140.
- Limited to feet, even in manual laborers.
- Histology shows epidermolytic hyperkeratosis, but not further clarified.

► **Focal palmoplantar and marginal gingival hyperkeratosis:**
- *MIM code:* 148730.
- Focal hyperkeratotic lesions both on palms and soles and mouth, especially marginal gingiva.

► **Acrokeratoelastoidosis (Costa):**
- *MIM code:* 101850.
- *Pathogenesis*: Unclear; both autosomal dominant inheritance and solar damage have been implicated.
- *Clinical features:* Distinct; white-yellow coalescent papules and plaques limited to lateral aspects of palms and soles.
- *Histology*: Marked damage to elastic fibers.
- *Differential diagnosis:* Punctate porokeratosis and *focal acral hyperkeratosis*, which is clinically identical but shows no elastic fiber defects on biopsy.

21.5 Linear or Striped Lesions

The usual explanation for linear or striped lesions is *mosaicism*—a common genetic phenomenon. During human development, the skin moves in a peculiar fashion to cover the growing trunk and limbs, producing a pattern known as *Blaschko lines*. Any time there is a mutation in a somatic gene during the early stages of development, linear lesions are produced, whether it be epidermal nevi (mutations in keratins or other epidermal growth control genes), large pigmented nevi, or others. Every female is a mosaic, because of the process of lyonization or random inactivation of one or other X chromosome during early embryonic life. Diseases such as incontinentia pigmenti, which are inherited in an x-linked dominant manner and caused by mutations in crucial genes, are fatal to those male embryos who only express the abnormal gene, and always produce clinical mosaics in women. Other mosaic lesions often not thought of as genetic include Becker nevus and its associated syndrome, nevus spilus, and linear and whorled hypermelanosis.

Incontinentia Pigmenti (IP)

► **Synonym:** Bloch–Sulzberger disease.
► **MIM code:** 308310.
► **Definition:** Uncommon syndrome with progressive linear lesions and associated ocular, skeletal, and CNS abnormalities.
► **Pathogenesis:** Mutation in the *NEMO* gene, modulator of NFκB, at Xq28; NEMO inhibits apoptosis, so IP patients have been described as pro-apoptotic. X-linked dominant inheritance; transmission from mother to daughter; mutation is lethal in males (except for Klinefelter syndrome).

► **Clinical features:**
- *Cutaneous findings:* Four phases of lesions all following peculiar linear and streaked pattern (100%):
  - At birth, vesicular stage with numerous eosinophils and associated urticarial plaques; also peripheral blood eosinophilia (Fig. 21.**9**).
  - In infancy, warty plaques, most often acral.
  - As adults, bizarre hyperpigmentation (*Chinese letter sign*) on trunk; blue-gray to brown shades.
  - Also white atrophic scars on legs, which neither tan nor sweat.
  - About 25% have aplasia cutis congenita (see below).

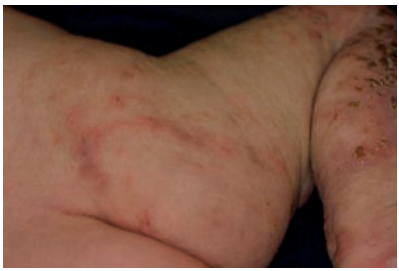


Fig. 21.**9** · Incontinentia pigmenti with linear erythematous and bullous lesions.

- *Dental anomalies* (50%): Delayed dentition, missing teeth (upper canines and premolars typically).
- *Ocular anomalies* (30%): Strabismus, optic nerve atrophy, blindness.
- *CNS anomalies* (25%): Mental retardation, delayed motor development, paraplegia.

► **Histology:** Blisters are rich in eosinophils; warty lesions show peculiar dyskeratotic keratinocytes; hyperpigmentation is result of incontinence of pigment.
► **Diagnostic approach:** Clinical examination, history of miscarriages, check mother's trunk and legs.
► **Differential diagnosis:**
- *Hypomelanosis of Ito.* Also known as IP achromians, incorrectly described as the "reverse image" of IP; white streaks on a dark normal background (p. 374).
- *Linear and whorled nevoid hypermelanosis:* Macular hyperpigmentation along Blaschko lines without underlying defects (p. 379).

► **Therapy:** Cutaneous lesions require no therapy; excellent dental and ophthalmologic care; monitor for developmental problems.

Focal Dermal Hypoplasia

► **Synonym:** Goltz syndrome.
► **MIM code:** 305600.
► **Definition:** Disorder limited almost exclusively to women, with multiple ectodermal and mesenchymal defects.
► **Pathogenesis:** Exact gene still controversial.

- **Clinical features:**
  - Linear skin lesions along Blaschko lines.
  - Areas with almost no dermis and outpouchings of fat.
  - Hypo- and hyperpigmented streaks and telangiectases.
  - Aplasia cutis congenita.
  - Periorificial papillomas.
  - Skeletal anomalies, most classic finding claw or lobster hand.
  - Dental anomalies.
  - Occasionally mental retardation.
- **Histology:** Striking finding; dermis is often only 1–2 cell layers thick, so that epidermis appears to be resting on subcutaneous fat.
- **Diagnostic approach:** Clinical examination, biopsy, radiography of long bones shows osteopathia striata (longitudinal streaks) in the metaphyses.
- **Differential diagnosis:** The individual fatty lesions can be confused with nevus lipomatosus; otherwise clinically distinctive.

Other X-linked Dominant Genodermatoses

- **MIDAS syndrome:** Combination of **mi**crophthalmia, **d**ermal **a**plasia, and **s**clerocornea.
- **Conradi–Hünermann–Happle syndrome (p. 339)**.
- **CHILD syndrome: C**ongenital **h**emidysplasia with **i**chthyosiform nevus and **l**imb **d**efects; peculiar large psoriasiform plaques, which often stop abruption at midline (p. 414).

Aplasia Cutis Congenita

- **Definition:** Congenital absence of skin and often subcutaneous tissue; may be solitary or associated with a long list of rare syndromes.
- **Pathogenesis:** Probably represents somatic mosaicism, as lines often follow Blaschko lines.
- **Clinical features:**
  - Most common presentation is punched-out ulcer on vertex of scalp (60%); 1–2 cm with erythematous base. Usually birth trauma is suspected, so documentation is crucial to avoid misunderstandings (and lawsuits). Heals with scarring and permanent alopecia.
  - Other sites include extremities and trunk; multiple lesions may be seen.
- **Diagnostic approach:** When other sites or multiple lesions present, likelihood of associated syndrome increases.
- **Therapy:** Disturbing lesions can usually be excised later in life.

Other Linear Lesions

- **Epidermal nevi** (p. 410) are also mosaics and thus usually linear. In some instances they are associated with underlying defects (epidermal nevus syndromes).
- **Lichen striatus (p. 289)**.
- **"Blaschkitis":** A number of inflammatory dermatoses (psoriasis, lichen planus, graft-versus-host disease) can follow Blaschko lines; the proposed explanation is that the patient's skin shows somatic mosaicism and only a part of the keratinocytes are susceptible to whatever triggers or modulates the dermatosis.

21.6 Ectodermal Dysplasias

Hundreds of diseases are listed as ectodermal dysplasias, defined as defects in one or more of the following structures: skin, adnexal glands, hair, nails, teeth. Many of the diseases discussed in this section qualify as ectodermal dysplasias. Only two common disorders are considered here as examples.

Anhidrotic Ectodermal Dysplasia

- **MIM codes:** 305100 (X chromosome); 224900 (autosomal recessive).
- **Definition:** Rare disorder with two causative genes both leading to defects in hair, teeth, and eccrine sweat glands.
- **Pathogenesis:** Defects in ectodysplasin binding are the problem. This member of the TNF family comes in two isoforms: EDA1, which binds to the EDAR receptor on chromosome 22a11-q13, and EDA2, which binds to XEDAR on the X chromosome.
- **Clinical features:**
  - *Classic triad:* Reduced sweating, hypotrichosis, hypo- or adontia.
  - *Typical facies* (*Popeye look*): Prominent forehead, saddle node, sunken cheeks, large ears, and thin hair. Mental retardation in 30–50%.
- **Diagnostic approach:** Clinical examination, check pedigree for consanguinity and check mother for focal areas of decreased sweating (mosaic pattern for carrier).
- **Therapy:** Supportive care; caution in hot weather because of inability to sweat.

Hidrotic Ectodermal Dysplasia

- **Synonym:** Clouston syndrome.
- **MIM code:** 129500.
- **Definition:** Disorder with defects in nails and hair, as well as palmoplantar keratoderma; autosomal dominant inheritance.
- **Pathogenesis:** Mutation in *GJB6* gene coding for connexin 30; located at 13q12.
- **Clinical features:** All patients have thickened, slowly growing yellow nails, often with paronychia. Transgrediens palmoplantar keratoderma with keratoses over the knees and elbows. Thin, easily broken hair. Teeth not involved. Normal sweating.
- **Diagnostic approach:** Clinical examination, family history usually positive.
- **Differential diagnosis:** Consider other syndromes with nail defects (p. 519).
- **Therapy:** File nails; treat keratoderma as on p. 345.

21.7 Epidermolysis Bullosa (EB)

Overview

- **Definition:** Group of disorders with mechanical defects leading to easy blistering, caused by defective structural proteins.
- **Classification:** Based on level of defect:
  - *EB simplex (epidermolytic EB):* Defects in keratins, other epidermal proteins.
  - *Junctional EB:* Defects in structures of the dermoepidermal junction.
  - *Dystrophic EB (dermolytic EB):* Defects in type VII collagen.
- **Diagnostic approach:** Clinical examination and family history can only point to possible diagnosis. Work together with specialized centers. Final diagnosis based on antigen mapping of skin biopsy and identification of genetic defect.

EB Simplex

Least disturbing form of EB; patients tend to easily develop blisters from minor mechanical trauma such as crawling on knees and elbows or (later in life) walking (Fig. 21.**10**). The first three disorders listed below all involve mutations in keratins 5 and 14, which are paired and expressed low in the epidermis, either in the basal layer or just above. All have autosomal dominant inheritance except the form associated with muscular dystrophy. In most instances, patients learn how to avoid and treat blisters and thus are able to cope well with life.

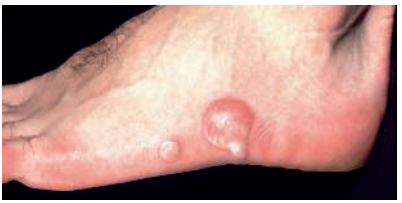


Fig. 21.**10** · Epidermolysis bullosa simplex.

- **EB simplex, Köbner type:**
  - Mutations in keratin 5 or 14.
  - Starts at birth of soon after; can appear anywhere on body.
  - No milia, scarring, or nail loss.
- **EB simplex, Weber–Cockayne:**
  - Mutations in keratin 5 or 14.
  - Onset of signs and symptoms in first two decades.
  - Problems limited to palms and soles; worse in summer, associated with hyperhidrosis; can scar.
  - Treating hyperhidrosis sometimes helps.
- **EB herpetiformis, Dowling–Meara:**
  - Mutations in keratin 5 or 14.
  - Onset just after birth; slight mortality rate.
  - Herpetiform, sometimes hemorrhagic blisters on trunk; later palmoplantar keratoderma, nail dystrophy, mucosal erosions.
- **EB simplex with mottled hyperpigmentation:**
  - Rare disease with keratin 5 mutation, generalized blisters, heals with hypopigmentation; corneal dystrophy, mental retardation.
- **EB simplex, Ogna:**
  - Mutation in plectin 1 gene; found in Scandinavia, Germany.
  - Blisters on extremities.
- **EB simplex with muscular dystrophy:**
  - Autosomal recessive inheritance; also involves plectin 1 mutation. Plectin is found in both hemidesmosomes and muscular fibers.
- **Other EB simplex subtypes:**
  - Autosomal recessive variant; also involves keratin 14 mutation.
  - EB simplex superficialis; perhaps collagen XVII.
  - EB simplex Jonkman; palmoplantar blisters, nail dystrophy; mutation in integrin β_4.

Junctional EB

- Mutations involve proteins involved in the formation of the dermoepidermal junction; all have autosomal recessive inheritance. Tend to scar.
- **Junctional EB, Herlitz type:**
  - Mutations in different subunits of laminin 5.
  - Formerly called lethal EB, but molecular biological studies have revealed a range from mild to severe involvement. Onset at birth. Progressive form is often fatal; characterized by distinctive vegetations on nape, axillae, periorificial locations. In the localized and inverse (limited to axilla, groin) subtypes, recurrent blisters but with better outlook. Oral blisters, dental anomalies, growth retardation.
- **Generalized atrophic benign EB (GABEB) (Hinter–Wolff type):**
  - Heterogenous; mutations in collagen XVII (bullous pemphigoid antigen 2), laminin 5 or integrin β_4.
  - Onset at birth, widespread blisters; nail loss, scarring alopecia, modest mucosal involvement; often improve over time.
  - Benign only in comparison to Herlitz.
- **Other forms of junctional EB:**.
  - Associated with pyloric atresia; mutations in integrin α_6 or β_4.
  - Localized mutations in collagen XVII.

Dystrophic EB

- Most severe form; mutations in type VII collagen, the main component of the anchoring fibrils in the papillary dermis; invariable scarring, often mutilating.
- **Dominant dystrophic EB:**
  - *Hyperplastic type, Cockayne–Touraine:*
    - MIM code: 131705.
    - Onset at birth; widespread blisters, heal with scars and milia. Also form hyperkeratotic lesions.
  - *Albopapuloid type, Pasini:*
    - MIM code: 131800.
    - Onset at birth; widespread blisters heal with scars and milia; mutilation of fingers and toes.
    - White papular scars on trunk.
  - Some sources no longer divide Cockayne–Touraine and Pasini as they have considerable overlap. There are also some minor variants in this group:
    - Pretibial dominant dystrophic EB.
    - EB pruriginosa.
    - Transient bullous dermolysis of the newborn.
- **Recessive dystrophic EB, Hallopeau–Siemens:**
  - MIM code: 226500.
  - Onset at birth; widespread blisters heal with scars and milia; mutilation of fingers and toes, clinically similar to severe dominant dystrophic forms.
  - Other finings include marked mucosal involvement, dental anomalies, scarring alopecia, anemia, growth retardation.

  Note: Two disastrous complications:
    - Scarring of hands and feet leads to formation of socks and mittens, as the skin grows together over the digits enclosing them in translucent sheets (Fig. 21.**11**).
    - Greatly increased risk of squamous cell carcinoma of the skin and mucosa.

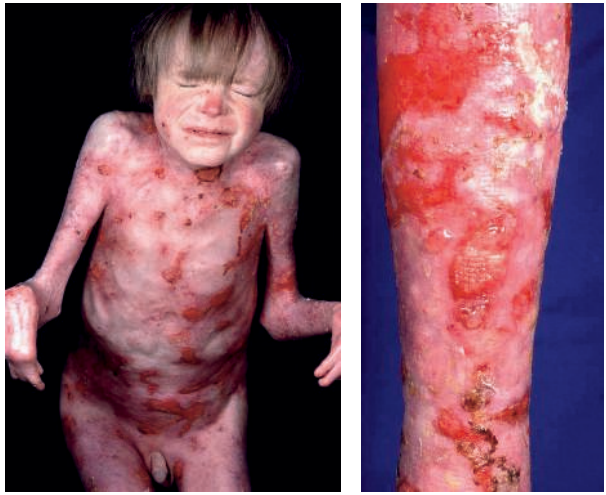


Fig. 21.**11** · **Dystrophic epidermolysis bullosa. a** With scarring and mitten formation of hands. **b** With scarring and erosions—a fertile ground for the development of squamous cell carcinomas.

Therapy

Patients with junctional and dystrophic EB are major therapeutic challenges. They are best treated in specialized centers. The only real therapy for such patients will be genetic manipulation to restore the missing proteins. In the meanwhile, perfect nursing care provided initially by experienced nurses who simultaneously teach the parents is the only approach. Modern dressings have technically made things easier, but even in developed countries, insurance companies sometimes refuse to pay the high costs associated with nursing care and bandaging material.

21.8 Diseases of Connective Tissue

Lipoid Proteinosis

- **Synonyms:** Urbach–Wiethe syndrome, hyalinosis cutis et mucosae.
- **MIM code:** 247100.
- **Definition:** Rare disease with deposits of hyaline material in skin and other tissues; autosomal recessive inheritance.
- **Epidemiology:** Uncommon, but large pedigrees exist in Sweden and South Africa, due to founder effect.
- **Pathogenesis:** Mutations in the *ECM1* (extracellular matrix protein) gene at 1q21, leading to deposition of type IV collagen and lipids; same mutation in lichen sclerosus (p. 217).

- **Clinical features:**
  - Initial finding often a hoarse voice because of vocal cord and tongue deposits.
  - Cutaneous lesions include waxy papules along edges of eyelids, which are thickened and have often lost their lashes.
  - Papules and nodule on face and trunk; sometimes plaques resembling morphea as well as hyperkeratoses over knees and elbows.
  - Seizures not uncommon.
- **Histology:** Deposits of PAS-positive amorphous material in the upper dermis.
- **Diagnostic approach:** Clinical examination, family history, biopsy.
- **Differential diagnosis:** Resembles erythropoietic protoporphyria but no photosensitivity and negative porphyrin studies.
- **Therapy:** Disturbing deposits can be removed from vocal cords; superficial destructive measures sometimes help skin lesions.

Ehlers–Danlos Syndrome

- **Definition:** Group of genetic disorders of collagen synthesis; see classification in Table 21.**1**.

Table 21.1 · **Classification of Ehlers–Danlos syndrome**

Type	Old code	Clinical findings	Inheritance	Defective protein
Classical	I, II	Hyperextensible skin, easy bruising, gaping scars, joint hypermobility, prematurity	AD	Type V collagen, tenascin
Hypermobility	III	Joint hypermobility, few skin findings	AD	Unknown
Arterial	IV	Thin skin with prominent veins, easy bruising, small joint hypermobility; risk of rupture of arteries, uterus, or bowel	AD	Type III collagen
Kyphoscoliosis	VI	Intraocular bleeding, severe scoliosis, marked skin and joint involvement	AR	Lysyl hydroxylase
Arthrochalasis	VIIA, VIIB	Marked joint involvement with subluxations, scoliosis, minimal skin involvement, growth retardation	AD	Type I collagen
Dermatosparaxis	VIIC	Marked skin fragility, bruising	AR	Procollagen-*N*-peptidase
Other	V, VIII, IX, X	See text		

AD = autosomal dominant; AR = autosomal recessive.

- **Epidemiology:** Incidence 1:5000.
- **Pathogenesis:** Collagen synthesis is complex, as collagen fibers consist of 3 chains that must be manufactured, modified, and combined. There are at least 25 different kinds of collagen. The situation is further complicated by the interactions between collagens, elastin, and the extracellular matrix. In Ehlers–Danlos syndrome, the defects are either in collagen or in the enzymes needed to process it.
- **Clinical features:**
  - The features of classic Ehlers–Danlos syndrome are hyperextensible skin, easy bruising, gaping thin scars, and joint hypermobility. Hematomas are common and may heal as fibrotic pseudotumors. Patients with other varieties of Ehlers–Danlos syndrome have distinguishing features, such as scoliosis or growth retardation, which usually allow them to be identified quickly.
  - Patients with classic Ehlers–Danlos syndrome are at risk for premature births and should be carefully monitored.
  - The only form associated with a shortened life span is arterial or type IV Ehlers–Danlos syndrome with mutations in type III collagen. These patients have thin skin so that the vessels and sebaceous glands are easily seen; the yellow sebaceous glands are often mistaken for the chicken skin of pseudoxanthoma elasticum (see below). They are at risk of fatal ruptures of arteries, uterus, or gastrointestinal tract.
  - The older groups of type V (X-linked), type VIII (periodontal), type X (fibrinonectin), and type XI (hypermobile large joints) are extremely rare and have not been clearly characterized. Old type X is now classified as a form of cutis laxa (see below).
- **Diagnostic approach:** Based on clinical examination and then detailed genetic evaluation. Histology is of no benefit; recent work has shown that the old clinical classification was often wrong.
- **Differential diagnosis:** Often patients with hypermobile joints are identified, for example among ballet dancers, gymnasts, or circus performers. In many instances, these individuals have no other defects and in the absence of genetic testing, should not be considered as having Ehlers–Danlos syndrome.
- **Therapy:** Avoid trauma, warn surgeons of need for meticulous suture work, monitoring during pregnancy, genetic counseling.

Marfan Syndrome

- **MIM code:** 305600.
- **Definition:** Disorder with defect in fibrillin leading to skeletal, cardiac, ocular, and cutaneous abnormalities; autosomal dominant inheritance.
- **Epidemiology:** Incidence 1:75000; occasionally identified unexpectedly in tall athletes following cardiac problems.
- **Pathogenesis:** Defect in fibrillin 1, a major component of elastic fibers.
- **Clinical features:**
  - *Skeletal*: Arachnodactyly, taller than average, arm span often greater than height, hyperextensible joints (easily injured), pectus excavatum, pes valgus. Characteristic elongated facies.
  - *Ocular*: Ectopia lentis (50–70%), myopia, heterochromic irises, retinal detachment.
  - *Cardiac*: Aortic valve insufficiency, aortic aneurysms, aortic rupture in first three decades is main threat to survival.
  - *Skin:* Many problems, but all minor; striae, elastosis perforans serpiginosa.
- **Diagnostic approach:** Cardiologic and ophthalmologic examination; genetic studies.

- **Differential diagnosis:** Congenital contractural arachnodactyly is similar but caused by mutation in fibrillin 2. Patients with MEN2B and homocystinuria are often described as marfanoid.
- **Therapy:** Monitoring of ocular and cardiac status; β-blockers and prompt surgery with aortic graft.

Cutis Laxa

- **Definition:** Group of disorders with defective elastic fibers leading to characteristic skin changes, as well as cardiac and pulmonary disorders.
- **Classification:** There are three types of inherited cutis laxa as well as acquired types:
  - *Autosomal recessive cutis laxa* (MIM code 219100): mutation in fibulin 5 gene at 14q32.1. Fibulin 5 is an elastic binding protein found on the surface of elastic fibers; severe systemic and cutaneous manifestations.
  - *Autosomal dominant cutis laxa* (MIM code 123700); mutations in either elastin gene at 7q11.2 or fibulin 5; primarily cutaneous manifestations.
  - *X-linked recessive cutis laxa* (MIM code 304150; formerly type IX Ehlers–Danlos syndrome or occipital horn disease); mutation in *ATP7A* gene coding for Cu^{2+} transport protein, also involved in Menkes syndrome; minimal skin changes.
  - *Acquired cutis laxa:* Very rare, may follows inflammatory dermatoses and be associated with monoclonal gammopathies; sometimes evidence for antibodies against elastic fibers.
  - *Penicillamine-induced cutis laxa:* Complication of treatment with long-term penicillamine for Wilson syndrome or cystinuria.
- **Clinical features:**
  - Unflatteringly described as "basset hound look." Patients have droopy skin, making them appear far older than their chronological age. Often ectropion.
  - Systemic problems include aortic dilation, pulmonary emphysema, pulmonary artery stenosis, and a tendency to multiple hernia and diverticula.
- **Histology:** Biopsy when stained for elastic fibers shows marked destruction or absence of these structural elements throughout the skin.
- **Diagnostic approach:** Clinical examination, biopsy.
- **Differential diagnosis:** Nothing else really looks like cutis laxa. *Mid-dermal elastolysis* is an acquired disease with fine wrinkling of the skin and loss of elastic fibers in the mid-dermis.
- **Therapy:** Monitor cardiac and pulmonary status; be alert to gastrointestinal complications; skin can be helped somewhat by cosmetic surgery as progression continues.

Anetoderma

- **Synonym:** Dermatitis maculosa atrophicans.
- **Definition:** Disorder with focal loss of dermal elastic fibers.
- **Pathogenesis:** Anetoderma is secondary to inflammation and destruction of classic fibers. Sometimes it follows an obvious disorder such as syphilis, lymphoma, or acne. More often, the initial disorder is unclear and the disease is subdivided into three types based on apparent precursor stage:
  - *Jadassohn type:* Initially erythematous lesions that later fade.
  - *Pellizari type:* Initially urticarial lesions.
  - *Schweninger–Buzzi type:* Anetoderma lesions develop without a visible precursor.

- **Clinical features:** The hallmark lesion is a 5–20 mm atrophic area which when palpated almost resembles a hernia, so that one can push the tip of the little finger into the depression. Lesions often hypopigmented.
- **Histology:** Normal epidermis, loss of elastin in dermis.
- **Diagnostic approach:** Clinical examination, often wise to take biopsy as ellipse with long axis including both normal and abnormal skin.
- **Differential diagnosis:**
  - White depressed lesions: morphea, lichen sclerosus et atrophicus, scars.
  - Histologic loss of elastin:
    - Acquired cutis laxa (clinically not macular).
    - Granulomatous slack skin (granulomatous inflammation, T-cell lymphoma).
- **Therapy:** Nothing good; disturbing individual lesions can be excised.

Pseudoxanthoma Elasticum

- **Definition:** Rare genodermatosis with calcification of elastic fibers in skin, eyes, and cardiovascular system.
- **Epidemiology:** Incidence 1:160 000.
- **Pathogenesis:** Inheritance usually autosomal recessive (MIM code 264800), but rarely and controversially reported as autosomal dominant. Mutation in *ABCC6* gene, which codes MRP6, a transporter protein primarily expressed in kidneys and liver, not skin and eyes. The working hypothesis is that it is needed to break down substances that damage elastin; when it fails to function, elastic fiber damage occurs. Pseudoxanthoma elasticum is also associated with thalassemia and sickle cell anemia, as well as amyloid elastosis and chronic renal failure. Penicillamine, L-tryptophan, and saltpeter can cause cutaneous pseudoxanthoma elasticum, but not systemic disease.
- **Clinical features:** Two main clinical features and confirmatory histology required for diagnosis:
  - *Cutaneous lesions:* 1–5 mm yellow flat-topped papules, resembling xanthomas, coalesce to produce patches in the flexural areas (neck, antecubital and popliteal fossae, axillae, groin). Skin in these areas folded and stiff. Occasionally periumbilical involvement. Sometimes discharge of chalky material from crusted lesions. Often elastosis perforans serpiginosa.
  - *Angioid streaks:* Classic retinal changes seen in 99% of patients; red-orange streaks reflecting tears in Bruch membrane. Also seen in sickle cell anemia, idiopathic thrombocytopenic purpura, acromegaly, some forms of Ehlers –Danlos syndrome, lead poisoning, Paget disease of bone.
  - Involvement of the ocular vessels leads to leakage and hemorrhage with resultant neovascularization, scarring. and visual loss. Even minor trauma to the orbit accelerates the process.
  - Involvement of medium-sized arteries in the limbs causes claudication; cardiac involvement leads to early myocardial infarcts; also hypertension and involvement of gastrointestinal and articular vessels.
- **Histology:** Twisted disrupted basophilic elastic fibers; von Kossa stain reveals marked calcification. On occasion, the calcified elastic fibers are discharged through defects in the epidermis (*perforating pseudoxanthoma elasticum*).
- **Diagnostic approach:** Clinical examination, consultation with ophthalmology and vascular surgery, skin biopsy usually most accessible. If pseudoxanthoma elasticum is considered but there are no skin findings, biopsy of a scar may reveal the same histologic changes in elastic fibers.
- **Differential diagnosis:** The neck changes may be confused with the thin skin and prominent sebaceous glands of type IV Ehlers–Danlos syndrome. Otherwise clini-

cally distinct. Perforating pseudoxanthoma elasticum is usually periumbilical, often in multiparous black patients or renal dialysis patients, and may be seen without any other stigmata of the disease.

- **Therapy:** No treatment for skin lesions; avoid trauma (contact sports) to reduce risk of ocular injury and hemorrhage; careful monitoring for cardiovascular disease.

21.9 Perforating Dermatoses

The concept of perforating dermatoses is fascinating but confusing. The idea that the skin can discharge undesirable dermal accumulations such as damaged collagen or elastic fibers, or any calcified tissues, through the epidermis seems logical. On the other hand, the idea that keratin can penetrate into the dermis in the absence of trauma is hard to fathom. Dermatologists have long memorized lists of perforating dermatoses; we consider the phenomenon to be more limited, as shown in Table 21.**2**.

Table 21.2 · **Perforating dermatoses**

Diseases with unquestioned perforation	Elastosis perforans serpiginosa Perforating pseudoxanthoma elasticum (see above) Perforating granuloma annulare (p. 292) All forms of cutaneous calcification
Diseases with folliculitis and/or epidermal defects	Perforating disease of renal dialysis (p. 330) and its variants: Perforating folliculitis Kyrle disease Reactive perforating collagenosis (p. 360)

Elastosis Perforans Serpiginosa

- **MIM code:** 130100.
- **Definition:** Dermatosis in which damaged elastic fibers are eliminated through the epidermis.
- **Pathogenesis:** Most patients have connective tissue defect (pseudoxanthoma elasticum, Marfan syndrome, Ehlers–Danlos syndrome) or Down syndrome. Also occurs in those taking penicillamine for Wilson disease; here different pattern to elastic fibers (*bramble bush branching*). Also occurs sporadically but most likely from fruste of pseudoxanthoma elasticum.
- **Clinical features:** Usually appears in adolescence; small delled papules arranged in a linear, annular or serpiginous pattern; usually located on neck, nape, or shoulders.
- **Histology:** Epidermal hyperkeratosis; channels through epidermis containing damaged elastic fibers, which also accumulate in the dermis.
- **Diagnostic approach:** Clinical examination, biopsy.
- **Differential diagnosis:** Porokeratosis of Mibelli, perforating granuloma annulare, perforating pseudoxanthoma elasticum.
- **Therapy:** Curettage or cryotherapy may help to flatten lesions; if small, excise.

Reactive Perforating Collagenosis

- **Definition:** Disease in which the spontaneous elimination of defect collagen occurs.
- **Pathogenesis:** Both inherited and familial forms have been identified; no genetic defect is known. We believe this disease does not exist, but is simply the result of many types of epidermal damage exposing the dermis. The two most recent papers in Germany have identified exuberant curettage of seborrheic keratoses and excessive use of keratolytics as possible causes. If the familial form exists, it features crusted lesions out of proportion to identifiable trauma.
- **Clinical features:** Crusted, inflamed papules and nodules, usually on the extremities. In some patients, there is so much crusting that the term *verrucous perforating collagenoma* is employed. Usually nearby scars from previous lesions.
- **Histology:** Epidermal defect; inflammation; collagen fibers in exposed dermis and among debris; identified with van Gieson or other collagen stains.
- **Differential diagnosis:** Lichen simplex chronicus, prurigo nodularis; artifacts.
- **Therapy:** Topical antibiotics, occlusive dressings to eliminate further manipulation.

21.10 Poikiloderma

Overview

- **Definition:** Poikiloderma is the combination of telangiectases, hypo- and hyperpigmentation, and atrophy, producing a mottled appearance. It is present in many disorders. Often the definition is stretched to include disorders with only some of these features. Poikilos is the Greek word for varied.
- **Classification:** There is no widely accepted classification, but a useful one is presented in Table 21.**3**. Differential diagnosis listed on p. 706.

Dyskeratosis Congenita

- **Synonym:** Zinsser–Cole–Engman syndrome.
- **MIM code:** 305000.
- **Definition:** Rare syndrome with poikiloderma, nail dystrophy, and oral leukoplakia with risk of squamous cell carcinoma.
- **Pathogenesis:** X-linked recessive manner inheritance; mutation in dyskeratin at Xq28; protein involved in ribosomal function. Also even rarer forms with autosomal recessive and autosomal dominant inheritance.
- **Clinical features:**
  - Nail dystrophy is first sign, usually before age 5; by age 10, most nails lost.
  - Poikiloderma, primarily mottled hypo- and hyperpigmentation with some telangiectases, on neck and thighs (dirty neck sign).
  - Oral leukoplakia with common development of squamous cell carcinoma
  - Pancytopenia, which is the usual cause of death.
- **Diagnostic approach:** Clinical examination; limited to males.
- **Differential diagnosis:** Fanconi syndrome is similar with reticulate hyperpigmentation and pancytopenia, but has skeletal defects and at least eight different genetic types.
- **Therapy:** Monitor oral lesions for malignant change; management by hematology; may benefit from bone marrow transplantation (ironically, skin changes look just like graft-versus-host disease).

Table 21.3 · Classification of poikiloderma

Disease	Comments
Congenital poikiloderma	Syndromes dominated by poikiloderma
Rothmund–Thomsen syndrome	Cataracts, photosensitivity, acral keratoses
Dyskeratosis congenita (see below)	Dystrophic nails, leukoplakia, squamous cell carcinoma, pancytopenia
Kindler syndrome	Poikiloderma plus epidermolysis bullosa-like fragility and blisters; mutation in kindlerin gene
Poikiloderma with blisters (Brain, Braun–Falco, Marghescu)	Blisters, keratoses
Hereditary acrokeratotic poikiloderma	Acral keratoses
Hereditary sclerosing poikiloderma	Prominent acral sclerosis
Syndromes with poikilodermoid features	
Bloom syndrome	Dwarfism, photosensitivity, lymphoma, leukemia
Ataxia-telangiectasia	Neurological findings, ocular and facial telangiectases
Xeroderma pigmentosum	Photosensitivity, multiple cutaneous malignancies; in some types, mental retardation
Fanconi syndrome	Multiple genes; reticulate hyperpigmentation, pancytopenia, skeletal defects
Acquired poikiloderma	
Radiation dermatitis	The prototype!
Mycosis fungoides	Some early lesions (poikiloderma atrophicans vasculare)
Parakeratosis variegata	Variant of mycosis fungoides with papules, telangiectases, reticular pattern but no atrophy.
Chronic graft-versus-host disease	Obvious history

21.11 Neurofibromatoses

Overview

The neurofibromatoses are a group of disorders having in common the presence of cutaneous neurofibromas. The most common member of the group is classical neurofibromatosis, also known as neurofibromatosis 1 or von Recklinghausen syndrome. Neurofibromatosis 2 features bilateral acoustic neuromas; other forms may be localized or linear.

Pathogenesis

The *NF1* gene on chromosome 17 encodes neurofibromin, a tumor suppressor gene, most extensively expressed in neural and glial tissue. Its absence leads to the disturbance in the GTP/Ras signal transduction pathway. The gene responsible for NF2 is merlin or schwannomin, located on chromosome 22, which binds membrane proteins to the cytoskeleton. In both instances, loss of heterozygosity is usually responsible for the development of tumors.

Neurofibromatosis 1 (NF1)

- **MIM code:** 162200.
- **Synonym:** von Recklinghausen disease.
- **Definition:** Disorder with multiple malformations and tumors involving skin, nervous system, and skeleton; autosomal dominant inheritance.
- **Epidemiology:** Common genodermatosis; incidence 1:3000; about 50% of cases are new mutations. Male:female ratio = 1.
- **Clinical features:**
  - ***Note:*** NF1 is characterized by three pathognomonic clinical findings: café-au-lait macules, neurofibromas, Lisch nodules of the iris.
  - *Hyperpigmentation* (99%):
    - *Café-au-lait macule* (99%). Tan, irregular, sharply bordered patches, usually several centimeters in diameter (Fig. 21.**12 a**) (p. 378). Six or more café-au-lait macules > 1.5 cm in an adult are one criterion for NF1. Lesions usually present at birth or develop in first year of life.
    - Axillary freckles (*Crowe sign*): Multiple small lentigines usually in axilla or groin; appear later than café-au-lait macules.
    - Large pigmented macules overlying plexiform neurofibromas.
  - *Multiple neurofibromas* (100%):
    - Always present on skin; may also involve nerves or internal organs.
    - Well-circumscribed soft fleshy papules or nodules, millimeters to centimeters in size, either cutaneous or subcutaneous. The tumors can usually be pushed into the subcutis (*door bell* or *buttonhole sign*) (Fig. 21.**12 b**).
    - Not present at birth; start to develop in second decade, flaring with puberty and pregnancy; continue to develop throughout adult life.
    - Typically pruritic; may be tender or painful.
    - Malignant change very rare; usually in larger tumors.
  - *Lisch nodules* (95%):
    - Pigmented hamartomas on the iris that develop in early childhood (Fig. 21.**12 c**); present before 6 years of age in 30%; in 95% of adults. Asymptomatic.
    - May be seen in patients with neurofibromin mutation and no skin findings.
- **Other findings (< 50%):**
  - *Skeletal changes:*
    - Reduced body size (50%).
    - Macrocephaly, both relative and absolute (30%).
    - Kyphoscoliosis (2%): S-shaped rotation scoliosis with prominent anterior angulation; early therapy mandatory.
    - Congenital *pseudoarthrosis* (0.5–1.0%). About half of all congenital pseudarthroses are caused by NF1; usually involve tibia or radius and more common in boys. (Pseudarthrosis is a nonhealing fracture that leads to the formation of a false joint.).

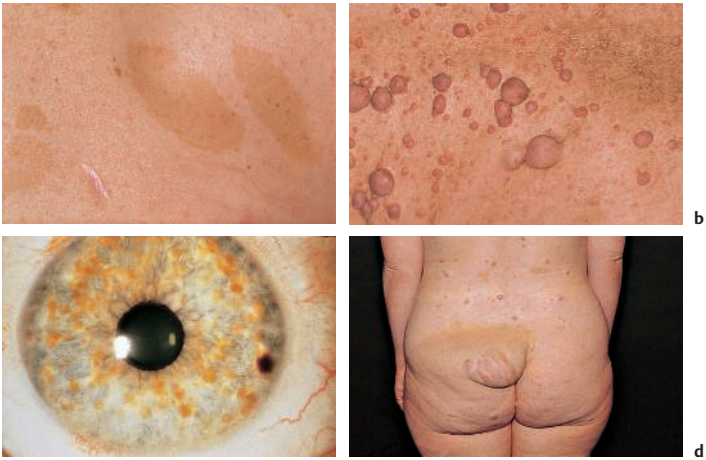


Fig. 21.**12** · **Neurofibromatosis 1. a** Café-au-lait macule. **b** Bultiple neurofibromas. **c** Lisch nodules. **d** Plexiform neurofibroma.

- *Nervous system tumors:*
  - CNS tumors (5–10%): Optic nerve glioma, astrocytoma, neurilemmoma, meningeoma, neurofibroma. Always search for optic nerve gliomas in patients with NF1.

▶ ***Note:*** No acoustic neuromas; they are a sign of NF2.

- *Other skin findings:*
  - *Pruritus:* Usually not limited to neurofibromas; can be extremely disturbing.
  - *Juvenile xanthogranuloma* (p. 469): If present, always exclude NF1; may be marker for increased risk of leukemia.
  - *Plexiform neurofibromas*: Congenital malformation consisting of masses of intersecting nerves (sack of worms on palpation); favor orbit periorbital region, nape, retropharyngeal, cervical, and mediastinal areas (Fig. 21.**12 d**). Often associated with segmental hypertrophy or large pendulous tumors; overlying skin often hyperpigmented. Risk of malignant transformation.
  - *Malignant neural tumors:* Generic name of *malignant peripheral nerve sheath tumor* probably best; features of both malignant neurofibroma and schwannoma. Most malignant neural tumors arise in NF1.
  - *Other tumors* (1–2%): Wilms tumor, rhabdomyosarcoma, leukemia (especially juvenile myelomonocytic leukemia), pheochromocytoma (always suspect if NF1 patient is hypertensive at early age).

    ▶ ***Note:*** Malignant tumors reduce life expectancy; the effect is greater in women.
  - *Mental retardation (30%):* Usually mild, trouble with speaking or reading.

► **Segmental neurofibromatosis:** Somatic mosaic; typically one segment of body, strictly respecting midline, features café-au-lait macules as well as cutaneous and systemic neurofibromas.

- **Diagnostic approach:**
  - The patient must be completely evaluated at the time of the initial diagnosis. Recommended tests include EEG, audiometry, ophthalmologic examination, CT of the skull and orbits, 24 hour urine for catecholamines and their metabolites, intelligence testing.
  - ***Note:*** Each of these tests has consequences for 5–10% of patients.
  - Later yearly evaluation to identify potential problems and insure prompt referral to other specialties.
- **Genetic counseling:**
  - *Patient with NF1:* Each child has 50% chance of having NF; both sexes at risk; 100% penetrance; no effective prenatal diagnosis because of huge size of NF gene.
  - *First-degree relatives:* Brother, sister, or child of NF patient who has no clinical signs of NF by 20th birthday has almost no risk of having an affected child.
- **Therapy:** No curative treatment. Neurofibromas that are bothersome can be excised and ablated with CO_2 laser. Ketotifen is often helpful for pruritus. Plexiform neurofibromas should be monitored for malignant change. Many systemic problems (scoliosis, hypertension) can be treated.

Neurofibromatosis 2 (NF2)

- **MIM code:** 101000.
- **Definition:** Syndrome featuring bilateral acoustic neuromas as well as other neural tumors; autosomal dominant inheritance.
- **Epidemiology:** Much less common that NF1; incidence 1:40000; also high degree of penetrance; male:female ratio = 1.
- **Clinical features:**
  - *Bilateral acoustic neuromas*: Schwann cell tumors that usually start in the vestibular nerve; signs and symptoms usually start after puberty with hearing loss (usually unilateral at first), loss of equilibrium and headache.
  - *Other neural tumors:* Schwann cell tumors of cranial and peripheral nerves, usually sensory branches. Meningiomas in skull and spinal canal. Gliomas usually low-grade; also plexiform neurofibromas.
  - *Cutaneous lesions:* About 50% have café-au-lait macules, axillary freckles, neurofibromas or sometimes cutaneous schwannomas. All skin changes less prominent than in NF1.
  - *Ophthalmologic findings:* Juvenile posterior or subcapsular cortical *cataracts* in >50%; these may appear before acoustic neuromas and are usually helpful in evaluating family members at risk. No Lisch nodules.
- **Diagnostic approach:** Dermatologists or ophthalmologists may be able to make the diagnosis first. Patients should be carefully followed for the development of acoustic neuromas. Gadolinium-enhanced MRI is considered gold standard in searching for these tumors.
- **Differential diagnosis:** Rare patients have multiple schwannomas (schwannomatosis) without clear evidence for NF2. They may be mosaics, or have other mutations.
- **Therapy:** Surgery for acoustic neuromas is not without risk; often residual disease (hearing loss or balance problems). Long-term follow-up required.

21.12 Tuberous Sclerosis

Overview

- **Synonyms:** Bourneville–Pringle disease, epiloia.
- **MIM codes:** 191100, 191092.
- **Definition:** Genodermatosis involving multiple organ systems including skin and CNS; autosomal dominant inheritance. Classical triad is adenoma sebaceum, epilepsy, and mental retardation.
- **Epidemiology:** Incidence 1:15 000; most cases are spontaneous mutations as many patients become institutionalized and do not have families.
- **Pathogenesis:** Two different genes are involved; hamartin for TSC1 and tuberin for TSC2. Both interact in the intracellular signaling pathway by encoding two subunits of a heterodimer signal transduction protein. Best example of how genetic studies identified (to everyone's surprise) two genes producing same clinical features.
- **Clinical features:**
  - *Neurological findings:*
    - Almost 100%; initially localized seizures, later generalized. The tubers are cortical and subcortical hamartomas; presumed focus for seizure activity.
    - Mental retardation (90%); severity highly variable; most common genodermatosis in institutionalized patients.
  - *Dermatologic findings:*
    - *Angiofibromas*: Present in > 90%. The facial angiofibromas are known as adenoma sebaceum—erroneously, as they are not sebaceous gland tumors but connective tissue tumors. Erythematous smooth papules favoring nasolabial fold and chin (Fig. 21.**13 a**). Often initially mistaken for acne if no other stigmata present. The subungual angiofibromas are known as Koenen tumors (Fig. 21.**13 b**). Also gingival angiofibromas.
    - *Connective tissue nevi*.
    - *Shagreen patch*: Patch usually in lumbosacral region, fancifully compared to pebbled pigskin surface of an American football (Fig. 21.**13 c**). Shagreen is a French leather with a similar appearance. Histologically proliferation of collagen.
    - *Forehead plaque:* Less common than shagreen patch; usually in more severely affected individuals; several cm erythematous elevated plaque.
    - *Hypopigmentation:*
    - *Ash-leaf macule*: Oval to pointed patches of hypopigmentation; caused by impaired transfer of melanosomes to keratinocytes. Present in infants. Best seen with Wood's light.
      - ***Note:*** Wood's light examination is indicated for all infants with unexplained seizures to exclude tuberous sclerosis.
    - Confetti-like and linear hypopigmentation less common.
  - *Visceral lesions:* CNS hamartomas (tubers), retinal hamartomas, calcified glial nodules, enamel defects, renal angiomyolipomas, cardiac rhabdomyomas; hyperostosis of inner table of skull.
- **Therapy:** No specific therapy possible. Neurologists most important in management for seizure control. Early educational testing and guidance to maximize opportunities. Angiofibromas can be treated with laser ablation or dermabrasion; tend to recur but can be re-treated.

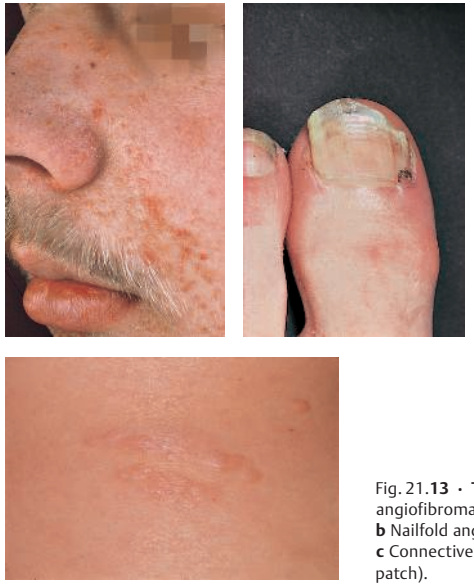


Fig. 21.**13** · **Tuberous sclerosis. a** Facial angiofibromas (adenoma sebaceum). **b** Nailfold angiofibroma (Koenen tumor). **c** Connective tissue nevus (shagreen patch).

21.13 Cancer-associated Genodermatoses

Overview

- There are a number of syndromes in which cutaneous findings provide early clues to the possible development of systemic malignancies (Table 21.**4**).

Note: Patients with multiple cutaneous tumors (adnexal or neural) should be suspected of having a genodermatosis and carefully evaluated. In addition, first-degree relatives should be checked.

Cowden Syndrome

- **Synonym:** Multiple hamartoma syndrome.
- **MIM code:** 158350.
- **Definition:** Genodermatosis with high risk of carcinoma of the breast with characteristic cutaneous findings and many associated systemic findings; autosomal dominant inheritance.
- **Epidemiology:** Very uncommon; incidence around 1:200000 in Western Europe.
- **Pathogenesis:** The involved gene is *PTEN* at 10p22–23; it plays a role in the phosphatidyl-inositol signaling pathway enhancing apoptosis; mutations in *PTEN* are seen in many disorders including juvenile polyposis, Lhermitte–Duclos syndrome (cerebellar "dysplasia"), and Bannayan–Riley–Ruvalcaba syndrome (rare cutaneous hamartoma syndrome). These disorders reflect artificially fixed points in a changing spectrum. *PTEN* is also mutated in many spontaneous carcinomas.

Table 21.4 · Cancer-associated genodermatoses

Genodermatosis	Clinical findings	Malignant tumors
Autosomal dominant inheritance		
Nevoid basal cell carcinoma syndrome	Multiple basal cell carcinomas, palmoplantar pits	Medulloblastoma, basal cell carcinoma
Birt–Hogg–Dubé syndrome	Multiple fibrofolliculomas	Renal cell carcinomas
Carney syndrome	Lentigenes, blue nevi, myxomas	Cardiac myxomas, testicular carcinomas
Cowden syndrome	Trichilemmomas, oral papules, acral fibromas	Carcinoma of breast, thyroid, GI tract
Familial melanoma-pancreatic carcinoma syndrome	Melanocytic nevi, often dysplastic	Malignant melanoma of skin and uvea, carcinoma of pancreas
Gardner syndrome	Epidermoid cysts, osteomas, fibromas, pigmented retinal epithelium	Carcinoma of colon; many others but uncommon
Howel–Evans syndrome	Palmoplantar keratoderma, leukokeratosis	Carcinoma of esophagus
Multiple leiomyomas	Multiple painful red-brown papules and nodules	Renal cell carcinoma, uterine leiomyomas
MEN1	Angiofibromas, connective tissue nevi (similar to tuberous sclerosis)	Parathyroid, pancreas, and pituitary tumors
MEN2B	Mucosal neuromas	Medullary thyroid carcinoma, pheochromocytoma
Muir–Torre syndrome	Sebaceous tumors and keratoacanthomas	GI, urogenital, and lung carcinomas; often multiple primary tumors
Neurofibromatosis 1	Café-au-lait macules, axillary freckles, neurofibromas	Malignant peripheral nerve sheath tumors, other rare soft tissue tumors, leukemia
Peutz–Jeghers syndrome	Periorificial lentigines	Intestinal, ovarian, and testicular carcinomas
Autosomal recessive inheritance		
Ataxia-telangiectasia	Ocular and facial telangiectases, severe ataxia, multiple infections	Leukemia, lymphoma, breast carcinoma, others
Bloom syndrome	Photosensitivity, telangiectases, dwarfism	Leukemia, lymphoma
Chediak–Higashi syndrome	Albinism	Lymphoma
Dyskeratosis congenita	Nail dystrophy, leukokeratosis, poikiloderma	Squamous cell carcinoma of mouth, leukemia
Fanconi anemia	Poikiloderma	Leukemia
Werner syndrome	Premature aging, growth retardation	Lymphoma

- **Clinical features:**
  - *Cutaneous findings:*
    - Multiple trichilemmomas (smooth to warty papules located primarily on face); type of adnexal tumor (p. 432).
    - Similar papules on oral mucosa, can coalesce producing cobblestone pattern.
    - Acral papules and fibromas.
    - All of these changes are likely part of a spectrum—not distinct lesions. Highly variable histology.
  - *Systemic findings:*
    - Macrocephaly, mild mental retardation, cerebellar changes (*Lhermitte–Duclos syndrome*).
    - *Gastrointestinal polyposis*: Hamartomatous, very low risk of malignant change.
    - *Breasts*: More than 75% of female patients have fibrocytic changes with at least 25% lifetime risk of carcinoma. Risk also increased in male patients.
    - *Thyroid gland*: 50% have adenomas or multinodular goiters; 3–10% risk of thyroid carcinoma.
- **Therapy:** Prophylactic mastectomy often recommended; otherwise close monitoring of breasts and thyroid gland, as well as colonoscopic monitoring.

Gardner Syndrome

- **Synonym:** Gardner syndrome is one manifestation of the familial polyposis syndrome.
- **MIM code:** 175100.
- **Definition:** Genodermatosis with a very high risk of carcinoma of the colon, as well as multisystem involvement; autosomal dominant inheritance.
- **Epidemiology:** Incidence of 1:15 000 in Holland; 25% new mutations.
- **Pathogenesis:** Mutations in *APC* (adenomatous polyposis of colon) gene, which is tumor suppressor gene controlling β-catenin.
- **Clinical features:**
  - *Skin:* Multiple epidermoid cysts (p. 407), sometimes with histological features of pilomatricomas (p. 432), favoring head and neck region. Sometimes massive. Usually appear in childhood. Also other soft tissue tumors, such as fibromas and lipoma. No malignant degeneration.
  - Osteomas (primarily mandibula, maxilla, petrous bone).
  - **C**ongenital **h**ypertrophy of **r**etinal **p**igment **e**pithelium (CHRPE) is earliest clinical sign.
  - Desmoid tumors, especially after abdominal surgery.
  - Intestinal polyposis, concentrated on colon but involving entire gastrointestinal tract; usually present in young adult life.
  - *Malignant tumors:*
    - 100% lifetime risk of carcinoma of the colon; may be multiple if prophylactic colectomy not performed.
    - Much less commonly carcinomas of liver, biliary tree, thyroid, and others.
- **Diagnostic approach:** History, presence of multiple epidermoid cysts or osteomas (dental radiographs); confirmed on colonoscopic examination.
- **Therapy:** Prophylactic colectomy; aspirin or NSAIDs may reduce development of new polyps; cysts and osteomas can be excised; desmoids following abdominal surgery are major problem with no effective treatment. Family members at risk should be followed.

Muir–Torre Syndrome (MTS)

- **MIM code:** 158320.
- **Definition:** Genodermatosis which is part of the hereditary nonpolyposis colon cancer (HNPCC) syndrome; combination of multiple sebaceous tumors and keratoacanthomas with multiple internal malignancies; autosomal dominant inheritance.
- **Epidemiology:** HNPCC is relatively common but MTS is rare; in other words, only a small number of HNPCC patients have cutaneous findings. The cancer family syndrome (Lynch syndrome) is an older term for the same disorder.
- **Pathogenesis:** Defects in a number of related DNA mismatch repair genes; the most common mutation in HNPCC syndrome is in MLH-1, but MSH-2 is more common in MTS. Somatic inactivation of second normal allele leads to microsatellite instability, a marker for genetic instability, and tumor growth.
- **Clinical features:**
  - *Skin:* Multiple sebaceous neoplasms and keratoacanthomas; often hard to clinically separate; papules and nodules, often with central dell or plug, favor midface (Fig. 21.**14**). Cystic sebaceous tumor, usually on back, is almost specific for MTS. Sebaceous carcinomas extremely rare.
  - *Malignant tumors:* Carcinoma of colon is most common (50%) but carcinomas involving lungs, urogenital tract, and other organs also possible. Tumors appear earlier than sporadic lesions, but have better prognosis. Most patients develop multiple tumors.

  Note: These patients do not have intestinal polyposis, making monitoring for colonic tumors more challenging.

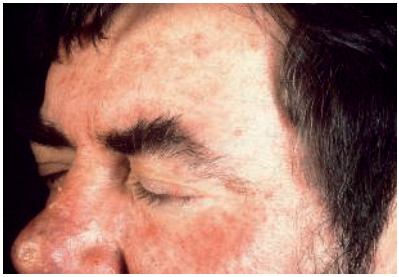


Fig. 21.**14** · Muir–Torre syndrome with multiple facial sebaceous tumors.

- **Diagnostic approach:** History, complete physical examination including gynecologic evaluation, colonoscopic examination; patients with multiple sebaceous tumors or keratoacanthomas should be carefully studied. Absence of specific gene products can be shown in skin biopsies, confirming diagnosis.
- **Therapy:** Appropriate treatment and follow-up for all tumors; screening and follow-up of family members at risk.

Peutz–Jeghers Syndrome

- **MIM code:** 175200.
- **Definition:** Genodermatosis featuring multiple lentigines, intestinal polyposis, and increased risk of carcinomas; autosomal dominant inheritance.

- **Pathogenesis:** Mutation in *STK11*, encoding a serine-threonine kinase growth control gene.
- **Clinical features:**
  - *Skin:* Multiple lentigines, usually periorificial (lips, oral mucosa, perinasal, periorbital, anogenital) as well as acrally. Appear early in life but often overlooked as freckles. Associated with pigmented nail streaks and occasionally hyperpigmented palmoplantar creases.
  - *Intestinal polyposis:* Jejunum is most often (90%) involved, but stomach, colon, rectum also affected (50%). Hamartomatous polyps with a small risk of malignant change. Main problems are intussusception and bleeding.
  - *Malignant tumors:*
    - Tumors of testes and ovaries most common; often peculiar histologic types.
    - Gastrointestinal tumors less common.
- **Diagnostic approach:** History, endoscopic examination, and follow-up; regular gynecologic or urologic examinations.
- **Differential diagnosis:** Many possibilities for multiple lentigines and systemic findings; exclude LEOPARD syndrome and Carney complex.
- **Therapy:** Surgical management as indicated; radical surgery rarely needed; examination and follow-up of family members at risk.

22 Disorders of Pigmentation

22.1 Overview

Definitions

- **Hyperpigmentation:** Increase in pigmentation.
- **Melanosis**, **hypermelanosis:** Increase in pigmentation due to excess melanogenesis.
  - ***Note:*** Hyperpigmentation and hypermelanosis are generally used as synonyms, although technically hyperpigmentation can result from other pigments in the skin.
- **Hypopigmentation**, **depigmentation:** Reduction (hypo-) or total loss (de-) of pigmentation.
- **Hypomelanosis**, **amelanosis:** Congenital reduction (hypo-) or total loss (a-) of pigmentation because of abnormal melanogenesis.
- **Leukoderma:** Hypo- or depigmentation following an inflammatory skin disease.
- **Pseudoleukoderma:** Less increase in pigmentation in diseased skin as compared to normal skin, following exposure to UV irradiation or exogenous pigments, producing a hypopigmented area (psoriatic leukoderma).
- **Dyschromatosis:** Literally, any abnormality in color of the skin; often refers to combination of hyper- and hypopigmentation; others use it to refer to pigmentary changes not related to melanocytes and melanin.
- **Poikiloderma:** Combination of atrophy, telangiectases, and hypo- as well as hyperpigmentation; classic example is radiation dermatitis.
- Unfortunately, these terms are not always used precisely. The critical distinctions are between:
  - *Congenital* and *acquired* changes.
  - *Hyperpigmentation:*
    - Excess melanin or other pigments (iron, silver, tattoos). If other pigments, then endogenous vs. exogenous.
    - Increased melanin production and transfer (café-au-lait macule) vs. increased number of melanocytes (lentigines, melanocytic nevi, malignant melanoma).
  - *Hypopigmentation:*
    - Loss of melanin (albinism) vs. loss of melanocytes (vitiligo).

Note: Examine the entire skin surface in patients with pigmentary abnormalities; use of the Wood's lamp helps to identify changes more readily.

Classification

- **Hypopigmentation:**
  - *Entire body:*
    - *Congenital:* Albinism, Chédiak–Higashi syndrome, Hermansky–Pudlak syndrome, phenylketonuria, homocystinuria, histidinemia.
    - *Acquired:* Panhypopituitarism.
  - *Widespread areas:*
    - *Congenital:* Piebaldism, Waardenburg syndrome, hypomelanosis of Ito (incontinentia pigmenti achromians).
    - *Acquired:* Vitiligo, postinflammatory hypopigmentation, idiopathic guttate hypomelanosis, systemic sclerosis (confetti hypopigmentation).

- *Localized:*
  - *Congenital:* Nevus depigmentosus, tuberous sclerosis (ash-leaf macules).
  - *Acquired:* Vitiligo, chemically induced depigmentation (cleansing compounds), postinflammatory hypopigmentation, halo nevus.

► **Brown hyperpigmentation:**
- *Diffuse:*
  - *Metabolic:* Hemochromatosis, Wilson disease, porphyria, hepatic failure, renal failure, Addison disease, tumors producing MSH or ACTH, ACTH therapy.
  - *Drugs or chemicals:* ACTH, amiodarone, antimalarials, arsenic, chlorpromazine, estrogens, minocycline, phenytoin, phenothiazine, psoralens (with UV); chemotherapy agents (busulfan, 5-fluorouracil, cyclophosphamide).
  - *Disease-related:* Systemic sclerosis, Whipple disease, mycosis fungoides, Sézary syndrome (melanoerythroderma).
- *Localized:*
  - *Tumors and nevi:* Freckle, lentigo, syndromes with lentigines (p. 385), café-au-lait macule, seborrheic keratosis, melanocytic nevus, Becker nevus, linear and whorled nevoid hypermelanosis, urticaria pigmentosa, acanthosis nigricans, epidermal nevus (some cases).
  - *Melasma*.
  - *Phototoxic dermatitis:* Berloque and meadow grass dermatitis.
  - *Medications:* Bleomycin (flagellate streaks), 5-fluorouracil (over veins).
  - *Burns*, *ionizing radiation*, *trauma*.
  - Postinflammatory hyperpigmentation following dermatoses or trauma.

► **Gray or blue hyperpigmentation:**
- *Diffuse:* Hemochromatosis, metastatic melanoma with circulating melanin, bismuth, silver, gold, systemic ochronosis.
- *Localized:* Nevus of Ota, nevus of Ito, mongolian spot, blue nevus, incontinentia pigmenti (late stage), macular amyloidosis, fixed drug reaction, erythema dyschromicum perstans, exogenous ochronosis.

22.2 Hypopigmentation

Albinism

► **Definition:** Family of disorders with disturbances in either melanin production or formation and transfer of melanosomes; typically affect skin and eyes; patients initially classified on clinical features but today defined by genetic studies. All inherited in autosomal recessive manner.

► **Epidemiology:** Overall incidence 1:20 000; all races affected.

► **Tyrosinase-negative albinism**.
- *MIM code:* 203100.
- *Pathogenesis:* Mutation in tyrosinase gene; melanosomes contain no melanin.
- *Clinical features:* Most severe form of albinism:
  - *Skin:* White hair, white to pale pink skin, no pigmented nevi, risk for UV-induced tumors (actinic keratoses, squamous cell carcinomas).
  - *Eyes:* Gray translucent iris, red reflex, photophobia, nystagmus, loss of vision.
- *Diagnostic approach:* Hair bulb negative for tyrosine, ophthalmologic examination.
- *Therapy:* Absolute sun avoidance or protection, dark glasses, regular dermatologic and ophthalmologic examinations.

- **Tyrosinase-positive albinism**.
  - *MIM code:* 203200.
  - *Pathogenesis:* Most common form of albinism; tyrosinase presence; melanin formed and melanosomes start to form but rarely mature completely.
  - *Clinical features:*.
    - *Skin:* White skin and hair at birth; later slight pigmentation, often yellow-red hair; may have few freckles.
    - *Eyes:* Some pigment presence; defects less severe than above.
  - *Diagnostic approach:* Hair bulb positive for tyrosinase, ophthalmologic examination.
  - *Therapy:* Sun protection and regular monitoring.
- **Yellow albinism**.
  - *MIM code:* 203100.
  - *Pathogenesis:* Lack of eumelanin synthesis with reduced pheomelanin synthesis.
  - *Clinical features:* Pale skin, freckles, can have pigmented nevi; pale yellow hair; iris with radial pigmentation; slight photophobia and nystagmus.
  - *Diagnostic approach:* Hair bulb positive for tyrosinase, ophthalmologic examination.
  - *Therapy:* Sun protection and regular monitoring.
- **Hermansky–Pudlak syndrome**.
  - *MIM code:* 203300.
  - *Pathogenesis:* Disease of diluted melanosomes, caused by mutations in at least seven different genes. Most common mutation is in *HPS1* gene; 1:20 Puerto Ricans are heterozygotes.
  - *Clinical features:* Blond hair, blue eyes, freckling, multiple melanocytic nevi. Nystagmus and photophobia. Bleeding disturbance because of lack of dense bodies in platelets. Patients with *HPS1* mutation have pulmonary fibrosis, granulomatous colitis, and renal insufficiency.
  - *Diagnostic approach:* Electron microscopy of platelets, identification of *HPS1* mutation or more complex studies if negative.
  - *Therapy:* Sun protection and regular monitoring. Should be managed by physician experienced with problem.

  Caution: Aspirin is contraindicated.
- **Chédiak–Higashi syndrome**.
  - *MIM code:* 214500.
  - *Pathogenesis:* Mutation in *LYST*, a gene controlling lysosome trafficking on chromosome 1q42.1–42.2. Giant lysosomes found in many cells including neutrophils, monocytes, hepatocytes and renal epithelial cells. Giant melanosomes in melanocytes.
  - *Clinical features:* Pale skin with silvery hair and blue-violet or light brown irises. Course complicated by multiple infections and risk of lymphoma (accelerated reaction); most die in first decade.
  - *Diagnostic approach:* Giant lysosomes can be identified in peripheral blood.
  - *Therapy:* Prompt treatment of infections; if donor is available, bone marrow transplantation.
- **Ocular albinism:** At least four types, inherited in several patterns. Pattern has ocular findings similar to oculocutaneous albinism but minimal skin findings. Still unclear why changes are limited to melanocytes of retinal pigment epithelium.
- **Phenylketonuria**.
  - *MIM code:* 261600.
  - *Definition:* Common metabolic disturbance in phenylalanine metabolism inherited in autosomal recessive manner.

- *Pathogenesis:* Because of mutations in phenylalanine hydroxylase, phenylalanine is not converted to tyrosine, but instead accumulates, blocking tyrosinase. This has two effects: (1) failure to produce adequate melanin, (2) toxic effects of increased phenylalanine.
- *Clinical features:*
  - Pale skin, blond hair, blue eyes.
  - Pseudo-scleroderma: diffuse areas of sclerosis.
  - Growth retardation.
  - Mental retardation; variety of neurological problems.
- *Diagnostic approach:* Prenatal screening is standard is most countries. Diagnosis can be made on cord blood (Guthrie test) or even diaper urine. Prenatal diagnosis possible.
- *Therapy:* Low-phenylalanine diet as soon as diagnosis is made; most defects not reversible.

► **Nevus depigmentosus**.
- *Definition:* Localized area of depigmentation, usually following Blaschko lines, caused by aberrant transfer of melanosomes.
- *Clinical features:* Sharply demarcated permanent area of depigmentation present at birth, which grows with child; usually respects midline.
- *Diagnostic approach:* History, clinical examination.
- *Differential diagnosis: Nevus anemicus* is pharmacologic nevus, which is pale because of vasoconstriction; thus nevus depigmentosus becomes red with rubbing; nevus anemicus does not.
- *Therapy:* Camouflage cosmetics or staining, as for vitiligo.

► **Hypomelanosis of Ito**.
- *Synonyms:* Incontinentia pigmenti achromians, pigment mosaic—Ito type.
- *Pathogenesis:* Not a single disease, but a manifestation of genomic mosaicism, and thus associated with wide variety of underlying defects, including mental retardation and severe neurological defects.
- *Clinical features:* Widespread areas of hypopigmentation following Blaschko lines; individual lesions identical to nevus depigmentosus.
- *Diagnostic approach:* History, extensive physical examination, cytogenetic testing.
- *Therapy:* None available.

► **Piebaldism**.
- *MIM code:* 172800.
- *Definition:* Uncommon genodermatosis with circumscribed hypomelanosis; autosomal dominant inheritance.
- *Epidemiology:* Incidence of 1: 20000; more common among Hopi Indians.
- *Pathogenesis:* Mutation in *KIT* gene on chromosome 4q12; *KIT* codes for the transmembrane receptor of a mast cell-stem cell growth factor.
- *Clinical features:*
  - Permanent and nonprogressive hypopigmented area involving forehead and upper chest and back, as well as extremities. Areas may develop freckles or lentigines.
  - White forelock (poliosis) and white medial eyebrows, usually noticed at birth.
  - No other systemic signs and symptoms.
- *Diagnostic approach:* History, complete physical examination; the Hopi patients were first diagnosed as having albinism as they were reluctant to disrobe for examiners.
- *Differential diagnosis:* Vitiligo, which is acquired.
- *Therapy:* None available.

- *Associated syndromes:* There are several forms of Waardenburg syndrome associated with piebaldism:
  - *Waardenburg syndrome I:* (MIM code 193500; mutation in *PAX3* gene with lateral displacement of the inner canthi (dystopia canthorum), broad nasal bridge, heterochromia irides (one blue eye, one brown eye), congenital deafness because of lack of migration of melanocytes to inner ear.
  - *Waardenburg syndrome IIA:* Lacks dystopia canthorum; otherwise similar.

Vitiligo

- **MIM code:** 193200.
- **Definition:** Acquired localized depigmentation of skin, hair, and occasionally mucosa, of unknown etiology, characterized by complete loss of melanocytes.
- **Epidemiology:** Prevalence around 1%; more obvious, but not more common, in dark-skinned individuals. Onset before 20 years of age in 50%; around $^1/_3$ of patients have affected family members.
- **Pathogenesis:** Etiology not well understood. Theories include:
  - Autoimmune destruction of melanocytes.
  - Neural pathways, because of relation to stress.
  - Metabolic abnormalities: accumulation of toxic metabolites.
  - "Self-destruct" action because of aberrant tetrahydrobiopterin and catecholamine synthesis.
- **Clinical features:**
  - Typical macule is oval or round, sharply circumscribed but with irregular border (Fig. 22.**1**). Size may range from a few mm to several cm. The border usually has the same color as normal skin; occasionally it is red or hyperpigmented. Early lesions may have areas of hypopigmentation rather than depigmentation (*trichrome vitiligo*).
  - Palms and soles are frequently involved; hairs less often.

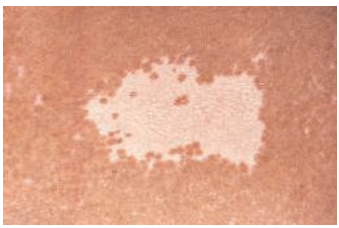


Fig. 22.**1** · Vitiligo: sharply bordered, irregular, completely depigmented macule.

- **Classification:** Degree of involvement highly variable, ranging from a few macules to almost complete depigmentation. The following classification is useful:
  - *Localized:*
    - *Focal:* One or more patches in the same area.
    - *Segmental:* Limited to a dermatome or Blaschko lines.
    - *Mucosal:* Only affected mucous membranes (rare).
  - *Generalized:*
    - *Acrofacial:* Distal extremities and facial, especially periorificial.
    - *Vulgaris (common):* Disseminated lesions without region predilection.
    - *Universal:* Complete or almost complete depigmentation.
- **Associated diseases:** Many autoimmune diseases are associated with vitiligo: either patients with vitiligo are more likely to be affected, or patients with the dis-

ease are more likely to have vitiligo. They include: hyperthyroidism, hypothyroidism, pernicious anemia, Addison disease, diabetes mellitus, alopecia areata, myasthenia gravis, uveitis (Vogt–Koyanagi–Harada syndrome), morphea, systemic sclerosis, halo nevus, malignant melanoma.

- **Prognosis:** Course highly variable and unpredictable. Spontaneous repigmentation that is cosmetically satisfactory for the patient occurs only rarely. Speckled repigmentation in a patch indicates that melanocytes from the outer root sheath of the hair follicle are producing melanin. Important to establish if the vitiligo is stable or progressive, as this influences choice of therapy.
- **Diagnostic approach:** See Table 22.**1**.
- **Differential diagnosis:** See Table 22.**2**.
- **Therapy:** The established therapy of vitiligo can be generously described as unsatisfactory. Table 22.**3** offers suggested approaches based on the patient's age.

Table 22.1 · **Vitiligo: diagnostic checklist**

History	Skin type?
	How long has depigmentation been present?
	Was there inflammation or other skin lesions prior to depigmentation?
	Any triggers—stress, systemic illnesses, sunburn, other skin trauma—occurring 2–3 months before depigmentation?
	Course—stable or progressive? Repigmentation?
	History of photosensitivity?
	How severe is emotional impact of vitiligo?
	Köbner phenomenon, halo nevi, or poliosis?
	Visual or ocular problems?
	Industrial or hobby exposure that could have caused chemically induced depigmentation?
	Family history of vitiligo?
	Personal or family history of premature graying (< 30 years of age) alopecia areata, thyroid disease, juvenile diabetes mellitus, pernicious anemia, connective tissue diseases, Addison disease, atopy?
	History of melanocytic nevi which have regressed?
	Medications (β-blockers can worsen vitiligo)
	Previous treatment effectiveness, side effects?
Physical examination	Wood's light examination including mucosal surfaces.
	Documentation of degree of involvement (whole body photography or diagrams; number of lesions < 5, > 20, > 100).
	Classification: Look for poliosis, achromotrichosis (white hairs in vitiligo patch), halo nevi, inflammatory border to lesions
	Ophthalmologic examination (40 % of patients have subclinical retinal pigmentary abnormalities)
Laboratory evaluation	Thyroid function tests including autoantibodies, anti-parietal cell antibodies, total IgE, ANA, glucose

Table 22.2 · Differential diagnosis of vitiligo

Diagnosis	Clinical features	Melanocyte abnormality
Nevus anemicus	Pale area because of vasoconstriction	None
Nevus depigmentosus	Localized hypomelanosis present since birth	Impaired transfer of melanosomes
Piebaldism	White forelock and depigmented areas	No melanocytes
Waardenburg syndrome	White forelock, depigmented areas, iris heterochromia, facial dysmorphism, deafness	No melanocytes, also missing in inner ear; autophagocytosis of melanocytes
Incontinentia pigmenti achromians	Hypopigmentation along Blaschko lines; often neurological abnormalities	Reduced melanocytes, abnormal melanosomes
Tuberous sclerosis	Ash-leaf macules, confetti depigmentation, adenoma sebaceum, connective tissue nevi, epilepsy, mental retardation	Normal numbers of melanocytes, abnormal transfer of melanosomes
Pityriasis alba	Facial depigmentation in atopic dermatitis	Normal numbers of melanocytes, abnormal transfer of melanosomes (reversible)
Postinflammatory hypopigmentation	Hypopigmentation following inflammatory dermatoses	Normal numbers of melanocytes, abnormal transfer of melanosomes (reversible); residual signs of inflammatory disease
Postinfectious leukoderma	After syphilis, lepra, pinta, yaws; white macules evolve from inflammatory lesions	Normal numbers of melanocytes, abnormal transfer of melanosomes (reversible); residual granulomatous inflammation
Pityriasis versicolor	Hypopigmented scaly macules; *Malassezia* spp. in skin	Normal numbers of melanocytes, abnormal transfer of melanosomes (reversible); hyphae and spores in stratum corneum (spaghetti and meatballs)
Systemic sclerosis	Confetti hypopigmentation	Reduced numbers of melanocytes
Idiopathic guttate hypomelanosis	Hypopigmented tiny macules on arms and legs in older individuals	Reduced numbers of melanocytes, photodamage
Chemically induced hypopigmentation	Appropriate history; hypo- or depigmented patches	Reduced to absent melanocytes

Note: Complete depigmentation is possible, using 20% monobenzyl ether of hydroquinone. The patient must be given detailed advice on lifelong use of sunscreens and irreversibility of action. The product is no longer available in the USA because it was too often used for localized hyperpigmentation and caused widespread, distressing depigmentation.

Table 22.3 · Treatment of vitiligo

Age	Clinical type	First choice	Options
< 5 years	Focal (< 5%)	Topical corticosteroids	None
	Segmental	None	None
	Widespread (< 5%)	Topical corticosteroids (+UVA)	UVB (311 nm), topical PUVA
> 5 years, adults	Focal (< 5%)	Topical corticosteroids (+UVA)	UVB (311 nm), topical PUVA, oral PUVA (> 12 years), minigrafts (if stable)
	Segmental	Minigrafts	Stains, self-tanning agents
	Widespread (> 5%)	UVB (311 nm)	Oral PUVA (> 12 years), topical corticosteroids (+UVA), L-phenylalanine (+UVA), minigrafts (if stable)
Adults	Eyelids, lips, nipples, penis	Minigrafts	Stains, tanning agents
	Resistant, involving > 80%	Total depigmentation	Stains, tanning agents

22.3 Brown Hyperpigmentation

Note: The major differential diagnostic consideration for all focal brown hyperpigmentation is a melanocytic nevus or malignant melanoma, as discussed in the next chapter. The lesions discussed below all feature increased melanin primarily in the basal layer of the epidermis. They are sometimes grouped together as *melanotic macules.*

Café-au-lait Macule

- **Definition:** Circumscribed tan macule, usually present at birth.
- **Clinical features:** Irregular tan macules and patches varying in size from 1 to many cm. More than five café-au-lait macules > 1.5 cm suggest neurofibromatosis 1, but the macules can be sporadic or associated with a variety of syndromes.
- **Histology:** Increased pigment in basal layer, normal number of melanocytes, giant melanosomes.

Syndromes with Café-au-lait Macules

- **Neurofibromatosis 1** (p. 362).
- **Neurofibromatosis 2** (p. 364).
- **Albright syndrome** (MIM code: 174800): Polyostotic fibrous dysplasia; endocrine abnormalities; and giant, more regular, pigmented patches reflecting mosaicism.
- **Watson syndrome** (MIM code: 193520): Mental retardation, pulmonic stenosis, axillary freckling.

- **Ataxia-telangiectasia:** (p. 453).
- **Bloom syndrome:** (p. 306).

Ephelides

- **Synonym:** Freckles.
- **Definition:** Localized hyperpigmentation caused by sun exposure; waxes and wanes with seasons.
- **Clinical features:** Much more common in skin types I and II; especially among redheads. Usually appear in childhood, flaring each summer; irregular brown macules of varying shades of tan and brown.
- **Histology:** Increased melanin, normal to reduced numbers of melanocytes.
- **Differential diagnosis:** Lentigines have an increased number of melanocytes and are permanent. Some patients with multiple lentigines (Carney complex) also have ephelides. Hyperpigmented plane warts occasionally mistaken for ephelides, but palpable.
- **Therapy:** Sunscreens, light avoidance, as freckles are marker for increased risk of skin cancers.

Becker Nevus

- More than a melanotic macule, although it clinically falls in this category until hypertrichosis appears at puberty. Best considered an organoid nevus (p. 412).

Linear and Whorled Nevoid Hypermelanosis

- Although nevoid hypomelanosis (nevus depigmentosus) is common, nevoid hypermelanosis usually following Blaschko lines is uncommon. Extensive lesions may be linear and whorled, but often one or two patches accompanied by a few macules is all that the patient displays. Search for underlying abnormalities warranted. Laser ablation of pigment possible.

Mucosal Melanotic Macules

- Irregular tan macules can be seen on the lips, penis, or labia. Harmless, but often confused with melanocytic nevi or malignant melanoma. On the genitalia, they often cause great concern. Biopsy is diagnostic, as there is only basal layer increase in melanin, without a proliferation of melanocytes. Once the diagnosis is secure, no treatment is needed, but patients may prefer excision or laser ablation.

Melasma

- **Synonyms:** Chloasma, mask of pregnancy.
- **Definition:** Combined epidermal and dermal hyperpigmentation of forehead, cheeks, and perioral area.
- **Epidemiology:** Common problem, almost exclusively limited to women; extremely prevalent in Latin America, among patients with mixed Indian/Spanish background. Pathogenesis: Risk factors include:
  - Sun exposure.
  - Pregnancy.
  - Use of oral contraceptives (or tumors secreting estrogens).
  - Rarely caused by phenytoin.

- **Clinical features:** Irregular brown hyperpigmentation, sometimes with blue tones, often speckled. Sometimes mask-like pattern. Typically worsens with sun exposure.
- **Histology:** Biopsy not needed, but shows increased epidermal melanin as with incontinence of pigment in papillary dermis.
- **Differential diagnosis:** Topical photosensitivity reactions can mimic melasma; sometimes both occur together, as when contact dermatitis develops to a sunscreen. Typical causes are berloque dermatitis (perfumes) and phenolated petrolatum.
- **Therapy:** Eliminate triggers (such as contraceptives), maximum sun protection/avoidance using physical screens, bleaching with 2–4% hydroquinone, azelaic acid, or topical retinoids (combinations possible).

Berloque Dermatitis

- **Definition:** Type of phytophotodermatitis caused by combination of phototoxic agent and sunlight.
- **Pathogenesis:** Berloque refers to the use of bergamot oil in perfumes; similar furocoumarins are present in many plants.
- **Clinical features:** Initially acute dermatitis following light exposure; then development of often bizarre hyperpigmented patches and streaks. When perfume is responsible, dripping streaks on neck and behind ear are classic.
- **Diagnostic approach:** Striking clinical picture usually gives answer.
- **Differential diagnosis:** Melasma.
- **Therapy:** Avoid triggers, maximum sun avoidance or protection, mild bleaching with azelaic acid.

Cronkhite–Canada Syndrome

- **MIM code:** 175500.
- Rare sporadic syndrome, most common in East Asia, featuring generalized gastrointestinal polyposis associated with malabsorption and wasting. Patients have brown hyperpigmentation of face, nape, nipples, and distal extremities, as well as nail dystrophy and alopecia. Cutaneous findings usually follow the systemic problems, which determine the management and course.

Acral Melanosis

- Rare acral hyperpigmentation seen in newborns; usually remains localized, but can later be more widespread.

22.4 Blue and Gray Hyperpigmentation

Erythema Dyschromicum Perstans

- **Synonym:** Ashy dermatosis.
- **Definition:** Poorly understood dermatosis with inflammatory phase and late postinflammatory dermal melanosis.
- **Epidemiology:** Almost limited to mixed-race individuals in Latin America.
- **Pathogenesis:** Divided opinions whether form of lichen planus or idiopathic dermatosis.

- **Clinical features:** Early lesions are erythematous macules favoring the trunk; they slowly evolve into blue-gray (ashy) macules with indistinct borders, often coalesce. Totally asymptomatic.
- **Histology:** Dermal deposits of melanin in macrophages.
- **Differential diagnosis:** Other forms of postinflammatory hyperpigmentation.
- **Therapy:** Nothing well established; both chloroquine and PUVA have proponents.

Alkaptonuria

- **Synonym:** Ochronosis.
- **MIM code:** 203500.
- **Definition:** Metabolic disturbance associated with arthritis and discoloration of cartilage and skin; autosomal recessive inheritance.
- **Pathogenesis:** Mutation in HGD (homogentisate 1,2 dioxygenase) leads to accumulation of homogentisic acid in urine and tissues.
- **Clinical features:**
  - Discoloration of tissues including cartilage by accumulations of homogentisic acid, leading to arthritis.
  - Discolored sclerae, auricular cartilage and nasal cartilage, giving blue tinge to overlying skin. Sometimes diffuse blue color.
- **Diagnostic approach:** Clinical examination; urine darkens dramatically on standing.
- **Differential diagnosis:** *Acquired ochronosis* is caused by abuse of hydroquinone bleaching agents, using either for too long or in too high a concentration; skin becomes darkened rather than lighter and dermal collagen is clumped and discolored.
- **Therapy:** Symptomatic management of arthritis; avoidance of sunlight, which exaggerates pigmentary changes.

Diffuse Melanosis with Metastatic Melanoma

- Rarely patients with metastatic malignant melanoma (p. 400) produce so much melanin in their tumors that it can be released into the circulation and settle out in all tissues, imparting a diffuse blue-gray color to the skin, as well as urine. A sign that death is near.

Deposition of Metallic Salts

- A number of heavy metals can be deposited in the skin, usually imparting various shades of blue and gray. The most common agents are shown in Table 22.**4**.

Argyria

- **Definition:** Deposition of silver in the skin and other tissues.
- **Pathogenesis:** Localized argyria results from the topical application of silver to skin or mucous membranes. Systemic argyria results from the ingestion of silver-containing medications or massive abuse of topical agents; 2–4 g of silver are required to cause problems. A number of topical and systemic agents containing silver are available in Germany, some over the counter. The most commonly used silver product, silver sulfadiazine or "burn butter," almost never causes argyria.
- **Clinical features:** Localized or diffuse blue-gray discoloration of skin.
- **Histology:** The silver particles are best found in the basement membrane of sweat glands.
- **Therapy:** No effective form of removal available.

Table 22.4 · Hyperpigmentation caused by heavy metals

Metal	Sources	Disorder
Silver	Nose drops, silver nitrate sticks	Argyria
Gold	Arthritis medication	Chrysiasis
Iron	Multiple blood transfusions, excessive ingestion	Siderosis
Arsenic	Fowler solution, skin tonics, old insecticides	Arsenical melanosis
Mercury	Topical bleaches or ophthalmic ointments Systemic exposure to fumes (hatters in past)	Hydrargyria: blue-gray discoloration, especially palmar creases Gingival hyperpigmentation
Lead	Paints with lead; in distant past, topical use of lead salts	Plumbism with gingival hyperpigmentation
Bismuth	Antacids; old syphilis medications	Bismuthism with stomatitis and dermatitis

Hyperpigmentation Caused by Medications

- **Amiodarone:** Diffuse blue-gray hyperpigmentation in sun-exposed areas, especially face (lipofuscin deposits).
- **Minocycline:** Following long-term use:.
  - Dark blue to black macules in acne scars or over cysts.
  - Hyperpigmented patches in light-exposed areas (slowly reversible); on occasion, diffuse disease.
  - Hyperpigmentation of mucosal surfaces, especially mouth.
  - Combination of both interaction with melanocytes and iron complexes.
- **Chemotherapy agents:**
  - *Generalized hyperpigmentation:* 5-fluorouracil, busulfan.
  - *Localized hyperpigmentation:* Adriamycin, bleomycin, cyclophosphamide, other alkylating agents, mithramycin, actinomycin D, various hormones.
  - *Lineare hyperpigmentation:* 5-Fluorouracil and many others (over veins), bleomycin (flagellate, presumably following scratching).
  - *Nail hyperpigmentation*: Adriamycin, cyclophosphamide, 5-fluorouracil, dacarbazine, mechlorethamine.
- **Antimalarials:** Chloroquine and hydroxychloroquine may cause gray hyperpigmentation, especially facial and pretibial, as well as on gingiva and palate. Quinacrine causes diffuse gray-yellow discoloration.

22.5 Reticular Hyperpigmentation and Dyschromatosis

Definitions

- **Reticular hyperpigmentation**: Net-like or lacy.
- **Dyschromatosis:** Combines hypo- and hyperpigmentation without the atrophy or telangiectases of poikiloderma.

Localized Reticular Hyperpigmentation

- **Acropigmentatio reticularis (Kitamura):** Rare disorder, primarily seen in Japan, with dominant inheritance; depressed reticulate macules on backs of hands and feet, palmoplantar pits, interrupted hieroglyphics; later spread centrally.
- **Dowling–Degos disease (reticular pigmented anomaly of the flexures):** Similar to Kitamura disease, but involves primarily axillae and groin; also inherited in autosomal dominant manner. Increased basal layer melanin.
- **Galli–Galli disease:** Similar to Dowling–Degos but with acantholysis histologically; also apparently has autosomal dominant inheritance.
- **Erythema ab igne:** Result of local exposure to heat (hand warmers, heating pads, sitting in front of heat source); combination of reticulate hyperpigmentation and livid vascular network. Melanin is dermal.

Generalized Reticular Hyperpigmentation

- **Naegeli–Franceschetti–Jadassohn syndrome** (MIM code: 161000): Rare disorder with autosomal dominant inheritance; reticulate hyperpigmentation of nape, axillae, groin, associated with palmoplantar keratoderma, hypohidrosis, and dental anomalies.
- **Dermatopathia pigmentosa reticularis** (MIM code: 125595): Extremely rare genodermatosis with autosomal dominant inheritance; atrophic reticulate hyperpigmentation of trunk and extremities, associated with nonscarring alopecia. Nail dystrophy and occasionally hypohidrosis.
- **Confluent and reticulated papillomatosis (Gougerot–Carteaud):** Pigmented patches and papules, sometimes with reticulated pattern, mainly on trunk: perhaps variant of pityriasis versicolor, as *Malassezia* spp. have been identified and lesions sometimes clear with antimicrobials.

Dyschromatoses

- **Dyschromatosis symmetrica hereditaria (Dohi)** (MIM code: 127400): Another Japanese genodermatosis with hypo- and hyperpigmented macules, believed to have autosomal dominant inheritance; prevalence of 1:100 000. Usually involves just the dorsal aspects of the extremities; about 20% have truncal lesions.
- **Dyschromatosis symmetrica universalis hereditaria** (MIM code: 127500): Variant of Dohi disease with widespread involvement.

23 Melanocytic Tumors

23.1 Benign Melanocytic Tumors

Overview

The first step in analyzing pigmented lesions is to decide if:

- **Only increased melanin is present:** Then one must think of brown hyperpigmentation (p. 378) including café-au-lait macule, freckles, Becker nevus, and mucosal pigmented macules. Sometimes the term *melanotic macule* is applied to this entire group, which is discussed in the preceding chapter on pigmentation.
- **Increased numbers of melanocytes are present:** This indicates lentigo, melanocytic nevus, or malignant melanoma.

23.2 Lentigenes

Lentigo Simplex

- **Definition:** Localized hyperpigmentation secondary to increase in melanocytes at the dermoepidermal junction.
- **Clinical features:** Sharply circumscribed, uniformly pigmented tan to dark brown macules; no relation to sun exposure (unlike freckles).
- **Histology:** Increased numbers of melanocytes at dermoepidermal junction; no nests. If nests (accumulations of more than three melanocytes) are seen, then preferred term is *nevoid lentigo, nevus incipiens* or, if more advanced, *junctional melanocytic nevus*.
- **Diagnostic approach:** It is not essential to know if a lesion is a lentigo or melanotic macule; a biopsy is not needed. If multiple lentigines are present, a variety of syndromes should be considered.
  - ***Note:*** Lentigines are permanent lesions and usually uniformly pigmented; ephelides (freckles) are paler, more irregular and vary with sun exposure, becoming more prominent in the summer.
- **Therapy:** None needed; if bothersome, cryotherapy or laser ablation, usually with erbium or ruby laser.

PUVA Lentigo

PUVA therapy induces a number of flat small irregular melanocytic lesions that persist for months or years after therapy. Histologically they show a proliferation of melanocytes at the dermoepidermal junction. The melanocytes are often atypical, and occasionally PUVA lentigenes may evolve into malignant melanoma. The lentigenes in xeroderma pigmentosum (p. 304) are very similar. Older adults may also develop irregular pigmented macules in sun-exposed skin, with proliferation of atypical melanocytes.

Syndromes with Lentigines

The following disorders should be considered in patients with multiple lentigines:

- **Multiple lentigines without associated findings**.
- **Multiple lentigines in mosaic pattern**.
- **LEOPARD syndrome** (MIM code 151100): Autosomal dominant inheritance; **l**entigines, **E**KG abnormalities, **o**cular hypertelorism, **p**ulmonary stenosis, **a**bnormal genitalia, **r**etarded growth, **d**eafness.
- **Carney syndrome** (MIM code: 160980): Autosomal dominant inheritance; also known as NAME syndrome: **n**evi (lentigines, blue nevi), **a**trial myxoma, **m**yxoid cutaneous tumors and **e**phelides (freckles). Two different responsible genes: CNC1 at 17q23, *PRKAR1A* gene encoding a protein kinase, and CNC2 at 2p16 with unknown product; patients may also have Cushing syndrome, as well as testicular and neural tumors.
- **Peutz–Jeghers syndrome (p. 369)**.
- **Axillary freckles** (also genital, perianal): Also known as Crowe sign; marker for neurofibromatosis.
- **Lentiginosis perigenito-axillaris of Korting:** Similar to axillary freckles, but no associated diseases.
- **Centrofacial lentiginosis of Touraine** (MIM code 151000): Autosomal dominant inheritance; association of midfacial lentigenes with mental retardation.
- **Mid-facial lentigenes in blacks:** common finding in light-colored, red-haired blacks; may also include freckles; no associated findings. May also be seen in whites as incidental finding.

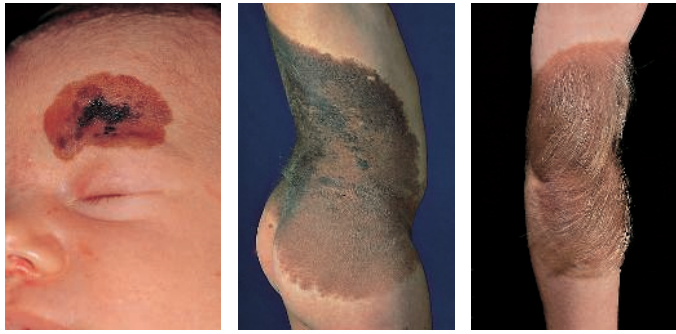
Solar Lentigo

Terminology is very confusing, but we consider these lesions to be flat seborrheic keratoses, which are discussed under benign epidermal tumors (p. 416).

23.3 Melanocytic nevi

Congenital Melanocytic Nevus

- **Synonyms:** Large lesions often called *bathing trunk nevus* or *giant hairy nevus*.
- **Definition:** Melanocytic nevus present at birth.
- **Epidemiology:**
  - 1% of newborns have melanocytic nevus; 1:20000 have lesion >10 cm; 1:500000 have giant melanocytic nevus.
  - Smaller (<1.5 cm) lesions with histological features of congenital melanocytic nevus can appear in infancy: tardive congenital melanocytic nevus.
- **Clinical features:**
  - Lesions are subdivided by size (Fig. 23.**1**): *Small:* <1.5 cm diameter; *medium:* 1.5–20 cm diameter; *large:* >20 cm diameter; the giant or bathing trunk lesions involve an entire body segment.
  - Most congenital melanocytic nevi are heavily pigmented, have a papillomatous surface and contain hairs. Few if any acquired melanocytic nevus have these features. At birth, the nevi may be less heavily pigmented or not have prominent hairs.
- **Histology:** Always junctional and dermal component; the junctional changes at birth are quite atypical and suggest a malignant melanoma until the history is



a b c

Fig. 23.1 · **Congenital melanocytic nevus. a** Medium-sized. **b** Giant. **c** Nevus pigmentosus et pilosus.

known; the dermal component usually extends deeply, often following adnexal structures.

- **Diagnostic approach:** Clinical examination; then dermatoscopy and photodocumentation.
- **Differential diagnosis:** Clinically unique when dark and hairy; at birth if tan, consider café-au-lait macule, nevus spilus, and early epidermal nevus.
- **Prognosis:** There is a risk of developing malignant melanoma, varying with the type of congenital melanocytic nevus:
  - *Large congenital melanocytic nevus:* Risk of malignant melanoma is around 10% (5–30%); tumors often develop in childhood as irregular, frequently amelanotic nodules in the midst of the tumor. They often arise deep and cannot be readily appreciated so prognosis is grim.
  - *Medium and small congenital melanocytic nevus:* Risk is much lower, clearly less than 5%. Change occurs in adult life. When a malignant melanoma develops within a preexisting nevus, often the precursor lesion was a small congenital lesion.

  ▶ ***Note:*** Despite this worrisome information, do not forget that the vast bulk of malignant melanoma develop spontaneously, rather than from a preexisting lesion.
- **Therapy:**
  - Two goals: (1) Avoid malignant melanoma; (2) cosmetic improvement, as patients with large disfiguring nevi have marked psychosocial problems.
  - Small and medium lesions can be excised, either in a single step or as part of a staged excision. If larger, skin expanders can be helpful to facilitate closure. Since the risk of malignant melanoma becomes higher in adult life, the procedure can be delayed until the child can cooperate.
  - Large lesions are a treatment problem. Often staged excision is not even an option because of the size. Early dermabrasion or curettage removes much of the melanocyte load and improves cosmetic appearance. Whether it reduces the risk of malignant melanoma remains controversial.
  - Patients should be followed yearly. Parents and then patients instructed in self-examination. Any new nodules are highly suspicious and should be excised.

Neurocutaneous Melanosis

- **Clinical features:** Patients with extensive or multiple congenital melanocytic nevi are at risk of having leptomeningeal involvement with drastic consequences:
  - Increased intracranial pressure and hydrocephalus.
  - Impingement on brain or spinal column with functional impairments.
  - Development of leptomeningeal malignant melanoma, which is almost invariably fatal.
- **Diagnostic approach:** Patients with extensive lesions crossing midline or in head and neck region should be subjected to imaging studies and then followed with ophthalmology and neurology.

Nevus Spilus

- **Synonym:** Speckled lentiginous nevus.
- **Definition:** Congenital lesion consisting of café-au-lait macule speckled with small melanocytic nevi.
- **Clinical features:** Irregular tan patch, several cm in diameter, with numerous small dark macules (lentigenes) or papules (melanocytic nevi) (Fig. 23.**2**). Rarely associated with systemic findings: *nevus spilus syndrome* with ipsilateral neurological findings such as hyperhidrosis or *phacomatosis pigmentokeratotica* (associated with nevus sebaceus).

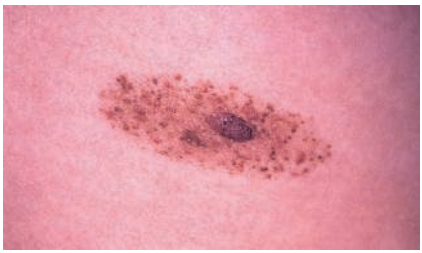
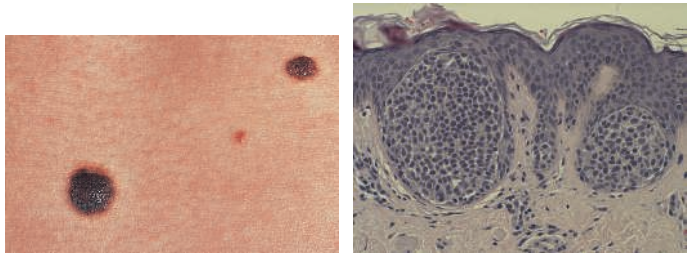


Fig. 23.**2** · Nevus spilus.

- **Histology:** The background skin contains increased melanin, while the darker spots have increased melanocytes, sometimes in nests.
- **Differential diagnosis:** Early in life, may be confused with Becker nevus or multiple lentigines in mosaic pattern; later distinctive.
- **Therapy:** Small lesions can be excised; otherwise follow and remove any darker component that is changing. The risk of malignant melanoma is very low.

Acquired Melanocytic Nevus

- **Definition:** Benign proliferation of melanocytes; most common human tumor.
- **Epidemiology:** Everyone has melanocytic nevi; lesions appear first at age 2–3 and their number usually stabilizes at about 30 years of age. Then some lesions may regress.
- **Pathogenesis:** Even though melanocytic nevi are so common, their pathogenesis is poorly understood. Accepted trigger factors include early sun exposure (uncommon in areas covered by two layers of clothing), hormones (puberty and pregnancy), and immunosuppression (flares following chemotherapy or in HIV/AIDS).



a b

Fig. 23.**3** · **a** Acquired melanocytic nevi. **b** Microscopic picture of junctional melanocytic nevus with nests of melanocytes in basal layer.

- **Clinical features:**
  - Average patient has 20–40 melanocytic nevi.
  - Start as homogenous tan macules, which gradually darken but almost never exceed 6 mm. Later become papules or nodules (Fig. 23.**3 a**).
  - Color varies from patient to patient, and from lesion to lesion, ranging from skin-colored to tan to red-brown to almost black. In general, older nevi tend to lose their color.
  - Surface may vary from papillomatous to smooth.

  ▶ ***Note:*** Size >1 cm or hair suggests a congenital melanocytic nevus.
- **Histology:** Traditionally divided into three types:
  - *Junctional*: Nests of melanocytes at dermoepidermal junction; nests are round to oval and all about the same size (Fig. 23.**3 b**).
  - *Compound*: Nests of melanocytes both at the dermoepidermal junction and through the dermis with varying patterns and degree of dermal involvement.
  - *Dermal*: No increase in melanocytes at dermoepidermal junction; limited to the dermis; older lesions may have areas with neuroid pattern, fat, or fibrosis.

  ▶ ***Note:*** Nonetheless, early nevi are usually junctional and old nevi most often dermal.
- **Diagnostic approach:** Careful clinical examination. If many lesions or atypical lesions are present, then photo-documentation and regular follow-up. Instruct patient on ABCDE rules (p. 389).
- **Differential diagnosis:** In most instances, the patient can make the diagnosis. The issue is always: Is there any reason to be suspicious of malignant melanoma? Older nonpigmented nevi may be mistaken for skin tags or neurofibromas.
- **Prognosis:** Patients with >50 melanocytic nevi have 5-fold increased melanoma risk; with >100, 10-fold increase.
- **Therapy:** Lesions that are likely to be traumatized, as well as those about which the patient is either worried or cosmetically bothered, can be excised.

Halo Nevus

- **Synonym:** Sutton nevus.
- **Definition:** Melanocytic nevus surrounded by hypopigmentation.
- **Pathogenesis:** A prominent host lymphocytic response attacks the nevus and may be responsible for its disappearance; at the same time, melanocytes and melanin in the adjacent epidermis are also destroyed. Often multiple; sometimes triggered by sunburn.

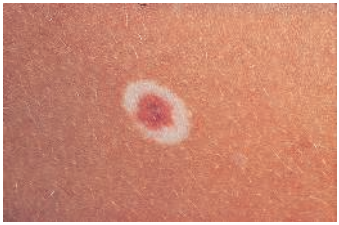
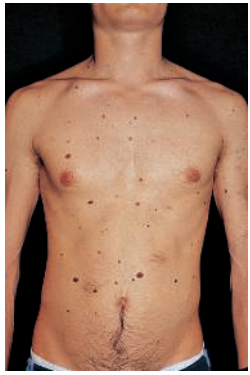


Fig. 23.**4** · Halo nevus.

- **Clinical features:** Papular melanocytic nevus surrounded by white halo (Fig. 23.**4**). Later nevus may fade or even disappear. Later, pigmentation comes back.
- **Histology:** Dense lymphocytic infiltrate that often obscures the residual melanocytes.
- ***Note:*** Halo nevi may also be the result of a host response to malignant melanoma. All patients with halo nevi should be checked for other suspicious pigmented lesions. In adults, ophthalmologic and genital examinations are indicated, along with total body examination.
- **Therapy:** Excision if desired; if multiple lesions, only excise those in which the nevus is atypical.

Dysplastic Nevus

- **Synonym:** Atypical nevus.
- **Definition:** Melanocytic nevi with irregular border, larger size, and collection of distinctive histological features.
- **Epidemiology:** 2–8% of whites have dysplastic nevi. They begin developing during puberty and continue to appear through out life. Dysplastic nevi may be sporadic or have autosomal dominant inheritance (dysplastic nevus syndrome).
- **Pathogenesis:** Hormones and sun exposure appear to be the major etiologic factors.
- **Clinical features:**
  - Dysplastic nevi (Fig. 23.**5 a**)and early malignant melanomas can be identified by the **ABCDE rule**; the criteria are most pronounced in melanoma.
    - **A**symmetry.
    - **B**order: irregular border, leakage of pigment.
    - **C**olor: multiple colors, best appreciated with dermatoscopy.
    - **D**iameter: >6mm.
    - **E**levating or **E**nlarging: a papule nevus is usually harmless; a flat nevus that grows or develops a nodular component is suspicious.
  - Dysplastic nevi may have a "fried egg" appearance: broad flat nevi (white of egg) with raised central portion (yolk).
  - Sporadic dysplastic nevi are commonly found on the palms, soles, breast, umbilicus, genital, and perianal regions.
- **Histology:** The histological features of dysplastic nevi are highly controversial. They include:
  - Junctional proliferation of melanocytes extending beyond the dermal component of the nevus (shoulder effect) often with fusion of adjacent nests (bridging).
  - Melanocytes in nests are often spindle-shaped.



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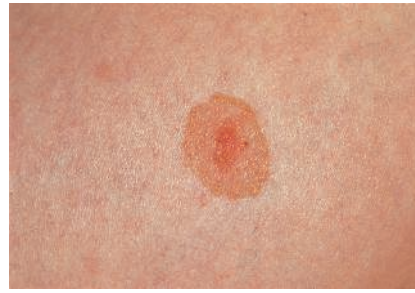


b

Fig. 23.5 · **a** Patient with multiple dysplastic nevi. **b** Dysplastic or atypical nevus.

- Fibrosis around the nests (lamellar fibrosis).
- Lymphocytic infiltrates.
- Atypia of melanocytes: most controversial point; some groups say no atypia; others grade degree of atypia (mild, moderate, severe).

Note: Many studies have shown that these criteria, greatly simplified here, are not reproducible, even between expert observers, or even by the same observer over a period of time. Almost every flat melanocytic nevus shows some of these features under the microscope.

- **Differential diagnosis:** Banal melanocytic nevus, malignant melanoma.
- **Therapy:** If a patient has only one or a small number of dysplastic nevi, excision is the simplest approach.

Dysplastic Nevus Syndrome

- **Synonyms:** B-K mole syndrome, familial atypical mole malignant melanoma syndrome, melanoma pancreas carcinoma syndrome.
- **MIM codes:** 155600, 606719.
- **Definition:** Syndrome with multiple dysplastic nevi, increased risk of malignant melanoma, and in some pedigrees increased risk of carcinoma of the pancreas or ocular malignant melanoma. Either familial or sporadic.
- **Epidemiology:** In contrast to sporadic dysplastic nevi, patients with multiple nevi are uncommon and those with a family history of melanoma even less common.
- **Pathogenesis:**
  - A number of genes have been associated with familial melanoma syndromes. The most common are mutations in *CDKN2A* (p16), a cyclin-dependant kinase inhibitor at 9p21, or in *CDK4*, a cyclin-dependent kinase, at 12q13. Both of these products help control the cell growth cycle. Some patients with p16 mutations also have an increased risk of pancreatic cancer; in well-established families, the risk of malignant melanoma is around 50% and pancreatic cancer, 17%. Many other loci and potential genes have been identified.
  - Still no consensus if multiple dysplastic nevi are markers for a predisposition to develop malignant melanoma or precursor lesions, likely to evolve into malignant melanoma. Most recent work points surprisingly more in the direction of marker than precursor.

Note: Not all families with an increased likelihood of malignant melanoma have dysplastic nevi.

- **Clinical features:** These patients have many, many dysplastic nevi—often more than 100, most common on the trunk, but also on protected sites such as scalp, breast, and bathing trunks area (Fig. 23.**5 b**).
- **Histology:** Identical to sporadic dysplastic nevus.
- **Therapy:**
  - Family history of atypical moles or malignant melanoma.
  - Complete body examination; dermatoscopic evaluation of atypical nevi.
  - Excision and histologic examination of especially large, irregular or changing nevi.
  - Documentation: Total body photographs, ideally digital; can be combined with computer-supported dermatoscopic examination in many systems, such as Dermascan or Fotofinder.
  - Follow-up every 6–12 months with excision of suspicious lesions.
- **Patient education:**
  - Self-examination.
  - Avoidance of excessive sun exposure.
  - Offer to examine first-degree relatives.

Note: :

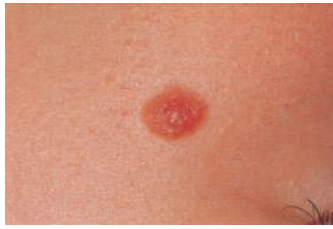
- Dermatoscopy with photodocumentation has proved to be most useful in identifying suspicious or changing dysplastic nevi.
- Even the most aggressive surgeon cannot cure patients with dysplastic nevus syndrome; many of their malignant melanomas develop de novo, not from preexisting nevi.

Spitz Nevus

- **Synonym:** Spindle and epithelioid cell nevus.
- **Definition:** Variant of benign melanocytic nevus with distinctive histologic pattern that features considerable atypia and is easily confused with malignant melanoma.

  Note: When Sophie Spitz described these nevi over 50 years ago, she used the term "benign juvenile melanoma," showing just what a histologic challenge these lesions present.
- **Epidemiology:** The vast bulk of Spitz nevi occur in children; about 1 % of histologically examined melanocytic nevi are Spitz nevi.
- **Clinical features:** Red-brown papule or nodule, often on face or upper trunk (Fig. 23.**6 a**). History of sudden growth. In adults, no typical appearance.
- **Histology:** Junctional or compound nevus with spindle cell and/or epithelioid pattern; symmetrical but with cellular and architectural atypia, including mitoses. Cells more normal at base with mitoses uncommon. Eosinophilic bodies at junction (*Kamino bodies*).
- **Differential diagnosis:** Two classic differential diagnostic considerations are mast cell tumor and juvenile xanthogranuloma; other possibilities include adnexal tumor, hemangioma, arthropod bite reaction, ordinary melanocytic nevus.
- **Therapy:** Excision.

Note: Atypical Spitz nevus describes lesions which cannot be separated with certainty from melanoma. They should be treated as would be a melanoma.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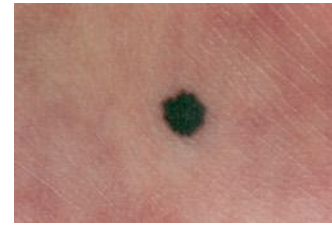

b

Fig. 23.**6** · **a** Spitz nevus. **b** Pigmented spindle cell nevus (Reed nevus).

Pigmented Spindle Cell Nevus

- **Synonym:** Reed nevus.
- **Definition:** Superficial heavily pigmented melanocytic nevus, sharing some features of Spitz nevus.
- **Clinical features:** Dark flat or slightly raised papule usually on extremities of young adults; more common in women (Fig. 23.**6 b**).
- **Histology:** Nests of spindle cells at the dermoepidermal junction with horizontal orientation parallel to skin surface. Marked melanin both in macrophages and in the epidermis, including stratum corneum.
- **Diagnostic approach:** Very distinctive starburst pattern on dermatoscopy.
- **Differential diagnosis:** Dysplastic nevus, malignant melanoma.
- **Therapy:** Excision.

Congenital Dermal Melanosis

There are a number of congenital lesions in which there are spindled melanocytes and melanin in the dermis, imparting a blue-gray color:

- **Mongolian spot:** Blue-gray sacral patch; common in black and Asian children; usually resolves by 5 years of age (Fig. 23.**7**). No biopsy needed, but very subtle presence of spindle-shaped melanocytes.
- **Nevus of Yamamoto:** Mongolian spot in extrasacral location, such as hands and feet; rare, and tends not to resolve.
- **Nevus of Ota (nevus fuscoceruleus ophthalmomaxillaris):** Common in Japanese; most often involves women; affects area served by 1st and 2nd branches of trigeminal nerve; sclera also pigmented. Usually present at birth; rare development of malignant melanoma. Major cosmetic problem in Japan, where it is relatively common.
- **Nevus of Hori:** Bilateral acquired nevus of Ota.

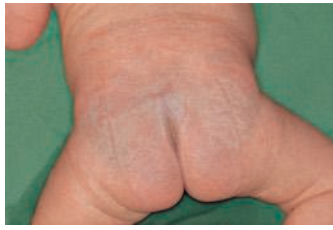
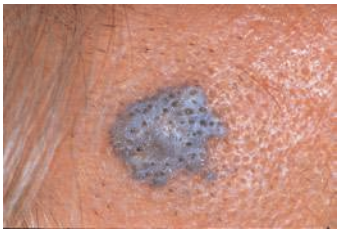


Fig. 23.**7** · Mongolian spot.

- **Nevus of Ito (nevus fuscoceruleus deltoideoacromalis):** Same as nevus of Ota, but affects shoulder girdle.
- **Therapy:** Ruby and alexandrite lasers are most helpful for destroying the dermal melanin.

Blue Nevus

- **Definition:** Benign tumor consisting of dermal proliferation of spindle-shaped melanocytes.
- **Clinical features:** Firm blue-gray to almost black flat-topped 1–2 cm papule; often acral or on face (Fig. 23.**8 a**). Cellular variant usually on buttocks, and larger.
- **Histology:**
  - *Ordinary blue nevus*: Spindle-shaped cells, varying degrees of melanin, sometimes in melanophages; junctional changes uncommon (Fig. 23.**8 b**).
  - *Cellular blue nevus*: Plump epithelioid cells and neuroid area, in deep dermis and often into subcutaneous fat; sometimes with satellite lesions. Mitoses and necrosis suggest a malignant blue nevus.
  - *Combined nevus*: Usually combination of blue nevus and compound nevus; no special clinical considerations.
  - *Deep penetrating nevus*: Variant or relative of blue nevus with both junctional nests and a spindle-cell proliferation that extends deep into the dermis, often along adnexal structures, or may involve subcutaneous fat.
- **Differential diagnosis:** Clinical: malignant melanoma, pigmented dermatofibroma, traumatic tattoo; histological: malignant melanoma, especially melanoma metastasis.
- **Therapy:** Excision.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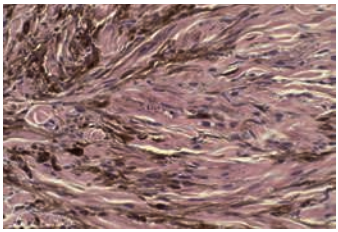
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Fig. 23.**8** · **a** Blue nevus. **b** Micrograph of blue nevus with marked melanin and spindle-shaped cells.

23.4 Malignant Melanoma

Overview

- **Synonym:** Melanoma (both terms used throughout this book).
- **Definition:** Malignant tumor of melanocytes.
- **Epidemiology:**
  - The lifetime risk of malignant melanoma for white Europeans increased dramatically from 1:1500 in 1935 to 1:75 in 2000, representing a doubling of incidence every 10–15 years (Fig. 23.**9**). In Australia and Southwestern USA, lifetime risk is 1:25. Uncommon in blacks and Asians (annual incidence 2–4/million).

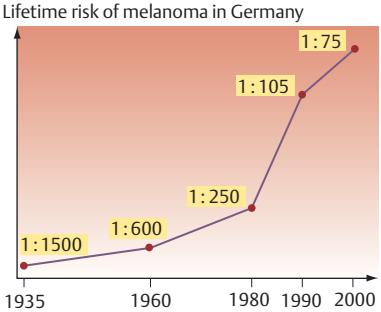


Fig. 23.**9** · Increasing incidence of malignant melanoma.

- Male:female ratio 1:1.5; uncommon in children; most occur between 30–70 years of age; varies with type.

► **Pathogenesis:** Risk factors include (up to 10%):
- Genetic predisposition (familial melanoma syndromes) (up to 10%).
- Excessive sun exposure and sunburns < 20 years of age, especially as infants.
- Number of melanocytic nevi (> 50), which correlates with childhood sun exposure.
- Presence of atypical melanocytic nevi.
- Skin types I and II (p. 50).
- About $^2/_3$ of malignant melanomas develop novo; $^1/_3$ arise in melanocytic nevi.

► **Biology:** Melanomas have two relatively distinct growth phases:
- *Horizontal or radial phase:* Melanoma starts with abnormal junctional melanocytes; expands laterally in most instances for long period of time; number of different clones can establish themselves with differing growth capabilities. Tumors in this phase rarely metastasize.
- *Vertical phase:* Tumor cells break through the basement membrane and begin to grow down into the dermis. Once the basement membrane has been bridged, the melanoma has the potential to metastasize.

► **Prevention:**
- Melanomas should be preventable tumors, as they develop in full sight of the patient and family in most cases.
- Two steps are essential for early detection of malignant melanoma:
  - Patients must learn how to identify suspicious melanocytic nevi and then to present promptly for evaluation and treatment.
  - Every physician must have an appreciation of the morphology of early malignant melanomas so that every visit to the doctor is a form of screening examination.

Clinical Features

There are four clinico-pathologic subtypes:

► **Superficial spreading melanoma (SSM):**
- Most common type; 60%; age peak 40–60 years.
- Irregularly pigmented, poorly circumscribed, often polycyclic macule or plaque; usually > 6 mm; over time frequently develops hypopigmented areas of tumor regression, as well as new nodules representing invasive tumors (vertical growth phase) (Fig. 23.**10**).

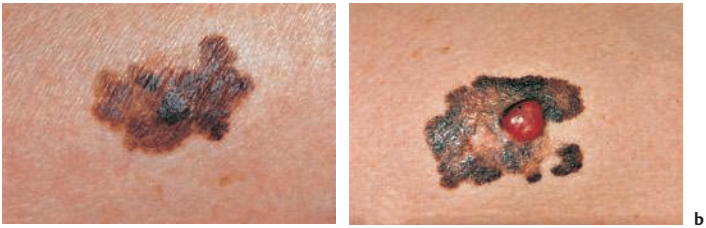


Fig. 23.**10** · **a** Superficial spreading melanoma. **b** Nodule and area of regression of the tumour shown in **a**.

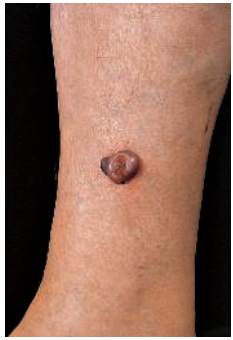
- Described by Fitzpatrick as "red, white, and blue" tumor.
- Usually on trunk in men; lower legs in women.
- *Differential diagnosis:* Pigmented Bowen disease, pigmented flat seborrheic keratosis, dysplastic nevus.

► **Nodular melanoma (NM):**
- About 20%; age peak 40–60 years.
- Dark-brown papule or nodule; rarely pink or skin-colored (amelanotic); frequently ulcerated (outgrows vasculature and is traumatized) (Fig. 23.**11 a**). Circumscribed, with little hint of peripheral spread.
- Prototype of vertical growth phase with very short period of horizontal spread.
- Prognosis usually worst because diagnosed at a thicker stage.

Caution: Nodular melanomas can be less than 6 mm in diameter.
- *Differential diagnosis:* Pigmented basal cell carcinoma, irritated seborrheic keratosis, porocarcinoma, pigmented squamous cell carcinoma, thrombosed vascular tumor (senile angioma), angiokeratoma, pyogenic granuloma, especially if nail fold and amelanotic, angiosarcoma.

► **Lentigo maligna melanoma (LMM):**
- About 10%; peaks > 60 years with increasing incidence until death.
- Areas of chronic light exposure; most often face.
- Large irregularly pigmented macule, often with areas of regression; as long as confined to epidermis, known as *lentigo maligna melanoma in situ*.
- When clinical nodule develops or tumor is found in dermis on microscopic examination, then LMM (Fig. 23.**11 b**).
- Better prognosis because of very long radial growth phase.
- *Differential diagnosis:* Pigmented actinic keratosis, solar lentigo (flat seborrheic keratosis).

► **Acral-lentiginous melanoma (ALM):**
- 5%; most common melanoma in dark-skinned individuals.
- Occurs on areas without hair follicles; otherwise resembles SSM or NM.
- Several clinical variants:
  - *Subungual melanoma:* May present as dark streak in nail, with streaks of pigment in nail fold (*Hutchinson sign*) and extension to finger tip; when amelanotic, may be mistaken for pyogenic granuloma (Fig. 23.**11 c**).
  - *Digital melanoma:* Typical on tips of toes or less often fingers; or less often palmoplantar; later lesions can be confused with tinea nigra (p. 121).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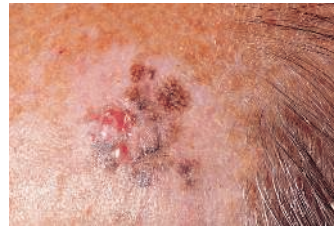
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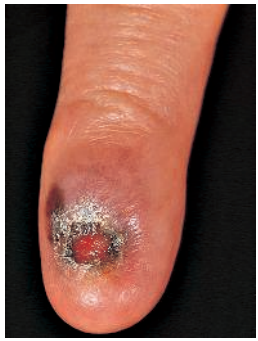
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Fig. 23.**11** · **a** Nodular malignant melanoma. **b** Lentigo maligna melanoma. **c** Acral-lentiginous melanoma.

Melanoma and Preexisting Nevi

- About 25% of melanomas show histological signs of preexisting melanocytic nevus.
- Of these nevi, 40% are congenital, 60% dysplastic.
- Giant congenital melanocytic nevi undergo malignant change early in life; smaller lesions much later.

Special Variants of Melanoma

- **Amelanotic malignant melanoma:** Skin-colored or pink; more often nodular or subungual, but any melanoma can be amelanotic. Extremely difficult to recognize; differential diagnostic considerations include vascular tumors, Spitz nevus, basal cell carcinoma.
- **Verrucous or polypoid malignant melanoma:** May at same time be amelanotic; verrucous, or papillomatous surface; almost always confused with seborrheic keratosis or verrucous nevus.
- **Mucosal melanoma:** Can involve mouth, pharynx, trachea, genitalia, and anorectal region; variants of ALM; usually recognized late in course and thus with dismal prognosis. Differential diagnostic considerations include benign racial hyperpigmentation, amalgam tattoos, and mucosal melanotic macules.

- **Uveal melanoma:** About 5% of melanomas; relatively good prognosis.
- **Meningeal melanoma:** Rare, occurs in patients with neurocutaneous melanosis.
- **Gastrointestinal melanoma**.
- **Metastatic malignant melanoma:** Metastases can be extremely hard to identify, as clinically they may be amelanotic or erythematous, while histologically they may be epidermotropic. When multiple lesions are present in a known melanoma patient (Fig. 23.**12**), the diagnosis is easier.
- **Occult melanoma:** Presents as metastatic disease with no evidence of primary tumor. Assumption is that primary melanoma has either undergone complete regression or was internal. Even at autopsy, mystery sometimes remains. Accounts for 5–8% of patients in referral centers.
- **Desmoplastic/neurotrophic melanoma:** Usually presents as LM of face or arms, but evolves into scar- or keloid-like lesion; diagnosis first made histologically.
  Caution: Be suspicious of facial keloid following removal of any poorly defined pigmented lesion.
- **Other histologic variants:** Melanomas may resemble ordinary or Spitz nevi under the microscope; making this diagnosis simply indicates a degree of uncertainty in the diagnosis. Balloon cell nevi and melanomas have large cells with clear cytoplasm; they are only identified histologically.

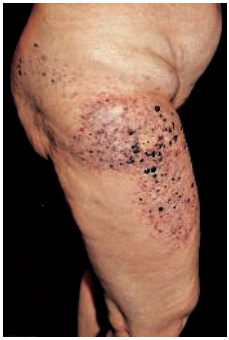

Fig. 23.**12** · Widespread cutaneous metastases from malignant melanoma.

Histology

The distinction between melanoma and atypical nevus is the most difficult one in dermatopathology. Some of the features favoring melanoma are:

- More single melanocytes than nests at the dermoepidermal junction.
- Atypical melanocytes at all levels of the epidermis.
- Atypical melanocytes in dermis.
- Mitoses, especially abnormal mitoses, in all levels of tumor; most worrisome at base.
- Lack of maturation of melanocytes in deeper levels.
- Asymmetry because of overall pattern, as well as variations in cell size, color and nature of infiltrate.
- **Immunohistochemistry:** No one specific melanoma marker. S100 has highest sensitivity but identifies melanocytes of all types and many other cell lines. HMB-45 and Melan A/Mart 1 are more specific (>90%) for malignant melanoma. Proliferation markers such as Ki-67/MIB 1 also useful.

Diagnostic Approach

- Clinical examination, dermatoscopy, and photo-documentation.
- Employ the ABCDE rules (see p. 389) to identify suspicious nevi and early malignant melanomas.
- Pruritus, bleeding, and ulceration are worrisome signs in nevi, but usually occur too late in the evolution of a melanoma to be of much help in improving outlook.
- Perform excisional biopsy if any suspicion of malignant melanoma exists; incisional biopsies should be reserved for rare cases of LMM that are too large for excision.
- As diagnostic certainty increases, more and more often the tentative diagnosis of malignant melanoma is made and the lesion excised with appropriate margins, avoiding a re-excision. Ultrasonography with a 20–50 MHz head can be used for preoperative assessment of tumor thickness but plays no role in diagnosing malignant melanoma.

Dermatoscopy

The principles of dermatoscopy are discussed in Chapter 2, but expanded here. Dermatoscopic examination usually make it possible to rapidly separate melanocytic lesions from other pigmented tumors such as pigmented basal cell carcinoma, dermatofibroma, seborrheic keratosis, and vascular tumors. It is also the most useful way to distinguish between benign and malignant melanocytic tumors, and certainly the most reliable way to monitor atypical pigmented lesions for changes over time, using computer-assisted photodocumentation and analysis.
The clinical criteria used for identifying melanoma, such as symmetry, border, and color, are partly transferable to a dermatoscopic examination (Tables 23.**1**, 23.**2**), but the dermatoscopy criteria are much more detailed and specific, so considerable experience and training is required (Figs. 23.**13–16**).

Differential Diagnosis

- The greatest clinical difficulties are provided by melanocytic lesions, especially dysplastic nevus, pigmented spindle cell nevus, Spitz nevus, blue nevus.
- Nonmelanocytic lesions may also be troublesome; they include pigmented actinic keratosis, pigmented basal cell carcinoma, irrigated seborrheic keratosis, pyogenic granuloma, thrombosed hemangioma, angiokeratoma, dermatofibroma.

Staging

- Once the diagnosis of malignant melanoma has been established, the following procedures are routinely employed for lesions > 1.00 mm in thickness and can be employed in selected cases for thinner lesions:
  - Routine laboratory evaluation.
  - Chest radiograph.
  - Sonography of regional lymph nodes, abdomen, pelvis, and retroperitoneum.
  - Sentinel lymph node biopsy.
  - In higher risk patients (stage IIB and higher), imaging studies (CT, MRI, PET) and tumor marker levels may be helpful.
- **Prognostic parameters:** The most important prognostic parameters are obtained from the histological interpretation of the excisional biopsy (T). The tumor thickness according to Breslow is reproducible and of prognostic significance, as is the presence or absence of ulceration. The Clark level is only rarely independently use-

Table 23.1 · Dermatoscopic criteria for melanoma

Pigment network	
Irregular	Irregular meshwork, with tumor progression—loss of network
Thickened trabeculae	Parts of the network become thickened
Other criteria	
Branched streaks	At the border of the lesion, the meshwork falls apart, leaving thickened dark brown-black remnant Histological equivalent: confluent pigmented melanocytic nests
Radial streaks and pseudopods	Further continuation of process with pigmented streaks extending into normal skin as residua of irregular pigment network. When thickened distally, known as pseudopods Histological equivalent: irregular pigmented nests at junction in periphery ***Caution:*** When radial streaks and pseudopods form a star burst pattern around tumor, diagnosis is usually pigmented spindle cell tumor (Reed tumor).
Black dots	Very dark, round-oval structures about 0.1 mm in diameter, mainly in periphery Histological equivalent: melanocytes or melanin in the stratum corneum
Veil	White veil-like areas over a dark background Histological equivalent: orthokeratosis or hyperkeratosis
Gray-blue areas	Gray-blue to gray-black areas are typically areas of regression in a melanoma Histological equivalent: areas of regression with melanophages in papillary dermis

Table 23.2 · Dermatoscopic risk estimation for melanocytic tumors (after Kenet and Fitzpatrick)

Risk group	Dermatoscopic criteria
Low risk	Regular pigment network, with no other melanoma criteria
Medium risk	Irregular pigment network, more prominent at periphery, with no other melanoma criteria
High risk	Irregular pigment network with other criteria (branched streaks, radial streaks, pseudopods, black dots, veil, and gray-blue areas)

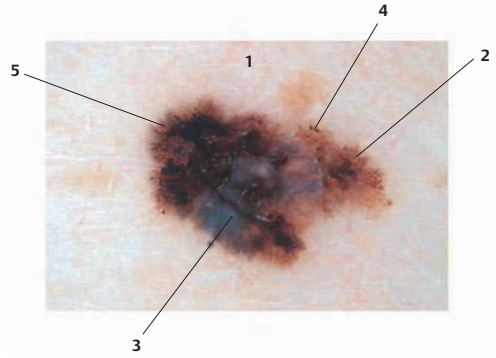

Fig. 23.**13** · **Dermatoscopy of malignant melanoma. 1** Asymmetry in all axes. **2** Atypical network. **3** Blue-white veil. **4** Irregular dots. **5** Irregular streaks at periphery (Image courtesy of Prof. Dr. Helmut Kerl MD, Graz, Austria.)

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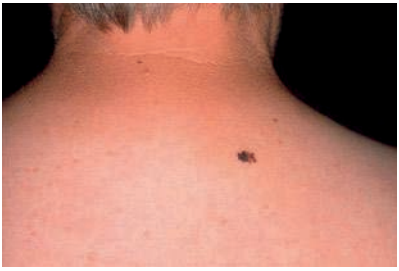

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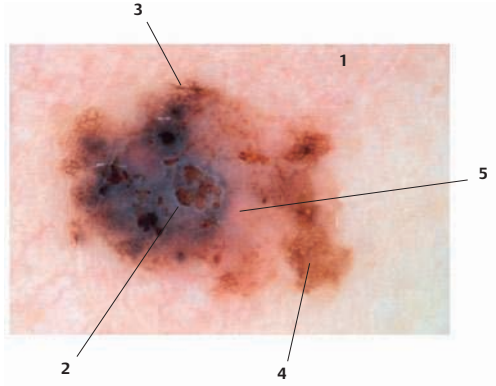


Fig. 23.**14** · **Malignant melanoma. a** Lesion on back. **b** Dermatoscopy of malignant melanoma shown in **a**: **1** Asymmetry in all axes. **2** Blue-white structures. **3** Irregular streaks. **4** Atypical network. **5** Dotted vessels. (Images courtesy of Prof. Dr. Helmut Kerl MD, Graz, Austria.)

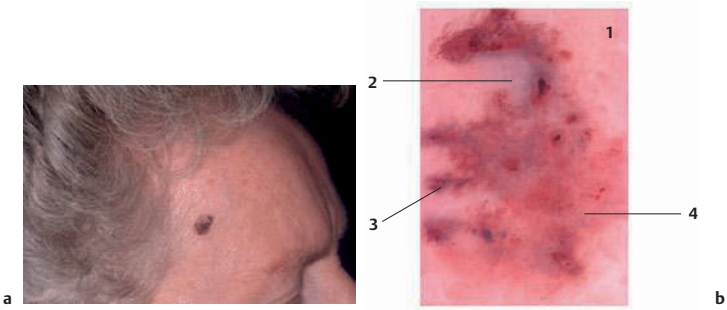


Fig. 23.**15** · **Malignant melanoma. a** Lesion on temple. **b** Dermatoscopy of malignant melanoma shown in **a**: **1** Asymmetry in all axes. **2** White structures. **3** Asymmetrically pigmented follicles. **4** Annular granular structures. (Images courtesy of Prof. Dr. Helmut Kerl MD, Graz, Austria.)

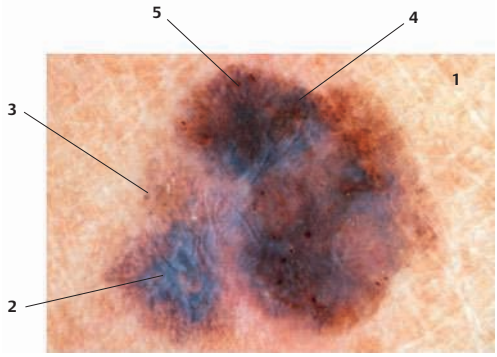


Fig. 23.**16** · **Dermatoscopy of malignant melanoma**. **1** Asymmetry in all axes. **2** Blue-white veil. **3** Irregular dots and globules. **4** Irregular blotches. **5** Irregular streaks. (Image courtesy of Prof. Dr. Helmut Kerl MD, Graz, Austria.)

ful, such as in selected body sites for tumors < 1.00 mm in thickness (Figs. 23.**17**, 23.**18**).

- When evaluating lymph nodes, the number of positive nodes and the degree of involvement (clinically apparent vs. clinically occult) are significant, as well as the presence of ulceration in primary tumor (N). In considering metastases (M), visceral metastases have a worse prognosis than cutaneous. See Tables 23.**3** and 23.**4**..

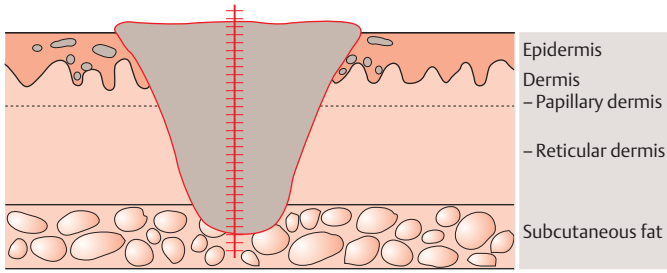


Fig. 23.**17** · Measuring the thickness of a tumor with an ocular micrometer to determine the Breslow depth. The measurement is taken from the stratum granulosum to the deepest point; melanoma cells extending along hair follicles are not measured.

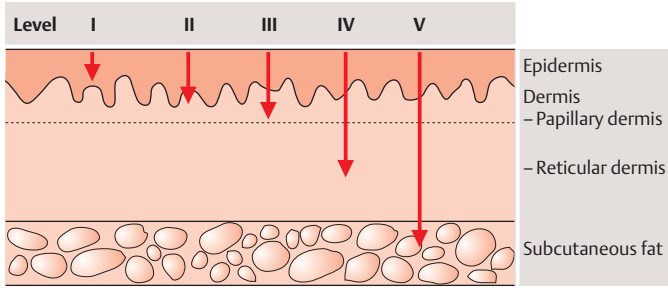


Fig. 23.**18** · Clark levels of malignant melanoma.

Table 23.3 · **TNM classification of malignant melanoma**

Primary tumor (T)		
T1	≤1.00 mm	a) without / b) with—ulceration or Clark level IV/V
T2	1.01–2.00 mm	a) without / b) with—ulceration
T3	2.01–4.00 mm	a) without / b) with—ulceration
T4	>4.00 mm	a) without / b) with—ulceration
Lymph nodes (N)		
N1a	Involvement of 1 LN with micrometastasis	
N1b	Involvement of 1 LN with macrometastasis	
N2a	Involvement of 2–3 LN with micrometastasis	
N2b	Involvement of 2–3 LN with macrometastasis	
N2c	Satellite or in-transit metastases without LN involvement	
N3	4 or more involved LN or satellite or in-transit metastases with LN involvement, or ulcerated primary tumor with LN involvement	

Table 23.3 · Continued

Lymph nodes (N)	
Micrometastasis	LN involvement detected with histologic examination, such as after sentinel LN dissection
Macrometastasis	Clinically palpable LN involvement or identified during surgical procedure
Distant metastases	
M1	Distant metastases in skin, LN, or subcutaneous fat with normal LDH
M2	Pulmonary metastases with normal LDH
M3	All other metastases, or any metastases with elevated LDH

LN = lymph node.
Based on American Joint Committee on Cancer (AJCC) criteria, 2002.

Table 23.4 · Staging of malignant melanoma with pathologic criteria

Stage	T	N	M	Criteria
0	Tis	N0	M0	Tis in situ melanoma
IA	T1a	N0	M0	T = 1.00 mm without ulceration
IB	T1b	N0	M0	T = 1.00 mm with ulceration or Clark level IV–V
	T2a	N0	M0	T 1.01–2.00 mm without ulceration
IIA	T2b	N0	M0	T 1.01–2.00 mm with ulceration
	T3a	N0	M0	T 2.01–4.00 mm without ulceration
IIB	T3b	N0	M0	T 2.01–4.00 mm with ulceration
	T4a	N0	M0	T > 4.00 mm without ulceration
IIC	T4b	N0	M0	T > 4.00 mm with ulceration
IIIA	T1–4a	N1a	M0	All T1–4a and 1 LN with micrometastasis
	T1–4a	N2a	M0	All T1–4a and 2–3 LN with micrometastasis
IIIB	T1–4a	N1b	M0	All T1–4a and 1 LN with macrometastasis
	T1–4a	N2b	M0	All T1–4a and 2–3 LN with macrometastasis
	T1–4b	N1a	M0	All T1–4b (with ulceration) and 1 LN with micrometastasis
	T1–4b	N2a	M0	All T1–4b (with ulceration) and 2–3 LN with micrometastasis
	T1–4a/b	N2c	M0	All T ± ulceration and in-transit or satellite metastases without LN involvement

Continued ▶

Table 23.4 · Continued

Stage	T	N	M	Criteria
IIIC	T1–4b	N1b	M0	All T1–4b (with ulceration) and 1 LN with macrometastasis
	T1–4b	N2b	M0	All T1–4b (with ulceration) and 2–3 LN with macrometastasis
	Any T	N3	M0	Any T with 4 or more LN with macrometastasis or any T with ulceration and macroscopic or in-transit metastases
IV	Any T	Any N	M1	Distant metastases

LN = lymph node.
Based on American Joint Committee on Cancer (AJCC) criteria, 2002.

Sentinel Lymph Node Biopsy

- Procedure recommended for tumors > 1 mm thickness.
- Sentinel lymph node is the first node in the regional drainage basin.
- Radioactive colloid injected about tumor with lymph node scintigraphy; then after period of time (4–24 hours), patent blue dye injected about tumor; scintigraphy and visual inspection for blue dye used to identify sentinel node (or nodes).
- Histologic status of sentinel lymph is of great prognostic importance; regardless of tumor thickness;
  - Negative SLN → 85% 5-year survival.
  - Positive SLN → 30% 5-year survival.
  - If SLN biopsy is positive, regional lymph node dissection is carried out.

Note: SLN biopsy is still a staging procedure; many studies are in progress to determine if it contributes to an improved survival..

Therapy

Malignant Melanoma

- Curable when recognized early and excised. When lymph node involvement or distant metastases occur, the prognosis is grave, although new therapeutic advances have increased the survival time for patients in this group.
- **Primary tumor:**
  - Excision is treatment of choice.
  - Margin of safety:
    - Tumors ≤ 1 mm thickness → 1 cm excision margin.
    - Tumors > 1 mm thickness → 2 cm excision margin.
- Melanomas on the face or in acral or anogenital sites may be excised using microscopic control of margins.
- **Adjuvant therapy:**
  - There is no proven increased survival for patients with any category of malignant melanoma following adjuvant chemotherapy, radiation therapy, or hyperthermic limb perfusion with chemotherapy agents.
  - All patients with high-risk melanomas (stage IIB or higher) should be offered adjuvant immunotherapy as part of a clinical study. The most promising agent is interferon-α_2, but the most effective regimen has yet to be determined.

Metastatic Malignant Melanoma

- Dismal outlook, with 6–9 months mean survival time.
- In-transit or satellite metastases should be surgically removed as far as possible. If multiple inoperable metastases are confined to a limb, hyperthermic perfusion with chemotherapy agents (for example with melphalan and TNF α) achieves a high remission rate (80%) but is fraught with complications and does not prolong life. Other possibilities include cryotherapy, laser ablation, topical immunotherapy.
- If LN metastases are identified, radical LN dissection is required. Adjuvant immunotherapy should be offered.
- **Radiation therapy** is the treatment of choice for bone and brain metastases. Isolated inoperable brain metastases (<3–5) should be irradiated individually with sterotactic convergence radiation. In addition, fotemustine 100 mg/m^2 i. v. can be added. Dexamethasone should also be administered to reduce brain edema.
- If there are multiple brain metastases, then whole brain irradiation can combined with chemotherapy including fotemustine 100 mg/m^2 i. v. on days 1, 8, and 15; then 5 week pause, combined with temozolomide 150–200 mg/m^2 orally every 4 weeks. Both agents cross the blood–brain barrier well.
- **Distant metastases:**
  - Dacarbazine (DTIC) 800 mg/m^2 i. v. every 4 weeks until progression occurs is the standard approved monotherapy, with about 20% response rate.
  - Polychemotherapy (many different regimens available) offers slightly higher response rates (20–30%) but with considerably more side effects.
  - High-dose interleukin (IL)-2 is a potential first line therapy in patients in good general health (high Karnofsky score).
  - Combined chemo- and immunotherapy (for example, DTIC, cisplatin, interferon-α and IL-2) achieves response rates as high as 50%. In individual cases, complete, long-lasting remissions are achieved. Such treatment should only be offered as part of a clinical study; with more than 1500 patients already treated, analysis shows a clear advantage over chemotherapy alone.
  - Solitary brain, liver, and lung metastases can be removed by surgery; 5-year survival up to 20% if truly only one metastasis.
  - Histamine increases the effect of IL-2 on liver metastases.
- **Experimental therapy:** Because of the dismal outlook for metastasis malignant melanoma, many experimental therapies are in development. Dendritic cell vaccination and gene therapy protocols are available, as well as administration of tumor-infiltrating lymphocytes and lymphokine-activated killer cells. All such approaches must be offered as part of clinical studies.
- **Follow-up:**
  - Clinical evaluation should be carried out every 3–6 months for 10 years, depending on the stage of the primary tumor. The current German guidelines are shown in Table 23.**5**.

    Note: Dermatologic evaluation must be part of all malignant melanoma follow-up, because patients with malignant melanoma have an increased risk of developing a second melanoma.
- **Early diagnosis of LN metastases:** Routine sonography (7.5–14 MHz) of in-transit area and regional nodes, coupled with fine needle aspiration, improves sensitivity.
- **Tumor markers:** S100, tyrosinase, and MIA all have been proposed as markers for recurrent disease. They may be better for following response to therapy than for discovering early metastases. In addition, false-positive results cause considerable anxiety and expense.

Table 23.5 · Follow-up of patients with malignant melanoma

Stage	Thickness	Clinical examination		LN sonography	Laboratory	Other imaging
		Years 1–5	Years 6–10			
I	< 1 mm	q. 6 mo.	q. 12 mo.	–	–	–
I + II	> 1 mm	q. 3 mo.	q. 6 mo.	q. 6 mo.	q. 6 mo.	–
III[a]		q. 3 mo.	q. 6 mo.	q. 3–6 mo.	q. 3–6 mo.	q. 6 mo.
IV[b]		prn	prn	prn	prn	prn

LN = lymph node.
a Frequency can be reduced after 3 years.
b All investigations for stage IV patients must be individualized.

► **Oncologic terminology:** The terms oncologists use to describe responses to therapy are often not known to patients and physicians. Some of the most common terms are shown in Table 23.**6**.

Table 23.6 · Oncologic terms for therapeutic responses

Complete remission (CR)	Disappearance of all signs of tumor for 4 weeks
Partial remission (PR)	Tumor reduction > 50% for 4 weeks
No change (NC) or stable disease	Tumor reduction < 50% or tumor progression < 25% or no change in parameters
Duration of remission	Period of time between achieving remission and recurrence of tumor
Total survival	Period of time between onset or therapy and death of patient
Recurrence-free survival	Period of time between tumor-free status and recurrence

24 Cysts and Epidermal Tumors

24.1 Cysts

Epidermoid Cyst

- **Synonyms:** Infundibular cyst, epidermal inclusion cyst, sebaceous cyst (common term, but completely incorrect).
- **Definition:** Cyst whose wall consists of stratified epithelium with stratum corneum.
- **Pathogenesis:** Most arise from the infundibulum, the upper part of the hair follicle above the site of entry of the sebaceous duct. Some are true inclusion cysts following trauma, usually to palms or soles, where a fragment of epidermis is embedded in dermis; others follow severe acne.
- **Clinical features:** Slowly growing, skin-colored, firm cystic structures, usually with visible central pore, ranging in size from 0.5 to 5.0 cm (Fig. 24.**1**). Most commonly on face or trunk. Two clinical variants include:
  - *Scrotal cysts*: Multiple epidermal cysts on scrotum, often calcified.
  - *Gardner syndrome* (p. 368): May present with multiple epidermoid cysts in childhood.

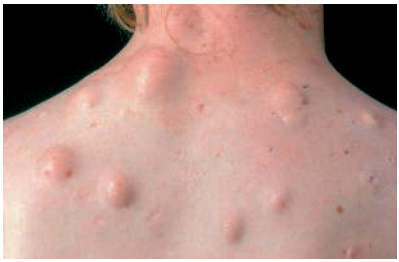


Fig. 24.**1** · Multiple epidermoid cysts.

- **Histology:** Cyst wall resembles normal epidermis with granular layer, inner layers thinner than basal layer, and stratum corneum; cyst contents are keratin arranged in layers. If cyst ruptures, keratin induces foreign body reaction with giant cells containing slivers of keratin (*cornflakes sign*).
- **Differential diagnosis:** Trichilemmal cyst.
- **Therapy:** Simple excision or extraction where small incision is made with scalpel or punch and then cyst contents extruded and cyst wall removed with curved forceps.
  Note: If the cyst wall is not completely removed, recurrences are more likely.

Milia

- **Definition:** Tiny variant of epidermoid cyst.
- *Pathogenesis:* Milia may be primary or secondary:
  - *Primary milia:* Tiny retention cysts of vellus hair follicle or rarely eccrine glands. Occasionally multiple and grouped: *plaque-like milia*.

- *Secondary milia:* Develop following trauma (dermabrasion) or subepidermal blistering diseases (bullous pemphigoid, porphyria cutanea tarda, junctional and dystrophic epidermolysis bullosa), presumably from small fragments of epithelium landing in dermis.

- **Clinical features:** 1–2 mm dome-shaped white-yellow papules, favoring face (cheeks, temples, periorbital).
- **Histology:** Exactly like epidermoid cyst; just smaller, except in rare cases of eccrine milia when sweat gland remnants can be seen.
- **Differential diagnosis:** Plane warts, xanthomas, syringomas.
- **Therapy:** Incision and expression of contents; laser ablation.

Trichilemmal Cyst

- **Synonyms:** Pilar cyst, isthmus-catagen cyst, wen.
- **Definition:** Cyst arises deeper in hair follicle with wall showing keratinization pattern without flattening of cells or granular layer.
- **Pathogenesis:** Often familial tendency; suggestion of autosomal dominant inheritance.
- **Clinical features:** Most lesions are on scalp (90%); rest on face, neck, upper trunk. 70% multiple; 30% solitary. Firmer than epidermoid cyst, no central pore; contents compact keratin with cheesy nature and smell.
- **Histology:** Keratinocytes in cyst wall show no tendency to flattening; abrupt transition to homogenous glassy keratin (trichilemmal keratinization). Often calcified.
- **Therapy:** See epidermoid cyst.

Proliferating Trichilemmal Cyst

- **Synonym:** Proliferating pilar tumor.
- **Definition:** Poorly understood tumor arising in connection with trichilemmal cysts. Some view tumor as benign; others consider it an extremely low-grade squamous cell carcinoma growing initially into a cyst cavity.
- **Clinical features:** Slow-growing nodule, sometimes eroded or ulcerated. More common in elderly women. Sometimes accompanied by other banal trichilemmal cysts. Can reach monstrous size.
- **Histology:** In early cases, remnants of cyst wall with atypical nests and strands of keratinocytes with trichilemmal keratinization extending into or toward cyst lumen. Later obliteration of cystic structure and appearance of squamous cell carcinoma.
- **Differential diagnosis:** Squamous cell carcinoma, pilomatrical carcinoma, basal cell carcinoma, malignant cylindroma.
- **Therapy:** Excision; follow-up as squamous cell carcinoma.

Dermoid Cyst

- **Definition:** Embryologic epidermal cyst containing adnexal structures; no relation to the benign ovarian teratoma known by the same name.
- **Pathogenesis:** Result of abnormal embryonic fusion, usually in midventral locations, leading to entrapment of epidermis in dermis.
- **Clinical features:** Midline cyst 1–4 cm present at birth; most common site is between eyes.
- **Histology:** Cyst wall shows normal epidermis with hairs, sweat glands, and rarely bone or even teeth.

- **Differential diagnosis:** Epidermoid or trichilemmal cyst; in newborn, ectopic neural tissue, vascular tumors.
  - ***Caution:*** Before surgery, consult an expert and carry out imaging studies on all suspected dermoid cysts to exclude ectopic neural tissue (nasal glioma, meningioma).
- **Therapy:** Excision.

Steatocystoma

- **Synonym:** True sebaceous cyst.
- **Definition:** Epithelial cyst whose wall contains small sebaceous glands.
- **Pathogenesis:** Multiple lesions may be inherited in autosomal dominant manner.
- **Clinical features:** Three clinical settings:
  - *Steatocystoma simplex:* Solitary often flaccid cyst, clinically identical to epidermoid cyst.
  - *Steatocystoma multiplex:* Multiple flaccid yellow cysts appearing usually at puberty favoring anterior chest, neck, axillae, genitalia.
  - *Oldfield syndrome:* Rarely steatocystoma are associated with intestinal polyposis, analogous to Gardner syndrome (p. 368); relationship controversial.
- **Histology:** Cyst wall usually collapsed and crenulated (notched) with tiny sebaceous glands.
- **Differential diagnosis:** *Eruptive vellus hair cysts* appear very similar, are usually somewhat smaller and more papular; they contain numerous vellus hairs as well as sebaceous glands. Some feel two conditions are part of a spectrum. *Keratocysts* are usually part of nevoid basal cell carcinoma syndrome (p. 435), but can also be sporadic. Identical to steatocystoma with crenulated cyst wall, but no sebaceous glands found.
- **Therapy:** Excision or laser ablation; systemic isotretinoin produces improvement in multiple lesions, usually short-lived when therapy is discontinued.

Ganglion

- **Synonym:** Digital mucous cyst (for special variant).
- **Definition:** Benign cyst arising from joint capsule or tendon, consisting of fibrous capsule containing mucinous material.
- **Pathogenesis:** Ganglion cysts can be viewed as herniations of synovial tissue.
- **Clinical features:** A true ganglion cyst is a soft tissue lesion occurring most commonly about the wrist. The ganglion variant familiar to dermatologists is the *digital mucous cyst,* a shimmering blue cystic structure almost always at the proximal border of a finger or toe nail. The associated nail is often distorted.
- **Histology:** A ganglion is a true cyst. The digital mucous cyst is a pseudocyst, as the mucinous joint fluid is surrounded by granulomatous response, not a cyst wall.
- **Diagnostic approach:** Larger cysts can be transilluminated. Digital cysts can be punctured; a clear gelatinous material oozes out.
- **Differential diagnosis:** The larger cysts over joints may be confused with lipomas, neuromas, chondromas, and exostoses. The digital lesion is clinically distinctive.
- **Therapy:** Ganglion cysts are usually removed by orthopedic or hand surgeons. The connection to a joint space is established with dye injection and then the connection tied off. The same procedure is often necessary for the digital mucous cyst, as other approaches such as drainage, intralesional corticosteroids, and superficial ablation often produce only short-term improvement.

Mucocele

Oral pseudocyst; results from bite or other trauma interrupting minor salivary gland duct with extravasation of mucinous material and histiocytic reaction. Presents as glistening dome-shaped nodule, usually as site of bite trauma. On histology, no cyst wall. Easily excised or otherwise destroyed. A *sialolith* or salivary duct stone may temporarily block off a duct, causing a mucocele-like swelling that resolves spontaneously as the obstruction clears.

24.2 Epidermal and Organoid Nevi

Epidermal Nevus

- **Synonym:** Verrucous nevus, nevus verrucosus.
- **Definition:** Focal area of abnormal epidermal development following Blaschko lines and having a variety of histologic patterns, sometimes associated with systemic abnormalities (*epidermal nevus syndrome*).
- **Pathogenesis:** There is considerable overlap between epidermal and organoid nevi, so both are considered together. A true epidermal nevus has an abnormal pattern of keratinization. Any mutation that can cause diffuse disturbances in keratinization (epidermolytic hyperkeratosis, Darier disease) or isolated lesions (porokeratosis) can also present as an epidermal nevus, the result of somatic mosaicism occurring early in embryonic life. Organoid nevi feature both epidermal and adnexal structures.
- **Clinical features:** An epidermal nevus is always present at birth, but sometimes not recognized as it may be flat, perhaps slightly pigmented, and only later become hyperkeratotic (Fig. 24.**2**). Soft and hard epidermal nevi can be distinguished; the former is papillomatous, similar to a skin tag or fleshy melanocytic nevus, while the latter is warty. Both may range in color from pale tan to dark brown. Most typical locations are face, neck, upper trunk.
- **Histology:** Typically, papillomatosis and varying degrees of hyperkeratosis.
- **Diagnostic approach:** History (present at birth), clinical examination; biopsy for confirmation.

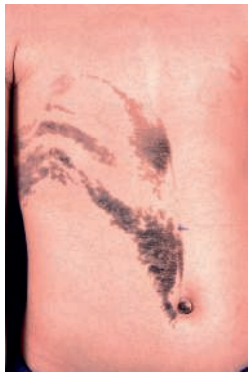


Fig. 24.**2** · Epidermal nevus.

- **Differential diagnosis:** Other epidermal nevi, other linear lesions. In the absence of history, a large seborrheic keratosis cannot be separated with certainty from a small epidermal nevus.
- **Therapy:** Excision (often serial excisions if large); dermabrasion, cryosurgery, and laser ablation may be successful for more superficial lesions.

ILVEN

- **Synonym:** ILVEN is an acronym for **i**nflammatory **l**inear **v**errucous **e**pidermal **n**evus.
- **MIM code:** 163200.
- **Epidemiology:** Women more often affected.
- **Pathogenesis:** ILVEN is exceptional in that it appears later in life. The suggestion is that there is a mutation in mosaic pattern, which predisposes certain areas of the skin to develop a dermatitic response.
- **Clinical features:**
  - Linear psoriasiform or dermatitic streaks, usually on extremities.
  - Appears later in life; not visible at birth.
  - ILVEN syndrome possible, association with other developmental anomalies.
- **Histology:** Without a history, easily mistaken for psoriasis or psoriasiform dermatitis with acanthosis, hyperkeratosis, and a dermal inflammatory cell infiltrate with exocytosis.
- **Differential diagnosis:** Other linear lesions especially lichen striatus.
- **Therapy:** Excision; treatment with antipsoriatic measures such as vitamin D analogues sometimes helpful.

Acantholytic Dyskeratotic Nevus

- **Synonym:** Segmental Darier disease, segmental Hailey–Hailey disease.
- **Pathogenesis:** Mosaic with mutation in *ATP2A2* gene (responsible for Darier disease) or *ATP2C1* gene (responsible for Hailey–Hailey disease). Described as type I mutation by Happle, as abnormal skin arises on background of normal skin. A type II segmental Darier disease, for example, occurs when a patient with Darier disease experiences loss of their normal allele in a mosaic pattern and develops even more severe skin disease in this location.
- **Clinical features:** Cannot be clinically separated from other epidermal nevi.
- **Therapy:** Excision when possible; otherwise, retinoids sometimes help, as they do for the systemic disorder.

Nevus sebaceus

- **Synonym:** Organoid nevus, Jadassohn nevus.
- **Definition:** Prototype of organoid nevus with increase in all epithelial components, especially the sebaceous glands.
- **Pathogenesis:** Once again, somatic mosaic with lesion following Blaschko lines.
- **Clinical features:** Nevus sebaceus is one of the few epidermal nevi that is clinically distinct (Fig. 24.**3**):
  - At birth, hairless yellow-orange plaque usually on scalp or temple.
  - At puberty, becomes thicker, nodular or verrucous.
  - Variety of tumors develop within nevus:
    - Trichoblastoma is most common.
    - Syringocystadenoma papilliferum also typical.
    - Basal cell carcinoma can occur, but extremely rare.

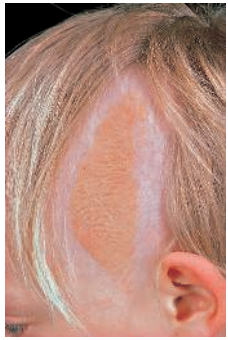


Fig. 24.**3** · Nevus sebaceus.

- **Histology:** Biopsies taken before puberty are relatively nondistinct, showing small sebaceous glands and sometimes abundant eccrine glands. When a thickened lesion is biopsied, then numerous sebaceous, eccrine, and apocrine glands, as well as abortive hairs, are seen beneath a papillomatous epidermis.
- **Diagnostic approach:** History, clinical examination; biopsy only needed if lesion is changing.
- **Differential diagnosis:** Other epidermal nevi, especially if not on scalp.
- **Therapy:** Excision.

Becker Nevus

- **Synonym:** Melanosis neviformis Becker.
- **Definition:** Type of organoid nevus with hyperpigmentation, increased hairs, and often increased smooth muscles.
- **Epidemiology:** Relatively common malformation.
- **Pathogenesis:** Type of organoid nevus involved hairs and smooth muscles; marked increase in androgen receptors explains flare at puberty. More easily recognized in men because of response to androgens. No increase in melanocytes.
- **Clinical features:**
  - Large patch or plaque; present at birth, but usually ignored. First sign is hyperpigmentation, but most dramatic change is growth of hairs during puberty (Fig. 24.**4**). Usually on trunk.
  - Hairs may become erect with rubbing if there is an associated *smooth muscle hamartoma* at base.
  - Area is hormonally sensitive; sometimes acne occurs, confined to nevus.

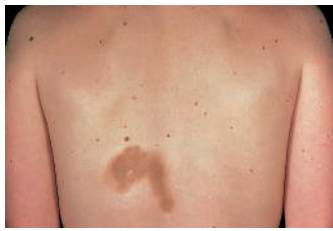


Fig. 24.**4** · Becker nevus.

- *Becker nevus syndrome:* Combination of one or more Becker nevi with ipsilateral breast hypoplasia, skeletal anomalies (ipsilateral shoulder girdle or arm hypoplasia, scoliosis, vertebral anomalies) and other cutaneous malformations.

- **Histology:** Increased basal layer melanin, normal number of melanocytes. Thick mature but normal hairs. In many cases, proliferation of arrector pili (smooth muscle).
- **Differential diagnosis:** Usually misdiagnosed as some form of melanocytic nevus; other possibilities include café-au-lait macule (early), nevus spilus, atypical dermal melanosis.
- **Therapy:** None needed; generally too large for excision.

Other Epidermal and Organoid Nevi

- **Hair follicle nevus:** Area of hypertrichosis with multiple hairs, often in immature stages and in peculiar groupings. When an accessory tragus (cartilaginous rest anterior to ear) is sectioned tangentially, it is often misinterpreted as hair follicle nevus.
- **Angora hair nevus:** Similar to hair follicle nevus, but with long hypopigmented hairs; not described as solitary finding but just in angora hair nevus syndrome.
- **Apocrine nevus:** Similar to nevus sebaceous but contains only excess apocrine glands.
- **Eccrine nevus:** Similar to nevus sebaceous but contains only excess eccrine glands.
- **Eccrine angiomatous hamartoma:** Linear lesion usually on legs, patients complain of localized hyperhidrosis; on biopsy, increased eccrine glands and small vessels.
- **Porokeratotic eccrine nevus:** Clinically multiple spines and plugs, which histologically show a parakeratotic column filling the eccrine duct ostia.
- **Nevus comedonicus:** Lesion with thick comedone-like epidermal invaginations but without inflammatory lesions of acne.
- **Munro nevus:** Local area of acne; contains same mutation in FGFR2 (fibroblast growth factor receptor) as in Apert syndrome (craniosynostosis, skeletal defects, and severe acne often involving extremities).

Epidermal Nevus Syndromes

The epidermal nevus syndromes feature some of the above mentioned nevi, in association with skeletal, neurological, and other developmental defects. They reflect somatic mosaicism, with mutation presumably occurring at an earlier embryonic stage leading to involvement of multiple systems.

Schimmelpenning–Feuerstein–Mims Syndrome

- **Synonym:** Nevus sebaceus syndrome.
- **MIM code:** 163200.
- **Definition:** Prototype of epidermal nevus syndrome with generalized nevus sebaceus and multiple anomalies.
- **Clinical features:**
  - Multiple nevus sebaceus, favoring scalp, but widespread, usually unilateral.
  - Pigmentary changes including café-au-lait macules and lentigines.
  - Ocular, cardiac, and skeletal anomalies; epilepsy; growth retardation.
- **Diagnostic approach:** Multidisciplinary diagnosis; skin biopsy may help confirm.
- **Differential diagnosis:** Proteus syndrome, other epidermal nevus syndromes.
- **Therapy:** Symptomatic depending on manifestations; nevus sebaceus can be excised.

Proteus Syndrome
- **MIM code:** 176920.
- **Definition:** Complex malformation syndrome; Proteus was a Greek god who could assume many different appearances.
- **Pathogenesis:** Lethal mutation that is viable only in the mosaic state. Still controversy over which gene is involved.
- **Clinical features:**
  - Ordinary epidermal nevi, but often extensive.
  - Large connective tissue nevi (p. 438), typically involving hands and feet.
  - Areas of hypoplasia of dermis or fat.
  - Vascular malformations and lipomas.
  - Disproportionate overgrowth of bone and soft tissue producing misshapen hands and feet.
  - Many other abnormalities, involving almost every organ system.

  Note: Joseph Merrick, the "Elephant Man," had Proteus syndrome, not neurofibromatosis.
- **Differential diagnosis:** A full-blown case is easy to diagnose; when only a few features are present, may be confused with vascular malformation syndromes.
- **Therapy:** Symptomatic; some problems amenable to surgical correction.

CHILD Syndrome
- **Mim code:** 308050.
- **Definition:** **C**ongenital **h**emidysplasia with **i**chthyosiform nevus and **l**imb **d**efects.
- **Pathogenesis:** Defect in *NHDSL* gene involved in sterol synthesis; located at X28; X-linked dominant inheritance, so only women are affected.
- **Clinical features:** Rare epidermal nevus syndrome with striking ichthyosiform or psoriasiform epidermal nevi which strikingly represent the midline, usually associated with ipsilateral skeletal defects. Favor body folds (*ptychotropism*). May wax and wane, so that some formerly considered the CHILD nevus a type of ichthyosis. Ipsilateral skeletal defects, as well as a variety of other systemic problems.
- **Histology:** Often very reminiscent of psoriasis; dermal papillae may contain foamy cells (*verruciform xanthoma,* p. 315).
- **Therapy:** Cutaneous lesions may improve with antipsoriatic therapy, such as vitamin D analogues.

Other Epidermal Nevus Syndromes
Systemic involvement has also been reported with Becker nevus, phacomatosis pigmentokeratotica (nevus spilus and nevus sebaceus), and angora hair nevus.

24.3 Benign Epidermal Tumors

Seborrheic Keratosis
- **Synonym:** Verruca seborrhoeica.
- **Definition:** Common verrucous pigmented tumor, usually after 40 years of age.
- **Epidemiology:** Very common; almost every 60-year-old has at least one seborrheic keratosis.
- **Pathogenesis:** Unknown; despite histologic similarities, not caused by human papillomavirus.

- **Clinical features (Fig. 24.5):**
  - *Flat type:* Smooth flat waxy plaques 0.5 to several cm on trunk; vary from tan to dark brown, sometimes with visible punctate inclusions *(horn pseudocysts)*.
  - *Acanthotic type:* Elevated dome-shaped, usually smooth, often heavily pigmented (*melanoacanthoma*) nodule with inclusions.
  - *Verrucous type:* Paler 0.5–1.5 cm tumor with warty surface but without the punctate papillary hemorrhage so typical of viral warts.
  - *Stalked type:* Pedunculated tags with surface changes of seborrheic keratosis, often in flexures or periorbital.
  - *Irritated seborrheic keratosis:* Inflamed or irritated keratosis, secondary to trauma, irritation, or infection; tend to be smoother and less pigmented, so difficult to recognize.
  - *Stucco keratoses:* Pale, small keratoses typical on shins and back of feet, but occasionally on forearms and hands. Usually mistaken for warts.
  - *Dermatosis papulosa nigra:* Heavily pigmented small papules on the cheeks of blacks; present in over 40% of individuals (who rarely have multiple seborrheic keratoses elsewhere). Not seen in whites.
  - *Leser–Trélat sign:* Sudden appearance of multiple small seborrheic keratoses and skin tags in adult is a variant of acanthosis nigricans (p. 485) and should raise the possibility of an underlying malignancy. Extremely rare; in adults with multiple seborrheic keratoses there is no cause for concern about cancer without a history of sudden eruption.

  Note: Seborrheic keratoses grow in crops; very unusual to see a solitary lesion. If a lesion is atypical (very dark, inflamed), look for other, more normal variants in the area.

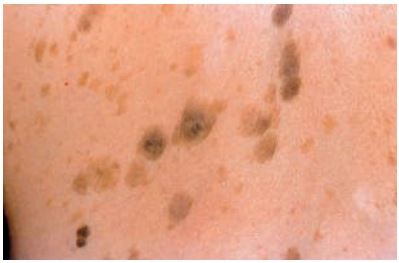


Fig. 24.5 · Multiple seborrheic keratoses.

- **Histology:** Unifying features are exophytic growth, acanthosis, and horn pseudocysts (epidermal invaginations filled with keratin). Degree of pigmentation varies. Some lesions very papillomatous with church spires (stucco keratosis, for example). Others show clonal proliferation of keratinocytes (*Borst–Jadassohn effect*).
- **Diagnostic approach:** Clinical examination; if questions, dermatoscopy is helpful.
- **Differential diagnosis:** Usually no differential diagnosis; sometimes common warts; if smooth or ulcerated, basal cell carcinoma; if heavily pigmented, melanocytic tumors.
- **Therapy:** Curettage is simplest; cryotherapy, dermabrasion and laser ablation are alternatives. Cryotherapy should be avoided for dark-skinned patients, such as those with dermatosis papulosa nigra, as postinflammatory hyperpigmentation is common.

Solar Lentigo

- **Synonyms:** Senile lentigo, actinic lentigo, old-age spot, liver spot.
- **Definition:** Common acquired lesion in older adults; number of synonyms makes it clear that there is lack of agreement on its exact nature. We few it as flat seborrheic keratosis in sun-exposed skin.
- **Clinical features:** Usually multiple, tan or brown macules with irregular shape on sun-exposed areas, especially backs of hands. Often a cosmetic problem. *Ink spot lentigo* is a variant with fine lines of pigment in skin folds, as if a drop of ink had been spilled on skin.
- **Histology:** Flat seborrheic keratosis with increased basal layer pigment (*dirty feet*), but no striking increase in melanocytes and definitely no nests.
- **Diagnostic approach:** If not clear with clinical examination and dermatoscopy, biopsy may be needed.
- **Differential diagnosis:** Pigmented actinic keratosis, Bowen disease, lentigo maligna melanoma in situ.
- **Therapy:** Cryotherapy, curettage, camouflage; laser ablation.

Lichenoid Keratosis

- **Clinical features:** Smooth erythematous papule or plaque, typically on décolletage, neck, or beneath breast.
- **Histology:** Dense lichenoid infiltrate at dermoepidermal junction; sometimes remnants of flat seborrheic keratosis or actinic keratosis.
- **Diagnostic approach:** Very difficult to diagnose clinically; dermatoscopy may help; otherwise biopsy.
- **Differential diagnosis:** Usually mistaken for basal cell carcinoma.
- **Therapy:** Excision.

Clear Cell Acanthoma

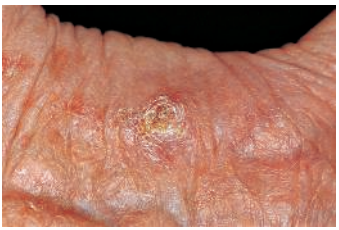
- **Synonym:** Degos tumor.
- **Clinical features:** Scaly plaque or nodule almost always on the shin of older individuals. Usually solitary, with no tendency to regress. No malignant potential.
- **Histology:** Numerous glycogen-rich keratinocytes give the epidermis a clear appearance and the tumor its name. Sharp transition from normal to clear epidermis. Also acanthosis and sometimes intraepidermal neutrophils, so confusion with psoriasis possible.
- **Differential diagnosis:** Poroma, dermatofibroma and old wart are most likely considerations; an amelanotic malignant melanoma must be excluded. Diagnosis always microscopic; some eccrine tumors, such as hidroacanthoma simplex, look quite similar.
- **Therapy:** Excision.

24.4 Carcinoma in situ

A carcinoma in situ is a neoplasm in which the tumor cells are confined to the epithelium of origin, without invasion of the basement membrane. If left untreated, progression to invasive carcinoma may occur.

Actinic Keratosis

- **Synonym:** Solar keratosis.
- **Definition:** UVB-induced carcinoma in situ.
- **Pathogenesis:** Mutations in a variety of genes including telomerase (delayed apoptosis, prolonged life) and TP53 (delayed apoptosis, accumulation of genetic damage).
- **Clinical features:**
  - 0.5–2.0 cm multiple sharply bordered irregular erythematous patches and papules with adherent scale, always in sun-exposed areas, more common in type I skin (Fig. 24.**6**).
  - ***Note:*** It is often easier to palpate actinic keratoses as "rough spots" than to try and see them.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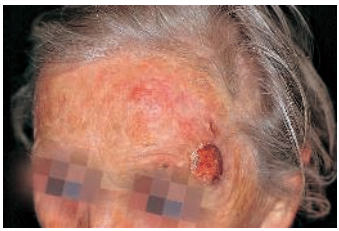
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Fig. 24.**6** · **a** Actinic keratosis. **b** With squamous cell carcinoma.

  - Early lesions (erythematous type) are 1–2 mm, with fine telangiectases only; the hykeratosis comes later.
  - Individual lesions may become irritated or inflamed (*lichenoid actinic keratosis*).
  - About 1% of actinic keratoses yearly are expected to change into invasive squamous cell carcinoma.
- **Histology:** Epidermis usually atrophic with hyperkeratotic scale, marked variation in size, and nuclear features of keratinocytes. Characteristic *pink and blue* as the hair follicles and eccrine ducts tend not to be involved so their keratin stains blue, while the intervening abnormal epidermis has pink, often parakeratotic keratin. Lichenoid actinic keratosis shows an intense dermoepidermal junction infiltrate. Bowenoid actinic keratosis shows more striking individual cell keratinization and atypia.
- **Diagnostic approach:** Strictly a clinical diagnosis; overdiagnosis results in an unneeded but harmless treatment; underdiagnosis is established at the regular follow-up all patients with actinic keratoses require.
- **Differential diagnosis:** In sun-exposed skin, few options. A flat pale seborrheic keratosis is identical clinically; hyperkeratotic lesions may be confused with warts.

Note: Actinic keratosis is the most common lesion underlying cutaneous horn. Other possibilities include squamous cell carcinoma, wart and seborrheic keratosis, but almost any tumor can be present at the base. Histological diagnosis always needed.

- **Therapy:**
  - Freezing with liquid nitrogen, ideally using a spray device and freezing for 5–10 seconds; you will soon acquire a feel for how long to freeze, depending on lesion thickness and location (more acrally and on scalp). In either case, lesions become necrotic and then peel or scab off.
  - Curettage with electrodesiccation or cautery, requires local anesthetic.
  - Excision, especially if thick, resistant to therapy or suspicious of squamous cell carcinoma.
  - *For numerous lesions:*
    - Topical 5-fluorouracil cream b.i.d. for 10–14 days; lesions become inflamed and red, then crust and peel off. All residual lesions (survivors) must be otherwise treated. Can be combined with topical tretinoin.
    - Topical imiquimod 3× weekly for 6 weeks.
    - Several other topical products available in USA: hyaluronic acid, masoprocol.
    - Trichloracetic acid peels, usually > 30%, and dermabrasion are more aggressive approaches.
  - *Photodynamic therapy:* Topical application of photosensitizing substance (usually methyl δ-aminolevulinic acid) followed by irradiation at a wavelength absorbed by agent. Can be used to identify and then to treat lesions that more readily absorb the photosensitizer.

Arsenic and Radiation Keratoses

These lesions arise in distinct clinical settings, tend to be more hyperkeratotic than actinic keratoses, and are generally more likely to progress to squamous cell carcinoma. They appear years after exposure to the carcinogen, but associated with arsenical melanosis or radiation dermatitis. Treatment is the same as for actinic keratosis.

Bowen Disease

- **Definition:** Squamous cell carcinoma in situ on the skin.
- **Pathogenesis:** Formerly most common triggers were radiation and arsenic; nowadays human papillomavirus (HPV) seems to be usual cause.
- **Clinical features:**
  - *Bowen disease:* Typically 1–3 cm slightly raised patch, tan to red-brown with variable scale. Most often truncal but can be anywhere (Fig. 24.**7**).
  - Over years, Bowen disease evolves into an invasive squamous cell carcinoma, known as *Bowen carcinoma*.
  - Lengthy debate over association of Bowen disease with internal malignancies; usually explained by linkage with past arsenic exposure.
- **Diagnostic approach:** Clinical examination, biopsy.
- **Differential diagnosis:**
  - Often mistaken for patch of dermatitis. Other possibilities include tinea, psoriasis, warts, actinic keratosis, superficial basal cell carcinoma, extramammary Paget disease.
  - Bowenoid papulosis (p. 71) is HPV-induced squamous cell carcinoma in situ of the genitalia; typically hyperpigmented; may undergo spontaneous regression.
- **Therapy:** Excision, curettage and electrodesiccation, laser ablation, or cryosurgery.

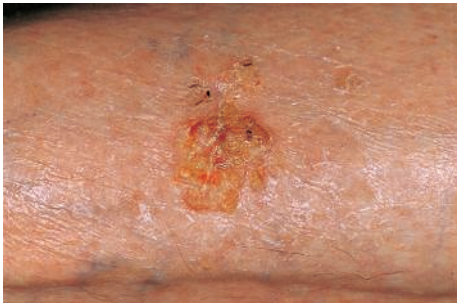


Fig. 24.**7** · Bowen disease.

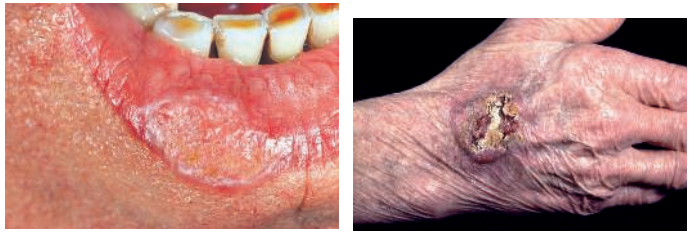
Erythroplasia of Queyrat

- **Pathogenesis:** Exactly the same as Bowen disease, but confined to mucous membranes.
- **Clinical features:** Velvety red patch typically on penis, vulva, perianal area, or mouth. Speckled leukoplakia in mouth is the combination of erythroplasia with dyskeratotic areas. Speckled red and white speckled pattern.
- **Diagnostic approach:** Clinical examination, biopsy.
- **Differential diagnosis:** Zoon balanitis, other forms of balanitis, psoriasis, lichen planus, fixed drug eruption.
- **Therapy:** Excision, superficial destruction; topical 5-fluorouracil under occlusion can be used in hair-free areas when surgery is not desired.

24.5 Malignant Epidermal Tumors

Squamous Cell Carcinoma (SCC)

- **Definition:** Malignant epidermal tumor arising from keratinocytes, with potential for local spread and metastasis.
- **Epidemiology:** Incidence 100:100000 in men; 50:100000 in women; increasing in frequency yearly. All statistics are distorted by how many actinic keratoses (SCC in situ) are counted.
- **Pathogenesis:** The main factor is UVB exposure, but there are many other factors including HPV (certainly types 16 and 18; others also implicated include 31, 33, and 38), radiation therapy, arsenic exposure, chemical carcinogens (tar, pitch), and immunosuppression (iatrogenic, HIV/AIDS).
- **Clinical features:** Usually present as hyperkeratotic papule or plaque, often with crust or ulceration (Fig. 24.**8**). Difficult to separate from precursor lesions. Growth rate and risk of metastasis are highly variable (Table 24.**1**); outlook is best for lesions on skin arising from actinic keratoses; worst for lip, penis, and vulva SCC.
- **Histology:** Keratinocytes are in disarray, with marked variation in cell size and nuclear features. Individual cell keratinization. Degree of keratinization reflects degree of differentiation and is used in staging schemes for some tumors such as



a b

Fig. 24.8 · **Squamous cell carcinoma. a** Early disease of lip. **b** Hand.

Table 24.1 · **Risk of metastasis for squamous cell carcinoma**

Form	Risk of metastasis (%)
Cutaneous, from actinic keratosis	0.1
Cutaneous, from Bowen disease	2 – 10
Mucous, from erythroplasia	20 – 40

oral cavity SCC. Downward growth of atypical keratinocytes into dermis and development of islands of atypical cells free from epidermis are unequivocal signs of progression to SCC.

- **Diagnostic approach:** Clinical examination and biopsy.
  - ***Note:*** Any actinic keratosis or other carcinoma in situ that is resistant to therapy or ulcerated should be suspected of being an SCC.
- **Differential diagnosis:** Keratoacanthoma, irritated seborrheic keratosis, basal cell carcinoma, warts, adnexal tumors as well as established precursor lesions such as actinic keratosis, Bowen disease, and erythroplasia, where question is—Has invasion occurred?.
- **Therapy:**
  - Excision with histologic control of margins. All other approaches are less than ideal; they include radiation therapy, photodynamic therapy, laser ablation, and cryosurgery. Some flexibility is reasonable when treating small actinic keratoses that show histologic invasion but are not clinically alarming, as their risk of spread is almost immeasurable. Utmost caution required when treating lip or genital lesions.
  - Inoperable or metastatic SCC are usually treated with palliative protocols borrowed from head and neck oncology programs. Typical agents include methotrexate or cisplatin combined with doxorubicin or 5-flurouracil.
- **Follow-up:** Patients should be checked every 3–6 months for 5 years, with the interval depending on risk of metastasis. Follow-up also includes checking for developing of additional tumors, as most patients have multiple SCC precursor lesions.

Verrucous Carcinoma

- **Definition:** Well-differentiated SCC with variety of clinical patterns and extremely low risk of metastasis.
- **Pathogenesis:** Few tumors have been more poorly understood. Verrucous carcinomas were long considered to be pseudocarcinomas, as their malignant potential is so low. In addition, they were described as "warty" but not virally induced. Now well established that they are low-grade cancers induced by HPV.
- **Clinical features:** Four distinct clinical forms:
  - *Ackerman tumor*: Indolent thick oral tumor; when multiple, *florid oral papillomatosis* is preferred term.
  - *Buschke–Löwenstein tumor* or *giant condyloma:* Large persistent destructive genital wart, involving scrotum, penis, vulva, vagina, cervix, or anus.
  - *Epithelioma cuniculatum*: Persistent destructive plantar wart usually on heel; cuniculatum refers to rabbit burrows, describing the invasive nature of the tumor.
  - *Papillomatosis cutis carcinoides (Gottron)*: Irregular nodules usually over shins; relationship to HPV not as clear as with other forms.
- **Histology:** Proliferation of keratinocytes, often with clear cytoplasm, sometimes papillomatous, with islands of keratinization and downward-pushing tumor masses; mitoses uncommon.
- **Diagnostic approach:** Clinical examination; any persistent verrucous lesion should be biopsied, especially in these locations. Often multiple biopsies and expert pathologic consultation required.
- **Differential diagnosis:** Large warts and other forms of SCC.
- **Therapy:** Surgical exesion; laser ablation for florid oral papillomatosis.
  - ***Caution:*** Laser smoke plume may contain HPV particles.
  - For advanced disease, treat as any other SCC.

Keratoacanthoma

- **Definition:** Peculiar tumor of keratinocytes, which often shows spontaneous regression but has histologic features of an SCC.
- **Epidemiology:** Tumor of elderly people.
- Pathogenesis: Rapid growth suggests viral etiology, but no HPV type definitely incriminated; other triggers include UVB, ionizing radiation, and chemical carcinogens. Expression of TP53 reduced. Most have follicular features, suggesting that a keratoacanthoma may involute just as the normal hair follicle does.
- **Clinical features:**
  - Usually on sun-exposed sites in fair-skinned individuals. Usually solitary.
  - Starts as innocuous papule; over weeks grows into characteristic delled nodule 1–3 cm in diameter with prominent central plug. Sharply defined; adjacent tissue always normal (Fig. 24.**9**).
  - Can evolve in cutaneous horn (p. 417).
  - Over months, most keratoacanthomas resolve spontaneously with scarring; unfortunately, some do not but behave as SCC.
- **Variants:**
  - *Giant keratoacanthoma*: Rare lesions reach several cm in size.
  - *Keratoacanthoma centrifugum marginatum:* Slowly expanding giant keratoacanthoma with prominent border and little tendency for regression.
  - Keratoacanthomas of nailbed and mucous are more likely verrucous carcinomas.

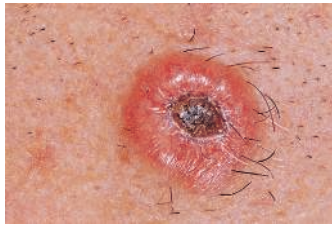


Fig. 24.**9** · Keratoacanthoma.

- **Histology:** Invaginated keratinocytic tumor with ground-glass cytoplasm, frequent mitoses, sometimes islands of tumor at base; most dermatopathologists hedge on the histologic diagnosis, suggesting that keratoacanthoma is likely, but that a SCC cannot be excluded with certainty.
- **Diagnostic approach:** If clinical suspicion is high, excisional biopsy is usually preferable. Punch biopsy not helpful.
- **Differential diagnosis:** Early stage: verruca or molluscum contagiosum; later, basal cell carcinoma, squamous cell carcinoma (less sharply defined).
- **Therapy:**
  - Observation rarely practiced because of risk of persistence and destructive behavior.
  - Simple excision most appropriate.
  - Laser ablation or cryosurgery also possible, if diagnosis has been histologically confirmed (as mentioned, difficult on biopsy).
  - Intralesional 5-fluorouracil (0.2–0.3 mL of 50 mg/mL, weekly for 6 weeks) is effective; intralesional methotrexate or bleomycin are alternatives.
  - For multiple keratoacanthomas:
    - Single dose of methotrexate 0.5 mg/ kg orally.
    - Acitretin 1 mg/kg daily for 4 weeks.

Multiple Keratoacanthomas

There are several syndromes with multiple keratoacanthomas:

- **Ferguson–Smith syndrome** (MIM code 132800): Rare syndrome with autosomal dominant inheritance, initially described in Scotland, in which patients develop hundreds of keratoacanthomas. Almost every patient has at least one invasive SCC. Also known as *multiple self-healing epithelioma syndrome*, but the name is misleading.
- **Eruptive keratoacanthomas (Gryzbowski):** Multiple eruptive keratoacanthomas over entire body; small (2–5 mm) papules, often without central plug; tend to heal with scarring and in some instances ectropion; some patients have immune defects.
- **Multiple keratoacanthomas (Witten–Zak):** Poorly defined group with multiple keratoacanthomas.
- **Muir–Torre syndrome** (p. 369): 30% of patients have multiple keratoacanthomas; many patients with Witten–Zak syndrome may fall into this group, as not all have accompanying sebaceous neoplasms.
  - ***Note:*** Always monitor patients with multiple keratoacanthomas for the development of internal malignancies.

Merkel Cell Carcinoma

- **Synonyms:** Merkel cell tumor, neuroendocrine carcinoma, trabecular carcinoma.
- **Definition:** Dermal or subcutaneous tumor apparently related to epidermal Merkel cell with rapid growth pattern.
- **Epidemiology:** Uncommon tumor, affecting elderly almost exclusively in sun-exposed skin. Female predominance.
- **Pathogenesis:** Tumor cells have many similarities to the epidermal neuroendocrine Merkel cells, so Merkel cell carcinoma is regarded as likely epidermal tumor.
- **Clinical features:** Rapidly growing blue-red nodules often with telangiectases; usually on face. Less than 10% truncal. Highly aggressive course, with 30–50% metastasizing and 10–20% leading to death (Fig. 24.**10**).
- **Histology:** Infiltrate of monomorphous indistinct (murky) blue-gray cells, often arranged in strands or trabeculae. Numerous mitoses. Neuron-specific enolase is positive; in contrast to metastatic small-cell tumor of the lung (which is otherwise identical), Merkel cell carcinomas expressed cytokeratin 20, as well as cytokeratins 8 and 18.
- **Differential diagnosis:** First recognize as separate tumor in the 1970s, previously diagnosed as anaplastic lymphoma; other possibilities include metastasis, sweat gland carcinoma, and amelanotic malignant melanoma.
- **Therapy:** Excision with 3 cm margins or micrographic surgery. Sentinel lymph node biopsy and postoperative radiation therapy are both becoming widely used. Metastases are treated with protocols similar to those employed for small-cell carcinoma of the lung, but with little success.

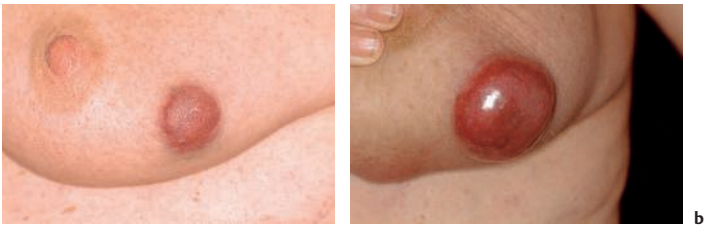


Fig. 24.**10** · **a** Merkel cell carcinoma. **b** Same patient three months later, having declined therapy.

25 Adnexal Tumors

25.1 Overview

- **Histogenesis:** The skin adnexal structures—eccrine, apocrine or sebaceous glands, hair follicles—can give rise to a baffling array of tumors, mimicking almost every cell and stage of adnexal development. The most common malignant human tumor, the basal cell carcinoma, usually shows signs or markers suggesting hair follicle differentiation, so it is included as a malignant adnexal tumor.
- **Localization:** The distribution of the different adnexal tumors follows that of the various normal structures; for example, eccrine tumors are expected on the palms and soles; follicular tumors are not. The classic tumor is a red-brown papule or nodule in the head and neck region.
- **Genetics:** Solitary adnexal tumors are sporadic events; most patients with multiple adnexal tumors have an autosomal dominant mutation that may lead to other cutaneous or even systemic abnormalities and can be transmitted to future generations. For example, a single trichilemmoma means little; multiple tumors suggest Cowden syndrome and a high risk of breast cancer.
- **Histology:** The tumor should be examined for clues to the line of differentiation:
  - *Eccrine:* Clear cells, myoepithelial cells, pores.
  - *Apocrine:* Decapitation secretion.
  - *Sebaceous:* Holocrine secretion, foamy cells.
  - *Follicular:* Hair germs, mimics of follicular structures.
  - When terms such as "resembling" or "derived from" are used below, they simply suggest how the tumors look microscopically. We recognize that the tumors may arise from stem cells and only share features with specific structures. There is also considerable controversy over the type of differentiation; for example, eccrine spiradenomas and cylindromas are caused by the same mutation in the Brooke–Spiegler syndrome, but one is considered eccrine; the other, follicular or apocrine.
- **Differential diagnosis:** In most instances, the differential diagnosis is other adnexal tumors and basal cell carcinoma. Only exceptions to this rule will be stated.
- **Therapy:** In almost every case, the treatment is excision.

25.2 Benign Tumors with Eccrine Differentiation

Eccrine Hidrocystoma

- **Definition:** Cyst derived from dermal component of eccrine duct.
- **Clinical features:** Translucent yellow or light blue cystic tumor, typically around eyes (Fig. 25.**1**). More common in women. Occasionally appear in crops suddenly, but then more likely reactive with ductal occlusion.
- **Histology:** Small cyst with colorless contents whose wall is composed of ductal cells.
- **Differential diagnosis:** Apocrine hidrocystoma.
- **Therapy:** Excision.

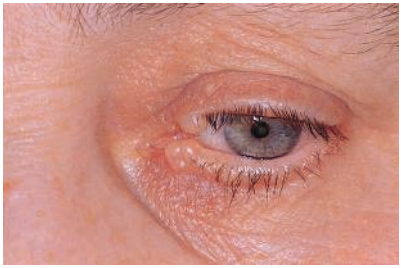


Fig. 25.**1** · Eccrine hidrocystoma.

Eccrine Poroma

- **Definition:** Tumor derived from the intraepidermal and/or upper dermal component of the eccrine duct.
- **Clinical features:** Skin-colored or erythematous solitary papule or nodule typically on soles (60%), palms (20%) or scalp (Fig. 25.**2**). Tends to be painful (because of location) and bleed (highly vascularized tumor). Usually appears in middle-aged adults.
- **Histology:** Strands of uniform cuboidal basaloid tumor cells arising from epidermis, containing ductal elements; if totally intraepidermal (*hidroacanthoma simplex*), if no epidermal connections (*dermal duct tumor*).
- **Differential diagnosis:** On the palms and soles, often mistaken for a wart; on the scalp, usually diagnosed as a vascular tumor.
- **Therapy:** Excision.

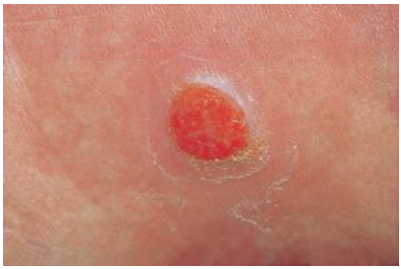


Fig. 25.**2** · Eccrine poroma on sole.

Syringoma

- **Definition:** Benign tumor that resembles the eccrine dermal duct.
- **Clinical features:**
  - More common in women, starting in puberty. Usually multiple skin-colored to yellow papules (Fig. 25.**3**). Most common site is periorbital, although axillae, umbilicus, and genital region also seen. Rarely on scalp, but then with alopecia.
  - *Eruptive syringomas:* Sudden onset of multiple papules usually on trunk; usually in young women. Sometimes spontaneous regression occurs. Occasionally inherited in autosomal dominant manner.

Fig. 25.**3** · Multiple syringomas in typical periorbital location.

- **Histology:** Small tubular structures in dermis surrounded by thickened connective tissue; thin epithelial strands (fancifully compared to tadpoles) also present.
- **Differential diagnosis:** Xanthelasma, other xanthomas, plane warts; on trunk, disseminated granuloma annulare, eruptive vellus hair cysts.
- **Therapy:** In most instances, best left alone; if cosmetically disturbing, a variety of destructive measures including laser ablation, dermabrasion or electrosurgery is possible. Recurrences are the rule.

Eccrine Spiradenoma

- **Definition:** Tumor from secretory component of eccrine sweat duct.
- **Epidemiology:** More common in women; may be multiple (Brooke–Spiegler syndrome).
- **Clinical features:** 0.3–5.0 cm intradermal solitary nodule with red-brown color; usually painful. Most often head, neck, upper trunk.
- **Histology:** Dense nests of basaloid epithelial cells associated with larger less dense cells producing rosette pattern.
- **Differential diagnosis:** Painful skin tumors; ANGEL mnemonic (p. 714).
- **Therapy:** Excision.

Clear Cell Hidradenoma

- **Synonym:** Eccrine acrospiroma.
- **Definition:** Solid-cystic eccrine tumor, dominated by secretory clear cells.
- **Clinical features:** 0.5–2.0 cm solid tumor; no favored sites.
- **Histology:** Nodules composed of clear tumor cells (glycogen-rich cells which have lost their content during fixation), admixed with small blue cells and myoepithelial cells.
- **Therapy:** Excision.

Mixed Tumor

- **Synonym:** Chondroid syringoma.
- **Definition:** Adnexal tumor with either eccrine or apocrine differentiation, ductal structures, and a prominent chondroid stroma.
- **Clinical features:** Typically 0.5–3.0 cm firm nodule in head and neck region.
- **Histology:** Ductal structures embedded in cartilage-like stroma; if decapitation secretion is seen, apocrine; otherwise, eccrine.
- **Therapy:** Excision.

25.3 Benign Tumors with Apocrine Differentiation

Accessory Nipple

- **Definition:** Congenital malformation with additional nipples formed along milk line; often erroneously considered a tumor and thus included here.
- **Pathogenesis:** Polythelia (multiple nipples) sometimes associated with Wilms tumor.
- **Clinical features:** Red-brown papules located along lines extending from axillae through nipples to groin. Soft brown asymptomatic papule; rarely identified clinically. Rarely may be tender, have discharge, or fluctuate with menstrual periods.
- **Histology:** Increased amount of smooth muscle fibers coupled with excessive mammary glands which are of apocrine origin.
- **Differential diagnosis:** Dermatofibroma, melanocytic nevus.
- **Therapy:** Excision.

Apocrine Hidrocystoma

- **Definition:** Cyst whose wall shows apocrine differentiation.
- **Clinical features:** Solitary cystic tumor, usually periorbital. May be dark blue to black (*hydrocystome noire*). On lid, may arise from glands of Moll.
- **Histology:** Cyst wall with apocrine secretion; may have hemorrhage or lipofuscin imparting color.
- **Differential diagnosis:** Eccrine hidrocystoma, thrombosed hemangioma, blue nevus, basal cell carcinoma.
- **Therapy:** Excision.

Hidradenoma Papilliferum

- **Definition:** Papillomatous adenoma with apocrine differentiation.
- **Clinical features:** Dermal nodule, usually on labia, generally asymptomatic, appears after puberty.
- **Histology:** Complex nodule of interlacing strands of glandular epithelium with decapitation secretion.
- **Differential diagnosis:** Endometriosis, Bartholin gland cyst, epidermoid cyst.
- **Therapy:** Excision.

Syringocystadenoma Papilliferum

- **Definition:** Papillomatous adenoma of distal apocrine duct, often with connection to epithelium.
- **Clinical features:**
  - Papule or plaque; usually red-brown, generally with central pore or erosion; 70% are on head.
  - Can be present at birth in linear arrangement.
  - Second most common tumor to development in nevus sebaceus (p. 411); 30% seen in this setting.
- **Histology:** Compound papilliferous tumor with stroma rich is plasma cells and almost always epidermal connection. Otherwise similar to hidradenoma papilliferum.
- **Therapy:** Excision.

Cylindroma

- **Synonym:** Turban tumor.
- **Definition:** Complex adenoma whose pattern of differentiation is disputed.
- **Clinical features:** Two separate patterns:
  - *Solitary cylindroma:*
    - Negative family history.
    - Several cm firm hairless tumor on scalp or less often face.
    - *Histology:* Nodules of basaloid tumor cells surrounded by a dense PAS-positive hyaline membrane.
    - *Therapy:* excision.
  - *Multiple cylindromas:*
    - Brooke–Spiegler syndrome.
    - Mutation in *CYLD1*, tumor suppressor gene, autosomal dominant inheritance.
    - Three different adnexal tumors may be present in same patient: cylindroma, spiradenoma, and trichoepithelioma.
    - *Clinical features:* On scalp, numerous flesh-colored to pink nodules, hairless; when numerous, fancifully compared to a turban (Fig. 25.**4**). Often trichoepithelioma in the midface and scattered spiradenoma; clinical distinction impossible with overlaps both clinically and histologically.
    - *Differential diagnosis:* Other multiple adnexal tumors, nevoid basal cell carcinoma syndrome; on scalp, trichilemmal cysts, metastases.
    - *Therapy:* Extremely difficult, complex surgical procedures (scalpectomy with grafting; dermabrasion, extensive laser ablation).

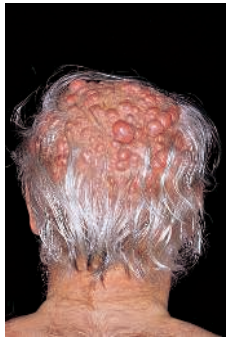


Fig. 25.**4** · Multiple cylindromas.

Nipple Adenoma

- **Synonyms:** Papillary adenoma, erosive adenomatosis of nipple, florid papillomatosis of nipple, subareolar duct papillomatosis.
- **Definition:** Adenoma of the milk ducts, usually associated with surface erosion.
- **Epidemiology:** Uncommon, usually in middle-aged women.
- **Clinical features:** Unilateral crust or erosion of nipple; often tender or burning.
- **Diagnostic approach:** Biopsy mandatory to exclude Paget disease.
- **Histology:** Cohesive mass in disarray composed of normal ductal and glandular elements.
- **Differential diagnosis:** Paget disease, Bowen disease, nipple dermatitis, psoriasis.
- **Therapy:** Excision.

Paget Disease of Breast

- **Definition:** Intraductal carcinoma of the breast extending to involve nipple with invasion of epidermis by malignant cells.
- **Epidemiology:** Almost exclusively limited to women.
- **Clinical features:** Unilateral sharply bordered area of crusting or erosion on nipple. Generally no underlying mass can be palpated.
- **Histology:** Epidermis contains numerous clear cells positive for carcinoembryonic antigen (CEA) and generally above the basal layer. Underlying intraductal tumor seen only rarely in biopsy.
- **Diagnostic approach:** Biopsy, breast examination, appropriate imaging studies.
- **Differential diagnosis:** Nipple adenoma, Bowen disease, nipple dermatitis, psoriasis; histologically, superficial spreading melanoma.
- **Therapy:** Surgery and follow-up management following guidelines for carcinoma of the breast.

Extramammary Paget Disease

- **Definition:** Intraepidermal growth of malignant adnexal tumor or underlying carcinoma, not located on the nipple.
- **Clinical features:** Most common site is anogenital region, where urogenital and rectal carcinomas must be excluded. Less often periumbilical (gastrointestinal carcinoma), axillary (breast carcinoma or apocrine carcinoma), external ear canal (ceruminous carcinoma).
- **Histology:** Identical to Paget disease of nipple.
- **Diagnostic approach:** Biopsy, search for underlying tumor.
- **Differential diagnosis:** Chronic dermatitis, Bowen disease.
- **Therapy:** Excision; often difficult to provide curative surgery because of extent of lesion, unclear margins and underlying tumor. Laser ablation and photodynamic therapy useful for palliation.

25.4 Benign Tumors with Sebaceous Differentiation

Ectopic Sebaceous Glands

- **Definition:** Sebaceous glands found on hairless surfaces.
- **Clinical features:** Most common are *Fordyce glands* or spots on lips: tiny yellow papules that are totally asymptomatic but sometimes annoy patient. Other common sites are nipple (*Montgomery tubercle*) and genitalia (labia and penis, where known as *Tyson glands*).
- **Therapy:** None needed.

Sebaceous Hyperplasia

- **Synonym:** Senile sebaceous hyperplasia.
- **Definition:** Most common sebaceous lesion; accumulation of enlarged, otherwise normal glands around a central follicle.
- **Clinical features:** Clinically distinctive, rosette of yellow tiny papules just beneath skin surface, arranged around a dilated hair follicle with central dell. Usually multiple, < 5 mm in size. More common in renal dialysis patients.

- **Differential diagnosis:** Basal cell carcinoma is usual mistake, but clinically distinctive.
- **Therapy:** None needed; excision is cosmetically disturbing; laser ablation possible. Some patients have hundreds; then systemic retinoids may provide some help.

Sebaceous Adenoma

- **Definition:** Dermal tumor comprised of normal sebocytes with some disarray in glandular organization.
- **Clinical features:** Solitary tumor, usually on head and neck region, frequently crusted; yellow color often not appreciated.
- **Histology:** Enlarged sebaceous lobules with an increased basaloid or undifferentiated peripheral zone; usually have connection to surface.
- **Differential diagnosis:** Basal cell carcinoma.
- **Therapy:** Excision.

Sebaceoma

- **Synonym:** Sebaceous epithelioma.
- **Definition:** Benign sebaceous tumor with marked loss of lobular pattern.
- **Clinical features:** No clinically distinct features; usually facial nodule in older adult.
- **Histology:** Basaloid tumor masses with at least foci of sebocytes and with no unequivocal signs of basal cell carcinoma.
- **Differential diagnosis:** Basal cell carcinoma, sebaceous adenoma.
  - ***Note:*** Unusual or multiple sebaceous tumors, especially cystic tumors, suggest Muir–Torre syndrome (p. 369).
- **Therapy:** Excision.

25.5 Benign Tumors with Hair Follicle Differentiation

Trichofolliculoma

- **Definition:** Organoid hair follicle tumor.
- **Clinical features:** One of the few adnexal tumors with distinctive clinical features: firm nodule with central pore through which pokes a bundle of wispy, fine hairs. Usually on scalp or face.
- **Histology:** Thickened dilated hair follicle with budding extending into dermis; some buds differentiate into complete follicles.
- **Differential diagnosis:** Melanocytic nevus, basal cell carcinoma.
- **Therapy:** Excision.

Trichoblastoma

- **Definition:** Recently defined group of hair follicle tumors, all featuring hair germs and matrical cells in varying patterns.
- **Clinical features:** No distinctive features; dermal nodule, usually in head and neck region.

- **Histology:** Crucial feature is basaloid tumor islands without peripheral palisading and without cleft formation (two hallmarks of basal cell carcinoma). Lesions may have large or small tumor nodules with lacy or sieve-like pattern, or with predominance of stromal proliferation (*desmoplastic trichoblastoma*). Adamantinoid trichoblastoma is clear cell tumor with rich lymphocytic infiltrate; also known as lymphadenoma.
- **Differential diagnosis:** Basal cell carcinoma; Ackerman has renamed BCC as trichoblastic carcinoma.
- **Therapy:** Excision.

Trichoepithelioma

- **Synonym:** Superficial trichoblastoma; if multiple, epithelioma adenoides cysticum.
- **Definition:** Most common benign hair follicle tumor; incomplete differentiation toward hair follicle.
- **Clinical features:**
  - *Solitary trichoepithelioma:*
    - Facial papule or nodule; not distinct.
    - *Histology:* Basaloid tumor strands and nests with small follicular cysts and without definite features of basal cell carcinoma.
    - *Differential diagnosis:* Overlaps with basal cell carcinoma.
    - *Therapy:* Excision.
  - *Desmoplastic trichoepithelioma:*
    - Flat-topped facial papule or plaque; very often on chin.
    - *Histology:* Similar to solitary lesion but with prominent desmoplastic stroma, thinner tumor stands.
    - *Differential diagnosis:* Clinically always mistaken for basal cell carcinoma; histologically shares features with syringoma and microcystic adnexal carcinoma.
    - *Therapy:* Excision.
  - *Multiple trichoepitheliomas:*
    - Brooke syndrome (part of Brooke–Spiegler syndrome [p. 428]) with mutation in *CYLD* gene but at different point.
    - Onset in puberty of multiple firm papules in perinasal and midface region; can also involve scalp, neck, and trunk.
    - Sometimes basal cell carcinomas develop amidst the otherwise benign lesions.
    - *Differential diagnosis:* Tuberous sclerosis, nevoid basal cell carcinoma syndrome, multiple syringomas, other adnexal tumors.
    - *Therapy:* Dermabrasion or laser ablation; recurrences common. If single lesion is worrisome, excision.

Trichoadenoma

- **Synonym:** Nikolowski tumor.
- **Definition:** Rare tumor, seemingly composed of many tiny trichilemmal cysts.
- **Clinical features:** Plaque or nodule, usually on head or neck; rarely buttocks.
- **Histology:** Dermal tumor with many tiny cystic spaces whose lining resembles follicular infundibulum.
- **Differential diagnosis:** Basal cell carcinoma, microcystic adnexal tumor, other adnexal tumors.
- **Therapy:** Excision.

Fibrofolliculoma/Trichodiscoma

- **Synonym:** Mantleoma.
- **Definition:** Benign tumors arising from mantle zone—perifollicular connective tissue just above entry of sebaceous duct.
- **Clinical features:**
  - Usually numerous 2–4 mm flesh-colored papules on face and trunk; solitary lesions hard to recognize.
  - Multiple lesions suggest Birt–Hogg–Dubé syndrome (p. 367).
- **Histology:** Fibrofolliculomas (or perifollicular fibromas) have a normal follicle with lacy branches surrounded by dense connective tissue stroma. A trichodiscoma represents the late stage of a fibrofolliculoma and has simply dermal fibrosis. The initial suggestion that a trichodiscoma was related to the hair disk (Haarscheibe) sensory organ common in animals was incorrect, but the name has been retained.
- **Diagnostic approach:** Patients with multiple tumors at risk for renal carcinoma.
- **Therapy:** Dermabrasion or laser ablation.

Pilomatricoma

- **Synonym:** Calcifying epithelioma of Malherbe; also written pilomatrixoma.
- **Definition:** Common cystic tumor with differentiation toward hair follicle matrix.
- **Epidemiology:** One of the most common childhood tumors, except for epidermoid cysts and lipomas, but also seen in adults.
- **Clinical features:** Firm 0.5–5.0 cm dermal nodule, almost always head and neck location especially anterior to ear or in eyebrows (Fig. 25.**5**). If superficial, has blue-red tones, may ulcerate and discharge pathognomonic chalky granules.
- **Histology:** Distinctive histological picture: dermal nodule with basaloid tumor cells, bland matrix with empty spaces (ghost cells), and usually calcification and peripheral inflammation.
- **Differential diagnosis:** Infected epidermoid cyst, actinomycosis, cutaneous osteoma, other adnexal tumors.
- **Therapy:** Excision.

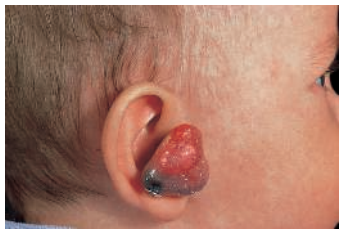


Fig. 25.**5** · Pilomatricoma.

Trichilemmoma

- **Definition:** Benign tumor with differentiation pattern suggesting outer root sheath.
- **Pathogenesis:** HPV implicated in solitary trichilemmomas, which may be old warts.
- **Clinical features:** Solitary warty tumor, usually facial; when multiple, consider Cowden syndrome (p. 367).

- **Histology:** Papillomatous tumor with thickened follicle containing numerous clear cells with basaloid band at periphery.
- **Differential diagnosis:** Wart, other adnexal tumors.
- **Therapy:** Excision.

25.6 Malignant Adnexal Tumors

- **Pathogenesis:** The only common malignant adnexal tumor is basal cell carcinoma. All others are very uncommon. Some appear to be malignant equivalents of benign tumors; *eccrine porocarcinoma* is one of the most common members of the group. Controversial if such tumors arise from benign tumor or are malignant from start with similar differentiation. Other malignant sweat duct tumors do not seem to have a benign equivalent. The malignant tumors are often very difficult to distinguish from squamous cell carcinoma and should be treated as such, with a risk for metastasis.
- Several malignant adnexal lesions have already been considered because they fit didactically better elsewhere; included in this group are proliferating trichilemmal cysts as well as Paget disease and extramammary Paget disease.

Basal Cell Carcinoma (BCC)

- **Synonym:** Basal cell epithelioma.
- **Definition:** Heterogenous group of low-grade malignant cutaneous tumors, characterized by differentiation markers usually associated with hair follicle development, locally aggressive but almost never metastatic.
- **Epidemiology:** Most common malignancy in humans: incidence 200/100 000 in men, 100/100 000 in women but gap narrowing. Incidence has doubled over past two decades. Most patients are > 50 years of age.
- **Pathogenesis:** The cell of origin of BCC has long been argued. Since it is the most common human malignancy, the question is not insignificant. Most BCC arise from epidermal cells differentiated in the direction of the primitive hair bulb. Thus the term *trichoblastic carcinoma* has been proposed but has not won acceptance. The main trigger appears to be UVB, but this is not the only factor, because BCCs are extremely uncommon on the backs of the hands where actinic keratoses are frequent. The underlying genetic mutations in BCC frequently involve the *PATCH* gene or other members of the sonic hedgehog signaling pathway, resulting in overexpression of transcription factor Gli1, as suggested by research in nevoid BCC syndrome.
- **Clinical features:**
  - ***Note:*** Key unifying clinical features of BCC include pearly nodules and telangiectases; always look for these (Fig. 25.**6 a**).
  - Most common site is face; 80% arise above the line connecting the corner of mouth to the ear lobe. Multiple lesions are more common on trunk. No mucosal lesions.
  - *Nodular BCC*: Most common variant, pearly, telangiectatic dome-shaped nodule or ring of papules; often with central ulceration (Fig. 25.**6 b,c**).
    - *Differential diagnosis:* Adnexal tumors.
  - *Superficial or multicentric BCC:* Flat, tan to red-brown patch, often with scaly and with a pearly border when carefully examined; usually on trunk; often a history of arsenic or radiation exposure (Fig. 25.**6 d**).
    - *Differential diagnosis:* Dermatitis, Bowen disease, extramammary Paget disease, psoriasis, tinea corporis.

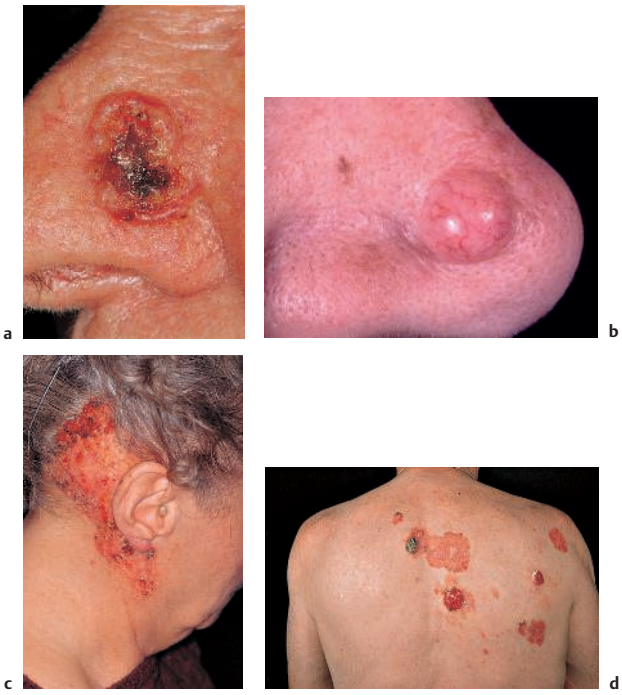


Fig. 25.**6** · **Basal cell carcinoma. a** On nose, showing typical pearly border. **b** Nodular BCC. **c** Large ulcerated BCC. **d** Multiple superficial BCC secondary to arsenic exposure.

- *Pigmented BCC:* Both nodular and superficial BCCs can be pigmented; melanin accumulates in tumor cells. More common in dark-skinned individuals. Rarely occurs in people with blue eyes.
  - *Differential diagnosis:* Malignant melanoma (dermatoscopy), melanocytic nevus, blue nevus, pigmented seborrheic keratosis, angiokeratoma.
- *Sclerosing (sclerodermiform) BCC:* Atrophic plaque, often with telangiectases or ulcer, but no other stigmata of BCC. Typically in lines of embryonic fusion around nose or ears. Desmoplastic dermal response far exceeds the proliferation of tumor cells. Margins difficult to determine clinically, causing treatment problems.
  - *Differential diagnosis:* Scar, desmoplastic trichoepithelioma, morphea.
- *Rodent ulcer:* Older name for predominantly ulcerated BCC usually on forehead or scalp, but sometimes in midface.
- *Ulcus terebrans:* Extremely aggressive BCC invading underlying structures such as large vessels, bones, even meninges; frequently fatal but mercifully rare. Causes of death include uncontrolled bleeding and infection.

- **Histology:** The histologic spectrum is as wide as the clinical. The unifying feature is collections of basaloid tumor cells with peripheral palisading and stromal retraction. The tumors may mimic many aspects of hair follicle differentiation:
  - *Nodular BCC:* Large tumor islands, sometimes with cystic degeneration, analogous to holocrine secretion.
  - *Keratotic BCC*: Hair follicle differentiation with keratinization.
  - *Adenoid BCC:* Glandular elements mimicking apocrine glands.
  - *Adamantinoid BCC:* Clear cell differentiation resembling enamel organ.
  - *Superficial or multicentric BCC:* Tiny buds arise from basal layer, mimicking primitive hair germ.
  - *Pigmented BCC:* Typical pattern but with excess melanin; no proliferation of melanocytes.
  - *Sclerosing (sclerodermiform) BCC:* Thin strands of basaloid tumor cells surrounded by thickened bundles of collagen.
- **Diagnostic approach:** Clinical examination and biopsy. Dermatoscopy is also helpful for pigmented or otherwise puzzling BCC. Fortunately BCC is a straightforward pathological diagnosis, even when clinical questions exist.
- **Therapy:** The aim is complete removal and thus a 100% cure, and as good a cosmetic result as can be obtained. There are many ways to achieve this gratifying goal:
  - Surgical excision with histologic control and cosmetic closure is the treatment of choice. Micrographic surgery should be employed for recurrent, sclerosing, or otherwise difficult BCC. Recurrence rate should be less than 5%, in expert hands.
  - Alternatives all have somewhat higher recurrence rates. They include:
    - *Cryosurgery:* Suitable for superficial BCC. Two freeze–thaw cycles should be used. Cryosurgery for nodular lesions is also possible, but requires a thermocouple so that tumor-killing parameters can be obtained. Disadvantages include lack of histologic control, recurrences, and scarring.
    - *Radiation therapy:* Best for elderly patients with numerous lesions or in difficult locations. Often recommended for lid lesions. 60–70 Gy, fractionate in 3–5 Gy administered 3–5× weekly. For deeper lesions, consult radiation therapy regarding electron beam therapy.
      - ***Note:*** Even around the eyes, surgical procedures now usually achieve better results than radiation therapy.
    - *Photodynamic therapy:* Useful for superficial and small lesions; new procedure, so long-term recurrence rates not well-established.
    - *Curettage and electrodesiccation or cautery:* Formerly widely used for superficial or small lesions; scarring and high recurrence rate limit its use today to exceptional situations.
    - *Laser ablation:* Lack of histologic control gives laser therapy the same disadvantages as curettage.
    - Topical imiquimod or 5-fluorouracil can be used over a long period of time, usually 3× weekly for 6 weeks, for superficial BCC.
  - There is no effective chemotherapy regimen for the rare cases of metastatic BCC. A standard approach is cisplatin 100 mg/m^2 every 3 weeks, perhaps combined with 5-fluorouracil. Fluids should be forced and 12.5 g of mannitol given just prior to cisplatin. Other regimens incorporate systemic retinoids.
- **Follow-up:** Every patient with BCC is likely to develop several more. Thus, at a bare minimum patients should be checked yearly; in the sunbelt of the USA, every 6 months is standard. New lesions can be identified and promptly treated at the same time as previous sites are monitored for recurrences.

Nevoid Basal Cell Carcinoma Syndrome

- **Synonyms:** Basal cell nevus syndrome, Gorlin–Goltz syndrome.
- **MIM code:** 109400.
- **Definition:** Genodermatosis with numerous BCC and multiple developmental anomalies; autosomal dominant inheritance.
- **Epidemiology:** One of more common tumor syndromes; incidence around 1:50000. About 25% of patients presenting with a BCC before 20 years of age will have this disorder.
- **Pathogenesis:** The defect is a mutation in the *PATCH* gene at 9q22.3, an important signal transduction gene involved in segmental regulation of embryologic growth and later of controlling hair follicle differentiation, explaining the combination of developmental defects and BCC.
- **Clinical features:**
  - Multiple BCC, often starting in childhood. Earliest lesions often on neck, resembling skin tags. Later lesions can take all forms of BCC; most common site is face.
  - *Palmoplantar pits:* Tiny hyperkeratotic lesions with a definite defect in epidermis. On careful inspection, appear different than palmoplantar keratoderma.
  - Epidermoid cysts are more common (especially acral ones), as are lipomas.
  - Developmental anomalies include odontogenic cysts of maxilla and mandible, dental defects, bifid ribs, scoliosis, hypertelorism, and frontal bossing.
  - Peculiar radiologic finding is calcification of the corpus callosum.
  - Most patients are normal, although both EEG abnormalities and mental retardation may occur.
  - Tumors include:
    - *Medulloblastoma:* Occurs in 5% of patients but accounts for less than 1% of childhood medulloblastomas. Appears before any other stigmata of syndrome. Patients require radiation therapy, which induces 1000 s of BCC in the radiation fields.
    - Ovarian fibromas and cardiac fibromas.
    - Mesenteric lymphatic cysts.
- **Diagnostic approach:** History (well over 50% have positive family history, as syndrome has little effect on reproduction), clinical examination; earliest clues are pits. Dental radiographs usually identify one or more cysts; other screening approaches; specialist consultation.
- **Differential diagnosis:** When complete, none; otherwise multiple BCC sporadically or after arsenic exposure. Rare syndromes with multiple adnexal tumors may also be similar.
- **Therapy:** Careful monitoring and prompt treatment of BCC when small. All the methods discussed above are appropriate except for radiotherapy, which must be avoided. Imiquimod appears useful for superficial lesions. Systemic retinoids may reduce the development of tumors, but have too many side effects for lifelong usage.

Microcystic Adnexal Carcinoma

- **Synonym:** Malignant syringoma.
- **Definition:** Carcinoma of eccrine ducts with characteristic tubular pattern and prominent stromal desmoplasia.
- **Clinical features:** Slowly growing deep nodule, usually lip or chin.
- **Histology:** Superficial component resembles syringoma with tiny cysts, while deeper component has basaloid strands of tumors often with perineurial entrapment. Little cytologic atypia or other features of malignancy.

Caution: Be extremely skeptical of the diagnosis of a solitary syringoma when the clinical lesion is a deep nodule; always re-excise.

- **Differential diagnosis:** Scar, sclerosing BCC.
- **Therapy:** Excision with control of margins; careful follow-up because of high risk of recurrence and slight risk of metastasis.

Eccrine Porocarcinoma

- **Clinical features:** Appear to develop from eccrine poroma; most common on feet; risk of regional lymph node involvement and distant metastasis. Generous excision and close follow-up mandatory. Metastatic disease treated as squamous cell carcinoma.

Other Malignant Adnexal Tumors

Table 25.1 · Other malignant adnexal tumors

Tumor	Derivation	Comments
Mucinous carcinoma	Eccrine	Periorbital tumor; tiny eccrine tumor islands in mucinous stroma
Aggressive digital papillary adenocarcinoma	Eccrine	Cystic tumor on fingers or toes; often requires amputation
Malignant spiradenoma	Eccrine	Only arises in background of Brooke–Spiegler syndrome
Adenoid cystic carcinoma	Apocrine	Red nodule usually on scalp; Swiss cheese pattern on histology; identical to salivary gland adenoid cystic tumor secondary metastasis must be excluded
Malignant cylindroma	Apocrine	Only arises in background of Brooke–Spiegler syndrome.
Apocrine carcinoma	Apocrine	Usually axilla; can have intraepidermal spread similar to extramammary Paget disease
Sebaceous carcinoma	Sebaceous	Two forms: Eyelid: frequent intraepidermal spread Trunk: nodular tumor
Pilomatrical carcinoma	Hair follicle	Does not develop from pilomatricoma; usually in adults
Lymphoepithelioma-like carcinoma	Hair follicle?	Remnants of adnexal structures with extensive lymphocytic infiltrate; keratin stains identify tumor stroma; treat as squamous cell carcinoma

26 Soft Tissue Tumors

26.1 Connective Tissue Tumors

Connective Tissue Nevus

- **Definition:** Localized lesion with increased amounts of collagen and/or elastin.
- **Epidemiology:** Uncommon solitary malformation; often associated with tuberous sclerosis (p. 365), MEN1 (p. 367), Proteus syndrome (p. 414), or Buschke–Ollendorff syndrome.
- **Clinical features:** Present at birth; sometimes first prominent after a few years. Usually a plaque over the lumbosacral region, unilateral, consisting of numerous 5–10 mm skin-colored papules and nodules.
- **Histology:** One of the few lesions where normal skin is needed for comparison; often useful to biopsy contralateral normal skin or include a tag of normal skin in elliptical biopsy. On H&E stain, dermis looks thickened; special stains confirm increase in collagen, elastin or both.
- **Differential diagnosis:** Often overlooked; only serious differential diagnostic consideration is organoid nevus (p. 410).
- **Therapy:** If small, excision; otherwise, none.

Buschke–Ollendorff Syndrome

- **Synonym:** Dermatofibrosis lenticularis disseminata.
- **MIM code:** 166700.
- **Definition:** Rare genodermatosis with multiple connective tissue nevi and bony changes; autosomal dominant inheritance.
- **Clinical features:**
  - *Dermatofibrosis lenticularis:* Multiple widely distributed small yellow-white papules.
  - *Skeletal system: Osteopoikilosis* features stippling and sclerotic foci in the epiphyses and metaphyses of long bones; asymptomatic, only detected by chance on radiologic examination.
- **Histology:** Skin lesions are connective tissue nevi, usually dominated by elastic fibers.
- **Diagnostic approach:** Skin biopsy and radiography of long bones.
- **Differential diagnosis:** Pseudoxanthoma elasticum.
- **Therapy:** None.

Elastofibroma Dorsi

- **Definition:** Subcutaneous tumor in adults with increased amounts of elastic fibers.
- **Pathogenesis:** Poorly understood; seems a result of trauma, as it is more common in manual laborers. New elastin may come from the periosteum; familial cases reported.
- **Clinical features:** Usually overlooked and found on autopsy; slow-growing firm nodules between scapula and thoracic wall in older adults.
- **Histology:** Indistinct nodule rich in elastic fibers and collagen bundles.
- **Differential diagnosis:** Clinically specific; histologically confused with keloid or connective tissue nevus.
- **Therapy:** None or excision.

Soft Fibroma

- **Synonyms:** Skin tag, acrochordon, fibroepithelial polyp, fibroma molle, fibroma pendulans.
  - ***Note:*** As is so often the case, the least important lesions have the most names.
- **Definition:** Harmless outpouching of epidermis and dermis.
- **Clinical features:** Some distinguish between three sizes of soft fibromas:
  - *Tiny:* Skin tags: 1–2 mm skin-colored stalked papules around eyes, neck, axillae (Fig. 26.**1**).
  - *Medium:* Roughly 5–10 mm stalked papule; no site of predilection.
  - *Large* (fibroma pendulans): 1–5 cm stalked soft tumor.
- **Histology:** The small lesions share some similarities with seborrheic keratoses and may have such surfaces changes. The medium and larger lesions are often older nevi and may contain a few nests of melanocytes. Otherwise, normal epidermis and dermis with increased vessels in a polypoid pattern.
- **Differential diagnosis:** Seborrheic keratosis, melanocytic nevus, neurofibroma.
- **Therapy:** Small lesions can be snipped off without anesthesia; medium and larger lesions are likely to have a central vessel that bleeds, so should be anesthetized and then removed by standard or scissor excision.

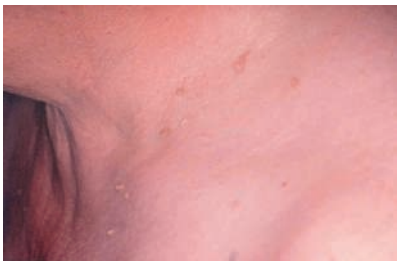


Fig. 26.**1** · Multiple skin tags.

Angiofibroma

- **Definition:** Benign proliferation of connective tissue and vessels; many different clinical lesions have same microscopic pattern:
  - *Fibrous papule of the nose:* Solitary flat-topped skin-colored 5–10 mm papule on distal aspect of nose.
  - *Adenoma sebaceum:* These marker lesions of tuberous sclerosis (p. 365) are actually angiofibromas.
  - Associated with *MEN1* (p. 367).
  - *Isolated angiofibromas*: 1–3 mm red papules on nose, nasolabial folds, and cheeks.
    - ***Note:*** Always check for tuberous sclerosis and MEN1, but isolated lesions far more common.
  - *Acquired digital fibrokeratoma:* Digital angiofibroma that acquires a unique collarette scale because of acral location.
  - *Pearly penile papules:* Tiny harmless angiofibromas at the base of glands in the coronal sulcus; often mistakenly treated as condylomata.
  - *Hirsuties vulvae:* Similar lesions forming fringe at line of transition from labia minor to vagina.

- **Histology:** Increased vessels and dermal fibrosis; can be subtle changes; biopsy is usually taken to exclude other possibilities, such as melanocytic nevus, wart, or basal cell carcinoma.
- **Therapy:** Genital lesions require no therapy. Solitary facial or digital lesions can be tangentially excised. Multiple lesions may be treated with dermabrasion or laser ablation, but recurrences common.

Perifollicular Fibroma

This term is synonymous with fibrofolliculoma and simply represents one stage in the evolution of tumors of the hair mantle region (p. 432). Marker for Birt–Hogg–Dubé syndrome (p. 367).

Dermatofibroma

- **Synonyms:** Histiocytoma, fibrous histiocytoma, sclerosing hemangioma, fibroma durum, nodular subepidermal fibrosis.
- **Definition:** Extremely common reactive fibrous proliferation.
- **Pathogenesis:** Two most common triggers appear to be arthropod assault and folliculitis.
- **Clinical features:** 5–10 mm firm tumor; almost always on legs (Fig. 26.**2**). Color varies from skin-colored through tan to red-brown or even dark brown. When one compresses a dermatofibroma from the sides, the lesion becomes depressed, rather than protruding as would a melanocytic nevus (*dimple sign* or *Fitzpatrick sign*).
  - ***Note:*** Multiple dermatofibromas, especially on other body sites, can be associated with systemic lupus erythematosus.
- **Histology:** The histologic spectrum of dermatofibroma is enormous and continuously being expanded. The classic lesion has a proliferation of fibroblasts with entrapment of collagen at the periphery, foci of hemosiderin, macrophages (histiocytoma), thickened vessels (sclerosing hemangioma), and reactive epidermal changes including acanthosis, increased melanin, and hair germs budding down from basal layer. The subcutaneous fat is usually not involved.
  - ***Note:*** A basal cell carcinoma over a dermatofibroma is almost always a mistaken diagnosis—instead, reactive proliferating hair germs are seen.

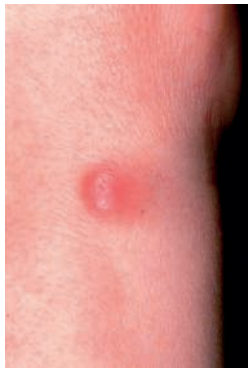


Fig. 26.**2** · Dermatofibroma.

- **Variants** include cellular changes (epithelioid, giant, granular, myxoid, desmoplastic or ossifying cells) as well as unusual patterns (giant or deep penetrating). The latter two patterns are associated with an increased recurrence rate and are sometimes described as fibrous histiocytomas.

Caution: Cellular dermatofibroma, cellular neurothekeoma, and plexiform fibrohistiocytic tumor are three dermatofibroma variants that require careful histiologic control of margins and follow-up.

Dermatomyofibroma

- **Synonyms:** Plaque-like dermal fibromatosis, Hügel tumor.
- **Definition:** Benign proliferation of myofibroblasts limited to dermis.
- **Clinical features:** Difficult to recognize; typically around shoulder girdle where it presents as large dermal plaque 1–2 cm in size of varying colors; some lesions 10–15 cm. Can also be palmoplantar.
- **Histology:** Proliferation of spindle cells (myofibroblasts) in dermis; poorly circumscribed and may impinge on subcutaneous fat but does not extend along fat septa; cells are usually actin-positive, suggesting smooth muscle or myofibroblastic differentiation.
- **Differential diagnosis:** Because of location and site, most important consideration is dermatofibrosarcoma protuberans. Other histologic possibilities: dermatofibroma, hypertrophic scar, keloid, leiomyoma; clinically larger lesions have been confused with morphea.

Hypertrophic Scars and Keloids

- **Definition:** Excessive connective tissue proliferation following an injury; a *hypertrophic scar* remains confined to the boundaries of the original insult, while a *keloid* proliferates beyond these limits.
- **Pathogenesis:** Predisposing factors include:
  - *Ethnic factors:* Far more common in blacks.
  - **Location:** Sternum, shoulders, neck (after thyroid operation), ear lobes (piercing), ankles, shins, over clavicle, edge of chin, and other sites where skin tension is generally increased.
  - **Type of injury:** Burns and infections more often form keloids, leading to contractures and impaired function, as well as considerable cosmetic defects.
  - The biologic reasons for the excess proliferation remain unclear, although most recent data shows that epidermal cytokines drive the dermal reaction.
- **Clinical features:** Firm skin-colored to red nodules and plaques rich in telangiectases. Keloids have irregular "fingers" growing at the periphery. Both may be tender, painful, or pruritic (Fig. 26.**3**).
- **Histology:**
  - *Normal scar:* Fibroblasts arranged in loose myxoid stroma; as healing proceeds, collagen fibers are laid down parallel to epidermis.
  - *Hypertrophic scar:* Fibroblasts scattered, admixed between myxoid stroma and dense collagen bundles.
  - *Keloid:* Similar to hypertrophic scar, but large amorphous bundles of eosinophilic collagen; later hyalinized.
- **Therapy:**
  - *Hypertrophic scar:* Improvement with time can be expected; cryotherapy may speed involution.
  - *Keloid:* No good therapy. Never make any bold promises of success. Possibilities include:

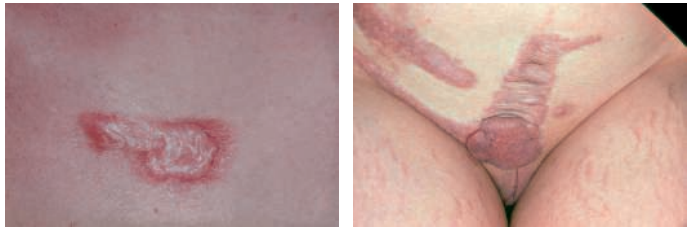


Fig. 26.3 · **Keloids. a** Hypertrophic scar with transition to keloid. **b** Large keloids.

- Injection of corticosteroids, ideally using a needleless injection system; use 2.5–5.0 mg triamcinolone/mL; inject every month for 6 months and reassess.
- Injections can be combined with cryotherapy; freezing the lesion 5 minutes before injection makes injecting physically easier and may have an additive effect.
- Pressure dressing with pressure > 24 mm Hg is useful for fresh wounds and especially for burn scars as prophylactic measure. Variety of pressure suits and wraps available.
- Tangential debulking excision can be combined with intralesional steroids, cryotherapy, and pressure dressings.
- Debulking can also be combined with postoperative radiation therapy; usually 10–20 Gy are given in 3–5 divided doses.
- Excision and coverage with skin graft can be considered only if it is certain that the new wound can heal under less skin tension with exogenous pressure applied and that the graft donor site can be placed under prophylactic pressure.

▶ ***Note:*** Simple re-excision almost never works and often worsens the problem greatly.

- Silicon gel sheeting for at least 12 hours daily; early studies were promising but recent ones less so.

Fibromatoses

▶ **Definition:** Confusing group of benign fibrous proliferations, which can be locally aggressive and tend to recur, but are not capable of metastasis.

▶ **Classification** (based on Enzinger and Weiss):

- *Superficial fibromatoses* (arise in fascia, grow slowly, relatively small):
  - Dupuytren contracture (palmar fibromatosis).
  - Ledderhose contracture (plantar fibromatosis).
  - Peyronie disease (penile fibromatosis).
  - Infantile digital fibromatosis.
  - Torticollis.
  - Gingival fibromatosis.
- *Deep fibromatoses* (desmoid tumors, arise from muscle aponeuroses, growing rapidly, are locally aggressive, but do not metastasize):
  - Extra-abdominal fibromatosis.
  - Abdominal fibromatosis.
  - Intra-abdominal fibromatosis.

- Pelvic fibromatosis.
- Mesenteric fibromatosis.
- Desmoids in Gardner syndrome (p. 368).
- Retroperitoneal fibromatosis (Osmond disease).

- **Clinical features:** The superficial lesions are characterized by firms nodules, bands, and strands of fibrous tissue, leading to tissue deviation (Peyronie disease or torticollis) or contractions (Dupuytren or Ledderhose disease).
- **Histology:** Irregular proliferations of myofibroblasts and fibroblasts; superficial variants usually parallel to the skin surface; deeper variants more cellular and highly irregular.
- **Differential diagnosis:** All connective tissue proliferations and tumors must be considered. The superficial lesions are clinically diagnosable; the deeper ones usually present as a mass and are harder to suspect.
- **Therapy:** All are hard to treat; infantile digital fibromatosis often resolves spontaneously. Fortunately, none are the direct responsibility of dermatologists.

Nodular Fasciitis

- **Definition:** Rapidly growing, histologically atypical reactive fascial proliferation.
- **Pathogenesis:** Trauma often appears to be trigger.
- **Clinical features:** More common in young adults; presents as rapidly growing tender nodule typically on ulnar aspect of forearm; variant in children on scalp (*cranial fasciitis*). Usually grows over 4–6 weeks, is larger than 3 cm, firm, and adherent to fascia. Spontaneous regression over 2 years.
- **Histology:** Myxoid stroma containing whorled arrangements of fibroblasts, some of which may be bizarre; periphery often contains inflammatory infiltrate.
- **Differential diagnosis:** Clinically lipoma usual consideration; histologically misdiagnosed as fibrosarcoma until entity firmly established.
- **Therapy:** None needed, but not clinically relevant, as excisional biopsy is done for diagnostic purposes.

Dermatofibrosarcoma Protuberans

- **Definition:** Low-grade malignant fibrous tumor always presenting in the skin.
- **Epidemiology:** Only common cutaneous sarcoma; prevalence 1/100 000.
- **Pathogenesis:** Usually specific reciprocal translation (17;22) (q22;q13) forming a ring chromosome; gene for type 1α1 collagen is placed under control of platelet-derived growth factor (PDGF), leading to excessive collagen deposition.
- **Clinical features:** Firm, slowly growing skin-colored or erythematous tumor, usually around shoulder girdle; resembles a scar (Fig. 26.**4**). Gradually develops multiple nodules and bizarre configuration.
  - ***Note:*** If a lesion looks like a scar but patient denies trauma or surgery, always consider dermatofibrosarcoma protuberans and sclerosing basal cell carcinoma.
- **Variants** include pigmented form (*Bednar tumor)* and juvenile form (*giant cell fibroblastoma*).
- **Histology:** Small bundles of fibroblasts and fibrocytes with storiform or radial pattern; infiltrate subcutaneous fat creating thickened septae and also have irregular peripheral spread. Mitoses uncommon. Tumor cells CD34-positive.
- **Diagnostic approach:** Adequate biopsy specimen essential; even if excision biopsy is impossible, provide a generous ellipse.
- **Differential diagnosis:** Deep or atypical dermatofibroma, leiomyosarcoma, myofibroblastic sarcoma.

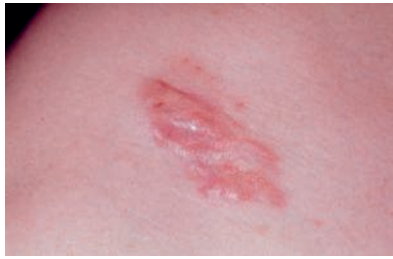


Fig. 26.4 · Dermatofibrosarcoma protuberans.

- **Therapy:** Best chance for cure is a complete initial excision with a 3 cm margin of safety. The excision should include the underlying fascia. Micrographic surgery is very useful in this setting, coupled with CD34 staining. Follow-up should be every 6 months.

Myofibroblastic Sarcoma

- **Definition:** Low-grade sarcoma usually involving the skin or less often subcutaneous connective tissue.
- **Clinical features:** Favors extremities, relatively well-circumscribed painless nodule without distinguishing features; rarely ulcerated. Can be locally aggressive; occasionally rapidly growing forms may metastasize.
- **Histology:** Fascicles of tumor cells, sometimes storiform or herringbone pattern, with varying degrees of nuclear atypia. The myofibroblasts are positive for smooth muscle actin and muscle-specific actin (HHF35), but usually negative for CD34.
- **Differential diagnosis:** Higher grade fibrosarcomas, dermatofibrosarcoma protuberans, leiomyosarcoma.

Malignant Fibrous Histiocytoma (MFH)

- **Definition:** Malignant soft tissue tumor with varying histologic patterns presumably derived from connective tissue elements.
- **Pathogenesis:** Controversial. For years it was considered the most common soft tissue tumor of adults, but now many of its variants have been reestablished as other sarcomas.
- **Clinical features:** Subcutaneous or deep soft tissue tumor; most common sites thighs and buttocks. Frequently recurs and can metastasize; cutaneous metastases occasionally seen.
- **Histology:** The best established variant is the myxoid MFH, also known as myxofibrosarcoma. Other patterns include inflammatory, xanthomatous, giant cell, and angiomatoid variants. Nuclear atypia and mitoses are common.
- **Differential diagnosis:** Other sarcomas.
- **Therapy:** Generous excision and follow-up every 6 months.

Atypical Fibroxanthoma

- **Definition:** Superficial malignant fibrous histiocytoma; dermal tumor with bizarre histologic pattern and low-grade malignant behavior.
- **Clinical features:** Usual lesion develops rapidly in sun-exposed skin of older patients; 1–2 cm erythematous, crusted lesion. Much less commonly similar le-

sions appear in younger patients without extensive sun exposure; these tend to grow slowly but achieve a greater size.
- **Histology:** Mixture of extremely bizarre spindled and epithelioid cells with wildly irregular nuclei embedded in fibrous stroma. Formerly considered a pseudomalignancy (*too bizarre to be malignant*), but now acknowledged as a low-grade malignancy.
- **Differential diagnosis:** Basal cell carcinoma, amelanotic melanoma, poorly differentiated squamous cell carcinoma, other sarcomas. Immunohistochemistry allows the exclusion of other possibilities, but there are no stains specific for atypical fibroxanthoma.
- **Therapy:** Complete excision; yearly follow-up.

Epithelioid Sarcoma

- **Definition:** Highly malignant sarcoma of uncertainty differentiation.
- **Clinical features:** Most patients are young adults; most typical sites are extremities and scalp. Firm subcutaneous nodules, sometimes ring-shaped and occasionally ulcerated. Recurrences and metastases are common, even years after removal of primary tumor.
- **Histology:** Cellular nodules with oval, polygonal, spindled, or epithelioid nuclei. Often necrosis with peripheral palisading, as well as hemorrhage and cyst formation. Vascular invasion common.
- **Differential diagnosis:** Early lesions often mistaken for granuloma annulare (annular, necrosis with peripheral palisading) or infections; later other sarcomas, especially synovial sarcoma, are the main consideration.
- **Therapy:** Generous excision is required; when limited to a distal limb, amputation is often required for cure.

26.2 Smooth Muscle Tumors

Overview

- **Definition:** Leiomyomas are benign smooth muscle tumors. They are often tender or painful; see ANGEL list (p. 714). Their classification is shown in Table 26.**1**.

Piloleiomyoma

- **Clinical features:** Usually start in puberty; red-brown 1–2 cm papules, usually multiple and on extremities; often tender.
- **Histology:** Bundles of dermal smooth muscle, resembling arrector pili muscles, but larger; nuclei are blunted or cigar-shaped.
- **Differential diagnosis:** Clinically mast cell tumor, Spitz nevus, adnexal tumor; histologically, neurofibroma.
- **Therapy:** Solitary or few lesions can be excised; unfortunately, usually so many that surgery is not an option. Phenoxybenzamine (10 mg 3–6 × daily) combined with nifedipine (10 mg t.i.d.) may relieve pain by relaxing smooth muscle fibers.
- **Multiple cutaneous leiomyomas** (MIM code 160800) have mutation in fumarate hydratase on chromosome 1q; also present in some solitary tumors. Such patients should be evaluated for leiomyomas elsewhere. Hereditary leiomyomatosis (MIM code 605839) has mutations in the same gene, but also uterine leiomyomas and leiomyosarcomas as well as papillary renal cell carcinomas.

Table 26.1 · Classification of cutaneous leiomyomas

Type	Frequency (%)	Origin
Piloleiomyoma	60	Arrector pili muscle
Genital leiomyoma	20	Dartos, other genital smooth muscle; may also arise from erectile muscle of nipple
Angioleiomyoma	20	Smooth muscle of vessel wall

Genital Leiomyoma

- **Clinical features:** Flat plaques, rarely larger than 2 cm.
- **Histology:** Same microscopic features as piloleiomyoma.
- **Differential diagnosis:** Cyst, fibroma; nipple adenoma.
- **Therapy:** Excision.

Angioleiomyoma

- **Clinical features:** Usually on the legs of middle-aged women; 1–2 cm painful subcutaneous nodule.
- **Histology:** Circumscribed nodular tumor consisting of bundles of smooth muscle surrounding thick-walled vessels.
- **Differential diagnosis:** Other subcutaneous masses—cysts, lipomas, fibromas.
- **Therapy:** Excision.

Cutaneous Leiomyosarcoma

- **Epidemiology:** Patients usually middle-aged; both sexes affected.
- **Clinical features:** Usually on trunk arising from arrector pili or extremities arising from vascular smooth muscle. Less often on breast or genitalia. Generally asymptomatic low-growing nodule, rarely ulcerated. Often overlooked.
- **Histology:** Same pattern as leiomyoma, but more nuclear atypia and mitoses. Very difficult histologic diagnosis.
- **Differential diagnosis:** Dermatofibrosarcoma protuberans, malignant fibrous histiocytoma; main problem is corresponding leiomyoma.
- **Therapy:** Excision with 1–2 cm safety margin and microscopic control of margins.
- **Prognosis:** Excellent prognosis for cutaneous and subcutaneous leiomyosarcomas; >95% 5-year survival. Follow-up every 6 months.

26.3 Tumors of Fat

Nevus Lipomatosus Superficialis

- **Synonym:** Hoffmann–Zurhelle nevus.
- **Definition:** Congenital malformation with islands of fat high in dermis.
- **Clinical features:** Grouped papules or plaque, usually around buttocks, with yellow tones (Fig. 26.**5**).
- **Histology:** Islands of normal fat in the dermis, often almost impinging on the epidermis; not uncommonly associated with melanocytic nevus.

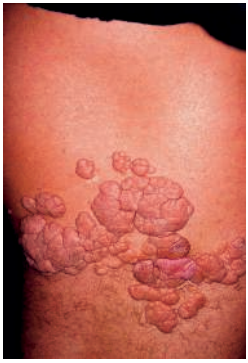


Fig. 26.5 · Nevus lipomatosus.

- **Differential diagnosis:** Connective tissue nevus; histologically, focal dermal hypoplasia.
- **Therapy:** Smaller lesions can be excised.

Lipoma

- **Definition:** Most common benign soft tissue tumor; accumulation of mature fat cells.
- **Clinical features:** Soft, lobulated, freely movable round or oval subcutaneous mass; usually appears in adult life; rarely symptomatic. Variants include:
  - *Angiolipoma:* Usually painful (see ANGEL p. 714), rich in small vessels that may have thromboses.
  - *Spindle cell lipoma:* Almost always on nape of older men; painless; bands of spindled fibrous cells admixed with fat cells.
  - *Mobile lipoma:* Usually on forearm; moveable over several cm; microscopically encapsulated; probably posttraumatic.
  - *Lumbosacral lipoma:* Congenital, often associated with spina bifida.
  - *Pleomorphic lipoma:* Clinically banal; histologically features giant cells and even lipoblasts.
- **Histology:** Normal fat tissue surround by a wispy fibrous capsule; variants as described above.
- **Differential diagnosis:** Cysts, other subcutaneous tumors.
- **Therapy:** Excision. In most cases, one can make an incision and manipulate out the lipoma; in other instances, complete excision required.

Multiple Lipomas

Two main groups:

- **Familial multiple lipomas** (MIM code 151900): Multiple lipomas, can be painful or disfiguring; possible association with diabetes mellitus. Individual troublesome lesions can be excised.
- **Dercum disease (adiposis dolorosa):** Puzzling condition with painful lipomas; limited to middle-aged women, often overweight. Lesions often angiolipomas.

Lipomatoses

- **Definition:** Multiple localized accumulations of fat, which may be symmetric or asymmetric.
- **Benign symmetric lipomatosis of Launois–Bensaude** (MIM code: 151800).
  - Type I: Cervical (Madelung neck).
  - Type II: Shoulder girdle; weightlifter form.
  - Type III: Pelvic (Engels).
  - Often associated with alcoholism and liver disease. Patients look muscular and healthy, but have paradoxical excess fatty deposits with other profound metabolic problems. No good treatment.
- Proteus syndrome (p. 414) often with multiple lipomas.
- **Michelin tire baby syndrome** (MIM code 156610): Extremely rare syndrome in which children develop multiple folds of skin resembling the advertising figure for Michelin tires; sometimes underlying fat tissue; in other instances fibrous tissue or smooth muscle. Often associated with mental retardation and other problems.

Hibernoma

- **Definition:** Benign tumor of embryonal brown fat.
- **Clinical features:** Tumor of young adults (not newborns); slowly growing asymptomatic tumor on trunk; can be large (5–10 cm).
- **Histology:** Fat cells are filled with many small vacuoles, typical of brown fat, which is also found in hibernating mammals.
- **Differential diagnosis:** Lipoma, liposarcoma.
- **Therapy:** Excision.

Liposarcoma

- **Definition:** Uncommon malignant tumor of fatty tissues.
- **Epidemiology:** Usually appear after age 40; do not develop from lipomas. Liposarcomas are the most common sarcoma, but are extremely rare in the skin.
- **Classification:** Based on histologic features: well-differentiated, myxoid, round cell and pleomorphic, with prognostic differences. Well-differentiated and myxoid have much better 5-year survival figures.
- **Clinical features:** Mass in deep soft tissues, retroperitoneum; about 5% of myxoid liposarcomas are cutaneous. Slowly growing subcutaneous mass; never clinically distinct.
- **Histology:** Useful in typing and thus in prognosis.
- **Therapy:** Radical excision.

26.4 Vascular Malformations and Tumors

Overview

Vascular embryogenesis is a complex process with many different types of aberrant vessel formation leading to *malformations.* Vascular *tumors* or new proliferations of vessels after birth are typically lobular and generally benign, although malignant and borderline variants are occasionally seen. The following primarily histopathological classification is useful, although we have varied from it slightly to group clinically similar disorders together:

- Malformations.
  - Capillary.
  - Venous.
  - Lymphatic.
- Dilated vessels.
- Hemangiomas and benign tumors.
- Tumors of glomus cells and pericytes.
- Borderline (low grade) malignant tumors.
- Malignant tumors.

Malformations

Nevus Flammeus

- **Synonym:** Port wine stain.
- **Definition:** Congenital localized vascular malformation consisting of dilated capillaries.
- **Classification:**
  - *Medial form:* Usually nape or forehead (stork bite nevus).
  - *Lateral form:* Follows peripheral or cranial nerve.
- **Clinical features:**
  - Circumscribed, flat pink or deeper red area; present at birth: grows with child. In adult life, tendency to thicken, develop papules.
  - Median lesions may regress during infancy; lateral ones do not.
  - Median lesions are not associated with other abnormalities; lateral ones may be.
- **Diagnostic approach:** Children with lateral lesions should be followed for vascular, neurologic, or orthopedic problems. Biopsy not needed.
- **Therapy:** Camouflage; capillaries can be destroyed with pulsed dye or copper vapor laser; later papules destroyed with Nd:YAG laser.

Sturge–Weber Syndrome

- **MIM code:** 185300.
- **Clinical features:**
  - Unilateral nevus flammeus in distribution of 1st or 2nd branch of trigeminal nerve with ipsilateral vascular abnormalities of meninges or cortex (Fig. 26.**6**).
  - Epilepsy (80%), mental retardation, contralateral hemiparesis, and muscle atrophy. CNS lesions may calcify.
  - Glaucoma, especially when 1st branch is involved.
- **Diagnostic approach:** Multidisciplinary approach with neurologic and ophthalmologic follow-up.
- **Therapy:** Nevus flammeus can be treated as outlined above.

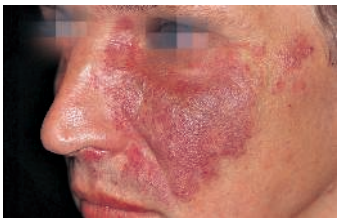


Fig. 26.**6** · Sturge–Weber syndrome.

Klippel–Trénaunay–Weber Syndrome
- **MIM code:** 149000.
- **Clinical features:**
  - Nevus flammeus involving a limb, with hypertrophy of underlying bones and muscles.
  - Frequent associated arteriovenous fistulas, potentially leading to high-output cardiac failure.
- **Diagnostic approach:** Angiologic evaluation to exclude shunts.
- **Therapy:** Many measures tried to limit distorted blood flow: ligation of anastomoses, microembolization, laser coagulation; in milder cases, compression stockings.

Venous Malformation
- **Synonym:** Cavernous hemangioma.
- **Clinical features:** Venous malformations are deeper, softer and unlikely to regress spontaneously. They are readily compressible. Because of their slow flow, venous malformations are subject to thromboses and thus can be painful. Thromboses almost unheard of in capillary and arterial malformations. Color of the overlying skin determined by depth of vascular structures.
- Multiple venous malformations may be familial.
- **Diagnostic approach:** Imaging studies to exclude arteriovenous shunts, thromboses, and internal malformations.
- **Differential diagnosis:** Hemangioma, nevus flammeus.
- **Therapy:** If limited to a limb, compression therapy and perhaps anticoagulants. Best active treatment is sclerotherapy, followed by surgery.

Congenital Lymphedema
- **Pathogenesis:** A "negative" vascular malformation, associated with defective or absent lymphatics leading to swollen limbs.
- **Clinical features:**
  - *Familial congenital lymphedema:*
    - *Synonym:* Nonne–Milroy syndrome.
    - *MIM code:* 153100.
    - *Pathogenesis:* Mutation in VEGF receptor 3 gene; autosomal dominant inheritance.
    - *Clinical features:* Lymphedema present at birth or infancy; usually involves both legs; associated with pleural effusions and ascites.
  - *Familial lymphedema praecox:*
    - *Synonym:* Meige syndrome.
    - *Pathogenesis:* Mutation in transcription factor in the forkhead family (*FOXC2*); autosomal dominant inheritance.
    - Onset in puberty; usually unilateral without other findings.
  - *Sporadic primary lymphedema:* No family history.
- **Differential diagnosis:** Much more common is lymphedema secondary to obstruction. Causes include filariasis, lymph node dissection, irradiation or involvement by metastatic disease, recurrent erysipelas.
- **Therapy:** Early and aggressive use of compression bandages or stockings; in more extreme cases, home compression machine is essential.

Lymphangiomas
- **Definition:** Group of lymphatic malformations and proliferations involving skin and soft tissue.

- **Clinical features:**
  - *Lymphangiectases:* Small dilated primarily clear vesicles; also known as cutaneous chylous reflux. Appear secondary to lymphatic obstruction or chronic lymphedema.
  - *Lymphangioma circumscriptum*: Congenital lesion that may first become apparent in childhood; multiple grouped vesicles, clear to red-blue, usually described as resembling frogspawn. Usually on extremities. Generally connect to deeper lymphatic vessels, so excision is often followed by recurrences. Smaller lesions can be treated with laser ablation or contact cryotherapy.
  - *Cystic hygroma:* Congential deep unilocular lymphatic malformation; typically involves soft tissue of face, neck; less often axilla or groin. Can be deforming. Surgery is difficult, but usually the most effective approach.

Caution: Patients with lymphangiomas and lymphedema are predisposed to cellulitis.

Dilated Vessels

Nevus Araneus

- **Synonym:** Spider nevus.
- **Definition:** Acquired vascular lesion consisting of central dilated arteriole and radiating capillaries.
- **Clinical features:**
  - 2–4 mm red papule from which extend fine telangiectases (thus spider nevus) (Fig. 26.**7**).
  - Usually face or décolletage.
  - Associated with pregnancy, liver disease, and CREST syndrome (p. 219).
- **Diagnostic approach:** If multiple lesions or sudden onset, search for cause.
- **Therapy:** Destruction of central vessel with laser or intense pulsed light source (IPL).

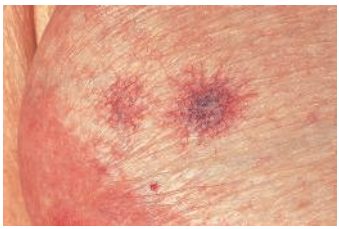


Fig. 26.**7** · Spider nevus.

Arteriovenous Fistula

- **Synonym:** Cirsoid aneurysm.
- Uncommon nodular vascular lesion, usually follows trauma. Often on forehead or distal extremities. Typically 1–2 cm nodule, which may pulsate or have auditory thrill. Histology shows vessels with extremely thick walls. Excision curative.

Venous Lake

- Common lesion on lips. Compressible, dome-shaped blue-pink nodule. When darker, occasionally mistaken for pigmented lesion. Harmless, but easily excised or ablated.

Telangiectases

► **Definition:** Irreversible dilation of cutaneous capillaries and postcapillary venules.

► **Classification (p. 706):**

- *Primary telangiectases* (congenital or without obvious cause):
  - Generalized essential telangiectases.
  - Unilateral nevoid telangiectasia syndrome.
  - Poikiloderma syndromes.
  - Ataxia-telangiectasia.
  - Hereditary benign telangiectases.
  - Hereditary hemorrhagic telangiectases.
  - Telangiectasia macularis eruptiva perstans (combination of telangiectases and mast cell disease).
- *Secondary telangiectases:*
  - Mycosis fungoides (poikiloderma vasculare atrophicans variant).
  - Rosacea.
  - Dermatomyositis.
  - Systemic sclerosis, especially CREST syndrome.
  - Lupus erythematosus.
  - Xeroderma pigmentosum.
  - Sun-damaged skin.
  - Erythema ab igne.
  - Portal hypertension.
  - Carcinoid syndrome.

Generalized Essential Telangiectases

► **Clinical features:** Common, usually found in middle-aged women, primarily on legs. Depending on severity. ranges from minor nuisance to major cosmetic problem. No associated findings.

Unilateral Nevoid Telangiectasia Syndrome

► **Clinical features:** Unilateral distribution of multiple spider nevi with prominent halos; usually starts in the shoulder girdle or upper arm region. May be congenital or acquired; latter usually in women and estrogen-driven (pregnancy, oral contraceptives). If troublesome in postmenopausal women, can be treated with antiestrogens; otherwise, laser destruction of individual lesions.

Hereditary Benign Telangiectases

► **MIM code:** 187260.

► **Clinical features:** Telangiectases with slight atrophy; often larger and thus venous. No associated hemorrhage or systemic problems. Likely autosomal dominant inheritance, but with expression primarily in women.

Hereditary Hemorrhagic Telangiectasia

► **Synonym:** Osler–Weber–Rendu syndrome.

► **MIM code:** 187300.

► **Definition:** Inherited disorder with cutaneous and mucosal telangiectases with tendency to bleeding.

► **Pathogenesis:** Autosomal dominant inheritance. Two well-established mutations in genes that interact with transforming growth factor-β to regulate small vessel growth: *HHT1* codes for endoglin gene at 9q34.1 while *HHT2* codes for activin receptor kinase 1 at 12q13. Other rarer genes also under consideration.

- **Clinical features:**
  - Most common presenting feature frequent nosebleeds in childhood.
  - During puberty, development of telangiectases, favoring oral and nasal mucosa, as well as internal organs; also on face, hands.
  - Internal complications include gastrointestinal bleeding (from telangiectases) and pulmonary arteriovenous fistulas, which serve as source of septic emboli for CNS.
- **Diagnostic approach:** History, physical examination including gastrointestinal studies, pulmonary imaging.
- **Differential diagnosis:** Fabry disease and other causes of multiple angiokeratomas.

Ataxia-telangiectasia

- **Synonym:** Louis–Bar syndrome.
- **MIM code:** 208900.
- **Definition:** Syndrome with profound neurological and immune defects associated with telangiectases.
- **Epidemiology:** Frequency 1: 40000; autosomal recessive inheritance. Carriers appear to have higher risk for internal malignancies.
- **Pathogenesis:** Mutation in *ATM* gene at 11q22.3, responsible for DNA surveillance and repair.
- **Clinical features:**
  - *Progressive cerebellar ataxia:* Major problem; children usually bedridden as infants.
  - *Telangiectases:* Almost always conjunctival at first, later facial or more widespread.
  - Other skin findings include café-au-lait macules, premature graying, sclerodermoid changes, and peculiar aggressive form of necrobiosis lipoidica.
  - Combined immune defect with defects in both humoral and cellular immunity, leading to multiple infections.
  - Endocrine problems—early-onset insulin-resistant diabetes mellitus.
  - Patients who survive infections have 100-fold increased incidence of malignancies, especially lymphoma and leukemia.
- **Prognosis:** Dismal; few survive childhood.
- **Therapy:** Bone marrow transplantation; if not available, then supportive care. Must be done early to minimize neurological defects.

Cutis Marmorata Telangiectasia Congenita

- **Synonyms:** Van Lohuizen syndrome, congenital generalized phlebectasia.
- **MIM code:** 219500.
- **Pathogenesis:** Sporadic disorder; cause unknown.
- **Clinical features:**
  - Present at birth; dilated vessels with striking marbled pattern that varies little with temperature. Most improve slowly over time. Can be associated with necrosis and ulcerations.
  - Midline nevus flammeus is sometimes marker.
  - About 30% of patients have systemic findings including limb hypo- or hypertrophy, craniofacial anomalies, glaucoma, and mental retardation.
- **Diagnostic approach:** History, clinical examination.
- **Therapy:** Nothing effective.

Angiokeratomas

- **Definition:** Capillary-lymphatic malformation in upper dermis associated with hyperkeratotic epidermis.
- **Clinical features:** Several clinically distinct forms:
  - *Solitary angiokeratoma:* Multihued or black hyperkeratotic papule, usually on legs of children; differential diagnostic considerations include melanocytic nevus and malignant melanoma (Fig. 26.**8**).

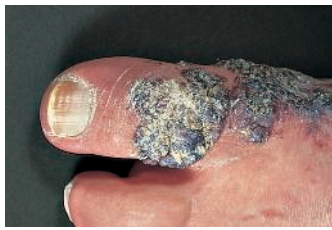


Fig. 26.**8** · Angiokeratoma.

  - *Angiokeratoma circumscriptum*: Verrucous blue-black plaque usually on extremities; present at birth, grows with patient. Can also be mistaken for malignant melanoma.
  - *Angiokeratoma of Mibelli*: Small blue-black hyperkeratotic papules of distal extremities, usually in children with acrocyanosis or cold injury; differential diagnosis including warts.
  - *Angiokeratoma Fordyce*: Tiny violet papules on scrotum or labia of older adults: differential diagnosis includes senile angioma when nongenital.
  - *Fabry disease:*
    - *Synonym:* Angiokeratoma corporis diffusum.
    - *MIM code:* 315500.
    - Pathogenesis: Mutation in *GLA* gene at Xq22 coding for α-galactosidase; X-linked recessive inheritance; lyosomal storage disorder.
    - *Clinical features:* Multiple angiokeratomas, typically starting around umbilicus; acral paresthesias, hypohidrosis, heat intolerance. Corneal dystrophy. Renal, cardiac, and CNS vascular problems.
    - *Differential diagnosis:* Osler–Weber–Rendu syndrome, senile angiomas.
    - *Therapy:* Enzyme replacement therapy possible.
  - Other metabolic diseases including fucosidosis, Kanzaki syndrome, and Spangler syndrome; check pediatric genetic sources.
- **Diagnostic approach:** Despite this puzzling list, the clinical pictures are usually quite distinct. A solitary or plaque-like lesion will usually be biopsied to exclude a pigmented lesion. Multiple scrotal or vulvar lesions are clear. Porokeratosis of Mibelli is usually overlooked. The metabolic disorders usually present with other findings, so the dermatologist rarely has the chance to make the diagnosis.
- **Therapy:** Individual small lesions can be destroyed with lasers; large plaques are best excised.

Hemangioma

- **Synonym:** Capillary hemangioma.
- **Definition:** Benign vascular tumor, which typically appears at birth or just thereafter.

- **Pathogenesis:** Sporadic event; angiogenesis is very active in utero and presumably perturbations in vascular growth control mechanisms are responsible.
- **Clinical features:**
  - Raised red to purple soft nodules that can become very large. About 30% can be seen at birth, but most appear later and all continue to grow (Fig. 26.**9**). Tumors can be compressed, but do not disappear with diascopy.

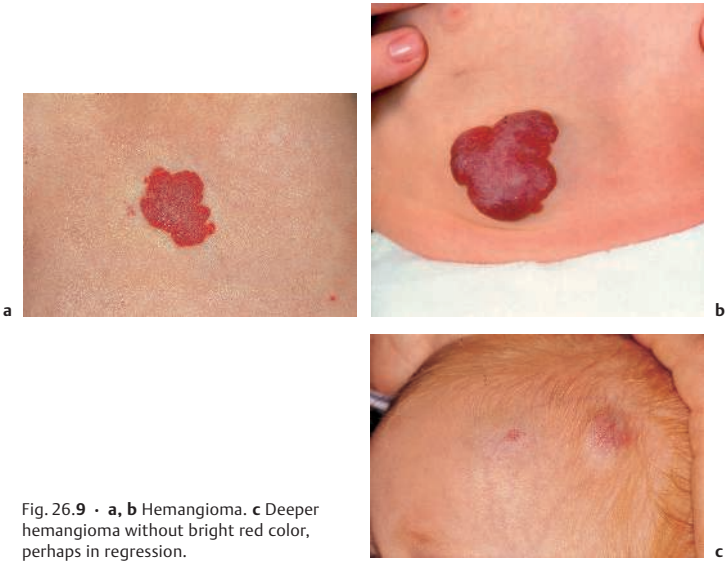


Fig. 26.**9** · **a, b** Hemangioma. **c** Deeper hemangioma without bright red color, perhaps in regression.

  - Those which appear after birth are 2–5 × more common in girls.
  - Congenital hemangiomas typically are large nodules with a rim of dilated vessels; they are divided into rapidly involuting and noninvoluting forms. No sex predilection.
  - Old distinction of capillary versus cavernous hemangioma rarely made today. The deeper vessels in cavernous lesions are usually venous malformations and do not regress.
  - Telangiectatic hemangiomas may mimic nevus flammeus, but continue to grow.
  - Complications include:
    - Obstruction of vital structures: eyes, nose, mouth.
    - *Bleeding:* Serious events surprisingly rare.
  - During the first months of life, hemangiomas can continue to grow. After about years of age, no further growth is anticipated and regression starts. It may take many years and often leaves behind scar or loose skin.
- **Diagnostic approach:** Clinical diagnosis:
  - ***Note:*** Three questions to separate hemangioma from malformation are listed in Table 26.**2**.

Table 26.2 · Separating hemangioma from malformation

Question	Hemangioma	Malformation
Present at birth?	Usually no; appears in first weeks of life	Yes
Growing?	Yes	No
Regressing?	Yes	No

- If multiple lesions are present, consider following problems:
  - Generalized eruptive hemangiomatosis: Multiple cutaneous lesions; no systemic involvement.
  - Diffuse neonatal hemangiomatosis: Multiple cutaneous lesions, plus cardiac, gastrointestinal, hepatic and pulmonary hemangiomas. Probably with hemorrhage, cardiac failure.
  - *PHACES syndrome:* **P**osterior fossa malformation, **h**emangiomas (mainly facial); **a**rterial, **c**ardiac, **e**ye, and **s**ternal anomalies.
  - Blue rubber bleb nevus syndrome (p. 458).

► **Therapy:**
- Small lesions can be treated with intense pulsed light source, pulsed dye or Nd:YAG laser (also intralesional); treatment should be started early, not awaiting growth phase.
- Contact cryotherapy is alternative approach; also done early.
- Residual lesions or scars best excised.
- Aggressive periorificial lesions:
  - Intralesional or systemic corticosteroids (prednisolone 20–30 mg daily for 2–3 weeks).
  - Interferon-α2 (systemic).
  - Sclerosing therapy or embolization also possible, but reserved for special centers.

▶ ***Note:*** The effectiveness of IPL and lasers has shifted the trend toward treating hemangiomas. Nonetheless, some parents may prefer to allow nature to take its course, especially for small truncal lesions, and they should be offered this option.

Senile Angioma

► **Synonym:** Cherry angioma.
► **Definition:** Common small capillary proliferation, usually appears in middle-aged adults.
► **Clinical features:** Small smooth ruby-red papules, usually on trunk and multiple. No associated findings.
► **Differential diagnosis:** Clinically distinct; if thrombosed, can be confused with pigmented lesions.
► **Therapy:** None needed; laser destruction easy if desired.

Pyogenic Granuloma

► **Synonym:** Eruptive hemangioma.
► **Definition:** Rapidly growing capillary hemangioma usually developing after trauma (Fig. 26.**10**).
► **Clinical features:**
- Typically eroded, often weeping or friable tumor that reaches several cm in size over week; history of trauma.

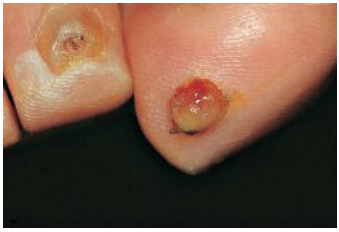


Fig. 26.**10** · Pyogenic granuloma.

- Many different clinical patterns:
  - Common on digits, especially nail folds.
  - Next most likely site is interdental gingiva, common during pregnancy (epulis of pregnancy).
  - Satellite lesions are common, as are satellite recurrences (central lesion removed; many small peripheral lesions recur).
  - Deeper pyogenic granulomas are often intravenous.

► **Histology:** Eroded epidermis; lobular proliferation of new vessels in dermis associated with neutrophilic infiltrate.
► **Diagnostic approach:** Sudden history, clinical appearance, histology.
► **Differential diagnosis:** Usually clinically distinct; nail lesions should always be studied histologically to exclude amelanotic malignant melanoma. Polypoid lesions on feet can be confused with Kaposi sarcoma. Satellite lesions usually cause concern; confused with metastases. In patients with HIV/AIDS, also consider bacillary angiomatosis.
► **Therapy:** Excision, cryotherapy, or any other destructive measures.

Tufted Angioma

► Uncommon lesion that clinically looks like bruise, but is persistent and slowly progressive. Histologic pattern very similar to pyogenic granuloma with multiple proliferative nodules. Associated with Kasabach–Merritt syndrome. Treatment difficult; options include surgery, laser ablation, and even ionizing radiation.

Acroangiodermatitis

► **Synonym:** Mali disease, pseudo-Kaposi sarcoma.
► **Definition:** Reactive dilated veins in areas of chronic venous insufficiency produce cutaneous nodules.
► **Clinical features:** Almost exclusively limited to ankles, dorsal aspect of feet; dark red to brown lichenoid papules and plaques, which may become confluent or ulcerate.
► **Histology:** Thickened epidermis over lying dermal proliferation of thick-walled vessels associated with hemosiderin deposition and fibrosis.
► **Diagnostic approach:** Usually obvious, if one appreciates the presence of chronic venous insufficiency. If any questions, biopsy.
► **Differential diagnosis:** Sporadic Kaposi sarcoma.
► **Therapy:** Compression therapy, possible excision.

Acquired Progressive Lymphangioma

► Another rare lesion that can cause differential diagnostic problems.
► Clinically resembles a slowly expanding bruise. Microscopically shows delicate vascular slits very similar to early Kaposi sarcoma.
► Treatment is excision or other destructive measures.

Blue Rubber Bleb Nevus Syndrome

- **MIM code:** 112200.
- **Definition:** Association of multiple cutaneous and gastrointestinal venous malformations.
- **Pathogenesis:** Most cases sporadic, but autosomal dominant inheritance.
- **Clinical features:**
  - Compressible blue nodules often tender (see ANGEL list, p. 714); present in infancy; involve trunk and extremities.
  - Associated gastrointestinal lesions usually bleed, leading to abdominal pain, anemia.
- **Diagnostic approach:** Gastrointestinal evaluation.
  - ***Note:*** Always search for gastrointestinal bleeding in patients with vascular lesions and anemia.
- **Therapy:** Individual painful lesions can be excised; sclerotherapy and laser ablation also possibilities.

Maffucci Syndrome

- **MIM code: 166000**.
- **Definition:** Combination of lymphatic–venous malformations and endochondromas.
- **Pathogenesis:** Mutations in *PTHR* gene at 3p22-p21.1; exact genetics unclear.
- **Clinical features:**
  - Multiple venous and lymphatic malformations, often favoring the extremities.
  - Vascular neoplasms, especially spindle cell hemangioendothelioma.
  - Endochondromas with a 20% risk of chondrosarcoma.
  - Short stature.
- **Diagnostic approach:** Careful monitoring for malignant change.
- **Therapy:** Vascular lesions treated as for venous malformations.

Glomus Tumor

- **Definition:** Benign tumor arising from the cutaneus glomus or Sucquet–Hoyer anastomosis; group of contractile cells responsible for arteriovenous shunting, especially in digits.
- **Epidemiology:** More common in men, although subungual more common in women.
- **Pathogenesis:** Usually sporadic; multiple lesions may be autosomal dominant inheritance.
- **Clinical features:**
  - Solitary lesions are tender red-blue tumors, often subungual or acral
  - Multiple lesions (*glomus malformations* or *glomangiomas*) are larger, compressible (more clearly associated with vessel spaces) and less likely to be painful (Fig. 26.**11**).
- **Histology:** Nests of small blue cuboidal cells in dermis, sometimes associated with vascular spaces. *Glomangiomyomas* have spindled rather than cuboidal cells.
- **Diagnostic approach:** Solitary lesions: see ANGEL list for painful tumors (p. 714); multiple lesions, gastrointestinal survey.
- **Therapy:** Excision.

Hemangiopericytoma

- **Clinical features:** Tumor of deep soft tissues with little dermatologic relevance.
- **Histology:** Classic histological picture of spindle cells and staghorn vessels; today felt to be reaction pattern seen in fibrous, neural, and smooth muscle tumors with different biological behaviors.

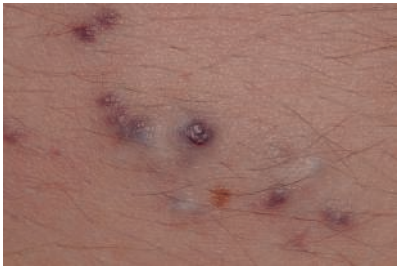


Fig. 26.**11** · Multiple glomus tumors.

Note: If confronted clinically with a tumor alleged to be hemangiopericytoma, seek expert dermatopathologic consultation.

Hemangioendotheliomas

- **Definition:** Vascular tumors of intermediate-grade biologic behavior; low-grade angiosarcomas.
- **Classification:** All are rare but some of dermatologic significance:
  - *Kaposiform hemangioendothelioma:* Spindle cell tumor of childhood; despite its rarity, most common tumor for Kasabach–Merritt syndrome (platelet consumption coagulopathy).
  - *Dabska tumor* (*malignant intravascular papillary angioendothelioma*): Head and neck tumor in children with intravascular tumor islands.
  - *Retiform hemangioendothelioma:* Tumor with hobnail endothelial cells; usually on distal extremities with slow, locally aggressive growth pattern.

Malignant Vascular Tumors

Angiosarcoma

- **Definition:** Sarcoma arising from vascular and lymphatic structures.
- **Pathogenesis:** Often caused by ionizing radiation, toxins (especially for hepatic angiosarcoma) or chronic lymphedema. Most recent studies show that lymphatic origin is likely.
- **Clinical features:** Several distinct clinical settings:
  - *Angiosarcoma of scalp:* Initially subtle, but relentless tumor of scalp; early lesions mistaken for vascular malformation; later nodules, ulceration; always extends far beyond apparent clinical margins, so difficult to cure.
  - *Angiosarcoma secondary to chronic lymphedema* (*Stewart–Treves syndrome*): Mostly common in edematous arm following mastectomy.
  - Postradiation angiosarcoma.
- **Histology:** Highly variable, ranging from benign lobular proliferations to spindle-cell rich areas to epithelioid areas with high mitotic rate and nuclear atypia. New vessels insinuate between strands of collagen.
- **Diagnostic approach:** Must think of disease and then biopsy.
- **Differential diagnosis:** Clinically, many ulcerated tumors such as malignant melanoma; histologically, Kaposi sarcoma.
- **Therapy:**
  - The only chance for cure is complete surgical excision, usually followed by consolidation radiation therapy.
  - Careful margin control; tumor often extends far beyond imagined borders; micrographic surgery valuable.

- Palliative radiation therapy if inoperable.
- Neither chemotherapy and interleukin-2 (intralesional and/or intravenous) has helped much.

► **Prognosis:** Five-year survival around 10%; both lymphatic and hematogenous spread.

Kaposi Sarcoma

► **Definition:** Virally induced, usually multifocal tumor with many clinical forms.

► **Pathogenesis:** Caused by human herpesvirus 8 (HHV-8); exact mechanism of tumor induction unclear but HHV-8 encodes many growth control genes. HHV-8 present in all forms of Kaposi sarcoma.

► **Clinical features:**

- *Classic Kaposi sarcoma*: Usually affects elderly men of Jewish or Mediterranean background; slowly growing red-brown patches and plagues on feet or legs (Fig. 26.**12**); when advanced, nodules, ulceration and rarely systemic involvement. Excellent prognosis.

Note: Patients tend to die with, rather than from, classic Kaposi sarcoma.

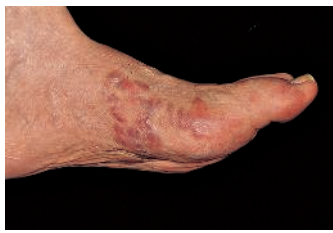


Fig. 26.**12** · Kaposi sarcoma—classic type.

- *Endemic (African) Kaposi sarcoma:* Several types:
  - Lymphadenopathic: Usually in children; resembles lymphoma; usually fatal.
  - Chronic localized or benign: Similar to classic.
  - Locally aggressive: Ulcerated cutaneous lesions; infiltration of bone.
  - Florid disseminated: Skin and visceral involvement.
- *Iatrogenic Kaposi sarcoma:* Associated with immunosuppression; resolves if immune status can be restored. Usually diffuse subtle lesions, but can resemble HIV-associated Kaposi sarcoma.
- *HIV-associated Kaposi sarcoma:* Disseminated Kaposi sarcoma, usually in men, often oral involvement or facial involvement, but can occur anywhere. Early lesions oval macules and papules that follow skin tension lines.

► **Diagnostic approach:**

- Biopsy to confirm diagnosis; then evaluate depending on clinical scenario.
- Exclude HIV infection; check HLA-DR status.
- Routine laboratory parameters and chest radiograph.
- Abdominal and lymph node sonography.
- Gastrointestinal examination as directed by signs and symptoms.
- Immune status.

► *Differential diagnosis:*

- Classic Kaposi sarcoma: Acroangiodermatitis, spindle cell hemangioma, Kaposiform hemangioendothelioma, leiomyosarcoma.
- HIV-associated Kaposi sarcoma: Bacillary angiomatosis.

- **Therapy:** Varies greatly with form:
  - *Local:*
    - Excision.
    - Cryotherapy (better for macular lesions).
    - Intralesional vincristine or vinblastine; also bleomycin.
    - Interferon-α.
    - Fractionated radiation therapy (20–30 Gy in 8–10 sessions).
    - Photodynamic therapy or laser ablation.
  - *Systemic:*
    - HAART.
    - Interferon-α 9 million IU subq. 3× weekly; watch for bone marrow toxicity.
    - Etoposide 100 mg/m^2 daily for 3 days; repeat every 28 days.
    - Liposomal doxorubicin 20 mg/m^2 every 28 days.
    - Polychemotherapy with doxorubicin 20 mg/m^2 and vincristine 2 mg every 2–3 weeks.

26.5 Neural Tumors

Overview

Neural tumors encompass a wide range of lesions, including:
- Malformations and hamartomas.
- Reactive processes.
- Benign neoplasms.
- Malignant neoplasms.

They may be sporadic or associated with systemic diseases such as neurofibromatosis or MEN2B.

Nasal Glioma

- **Definition:** Embryologic herniation of CNS tissue.
- **Clinical features:** Nodule present at birth, usually at root of nose (nasion), flesh-colored, representing outpouching of CNS with incomplete midline closure.
- **Histology:** Glial tissue with astrocytes; no neurons.
- **Diagnostic approach:** Careful evaluation prior to surgery.
  - ***Caution:*** All midline congenital lesions should be evaluated in multidisciplinary fashion with imaging studies to exclude connection to underlying neural structures. Cutting unprepared in neural tissue is not a pleasant experience.
- **Differential diagnosis:** Vascular malformation, dermoid cyst, lipoma.
- **Therapy:** Excision by neurosurgery.

Cutaneous Meningioma

- **Definition:** Benign tumor of meningeal tissue.
- **Pathogenesis:** In contrast to glioma, no brain tissue is involved, just meninges.
- **Clinical features:** Three forms:
  - *Primary cutaneous meningioma* (*ectopic meningothelial hamartoma*): Present at birth; located on scalp, forehead (then similar to nasal glioma), or paravertebral region. Highly vascular; can be mistaken for angiosarcoma. Good prognosis.
  - *Secondary cutaneous meningioma:* Local spread of CNS meningioma either via erosion of skull or following surgery to involve skin. Outlook that of underlying tumor.

- *Peripheral meningioma* (*ectopic meningioma*): Meningeal remnants along the tracts of cranial or peripheral nerves; usually in adults. Typical sites include scalp, perinasal, periauricular, and periorbital. Troublesome because of compression and destruction of vital structures.
- In each case, dermal or subcutaneous plaques, 2–10 cm, on scalp or following nerves.

► **Diagnostic approach:** Once again, exclude underlying defects.
► **Therapy:** Excision.

Neurofibroma

► **Definition:** Benign tumor of peripheral nerve sheath.
► **Pathogenesis:** Neurofibromas can be solitary or when multiple associated with neurofibromatosis 1 (p. 362).
► **Clinical features:** A solitary neurofibroma is a soft compressible tumor, usually identified in young adult.
► **Histology:** Dermal spindle cell tumor, nuclei are long and wavy, often rich in mast cells.
► **Diagnostic approach:** Histology; then exclude neurofibromatosis.
► **Differential diagnosis:** Usually mistaken for weakly pigmented melanocytic nevus or skin tag.
► **Therapy:** Excision.

Neurilemmoma

► **Synonym:** Schwannoma.
► **Definition:** Benign tumor of Schwann cells.
► **Pathogenesis:** Both neurofibroma and neurilemmoma are Schwann cell tumors; why they look so different is unclear.
► **Clinical features:** Neurilemmomas can be sporadic, associated with neurofibromatosis 2 (p. 364), or multiple without other findings (*schwannomatosis*).
- They are associated with a nerve, most commonly the acoustic nerve.

► ***Note:*** Bilateral acoustic nerve neuromas always suggest neurofibromatosis 2.

- Confusingly, neurilemmomas are also seen in neurofibromatosis 1. Sporadic neurilemmomas are usually on the extensor aspects of the extremities associated with peripheral nerves. Typically 2–5 cm firm nodule, sometimes tender.

► **Histology:** Circumscribed tumor with orderly array of nuclei (*Antoni pattern*) sometimes surrounding accumulations of collagen (*Verocay bodies*). Usually nerve associated with specimen.
► **Diagnostic approach:** Histology; exclude neurofibromatosis 2.
► **Differential diagnosis:** Other painful tumors (see ANGEL list p. 714); lipoma, epidermoid cyst, neurofibroma, rheumatoid nodule.
► **Therapy:** Excision.

Granular Cell Tumor

► **Synonym:** Abrikosov tumor; granular cell myoblastoma no longer appropriate; in infants, congenital epulis.
► **Definition:** Benign Schwann cell tumor with characteristic granular cytoplasm.
► **Clinical features:**
- In infants, tumor of oral mucosa, usually palate.
- In adults, solitary tumor most commonly on tongue, frequently associated with overlying pseudoepitheliomatous hyperplasia leading to mistaken diagnosis of squamous cell carcinoma.

- As solitary cutaneous lesion, no site of predilection; 1–2 cm skin-colored nodule; simply a surprise when histologic report comes back.

► **Histology:** Dermal tumor with nests and strands of epithelioid cells with granular cytoplasm.
► **Therapy:** Excision.

Perineurioma

► **Synonym:** Nerve sheath myxoma.
► **Definition:** Benign tumor of perineurium—fibrous component of nerve sheath.
► **Clinical features:** Solitary asymptomatic tumor, usually in adult women; often acral. Painless; no connection to neurofibromatosis.
► **Histology:** Combination of cut-onion pattern and myxoid areas in circumscribed dermal tumor.
► **Therapy:** Excision.

Traumatic Neuroma

► **Definition:** True neuroma, resulting from trauma to peripheral nerve.
► **Clinical features:** Dermal tumor, usually asymptomatic, but can be tender. Several clinical variants including:
- *Morton neuroma:* Painful tumor between metatarsal bones.
- *Pacinian neuroma:* Painful tumor on distal aspect of fingers; microscopically rich in Pacinian corpuscles (pressure receptors).
- *Rudimentary digit:* Following intrauterine autoamputation of accessory digit, sometimes neuroma remains on lateral aspect of 5th digit.

► **Histology:** Benign neural fibers in fibrous stroma, sometimes with obvious scar formation.
► **Differential diagnosis:** If painful, see ANGEL list p. 714).
► **Therapy:** Excision.

Mucosal Neuromas

► **Definition:** True neuroma associated with MEN2B syndrome (p. 367).
► **Clinical features:** Multiple soft nodules on tongue, lips; enlarged conjunctival nerves may lead to spontaneous lid eversion (Gorlin or everted lid sign).
► **Histology:** Circumscribed submucosal neural tissue.
Caution: Be suspicious of diagnosis of traumatic neuroma in the mouth. Oral trauma usually leads to bite fibroma, not bite neuroma. Always check patients for MEN2B because of risk of medullary thyroid carcinoma and phaeochromocytoma.
► **Therapy:** Excision if painful or troublesome.

Soft Tissue Ependymoma

► **Definition:** Soft tissue tumor arising from ependymal rests; potentially malignant.
► **Clinical features:** Slowly growing mass, almost always over sacrum or coccyx in child or young adult, associated with spina bifida and other signs of incomplete spinal closure. About 20% behave in malignant fashion with metastases; rest are locally aggressive.
► **Histology:** Poorly circumscribed myxoid-papillary dermal tumor.
► **Differential diagnosis:** Often mistaken for pilonidal cyst or sinus.
► **Therapy:** Generous excision and careful monitoring.

Malignant Peripheral Nerve Sheath Tumor

- **Synonyms:** Neurofibrosarcoma, malignant schwannoma, MPNST.
- **Pathogenesis:** Half of MPNST arise in patients with neurofibromatosis; the tumors arise from plexiform neurofibromas, not from ordinary cutaneous neurofibromas; most common in men in their 30s. Sporadic MPNST occur in an older population without gender predilection. Trunk and head are most common sites. Rarely following ionizing radiation.
- **Clinical features:** Deep, aggressive tumor without distinctive clinical features unless neurofibromatosis is present.
- **Histology:** Pleomorphic tumor, sometimes with residua of benign precursor, often with myxoid areas and frank nuclear atypia.
- **Therapy:** Generous excision and careful monitoring; five-year survival less than 50% with better outlook for sporadic tumors.

27 Other Cutaneous Tumors

27.1 Mast Cell Disorders

Overview

Mast cells are derived from the bone marrow and then populate many organs, including the skin. They are typically in a perivascular location and release a variety of mediators in response to both immune and nonimmune stimulation. Mast cells contain granules; the main mediators in these organelles are histamine and heparin. In addition, a variety of cytokines and prostaglandins are released. Most cutaneous mast cell disease is limited to the skin; in rare instances, the bone marrow or other organs are involved. Many cases of mast cell proliferation are caused by mutations in the c-*kit* gene.

Classification

- **Cutaneous mastocytosis:**
  - Mastocytoma.
  - Urticaria pigmentosa.
  - Diffuse cutaneous or bullous mastocytosis.
  - Telangiectasia macularis eruptiva perstans.
- **Systemic mastocytosis:**
  - Extracutaneous mastocytoma.
  - Indolent systemic mastocytosis, with variant of smoldering mastocytosis.
  - Systemic mastocytosis with associated hematologic non–mast cell lineage disorder.
  - Aggressive systemic mastocytosis.
  - Mast cell leukemia.
  - Mast cell sarcoma.

Mastocytoma

- **Definition:** Localized mast cell accumulation, usually in dermis.
- **Epidemiology:** Often present at birth, but can appear in childhood.

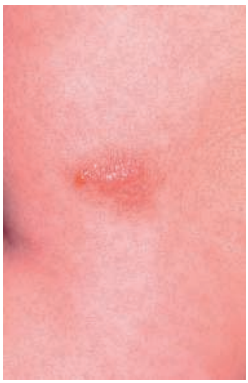


Fig. 27.**1** · Mastocytoma.

- **Clinical features:** Red-brown papule or nodule; may urticate or blister when rubbed (*Darier sign*) (Fig. 27.**1**). Occasionally multiple lesions.
- **Histology:** Dermal nodule of uniform cuboidal cells whose granules can be seen with Giemsa or toluidine blue staining. Histologically can be confused with dermal nevus.
- **Differential diagnosis:** Spitz nevus, juvenile xanthogranuloma.
- **Therapy:** None needed; if troublesome, excision.

Urticaria Pigmentosa

- **Definition:** Multiple mast cell lesions in the skin; may be associated with systemic mast cell disease.
- **Clinical features:** Red-brown 1–5 mm disseminated macules or papules; Darier sign positive as lesions easily urticate releasing mast cell mediators (Fig. 27.**2**). Sometime release severe enough to cause systemic signs and symptoms (hypotension, tachycardia, headache, dizziness). In children, likelihood of spontaneous remission; in adults usually permanent with risk of systemic disease.

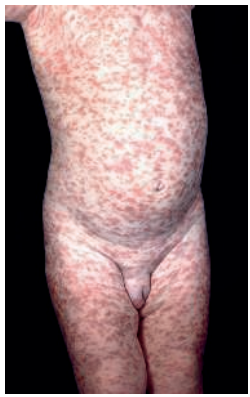


Fig. 27.**2** · Urticaria pigmentosa.

- **Histology:** Increased dermal mast cells, usually perivascular, but smaller accumulations than mastocytoma.
- **Differential diagnosis:** When patients describe signs and symptoms, mistaken diagnosis of allergic urticaria often made. Careful clinical examination usually points in the right direction.
- **Therapy:** Trial of PUVA; if effective, maintenance therapy needed. Systemic antihistamines and high-potency topical corticosteroids under occlusion.

Diffuse Cutaneous Mastocytosis

- Rare form usually seen in infants < 3 years of age; may present as erythroderma or widespread bullae. Clinically can be very alarming, but usually resolves spontaneously.

Telangiectasia Macularis Eruptiva Perstans

- Another rare variant, seen in adults, with diffuse red-brown macules and multiple telangiectases. Patients have significant risk of systemic involvement.

Indolent Systemic Mastocytosis

- **Definition:** Mast cell proliferation in multiple organs, usually coupled with urticaria pigmentosa.
- **Clinical features:** Main symptoms are usually produce by histamine release. A number of medications, such as codeine, can cause mast cell degranulation. The following organ systems most like to be involved:
  - *Gastrointestinal tract:* Nausea, vomiting, diarrhea, duodenal ulcer. Endoscopy and biopsy usually needed for diagnosis.
  - *Bone:* Pain and osteoporosis main findings; bone biopsy or scintigraphy.
  - *Bone marrow:* Proliferation of mast cells or other marrow elements.
  - Hepatosplenomegaly or lymphadenopathy may also be seen.
- **Therapy:** Combined treatment with H1 and H2 blockers; oral cromolyn sodium, a mast cell stabilizer, may help gastrointestinal manifestations but is not absorbed to benefit other organs. If indications of mast cell leukemia or other hematologic involvement, refer to a hematology center with special interest in mast cell disease.

27.2 Histiocytoses

The histiocytoses include two separate lineages of diseases—Langerhans cell histocytosis and macrophage disorders. Both Langerhans cell and macrophages are derived from the bone marrow but fulfill different functions. Langerhans cells are dendritic cells involved primarily in antigen presentation, while macrophages are phagocytic cells. There are overlaps both among normal cells and the different disease states. The different histiocytoses can be readily separated with a small battery of special stains, as shown in Table 27.**1**.

Table 27.1 · Simple classification of histiocytoses

Disease	S100[a]	CD1a[a]	CD68[b]	EM (BG)[c]
Langerhans cell disease	+	+	–	+
Sinus histiocytosis with massive lymphadenopathy	+	–	–	–
Macrophage disorders (xanthogranulomas)	–	–	+	–

a S100 and CD1a are reliable markers for Langerhans cells.
b CD68 is the best macrophage marker but others are available.
c Electron microscopy to search for Birbeck granules was formerly the gold standard for identifying Langerhans cells.

Langerhans Cell Histiocytosis (LCH)

- **Synonym:** Langerhans cell disease; formerly known as histiocytosis X.
- **Definition:** Group of disorders featuring proliferation of Langerhans cells with varying degrees of systemic involvement.

- **Epidemiology:** All forms of LCH are rare; incidence is around 4/1 000 000.
- **Pathogenesis:** The proliferations of Langerhans cells are clonal, but in many instances, spontaneous regression occurs, so LCH is somewhere between a malignancy and a reactive proliferation.
- **Clinical features:** There are four clinical forms with extensive overlap:
  - *Hashimoto–Pritzker disease* (*congenital self-healing reticulohistiocytosis*): Nodules present at birth, which almost always regress; differential diagnostic considerations include TORCH disorders (p. 65), mastocytoma, congenital leukemia.
  - *Letterer–Siwe disease:* Widespread disease; most common in infants and children; purpuric scaly papules, favoring scalp, seborrheic areas and flexures (Fig. 27.**3**). High likelihood of systemic involvement. Can appear in adult life.

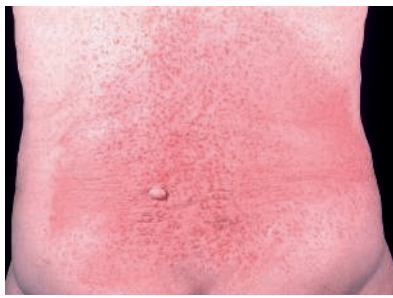


Fig. 27.**3** · Langerhans cell histiocytosis, Letterer–Siwe form

  - *Hand–Schüller–Christian disease:* Classic triad of diabetes insipidus, exophthalmos, and bony defects; usually self-limited.
  - *Eosinophilic granuloma:* Single or limited number of lesions usually involving bone; more common in adults.
- **Histology:** All have same microscopic picture; infiltrate of large epidermotropic cells with kidney-shaped nuclei, often admixed with eosinophils; S100 and CD1a positive. Identification of Birbeck granules no longer required for diagnosis.
- **Diagnostic approach:** Clinical examination, biopsy. The prognosis depends on the number of organs with functional impairment; most crucial are bone marrow, liver, lungs and spleen. Isolated pulmonary LCH occurs in adult smokers and rarely has any cutaneous findings.
- **Differential diagnosis:** In infants, seborrheic dermatitis, diaper dermatitis or candidiasis; later Darier disease.
  - ***Note:*** Always biopsy infants with purpuric diaper dermatitis or seborrheic dermatitis not responsive to treatment.
- **Therapy:** Mild or localized disease responds to topical steroids, topical nitrogen mustard is effective but generally avoided in children. Localized lesions are sensitive to radiation therapy or curettage. Systemic disease treated with standard regimen of vinblastine and corticosteroids, or under protocol (consult tertiary centers).
- **Prognosis:** 30% clear completely; 60% resolve with residua, and 10% die.

Indeterminate Cell Histiocytosis (ICH)

In the past, patients with LCH who did not have Birbeck granules were described as having ICH. Today, the indeterminate cell is no longer recognized and electron microscopy is rarely performed. ICH is now used to describe cases with overlapping histological features of LCH and macrophage disorders; usually clinically the cases represent widespread xanthogranulomas.

Sinus Histiocytosis with Massive Lymphadenopathy

- **Synonym:** Rosai–Dorfman disease.
- **Definition:** Uncommon disorder, usually affecting children with massive lymphadenopathy.
- **Pathogenesis:** Etiology unknown.
- **Clinical features:** Most striking presenting finding is massive lymphadenopathy. About 10% of these patients has cutaneous red-brown papules and nodules. The skin and soft tissues are the most common sites of nonnodal SHML.
- **Histology:** Appearance likened to "lymph node within the skin"; proliferation of lymphocytes and large clear sinus histiocytes that ingest the lymphocytes (*emperipolesis*).
- **Differential diagnosis:** Cutaneous lesions not clinically distinct; if solitary, possibilities include juvenile xanthogranuloma, Spitz nevus, mastocytoma, melanocytic nevus.
- **Therapy:** No established treatment for systemic disease; about 10% of patients succumb. Individual skin lesions can be excised.

Macrophage Disorders

The prototypical macrophage disorder is juvenile xanthogranuloma. The rest of the diseases are very uncommon; they may be divided into solitary and local variants, and further classified on what type of macrophage (foamy, ground glass, spindle) dominates. This entire group is sometimes referred to as non-Langerhans cell histiocytosis.

Juvenile Xanthogranuloma

- **Epidemiology:** Most common in infants and small children, but can appear in adults.
- **Clinical features:** Yellow to red-brown nodules; favors scalp, trunk or flexures. Number may range from 1 to >20. In children, almost always resolve spontaneously. Variants include plaque-like, disfiguring, and subcutaneous forms. Occasionally ocular involvement with hemorrhage and glaucoma.
  - ***Note:*** It is wise to refer all children with juvenile xanthogranuloma to the ophthalmologist.
- **Histology:** Infiltrate of small macrophages, CD68 positive and CD1a negative; occasionally focal S100 positivity. Touton giant cells almost always present (larger wreathed giant cells with lipids inside wreath), as well as eosinophils.
- **Diagnostic approach:** Rare association between juvenile xanthogranuloma, neurofibromatosis 1, and juvenile myelomonocytic leukemia. Check all patients for café-au-lait macules.
- **Differential diagnosis:** Spitz nevus, mastocytoma.

Multicentric Reticulohistiocytosis

- **Epidemiology:** Rare disease, most common in middle-aged women.
- **Clinical features:** Skin-colored to red-brown papules and nodules over joints, resembling rheumatoid nodules; sometimes tiny papules along nail fold (*coral bead sign*). Destructive arthritis, associated autoimmune diseases (lupus erythematosus) as well as occasional paraneoplastic marker.
- **Histology:** Infiltrate of multinucleated giant cells with haphazardly arranged nuclei and ground glass cytoplasm; same changes may be seen in synovium.
- **Differential diagnosis:** Sarcoidosis, rheumatoid arthritis, tuberous and tendinous xanthomas.
- **Therapy:** No satisfactory treatment; methotrexate usually employed; anti-TNF biologicals show promise.

Other Rare Macrophage Disorders

Other diseases with a similar histologic profile are listed in Table 27.**2**. In each instance, solitary lesions can be excised while multiple lesions are not easily influenced..

Table 27.2 · **Rare macrophage disorders**

Disease	Comments
Benign cephalic histiocytosis	Multiple small xanthogranulomas in mid-face of small children; resolves spontaneously
Generalized eruptive histiocytosis	Multiple small red-brown papules which wax and wane; may evolve into other members or group or serve as paraneoplastic marker
Solitary reticulohistiocytoma	Variant of xanthogranuloma with ground class giant cells; not associated with systemic signs and symptoms
Papular xanthoma	Solitary or limited number of foamy xanthogranulomas with normal serum lipid studies; normolipemic xanthoma
Xanthoma disseminatum	Multiple normolipemic xanthomas
Spindle cell xanthogranuloma	Large nodule usually mistaken histologically for dermatofibroma
Progressive nodular histiocytosis	Patients with multiple spindle cell and papular xanthomas; extremely rare

28 Cutaneous Lymphomas and Leukemia

28.1 Benign Lymphocytic Infiltrates

Overview

- **Definition:** Benign reactive lymphocytic infiltrate, which must be distinguished from a lymphoma.
- **Classification:** The old term "pseudolymphoma" only causes confusion. Many of the lesions formerly diagnosed as pseudolymphoma have turned out to be low-grade B-cell lymphomas; one example is marginal zone lymphoma. There are nonetheless several situations where benign lymphocytic infiltrates do occur in the skin. All lesions are clinically similar, presenting as red-brown nodules.
  - *Lymphadenosis cutis benigna:* Proliferation associated with *Borrelia burgdorferi* infection (p. 94). Nodules, often involving earlobe or nipple, resolve with antibiotic therapy. Infiltrate of CD20+ B cells with both κ and λ light chains and regular germinal centers.
  - *Lymphocytic infiltration of Jessner–Kanof:* Erythematous nodules and plaques, often facial, which on biopsy show abundant CD4+ helper T cells and mucin. In many instances, this disease is actually lupus tumidus (p. 206) and may respond to corticosteroids or antimalarials.
  - Reactions to arthropod assaults (tick bites, nodular scabies) and viral infections (molluscum contagiosum) can be misinterpreted as lymphomas if the history is not available; mixed collection of lymphocytes, often with eosinophils (p. 130).
  - Vascular tumors may have such an intense lymphocytic infiltrate that the underlying abnormal vessels are obscured; two dramatic examples are:
    - *Angiolymphoid hyperplasia with eosinophilia*: Typically facial nodules featuring vessels lined by thick epithelioid (hobnail) endothelial cells, associated with a dense infiltrate of lymphocytes and eosinophils.
      - ***Note:*** This disorder is sometimes erroneously designated *Kimura disease*; the latter is a systemic disease found in the Far East which rarely has cutaneous findings and is not relevant for Western physicians.
    - **A***cral* **p***seudolymphomatous* **a***ngiokeratoma of* **ch***ildren (APACHE syndrome)*: Acral papules in children; mixed lymphocytic infiltrate around superficial vessels.
    - Rarely drugs, foreign bodies, or allergic contact dermatitis may induce a lymphocytic infiltrate, but such lesions are much less common than the other categories.
- **Differential diagnosis:** The most important exclusion is a true lymphoma. Molecular biologic analysis including clonality studies can be crucial, if a typical history is not available. Other possibilities include polymorphous light eruption, tinea, leukemic infiltrates, Kaposi sarcoma, angiosarcoma, adnexal tumors.

28.2 Primary Cutaneous Lymphomas

Overview

- Primary cutaneous lymphomas manifest themselves primarily in the skin and are confined there initially without evidence of nodal or systemic involvement. They may be either B-cell or T-cell lymphomas, presumably with skin-specific homing mechanisms.
- **Epidemiology:** Very rare; incidence 1–2/100 000, but has increased in recent years.
- **Pathogenesis:** Many different factors appear involved, including persistent antigen stimulation (*Borrelia burgdorferi, Helicobacter pylori* for intestinal tumors) for B-cell lymphomas and transforming viruses (HTLV1, Epstein–Barr virus) for T-cell lymphoma. Genetic instability, immunosuppression, and carcinogens all play a role.

Classification

- Recently a working committee unified the classifications used by the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC), as shown in Table 28.**1**. We will follow this classification and not attempt to cross-reference to older or alternate schemes.
- The frequency and 5-year survival for the most common cutaneous lymphomas in the WHO/EORTC classification are shown in Table 28.**2**.

Table 28.1 · **WHO-EORTC classification of cutaneous lymphomas**

Cutaneous T-cell and NK-cell lymphomas
Mycosis fungoides
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma*
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Cutaneous γ/δ T-cell lymphoma (provisional)
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)

Table 28.1 · Continued

Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other
Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma) †

Table 28.2 · Relative frequency and disease-specific 5-year survival of 1905 primary cutaneous lymphomas

WHO/EORTC classification	Number	Frequency (%)	Disease-specific 5-year survival (%)
Cutaneous T-cell lymphoma			
Indolent clinical behavior			
Mycosis fungoides	800	44	88
Folliculotropic MF	86	4	80
Pagetoid reticulosis	14	<1	100
Granulomatous slack skin	4	<1	100
Primary cutaneous anaplastic large cell lymphoma	146	8	95
Lymphomatoid papulosis	236	12	100
Subcutaneous panniculitis-like T-cell lymphoma	18	1	82
Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma †	39	2	75
Aggressive clinical behavior			
Sézary syndrome	52	3	24
Primary cutaneous NK/T-cell lymphoma, nasal type	7	<1	NR
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma †	14	<1	18
Primary cutaneous γ/δ T-cell lymphoma †	13	<1	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified #	47	2	16
Cutaneous B-cell lymphoma			
Indolent clinical behavior			
Primary cutaneous marginal zone B-cell lymphoma	127	7	99
Primary cutaneous follicle center lymphoma	207	11	95

Continued Table 28.3 ▶

Table 28.2 · Continued

WHO/EORTC classification	Number	Frequency (%)	5-year survival (%)
Cutaneous B-cell lymphoma (Continued)			
Intermediate clinical behavior			
Primary cutaneous diffuse large B-cell lymphoma, leg type	85	4	55
Primary cutaneous diffuse large B-cell lymphoma, other	4	< 1	50
Primary cutaneous intravascular large B-cell lymphoma	6	< 1	65

NR indicates not reached. * Data are based on 1905 patients with a primary cutaneous lymphoma registered at the Dutch and Austrian Cutaneous Lymphoma Group between 1986 and 2002.
† Primary cutanous peripheral T-cell lymphoma, unspecified excluding the three provisional entities indicated with a double dagger (#).

28.3 Primary Cutaneous T-cell Lymphomas

Mycosis Fungoides

- **Definition:** An epidermotropic cutaneous T-cell lymphoma characterized by a proliferation of small to medium-sized CD4+ t cells with cerebriform nuclei.
- **Epidemiology:** Male:female ratio 2–3:1; typically starts after 50 years of age, but can be seen in younger patients.
- **Clinical features:**
  - *Patch stage*: Macules and patches, slightly erythematous and scaly, often with cigarette paper surface (wrinkled appearance, also called pseudoatrophy); sites of predilection include buttocks, trunk, upper thighs, upper arms (Fig. 28.**1 a**). Less often involvement of flexures, scalp, and palms.
  - ***Note:*** If confronted with erythematosquamous plaques with varying shades of color, always think of mycosis fungoides.
  - *Plaque stage*: Gradual thickening of patches with increased scale (Fig. 28.**1 b**).
  - *Tumor stage*: Usually after many years, abrupt development of thick, often ulcerated tumors arising from the plaques (Fig. 28.**1 c**).
- **Variants:**
  - *Folliculotropic mycosis fungoides*: Malignant T cells are highly concentrated in and about hair follicles; often mucinous deposits in follicles, which are then destroyed producing alopecia; two synonyms are *mucinosis follicularis* and *alopecia mucinosa*.
  - *Granulomatous slack skin*: Granuloma formation and destruction of elastic fibers leads to pendulous skin, especially in flexures; also seen with Hodgkin lymphoma.
  - *Pagetoid reticulosis:* Two clinical patterns:
    - Classic *Woringer–Kolopp* pagetoid reticulosis: One or few acral plaques; sharply bordered, scaly, stable.
    - Disseminated *Ketron–Goodman* pagetoid reticulosis: Widespread plaques without patch stage lesions or pruritus; most do not distinguish this form from mycosis fungoides.

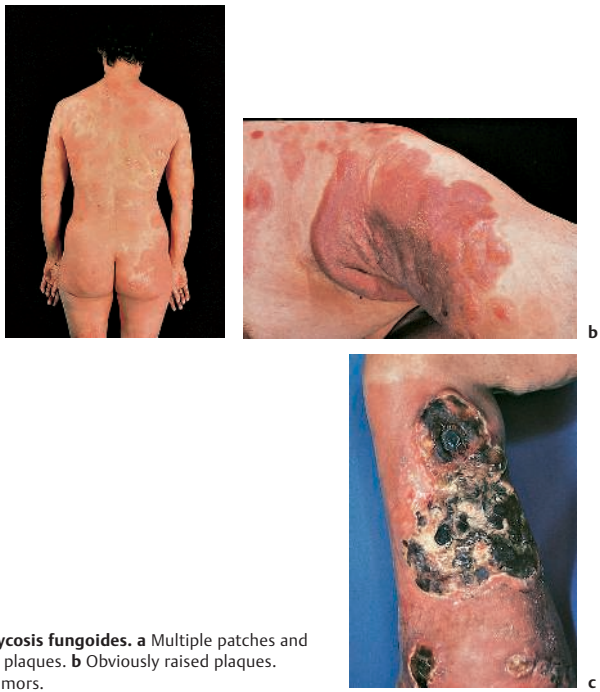


Fig. 28.**1** · **Mycosis fungoides. a** Multiple patches and slightly raised plaques. **b** Obviously raised plaques. **c** Ulcerated tumors.

► **Histology:**
- *Patch stage:* Perivascular or confluent subepidermal infiltrate of lymphocytes, some with atypical cerebriform nuclei. Some cells enter the epidermis and may form small collections (*Pautrier microabscess*). The cells are usually T-helper cells of memory type (CD3+, CD4+, CD8-, CD45 RO+, CD30-). Rarely CD8+ tumor cells.
- *Plaque stage:* Dermal infiltrate is thicker and more pleomorphic, with lymphocytes, histiocytes, eosinophils and sometimes plasma cells. Epidermotropism is more prominent.
- *Tumor stage:* Nodular dermal infiltrate of clearly atypical cerebriform lymphocytes with other cells admixed.
- *Granulomatous slack skin:* Destructive granulomas with loss of elastic fibers; infiltrates of malignant T cells.
- *Pagetoid reticulosis:* More epidermotropism of atypical T cells, thus mimicking Paget disease.
- *Molecular biology*: Using PCR a clonal T-cell proliferation can be shown in the skin in 80% of cases and in the blood in > 50%. Presence of a clone at time of diagnosis is associated with poorer prognosis.

► **Staging:**
- Staging is based on a modified TNM (Bunn and Lamberg, 1979) shown in Tab. 28.**3**.
- *T (Skin):* The most advanced lesions are used for staging.

Table 28.3 · Staging of mycosis fungoides (based on Bunn and Lamberg, 1979)

Stage	TNM	Clinical features
IA	pT1 N0 M0	Patch and plaque lesions, < 10% of body surface
IB	pT2 N0 M0	Patch and plaque lesions, > 10% of body surface
IIA	pT1–2 N1 M0	Skin involvement as in I, but lymphadenopathy without histologic evidence of involvement
IIB	pT3 N0–1 M0	Tumors ± lymphadenopathy without histologic evidence of involvement
III	pT4 N0–1 M0	Erythroderma ± lymphadenopathy without histologic evidence of involvement
IVA	pT1–4 N2–3 M0	All skin involvement ± lymph nodes with histologic evidence of lymphoma
IVB	pT1–4 N0–3 M1	Visceral involvement; histologically proven

- *N (Lymph nodes):*
  - N1: clinically palpable nodes without specific lymphoma cells (*dermatopathic lymphadenopathy*).
  - N2: nodes contain lymphoma cells; need not be dramatically enlarged.
  - N3: nodal architecture destroyed by lymphoma cells; nodes usually enlarged.
  - Involvement of deeper lymph nodes (para-aortal, mediastinal) occurs late and is associated with short survival.
- *M (Metastases):* Histologically proven internal organ involvement.

► **Diagnostic approach:** The diagnosis of patch-stage mycosis fungoides is difficult. Often a certain diagnosis cannot be made even when clinical, histological, and molecular biological information is combined.

- Patients should be checked every 4–12 months. Baseline skin biopsy, lymph node evaluation, and laboratory studies essential.
- If skin lesions appear to thicken, re-biopsy is indicated.
- Lymph nodes should be assessed with sonography and suspicious ones excised.
- Once plaque or tumor stage is reached, chest radiography and abdominal sonography, as well as more directed imaging studies, become essential.

► **Differential diagnosis:**

- *Patch stage:* Nummular dermatitis, tinea corporis, large-patch parapsoriasis.
- *Plaque stage:* Psoriasis, subacute cutaneous lupus erythematosus, pityriasis lichenoides chronica.
- *Tumor stage:* Other lymphomas, leukemic infiltrate.
- *Pagetoid reticulosis: Clinical:* tinea corporis, psoriasis, Bowen disease, other papulosquamous diseases; *histological:* superficial spreading melanoma, Paget disease, Bowen disease.

► **Therapy:**

- PUVA therapy; initially 4 × weekly, then once response has been seen, gradual reduction until complete clinical remission.
- Interferon-α2a (9 million IU subq. 3 × weekly); in decreasing doses, for maintenance therapy.
- When PUVA and interferon are combined, treatment time is reduced and longer remissions are induced.
- Topical application of nitrogen mustard or BCNU is also highly effective and widely used in the USA.

- Solitary tumors can be irradiated (30 Gy fractionated into 2–3 Gy doses or electron beam).
- Biologicals such as cytokines (e.g., interleukin-12), traditional and new retinoids (bexarotene) and receptor-targeted cytotoxic fusion proteins (denileukin diftitox) are increasingly being used, but the exact role of these agents remains to be determined.
- Polychemotherapy should be considered in the case of unequivocal lymph node or internal organ involvement.

► **Prognosis:** 5-year survival is 88%, but a more detailed view is instructive (Table 28.**4**).

- Patients with limited patch-stage mycosis fungoides have same survival as age-matched controls. Patients can rapidly progress after years of stable mild disease. Outlook in tumor stage is dismal.

Table 28.4 · **Survival of patients with mycosis fungoides**

Stage	Median survival (years)
Ia	Normal
Ib/IIa	13
IIb/III	4
IV	1.5

Sézary Syndrome

► **Definition:** Leukemic form of cutaneous T-cell lymphoma with triad of erythroderma, generalized lymphadenopathy, and abnormal circulating T cells in peripheral blood ($<$ 1000 Sézary cells/mm^3 and/or expanded T-cell population with aberrant phenotypes).

► **Clinical features:** Erythroderma accompanied by intense pruritus, alopecia, palmoplantar hyperkeratosis, and alopecia.

► **Histology:** Most cases shows same changes as plaque stage mycosis fungoides. Infiltrate more monotonous and usually epidermotropic, but rarely only perivascular infiltrate with atypical cells. Lymph nodes show extensive replacement of normal architecture by atypical T cells.

- *Peripheral blood:* Standard for diagnosis is presence of $>$ 1000 Sézary cells/mm^3, FACS analysis with CD4+/CD8+ ratio $>$ 10:1, expanded T-cell population with loss of CD2, CD3, or CD5 and proof of clonality. Some Sézary cells can be found in peripheral blood in a patient with severe atopic dermatitis and other inflammatory diseases.

► **Differential diagnosis:** Other forms of erythroderma (p. 282).

► **Therapy:** Extracorporeal photophoresis, methotrexate (0.3 mg/kg weekly), PUVA, combination therapy with chlorambucil and prednisolone for more advanced disease.

► ***Note:*** Do not forget symptomatic therapy of erythroderma: topical corticosteroids, wet dressings, oral antihistamines.

► **Prognosis:** Dismal; median survival time 2–4 years.

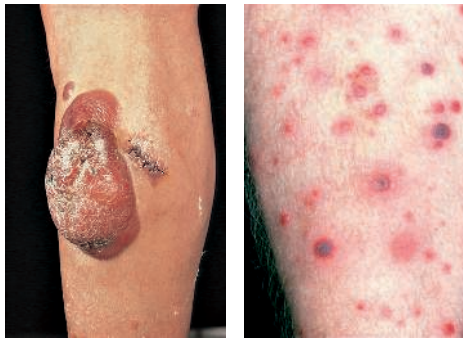
Primary Cutaneous CD30-positive Lymphoproliferative Disorders

Primary Cutaneous Anaplastic Large Cell Lymphoma (C-ALCL)

- **Definition:** Low-grade cutaneous lymphoma in which most of the large malignant cells express CD30.
- **Clinical features:** One or more red-brown nodules, which are often ulcerated (Fig. 28.**2a**). About 20% with dissemination. Individual lesions may regress. Visceral involvement uncommon.
- **Histology:** Diffuse, nonepidermotropic infiltrates; tumor cell morphology varies from anaplastic to pleomorphic or immunoblastic. >75% of cells are CD30+, usually CD4+, CD8–. Loss of typical T-cell markers (CD3, CD5) as well as expression of cytotoxic granules is common. Unlike systemic CD30+ lymphoma, most C-ALCL express cutaneous lymphoid antigen (CLA) but not epithelial membrane antigen (EMA) or anaplastic lymphoma kinase (ALK). Tumor cells usually clonal.
- **Diagnostic approach:** Clinical examination, histology, molecular biology. Once diagnosis is established, follow up every 3–4 months. Baseline and yearly staging (chest radiography, sonography of abdomen and lymph nodes) to exclude systemic involvement. Lymph node involvement alone is not poor prognostic sign.
- **Differential diagnosis:** Other lymphomas, skin metastases, leukemic infiltrates.
- **Therapy:** Excision or ionizing radiation for individual lesions; total dose 30 Gy. If more widespread, PUVA, interferon-α combination therapy. For advanced disease, polychemotherapy or denileukin diftitox.
- **Prognosis:** Good; 5-year survival 90%.

Lymphomatoid Papulosis

- **Definition:** Multifocal chronic, recurrent self-healing papulonecrotic or papulovesicular skin disease with histologic features suggesting a CD30+ lymphoma.
- **Clinical features:** Rapidly growing red-brown papules and nodules; sometimes papulonecrotic resembling pityriasis lichenoides et varioliformis acuta; picture varies from single large nodules to multiple lesions that may be pruritic; heal with atrophic scars (Fig. 28.**2b**).
- **Histology:** Three histologic types:
  - A: mixed inflammatory infiltrate with nests of CD30+ T cells.
  - B: resembles mycosis fungoides.
  - C: resembles large cell, anaplastic T-cell lymphoma.



a **b**

Fig. 28.**2** · **a** CD30+ cutaneous T-cell lymphoma. **b** Lymphomatoid papulosis.

- Molecular biology studies usually reveal a T-cell clone in the skin, sometimes also in peripheral blood.

► **Diagnostic approach:** Histologic picture most be combined with clinical history of regression. Multiple biopsies over time required to rule out associated lymphomas. If clinical history is clear, no staging required.
► **Differential diagnosis:** Other lymphomas, pityriasis lichenoides et varioliformis acuta.
► **Therapy:** PUVA; methotrexate 0.2–0.3 mg/kg weekly is amazingly effective, but often not appropriate for young patients.
► **Prognosis:** Excellent; 5-year survival about 95%.

Subcutaneous Panniculitis-like T-cell Lymphoma

► **Definition:** Cytotoxic T-cell lymphoma with presence of primarily subcutaneous infiltrates of pleomorphic cells of variable size, many macrophages and often the hemophagocytic syndrome.
► **Pathogenesis:** A more aggressive γδ and a more indolent αβ CD8+ subtype exist. The former is best classified under γδ lymphomas; only the latter αβ subtype is considered here.
► **Clinical features:** All ages are affected and both sexes are at equal risk. There are subcutaneous plaques and tumors, usually involving the legs (just as with inflammatory panniculitis) and sometimes with systemic signs and symptoms.
► **Histology:** Atypical pleomorphic T cells in the subcutaneous fat, often rimming individual lipocytes.
► **Therapy:** Systemic corticosteroids or doxorubicin-based chemotherapy.

Extranodal NK/T-cell Lymphoma, Nasal Type

► **Definition:** Lymphoma composed of small, medium or large cells with NK-cell phenotype, or more rarely of cytotoxic T cells.
► **Epidemiology:** Skin is second most common site after nose. Almost all cases are positive for Epstein–Barr virus.
► **Clinical features:** Involves nose, midface, upper airways (old *lethal midline granuloma)*; cutaneous lesions usually nodules or plaques, which can become bullous or necrotic. Peripheral lymphadenopathy often absent.
  - Systemic involvement includes gastrointestinal tract, hepatosplenomegaly, lungs (lymphomatoid granulomatosis), bone marrow infiltration with pancytopenia.
  - Sometimes associated with hemophagocytic syndrome (*histiocytic medullary reticulosis).* Often "B symptoms" such as fever, weight loss.

► **Histology:** Highly variable; atypical lymphocytes of varying sizes, often angiocentric; CD56+, CD2+, CD3–, CD3ε in cytoplasm; express granzyme, perforin and TIA. Clonal population; TCR in germline configuration.
► **Differential diagnosis:** Varies with site; other lymphomas, pother forms of panniculitis, vasculitis (Wegener granulomatosis).
► **Therapy:** Polychemotherapy; usually CHOP, BACOP, or research protocols.
► **Prognosis:** Poor, but varies with disease type.

Other Primary Cutaneous T-cell Lymphomas

► **Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma:** Proliferation of epidermotropic CD+ cytotoxic T cells with aggressive clinical behavior.
► **Cutaneous γδ+ T-cell lymphoma:** Proliferation of γδ+ t cells with development of ulcerated plaques and tumors, particular on extremities, with poor prognosis.
► **Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma:** Proliferation of small or medium-sized T cells without a history of mycosis fungoides. Mainly nodules or plaques with 5-year survival 60–80%.

28.4 Primary Cutaneous B-cell Lymphomas

Primary Cutaneous Follicle Center Cell Lymphoma

- **Definition:** Low-grade B-cell lymphoma of neoplastic follicle center cells, typically found on head and upper trunk.
- **Clinical features:** Picture variable; small nodules with erythema, red-brown plaques with little epidermal involvement, grouped papules (Fig. 28.**3**). On the trunk, tumors likely to be surrounded by erythema. Disseminated skin disease unusual.

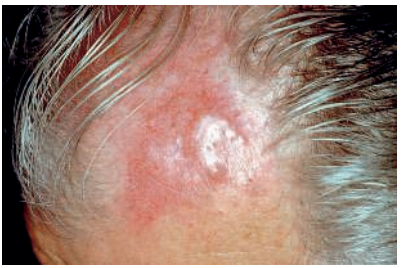


Fig. 28.**3** · Follicle center cell lymphoma.

- **Histology:** Both follicular pattern and diffuse infiltrates without epidermotropism. Variable mixture of small centrocytes and centroblasts, sometimes admixed with larger centrocytes; also reactive T cells. Immunophenotype CD20+, CD79a+; bcl-6+, bcl-2–. λ/κ ratio usually shifted, but light chains not always expressed. Skin infiltrate usually clonal, but no clonality seen in peripheral blood.
- **Diagnostic approach:** Clinical features, histology, molecular biology; baseline and yearly imaging (chest radiograph, sonography of abdomen and lymph nodes); bone marrow examination at time of diagnosis and with any change in peripheral blood picture or suggestion of systemic involvement.
- **Differential diagnosis:** Dermatofibrosarcoma protuberans, other lymphomas, leukemic infiltrates.
- **Therapy:** Ionizing radiation (30 Gy in 10 fractions); excision of solitary lesions; anti-CD20 monoclonal antibody therapy, interferon-α2.
- Excellent; 5-year survival 95%.

Primary Cutaneous Marginal Zone Lymphoma

- **Definition:** Primary cutaneous lymphoma derived from the lymphocytes of the marginal zone surrounding the follicle; formerly immunocytoma or primary cutaneous plasmacytoma.
- **Clinical features:** Male:female ratio 10:1; usually >50 years of age; no systemic signs and symptoms. Single or multiple cutaneous or subcutaneous red-brown papules and nodules; favor the trunk (70%); associated with worse prognosis are involvement of the head and neck (20%) or disseminated disease (10%).
- **Histology:** Dermal infiltrate with sparing of the papillary dermis (*grenz zone*). Nodular or diffuse pattern with small lymphocytes, plasmacytoid cells, and plasma cells, often extending into subcutaneous fat. Involvement of sweat gland or hair follicles in 90%. About 50% have reactive follicles. Tumor cells are CD20+, CD79a+, CD5–, CD10–, bcl-2–; λ/κ shift; monoclonality of heavy chain usually demonstrable; CD30+ cells at margin.

- **Diagnostic approach:** Clinical features, histology, molecular biology; baseline and yearly imaging (chest radiograph, sonography of abdomen and lymph nodes); bone marrow examination at time of diagnosis and with any change in peripheral blood picture or suggestion of systemic involvement.
- **Differential diagnosis:** Other lymphomas, metastases, leukemic infiltrates.
- **Therapy:** Excision if possible; otherwise ionizing radiation or electron beam (30 Gy total dose). Systemic therapy with anti-CD20 antibodies.
- **Prognosis:** Even with appropriate treatment, 30% relapse rate. 25% have extracutaneous involvement (parotid gland, subcutaneous fat, gastrointestinal tract, spleen, bone marrow, lymph nodes, orbit, thorax. Outlook excellent; 5-year survival 90%.

Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type

- **Definition:** Aggressive cutaneous B-cell lymphoma with a predominance or confluent sheets of centroblasts and immunoblasts, almost always located on legs.
- **Clinical features:** Most patients are older women. Rapidly growing red-brown nodules and plaques on legs; often ulcerated (Fig. 28.**4**). Prompt lymph node involvement on same side and then systemic spread.

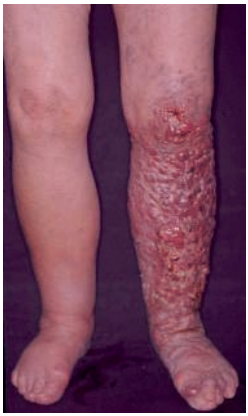


Fig. 28.**4** · Diffuse large B-cell lymphoma, leg type.

- **Histology:** Diffuse, nonepidermotropic infiltrate of large blasts with large nucleus and prominent central nucleolus; CD20+, CD79a+ and monotypic Ig expression. Bcl-2+, MUM–1+. No t(14;18) translocation as in noncutaneous large cell B-cell lymphoma. Tumor cells monoclonal.
- **Diagnostic approach:** Clinical examination, biopsy, extensive staging and close follow-up.
- **Differential diagnosis:** Other lymphomas, metastases, leukemic infiltrates. A comparison between primary cutaneous follicle center lymphoma and primary cutaneous diffuse large b-cell lymphoma, leg type is given in Table 28.**5**.
- **Therapy:** Polychemotherapy, usually anthracycline based; excision, ionizing radiation (30 Gy); radioactively labeled anti-CD20 antibodies (ibritumomab tiuxetan), or rituximab.
- **Prognosis:** Modest; 5-year survival 50%.

Table 28.5 · Characteristic features of primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous diffuse large B-cell lymphoma (PCLBCL), leg type

	PCFCL	PCLBCL, leg type
Morphology	Predominance of centrocytes that are often large especially in diffuse lesions Centroblasts may be present but not in confluent sheets Growth pattern may be follicular, follicular and diffuse, or diffuse (a continuum with distinct categories or grades)	Predominance of confluent sheets of medium-sized to large B cells with round nuclei, prominent nucleoli and course chromatin resembling centroblasts or immunoblasts Diffuse growth pattern
Phenotype	Bcl-2: ∓ Bcl-6: + CD10: ∓ Mum-1: –	Bcl-2: ++ Bcl-6: ± CD10: – Mum-1: +
Clinical features	Middle-aged adults Localized lesions on head or trunk (90%); multifocal lesions rare	Elderly, especially women Lesions localized to legs, usually below knees. Rare cases away from leg (10%).

CD4+, CD56+ Hematodermic Neoplasm (Blastic NK-cell Lymphoma).

- **Definition:** Blastic NK-cell lymphoma is a clinically aggressive neoplasm with a high incidence of cutaneous involvement and risk of leukemic dissemination.
- **Pathogenesis:** More recent studies suggest a plasmacytoid dendritic cell precursor; thus the names *CD4+, CD56+ hematodermic neoplasm*, and *early plasmacytoid dendritic cell leukemia/lymphoma* have been proposed.
- **Clinical features:** Blastic NK-cell lymphoma presents commonly in the skin with solitary or multiple nodules with or without extracutaneous disease. Moist patients, even if presenting with only cutaneous findings, rapidly develop involvement of bone marrow, lymph nodes, peripheral blood, and extranodal sites.
- **Histology:** Nonepidermotropic monotonous infiltrates of medium-sized cells with finely clumped chromatin. Immunophenotype is CD4+, CD56+, CD8-, CD7 ±, CD2∓, CD45RA+; the cells do not express surface and cytoplasmic CD3 or cytotoxic proteins. TCR is in germline configuration.
- **Therapy:** Systemic chemotherapy usually leads to complete remission but is soon followed by relapses that are not responsive. Median survival 14 months.

Hodgkin Lymphoma

- **Definition:** Hodgkin lymphoma (HL) is a common primarily nodal lymphoma with characteristic large tumor cells.
- **Pathogenesis:** Sometimes Epstein-Barr virus implicated.
- **Clinical Features:** HL rarely involves skin, and then usually secondary to either direct spread from involved lymph nodes or hematogenous spread. Primary cutaneous HL is extremely rare. Patients with HL often have pruritus and are predisposed to viral infections such as herpes zoster and warts.
- **Histology:** The distinctive tumor cell in HL is the Reed-Sternberg cell. Most often B-cell lineage although sometimes T-cell, then with overlaps with other CD30-

positive lymphoproliferative disorders. Inflammatory background and pattern variable.

- **Therapy:** Both radiation therapy and systemic chemotherapy are highly effective for nodal disease. Cutaneous lesions also respond well to ionizing radiation.

28.5 Leukemia and the Skin

Overview

In sharp contrast to lymphomas, no attempt is made to classify leukemias on the basis of cutaneous findings. Bone marrow examination and detailed cytological, immunohistochemical, and molecular biologic analysis is required. Leukemias are divided into myeloid and lymphocytic types, with many subtypes. Some diseases, such as the hematodermic neoplasm mentioned just above or chronic lymphocytic leukemia (CLL) can be classified as either lymphomas or leukemias, depending on the manner of presentation. The cutaneous lesions associated with leukemia can represent either specific infiltrates with leukemic cells in the skin or nonspecific changes secondary to anemia, immunosuppression, and chemotherapy.

Leukemia Cutis

- **Clinical features:** Leukemic infiltrates are typically red-brown nodules, sometimes with a blue hue, similar to other metastases but often with a more florid course. They may occasionally precede other signs and symptoms but more often herald failed therapy or a relapse. There are many distinctive clinical patterns to leukemic infiltrates, including:
  - Gingival infiltrates.
  - Bullous, ulcerated, and hemorrhagic lesions.
  - Leonine facies with symmetrical facial infiltrates, often in CLL.
  - Involvement of scars.
- **Granulocytic sarcoma:** Specific infiltrate of acute myeloid leukemia, which often precedes any other findings. Typically a facial, especially periorbital, mass in young adult. The biopsy surface, when cut in the pathology laboratory, develops a green color because of the presence of myeloperoxidase, so these tumors were initially designated as *chloroma*.

Nonspecific Findings

- **Clinical features:** Almost all patients with leukemia have cutaneous findings at some point. Typical changes include:
  - Purpura, hemorrhage, and ecchymoses because of impaired bone marrow function from disease and chemotherapy.
  - Wide variety of infections.
  - Atypical Sweet syndrome (p. 249) and pyoderma gangrenosum (p. 251).
  - Severe arthropod assault reactions.
  - Urticarial exanthems.
  - Broad spectrum of chemotherapy reactions because patients typically receive high-dose regimens. Examples include:
    - Mucositis.
    - Hair loss.
    - Acral erythema.
    - Lymphocyte recovery rash (occurs as lymphocytes begin to repopulate body after aggressive treatment).

► **Histology:** A standard problem is to determine if a maculopapular or urticarial rash represents a specific or nonspecific finding. Modern techniques have made it easier to identify leukemic cells in the skin, but the question remains: If a patient has >90% circulating leukemia cells and develops a drug reaction, the infiltrating cells in the skin will contain leukemic cells, but is the infiltrate is reactive or specific?

Signs of Selected Leukemias

The list is in Table 28.**6** is not exhaustive, but indicates how some of the common leukemias may involve the skin.

Table 28.6 · **Cutaneous signs of selected leukemias**

Leukemia	Skin findings
Acute leukemias	
Acute myeloid leukemia	Leukemia cutis in 10% Oral infiltrates in >50% Granulocytic sarcoma in young adults
Acute juvenile myelomonocytic leukemia	Association with neurofibromatosis; perhaps increased if juvenile xanthogranulomas are also present
Acute myelomonocytic leukemia	More likely to have fewer large nodules
Adult T-cell leukemia/lymphoma	Papules and nodules in >50% Patches as in mycosis fungoides rare Infective dermatitis (severe recalcitrant disease with lymphadenopathy in Jamaican children)
Acute lymphocytic leukemia	Leukemia cutis very uncommon
Chronic leukemias	
Chronic myeloid leukemia	Infiltrates uncommon; atypical Sweet and pyoderma gangrenosum may herald blast crisis
Chronic lymphocytic leukemia	Infiltrates common; often leonine facies Exaggerated reaction to arthropod assault (often bullous, on shins, may mimic bullous pemphigoid)
Hairy cell leukemia	Atypical Sweet, pyoderma gangrenosum and vasculitis may be seen; infiltrates rare
Polycythemia vera	Pruritus after warm bath Erythromelalgia (pain in fingers with vasodilation) Hyperviscosity syndrome with vessel occlusion and infarcts

29 Paraneoplastic Disorders

Overview

There ae a number of dermatologic conditions that should suggest the presence of an underlying malignancy. Some point to cancer-associated genodermatoses, others to acquired diseases associated with an increased incidence of malignancy (dermatomyositis or paraneoplastic pemphigus). Finally, there are conditions presumably caused by biologically active products manufactured by tumors. Schnyder established criteria for such conditions. They include:

- No other explanation for the skin finding.
- Skin changes improve with cancer treatment and may reappear if cancer recurs.
- Skin changes appear at about the same time as the systemic cancer; they may precede any clinical manifestations of the underlying malignancy.
- Statistical connection is shown.

Four of the most dramatic conditions are discussed below.

Acanthosis Nigricans

- **Definition:** Velvety hyperpigmentation of axilla, groin, and nape.
- **Pathogenesis:** Tumor-related acanthosis nigricans results from the secretion of insulin-like growth factor (IGF) or closely related proteins by the tumor; other forms involve abnormalities of IGF or insulin receptor.
- **Classification:**
  - *Malignant acanthosis nigricans:*
    - Usually involves adults > 40 years of age.
    - Sudden onset.
    - May also involve palms and soles (*tripe palms*) or mouth.
    - Most common tumor is carcinoma of the stomach (65%) or other gastrointestinal tumors.
    - Acanthosis nigricans typically improves with tumor therapy.
    - Possibly related findings:
    - *Leser–Trelat sign*: Eruptive skin tags and tiny seborrheic keratoses; similar mechanism, often occurs in same patient.
    - *Florid cutaneous papillomatosis:* Same changes but widespread rather than flexural.
- *Endocrine acanthosis nigricans:* Patients with insulin-resistant diabetes, because of acquired loss of function of insulin receptor, associated with collagen–vascular disorders and hyperandrogenism.
- *Syndromes with acanthosis nigricans:* Usually reflect abnormalities in insulin receptor or insulin-like growth factor secretion; often with associated lipodystrophy (p. 538).
- *Pseudo acanthosis nigricans*: Mild hyperpigmentation in obese individuals; more common in dark-skinned individuals and in the tropics.
- *Drug-induced acanthosis nigricans:* Most common trigger is nicotinic acid when used to treat hyperlipidemia.
- **Histology:** Not acanthotic and not hyperpigmented; microscopically looks like many small seborrheic keratoses.
- **Diagnostic approach:** Clinical examination, biopsy, always exclude diabetes mellitus. In adults without any obvious explanation, extensive tumor search is justified including imaging of gastrointestinal tract, CEA, α-fetoprotein;

- **Therapy:** Treat underlying problem, lose weight; topical retinoids may bring modest improvement in syndromic or endocrine acanthosis nigricans, but are irritating.

Erythema Gyratum Repens

- **Definition:** Characteristic migratory erythema with distinctive pattern.
- **Clinical features:** Rapidly changing "wood grain" pattern usually on trunk; extremely uncommon (Fig. 29.**1**). Not associated with any distinctive tumor.
- **Diagnostic approach:** Extensive tumor search always warranted.
- **Differential diagnosis:** Other figurate erythemas (p. 285).
- **Therapy:** No therapy possible.

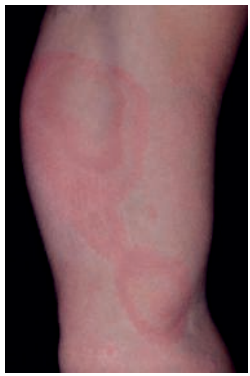


Fig. 29.**1** · Erythema gyratum repens.

Hypertrichosis Lanuginosa acquisita

- **Definition:** Generalized growth of lanugo hairs in an adult; obligate neoplastic marker.
- **Clinical features:** Extremely rare condition, more common in women. Relatively sudden onset of growth of thin silvery hairs. Often starts on face. The underlying tumor can precede, accompany, or follow the growth of hairs. Most common associated tumors are colon and rectal carcinomas (25%), bronchial carcinoma (25%), cervical carcinoma (10%).
- **Differential diagnosis:** Almost none; other causes of acquired diffuse hypertrichosis are discussed on p. 513.
- **Therapy:** Hairs can be removed with depilatories or shaving.

Necrolytic Migratory Erythema

- **Synonyms:** Glucagonoma syndrome, erythema necroticans migrans.
- **Definition:** Circinate and periorificial erythema and scaling associated with islet cell tumor of the pancreas producing glucagon.
- **Clinical features:** On trunk and extremities, 1–4 cm erythematous patches often with central blister or necrosis; in the flexures and about the mouth, erosions and crusts.

- **Histology:** High epidermal necrosis (reversal of staining) with neutrophilic infiltrate.
- **Diagnostic approach:** Clinical examination, biopsy; for screening, blood sugar; then glucagon level and imaging studies.
- **Differential diagnosis:** Acrodermatitis enteropathica (zinc levels may be reduced in both conditions); candidiasis.
- **Therapy:** Ideally surgery; unfortunately many tumors are discovered too late for curative surgery; palliative chemotherapy with variety of substances possible.

Other Cutaneous Markers of Malignancy

Many conditions that can on occasion indicate an underlying malignancy are listed in Table 29.1. They are less reliable markers than discussed above, but should never be overlooked. See also the cancer-associated genodermatoses (p. 367), as they are not repeated here.

Table 29.1 · Cutaneous markers of malignancy

Marker	Skin findings	Underlying malignancy	Strength of association[a]
Acanthosis nigricans	See above		
Bazex acrokeratosis	Psoriasiform lesions on fingers, toes, nose, ears	Carcinoma, usually upper airway	>95%
Dermatomyositis	Gottron papules, heliotrope eyelids, photosensitivity	Carcinoma, often ovarian	~15% in adults
Digital ischemia	Raynaud phenomenon, gangrene, other signs of cryoglobulinemia	Hematologic malignancies	Rare
Erythema annulare centrifugum	Slowly expanding annular erythematous plaques	Carcinomas, lymphomas	Rare
Erythema gyratum repens	See above		
Erythroderma	Diffuse erythema and widespread desquamation	Lymphomas (especially mycosis fungoides, Sézary syndrome); carcinomas	~25%
Florid cutaneous papillomatosis	Diffuse acanthosis nigricans-like changes	Carcinomas	>95%
Follicular mucinosis	Boggy plaques, usually on scalp	Mycosis fungoides (perhaps early lesion)	>75%
Flushing	Sudden diffuse erythema	Carcinoid tumors, other secretory carcinomas	Common
Hyperpigmentation	Diffuse or localized darkening	Metastatic melanoma with melanin in serum; rarely other tumors	Rare

Continued Table 29.1 ▶

Table 29.1 · Continued

Marker	Skin findings	Underlying malignancy	Strength of association[a]
Hypertrichosis lanuginosa acquisita	See above		
Leser–Trelat sign	Eruptive skin tags and small seborrheic keratoses	Carcinomas	>95%
Necrobiotic xanthogranuloma	Red-yellow nodules, almost always periorbital	Gammopathy	>95%
Necrolytic migratory erythema	See above		
Pachydermoperiostosis	Thickened digits, periostosis	Carcinoma of lung	Common
Panniculitis	Painful subcutaneous nodules, fat necrosis	Carcinoma of pancreas	Uncommon
Palmoplantar keratoderma	1) Acquired thickening and scaling of palms and soles	Carcinomas	Rare
	2) Congenital keratoderma and leukokeratosis (Howel–Evans syndrome)	Carcinoma of esophagus	>95%
Paraneoplastic pemphigus	Oral erosions, cutaneous lesions that overlap between lichen planus and erythema multiforme	Lymphoma, Castleman tumor, thymoma	>95%
Pruritus	Intense itching without explanation	Hodgkin lymphoma, many others	Rare
Pyoderma gangrenosum	Aggressive undermined ulcers without clear cause	Gammopathy (usually IgA)	<25%
Sweet syndrome	Succulent red nodules and neutrophilia	Leukemia, especially hairy cell type	Unclear ~50%
Thrombophlebitis	Recurrent superficial thrombophlebitis (Trousseau sign)	Carcinoma of pancreas	>25%
Tripe palms	Acute pebbly palms and soles; analogous to acanthosis nigricans	Carcinomas	>95%
Xanthomas, diffuse plane	Large sheets of xanthomatous infiltration	Gammopathy	>95%
Zoster	Severe or generalized zoster in young adult	Lymphoma, leukemia (HIV infection)	Uncommon

a This column refers only to the strength of the association, not to the frequency of the finding. Based on Table 65.**3** in Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC. *Dermatology* (Springer, Berlin, 2000).

30 Diseases of the Lips and Oral Mucosa

30.1 Inflammation and Leukoplakia

Cheilitis

- **Definition:** Inflammation of the lips.
- **Clinical features:** Lip inflammation is similar to dermatitis elsewhere; features include erythema, scaling, and fissuring. The inflammation frequently involves the neighboring skin and is often impetiginized.
- **Classification:** There are many different causes of cheilitis; all appear quite similar.
  - *Irritant cheilitis:* Very common; result of repeated lip licking, biting or sucking; also caused by exposure to UV light, wind, and cold.
  - *Allergic contact cheilitis:* Most common causes are allergens in lipsticks (colophony).
  - *Atopic cheilitis:* Often worsened by lip licking and biting; characterized by frequent deep median fissures in lower lip.
- **Diagnostic approach:** Exclude atopy and allergic contact cheilitis; use special patch testing tray for typical lip allergens—lipsticks, topical medications (herpes ointments), fingernail polish, toothpastes, mouthwashes.
- **Differential diagnosis:** Lupus erythematosus, lichen planus, actinic cheilitis.
- **Therapy:** Avoid triggering factors and allergens; apply white petrolatum for protection; if severely inflamed, use corticosteroid ointment.

Angular Cheilitis

- **Synonym:** Perlèche.
- **Definition:** Inflammation at corners of mouth.
- **Pathogenesis:** In infants, usually from drooling; in children and young adults, infectious (*Candida albicans* or bacteria); other adults, poorly fitting dentures with drooling; all age groups, trauma during dental care; rarely vitamin or nutrient deficiency.
- **Clinical features:** Erythema, fissures, and maceration at corners of mouth.
- **Diagnostic approach:** Exclude candidiasis and bacterial infections; have dentures checked. Serum iron level and ferritin if other signs of bleeding or malnutrition.
- **Therapy:** Treat with protective (zinc oxide) or anticandidal paste.

Granulomatous Cheilitis

- **Definition:** Swelling of lip with granulomatous inflammation.
- **Pathogenesis:** Can be idiopathic or part of Melkersson–Rosenthal syndrome.
- **Clinical features:** Initially episodic swelling of lips; later more permanent. Rarely, swelling of other areas such as tongue, cheeks, eyelids, or forehead.
  - *Melkersson–Rosenthal syndrome*: Associated diagnostic features include Bell palsy (facial never paralysis) and furrowed tongue. Occasional lymph node involvement with granulomas (p. 291).

- **Histology:** Lymphocytic infiltrate, often rich in plasma cells; small granulomas can usually be detected.
- **Diagnostic approach:** Clinical triad, biopsy.
- **Differential diagnosis:** Sarcoidosis, recurrent erysipelas, herpes simplex, angioedema.
- **Therapy:** Intralesional corticosteroids (triamcinolone 2.5 mg/mL diluted in lidocaine); if unsuccessful, short burst of systemic corticosteroids or clofazimine 100 mg daily for 3–6 months (urine turns red-orange). Once less active, reduction surgery on lip may be required.

30.2 Leukoplakia

- **Definition:** White patch on mucous surface, which will not rub off. (Definition designed to exclude candidiasis, which usually can be rubbed off.) The white color is caused by moist hyperkeratosis.
- **Classification:** There are many different types of leukoplakia:
  - *Inherited:* White sponge nevus is best example.
  - *Acquired:*
    - Infections (Epstein–Barr virus and oral hairy leukoplakia in HIV/AIDS, oral warts).
    - Exogenous agents (tobacco, trauma).
    - Other disorders (lichen planus).

  Note: Confusion can arise from thr use of the term leukoplakia as synonymous with squamous cell carcinoma in situ of the mucosa. This is a more restricted meaning. Selected examples of the different types of leukoplakia are discussed below.
- **Clinical features:** In most instances, the nature of leukoplakia can be established clinically. For example, white linear streaks on the buccal mucosa at the level of the bite line are almost always frictional and reactive. Lesions along the lower labial mucosa where chewing tobacco is held are very often in-situ carcinomas. Verrucous lesions, speckled leukoplakia (mixture of red and white areas), or ulcerated areas are also likely to represent malignant change.

  Caution: In all instances, when the diagnosis of leukoplakia is made, the possibility of a intraepithelial carcinoma should be considered and excluded with a biopsy if clinically needed.
- **Histology:** Microscopic picture can vary from reactive hyperplasia through carcinoma in situ to frankly invasive squamous cell carcinoma. Even when an underlying disorder such as lichen planus is identified, the risk of a secondary squamous cell carcinoma is not completely excluded.
- **Therapy:** Treatment depends on underlying diagnosis.

White Sponge Nevus

- **Definition:** Localized area of marked hyperkeratosis; present since birth and stable.
- **Pathogenesis:** Mutations in keratin type 4 or 13; the major forms expressed in the mucosal basal layer; autosomal dominant inheritance.
- **Clinical features:** Thickened, wave-like or folded plaques on the oral and nasal mucosa; sharply bordered and permanent. Less often vaginal or anal involvement. Rarely symptomatic.
- **Therapy:** No effective therapy available.

Human Papillomavirus (HPV) Infections

- **Pathogenesis:** Selected HPV types can thrive on mucosal surfaces; examples include HPV 2 and 4 (warts), HPV 6 and 11 (condylomata acuminata), and HPV 13 and 32 (Heck disease).
- **Clinical features:** The clinical distinctions are usually more a matter of degree. Warts may appear more papillomatous or elongated than condylomata. Heck disease usually occurs in Eskimos or Native Americans; patients have 100s of small oral papillomas.
- **Therapy:** Many of the usual wart treatments are difficult to use. Local destruction (electrosurgery, laser) and meticulous hemostasis is the usual approach.

Carcinoma in Situ of the Lip

One must distinguish between carcinoma in situ of the lip, usually caused by sun exposure and a dermatologic problem, and carcinoma in situ of the oral mucosa, usually caused by tobacco exposure and a management responsibility of oral surgeons and otorhinolaryngologists, but often a diagnostic challenge for dermatologists.

- **Synonym:** Actinic cheilitis.
- **Pathogenesis:** Completely analogous with actinic keratosis; UV-induced carcinogenesis. Nicotine use and immunosuppression may be co-factors. Only difference is that risk of invasive squamous cell carcinoma is greater on lip than skin.
- **Clinical features:** Almost exclusively involves lower lip; early lesions may simply feel rough to patient or be slightly white; later lesions can be thickened, erythematous or ulcerated.
- **Histology:** Atypical keratinocytes in epithelium, but no evidence of invasion into lamina propria.
- **Therapy:** Early lesions can be treated with cryotherapy or laser ablation; any thickened or ulcerated lesions should be biopsied first. More advanced disease usually treated by vermilionectomy (excision of epithelium of lip) with coverage either with a mucosal advancement flap or by secondary intention.

Carcinoma of the Lip

- **Definition:** Invasive squamous cell carcinoma of the lip with potential for metastasis.
- **Classification:** Shown in Table 30.**1**.

Table 30.1 · **Classification of carcinoma of the lip**

Stage	Tumor thickness
T1	< 5 mm
T2	5–10 mm
T3	10–20 mm
T4a	> 20 mm thickness, < 20 mm diameter
T4b	> 20 mm thickness, > 20 mm diameter

- **Clinical features:** On lower lip and usually with history of previous treatment of actinic cheilitis. Verrucous, eroded, ulcerated papule or nodule.
- **Diagnostic approach:** History, clinical examination; sonographic evaluation of regional lymph nodes; chest radiograph.

- **Differential diagnosis:** Other causes of leukoplakia; other lip tumors, such as keratoacanthoma and basal cell carcinoma.
- **Therapy:**
  - Excision with careful control of margins; ideally micrographic surgery.
  - Radiation therapy if inoperable or impossible to completely excise.
  - If lymph nodes are involved, neck dissection.
  - Consideration of chemotherapy depending on status of excision and lymph nodes; mandatory for systemic involvement.
- **Follow-up:** Every 3 months, with sonography every 6 months and yearly chest radiograph.
- **Prognosis:** Highly variable; 5-year survival for T1 is 80%; T4, 20%.

30.3 Lesions of Tongue

Furrowed Tongue

- **Synonyms:** Plicated tongue, scrotal tongue
- **Pathogenesis:** Unknown; in rare cases associated with Melkersson–Rosenthal syndrome.
- **Clinical features:** Thickened tongue with deep furrows and splits that look as if they should hurt but are asymptomatic. Appearance often very distressful to patient, as is the name "scrotal tongue," which should be avoided.
- **Therapy:** Nothing satisfactory.

Geographic Tongue

- **Synonyms:** Migratory glossitis, exfoliatio linguae areata.
- **Definition:** Migratory areas of loss of relief of tongue.
- **Clinical features:** Name comes from resemblance to a map with red smooth areas with white borders; totally asymptomatic but sometimes scares patient; patient changes over hours to days (Fig. 30.**1**). Usually idiopathic, but occasionally associated with severe psoriasis.

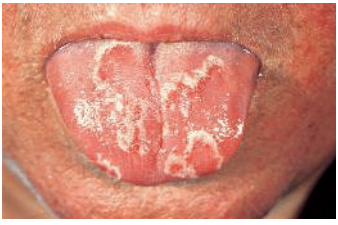


Fig. 30.**1** · Geographic tongue.

- **Histology:** Atrophic epithelium with exocytosis of neutrophils.
- **Differential diagnosis:** Candidiasis, other forms of glossitis (as found in deficiency states, for example).
- **Therapy:** None available.

Black Hairy Tongue

- **Synonym:** Lingua villosa nigra.
- **Definition:** Discoloration of dorsal surface of tongue with elongated papillae.
- **Pathogenesis:** Unknown; smoking and poor oral hygiene may play role, but many patients have no risk factors. May be secondary to pertubation of normal flora during antibiotic therapy. May be more common in HIV/AIDS, but not to be confused with oral hairy leukoplakia.
- **Clinical features:** Dorsal surface of tongue is discolored; long threads are elongated papillae; may bother patient (Fig. 30.**2**).
- **Diagnostic approach:** Clinical examination.
- **Therapy:** Exclude predisposing factors; clean tongue regularly with soft toothbrush. If not helpful, paint with 20% urea solution before brushing, to soften.

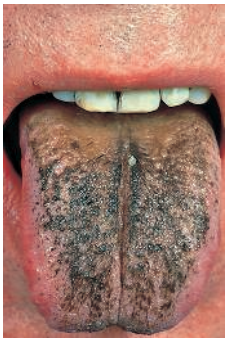


Fig. 30.**2** · Black hairy tongue.

Oral Hairy Leukoplakia

- Almost 100% specific for HIV/AIDS. Result of mixed infection with Epstein–Barr virus most important, but both HPV and *Candida albicans* associated. Fine filaments or "hairs" at lateral edge of tongue. Harmless, but difficult to treat (p. 161).

Glossodynia

- **Definition:** Sensation of burning or discomfort of tongue in the absence of physical findings.
- **Epidemiology:** Most patients are middle-aged women; often they display obsessive-compulsive personality traits.
- **Clinical features:** By definition, the examination is normal. Search for signs of candidiasis, aphthae, blistering diseases.
- **Diagnostic approach:** Culture of mouth and stool for *Candida albicans* frequently recommended; one must be careful since *Candida albicans* can be transiently present in the mouth and stool of almost everyone. Similarly, vitamin and mineral deficiencies may rarely be responsible, but repeated testing often convinces patients that they require special diets and supplements.
- **Therapy:** Short trials of anticandidal agents or vitamin supplements may be indicated in some patients. Antidepressant therapy is also occasionally helpful, but usually resisted by patients.

30.4 Epulis

- **Definition:** General name for any gingival tumor.
- **Clinical features:** There are many different types:
  - *Congenital epulis:* Benign soft tumor, present at birth; usually on maxilla; histologically resembles a granular cell tumor (p. 462).
  - *Epulis fissurata:* Also known as fibrous inflammatory hyperplasia; reactive process at edge of ill-fitting denture.
  - *Epulis granulomatosa:* Pyogenic granuloma (p. 456) of gingiva; more common in pregnancy or following trauma.
  - *Giant cell epulis:* Posttraumatic reaction; tumor rich in giant cells and fibrous stroma; also known as peripheral giant cell reparative granuloma.
- **Diagnostic approach:** If the clinical diagnosis is not apparent, biopsy is needed.
- **Therapy:** Eliminate predisposing factors; surgical removal.

30.5 Aphthous Stomatitis

- **Definition:** Common disorder with small usually painful recurrent oral ulcers with characteristic clinical appearance.
- **Synonyms:** Aphthae (singular aphtha), canker sore, recurrent aphthous stomatitis (RAS).
- **Pathogenesis:** Cause unknown; stress appears trigger, as does trauma, but variety of autoimmune and vasculitic processes also suggested, with TNFα appearing to be common mediator. Less common in smokers; more common in HIV/AIDS.
  Clinical Features:
  - Small round or oval ulcers covered with gray exudate and surrounded by erythematous halo. Usually heal over 7–10 days without scarring.
  - Several clinical variants:
    - Minor type: One or more aphthae, common recurrences.
    - Herpetiform type: Same as minor, but lesions arranged in herpetiform fashion but no evidence for herpes simplex virus infection.
    - Major type: Larger more severe ulcers which usually cause scarring. Also known as Sutton aphthae or periadenitis mucosa necrotica recurrens.
  - Bipolar aphthae: Combination of oral and genital aphthae with no sign of other systemic disease.
  - Multiple aphthae also one of diagnostic criteria for Behçet syndrome (p. 256) and associated with cyclic neutropenia where aphthae and drop in WBC occur every few weeks.
- **Diagnostic Approach:** Strictly clinical diagnosis; biopsy does not help.
- **Differential Diagnosis:** Always exclude Behçet syndrome or bipolar aphthae if multiple lesions are presence or recurrences frequent. Recurrent herpes simplex infections only rarely intraoral and aphthae do not involve lips, but confusion persists.
- **Therapy:** No good therapy; try topical anesthetics, corticosteroids or pledgets soaked in tetracycline solution. Rarely systemic corticosteroids necessary; thalidomide highly effective, blocking TNFα but not often used.

31 Diseases of the Hairs and Scalp

A classification of hair disorders is shown in Table 31.1.

Table 31.1 · Classification of hair disorders

Hypertrichosis	
Localized	*Diffuse*
Faun tail nevus	Hirsutism
Becker nevus	Hypertrichosis lanuginosa acquisita
Hair nevus	Congenital hypertrichosis
Drug-induced hypertrichosis[a]	Drug-induced hypertrichosis
Hypertrichosis associated with metabolic and endocrine disorders[a]	Hypertrichosis associated with metabolic and endocrine disorders
Posttraumatic/postinflammatory hypertrichosis	
Trichomegaly (excessive eye lashes)	
Alopecia	
Localized	*Diffuse*
Nonscarring	
Alopecia areata	Diffuse alopecia areata, alopecia totalis, alopecia universalis
Trichotillomania	Androgenetic alopecia[b]
	Androgen-induced alopecia[b]
Traction alopecia	Hormonal imbalance
Infections (tinea capitis, folliculitis)	Anagen effluvium: toxins (chemotherapy, poisons)
	Telogen effluvium: major illnesses, polytrauma, high fevers, post-partum effluvium, drug-induced, "stress"-induced effluvium
	Loose anagen hair
Scarring	
Lichen planus	Pseudopelade of Brocq
Frontal fibrosing alopecia (Kossard)	Keratosis follicularis spinulosa decalvans
Chronic cutaneous lupus erythematosus	
More severe or advanced infections (deep tinea capitis, massive folliculitis, zoster)	
Physical, chemical or mechanical alopecia	
Aplasia cutis congenita	
Epidermolysis bullosa—junctional, dystrophic or acquired	

Continued Table 31.1 ▶

Table 31.1 · Continued

Alopecia (Continued)	
Localized	*Diffuse*
Hair shaft abnormalities	
Isolated	*Associated with syndrome*
Monilethrix	Netherton syndrome
Trichorrhexis nodosa	Menkes syndrome
Pili torti	Trichothiodystrophy
	Ectodermal dysplasia syndromes

a Can be either localized (then usually symmetrical) or diffuse.
b Diffuse, but follows a genetically determined pattern (hair loss only in androgen-sensitive scalp hair follicles; hair retained in androgen-insensitive occipital hair follicles).

31.1 Alopecia: Overview

Definitions

- **Atrichosis or atrichia:** Congenital complete absence of hairs.
- **Hypotrichosis:** Congenital reduction in number of hairs.
- **Effluvium:** Sudden loss of hair.
- **Anagen effluvium:** Loss of hairs during their growth phase.
- **Telogen effluvium:** Loss of resting hairs.
- **Alopecia:** Acquired loss of hair; may be partial or complete; scarring or nonscarring.

Diagnostic Approach

- Diagnostic methods are summarized in detail on p. 34.
- Far and away the most common alopecia is androgenetic alopecia. The only other fairly common problems are alopecia areata and telogen effluvium. All other alopecias (scarring alopecia, infections, hair shaft anomalies) are uncommon.
- ***Note:*** Every slowly progressive diffuse hair loss in women, as well as every telogen effluvium or slow regression of temporal hair line in men, as long as there is no suggestion of scarring, should be considered as androgenetic alopecia until proven otherwise and so treated. This diagnosis is correct for the vast majority of both men and women who complain of losing hair.

Differential Diagnosis

If you are having trouble, always consider these possibilities:
- Trichotillomania—easy to overlook.
- Diffuse alopecia areata is not so rare; often the patients can remember a solitary lesion, perhaps years in the past.
- Many patients have both androgenetic alopecia and telogen effluvium (caused by abnormal thyroid function, dietary defects, iron deficiency, zinc deficiency, medications).

- Both severe androgenetic alopecia and psoriatic alopecia can rarely show scarring on biopsy.
- Always think of unexpected toxin exposure—accidental, suicidal, or homicidal.

Practical Tips for Patient

Note: Always take the patient's concerns seriously. Loss of hair is a great problem to many people. They may worry not only about their appearance, but about the possibility of an underlying malignancy or serious disease, as well as poisoning or other environmental hazards.

Always ask about and discuss the following topics:

- **Hair washing:** Daily hair washing, using a mild shampoo, is fine. Discrete dandruff and pruritus is often a clue that washing could be more frequent. Lack of care may also increase the telogen rate. It is always appropriate to use conditioners and rinses.
- **Cosmetics:**
  - Cutting, coloring, and gentle permanent waves without tight curlers scarcely influence hair growth. Hair sprays are also harmless.
  - Aggressive permanent waving or frequent blow-drying damages the hair shafts, but does not influence hair growth. When hair dyes (usually paraphenylenediamine) or other products cause allergic contact dermatitis, the telogen rate is increased and hair growth is affected.
  - Hairstyles where tension is applied to hairs (corn rows, long pigtails, tightly wound styles) can drive anagen hairs into telogen. If employed for long periods of time they cause traction alopecia, which in rare cases can scar and then became permanent.
- **Diet:**
  - Almost every patient is convinced that diet plays a great role in hair growth; this issue must be addressd in every case.
  - Patients with eating disturbances or on crash diets almost always have telogen effluvium. When a careful history is obtained in young women with diffuse hair loss, dietary factors play a role in at least 25%. Gelatin capsules are popular, but there is no evidence that they offer an advantage over a well-balanced, protein-rich diet.
  - At least 20% of young women have an iron deficiency because of blood loss during menses. Low iron levels increase the sensitivity of the follicle to androgens; daily iron replacement is safe and often helps.
  - Even in the absence of iron deficiency and associated anemia, low ferritin levels raise an anagen follicle's sensitivity to various hair growth-inhibitory agents (e.g., androgens, thyroid abnormalities, drugs). Therefore, measuring ferritin, and raising it to a level well above the lower normal range by oral iron substitution therapy, is always advisable.
  - Biotin and zinc deficiencies are rarer than is often assumed. Zinc deficiency rarely causes isolated hair problems. Biotin also appears to play a minor role. However, supplementation with either material, even in the absence of a manifest deficiency, can be helpful. Any zinc deficiency should be corrected, because zinc is a co-factor of numerous important enzyme systems.

31.2 Congenital Alopecia and Hypotrichosis

Total Congenital Alopecia

- **Isolated:** At birth, normal hairs, but later complete loss of all hairs with atrophy of sebaceous glands; autosomal recessive inheritance.
- **Associated defects:** Seen with several ectodermal dysplasia syndromes; most common is hidrotic ectodermal dysplasia (complete alopecia, palmoplantar keratoderma, thickened nails); also seen in progeria.
- **Papular atrichia with cysts:** At birth, normal hairs. During puberty, onset of hair loss in face and scalp, later complete alopecia with many tiny papules that are epidermoid cysts. Defect in *hairless* gene at 8p21.2.

Localized Congenital Alopecia

- **"Negative" nevus:** Area lacking hair follicles from birth.
  - ***Note:*** Nevus sebaceus (p. 411) frequently presents at birth as a bald patch on the anterior scalp line. On biopsy, follicles are always seen, and during puberty, the lesion thickens and becomes more clinically apparent.
- **Aplasia cutis congenita** (p. 350): Usually isolated finding but can be associated with number of syndromes; typically area on vertex where skin fails to fuse, leaving atrophic scar.
- **Scarring alopecia** can be seen with a variety of other syndromes, including incontinentia pigmenti.
- **Temporal triangular alopecia:** Congenital loss of hair in triangular pattern, usually unilateral, nonscarring. Similar lesions may be seen over suture lines or as part of cowlick.

Congenital Hypotrichosis

- **Hypotrichosis congenita:**
  - *Autosomal dominant form* (hypotrichosis simplex of the scalp): normal scalp hair at birth and in early childhood, but noticeable hair loss by start of school.
  - *Autosomal recessive form:* Normal hair at birth, but soon thereafter loss of scalp hairs as well as eyebrows and eyelashes.
- **Hypotrichosis can be seen with many syndromes, including:**
  - Hidrotic ectodermal dysplasia (p. 351).
  - Anhidrotic ectodermal dysplasia (p. 351).
  - Syndromes with hair shaft anomalies (p. 510).
  - Rothmund–Thomson syndrome (p. 306).
  - Disorders of amino acid metabolism (p. 315).

31.3 Diffuse Nonscarring Alopecia

Telogen Effluvium

- **Definition:** Sudden loss of hairs because of altered hair growth cycle, with premature shift of hairs into catagen and then telogen phase.
- **Pathogenesis:** We do not view telogen effluvium as a disease, but as a symptom, almost always reflecting a trigger event.
  - *Androgenetic alopecia:* Most common cause is flare of androgenetic alopecia, in both men and women.

Note: Telogen effluvium may also be the only sign of a developing androgenetic alopecia where the terminal-to-vellus hair conversion has not yet occurred.

- *Thyroid dysfunction*: Always check thyroid function tests; sometimes normal values in patients on thyroid replacement can still be associated with unexplained hair loss, requiring more detailed endocrinologic studies.
- *Sudden drop in estrogen levels:* Delivery, miscarriage, or discontinuing oral contraceptives.
- *Inadequate diet:* Always ask about eating disturbances, crash diets, or other peculiarities.
- *Iron deficiency:* May be first sign of modest iron deficiency with only abnormal ferritin levels and no laboratory signs of anemia.
- *Scalp diseases:* Seborrheic dermatitis; less often psoriasis, tinea capitis or allergic contact dermatitis.

Note: Any inflammatory scalp disease increases the shift into telogen phase and thus the rate of hair loss; thus prompt and aggressive treatment required.

- *Medications:* Most common are β-blockers, cimetidine, antithyroid drugs, ACE inhibitors, lipid lowering agents, amphetamines, retinoids, NSAIDs.
- Other possible causes include:
  - Severe acute illnesses, infections, high fever, general anesthesia.
  - Hyperprolactinemia (especially if associated with late-onset acne).
  - Malabsorption and inflammatory bowel disease.
  - Endocrine disorders (Addison disease, Hashimoto thyroiditis).
  - Chronic diseases (connective tissue disorders, chronic infections, malignancies).
  - Psycho-emotional stress.

► **Clinical features:** Typically patient describes markedly increased diffuse hair loss during hair washing and combing, well above the previously observed level. If flare of underlying androgenetic alopecia, often—but not always —the characteristic pattern can be seen.

► **Diagnostic approach:** Examine hairs, trichogram shows >25% telogen hairs (in extreme cases, 80–90%); laboratory screening (complete blood count [CBC], sed rate, liver function tests, renal status, iron, ferritin); more directed testing based on history.

► **Differential diagnosis:**

- *Anagen effluvium*: Hairs are damaged and lost during growth phase; bayonet hairs without telogen bulb; usual causes chemotherapy, radiation therapy, sepsis; rarely seen with alopecia areata.
- *Intoxication*: Actual poisoning by thallium or arsenic rarely seen, but many patients convinced they are being poisoned by amalgam, environmental factors, dietary exposure, or (especially problematic) occupational exposures. Careful documentation and discussion required. Usually the underlying disease is ndrogenetic alopecia.

► **Therapy:** Usually no therapy is needed. Most patients accept the message that underlying factors must be corrected and nature given time to restore cycle. In women with androgen-induced telogen effluvium, solutions containing 17-estradiol induce prolongation of anagen phase and are effective.

Androgen-induced Alopecia

► **Definition:** Hair loss because of an endocrine abnormality with increased circulating androgen levels.

► **Epidemiology:** Disease of women.

► **Pathogenesis:** Causes of excesses androgens include ovary (secretory tumors, polycystic ovary disease), adrenal gland (many corticosteroids have androgenetic

function), and pituitary (excess secretion of regulatory hormone). In about 50% of cases, combined ovarian and adrenal hyperfunction. Always exclude adrenogenital syndrome (p. 319).

- **Clinical features:** Diffuse alopecia often starting in centroparietal region, associated with seborrhea; hirsutism (hypertrichosis of beard area, breasts).
- **Diagnostic approach:** General examination; determination of dehydroepiandrosterone sulfate (DHEAS), testosterone, free testosterone, sex hormone binding globulin (SHBG), prolactin levels; trichogram or phototrichogram.
- **Differential diagnosis:** Androgenetic alopecia, diffuse alopecia areata, SAHA syndrome (**s**eborrhea, **a**cne, **h**ypertrichosis, **a**ndrogen-induced alopecia).
- **Therapy:** Treat underlying disease; antiandrogens including cyproterone acetate combined with ethinyl estradiol or chlormadinone acetate.

Androgenetic Alopecia

- **MIM code:** 109200.
- **Definition:** Physiologic process with increased follicle sensitivity to androgens leading to change from terminal to vellus hair follicles with distinct patterns of alopecia, often associated with telogen effluvium.
- **Epidemiology:** At least 80% of men and 60% of women have detectable androgenetic alopecia by 60 years of age.
- **Pathogenesis:** Polygenic inheritance; variable penetrance. The hair follicles have increased numerous of androgen receptors in typical patterns as well as increased activity of 5-α-reductase type II, leading to increased androgen sensitivity. Dihydrotestosterone also causes shift to telogen hairs.
- *Clinical features:* Thinning of hair without scalp disease; two classic pattern schemes used for grading (Figs. 31.**1**, 31.**2**):
  - *"Male pattern"* (after Hamilton).
  - *"Female pattern"* (after Ludwig).

  ▶ ***Note:*** Overlap forms are common in both sexes.
- **Diagnostic approach:** Usually obvious, but many younger patients are skeptical and disappointed in the diagnosis. In men, usually receding frontal hairline; in women, more diffuse thinning and retention of frontal pattern. Vellus hairs usually prominent in areas of loss; hairs are thinner and remain shorter. In women, often associated with telogen effluvium.
  - Patients may complain that hairs are finer and grow more slowly, while at other body sites, hair growth may be increased. Often seborrhea more prominent than previously.
  - Family history is almost always positive, if one is persistent enough. Many patients initially say that no one in the family was bald, but this typically means only that their father had a relatively full head of hair. Ask about hair loss in grandparents, uncles, aunts.

    ▶ ***Note:*** If the clinical diagnosis seems likely but the patient is skeptical, studying old photographs with the patient is often very helpful.
  - Trichogram or phototrichogram reveals reduced anagen/telogen ratio, frontal > occipital. Only valuable if rigorously standardized, quality-controlled, and done professionally. In clinical routine, both techniques are dispensable for making a correct diagnosis.
  - Hormone levels usually normal. Studies only needed when hirsutism, virilization, menstrual problems, infertility, galactorrhea, or other indications of endocrine abnormalities are present. Then DHEAS, free testosterone, SHBG, prolactin, thyroid function; hormone studies should be done on day 3–7 of cycle, or ideally after not taking oral contraceptives for 3 months.

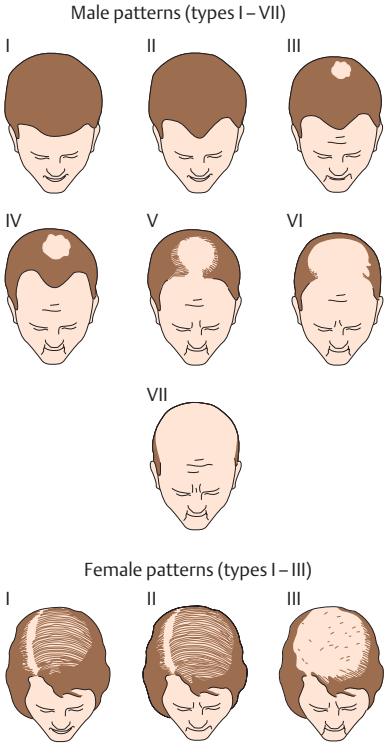


Fig. 31.**1** · Androgenetic alopecia: male pattern (after Hamilton) and female pattern (after Ludwig); men can also develop the Ludwig pattern and women the Hamilton pattern.

Fig. 31.**2** · Severe androgenetic alopecia in a women.

► **Differential diagnosis:** Diffuse alopecia areata, androgen-induced alopecia.

► **Therapy:**

- Most important step is adequate discussion with patient. Explain that process is physiologic, normally slow, with occasional bursts. Since the hairs are not lost but converted to vellus hairs, there is good hope that an efficient therapy can be developed to re-convert them. *Be optimistic!*.
- *Treatment of men:*
  - Topical estrogens are ineffective and may lead to gynecomastia. Systemic antiandrogens have too many side effects including testicular atrophy, impotence, and feminization (and are therefore only indicated in transsexual men).
  - *Minoxidil* is a systemic vasodilator, used for severe hypertension, which causes hypertrichosis. Topical minoxidil 2–5% solution is effective in androgenetic alopecia. Minoxidil can also be compounded (p. 697), but considerable care is required as it is poorly soluble. After 4–12 months of usage, hair loss may be stabilized and some regrowth of terminal hair shafts seen in frontal and vertex vellus regions. Side effects include hypertrichosis in undesired locations (face, nipples), allergic contact dermatitis and hypotension.

    ▶ ***Note:*** Patients must understand that once minoxidil is stopped, hair loss starts again, and that maintaining the status quo, rather than dramatic regrowth, is the goal.
  - Systemic finasteride (5-α-reductase type II inhibitor) is the most effective therapy available. 1 mg/daily "forever" is the dosage. It blocks conversion of testosterone into dihydrotestosterone, the active agent in androgenetic alopecia. Side effects during short-term use (1–3 years) are minimal; the inhibitor is highly specific and even effects on libido are quite rare. The long-term effects over 30 years are still unpredictable. Once stopped, there is rapid progression of hair loss at the pretreatment level.
  - Topical 17-α-estradiol is often employed in Germany; it does not exert estrogen effects, yet may inhibit 5-α-reductase activity and therefore is a safe, but not highly effective, treatment.
  - Combination therapy makes sense and appears more effective, yet has not been rigorously tested; minoxidil and/or 17-α-estradiol solution (men) combined with finasteride.
  - Supportive care includes appropriate grooming, aggressive treatment of seborrheic dermatitis, and avoiding medications that could increase hair loss.
  - Be alert to co-factors such as thyroid disease; appropriate endocrinologic management can help slow progression of hair loss.
  - *Hair transplantation:* Effective technique that depends on donor dominance; plugs or micrografts of hairs taken from an area where androgenetic alopecia does not occur can be transplanted to bald areas and hairs will continue to grow.

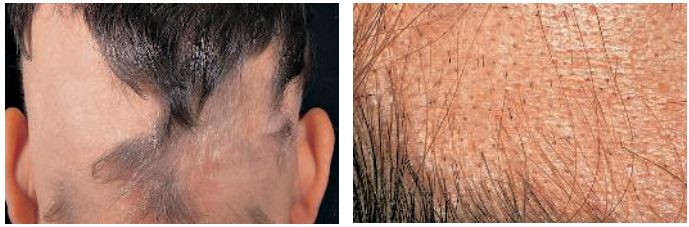
    ▶ ***Note:*** Hair transplants should be done by experienced surgeons, and only in patients in whom the degree and progression of baldness can be assessed. Continued treatment with minoxidil and/or finasteride should also be considered.
- *Treatment of women:*
  - Topical estrogens may be of value. A 17-α-estradiol solution is available commercially in Germany, or appropriate solutions for women and men can be compounded (p. 694). The solutions are applied to scalp and massaged in for 10 minutes daily. Trial of therapy for at least 4 months.
  - Minoxidil also useful; at least 6 months trial, better 12; more risk of facial hypertrichosis in women.

- Systemic antiandrogens can be employed, always in conjunction with oral contraceptives in premenopausal women and usually with monitoring by gynecologist. Various combinations and dosages of cyproterone acetate and chlormadinone are available in Europe but not in the USA.
- Topical antiandrogens are under development. Agents such as spironolactone, ketoconazole, cimetidine or dexamethasone have systemic antiandrogen effects but do little, if anything, topically.
- Hair transplantation usually not indicated in women because of their more diffuse thinning and the impossibility of reliably determining the border between androgen-sensitive and insensitive hair follicles.
- Same supportive measures as in men; also consider iron, zinc, and biotin supplementation.
- Monitor success with hair counts, trichogram or phototrichogram; learning that hair loss is decreasing has immense emotional value for the patient.

31.4 Localized Nonscarring Alopecia

Alopecia Areata

- **MIM code:** 104100.
- **Definition:** Sudden localized hair loss without clinically visible inflammation; variety of clinical patterns.
- **Epidemiology:** Prevalence in the USA is 0.1–0.2%, with an estimated lifetime risk of developing alopecia areata of 1.7%. About 20% of patients with alopecia areata report a positive family history for the disease.
- **Pathogenesis:** Alopecia areata is most likely an organ-specific autoimmune disorder, with autoaggressive T cells possibly directed against melanocytes in the anagen follicle. Likely association with other autoimmune diseases such as vitiligo, Hashimoto thyroiditis, and diabetes mellitus; also seen with other thyroid diseases and atopy, as well as with Down syndrome and Turner syndrome, but causal relationship not proven. Despite the severity of the immunologic attack, follicles are only very rarely destroyed and can therefore fully recover. Alopecia areata is so variable that some consider it to be a family of diseases. It occasionally follows severe physical or emotional stress.
- **Classification:**
  - *Alopecia areata circumscripta*: One or several areas of alopecia on scalp or beard.
  - *Alopecia totalis:* Loss of most or all of scalp hair, sometimes with loss of eyebrows and eyelashes.
  - *Alopecia universalis:* Loss of all scalp and body hair.
- **Clinical features:**
  - Round to oval sharply circumscribed areas of hair loss without inflammation (Fig. 31.**3**). Usually starts as single lesion; most often spontaneous resolution. In others, expansion of lesion or development of new patches.
  - *Ophiasis*: Band-like loss from ear to ear across the nape; poor prognostic sign.
  - Scalp sometimes slightly swollen; doughy or puffy feeling.
  - *Exclamation point hairs*: Broken-off 1–2 mm hairs at periphery of patch; when plucked, look like exclamation point with thick bulb.
  - *Cadaver hairs:* Hairs broken before they reach surface; also sign of activity and progression.
  - Focal areas of *poliosis* (grey hairs) where previous patches have regrown.



a b

Fig. 31.3 · **a** Alopecia areata. **b** Exclamation point hairs.

- *Pitted nails* present in around 20% of adults and up to 50% of children with alopecia areata; association with twenty-nail dystrophy (trachyonychia, p. 524); other nail problems less likely. Rare reports of keratitis and hypohidrosis.

► **Histology:** Only indicated for confirmation of suspected diffuse variant of alopecia areata. In early stage, dense lymphocytic infiltrate about lower follicles ("swarm of bees" pattern around anagen hair bulb) and increased number of catagen follicles; later, miniaturization of follicles. If infiltrates present, strong support for diagnosis; their absence does not rule out the possibility of alopecia areata.

► **Diagnostic approach:** History (previous lesions, overlooked lesions in beard area); clinical examination (polished areas with exclamation point or cadaver hairs).

► ***Note:*** Use hand lens (dermatoscope) to better visualize exclamation point and cadaver hairs as well as fully maintained follicle orifices (disappear in scarring alopecias); always do pull test at edge of lesion (if positive, high likelihood of progression).

- Biopsy rarely needed. Laboratory examination probably not justified for single lesion, but if disease is progressive or persistent or negative prognostic factors present, then CBS, sed rate, thyroid function (highest yield), search for autoantibodies (ANA, parietal cell, mitochondrial, thyroid); if otherwise sick or lymphadenopathy, or if very many, small, only partially alopecic areas visible, then syphilis serology.

► ***Note:*** Check blood pressure. Alopecia areata tends to be more aggressive in young patients from families with high prevalence of hypertension.

► **Differential diagnosis:** Trichotillomania, tinea capitis, syphilitic alopecia, scarring alopecia.

► ***Note:*** Combinations of alopecia areata and trichotillomania occur, especially in children.

► **Prognosis:** The outlook is variable; 35–60% experience spontaneous remission in 2 years. Unfavorable signs are:

- Positive personal or family history for atopy, alopecia areata, or autoimmune diseases.
- Onset before puberty.
- Rapid progression.
- Widespread recurrence.
- Persistence for > 2 years.
- Ophiasis (alopecia areata involving temporal ands occipital margins of scalp in a continuous band).
- Involvement of eyelids or eyelashes.
- Pitted nails.

- **Therapy:**
  - Aggressiveness of therapy adjusted to risk factors and prognosis.
  - Explain course to patient; initially only vellus hairs (peach fuzz) will be seen; regrowth of terminal hairs takes 6–18 months, depending on hair length.
  - Address underlying issues if any have been identified, such as atopy or thyroid disease.
  - No curative therapy; two main strategies to alter immune picture around follicles—immunosuppression with corticosteroids or immunomodulation via intentional allergic contact dermatitis.
  - Single or few lesions less than 6 months in age:
    - High potency topical corticosteroid solution or gel b.i.d.
    - Triamcinolone acetate 2.5 mg/mL in lidocaine; infiltrate lesion, especially the periphery, and repeat in 4–6 weeks. More than two injections leads to increased risk of atrophy.
    - Add zinc aspartate 50 mg b.i.d. as adjuvant therapy.
    - Consider short burst of systemic corticosteroids in patient with two or more unfavorable prognostic factors. Typical regimen prednisolone for 1 week is 75–75–50–25–25–10–10 mg, then 3 weeks pause. Repeat for three cycles; then re-assess and either offer another three cycles or stop. Carefully consider contraindications and side effects (hypertension, worsening of diabetes mellitus, glaucoma, many others).
- Long-term systemic treatment with corticosteroids or cyclosporine can induce hair growth, but it is not stable and the side effects of continued therapy are unacceptable.
- Anthralin irritant therapy can be combined with corticosteroid bursts and oral zinc. Use either 1–3% anthralin cream or 2–5% anthralin stick applicator. Apply daily; starting for 5 minutes and increasing in 5 minute increments until irritation is induced or 8 hours is reached. If no irritation, can also increase concentration. Then continue on daily basis, removing the anthralin one burning occurs. Regrowth takes 4–8 weeks to begin after irritation has been induced. Side effects include discoloration and nuchal lymphadenopathy.
- If all these approaches have failed despite appropriate usage, then consider inducing contact allergy to diphenylcyclopropenone (*Happle regimen*). Extensive counseling required, as this method is still regarded as experimental:
  - Sensitization with 2% diphenylcyclopropenone applied to scalp with adhesive bandage.
  - Observe positive response; if none occurs, repeat.
  - After 2 weeks, begin treatment starting with 0.0001% solution and slowly working up to 0.5%. Make every effort to maintain a mild allergic contact dermatitis. Explain to patient that occasional severe reactions are hard to avoid; blisters and pigmentary changes can occur.
  - Over months of mild irritation, hair regrowth usually starts.
  - Other possibilities include:
    - PUVA or UVB therapy.
    - Minoxidil.
    - Topical immunomodulatory agents (tacrolimus, pimecrolimus).
  - ***Note:*** In children, the main options are topical corticosteroids, anthralin, and oral zinc.

Trichotillomania

- **Definition:** Localized alopecia secondary to plucking, cutting, or rubbing away hairs.
- **Clinical features:**
  - Poorly circumscribed areas of with broken-off hairs; occasionally follicular hemorrhages. Pull test is negative and trichogram shows few telogen hairs.
  - In infants, an almost normal habit of no consequence. May also induce nuchal alopecia simply by rubbing their heads on mattress or pillow. In older children or adults, usually associated with psychiatric disturbances, in the general category of obsessive-compulsive disorder. Clinically tends to be more diffuse than in small children; sometimes entire scalp involved and patient presents with wig.
- **Histology:** Biopsy shows perifollicular hemorrhage and damaged follicles; useful to exclude alopecia areata.
  - ***Note:*** Bear in mind the possibility of trichophagia and the formation of hair ball (trichobezoar) in the gastrointestinal tract, which can cause obstruction and other signs and symptoms.
- **Therapy:** Confronting the patient with the diagnosis may help in mild cases. Most teenagers and adults require psychiatric support and therapy. Often manifestation of conflict between child and parents, making management even more difficult.

Self-induced Alopecia

There are several other forms of self-induced alopecia in which there is no underlying psychological problem:

- **Traction alopecia:** Hair loss secondary to tight hair styles, such as corn rows in blacks, tight braids, or long, heavy ponytails. If not interrupted, can progress to scarring and permanent hair loss.
- **Pressure alopecia:** Hair loss from tightly-fitting helmets, hats, sweat bands, or the like.
- **Massage alopecia:** Hair loss following over-aggressive or ritually repeated hair massage.

31.5 Scarring Alopecia

Overview

- **Definition:** Irreversible damage to hair follicles leading to scarring and permanent alopecia.
- **Pathogenesis:** Many causes including autoimmune diseases (chronic cutaneous lupus erythematosus [discoid], lichen planus, less often morphea or systemic sclerosis), infections (bacterial, fungal, viral), tumors (mycosis fungoides, follicular mucinosis), exogenous factors (ionizing radiation, trauma, overaggressive hair care), embryological defects (aplasia cutis congenita). In some instances, no causative agent is identifiable (*pseudopelade).* In our experience, however, most cases of pseudopelade represent end-stages of lichen planopilaris (most common) or chronic cutaneous lupus erythematosus (less common).
- **Diagnostic approach:** The key is not to overlook clinical signs of scarring. Use of the dermatoscope is a priceless, but far too rarely employed, tool for identifying such signs—disappearance of follicular ostia, along with shiny, thin scalp epider-

mis that has lost its normal surface patterning. Bundles of hairs produced by hair follicles that have become fused by autoaggressive inflammation (*toothbrush sign,* as hairs resemble grouped bristles of toothbrush) are also a frequent sign of scarring alopecia.

- Always look for signs of associated diseases elsewhere on the skin. Sometimes much easier to identify lupus erythematosus or lichen planus on the skin than on the scalp. Also check mouth and nails for discrete signs of lichen planus. Scalp biopsy is always indicated when scarring alopecia is suspected, but quite often is not as helpful as expected. The main reason for that is a wrong biopsy technique (p. 27). Advanced scarring alopecia, no matter how perfect your biopsy is and whatever its cause, looks puzzlingly similar in most cases.
- **Differential diagnosis:** Late disease looks the same, no matter what the cause. Always systematically consider all of the pathogenetic possibilities discussed above, and look for indications to the presence of these problems elsewhere on the skin, mucosa, or nails.
- **Therapy:** If the cause is identified, then it should be treated promptly and aggressively to minimize the amount of scarring. Once scarring has occurred, there is no treatment other than perhaps an attempt at hair transplantation—yet only in the absence of active inflammation and once the alopecia has stopped progressing.

Chronic Cutaneous Lupus Erythematosus (CCLE)

- **Synonym:** Discoid lupus erythematosus.
- **Clinical features:**
  - Scalp involvement is common in CCLE, especially among black women.
  - Early lesions show erythema, follicular plugging, and scale; later hypopigmentation, atrophy, and scarring alopecia (Fig. 31.**4**).

  Caution: In rare cases, CCLE can evolve into a squamous cell carcinoma, so always do a biopsy in patients with chronic disease and a changing clinical picture.

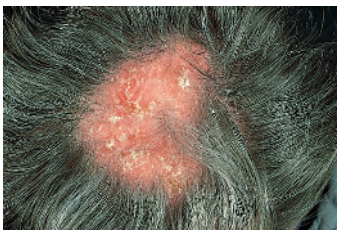


Fig. 31.**4** · Scarring alopecia: chronic cutaneous lupus erythematosus.

- **Histology:** Follicular scarring, lymphocytic infiltrates about remaining follicles, epidermal atrophy, telangiectases, mucin deposition, on direct immunofluorescence (DIF) may see lupus erythematosus band.
- **Therapy:**
  - High-potency topical or intralesional corticosteroids (triamcinolone 2.5–5.0 mg/mL in lidocaine). If lesions are hyperkeratotic, then a salicylic acid scalp ointment applied overnight and washed out thoroughly may remove scale and help increase penetration of corticosteroids.
  - If no response, then more rapidly to systemic therapy. Often scalp disease in CCLE is self-limited, so aggressive intervention is warranted. Most useful are

corticosteroid pulse therapy or cyclosporine for a limited time period. Antimalarials are another possibility, but have a slow onset of action and are less suited for the immediate task of arresting scarring.
- Chronic immunosuppressive therapy is not appropriate for scarring alopecia.
- Patients should wear a hat and use high protection factor sunscreens.

Lichen Planus

- **Synonym:** Lichen planopilaris, lichen follicularis, Graham–Little syndrome.
- **Epidemiology:** Scalp involvement in 30–60% of patients with lichen planus; usually middle-aged adults. More common in patients with persistent diseases.
- **Clinical features:** Follicular or perifollicular hyperkeratoses, usually multiple, evolving into atrophic patulous follicles, sometimes with erythematous rim, and then permanent scarring.
- **Histology:** Dense lymphocytic infiltrate both around residual follicles and sometimes along dermoepidermal junction; epidermis normal with prominent granular layer, no mucin; on direct immunofluorescence, colloid bodies more likely.
- **Therapy:**
  - High-potency topical or intralesional corticosteroids with salicylic acid ointments.
  - If nonresponsive or rapidly advancing, consider short burst of systemic corticosteroids, perhaps combined with acitretin (0.3–0.5 mg/kg).

Infections

Sometimes the cause of the inflammation leading to scarring is known:
- Tinea capitis (p. 108).
- Furuncle, carbuncle (p. 74).
- Herpes zoster (p. 61).

Folliculitis Decalvans

- **Definition:** Scarring alopecia with follicular inflammation and usually pustules.
- **Epidemiology:** In men, usually starts in young adult life; in women, somewhat later.
- **Pathogenesis:** Divided opinions if bacteria play a primary or secondary role. Possibly a hypersensitivity reaction against persistent bacterial antigens with continued, autoaggressive immune responses.
- **Clinical features:** Pustules, erythema, scarring and sometimes marked seborrhea (Fig. 31.**5**).
- **Histology:** Dense neutrophilic infiltrates with destruction of follicles; often rich in plasma cells.

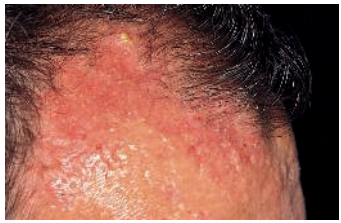


Fig. 31.**5** · Folliculitis decalvans.

- **Diagnostic approach:** Culture often identifies *Staphylococcus aureus*. Biopsy and DIF useful to exclude lupus erythematosus.
- **Therapy:**
  - Despite the confusing pathophysiology, empiric antibiotic therapy seems the best approach.
  - Rifampicin 300 mg b.i.d., often combined with clindamycin 300 mg b.i.d. for 2 weeks; then rifampicin alone for another 6–8 weeks. Clarithromycin or ciprofloxacin can replace clindamycin.
  - Metronidazole 500 mg t.i.d. combined with clindamycin 300–600 mg b.i.d. for 3 weeks.
  - If antibiotics are not effective, then consider prednisolone pulse therapy combined with isotretinoin.

Follicular Mucinosis

- **Synonym:** Preferred term is folliculotropic mycosis fungoides; alopecia mucinosa.
- **Definition:** Alopecia associated with lymphocytic infiltrate of hair follicle and intrafollicular mucin deposition.
- **Pathogenesis:** In adults, almost always follicular mycosis fungoides; in children, controversial if perhaps a self-limited form exists. Often mycosis fungoides appears years after the follicular mucinosis (p. 474).
  - ***Note:*** If the diagnosis of follicular mucinosis is made, the patient must be examined completely and then followed for development of mycosis fungoides.
- **Clinical features:**
  - *Acute form:* 2–5 cm boggy plaques without hairs; usually on face or scalp. Most common in children, young adults. Spontaneous healing may occur over 1–2 years.
  - *Chronic form:* In addition, keratotic papules on extensor surfaces or trunk associated with hair loss; often mucinous substance can be expressed.
- **Histology:** Folliculotropic infiltrate of T cells together with mucin deposition in follicles or epidermis. If atypical lymphocytes or clonal rearrangement of T-cell receptor present, then regard as mycosis fungoides.
- **Therapy:**
  - If chronic lesion or older adult, treat as mycosis fungoides with PUVA or ionizing radiation (20–30 Gy fractionated over 3–4 weeks) combined with interferon-α-2b.
  - If acute lesion in child with no histological evidence for mycosis fungoides, can treat with intralesional steroids. If no response, consider short burst of systemic corticosteroids or dapsone 50–100 mg daily (following hemoglobin level). Follow patient even if remission occurs.

Pseudopelade of Brocq

- **Definition:** Scarring alopecia in absence of identified causative agent.
- **Pathogenesis:** May be the end stage for lichen planus or lupus erythematosus; no convincing evidence available that this really is a specific disease unrelated to other forms of scarring alopecia; possibly an exaggerated form of (physiological) "programmed organ deletion" of hair follicles.
- **Clinical features:** Small confluent atrophic scarred areas (likened to "tracks in the snow"), usually occipital or parietal. Typically bundles of hairs remaining (Fig. 31.**6**). Hair follicles hard to see; affected areas smooth and glistening, sometimes pruritic.

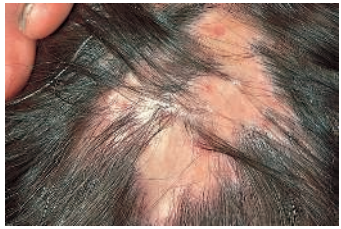


Fig. 31.**6** · Pseudopelade of Brocq.

- **Histology:** Reduced number of follicles with scarring and no evidence for lupus erythematosus or lichen planus.
- **Therapy:**
  - Treat underlying disease.
  - If none seen, empiric use of antibiotics or antimalarials.
  - Symptomatic treatment with wig. Hair transplantation or scalp reduction can be considered if disease is completely quiescent.

31.6 Hair Shaft Anomalies

Definitions

There are a number of structural defects in the hair shaft; some inherited, others acquired. Figure 31.**7** illustrates the most common variants.

- **Trichoptilosis:** Hairs split and feathered.
- **Trichoclasis:** Tranverse split in hair with retained cuticle.
- **Trichoschisis:** Smooth transverse split in hair, associated with trichothiodystrophy.
- **Trichorrhexis nodosa:** Localized longitudinal splitting of shaft; frayed ends pushed upon one another (compared to two paint brushes pushed into one another), causing nodules along shaft.
- **Trichonodosis:** Knots and loops in shaft.
- **Trichorrhexis invaginata:** Distal shaft pushed into bulbus receptacle on proximal shaft (*bamboo hair*); associated with Netherton syndrome (atopy, ichthyosiform skin changes; p. 195).
- **Pili torti:** Hair that is flattened and twisted upon its long axis.
- **Monilethrix:** Shaft has alternate swellings (nodes) and constrictions (lacking medulla), producing beaded effect. Nodal interval 0.7–1.0 cm.
- **Pseudomonilethrix:** Appears similar to monilethrix, but parts of shaft are irregular with nodes while other areas are regular.
- **Pili annulati:** Disturbance in hair color with alternating pigmented and nonpigmented areas. May be confused with pili torti.

Diagnostic Approach

- **Hair shaft anomalies**:
  - *With increased fragility:* Monilethrix, pseudomonilethrix, poli torti, Menkes syndrome, Netherton syndrome, trichorrhexis nodosa, trichothiodystrophy.
  - *With normal stability:* Pili annulati, wooly hair, uncombable hair syndrome.

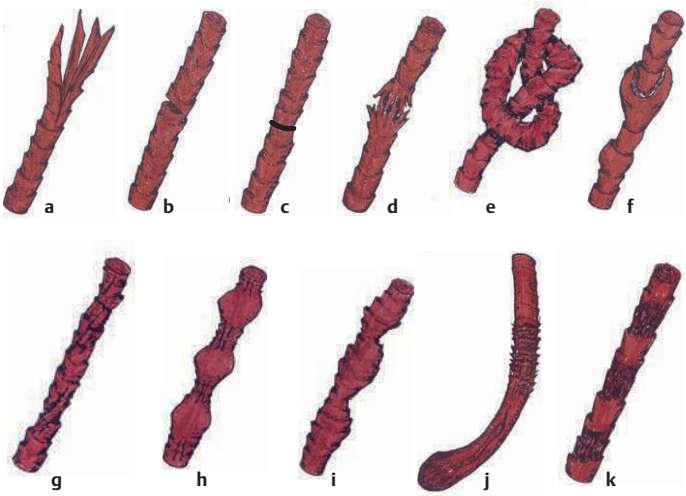


Fig. 31.7 · **Hair shaft anomalies (after Whiting). a** Trichoptilosis. **b** Trichoclasis. **c** Trichoschisis. **d** Trichorrhexis nodosa. **e** Trichonodosis. **f** Trichorrhexis invaginata. **g** Pilus tortus. **h** Monilethrix. **i** Pseudomonilethrix. **j** Loose anagen hair syndrome. **k** Pilus annulatus.

Therapy

In most instances, no therapy except "tender loving care." Patients should be encouraged to use mild shampoos, with rinses and conditioners to make hairs less likely to tangle or split.

Monilethrix

- **MIM code:** 158000.
- **Pathogenesis:** Mutations in human hair keratins (HB1 or HB6), both on chromosome 12q13; autosomal dominant inheritance.
- **Clinical features:**
  - Normal hair at birth, but in the first months hairs begin to break off 1–2 cm above the surface, more prominent on occiput, where small erythematosus follicular keratoses also develop.
  - Sometimes spontaneous improvement in puberty or pregnancy.
  - Occasionally eyelids, eyelashes, and body hair affected.
  - Often associated with keratosis pilaris and nail changes; rarely dental anomalies and juvenile cataracts.
- **Diagnostic approach:** Sometimes clinically inapparent, but abnormalities identified with microscopy or scanning electron microscopy.
- **Therapy:** No satisfactory therapy; supportive care.

Pseudomonilethrix

- Inherited autosomal dominant form, most common in South Africa. The hair shafts vary greatly in caliber, are flattened, turned on their long axes, and very fragile. Usually appears in childhood. Acquired form appears later, believed secondary to trauma or aggressive hair care.

Pili Torti

- Many different forms, all with same defect of flattening and twisting of shaft along long axis.
- **Isolated pili torti:** Autosomal dominant inheritance. Hairs very fragile, apparent in infancy.
- Associated with:.
  - *Menkes kinky hair syndrome* (p. 317): abnormal copper uptake, mental retardation, pili torti.
  - *Bjornstad syndrome:* Sensory deafness and pili torti.
  - *Crandall syndrome:* Sensory deafness, hypogonadism, pili torti.

Loose Anagen Hair Syndrome

- **MIM code:** 600628.
- **Definition:** Disturbance in binding between hair shaft and inner root sheath; autosomal dominant inheritance with variable expressivity.
- **Clinical features:** At birth, hairs are normal. By 4–6 years of age, fine blond hairs that are easily extracted; more common in girls.
- **Diagnostic approach:** Light pull test is very positive; on trichogram, almost all the hairs are anagen.
- **Therapy:** No effective treatment, but self-limiting disease; in almost every patient, by puberty the hairs are firmly anchored again.

Trichothiodystrophy

- **MIM code:** 601675.
- **Definition:** Combination of sulfur-deficient hair with complex series of associated defects.
- **Pathogenesis:** Mutations in same DNA repair genes responsible for xeroderma pigmentosum (p. 304); in autosomal recessive inheritance. Mutations at some sites in genes cause xeroderma pigmentosum; at others, trichothiodystrophy.
- **Clinical features:** The hair findings are the unifying clinical feature.
  - The hairs are easily broken, so patients present with both focal and diffuse alopecia, often involving nonscalp hairs. When examined under polarized light, the hairs are banded (*tiger tail sign*).
  - Associated defects include **p**hotosensitivity, **i**chthyosis, **b**rittle hair, **i**nfertility, **d**evelopmental delay, **s**hort stature. The initial letters are variously combined to create BIDS, IBIDS, PIBIDS; *Tay syndrome* is another name for IBIDS.
  - Despite the relationship to the xeroderma pigmentosum gene, there is no increased incidence of skin cancers.
- **Diagnostic approach:** Exact genetic analysis available in specialized centers.
- **Therapy:** Multidisciplinary management; no treatment for hair except gentle care.

Other Hair Shaft Anomalies

- **Pili multigemini:** Multiple hairs arise from same follicular unit; very common in dogs.
- **Trichostasis spinulosa:** Multiple vellus hairs rolled up inside dilated follicle with comedo plug; more common in sebaceous areas, sun-damaged skin; almost normal on nose.
- **Woolly hair:** Hairs are excessively curled, fancifully compared to sheep wool, scalp hair of blacks, or even fiberglass; may be inherited (MIM code 194300) or acquired; diffuse or localized (*woolly hair nevus*). Also associated with Naxos syndrome (MIM code 601204: palmoplantar keratoderma, cardiomyopathy, defect in plakoglobin).
- **Hair casts:** Small white keratinous sheaths around the hair shaft; may slide; differential diagnostic considerations include nits and trichomycosis axillaries.

31.7 Hypertrichosis

Overview

- **Definition:** Growth of hairs that are longer, thicker or more numerous than the location, age, and racial background of the patient would predict. Usually there is a switch from vellus to terminal hairs; in acquired hypertrichosis an anagen shift is usually present.

Hypertrichosis Lanuginosa

- Lanugo hairs have a thin depigmented shaft. They are present in utero during months 3–7, but normally shed by birth and replaced by terminal or vellus hairs.
- **Hypertrichosis lanuginosa congenital:**
  - MIM code: 145700.
  - Uncommon genodermatosis in which newborn is covered by long lanugo hairs, which are not shed and replaced, but continue to grow. Patient typically winds up with a silvery coat of hairs 10 cm long.
- **Hypertrichosis lanuginosa acquisita:** Obligatory paraneoplastic marker (p. 486). Any patient who shows this should be subjected to a rigorous and systematic tumor search.

Generalized Hypertrichosis

- There are many causes for diffuse excess numbers of terminal hairs. In all of these disorders, there are still local (regional differences) but the entire body seems affected.
- **Hereditary:** Porphyria cutanea tarda and porphyria variegata (primarily facial), mucopolysaccharidoses, chromosome abnormalities (trisomy 18).
- **Endocrine:** Pituitary and thyroid disorders.
- **Eating disorders** (especially anorexia nervosa), malabsorption, fetal alcohol syndrome.
- **Medications:** Cyclosporine, minoxidil, phenytoin are most common; others include diazoxide, streptomycin, corticosteroids, penicillamine, psoralens.

Localized Hypertrichosis

- **Nevi** including:
  - *Hair nevus*: Uncommon and disputed but sometimes localized area with excess hair follicles and no other abnormalities; if papule in front of ear, search carefully for associated cartilage suggesting accessory tragus with enormous number of vellus hairs.
  - *Becker nevus*: Localized mosaic area of increased melanin and increased hair growth. Often relatively hairless until puberty, can be associated with localized acne or underlying smooth muscle hamartoma with cutis anserina (*goose bumps*) as smooth muscles contract (p. 412).
  - *Faun tail nevus:* Localized hair growth over sacrum fancifully resembling a fluffy tail, but a most serious marker for potential underlying spinal cord defects or spina bifida. Neurological and radiological work-up mandatory.

31.8 Hirsutism

Overview

- **Definition:** Increased growth of terminal hairs in women in androgen-dependent areas, producing male-like hair growth pattern. *Virilization* is the association of hirsutism with other signs of male development, such as voice deepening, clitoral enlargement, increased muscles, loss of breast tissue, acne, and androgenetic alopecia.
- **Pathogenesis:** The main causes of hirsutism are summarized in Table 31.**2**.
  - ***Note:*** Most cases of hirsutism are physiologic; in many ethnic groups, female body hair does not fit the current Western beauty standard, leading to psychosocial problems as people move between cultures.
  - ***Note:*** Hirsutism combined with androgenetic alopecia can be a sign of elevated prolactin levels, typically caused by neuroleptic agents, polycystic ovary syndrome, or prolactinoma (usually a small tumor not otherwise symptomatic).

Diagnostic Approach

- **History:**
  - Onset, course of excessive hairs; family history (hair patterns of other women in family).
  - Menstrual history; pregnancies.
  - Symptoms of virilization?.
  - Medications?.
  - History of thromboses (contraindication to estrogen therapy).
- **Examination:**
  - Signs of virilization, Cushing disease, acromegaly, galactorrhea (Fig. 31.**8**).
  - Complete physical examination; palpate ovaries, Pap smear, breast check.
  - *Laboratory:* DHEAS, free testosterone, SHBG, prolactin; others as indicated. Testosterone >2 ng/mL suggests ovarian tumor; DHEAS >9000 ng/mL suggests adrenal tumor.
  - ***Note:*** If it is not completely clear that the patient has idiopathic hirsutism, refer to endocrinologist or gynecologist for a second opinion.

Table 31.2 · Causes of hirsutism

	Functional	Neoplastic
Endocrine		
Ovarian	Polycystic ovary disease	Variety of functional tumors (hilar cell or Leydig cell, luteoma, arrhenoblastoma
Adrenal gland	Congenital adrenal hyperplasia, idiopathic adrenal hyperandrogenism	Adenomas and carcinomas
Pituitary		Cushing disease, acromegaly, adrenogenital syndrome, prolactinoma
Nonendocrine		
Idiopathic	Most common; genetic-ethnic variation	
Medications	Phenytoin, androgens (danazol, stanozolol, body building pills), corticosteroids, ACTH, oral contraceptives (progesterone has androgen action), metyrapone (used for diagnostic purposes only, so unlikely)	
Achard–Theirs syndrome	Virilization and adult-onset diabetes mellitus in postmenopausal women because of excess adrenocortical androgens	
SAHA syndrome	Seborrhea, acne, hypertrichosis/hirsutism, alopecia; group of disorders with either elevated androgen levels or increased androgen sensitivity	

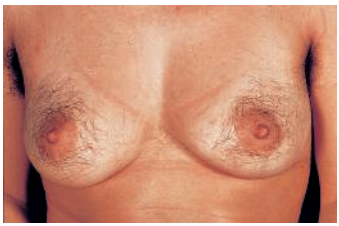


Fig. 31.**8** · Hirsutism.

Therapy

- **Treat underlying disease**.
- **Removal of hairs:**
  - Shaving, wax epilation, chemical epilation (thioglycolate commercial products or compounded, p. 700).
  - Bleaching (6–10% hydrogen peroxide in water).
  - *Electrolysis:* Destruction of individual hair follicles with electrocoagulation or diathermy; time-consuming; frequent re-treatment; works on white or gray hair.
  - *Epilation with lasers* (diode or Nd:YAG) or intense pulsed light source; only works on pigmented hairs but much faster and more effective. Clearly the method of the future.
  - Eflornithine (topical) effective but only as long as used; also expensive.
  - Ionizing radiation **contraindicated**.

  ▶ ***Note:*** The problem with all attempts at permanent hair removal is that bulge (hair stem) cells are hard to destroy and multiple treatments are often required. Also, complete destruction of these important stem cells ("bone marrow of the skin") does not appear an inherently good idea, since they are needed during wound healing and epidermal regeneration after burn wounds.
- **Hormone therapy:**
  - *Hormones that antagonize androgens:* Corticosteroids or estrogens.
  - *Primary antiandrogens:*
    - Cyproterone acetate.
    - Chlormadinone acetate.
  - *Miscellaneous agents with secondary antiandrogen activity:* Spironolactone, ketoconazole, cimetidine.
  - *5-α-Reductase inhibitor*: Finasteride is not approved for women but effective; must be used with effective contraception because of risk of malformations in male fetuses.
  - *Combination therapy*: Many combinations of estrogens and either cyproterone acetate or chlormadinone acetate are available in Europe.

31.9 Diseases of the Scalp

Dandruff

- **Definition:** Pityriasis capitis.
- **Clinical features:** Familiar fine scale present on scalps of most adults; uncommon in children. Gradual transition with seborrheic dermatitis, in which case erythema or pruritus may be present, as well as involvement of paranasal and retroauricular regions and external ear canal.
- **Therapy:** Medicated "dandruff" shampoos with zinc pyrithione, selenium sulfide, climbazole, octopirox, ketoconazole, and/or tar. Patients should be encouraged to switch between shampoos to reduce tachyphylaxis (product not working after repeated use).

Oily Scalp

- **Synonym:** Seborrhoea oleosa.
- **Clinical features:** Likely a variant of seborrheic dermatitis. Patients have very oily skin and hair; often associated with androgenetic alopecia, as androgens stimulate sebum production.
- **Therapy:** Keep hairs cut short, same shampoos as above; if insufficient, use topical estrogens in alcoholic vehicle.

Seborrheic Dermatitis

- In our view, both of the above conditions are closely related to seborrheic dermatitis, a combination inflammatory condition that overlaps with psoriasis.
  - ***Note:*** Treating seemingly minor degrees of scalp inflammation (such as mild seborrheic dermatitis) is essential in managing hair loss, because inflammation causes a telogen shift and thus exacerbates the hair loss.

32 Diseases of the Nails

32.1 Introduction

Anatomy (Fig. 32.1)

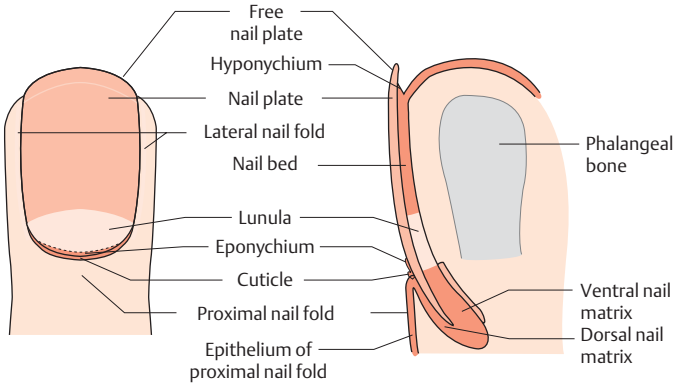


Fig. 32.1 · Anatomy of the nail apparatus.

Components of the Nail

- **Epidermis of dorsal nail fold:** Skin at proximal end of nail; folded upon itself.
- **Cuticle:** Sheet of cells that seals proximal nail fold.
- **Nail matrix:** Epithelium that keratinizes without granular layer (onycholemmal keratinization); the lunula is the most distal aspect of the nail matrix, visible through the nail plate.
- **Nail bed:** Produces a thin sheet of parakeratotic keratinocytes attached to deep surface of nail plate; perhaps helps in attachment, which is also facilitated by a system of ridges and furrows (zipper effect).
- **Hyponychium:** Skin at point of separation of nail plate from nail bed; lacks dermatoglyphics.

  Note: Nails grow slowly; replacement requires 6–12 months for fingernails and 12–18 months for toenails. Thus any therapeutic effects on the nails are not easily noticed, and treatment requires much patience on the part of physician and patient alike.

Common nail abnormalities (Fig. 32.2)

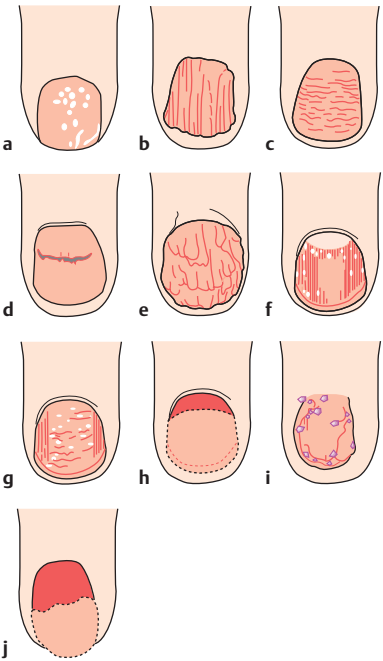


Fig. 32.2 · **Common nail changes. a** Pits. **b** Longitudinal grooves. **c** Transverse grooves. **d** Beau lines. **e** Trachyonychia. **f** Punctate leukonychia. **g** Longitudinal leukonychia. **h** Onychoschisis. **i** Lichen planus nail. **j** Distal onycholysis.

32.2 Congenital Nail Anomalies

Pachyonychia Congenita

- **MIM codes:** 167200; 167210; 260130.
- **Definition:** Group of genodermatoses involving keratin mutations with thickened nails and variable associated findings; pachys means thick.
- **Pathogenesis:** Two well established types:
  - Jadassohn–Lewandowsky type (PC1): Mutations in keratins 16 and 6A.
  - Jackson–Lawler type (PC2): Mutations in keratins 17 and 6B.
- **Clinical features:** Thickened and friable finger and toenails; palmoplantar hyperkeratosis and often hyperhidrosis. PC1 patients have oral leukokeratosis; PC2 patients have steatocystomas, alopecia, and natal teeth. Other clinical forms very rare, poorly established.
- **Therapy:** Abrasion of nail with rotary sander; keratolytics, including high-concentration urea ointments; if severe, acitretin may produce temporary improvement.

Isolated Congenital Nail Dystrophy

- **MIM code:** 605779.
- Autosomal dominant inheritance; gene locus 17p13. Patients have thin nail plates with longitudinal grooves and sometimes koilonychia. No associated findings.

Nail–Patella Syndrome

- **Synonym:** Onycho-osteodystrophy.
- **MIM code:** 161200.
- **Definition:** Uncommon genodermatosis with nail and skeletal anomalies.
- **Pathogenesis:** Mutation in *LMX1B* gene at 9q34.1 coding for LIM homeo domain, a growth control gene important in dorsa–ventral patterning of the limbs.
- **Clinical features:**
  - Dystrophic nails; triangular lunulae; longitudinal grooves, splitting and even anonychia (complete or partial); worse on thumbs, which are sometimes exclusively involved.
  - Skeletal findings include absent or hypoplastic patellas (seen on prenatal ultrasonography), which lead to unstable knees; also abnormal iliac horns, scapulas, and elbows. 25–40% have progressive nephropathy and some require dialysis or transplantation.
- **Therapy:** None for nail findings.

Other Genodermatoses with Nail Anomalies

Many other genodermatoses may have abnormal nails. Examples include:
- Non-bullous congenital ichthyosiform erythroderma.
- Darier disease.
- Hailey–Hailey disease.
- Hidrotic ectodermal dysplasia.
- Focal dermal hypoplasia.
- Junctional and dystrophic forms of epidermolysis bullosa.
- Dyskeratosis congenita.

Other Inherited Nail Anomalies

- **Pitted nails**, as well as longitudinal and transverse grooves, can be inherited. Diagnosis made when present early in life and with positive family history, as all are most often acquired.
- Various forms of **anonychia:** Partial or complete absence of nail from birth (In contrast, **onychotrophy** should be reserved for nails that are initially normal and then become thinned or even lost.).
  - ***Note:*** Anonychia is associated with a wide variety of ectodermal dysplasia syndromes. Always look for associated hair, tooth, and skin findings.

32.3 Nail Apparatus Infections

Acute Paronychia

- **Definition:** Acute infection of nail fold.
- **Pathogenesis:** Most often bacterial infection, facilitated by damage to cuticle; less often herpes simplex; rarely iatrogenic (patients receiving systemic retinoids).

- **Clinical features:**
  - Painful swelling of proximal or lateral nail fold region; cuticle usually missing. When staphylococcal, can be bullous (*bulla repens*) and extend under the nail.
  - *Herpetic whitlow:* Intensely painful swelling; usually with blisters; if child, often with oral herpetic infection and thumbsucking; in adults, formerly common in dentists, today rare.
- **Diagnostic approach:** Culture and sensitivity for bacteria; direct immunofluorescence test for herpes simplex virus.
- **Differential diagnosis:** Felon or panaritium refers to a deeper digital infection, often following puncture injury (human or cat bite, trauma). Has potential to spread along fascial planes and tendon sheaths, so requires management by hand surgeon.
- **Therapy:** If bacterial, incision and drainage; systemic antibiotics; if viral, no manipulation, systemic antivirals.

Blistering Dactylitis

- **Definition:** Streptococcal infection of fingertips.
- **Pathogenesis:** No explanation for limited localization of infection.
- **Clinical features:** Patients present with asymptomatic distal digits that are swollen and may evolve with blisters. More proximal involvement also possible. Most common in children.
- **Differential diagnosis:** Important to distinguish from paronychia or other nail fold infection because of rapid response to antibiotics.
- **Therapy:** Oral penicillin or other antistreptococcal antibiotics. Blisters can be drained.

Chronic Paronychia

- **Definition:** Chronic infection of the nail fold.
- **Epidemiology:** Very common disorder, most often seen in women 30–60 years of age.
- **Pathogenesis:** The two most important factors are repeated exposure to water and a damaged cuticle. The usual causative agent is *Candida albicans*; secondary infection with *Staphylococcus aureus* and *Pseudomonas aeruginosa* (dark nail) also occurs.
- **Clinical features:** Thumb and index finger are most often involved. Usually starts as slight swelling of proximal nailfold, then loss of cuticle and discharge of pus from under the nailfold. Once the cuticle is damaged, water, irritants, and microorganisms all cause trouble.
- **Diagnostic approach:** Smears for culture and sensitivity; search for both bacteria and yeast; secondary contaminants common.
- **Therapy:** Treatment of chronic paronychia is difficult, requiring patience on the part of both patient and physician. Important steps include:
  - Reducing exposure to moisture and other irritating factors. Elimination is impossible for domestic workers, and difficult in many industrial settings.
  - Protection of nail fold:
    - Gloves, ideally washable cotton gloves underneath rubber gloves.
    - Disposable vinyl gloves when working with fruits and vegetables.
    - No direct contact with cleaning fluids, solvents, paints.
    - After exposure, wash hands with mild soap, rinse extensively.
    - Do not manipulate cuticle.
    - In the evenings, apply thick ointment to cuticle area.

- Use topical antimycotic agents q.i.d. and after exposure; ointments adhere better but solutions penetrate better; let patient try both. If bacterial infection is identified, then topical antibiotics.
- Bacterial infections may require culture-directed systemic antibiotics; systemic antimycotic agents seldom needed.

Onychomycosis

- **Definition:** Fungal infection of the nail apparatus.
- **Epidemiology:** 20–30% of adults >40 years of age have onychomycosis, usually involving toenails.
- **Pathogenesis:** Dermatophytes are most common cause (>80%) (*tinea unguium*) but also yeasts (8%) and molds (6%).
  Caution: If patient is young and has multiple or severe candidal infections of nail folds and nails, think of chronic mucocutaneous candidiasis or other immune defects.
- **Clinical features:** Three common clinical patterns can be seen:
  - *Distal subungual onychomycosis:* Most common form; the fungus penetrates the hyponychium and cross along the ventral nail surface, causing onycholysis and crumbling. Entire nail can become involved (Fig. 32.**3**).

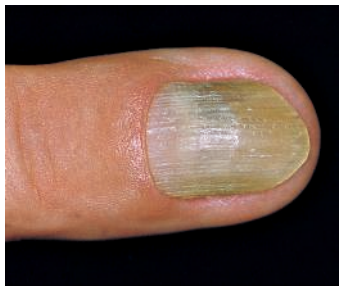


Fig. 32.**3** · Onychomycosis caused by a mold.

  - *Superficial white onychomycosis:* Infection of dorsal surface of nail plate causing scaly white spots.
  - *Proximal subungual onychomycosis:* Penetration occurs at proximal nail fold, leading to severe nail dystrophy with diffuse involvement.
- **Diagnostic approach:** Clippings from dystrophic nail for microscopic examination; periodic acid–Schiff (PAS) staining of histologic sections both easier and more effective than KOH examination. Culture of nail is gold standard.
- **Differential diagnosis:** Psoriasis, trauma.
- **Therapy:**
  - Topical therapy (antifungal nail polish) only suitable for superficial, minimal disease.
  - Systemic antifungal agents offer the best chance of cure:
    - Terbinafine for anthrophilic dermatophytes: 250 mg daily for 2 weeks.
    - Fluconazole for yeasts and dermatophytes: 150 mg weekly for 3–6 months.
    - Itraconazole for yeast, molds and mixed infections: 200 mg daily for 3 months or 200 mg b.i.d. for 7 days, then 21 days vacation; repeat for total of three or four courses.

Note: There are many other regimens and recommendations; the three listed above are clearly the best agents, and we have found these regimens most effective.

- In Germany, shoes are treated with formaldehyde solutions in sealed plastic bags for several days to reduce risk of re-infection.
- Nail removal almost never needed. Surgical removal painful and may damage matrix, leading to permanently dystrophic, susceptible nails. In addition, patients perceive nail removal as a cure, which it is not.
- If a patient cannot tolerate systemic therapy, then the nail can be removed by softening with a 40% urea ointment (p. 697) for a week followed by extraction and treatment with topical antimycotic agents. Once a nail starts to form, topical antifungal agents should be applied.
- Nail polish can be used without problems.

Note: The biggest problem in treating onychomycosis is recurrence. There are many possible explanations:

- Reinfection from shoes, environment (swimming pools, saunas), or other individuals.
- Biological predisposing factors (impaired immunity, anatomic disturbances such as overlapping or tightly compressed toes).
- Persistent microorganisms "hiding" from the systemic agents.
- In any event, it is wise to warn patient about likelihood of recurrence (at least 50%) and never promise a cure. In addition, the chance of cure drops with age.

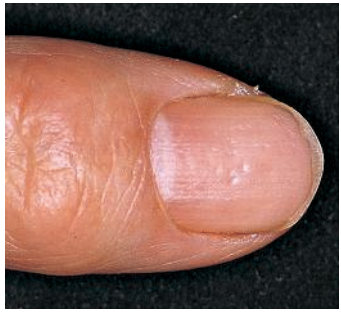
32.4 Acquired Nail Changes

Onychodystrophy

- **Definition:** Generic term for any change in color, texture or structure of nails. In addition to distorted growth, other common findings include pits, ridges, and loss of sheen (Fig. 32.**4 a**).
- **Pathogenesis:** Common causes of onychodystrophy include:.
  - Trauma.
  - Nail biting.
  - Nervous tic or other manipulation of nail or cuticle.
  - Postinflammatory (chronic dermatitis or paronychia).
  - Psoriasis (subungual debris, nail pits, oil spots).
  - Lichen planus (atrophy of nail plate, sometimes trachyonychia).
  - Ischemic vascular disease.

Leukonychia

- **Definition:** White discoloration of nail caused by alteration of light reflection because of defective keratinization.
- **Clinical features:** Many forms (Fig. 32.**4 b**), including:
  - *Leukonychia punctata:* Very common; more often dominant hand; probably microtrauma.
  - *Total leukonychia:* Rare, may be genetic; occasionally traumatic (exposure to strong acids).
  - *Striate leukonychia:* Longitudinal white bands may reflect disorder of keratinization (Darier or Hailey–Hailey disease) or be traumatic.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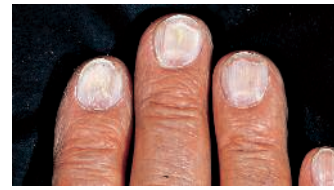
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Fig. 32.4 · **a** Pitted nails. **b** Leukonychia.

- *Transverse leukonychia:*
  - Transverse white bands usually from trauma (typist's nails in the past, excessive manicuring, picking at proximal nail fold).
  - Mees lines: White lines from nail matrix affects of high fever or toxic exposure (arsenic).

  Note: Isolated longitudinal leukonychia may reflect an underlying nail bed tumor.
- *Apparent leukonychia* is the result of nail bed changes in vascularization or onycholysis. The nail itself is not altered:
  - *Terry nail:* White nail seen with cirrhosis.
  - *Muehrcke nail:* White bands in hypoalbuminemia.
  - *Lindsay nail (half and half nail):* Proximal whiteness in uremia.
  - *Distal onycholysis:* Most common cause of distal leukonychia.

► **Therapy:** Other than eliminating underlying cause, no treatment is possible.

Trachyonychia

► **Synonym:** Twenty-nail dystrophy; trachys means rough.
► **MIM code:** 161050.
► **Definition:** Uncommon congenital nail dystrophy with autosomal dominant inheritance.
► **Clinical features:** All nails have longitudinal grooves, are dull, fragile, and have adherent scales. Onset in early childhood.

Note: Involvement of one or several nails can occur in psoriasis, lichen planus, alopecia areata, or sporadically.

► **Therapy:** No effective therapy; most patients improve with time.

Median Nail Dystrophy

► Longitudinal central defect in thumb nail, often bilateral, may be associated with enlarged lunula. Defect may be feathered or branched. Presumed posttraumatic. No effective therapy.

Beau Lines

- **Definition:** Transverse lines or grooves in nail.
- **Pathogenesis:** Causes include trauma, skin diseases (atopic dermatitis), systemic illnesses (hepatitis, pellagra, acute lupus erythematosus), medications (chemotherapy)—in sum, anything that can disturb nail matrix.
- **Clinical features:** The grooves or lines move distally; the distance from the nail fold lets one assess the time of trauma. In cancer chemotherapy patients, the ridges sometime mirror the multiple courses of chemotherapy.

Onycholysis

- **Definition:** Separation of nail from nailbed.
- **Pathogenesis:** Causes include psoriasis, dermatitis, fungal infections; medications (for example *photo-onycholysis* from tetracyclines or psoralens), thyroid disease, other metabolic disturbances; rarely inherited.
  - *Idiopathic onycholysis* is most common among women; painless separation of nail without apparent cause. Typically, the distal third separates and underlying nail bed becomes darker and thickened.
- **Diagnostic approach:** Fungal culture to exclude distal subungual onycholysis.
- **Therapy:** Cut nail very short to reduce leverage encouraging separation; even in absence of positive studies, apply antifungal solution b.i.d. Usually self-limited process.

Onychogryphosis

- **Definition:** Thickened, distorted, claw-like nail.
- **Pathogenesis:** Usually in elderly; factors include trauma, poorly fitting shoes, neglect, impaired vascular supply, onychomycosis.
- **Clinical features:** Most often great toes; nails dramatically thickened and claw-like (Fig. 32.**5 a**).
- **Therapy:** Removal of nail using urea paste; if peripheral circulation is intact, surgical removal and matrix destruction is another possibility. Then, roomy footwear and routine clipping.

Ingrown Nail

- **Synonym:** Unguis incarnatus.
- **Definition:** Penetration of nail plate into tissue of lateral nail fold.
- **Pathogenesis:** Almost always involves great toes. Causes include congenital malformation of nail (pincer nail), improper trimming, tightly fitting shoes, and hy-

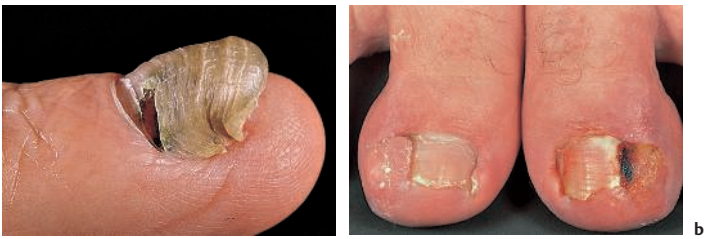


Fig. 32.**5** · **a** Onychogryposis. **b** Ingrown toenails.

pertrophy of the lateral lip of the great toe because of pressure from an overlapping second toe.
- **Clinical features:** Distorted nail with swelling, pain, and granulation tissue along the lateral nail fold (Fig. 32.**5 b**).
- **Therapy:**
  - *Mild cases:* Eliminate pressure, trim nail; topical antiseptics as foot soaks or on small piece of cotton wool pushed under affected nail.
  - *Moderate cases:* May benefit from nail brace, shifting pressure away from lateral aspects; applied by podiatrist.
  - *Severe cases:* Emmert procedure, where lateral nail fold is excised and lateral aspect of nail matrix destroyed.

Clubbing

- **Synonyms:** Hippocratic nails, drumstick fingers.
- **Definition:** Thickened distal digits with rounded nails; first described by Hippocrates.
- **Pathogenesis:** Most often associated with chronic pulmonary disease, but can reflect wide variety of underlying disturbances. Acquired clubbing almost always means systemic disease.
  - *Pachydermoperiostosis* (*primary hypertrophic osteoarthropathy*, *Touraine–Solente–Golé syndrome*): Combination of thickened skin of the scalp (cutis verticis gyrata), hyperhidrosis, periosteitis, enlarged hands and feet, and clubbing.
  - *Hypertrophic pulmonary osteoarthropathy* (*Marie–Bamberger syndrome*): Combination of distal osteitis and clubbing secondary to chronic cardiac or pulmonary disease.
- **Clinical features:** The tip of the digit is swollen and the nail is curved over the end. *Lovibond angle* (the angle between the nail and the nail bed) is $> 180°$.
- **Therapy:** Treat underlying disease, sometimes nails also improve.

Koilonychia

- **Definition:** Spoon-shaped nails.
- **Pathogenesis:** Many causes: normal variant in infants; in adults associated with iron deficiency (Plummer–Vinson syndrome), other deficiencies, occupational trauma, impaired circulation in elderly.
- **Clinical features:** Reverse of clubbing; the nail is depressed in its mid-portion and then elevated again distally.
- **Therapy:** Treat underlying diseases; biotin 5 mg daily is frequently tried in Germany.

Yellow Nail Syndrome

- **MIM code:** 153300.
- **Definition:** Triad of primary lymphedema, bronchopulmonary disease, and yellow nails.
- **Pathogenesis:** Mutation in forkhead family transcription factor MFH1 (*FOXC2*); autosomal dominant inheritance; overlaps with other forms of lymphedema caused by mutations in same gene.
- **Clinical features:** Nails are slow-growing, overly curved and yellow, often with onychodystrophy. Lymphedema and bronchiectasis are associated findings.
- **Therapy:** Prompt attention to pulmonary problems, compression for lymphedema; nails are least problem.

Nail Tumors

- The list of nail tumors is long. They can cause longitudinal discoloration or deformations.
- Examples include wart, digital mucous cyst, pyogenic granuloma, glomus tumor, fibroma, subungual exostosis, subungual epidermoid cyst, enchondroma, Bowen disease, keratoacanthoma, squamous cell carcinoma, melanocytic nevus, acral-lentiginous malignant melanoma.

Caution: Subungual malignant melanoma (Fig. 32.**6**) is often diagnosed too late; always think of the possibility when a longitudinal dark streak appears in an adult nail. It is difficult to distinguish between a streak caused by a nevus and that from a melanoma; often an excisional biopsy is needed in adults. In children who are developing nevi elsewhere, one can usually assume the streak is from another nevus. When the pigment extends to the nail fold or finger tip (*Hutchinson sign*), melanoma is probable. Dermatoscopy is also helpful. The main differential diagnostic consideration is a subungual hematoma, which can almost always be identified with dermatoscopy.

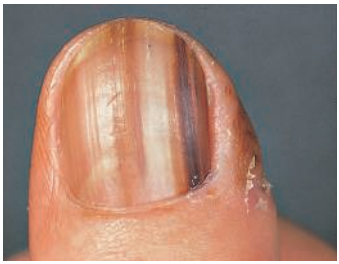


Fig. 32.**6** · Subungual malignant melanoma.

33 Disorders of Sweat Glands

Hyperhidrosis

- **Definition:** Increased eccrine sweating.
- **Classification:**
  - *Emotional (cortical) hyperhidrosis:* Usually localized to axillae, groin, palms, and soles.
  - *Thermoregulatory (hypothalamic) hyperhidrosis:* Usually diffuse, such as sweating when hot or active, or with variety of metabolic triggers, infections, vascular or neurological diseases.
  - *Gustatory hyperhidrosis:* Reflex hyperhidrosis following eating or other sensory stimulation; can be generalized but most often localized to distribution of auriculotemporal nerve following injury or parotid gland surgery.
- **Clinical features:** Hyperhidrosis causes a variety of problems. "Sweaters" are unable to work with metals and often avoid social contacts.
- **Diagnostic approach:** Diagnostic usually made easily on history; starch iodide or gravimetric testing can be used to monitor therapy.
- **Differential diagnosis:** Exclude underlying diseases (diabetes mellitus, hyperthyroidism, pheochromocytoma, and many others) that can cause hyperhidrosis.
- **Therapy:**
  - *Aluminum salts:*
    - Extra-strength ordinary antiperspirants.
    - 15–20% aluminum chloride solution or compounded mixture (15.00% $AlCl_3.6H_2O$, 2.50% hydroxyethyl cellulose to thicken, 82.5% distilled water).
    - Apply to axillae each evening for 5 nights; rinse in morning; then use 1–2×weekly. Main problem is irritation; can discolor fabrics. Do not use immediately after shaving. For palms and soles, can use 30%.
  - T*ap water iontophoresis:* 10–15 mA; easier for palms and soles.
  - *Botulinum toxin injections:* Effective for axillae, as well as palms and soles, but far less painful in axillae.
  - *Surgery (only for axillae):* Subcutaneous curettage of sweat glands, suction removal or excision; sympathetectomy is last resort.

Miliaria

- **Definition:** Erythematous papules associated with sweat duct occlusion following heat exposure.
- **Epidemiology:** Miliaria are most common in first week of life as infant adjusts to environment; also occur in any age with excessive heat, sweating, occlusion, or combinations thereof.
- **Pathogenesis:** The eccrine sweat pore become macerated and then occludes the duct. This leads to superficial clear vesicles (*miliaria crystallina)* or deep, more painful red papules or nodules (*miliaria rubra*). Most common sites trunk, neck; in occluded areas (sporting equipment).
- **Differential diagnosis:** Usually mistaken for folliculitis or one of its variants. *Neutrophilic eccrine hidradenitis* is closely related, occurs with chemotherapy or episodically in children; extreme miliaria with inflammatory response.
- **Therapy:** Cooling measures, zinc oxide lotion.

Bromhidrosis

- Unpleasant odor usually caused by axillary sweat. Interaction of apocrine and eccrine sweat probably responsible. Factors such as medications (DMSO), garlic, or amino acid disorders affect only eccrine sweat. Co-factors include improper hygiene, secondary bacterial and fungal infections, as well as nonabsorbent clothing. Mainstay of treatment is to reduce sweating, as for hypohidrosis.

Pseudobromhidrosis

- Delusion of unpleasant body odor, when none is present. A monosymptomatic delusion, similar to acarophobia. Very difficult to manage; approach only in cooperation with psychiatry.

Chromhidrosis

- Discoloration of eccrine or apocrine sweat. Normal eccrine sweat is always colorless; discoloration is the result of colored salts on the skin (copper miners), infections with chromogenic microorganisms (*Corynebacterium*), or other subtle exposure to dyes. Apocrine sweat, on the other hand, is rich in lipofuscin and can be discolored intrinsically, or secondary to metabolic diseases (ochronosis) or medications (clofazimine).

Fox–Fordyce Disease

- **Definition:** Pruritic papules in axillae and anogenital region.
- **Pathogenesis:** Uncommon disease, almost limited to women; probably apocrine miliaria with plugging of follicle and secondary inflammation.
- **Clinical features:** Intensely pruritic papules in axillae and inguinal region.
- **Differential diagnosis:** Folliculitis.
- **Therapy:** No good treatment; some patients improve with oral contraceptives; high-potency topical corticosteroids may suppress itch. If small area affected, excision can be tried.

34 Diseases of Sebaceous Glands

34.1 Acne

- **Definition:** Multifactorial disease primarily of teenagers with follicular plugging and inflammation.
- **Epidemiology:** Most common skin disease; affects almost every individual. Most commonly in puberty, but special forms seen in other age ranges.
- **Pathogenesis:** Many different factors play a role:
  - Altered hormonal status with increased androgens in men and increased androgenic properties of progesterone and other hormones in women.
  - Follicular keratinization: Hyperkeratotic plugs form in follicle opening.
  - Hyperplasia of sebaceous glands with increased sebum production, secondary to hormonal changes.
  - Colonization of follicles by *Propionibacterium acnes*, which produces lipases splitting free fatty acids and releasing inflammatory mediators.
- **Clinical features:**
  - *Acne vulgaris:* Traditionally divided into two overlapping subcategories:
    - *Acne comedonica:* Primarily open comedones (whiteheads) and closed comedones (blackheads). Comedones develop only in sebaceous follicles concentrated on face, chest, and mid-back, which have small hairs and large sebaceous glands. Black color is melanin from follicle, not dirt. Most common sites for comedones are forehead, cheeks, perioral region (Fig. 34.1 **a, b**).

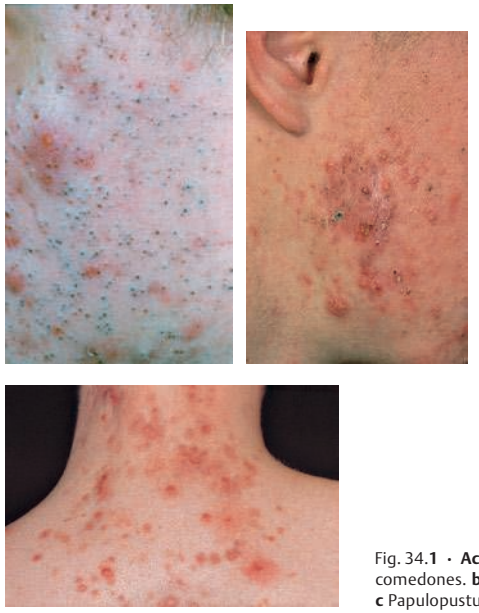


Fig. 34.1 · **Acne vulgaris. a** Primarily comedones. **b** Comedones and pustules. **c** Papulopustular stage.

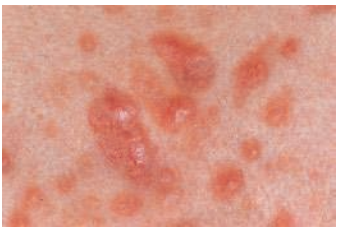
– *Acne papulopustulosa:* Follicular pustules or inflammatory papules; comedones rupture, neutrophils are attracted, and process accelerated (Fig. 34.**1 c**).

► *Acne variants with marked inflammation:*

– *Acne conglobata:* Features inflammatory nodules and pseudocysts with marked scarring; typical sites are face, sternum, and back in young men (Fig. 34.**2 a**).
– *SAPHO syndrome:* **S**ynovitis, **a**cne conglobata, **p**almoplantar pustulosis, **h**yperostosis, and **o**steitis; sternoclavicular joints most common bony sites.
– *Acne inversa:* Furunculoid lesions in axilla, groin, perianal region, and submammary area with sinus tracts and fistulas.

Note: Almost all "chronic furunculosis" of these sites is acne, not recurrent bacterial infections. The old name of *hidradenitis suppurativa* is no longer appropriate.

– *Acne tetrad:* Combination of acne conglobata, acne inversa, perifolliculitis capitis abscedens et suffodiens (sterile dissecting folliculitis of scalp), and pilonidal sinus; more common in men.
– *Acne fulminans:* Sudden severe acne with systemic signs and symptoms (fever, leukocytosis, osteomyelitis, pericarditis); patients present with severe acne conglobata with necrosis of lesions leaving gelatinous debris (Fig. 34.**2 b**); often tender sternoclavicular joints; treated initially with high-dose corticosteroids to control inflammation; then retinoids.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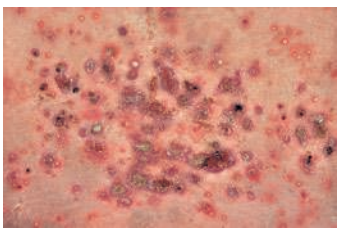
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Fig. 34.**2** · **a** Acne conglobata with cysts. **b** Acne fulminans.

• *Other special forms of acne:*

– *Mallorca acne* (*acne aestivalis*)*:* Acne flare of acne following sun intense sun exposure; often winter vacations among Europeans; comedones produced by combination of heat, sweating, and occlusive sun screens; probably variant of polymorphous light eruption (p. 300).
– *Contact acne:* Caused by comedogenic makeup and other skin care products, as well as tars and other industrial contacts.
– *Chloracne:* Systemic or topical exposure to halogenated hydrocarbons causes severe comedonal acne, often permanent, as well as liver disease; mass industrial exposure (Seveso accident), military use (Agent Orange in Vietnam war), or intentional poisoning (Ukrainian presidential election in 2005).
– *Acne neonatorum:* Acne as a result of elevated hormone levels in utero with sebaceous gland hyperplasia; resolves spontaneously.
– *Acne infantum:* Onset age 3–6 months; caused by elevated levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone; always rule out endocrine disorder; check free and total testosterone, DHEA, DHEAS, LH, FSH.

- *Acne excoriée des jeunes filles:* Mild acne in young women with overaggressive self-manipulation leading to excoriations and erosions.
- *Mechanical acne:* Head bands, shoulder pads, and many other items causing occlusion and pressure can induce comedones.
- *Late-onset acne* (*acne tarda*): Onset of acne in women well past puberty; always exclude hyperprolactinemia and polycystic ovary syndrome.
- *Localized acne:* Two situations where acne can be limited to patch of nonfacial skin as variant of epidermal nevus (p. 412):
  Munro nevus: Mosaic defect in FGFR2 with localized acne
  Becker nevus: Androgen-sensitive epidermal mosaic, often with hypertrichosis and localized acne.

• *Medication-induced acne:* Details are given in Table 34.**1**. In almost all instances, the reaction is acneiform, with follicular papules or pustules but not comedones.

Table 34.1 · **Medications causing acne**

Category	Examples
Hormones	Corticosteroids, androgens, oral contraceptives (progesterone dominant), body-building steroids
Antiepileptic medications	Trimethadione, phenytoin, and related compounds
Halogens	Compounds with bromides, iodides
Antabuse	Disulfiram
Anti-TB drugs	Isoniazid, ethionamide, rifampicin
Psychopharmaceuticals	Lithium, amitriptyline, barbiturates
Immunosuppressive agents	Cyclosporine
Monoclonal antibodies	Cetuximab (EGFR inhibitor)
Thyroid-suppressive agents	Thiouracil
Antibiotics	Tetracyclines (rarely, but then a clinical problem)

▶ ***Note:*** Not all diseases with comedones are acne. *Favre–Racouchot disease* (nodular elastosis with cysts and comedones) is caused by chronic UV exposure but always has comedones without inflammation. *Nevus comedonicus* is a form of epidermal nevus with comedones but no inflammation. In addition, not all diseases with acne in their name belong in the acne family. *Acne urticata* is facial excoriations without acne, while *acne varioliformis*is a form of folliculitis limited to the frontal hairline.

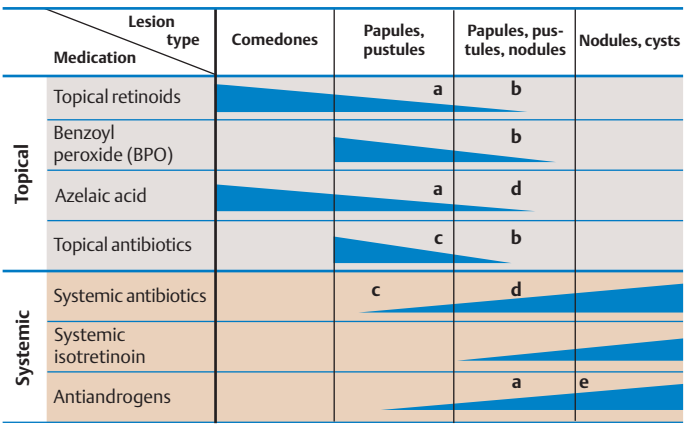
▶ **Prognosis:** The course and prognosis of acne is highly variable. It is impossible to look at a patient and say "You will have trouble for only a few months." All acne causes scars, but the more promptly the disease is treated, the less severe the scarring is likely to be. It is a very emotionally distressing disease, especially for teenagers already at a difficult stage of life. Few groups of patients are more grateful than acne patients, who usually respond promptly to a variety of measures but then require long-term treatment and support.

▶ **Therapy:** The main principle of acne therapy is that there are many options; the treatment plan should be adjusted to the severity and course of the acne. Combination therapy is usually required. Our therapeutic approach is summarized in Table 34.**2** and Fig. 34.**3**.

Table 34.2 · Choice of acne treatment based on clinical features

	Substance	Comedones	Seborrhea	Pustules	Inflammation
Topical	Azelaic acid	++	–	++	+
	Benzoyl peroxide	(+)	–	+++	(+)
	Adapalene	+++	–	(+)	++
	Tretinoin	+++	–	(+)	–
	Antibiotics	(+)	–	+++	+
Systemic	Tetracycline	(++)	–	+++	+
	Isotretinoin	+++	+++	(+++)	++
	Antiandrogens	++	+	(+)	?

– = no effect; + = effective; ++ = very effective; +++ = extremely effective; (+) = indirect effect;?= unclear effect.



a = Combine with BPO or topical antibiotics
b = Combine with systemic antibiotics or antiandrogens
c = Combine with topical retinoids
d = Combine with antiandrogens
e = Combine with systemic antibiotics and isotretinoin

Fig. 34.**3** · Strategies for acne therapy (after Orfanos and Garbe).

- *General measures:* Always discuss the following points with patients and parents (if patient agrees):
  - Diet is not a major factor. Patients should eat what they enjoy.
  - Lack of cleanliness is not the crucial issue. Gentle mild cleansing twice daily is completely adequate. There is no reason to buy expensive cleansers. Abrasive cleansers can be too irritating.

- *Topical therapy:*
  - *Topical retinoids:* Far and away the best treatment for comedones. Since all acne lesions develop from comedones, almost every acne patient benefits from topical retinoids. Several forms are available; the most widely used is tretinoin, but isotretinoin and adapalene are also available and less irritating. Tretinoin comes in various concentrations as a cream and gel. It must cause a bit of irritation to be effective. It should be used in the evening because it is slightly photosensitizing. Easily combined with other products for morning use.

Caution: Acne almost always flares as topical retinoid therapy is started. Always warn the patient.

  - Benzoyl peroxide 5–10%: Also comes as wash, cream, water-based gel, or alcoholic gel; can be used as monotherapy b.i.d. or mornings in combination with topical retinoids; bleaches hair and clothes, slightly irritating; no resistance of microorganisms.
  - *Topical antibiotics:* Antibiotics are used to inhibit *Propionibacterium acnes* and reduce the lipolytic acne, decreasing follicular irritation. The most widely used topical antibiotics are erythromycin and clindamycin. Topical usage avoids systemic side effects, but antibiotic resistance does develop, not only by *Propionibacterium acnes* but also by other organisms in the patient's environment. Erythromycin is available as combination product with zinc or isotretinoin.
  - *Azelaic acid 20%:* Effective against comedones and inflammation; almost without irritation; good choice for sensitive skin.

Note: No topical agent or regimen effectively reduces sebum production.

- *Systemic therapy:*
  - *Antibiotics:* Usual choice is tetracyclines, generally minocycline 50–100 mg daily (low phototoxicity, occasional hypersensitivity reactions) or doxycycline 50–100 mg daily (more photosensitivity). Both are much easier to administer than ordinary tetracyclines. Other problems include staining of erupting teeth (do not use under age 12), and selection of resistant bacterial strains. May cause gram-negative folliculitis with painful pustules and nodules on mid-face and chin. Alternatives include erythromycin and other macrolides. Widely used for many years, but now much more reluctance; typical course 2–3 months.
  - *Hormones:* Both estrogens and antiandrogens can play a positive role in female patients. Usually combination employed.
  - *Isotretinoin* is the only sebostasis agent, inhibits comedo formation and has immunomodulatory actions. It is indicated for severe acne, but highly effective in all forms. Usual dosage 0.5–1.0 mg/kg for 3–6 months. Detailed recommendations (p. 622).

Caution: Isotretinoin is teratogenic. Female patients must employ effective contraception under the guidance of a gynecologist, with pregnancy testing before initiation of therapy. Do not bend the rule; assume the worst.

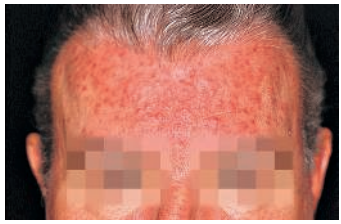
  - Other cautions include:
    Do not combine with tetracyclines because of risk of pseudotumor cerebri
    Watch for elevated cholesterol, triglycerides, and liver function tests
    Be aware of likelihood of skeletal pain in physically active patients; always question patients about sporting activities; if competitive athletes, treat in off-season.

- *Supplementary measures:*
  - Light chemical peels with α-hydroxy acids (AHA) or other mild agents are sebostatic and help with superficial scars.
  - Surgical management of scars requires individual adjustment; can include laser ablation, dermabrasion, cryotherapy, collagen injections.
  - Acne inversa usually requires surgery.

34.2 Rosacea

- **Definition:** Chronic inflammatory facial dermatosis in adults.
- **Epidemiology:** Common disorder, more often seen in fair-skinned individuals (skin types I–II, "curse of the Celts").
- **Pathogenesis:** Unclear; not related to acne despite superficial similarities as no comedones are present. Key factors include flushing (vascular reactivity) and inflammation. Genetic predisposition; other factors may include *Demodex folliculorum*.
- **Clinical features:**
  - *Stage I:*
    - Flushing; vascular dilation; triggered by alcohol, spicy foods, caffeine, nicotine, hormonal change, UV light, heat and cold. In early stages, reversible.
    - Persistent erythema; telangiectases but no comedones or pustules.
  - *Stage II:*
    - Persistent erythema, papules and pustules (Fig. 34.**4 a**). Does not respect the hairline (as does acne). Usually mid-facial; only rarely involves chest or trunk.
  - *Stage III:*
    - May develop independent of earlier stages; perhaps mediated by TGF-β.
    - Rhinophyma: swollen nose with sebaceous gland hyperplasia and fibrosis, usually red because of telangiectases (Fig. 34.**4 b**).
  - *Special variants:*
    - *Ocular rosacea:* Patients may have blepharitis, conjunctivitis, iridocyclitis, or keratoconjunctivitis without obvious rosacea; usual scenario is lid rosacea plus ocular problems (Fig. 34.**4 c**). Complain of foreign body sensation or photophobia.

      Caution: Untreated, ocular rosacea can advance to severe keratitis with corneal scarring.
    - *Rosacea fulminans* (*pyoderma faciale*): Severe inflammatory reaction, analogous to acne fulminans. Young women with sudden severe conglobate disease with necrosis but without comedones.
    - *Lupus miliaris disseminatus faciei:* Tiny brown papules periorbital region; granulomatous histology.
    - *Steroid rosacea:* Topical corticosteroids may induce a rosacea-like picture; more often they are responsible for perioral dermatitis.
- **Histology:** Biopsy rarely needed, but may show granulomatous changes including caseation; thus often confusion over relationship of rosacea and tuberculosis.
- **Diagnostic approach:** History, clinical examination.
- **Differential diagnosis:**
  - Acne is always mentioned first, but easy to tell them apart; different age groups, and rosacea has no comedones.
  - *Perioral dermatitis:* Different clinical picture but exact relationship to rosacea still unclear.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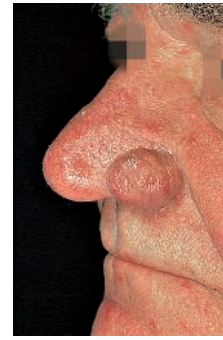
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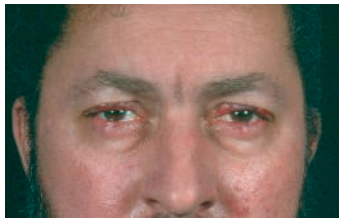
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Fig. 34.4 · **a** Rosacea. **b** Rhinophyma. **c** Ocular rosacea.

- Rosacea and seborrheic dermatitis frequently present in same patient.
- In past, relationship to tuberculids was confusing. Today granulomatous rosacea is an accepted histologic variant; lupus miliaris disseminatus faciei is regarded as periocular granulomatous rosacea and not a form of tuberculosis.
- Demodicosis often complicates rosacea; pustules may be full of mites. More controversial is primary inflammatory condition caused by *Demodex folliculorum* mimicking rosacea; if it exists, then pustules on normal skin without the underlying erythema.

Note: Always ask and ask again about the use of topical corticosteroids, a frequently overlooked trigger.

► **Therapy:**

- *Stage I:* Topical metronidazole gel; commercially available in most countries or can be compounded (p. 695). Apply b.i.d. Alternatives include topical erythromycin, which is less effective. Use sun screens; avoid triggers if any seem clinically relevant.

Caution: Topical corticosteroids are absolutely contraindicated in rosacea. They are responsible for worsening in many cases.

- *Stage II:*
  - Systemic antibiotics, usually minocycline 50 mg daily or b.i.d for 3 months. Tetracycline 250 mg q.i.d. on empty stomach for 3 months. In either case, can gradually taper dose.
  - Isotretinoin 0.2–1.0 mg/kg for 6 months; not with tetracycline.
  - Short burst of systemic corticosteroids plus isotretinoin for rosacea fulminans.
- *Stage III:* Surgical invention; debulking with scalpel, dermabrasion, or laser ablation.

34.3 Perioral Dermatitis

- **Definition:** Papular dermatitis primarily involving perioral region, with distinctive pattern.
- **Epidemiology:** Most common in young women.
- **Pathogenesis:** Controversial. Most patients present having used topical corticosteroids, which are agreed to be a causative factor. But for what condition did the patient receive the corticosteroids, and how does one explain the occasional patient who has never used corticosteroids? Two likely lines of evidence: overuse of moisturizers leads to follicular occlusion and reaction; problem worse in those with atopic diathesis.
- **Clinical features:**
  - Tiny 1–3 mm erythematous papules and pustules without comedones Fig. 34.**5**); grouped around mouth with distinctive grenz zone between vermilion and first lesions; true name *peri-perioral dermatitis*.
  - May also be periorbital or perinasal.
- **Diagnostic approach:** Clinical examination, history of corticosteroid use.
- **Differential diagnosis:** Rosacea, demodicosis, folliculitis.
- **Therapy:**
  - Absolute prohibition of topical corticosteroids.
  - ***Note:*** Explain to patient that her disease will flare initially because of "steroid withdrawal," but that she must resist the temptation to restart topical corticosteroids. This is the classic nightmare in treating perioral dermatitis—the patient has an ample supply of corticosteroids and re-employs them, with the expected flare.
  - Short course of systemic antibiotics; tetracycline or erythromycin for 6 weeks.
  - Topical immunomodulatory agents may also be helpful in early weeks.
  - Choose just one, bland moisturizer.

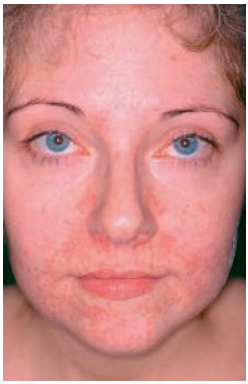


Fig. 34.**5** · Perioral dermatitis.

35 Diseases of Subcutaneous Fat

35.1 Lipodystrophy and Lipoatrophy

Overview

Definition: Group of disorders with localized or generalized changes in fat. Frequent overlaps between dystrophy and atrophy:

- *Lipodystrophy:* Includes both increase in fatty tissue, abnormal distribution of fat, or disappearance of fat.
- *Lipoatrophy:* Refers exclusively to loss or disappearance of fatty tissue.

Congenital Lipodystrophy

- **Congenital generalized lipodystrophy (CGL)** (Berardinelli–Seip syndrome); rare disorder; autosomal recessive inheritance, with two different mutations:
  - *CGL1* (MIM code 608594): mutation in *AGPAT2* at 9q34.3.
  - *CGL2* (MIM code 269700): mutation in seipin at 11q13.
  - Widespread loss of fat, extensive acanthosis nigricans, hirsutism, acromegaly, insulin resistance with extremely high insulin levels and hypertriglyceridemia.
- **Familial partial lipodystrophy (FPLD)**: Three types recognized in OMIM, although not all agree with splitting. All feature localized loss of fat with some degree of excess fat at other sites:
  - *FPLD1 (Köbberling type, MIM code 608600):* Mutation unknown. Loss of adipose tissue on extremities with normal or increased amounts on face, neck, and trunk.
  - *FPLD2 (Dunnigan type, MIM code 151660):* Mutation in lamin A/C; autosomal dominant inheritance. Patients lose fat over their limbs and trunk, developing a pseudomuscular appearance, but at same time have increased deposits on the neck and sometimes labia. They are insulin-resistant and usually develop diabetes mellitus and elevated triglycerides; acanthosis nigricans and hirsutism may also occur.
  - *FPLD3:* Similar to type 2, but with mutations in *PPARG* gene.
- **Partial progressive lipodystrophy (MIM code 608709, Barraquer–Simons syndrome):** Genetic basis unclear. Loss of fat on face, trunk, and arms, producing starved appearance, with normal distribution on buttocks and legs; have associated IgG antibody against C3 (C3 nephritogenic factor) leading to renal disease in about 50%.

Acquired Lipodystrophy

- Most common cause today is truncal and nuchal lipodystrophy in HIV/AIDS patients; etiology unclear, but in many instances secondary to highly active antiretroviral therapy (HAART).
- Buffalo hump and moon facies of Cushing syndrome are classified by some as lipodystrophy.
- Acquired generalized lipoatrophy (Lawrence syndrome) resembles Berardinelli–Seip syndrome but starts in adult life, following severe systemic illness. Very rare.
- **Localized disease:**
  - Following injections of corticosteroids; rarely other medications.
  - Secondary to panniculitis (inflammatory lipoatrophy).

- *Lipoatrophia semicircularis*: linear depressed bands on thighs of women; in most instances posttraumatic (tight pants, water-skiing tow ropes).
- *Lipodystrophia centrifugalis abdominalis infantilis*: Idiopathic disorder in Japanese infants with loss of subcutaneous fat starting in groin or axilla and spreading to trunk.

► **Differential diagnosis:** Sometimes it is difficult to tell which layers of skin are deficient; for example:
- Atrophoderma of Pasini–Pierini: atrophic morphea.
- Hemifacial atrophy (Parry–Romberg): extensive loss of tissue on one side of face including skin and muscle, as well as fat; also probably extreme morphea variant.

35.2 Panniculitis

Overview

► **Definition:** Inflammation of the subcutaneous fat.
► **Classification:** There are many different ways to classify panniculitis:
- *In order of frequency:*
  - Erythema nodosum is common.
  - All the others are extremely rare.
- *Clinically:*
  - On the shin: usually erythema nodosum.
  - On calf, above knee, or not on legs: Consider other possibilities.
- *Histologically:*
  - Septal versus lobular.
  - With or without vasculitis.

A working classification is shown in Table 35.**1**.

Table 35.1 · **Classification of panniculitis**

Septal	*Without vasculitis*	Erythema nodosum
		Connective tissue panniculitis
	With vasculitis	Superficial thrombophlebitis
		Polyarteritis nodosa
Lobular	*Without vasculitis*	Pancreatic
		Lymphoma
		Traumatic (cold, injections, injuries)
		Neonatal fat necrosis
		α_1-Antitrypsin deficiency
		Infectious
		Lipoatrophic panniculitis (Rothman–Makai lipogranulomatosis, other variants)
		Lupus erythematosus (lupus profundus)
		Sarcoidosis
		Weber–Christian disease (idiopathic)
	With vasculitis	Erythema induratum/nodular vasculitis

► **Diagnostic approach:**
- If not erythema nodosum, do biopsy. Take a long thin ellipse through the subcutaneous fat, not a punch biopsy, and label the specimen clearly as "rule out panniculitis." Otherwise, many dermatopathology laboratories routinely trim the fat from specimens.
- If the lesion drains oily liquid when incised, suspect liquefying panniculitis, which almost always means α_1-antitrypsin deficiency or artifact.
- Many special clues from the histology:
  - Lobular vs. septal; vasculitis or not.
  - Plasma cells: lupus erythematosus.
  - Saponification: pancreatic disease.
  - Foreign bodies: factitious disease.
  - Organisms: infections.
  - Atypical lymphocytes: lymphoma.

► ***Note:*** Always consider the possible triggers and underlying diseases when confronted with panniculitis. Few disorders display more interplay between the skin and systemic disease.

Erythema Nodosum

► **Definition:** Self-limited panniculitis with sudden onset of red-brown, bruise-like patches and nodules on shins; usually reactive.

► **Epidemiology:** Female:male ratio 3–5:1; typically young adults.

► **Pathogenesis:** Triggers include:
- *Medications:* Oral contraceptives, penicillin, other antibiotics, salicylates, bromides, iodides, immunotherapy agents (vaccines, hyposensitization regimens).
- *Infections:*
  - *Bacteria:* Most common are streptococcal and mycobacterial infections, as well as brucellosis, yersiniosis, and chlamydial infections (psittacosis), but almost every bacterial infection has been associated with erythema nodosum. *Erythema nodosum leprosum* is a late reactive stage and not true erythema nodosum.
  - *Deep fungal:* Most patients with coccidioidomycosis or histoplasmosis have erythema nodosum; also with blastomycosis and sporotrichosis.

! ***Caution:*** Always take travel history. If a young adult returns from holidays in southwestern desert areas of the USA (California, Arizona, New Mexico) and has erythema nodosum, the risk of acute coccidioidomycosis is considerable. If the patient is pregnant and not treated, the risk to the child is also significant.
  - *Viral:* Hepatitis B, hepatitis C.
- *Malignant diseases:* Rare marker for Hodgkin lymphoma, other lymphomas, leukemias, and following radiation therapy.
- *Chronic inflammatory diseases:* Inflammatory bowel disease, Behçet syndrome, and Reiter syndrome can all present with erythema nodosum.
- *Sarcoidosis,* especially *Löfgren syndrome:* Sarcoidosis with hilar lymphadenopathy, arthritis, and erythema nodosum.
- *Pregnancy*.

► **Clinical features:**
- *Prodrome:* Fever, chills, perhaps joint pain; varies with trigger.
- *Skin findings:* Usually multiple, bilateral bruise-like tender or painful nodules and plaques covered by a smooth epidermis (Fig 35.**1**). Almost always on shin; rarely thighs, arms. May be associated with continuing fever, malaise, or arthritis. Resolve after weeks.

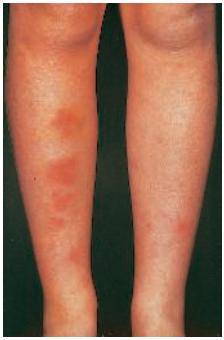


Fig. 35.**1** · Erythema nodosum.

- *Special variants:*
  - *Erythema nodosum migrans:* Multiple smaller nodules, evolve into rapidly spreading plaques with central healing. *Subacute nodular migratory panniculitis* (Vilanova–Piñol-Aquadé) is the same or similar.
  - *Erythema nodosum chronicum:* Otherwise typical lesions but persistent.
  - *Nodose erythema:* Refers to clinically atypical lesions such as those located on calves and not shins.
- **Histology:** Thickened septae, granulomas, giant cells, fat lobules relatively spared.
- **Diagnostic approach:** Examination, detailed history, screening laboratory work (streptococcal screen, pregnancy test, chest radiograph, tuberculosis skin test) and others as directed by history.
- **Differential diagnosis:** Other forms of panniculitis, Sweet syndrome, necrobiosis lipoidica, granuloma annulare, pernio (usually on feet).
- **Therapy:**
  - Compression stockings, NSAIDs; if severe, bed rest if possible (most young mothers cannot get bed rest).
  - High-potency corticosteroids under occlusion.
  - No systemic steroids, as they may mask underlying signs and symptoms; exception is acute sarcoidosis.

Erythema Induratum

- **Synonyms:** Bazin disease, nodular vasculitis.
- **Definition:** Panniculitis associated with granulomatous vasculitis involving mid-sized vessels.
- **Epidemiology:** Almost limited to adult women.
- **Pathogenesis:** Controversial; relationship to tuberculosis not firmly established. *Mycobacterium tuberculosis* DNA is rarely identified in lesions. The issue is nodular vasculitis—same clinical appearance but no evidence for tuberculosis.
- **Clinical features:** Firm nodules almost always on back of legs. Tend to ulcerate and heal with scars.
- **Histology:** Granulomatous vasculitis.
- **Differential diagnosis:** Other forms of panniculitis; erythema nodosum never ulcerates.

- **Therapy:** Compression stockings, NSAIDs; wound care if ulcerated.
  - If evidence in history or examination for tuberculosis, then consider tuberculostatic therapy.

Other Forms of Panniculitis

Most of these diseases are very rare, and many are covered elewhere in this book. Here are just a few tips:

- Both **pancreatitis** and **pancreatic neoplasms** can cause panniculitis. The pancreatic enzymes cause saponification.
- **α_1-Antitrypsin deficiency:** Consider with liquefying panniculitis, when several members of same family have panniculitis; responds to dapsone; patients should be warned about smoking and pulmonary disease.
- **Lymphoma:** Subcutaneous lymphomas are usually T-cell in origin (p. 479). Erythrophagocytosis is not uncommon. Histiocytic cytophagic panniculitis is in almost all cases subcutaneous panniculitis-like T-cell lymphoma. Rare disorders exist with virally triggered hemophagocytosis and fat involvement.
- **Trauma:** Cold panniculitis is common, ranging from popsicle panniculitis (children sucking icy desserts) of the cheeks to neonatal fat necrosis, a benign condition. Fat is a favored site for injection of materials, ranging from silicone for cosmetic enhancement to feces, urine, and even more bizarre materials to induce artifactual disease.
- True infectious panniculitis is uncommon; in most instances infections trigger erythema nodosum.
- **Lupus profundus** (p. 206): Usually signs of lupus erythematosus elsewhere, but sometimes isolated. Panniculitis plus overlying mucin or epidermal atrophy, or rich in plasma cells, should suggest lupus erythematosus.
- **Weber–Christian disease** (relapsing febrile nodular nonsuppurative panniculitis) is controversial; probably most cases reflect α_1-antitrypsin deficiency, pancreatic disease, or lymphoma. Before making this diagnosis, investigate the patient extensively and observe for at least 6 months.

36 Anogenital Diseases

36.1 Anal and Perianal Diseases

Hemorrhoids

- **Definition:** Hyperplasia of the physiologic hemorrhoidal vascular complex, which is an erectile tissue essential in maintaining rectal continence. In the USA, such hemorrhoids are referred to as internal hemorrhoids.
- **Epidemiology:** Every adult has some degree of hyperplasia of these normal structures.
- **Pathogenesis:** Factors leading to signs and symptoms of disease include chronic constipation with straining for bowel movements, genetic predisposition, low-fibre diets, and abuse of laxatives.
- **Clinical features:** Hemorrhoids are divided into four grades:
  - *Grade I:* Enlarged cushions of hemorrhoidal complex, visible on proctoscopic examination.
  - *Grade II:* Hemorrhoids can prolapse through anal canal, but retract spontaneously.
  - *Grade III:* Hemorrhoids frequently prolapse but can be repositioned.
  - *Grade IV:* Permanent anal prolapse.
- **Diagnostic approach:**
  - Careful inspection, ideally after bowel movement, and with pressing.
  - *Palpation:* Grade II can be palpated, as can thrombosed lesions.
  - Proctoscopic examination, ideally with Blond proctoscope, which has side opening into which hemorrhoids may prolapse. Routine proctoscopy can overlook hemorrhoids.

  Note: Never be content to blame rectal pain or bleeding on hemorrhoids. A complete examination is necessary to exclude other conditions, such as a carcinoma of the rectum.
- **Therapy:**
  - High-fibre diet.
  - Anal exercises; tightening anal sphincter for 10–20 seconds repeatedly several times a day, perhaps tightening against anal dilator.
  - Destruction with rubber band ligature, sclerosing solution, infrared coagulation or operation, depending on severity.

  Caution: Hemorrhoidal ointments and suppositories cannot address the underlying problem. They may provide temporary relief from pain and pruritus, but have a high risk of causing allergic contact dermatitis.

Anal Vein Thrombosis

- **Synonym:** Pile, external hemorrhoid.
- **Definition:** Sudden painful thrombosis of external anal vein.
- **Clinical features:** Blue-purple nodule, often eroded, very tender; on anal ring; often appears after defecation.
- **Therapy:** Incision and expression of clot, NSAIDs, sitz baths.

Anal Tags

- **Clinical features:** Lax, fibrotic skin folds, usually the long-term sequelae of thrombosed anal veins. They may become inflamed or irritated, as well interfering with continence.
- **Therapy:** Symptomatic lesions easily excised.

Anal Fissure

- **Definition:** Extremely painful fissure or ulcer in anal canal.
- **Pathogenesis:** Controversial; increased sphincter tone plays a role, but other factors unclear.
- **Clinical features:**
  - Fibrinous fissure or ulcer with callused border; almost always at 6 o'clock position with patient in dorsal lithotomy position.
  - Extremely tender; pain after completion of bowel movement almost unbearable; patients tend to resist bowel movements and become constipated, worsening problem.
  - Increased sphincter tone, sentinel pile (proximal hypertrophic anal papilla).
- **Therapy:**
  - Apply local anesthetic before attempting examination; sometimes injection is required.
  - Acute fissures can be painted with 1% aqueous silver nitrate solution.
  - 2% nitroglycerine ointment is sometimes helpful; can cause headaches. Apply t.i.d.–q.i.d. In theory, sphincter is relaxed and dilated.
  - Injection of botulinum toxin also appears to relax sphincter tone.
  - Chronic or unresponsive fissures must be excised; wide variety of surgical approaches available.

Perianal Dermatitis

- **Definition:** Dermatitis in perianal region; usually extremely pruritic.
- **Epidemiology:** Common; many patients do not present to physician.
- **Pathogenesis:** Many causes, including:
  - Anal incontinence with irritation of perianal skin by anal discharge.
  - Inadequate anal hygiene.
  - Allergic contact dermatitis to cleansing tissues, hemorrhoidal preparations, other medications.
- **Clinical features:** Few clues to cause on clinical examination; erythema, maceration, fine fissures. Often excoriations; some patients complain of considerable interference with work, social life, or sleep.
- **Diagnostic approach:** Look for skin disease elsewhere, complete proctologic examination, patch testing, stool examination for ova and parasites, cultures of stool and perianal skin for yeasts and dermatophytes; if disease persists, biopsy.
- **Differential diagnosis:** See summary in Table 36.**1**.
- **Therapy:** Improve hygiene, eliminate triggers, short course of mid-potency corticosteroid ointment; use zinc oxide paste for long-term protection.
  - ***Note:*** Important to discourage the patient from overenthusiastic cleansing, which can often worsen the problem and develop into a neurosis.

Table 36.1 · Differential diagnosis of perianal disease

Disease	Clinical features
Candidiasis	Macerated patches with erosions and peripheral pustules
Tinea inguinalis	Involves medial thigh, not scrotum or labia; scaly patch with prominent erythematous border
Psoriasis	Red macerated plaques without characteristic silvery scale; very difficult to diagnose without other signs of psoriasis
Seborrheic dermatitis	Look for clues elsewhere; sometimes worst in perianal region
Lichen planus	Often eroded and intensely pruritic
Lichen sclerosus	Both girls and women may have genital and perianal involvement; often hemorrhagic; in children mistaken for child abuse
Atopic dermatitis	Search for other stigmata; sometimes primarily here in adults
Contact dermatitis (allergic, toxic)	Erythema, scale, papulovesicles; appropriate history (usually hemorrhoid creams)
Other causes of anal dermatitis	Hemorrhoids, anal tags, worms, anal polyp, anal fissure, anal fistula—because of the risk of rectal carcinoma, every patient with an unclear perianal dermatitis deserves a proctologic examination
Condyloma acuminata	White papillomatous papules which can coalesce or become macerated
Extramammary Paget disease	Weeping eroded plaques, perianal or inguinal, associated with underlying adenocarcinoma in some cases
Bowen disease	Erythematous plaques; formerly common in patients who had received ionizing radiation for psoraisis
Condylomata lata	Eroded weeping broad-based plaques; perianal and intertriginous; lesion of secondary syphilis
Crohn disease	Draining sinus tracts and fistulas

Perianal Lesions

- Many of the same diseases affecting the genitalia also involve the perianal region. Always think of the possibility of rectal disease with secondary perianal problems.

Pruritus Ani

- **Definition:** Perianal pruritus without visible skin changes.
- **Pathogenesis:**
  - Most common causes are eating spicy foods and improper anal hygiene.
  - All of the conditions that cause anal dermatitis can also cause pruritus ani.
  - Other factors include pinworms, candidiasis, food allergies, emotional factors.
- **Clinical features:** In true pruritus ani, nothing is to be seen.

- **Diagnostic approach:** Careful examination to exclude anal and rectal diseases, especially those causing stool incontinence; search for condyloma; culture stool and skin for *Candida albicans*; patch testing.
- **Therapy:**
  - Few diseases are as burdened with emotional overtones as pruritus ani. Patients are hesitant to discuss the problem. Often there are hidden guilt factors, such as anal intercourse or other forms of penetration.
  - ***Caution:*** Always consider child abuse in children who complain of pruritus ani or anal pain.
  - Bland, high-fibre diet.
  - Some individuals develop severe pruritus from the tiny residual amounts of stool left behind after cleansing with toilet paper, and must plan their activities so that they can clean the area adequately.
  - Topical antipruritic agents, such as polidocanol ointment in nonsensitizing base.
  - Systemic sedating antihistamines in the evening.

36.2 Diseases of Male Genitalia

There are many diseases that may involve the male genitalia. We will only touch upon some of the most common.

Balanitis

- **Definition:** Inflammation of the glans penis. *Balanoposthitis* refers to inflammation of the glans and prepuce, which is the more likely clinical setting.
- **Pathogenesis:** The main risk factor is the presence of an occlusive foreskin. Other factors include infections, diabetes mellitus (with glycosuria), immunosuppression, lack of cleanliness (with irritation from smegma), excessive trauma, and underlying skin diseases such as atopic dermatitis or psoriasis. The most common infectious organism causing balanitis is *Candida albicans*, but trichomonas, herpes simplex, *Chlamydia*, and many others can play a role. Another factor is allergic contact dermatitis to hygiene items, topical medications, or latex.
- **Clinical features:** Acute balanitis features erythema, pain, and often a weeping discharge. In many instances it may be accompanied by phimosis. Always search for lymphadenopathy or ulcerations as clues to infections. Chronic balanitis is usually candidal and often occurs in diabetics.
- **Diagnostic approach:** Culture for bacteria (often mixed infections) and yeasts. If any question, syphilis serology. If urethral discharge, culture for gonorrhea.
- **Differential diagnosis:** The differential diagnostic considerations are shown in Table 36.**2**.
- **Therapy:**
  - Treat underlying disease.
  - Always use lotions or thin creams; heavy pastes or ointments cause additional "debris" to accumulate beneath the foreskin and exacerbate the problem.
  - Wicking is essential in uncircumcised men. A strip of moistened gauze 1–2 cm wide is placed in coronal sulcus and the foreskin is pulled over it. Tap water suffices; high concentrations of disinfectants under occlusion (from the foreskin) can lead to necrosis.
  - If no diagnosis is apparent, then assume *Candida albicans* is involved and use imidazole lotion or cream b.i.d.
  - Chronic persistent balanoposthitis may require circumcision.

Table 36.2 · Differential diagnosis of balanitis

Disease	Clinical features
Chronic irritative balanitis	Erythema, maceration, painful; more common in uncircumcised; more common when partner has discharge
Candidal balanitis	Pustules are peripheral; partner history? diabetes mellitus?
Contact dermatitis	Erythema, pruritus, appropriate history; condoms, hygiene products
Herpes genitalis	Grouped blisters on erythematous base, rapidly pustular, painful, history of recurrences
Psoriasis	Red macerated plaque; look for psoriasis elsewhere; can be solitary or just associated with arthritis
Lichen planus	Eroded plaque; look for lichen planus elsewhere; can be solitary
Lichen simplex chronicus	Area of persistent rubbing, exaggerated skin markings; occasionally on penis
Plasma cell balanitis (Zoon)	Circumscribed smooth red plaque; almost always in uncircumcised; biopsy diagnosis
Erythroplasia of Queyrat	Circumscribed velvety red plaque; variant of squamous cell carcinoma in situ; biopsy diagnosis
Erythema multiforme	Target lesions on extremities, palms and soles; sometimes on glans penis; blue-violet center with white intermediate zone and erythematous rim
Lichen sclerosus	White sclerotic area on glans or inner prepuce; common cause of phimosis; also known as balanitis xerotica obliterans
Circinate balanitis	Erythematous erosions with white periphery; associated with Reiter syndrome (reactive arthritis, keratoderma blennorrhagicum, signs of psoriasis)
Fixed drug eruption	Red-brown patch or plaque; history of recurrence in exactly the same site with ingestion of same drug

Human Papillomavirus (HPV) Infections (p. 70)

- **Clinical features:** In the anogenital lesion, HPV on mucosal or transitional surfaces or in occluded or macerated areas are white and thus often not instantly recognized as warts; they are also generally designated condylomata acuminata. Intrameatal warts are not uncommon; they may cause dysuria or even mild obstruction with a distorted stream of urine. Similar lesions on the shaft of the penis are usually darker.
- **Histology:** Some lesions may show squamous cell carcinoma in situ; they are known as *bowenoid papulosis* (p. 71). Despite the worrisome histologic appearance, many of these lesions resolve spontaneously. Biopsy of genital warts is usually not needed, but should be considered in recalcitrant lesions.

- **Differential diagnosis:** HPV infections of the genitalia are common, but they are also often misdiagnosed. Table 36.**3** shows just some of the conditions that are erroneously diagnosed as "warts" in the anogenital region.
- **Therapy:** Mucosal warts respond more readily to topical agents such as podophyllotoxin or imiquimod.

***Table 36.3* · Differential diagnosis of genital warts**

Disease	Clinical features
Bowenoid papulosis	Variant of condylomata acuminata, larger lesions, often on shaft of penis or labia minora; histologically squamous cell carcinoma in situ; some regress, others become squamous cell carcinoma
Molluscum contagiosum	Skin-colored 1 – 5 mm delled papules, often grouped
Free sebaceous glands	Tiny yellow papules on prepuce or labia minora
Pearly penile papules	Tiny angiofibromas in sulcus of glands; often mistaken for warts; harmless; female equivalent is hirsuties vulvae
Lichen planus	Polygonal violet flat-toped papules, lacy white network often seen on glans or labia minora; pruritic
Lichen nitidus	Miniscule white papules; favor penis shaft
Condylomata lata	Eroded weeping broad-based plaques; perianal and intertriginous; lesion of secondary syphilis

Penile Ulcers

- **Pathogenesis:** Genital ulcers are a major problem because they are often transmissible, painful, interfere with sexual intercourse, and may reflect a serious underlying disease (syphilis, chancroid).
  - ***Note:*** Genital ulcers are often overlooked in women. This is reflected in the transmission of herpes simplex by asymptomatic women and in the lower incidence of chancres in female syphilis patients.
- The causes of penile ulcers include infections, trauma, aphthous diseases (both idiopathic genital ulcers and Behçet syndrome), squamous cell carcinoma, and especially artifact.
- **Clinical features:** Classically the distinction is made between the relatively painless firm, punched-out chancre of syphilis (hard ulcer) and the soft, jagged, painful ulcer of chancroid. The most common genital ulcers are caused by herpes simplex virus; they are typically small, grouped erosions, as the vesicular stage is often overlooked.
- **Diagnostic approach:** Always take a careful history, check other mucosal sites (mouth, rectum, conjunctiva), and consider trauma and artifact. If the diagnosis is not 100% clear, do syphilis serology and bacterial culture.
- **Differential diagnosis:** The same infections and other problems create genital ulcers in women, but the risk of their being overlooked is greater. Thus, we discuss penile ulcers as prototypical of all genital ulcers. The differential diagnostic considerations are shown in Table 36.**4**.
- **Therapy:** Treat underlying disease. Genital ulcers heal rapidly; avoid occlusive medications, which are messy and so often not employed by patient.

Table 36.4 · Differential diagnosis of penile ulcers

Disease	Clinical features
Herpes genitalis	Grouped blisters on erythematous base, rapidly pustular, painful, history of recurrences; most common cause of small penile blisters
Chancre	Firm hard, button-like lesion with superficial erosion; usually painless
Chancroid	Painful, dirty, genital ulcer with ragged edges
Lymphogranuloma venereum	Small solitary soft erosion; often overlooked; main finding lymphadenopathy
Pyoderma	Painful dirty ulcer; often arises after traumatic sexual intercourse, zipper injury
Squamous cell carcinoma	Irregular tumor, often ulcerated, almost invariably in uncircumcised individuals
Behçet syndrome	Recurrent aphthae, genital ulcers; more common in Asia and Middle East; genital lesions often large and persistent
Artifact	Bizarre morphology; penis is favored site for injections, chemical burns, other self-induced changes
Fournier gangrene	Sudden aggressive ulcer; necrotizing fasciitis of the genitalia; mixed bacterial infection; associated with trauma, surgery, systemic infections

Sclerosing Lymphangiitis

A peculiar condition in which the lymphatics (or on occasion veins) of the penile shaft become irritated or inflamed. Not infectious, but often follows sexual intercourse, presumably because of trauma. Presents as painful cord, easily felt because of lack of subcutaneous tissue. No treatment required; NSAIDs are sometimes helpful.

36.3 Diseases of Female Genitalia

Vaginitis

Vaginal infections rarely present to the dermatologist. Nonetheless, it is important to inquire about vaginal discharge whenever confronted with a vulval dermatitis, as the drainage may be irritating. Similarly, partners of women with vaginitis are likely to develop balanitis. The most common infectious causes of vaginitis are *Candida albicans*, *Trichomonas vaginalis*, and *Gardnerella vaginalis*, which causes bacterial vaginosis with its characteristic fishy smell. *Chlamydia*are more likely to cause cervicitis, while *Neisseria gonorrhoeae* can lead to a purulent discharge, especially in children whose vaginal epithelium better supports the infection.
Chronic vulvovaginitis has many overlaps with chronic balanitis; diabetes mellitus and obesity are particular risk factors, while *Candida albicans* is frequently present and should be treated. Allergic contact vaginitis also occurs, triggered primarily by feminine hygiene products and latex, but most such reactions are irritant in nature.

Foreign bodies are another consideration, especially in children, who are also occasionally irritated by bubble baths.

Atrophic vaginitis is a problem that may involve dermatologists. Every women experiences some degree of vaginal atrophy after the menopause, with thinning of the epithelium and a rise in pH favoring Gram-negative, anaerobic bacteria. If a discharge is present, it is watery. Topical estrogens or estrogen vaginal suppositories are the usual treatment. Some of these patients have lichen sclerosus, as discussed below.

Vulvar Dermatitis

When confronted with a patient with vulvar dermatitis, the two most important issues are:

- Presence of vaginal discharge with irritation.
- Evidence of underlying skin disease such as:
  - *Atopic dermatitis:* Many women with chronic vulvar dermatitis have other stigmata of atopic dermatitis.
  - *Psoriasis:* Classic intertriginous disease, may involve vulva almost exclusively; look for other clues (nails, scalp).
- Some rare diseases also regularly involve the vulva. Examples include necrolytic migratory erythema as a marker for glucagonoma and acrodermatitis enteropathica as a sign of zinc deficiency.
  - ***Note:*** Always consider nutritional deficiencies and eating disorders when confronted with vulvar dermatitis.
- **Therapy:** Treatment is based on identifying and correcting the underlying disorder. To control pruritus, topical corticosteroid and anesthetics (polidocanol) lotions or creams are useful.

Lichen Sclerosus

This common inflammatory dermatosis often involves the vulva in both small girls and older women. The clinical picture is distinctive, with an ivory-white plaque usually with a violaceous ring. In the genital area, a "figure 8" pattern occasionally occurs as the disease involves both the anus and the vaginal orifice (p. 217).

A careful search for clues to lichen sclerosus is indicated in several clinical settings:

- **Potential child abuse:** Because of the abnormal connective tissue in papillary dermis, patches of lichen sclerosus frequently show hemorrhage. When periorificial, the findings can be confused with sexual abuse.
- **Vulvar pruritus and pain:** The affected skin is more fragile and easily damaged by irritants or physical trauma. In addition, late lesions are sclerotic and atrophic producing a restricted vaginal orifice and pain on intercourse.
- **Vaginal atrophy** often reflects overlooked lichen sclerosus.
- **Vulvar lichen sclerosus** is rarely a site for the development of squamous cell carcinoma. Keratotic or ulcerated lesions in this setting must always be biopsied.
- **Therapy:** Surprisingly, topical corticosteroids (usually high potency) and topical calcineurin inhibitors are more effective than topical estrogens.

Pruritus Vulvae and Vulvodynia

- **Definitions:** Although there are overlaps and cases that are hard to define, it is clinically helpful to separate two conditions:
  - *Pruritus vulvae:* Intense vulvar itching, with almost invariably secondary excoriations or lichenification.
  - *Vulvodynia:* Vulvar burning or pain, usually associated with pain on intercourse (*dyspareunia*).

- **Pruritus vulvae:** Most often reflects underlying pruritic dermatosis (atopic dermatitis, contact dermatitis, lichen sclerosus), vaginal discharge, infestation (scabies), or underlying cause of pruritus (renal disease, diabetes mellitus). Always check for what is being applied topically, taking detailed and persistent history. Physical examination should include perianal region, as rectal discharge can also lead to vulvar irritation. Sometimes biopsies are useful to identify clinically subtle lichen sclerosus or even bullous pemphigoid in the elderly. Search for any erosions, ulcerations, or scars, as they might point to herpes genitalis or aphthae. In some instances, one finds no cause.
  - ***Note:*** Pruritus vulvae can simplistically be viewed as lichen simplex chronicus of the female external genitalia. No matter what the cause, a chronic itch–scratch cycle develops and lichenification is the result.
  - *Therapy:* Topical corticosteroids or anesthetics are most useful; they can be combined with systemic antihistamines or even antidepressants, depending on the severity.
- **Vulvodynia:** A much more difficult problem. Generally no positive physical findings. Classic symptom is pain or burning.
  - ***Note:*** A patient with vulvodynia generally corrects a physician who asks "How long have you been *itching?*" They feel pain, not itching.
  - One must search for any signs of dermatologic disease that could explain the pain. Sometimes when the vulvar vestibule (area between labia minora where urethra and vagina open) is exquisitely sensitive, the diagnosis of vulvar vestibulitis is made. Some then treat for HPV infection of the vestibule, but results have been clinically less than impressive.
- **Therapy:** Try to work together with a gynecologist and psychotherapist interested in this extremely challenging and time-consuming clinical problem. Most patients do not benefit from topical therapy, and require antidepressants or other psychotropic medications.

37 Phlebology

37.1 Anatomy and Function of Leg Veins

Anatomy of the Leg Vein System (Fig. 37.1)

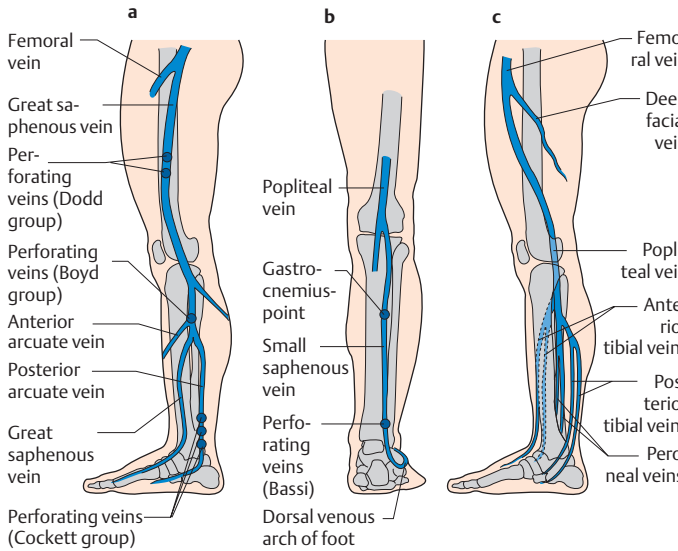


Fig. 37.1 · **Anatomy of the leg veins. a** Epifascial greater saphenous vein with most important perforating veins. **b** Epifascial lesser saphenous vein with most important perforating veins. **c** Deep subfascial veins.

There are two systems of leg veins, both containing unidirectional valves directing the blood flow upward:

► **Superficial epifascial veins:**

- Two major veins, great saphenous vein and small saphenous vein, as well as their branches.
- The *great saphenous vein* runs into front of the medial malleolus and along the medial aspect of the leg to the groin where it joins the femoral vein at the *saphenofemoral junction*; it is the longest vein in the body.
- The *small saphenous vein* runs from above the lateral malleolus over the calf to join with the popliteal vein at the sapheno-popliteal junction in the popliteal fossa.
- The *posterior arcuate vein* (posterior saphenous vein) is the most important smaller vein; it runs from behind the medial malleolus up the calf and joins the great saphenous vein. It has connections to the *subfascial posterior tibial vein*

(Cockett perforating veins); incompetent valves in this system are a major cause of venous leg ulcers.

- **Deep subfascial veins:**
  - The deep veins of the lower leg are paired with the corresponding arteries; they include the *anterior tibial*, *posterior tibial*, and *peroneal veins*.
  - Above the knee, the deep veins are the *popliteal*, *superficial femoral*, and *deep femoral veins*.
  - Anatomic variants are common in this system.
- **Perforating veins** connect the two systems; their valves direct the blood flow to the deep system.

Function of Leg Veins

- **Muscle pump:** The energy for venous return is provided primarily by the pumping action of the leg muscles combined with the unidirectional valve system. Each time the muscles contact, venous blood is directed upward and inward. Adequate contraction of the muscle pump depends on a fully flexible ankle joint.
- **Other factors:** The arterial pressure plays little part. Each step empties the venous pads of the soles.

37.2 Varicose Veins

Overview

- **Definition:** Varicosities are dilated superficial veins. They are divided into primary and secondary forms.

Primary Varicose Veins

- **Definition:** Varicose veins that develop without an apparent cause.
- **Epidemiology:**
  - Female:male ratio 2:1; onset usually 20–30 years of age.
  - Strong family predisposition.
  - By age 70, 70% of women and 60% of men are affected; in 70%, both legs are involved.
  - Co-factors include number of pregnancies, occupation requiring prolonged standing, and obesity.
- **Pathogenesis:** The wall is dilated to an extent that the valves are no longer competent. This starts a vicious cycle of reflux, further dilation, and impaired return.
- **Clinical features (Figs. 37.2, 37.3):**
  - *Starburst or spider varicosities:* Fine microvaricosities usually located on inner aspect of calf and outer aspect of thigh. When arranged along edge of foot, known as *corona phlebectatica paraplantaris* (venous crown).
  - *Reticular varicosities:* Netlike dilated superficial veins without hemodynamic consequences.
  - *Accessory varicosities:* Involve branches of the main veins; often asymptomatic but hemodynamically significant.
  - *Truncal varicosities* (*saphenous vein varicosities*)*:* Involve the major veins of the leg; in 70% of cases associated with incompetent perforating veins; hemodynamically significant.
  - The classification of varicosities devised by Hach is shown in Table 37.**1** and Fig. 37.**4**.

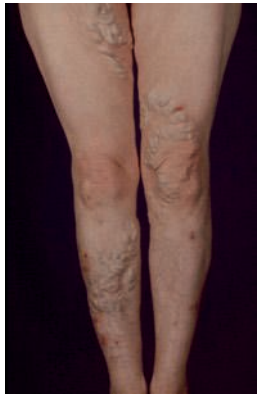


Fig. 37.**2** · Prominent varicosities involving major veins.

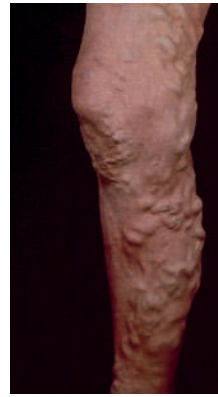


Fig. 37.**3** · Closer view of marked varicosities.

Table 37.1 · **Level of insufficiency of major veins**

Reflux	Grade
Great saphenous vein	
One handsbreadth below junction	I
Above the knee	II
Below the knee	III
To the ankle	IV
Small saphenous vein	
Below the knee	I
Mid-calf	II
To the ankle	III

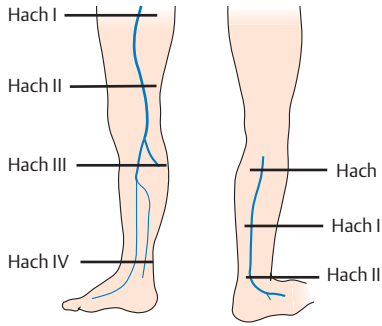


Fig. 37.**4** · Level of venous insufficiency (after Hach).

Secondary Varicose Veins

- **Definition:** Varicose veins secondary to a known cause.
- **Pathogenesis:** The most common cause of secondary varicosities is the *postthrombotic syndrome*. Uncommon causes are angiodysplasias (vascular malformation syndromes) and other underlying diseases, such as connective tissue defects. In the postthrombotic syndrome, a deep venous thrombosis leads to damage to the valves and reflux, which then places excess demands on the perforating and collateral veins. Over years the perforating and then epifascial veins become dilated and incompetent. In both primary and secondary varicosities, the number of incompetent perforating veins is the best correlate for the degree of hemodynamic compromise.
  - ***Note:*** Suprapubic varicosities are almost always a sign of a pelvic vein thrombosis. They are occasionally confused with an inguinal hernia.
- **Chronic venous insufficiency:** The reduced venous return is hemodynamically significant and causes clinical disease, divided into three stages (after Widmer):
  - *Stage I:* Corona phlebectatica paraplantaris.
  - *Stage II:* I + atrophie blanche, hemosiderin deposits, dermatosclerosis, stasis dermatitis.
  - *Stage III:* II + ulceration.

Complications

- Thrombophlebitis, varicophlebitis.
- Rupture of varicose veins with minor trauma.
- **Arthrogenic stasis syndrome:** Thickening of skin and pain restrict motion of ankle joint, starting a vicious circle of inadequate pumping and then worsening problems. The impaired mobility of the ankle joint later becomes the most important obstacle to ulcer healing.
- Venous leg ulcer (ulcus cruris venosum, stasis ulcer).
- Muscle atrophy, subcutaneous bone dysplasia.

Diagnostic Approach

Detailed information on the phlebologic diagnostic process is given on p. 39. The most useful approach for chronic venous insufficiency is Doppler and duplex sonography. Other approaches such as light reflection rheography (LRR), digital photoplethysmography (DPPG), and venous plethysmography (resting and dynamic) can be used as indicated. When deciding on the possibility of surgery for the postthrombotic syndrome with secondary varicosities, invasive phlebodynametry (actual measurement of venous pressure with intravascular needle) is often required. Phlebography is usually not necessary when the above approaches are employed.

Therapy

- **Basic principles:**
  - Regular compression therapy is the mainstay of treating varicosities.
  - Varicosities in the great and small saphenous vein require surgical correction.
  - Accessory vein varicosities can be treated surgically or sclerosed.
  - Reticular and starburst veins can be treated with sclerotherapy, or in the case of starburst veins, with laser ablation.
  - Incompetent perforating veins should be interrupted surgically.
  - Vein stripping (Babcock procedure) can produce long-term improvement.

- Most venous leg ulcers heal with compression therapy. When accompanying varicose veins are treated, most ulcers heal more rapidly.

► **Procedure depending on phlebologic evaluation:**

1 *No deep reflux but varicosities:* LRR or DPPG indicate improvement possible, then:
   – Remove incompetent vein segments surgically.
   – Strip the main vein and then either excise or sclerose the accessory veins.
   – General, regional or tumescent local anesthesia can be employed.
   – If varicosities recur, repeat operation possible.
2 *Deep reflux and varicosities:* LRR or DPPG indicate improvement possible, then:
   – Completely remove varicosities as above.
   – If the reflux in the deep veins stops, then life-long compression not required.
3 *Deep reflux and varicosities:* LRR or DPPG indicates no improvement possible, then:
   – Life-long compression therapy required.

▶ ***Note:*** Patients with compensated varicose veins *can* be treated; those with chronic venous insufficiency *must* be treated.

► **Operative approach to venous leg ulcers:** The entire surgical palette discussed above can be employed when leg ulcers are present. Prompt therapy of chronic venous insufficiency should hopefully prevent advancement to stage III disease. In addition, early surgery reduces the likelihood of deep vein insufficiency. If a complete stripping is not possible or has already been accomplished, then options include:

- Sclerosis of veins about the ulcer.
- Ligature of isolated perforating veins, especially those in Cockett group.
- Endoscopic subfascial resection of perforating veins is another alternative when severe dermatosclerosis or a leg ulcer is present; recurrences are not uncommon.
- Radical excision of ulcus to fascia and paratibial fasciotomy are seldom used.
- Shaving excision of ulcer followed by mesh grafting offers the chance of long-term relief.
- If all other procedures have failed, split-skin grafting and compulsive compression therapy will shorten the healing time.

► **Alternative surgical methods:** There are a number of new promising approaches that have not been clinically validated and must still be regarded as experimental:

- *CHIVA* (**c**onservative and **h**emodynamic method for **v**enous **i**nsufficiency on an **a**mbulatory basis): After duplex sonographic mapping, all perforating veins are tied off under local anesthesia but no attempt is made to remove the varicosities, which regress somewhat on their own.
- *Endoluminal laser therapy:* The great saphenous vein is exposed or entered percutaneously just below the knee. A glass fiber is advanced to the junction. Then, with tumescent local anesthesia, the vein is coagulated with a diode laser while the glass fiber is slowly retracted.
- *Radiowave sclerosis:* Similar to the endoluminal laser therapy, but the vein is destroyed with a disposable catheter attached to a high-frequency electrosurgical unit.
- *Valvuloplasty*: The junction is exposed and the great saphenous vein wrapped with a Gore-Tex cuff or partially ligated so that its valve system functions once again.

37.3 Inflammation of Veins

Superficial Thrombophlebitis

- ***Note:*** When speaking with patients, always emphasis the difference between *thrombophlebitis* (inflammation of vein) and *phlebothrombosis* (primary thrombosis, far more serious).
- **Pathogenesis:** The elements of the *Virchow triad* (vessel wall damage, increased coagulability, delayed blood flow) remain the crucial factors for thrombosis.
- **Clinical features:** Erythematous warm and tender cord without generalized signs and symptoms. Most common on calf in area of varicosities; uncommon without accompanying varicose disease. Also may develop on arm following long-term intravenous therapy.
- **Diagnostic approach:** History, clinical examination.
- **Differential diagnosis:** Erythema nodosum, erysipelas, phlebothrombosis.
- **Therapy:** Compression therapy with class II stockings or relatively firm elastic wraps. No bedrest. NSAIDs. If ascending, prophylactic heparinization. If the junction is involved, emergency surgery; if the thrombosis enters into the deep venous system, then treatment as below.

Varicophlebitis

- **Definition:** Localized phlebitis in a varicose vein.
- **Clinical features:** Tender, long, firm thrombosis in a varicosity of one of the major veins. May be localized or widespread. When the great saphenous vein is involved on the thigh, both deep vein involvement and pulmonary emboli may occur.
- **Therapy:** Standard therapy as above; also consider operative removal of primary varicosity or incision with expression of thrombus.

Thrombophlebitis Saltans

- **Definition:** Recurrent thrombophlebitis in nonvaricose veins; involves both arms and legs.
- **Epidemiology:** Most common in young men.
- **Clinical features:** Involvement of both arms and legs should always suggest trouble when dealing with thrombophlebitis.
- **Diagnostic approach:** Check for underlying vasculitis (Bürger syndrome).
  Caution: Thrombophlebitis saltans can be a paraneoplastic marker, especially for lung and pancreas carcinomas.
- **Therapy:** NSAIDS; if Bürger disease is present, consider systemic corticosteroids or immunosuppressive agents.

Mondor Disease

- **Definition:** Thrombophlebitis of the thoracoepigastric vein.
- **Pathogenesis:** Unknown.
- **Clinical features:** Sudden onset of firm, tender cord up to 40 cm long on the lateral thoracic wall.
- **Diagnostic approach:** Pathognomonic clinical picture.
- **Therapy:** Nothing or NSAIDS. Lesion resolves spontaneously over weeks.

37.4 Deep Venous Thromboses

Arm Vein Thrombosis

- **Classification:**
  - Subclavian-axillary vein thrombosis (Paget–Schroetter syndrome).
  - Thrombosis as complication of venous catheterization.
  - Thrombosis secondary to predisposing conditions.
- **Clinical features:** Subclavian–axillary vein thrombosis typically affects young men; the most common cause is thoracic inlet syndrome. The onset is usually slow with pain, swelling, and a sense of heaviness, as well as loss of strength. The veins in the shoulder region may be more prominent and cyanosis of the limb can develop.
- **Complications:** Pulmonary emboli develop in 10%; rarely life-threatening. Post-thrombotic features very uncommon.
- **Diagnostic approach:** Compression sonography or duplex sonography; if not clear, phlebography. D-dimer test.
- **Differential diagnosis:** External of axillary vein by tumors, metastases, scars, following radical mastectomy, callus formation after clavicular facture, substernal thyroid tissue, and cervical rib.
- **Therapy:**
  - Low molecular weight heparin and coumarin; once the INR is in the range 2–3 for 2 days, then heparin can be discontinued (see below).
  - Thrombolysis or surgery in early phase in young patients.
  - In thoracic inlet syndrome, surgical correction usually possible.

Deep Vein Thrombosis (DVT)

- **Synonyms:** Phlebothrombosis, deep leg vein thrombosis.
- **Pathogenesis:** Risk factors include trauma, lack of physical activity (especially absolute bedrest), aberrant coagulability (following surgery, miscarriage, or pregnancy), use of oral contraceptives, underlying malignancy, smoking, long airplane flights, and excessive physical activity in poorly trained individuals (Sunday mountain climbers).
- **Clinical features:**
  - In nonhospitalized patients, onset usually dramatic. In hospitalized patients, often slow and easily overlooked.
  - Sense of heaviness and tension, tugging pains, pain in the groin or flank, fatigue, anxiety, increased pulse.
  - Leg may be livid or show prominent veins.

  Caution: May present as pulmonary embolus.
  - *More severe forms:*
    - *Phlegmasia cerulea dolens:* Acute fulminating DVT with reactive arterial spasm, cyanosis and edema; multiple veins may be involved.
    - *Phlegmasia alba dolens:* Femoral vein phlebitis leading to limb swelling and pallor.

  Note: If a patient has unexplained calf pain, leg edema, tense muscles or tenderness, always think of DVT.
- **Diagnostic approach:**
  - Clinical diagnosis extremely difficult and unreliable; must always be confirmed.
  - *D-dimer test:*
    - Fibrin split products, which always appear when clotting occurs.

  - Always positive after surgery, infections (erysipelas); return to normal after 2–3 days.
  - Available as rapid screening test or can be quantitatively determined.
  - Only for screening test to exclude diagnosis.
- *Compression sonography:*
  - Method of choice.
  - If diagnosis unclear, repeat after short period of time or do phlebography. Doppler sonography and vein compression plethysmography are only sensitive for pelvic vein thrombosis.

► **Differential diagnosis:** Sport injuries, hematomas, thrombophlebitis.

► **Therapy:** (p. 676).

- Subcutaneous heparinization with a low molecular weight heparin (for example, fraxiparin 0.1 mL/0 kg b.i.d. subq.). On first or second day, also start coumarin with a goal of INR 2–3. Once the INR level has been obtained for 2 days, heparin can be stopped.

Caution: Check platelets before starting heparin therapy and then weekly, because of risk of heparin-induced thrombocytopenia (HIT).

- Duration of therapy 6 months for thrombosis below pelvis; 12 months for pelvic vein thrombosis or recurrence.
- Compression therapy with compression bandages and then once edema has resolved, compression stockings class II.
- Bed rest for 5 days in the case of pelvic vein thrombosis.
- In younger patients, thrombolysis or operative thrombectomy should be considered. If an operation is planned, then nonfractionated heparin should be administered by continuous i.v. infusion, as it is more easily counteracted with protamine sulfate.

Note: Calf vein thrombosis may require less aggressive therapy (p. 676).

► **Complications:**

- *Pulmonary embolus:*
  - Clinical signs and symptoms include tachycardia, dyspnea, right-sided cardiac overload, oxygen saturation $< 92\%$, pain. About 10% of untreated DVT patients develop clinically apparent pulmonary emboli.
  - Diagnostic procedures include EKG, scintigraphy, sonography, chest radiograph, and pulmonary artery angiography.
- Later complications include development of secondary varicosities or postthrombotic syndrome.

Postthrombotic Syndrome

► **Definition:** Chronic venous insufficiency of leg following phlebothrombosis.

► **Pathogenesis:** Following postthrombotic recanalization with valve defects, there is usually a period of years without problems, then development of incompetent perforating veins and secondary varicosities. The chronic venous insufficiency leads to disturbances in microcirculation with tissue damage including ulceration, obliterating lymphangiopathy, and arteriolar occlusion.

► **Clinical features:** Initially pitting edema, later induration. Small varicosities and blowout veins as first signs of incompetent perforating veins. Other signs of stasis are *atrophie blanche* (white atrophic scars) and *purpura jaune d'ocre* (yellow-brown chronic purpura about ankles) (Fig. 37.**5**).

► **Therapy:** Life-long use of compression stockings (Table 37.**2**) or compression bandages. Usually a below-the-knee stocking is sufficient.

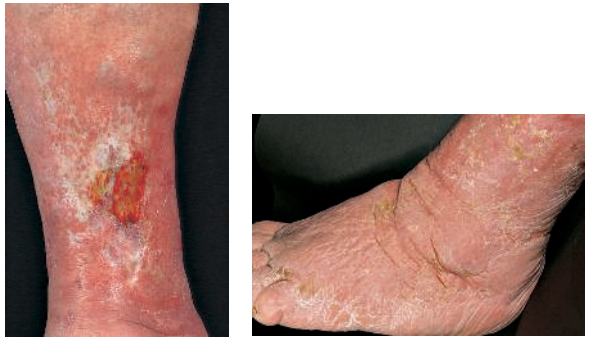

a b

Fig. 37.**5** · **a** Atrophie blanche with ulceration. **b** Dermatosclerosis and verrucous edema in postthrombotic syndrome.

Table 37.2 · **Classes of compression stockings**

Class	Features
I	Light compression, pressure 15 – 20 mmHg, mild superficial effect
II	Medium compression, pressure 23 – 32 mmHg, moderate superficial effect
III	Strong compression, pressure 34 – 36 mmHg, superficial and deep effects
IV	Very strong compression, pressure > 49 mmHg, marked deep effects

37.5 Stasis Dermatitis and Venous Leg Ulcers

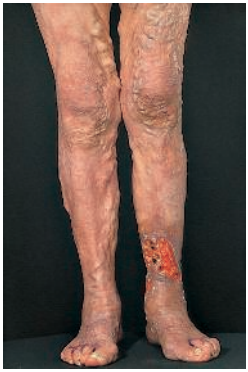
Overview

- **Pathogenesis:** Crucial factor is reduced tissue oxygen levels caused by venous hypertension and stasis.
- **Clinical Features:** Venous ulcers are usually on medial side of ankle; they can vary greatly in size and clinical appearance (Fig. 37.**6**).
- **Diagnostic approach:** Evaluation to rule out arterial and neuropathic ulcers, as well as ulcerated tumors and trauma. Differential diagnostic considerations for leg ulcers are listed on p. 728.

Note: The biggest mistake is to overlook an ulcerated tumor (basal cell carcinoma, squamous cell carcinoma, amelanotic malignant melanoma, lymphoma); if in doubt or if ulcer fails to respond, always biopsy.

Therapy

- **Overview:**
  - Compression therapy, mobilization, and consideration of surgical measures to eliminate varicosities.
  - Stage-adjusted management of venous ulcer with moist wound therapy with goals of cleaning, encouraging granulation, and facilitating re-epithelialization.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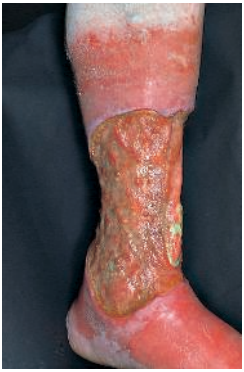

b

Fig. 37.6 · **a** Bilateral varicosities with venous leg ulcer. **b** Extensive venous leg ulcer.

Caution: Avoid use of topical agents with potential for contact sensitization; rare use of topical antibiotics; systemic antibiotics only for clinically apparent infection, then short-term and culture-directed.

► **Compression and mobilization:**

- Firm compression bandages; maximal variant is Unna boot (zinc paste bandages).
- Variety of stockings available for ulcer care.
- Mobilization; physical therapy to retain mobility of ankle joint because of its crucial role in pumping.
- Consider manual or instrumental lymphatic drainage.

Note: Meticulous attention to compression and mobilization is the cornerstone of all effective venous leg ulcer treatment.

► **Topical therapy around ulcer**.

- *Goals:* Clean and protect nonulcerated periphery, treat underlying dermatitis.
- *Cleansing:* Daily washing in tub or shower; moist compresses with physiologic saline (0.9%). Compresses with 5.0% saline are more effective but may be irritating or painful. Olive oil is useful for removing crusts and residual creams or ointments.
- *Superinfection with exudation:* Antiseptic solutions with moist compresses.

Note: Moist compresses left on until almost dry are much more effective for débridement than soaking.

- *Resistant infections:* Culture and sensitivity; then consider fusidic acid ointment or mupirocin ointment. In most instances, systemic antibiotics are preferable.
- *Dermatitis therapy:*

Note: Always exclude allergic contact dermatitis caused by topical agent or preservative. Common allergens include balsam of Peru, wool wax alcohols, cetyl sterol alcohol, emulgators, preservatives (parabens), antibiotics (especially neomycin, gentamicin, chloramphenicol). Use of any of these agents should be considered carefully.

- If the dermatitis is dry, use a corticosteroid ointment or emollient cream. A useful compound is betamethasone valerate 0.1% in white petrolatum (p. 692).
- If the dermatitis is moist or weeping, then clioquinol lotion or cream (p. 691) is helpful.

- *Skin protection:* Zinc oxide paste or white petrolatum can be applied to normal skin around the ulcer.

Caution: White petrolatum has an occlusive effect, which encourages the growth of bacteria. It must always be combined with appropriate cleansing.

► **Topical therapy of ulcer:** Goals are pain relief, cleansing, encouragement of granulation, encouragement of reepithelialization, protection.

- *Pain relief:*
  - Topical anesthetics before cleansing (EMLA under occlusion for 45 minutes); alternatively, local anesthetic solution injected beneath ulcer.

Caution: Lidocaine creates an alkaline environment, favoring bacterial growth and inhibiting keratinocyte proliferation.

  - Analgesics (usually NSAIDs suffice).
  - Choose dressings that are easy to remove. If dressing is adherent, soak with tap water or physiologic saline for 5–10 minutes.
- *Cleansing:*
  - *Physiologic-osmotic:* NaCl solution in increasing concentrations (0.9%–2%–5%–10%) or crystalline sugar.
  - *Antiseptic solutions:* H_2O_2:H_2O 50:50, 0.1–0.5% methylrosaniline chloride aqueous solution (p. 697); always rinse with physiologic saline.
  - *Mechanical debridement:* Curettage after adequate anesthesia.
  - *Autolytic debridement:* Alginate or hydrocolloid dressings.
  - *Enzymatic debridement:* Many available, none clearly superior; possibilities include streptokinase/streptodornase, collagenase, and papain-urea-chlorophyll.
  - *Absorption:* Activated charcoal granules, also available with additional silver, other compounds.

Note: Most of the cleansing measures also stimulate granulation tissue.

- *Encouragement of granulation:*
  - *Physiologic-osmotic:* 5–10% saline solution, sugar or sugar:sand mixtures.
  - *Mechanical debridement:* scarification of periphery with scalpel and then airtight occlusion.
  - *Increase perfusion:* Infrared light, Nd:YAG laser, or physical activity.
  - *Moist wound care:* Polyurethane foams, alginate pads.
  - *Vacuum closure technique:* Polyurethane foam is applied, covered with occlusive membrane and then placed under suction pressure with pump or vacuum bottle. Often painful at start.
- *Encouragement of epithelialization:*
  - *Moist wound care:* Hydroactive gel or hydrocolloid dressing.
  - *Impregnated gauze nonadhering dressings.*
  - *Autologous keratinocyte cultures*, if technically possible.
  - *Protargol zinc paste:* 0.1% silver nitrate, 30.0% zinc oxide, 69.9% white petrolatum.
- *Protection:* Zinc oxide paste or ointment, panthenol ointment.

► **Rheologic therapy:** If there is an arterial component, consider low-dose aspirin, low-dose heparin, pentoxifylline; prostacyclin infusions possible but value not proven. Foot of bed should be lower than head, and no compression therapy if arterial systolic pressure at ankle < 80 mm Hg. Check for hyperviscosity syndrome and treat.

Note: Always maximize treatment of accompanying varicosities, venous insufficiency, or arterial disease; otherwise an ulcer will take much longer to heal. Be alert to accompanying neuropathies. If response is slow, check again to be sure you have identified the cause correctly.

37.6 Phlebologic Surgery

- **Preoperative planning:**
  - Exact diagnosis incorporating Doppler and duplex ultrasonography, as well as phlebography. To document function of deep and pelvic veins, ascending press phlebography is best.
  - Identify all incompetent veins, including perforating veins and accessory, collateral, or atypical main veins.
  - To reduce complications, usually best to operate on just one leg; the other one can then be addressed in 6–8 weeks. This approach minimizes the postoperative restriction of motion,
- **Operative approach for varicosities:**
  - **Procedure:** Recommended procedures are shown in Table 37.**3**.

Table 37.3 · **Operative approach to varicosities**

Stage (after Hach)	Procedures
I	Crossectomy of the great saphenous vein/small saphenous vein
II	Crossectomy of the great saphenous vein/small saphenous vein and stripping with Babcock method to knee
III	Crossectomy of great saphenous vein and stripping to mid-calf Crossectomy of small saphenous vein and stripping of the complete posterior calf
IV	Crossectomy of great saphenous vein and stripping of entire calf

- **Technique:**
  - On the evening before the operation, mark the junctions and the course of the major veins, as well as the perforating veins and other varicosities; shave the groin and thighs.
  - After sterile preparation and draping, incision to expose the oval fossa of the thigh. Exposure of the junction of the great saphenous vein and the femoral vein. Tie off all contributing branches; then suture ligation of great saphenous vein with additional safety ligature.

  Caution: Place ligatures carefully so as not to reduce lumen of femoral vein.
  - If possible, insert stripper into the distal great or small saphenous vein and then advance it in direction of venous valves. Retrograde insertion increases risk of damaging vein wall. Always advance stripper slowly and control its progress with palpation.

  Caution: Do not introduce stripper via perforating veins.
  - Once the stripper has been passed and its head attached, dissect out and ligate the perforating and accessory veins. Then extract the stripper, removing the vein, and immediately applying compression dressings. This minimizes blood loss.
- **Postoperative care:** Compression therapy with custom-fitted class II stockings for 8–10 weeks. Thereafter consider sclerotherapy of accessory varicosities.

  Caution: Recurrent varicosities should always be treated on an inpatient basis because of the risk of excessive bleeding.

Venous Leg Ulcer

- **Chronic venous ulcer:**
  - Conservative antiseptic therapy, closing the skin defect.
  - Simultaneous attention to incompetent main, accessory, or perforating veins will speed heeling.
- **Marked dermatolipofascial sclerosis:**
  - Radical fasciectomy to relieve pressure.
- **Less severe changes:**
  - Endoscopic subfascial dissection of perforating veins is often just one.
  - Sufficient to allow healing of ulcer.
- **Large infected ulcers:** *Vacuum sealing method* offers excellent approach following radical excision of ulcer to condition base. Its use can greatly reduce the time a patient is immobilized.

38 Occupational Dermatoses

38.1 Overview

- Skin disorders are the second most common cause of occupational disability in most developed countries accounting for around 25% of days lost. (The most common is musculoskeletal problems, accounting for around 50%.).
- Scandinavian studies suggest an incidence of 5–15:10000. The vast bulk of this is occupational allergic-irritant dermatitis of the hands.

38.2 Occupational Hand Dermatitis

- **Epidemiology:** About 1% of the population has hand dermatitis. In working populations, the prevalence may exceed 10%. Some professions at very high risk include:
  - Beauticians/hairdressers and barbers.
  - Bakers.
  - Gardeners and florists.
  - Machinists.
  - Construction workers.
  - Dental technicians.
  - Other health care personnel.
- **Pathogenesis:** The vast bulk of occupational hand dermatitis is irritant in nature. Typical irritants include soaps, cutting oils, and other petroleum products. Prolonged immersion of hands in water is also a factor, by greatly damaging the barrier and facilitating entry by other agents. Strong irritants cause chemical burns and are usually recognized and avoided. Frequent exposure to minor irritants is the usual scenario.
  - Allergic contact dermatitis may rise on the background of irritant dermatitis or independently. Typical allergens include:
    - Rubber components.
    - Epoxy resins.
    - Chromate.
    - Aromatic amines (parabens, hair dyes).
    - Fragrances.
    - Preservatives.
- **Clinical features:** The diagnosis and treatment of hand dermatitis is covered in detail (p. 200).
  - ***Note:*** Assume every case of hand dermatitis is potentially occupational, and detail the information in your history. This will both allow you to intervene early and institute preventive measures, perhaps even for other employees, and save you much anguish later when contacted by the employer or workmen's compensation bureau.
- **Diagnostic approach:**
  - Search for preexisting or aggravated skin diseases. Both atopic dermatitis and psoriasis can cause problems. The issue is always whether the disease was already present but made worse by the occupational exposure, or was "caused" by the job. Understandably, the distinction is difficult and the financial impact on the employee, employer, and insurer is immense.

- Document what happens to the dermatitis on nonworking days, weekends, and during vacation.
- Is there distant spread to sites beyond the hands? This hints at allergic contact dermatitis.
- Do patch testing. This information will be required in almost every case. Obtain detailed instructions on how to test for the specific materials with which the patient has contact. Two common errors are:
  - Blind reliance on standard patch test series (p. 43).
  - Failure to properly dilute suspected substances, thus causing irritant reactions instead of testing for allergic ones.

► **Differential diagnosis:** The initial diagnosis is easy. One should exclude tinea and psoriasis.

► **Therapy:** The treatment is standard, including emollients, topical corticosteroids, and in severe cases systemic corticosteroids or other immunosuppressive agents. In addition, in almost all cases, the patient must be temporarily excused from work.

► **Prophylaxis:** The ideal approach is avoidance or prophylaxis. This can take many forms:

- *Primary prevention:*
  - Advise patients with atopic dermatitis not to enter high-risk professions.
  - Screen individuals entering high-risk professions for preexisting skin diseases and teach them about skin protection and avoidance maneuvers.
  - Be sure appropriate protective measures are available in the workplace, including protective gloves and skin barrier creams. Using a fluorescent marker in the hand cream and a Wood's light, patients can be shown how to apply their protective creams correctly.

  ▶ ***Note:*** The three-step approach to skin protection involves protection, cleansing, and maintenance care.
- *Secondary prevention:*
  - Prompt attention to early irritant hand dermatitis, with increased emphasis on protection and maintenance to avoid severe disease.
  - In Germany, all physicians are required to refer patients in whom an occupational hand dermatitis is suspected to a qualified dermatologist for expert assessment and management.
  - Working with trades unions and employers, it is often possible to remove potential allergens or irritants from the workplace and find suitable replacements.
- *Tertiary prevention:*
  - Once the disease is severe, patients can be taught how to deal with it better or retrained in other professions.

38.3 Occupational Contact Urticaria

► Contact urticaria (p. 172) is a common problem among bakers, veterinarians, food handlers, and health care workers.

► Nonimmune contact urticaria is more common and represents a reaction to chemicals such as sorbic acid. Immune contact dermatitis involves a reaction to protein constituents, such as those in meats, foods, animal dander, or especially latex.

► Latex has an interesting history. In the 1980s, with increased interest in preventing hepatitis B and the advent of HIV/AIDS, the demand for natural rubber latex (NRL)

gloves rose dramatically. With the introduction of cheaper manufacturing methods in Asia, producing NRL gloves with a high protein content, latex allergy dramatically increased in the 1990s, with sensitization rates up to 20% in hospital personnel. New regulations limiting the amount of protein in NRL gloves to $< 200\,\mu g/g$ (low-protein gloves) and the provision of powder-free NRL gloves have reversed the trend, with sensitization rates dropping in most series.

- In most instances, the patients suffer from contact urticaria initially. Later, latex allergy may lead to life-threatening reactions as some patients develop anaphylaxis.
- The diagnostic approach includes specific IgE testing and then prick testing with a latex extract. The sensitivity of the specific IgE testing has been greatly increased to around 70% by using recombinant Hev b 5 and Hev b 13 (Hev refers to *Hevea brasiliensis*, the rubber tree), which are the major latex allergens. The sensitivity and specificity of prick testing depends on the allergen extract used, and may vary depending on its origin.

38.4 Other Occupational Dermatoses

Infections

- **Bacterial infections:**
  - *Staphylococcal and streptococcal infections:* Any profession exposed to minor trauma, such as butchers, farmers, construction workers; more serious problem in health care workers because of risk of resistant strains and possibility of further transmission.
  - *Anthrax:* Contact with infected animals or hides contaminated with spores can cause local inoculation or pulmonary disease.
  - *Erysipeloid: Erysipelothrix rhusiopathiae* is present in many animals; inoculation injury for hunters, butchers.
- **Viral infections:**
  - *Warts:* Human papillomavirus 7 and occasionally other strains cause butchers' warts.
  - *Orf:* Parapox virus common in sheep and goats can be transmitted to farmers, shepherds, and veterinarians.
  - *Milker's nodule:* Closely related to orf, but infects udders of cows and is transferred to dairy farmers and veterinarians.
- **Fungal diseases:**
  - *Candidiasis:* Candidal paronychia are common in bakers and food handlers.
  - *Sporotrichosis:* Inoculation of plant material can transfer *Sporothrix schenckii* to gardeners, forestry workers.
  - *Dermatophyte infections:* Those around cattle often acquire severe but self-limited infection with *Trichophyton verrucosum* during first period of exposure.

Acne (p. 530)

- **Chloracne:** Caused by exposure to halogenated hydrocarbons, such as dioxin, chloracne features closed comedones and cysts, as well as hyperpigmentation. Exposure may be via military service (Agent Orange pesticide exposure in Viet Nam), contaminated foods, industrial accidents (Seveso accident), or even poisoning as occurred in a prominent Ukrainian politician in 2005.
- **Tar acne:** Pitch, tar, and oils can cause comedonal or pustular acne. Today cutting oils are most common; be suspicious when acneiform lesions are seen on anterior thighs or abdomen where oils can be splashed.

Skin Cancers

- **UV exposure** is the most common cause, playing a role in skin cancers across the range of occupations including pilots, farmers, military personal, athletes, welders, and many others.
- **Hydrocarbons**, such as pitch, tar, and other compounds, may also cause skin cancers. The first known report of occupational cancer was scrotal cancer in chimney sweeps. Today risk groups include road construction workers, roofers, and refinery workers.
- **Arsenic** exposure in mining activites in areas such as Taiwan and Argentina, as well as in industrial processes, can cause skin cancers. Today most exposure worldwide is through contaminated ground water in Bangladesh.

Vibration Syndrome

- The use of tools with marked vibration such as jackhammers, stamping machines, or chain saws may lead to vasospasm or white fingers. Smoking and cold weather are co-factors. The spasm is different from Raynaud syndome in that it is asymmetrical. Raynaud syndrome and acro-osteolysis can be induced by exposure to vinyl chlorides, while systemic sclerosis with Raynaud syndrome can be caused by exposure to silica.

39 Skin Diseases in Different Age Groups

39.1 Skin Diseases in Pregnancy

Overview

- Many skin changes occur during pregnancy. They can be grouped into physiologic variations, changes in preexisting dermatoses, and pregnancy-specific dermatoses.

Note: Remember that what is common in nonpregnant patients is also common in pregnancy. Always think of common diseases first—atopic dermatitis, acne, and scabies are all commonly misdiagnosed as other, more exotic conditions.

- **Physiologic changes:** Most are likely caused by hormonal changes:
  - Striae distensae.
  - Hyperpigmentation of nipples, genitalia, and perianal region. Linea alba (midline of abdomen) darkens and is known as *linea nigra*. Facial hyperpigmentation known as *melasma* or "*mask of pregnancy*" (p. 379).
  - Seborrhea, hyperhidrosis, hypertrichosis.
  - Androgenic alopecia may improve with increased levels of estrogens.
  - Postpartum telogen effluvium.
  - Eruptive vascular lesions (nevus araneous or vascular spiders) and palmar erythema.
- **Changes in pre-existing or latent dermatoses:**
  - Darkening, growth and perhaps increase in number of melanocytic nevi.
  - Growth of neurofibromas.
  - *Tend to improve:* Acne, acne inversa, psoriasis and sarcoidosis.
  - *May improve or worsen:* Atopic dermatitis, pustular psoriasis.
  - *Tend to worsen:* Autoimmune collagen-vascular disorders (lupus erythematosus, dermatomyositis, systemic sclerosis), autoimmune bullous diseases (fetal involvement possible via transplacental transfer of antibodies), invasive or metastatic melanoma, porphyria cutanea tarda, Ehlers–Danlos syndrome, pseudoxanthoma elasticum, viral and fungal infections.
- **Pregnancy-specific dermatoses**.

Cholestasis of Pregnancy

- **Synonym:** Pruritus of pregnancy.
- **Pathogenesis:** Common disorder occurring in up to 2% of pregnancies; idiosyncratic hormonally driven reduction in bile transport.
- **Clinical features:** Presents with intense pruritus in second or third trimester; rarely accompanied by dark urine or jaundice. No problems in mother, but slight increase in fetal mortality and prematurity. Likely to recur in subsequent pregnancies and perhaps with oral contraceptives.

  Note: The most common cause of jaundice in pregnancy is viral hepatitis.
- **Diagnostic approach:** Elevated bilirubin with possible mild elevations in AST, ALT; any other changes should mandate search for other liver disease.
- **Differential diagnosis:**
  - *Pruritus:* Look for other signs of pruritic diseases, such as scabies or atopic dermatitis.

- *Jaundice:* Hyperemesis gravidarum, viral hepatitis, acute fatty liver of pregnancy.
- *Jaundice + thrombocytopenia:* HELLP syndrome (**h**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelets).

► **Therapy:** Cholestyramine 8–12 g daily in 2–3 divided doses for itch. Vitamin K if hypoprothrombinemia develops. Consider induction of labor.

Erythema Nodosum Gravidarum

► Just as erythema nodosum occasionally appears correlated with menses or oral contraceptives, sometimes it appears in the first trimester or early second trimester without apparent cause. Patient must be investigated just as any other patient with erythema nodosum (p. 540). If secondary to pregnancy, usually resolves by third trimester but may recur with subsequent pregnancies or hormone exposure.

! ***Caution:*** NSAIDs should not be used in the third trimester; they may cause premature closure of the ductus arteriosus.

Pemphoidus Gestationis

This is the most specific dermatosis of pregnancy, an autoimmune bullous disease that may also transiently affect the newborn (p. 238).

Pruritic Urticarial Papules and Plaques of Pregnancy

► **Synonym:** PUPPP (acronym), polymorphic eruption of pregnancy.
► **Definition:** Intensely pruritic eruption, usually occurring in last trimester.
► **Clinical features:** The distended abdomen is the most common site; sometimes the urticarial papules and plaques preferentially involve the striae. May also involve trunk, thighs, and upper arms. No other signs and symptoms and no complications. Resolves after delivery. No risk to child.
► **Histology:** Not diagnostic. Superficial and deep perivascular lymphocytic and eosinophilic infiltrates. Sometimes spongiosis or acanthosis.
► **Therapy:** Topical corticosteroids; in rare cases, systemic corticosteroids needed.

Prurigo Gestationis

► **Definition:** Association of intense pruritus in third trimester with excoriations and prurigo papules.
► **Pathogenesis:** Many of these patients have atopic diathesis, and their skin diseases flares in pregnancy.
► **Clinical features:** Marked pruritus, excoriations, erosions, prurigo nodules.
► **Diagnostic approach:** No specific clinical or histologic criteria.
► **Differential diagnosis:** Exclude hepatic disease (cholestasis of pregnancy occurs early but hyperemesis, HELPP occur late), folliculitis and other pruritic dermatosis (scabies). Search for stigmata of atopy.
► **Therapy:** Symptomatic topical antipruritic measures.

Impetigo Herpetiformis

► **Definition:** Severe annular pustular psoriasis (p. 265) in pregnancy.
► **Pathogenesis:** Unknown, but may be associated with or lead to hypoparathyroidism.
► **Clinical features:** Erythematous patches with peripheral pustules and central scales favoring abdomen or upper inner thighs. Systemic signs and symptoms in-

cluding fever, chills, nausea and vomiting; in some cases hypocalcemia with tetany. Potentially fatal, and increased fetal mortality.
- **Histology:** Intraepidermal accumulations of neutrophils without evidence for infectious agents.
- **Diagnostic approach:** Clinical examination, history of psoriasis, leukocytosis, elevated sed rate, calcium level, exclude hypoparathyroidism.
- **Differential diagnosis:** Occasionally described in nonpregnant patients; then we prefer diagnosis of pustular psoriasis. IgA pemphigus may appear similar; consider immunofluorescence studies.
- **Therapy:** Multidisciplinary management with obstetrician and pediatrician. Systemic corticosteroids and meticulous supportive care, usually in hospital, are required.

39.2 Dermatoses in Childhood

The differential diagnostic considerations for the classic childhood exanthems are shown in Table 39.1.

Table 39.1 · Classic exanthems

	Diagnosis	Clues
1	Measles	Fever, sniffles, cough, skin changes start behind ears, Koplik spots
2	German measles (rubella)	Resembles common cold, skin changes start on face, lymphadenopathy
3	Scarlet fever (scarlatina)	Starts on neck, favors flexures, pharynx dark red, tonsils enlarged/inflamed, white strawberry tongue
4	Dukes disease	No longer diagnosed
5	Erythema infectiosum (fifth disease)	Begins on trunk, later face ("slapped cheeks"), sometimes lacy pattern on arms, pharyngitis, fever, malaise
6	Roseola infantum (exanthem subitum, sixth disease)	Infants, sudden high fever, as the fever resolves, pale red macules on trunk which last about 1 day, no lymphadenopathy
	Varicella (chickenpox)	1–2 cm oval erythematous macules with central blister, lesions in various stages, scalp and oral mucosa affected, palms and soles spared, pruritic

Classic Childhood Exanthems

Traditionally, there were six childhood exanthems. Many have become rare today because of immunization or the wider use of antibiotics, and nowdays most childhood exanthems are caused by Cocksackie and enteroviruses. The left-hand column indicates the numbers attached to the classic exanthems over 100 years ago. The terms "fifth disease" and "sixth disease" are still occasionally used.
Most of these have fortunately become uncommon because of effective immunizations. The ill-advised trend of avoiding immunizations in many developed countries has led to increasing numbers of all the exanthems in recent years.

Measles

- **Synonym:** Morbilli.
  - ***Note:*** The name rubeola means measles in German and English, but rubella in French and Spanish—thus best avoided.
- **Definition:** Acute viral infection of childhood with typical exanthem and severe general signs and symptoms.
- **Pathogenesis:** Measles virus is a paramyxovirus, spread by droplets. Highly infectious; over 90% of infected individuals are clinically ill.
- **Clinical features:** Three stages:
  - *Incubation period:* 9–12 days.
  - *Prodrome*: 3–4 days.
    - Fever, runny nose, cough, conjunctivitis (worse on lids, making eyes appeared circled), photophobia.
    - Tiny white spots on buccal mucosa (Koplik spots) persist into exanthem phase. Patchy erythema of palate (3–4 days).
  - *Exanthematous phase:* 3–4 days.
    - Initially fever disappears, but then recurs.
    - Maculopapular exanthem starts behind ears and on forehead; later spreads to neck and trunk and finally to extremities including palms and soles. Initially pale, but becomes deep red and may scale.
    - Complications include encephalitis, pneumonia, otitis media, and as delayed effect, subacute sclerosing panencephalitis.
- **Diagnostic approach:** Clinical features, exposure, lack of immunization; increase in titer of IgG antibodies.
- **Differential diagnosis:** Rubella, other viral infections, scarlet fever.
- **Therapy:** Supportive care, bedrest, antipyretics; in severe cases or with complications, antibiotics or immunoglobulins.
- **Prophylaxis:** Immunization is part of MMR (measles, mumps, rubella) administered at 12–15 months. This provides long-term immunity, as does primary infection.

Rubella

- **Synonyms:** German measles, 3-day measles.
- **Definition:** Common relatively mild viral infection of children and young adults; causes severe fetal damage if contracted in early pregnancy.
- **Pathogenesis:** Rubella virus is a togavirus, spread by droplet infection with high infection rate, but more asymptomatic cases than measles.
- **Clinical features:**
  - *Incubation period:* 14–21 days.
  - *Prodrome:* Minimal complaints, mild common cold; 3–4 days.
  - *Exanthematous phase:* 2–3 days.
    - Starts on face; erythematous macules and papules with pale periphery; spread rapidly to neck, trunk, and extremities; disappear over 3 days (much more transient than measles).
    - Prominent retroauricular, occipital, and cervical lymphadenopathy; sometimes tender.
    - Complications include fetal defects in first 16 weeks of pregnancy (*Gregg syndrome*: ocular, hearing, and cardiac problems), as well as purpura, encephalitis, and in adults arthritis.
- **Diagnostic approach:** Clinical features, lack of immunization, increase in IgG or IgM titers; prenatal diagnosis of viral RNA in amniotic fluid or later fetal blood antibodies possible.

- **Differential diagnosis:** Measles, other viral exanthems, scarlet fever.
- **Therapy:** None needed; with complications, immunoglobulin available. Isolation from pregnant or potentially pregnant women. If pregnant patient is exposed, multidisciplinary consideration for immunoglobulin; only helps if given before exanthem develops.
- **Prophylaxis:** Immunization with MMR. All girls who do not have titers by puberty must be immunized to reduce risk of fetal malformations.

Scarlet Fever

- **Definition:** Generalized exanthem caused by erythrogenic toxins from group A streptococci.
- **Epidemiology:** Most patients are children < 10 years of age.
- **Clinical features:**
  - The cutaneous and mucosal features in scarlet fever appear 1–2 days after the pharyngitis and tonsillitis. Patients are ill with fever, chills, and malaise.
  - *Enanthem*: The pharynx is usually dusky red, when enlarged, inflamed tonsils. The tongue initially has a white cover, then the red papillae become apparent (*white strawberry tongue*), and then later the coating is shed, revealing a red swollen tongue (*strawberry tongue*).
  - *Exanthem*: The rash usually starts on neck and spreads to trunk and extremities. After 2 days, spread is complete. The flexures are most prominently affected (*Pastia lines*), while the palms and soles are spared. Running one's hand over the skin is described as the "*sandpaper sign*." The erythema resolves after 3–5 days, followed by widespread shedding, most noticeable on the palms and soles.
- **Complications:** Glomerulonephritis, rheumatic fever, otitis, sinusitis.
- **Diagnostic approach:** Throat culture.
- **Therapy:** Penicillin V–K 250 mg t.i.d. for 10 days; acutely ill children may benefit from initial intramuscular dose.

Erythema Infectiosum

- **Synonym:** Fifth disease.
- **Definition:** Infection with parvovirus B19 causing fever and distinctive skin reaction pattern.
- **Epidemiology:** Occurs between 5 and 10 years of age; moderately contagious, occurs in epidemics; 50% of teenagers have immunity.
- **Pathogenesis:** B19 has affinity for bone marrow erythropoietic cells via P antigen. Causes considerable problems in pregnancy, as well as in patients with chronic anemia and immunosuppression, especially bone marrow transplantation patients.
- **Clinical features:**
  - Two classic skin findings:
    - *Slapped cheek sign:* Erythema of cheeks, sometimes figurate.
    - *Garland sign:* Reticulate erythema of extensor surfaces of arms.
    - Both may be missing, and patient may have pruritus and a maculopapular exanthem
  - Associated findings include fever, lymphadenopathy, pharyngitis.
  - Infection in children with chronic anemia, bone marrow transplantation patients, and other immunosuppressed patients can lead to *aplastic crisis*.
  - Infection in pregnancy may lead to fetal death (first trimester), hydrops (second trimester), or transient aplastic anemia (third trimester).

- **Diagnostic approach:** In child or adult, if any clinical question, check IgM antibodies or PCR for viral DNA, especially if contact with pregnant individual. In pregnancy, multidisciplinary approach with fetal ultrasound monitoring, search for antibodies and viral DNA.
- **Differential diagnosis:** Other viral exanthems, especially when classic findings not present.
- **Therapy:** Symptomatic.

Exanthema Subitum

- **Synonyms:** Exanthem subitum, roseola infantum, sixth disease.
- **Definition:** Viral infection of small children with high fever and transient rash.
- **Epidemiology:** Usually affects children 6 months–3 years of age; caused by human herpesvirus 6 (HHV-6) (and less often HHV-7). Runs in epidemics.
- **Clinical features:**
  - Sudden high fever (40 °C) lasting 3–5 days, with child surprisingly asymptomatic. Enanthem possible.
  - As fever breaks, pale pink-red macules on trunk lasting 1 day.
  - No lymphadenopathy or other associated findings.
- **Diagnostic approach:** Usually clinical diagnosis, but leukopenia, IgM antibodies and HHV can be identified.
- **Differential diagnosis:** Many other viral exanthems.
- **Therapy:** Symptomatic.

Other Childhood Exanthems

Erythema Toxicum Neonatorum

- **Definition:** Common erythemato-squamous eruption of first week of life.
- **Epidemiology:** Present in up to 50% of infants; usually starts 1–2 days after birth.
- **Clinical features:** Erythematous macules on trunk and extremities; associated with wheals and pustules; harmless and not toxic.
- **Diagnostic approach:** Smear from pustule rich in eosinophils.
- **Differential diagnosis:**
  - *Neonatal pustular melanosis*: Possible variant of erythema neonatorum, more common in dark-skinned infants; pustules plus scaly hyperpigmented macules representing older lesions.
  - *Impetigo:* Child sick, smear contains neutrophils.
  - *Miliaria:* Usually occurs later, often intertriginous or on trunk.
  - If purely pustular, consider neonatal *herpes simplex* and *Candida* infections.
  - If child is older, consider *infantile acropustulosis*.
- **Therapy:** None required.

Gianotti–Crosti Syndrome

- **Synonyms:** Infantile acrodermatitis, papular acrodermatitis of childhood, acrodermatitis papulosa infantum.
- **Definition:** Acral viral exanthem caused by many different agents.
- **Epidemiology:** 90% of patients are < 4 years of age.
- **Pathogenesis:** Initially associated with hepatitis B, but now clear that many different viruses can cause same clinical picture. Most common cause in countries where hepatitis B immunizations are used is Epstein–Barr virus. Some form of aberrant immune response, seen only in small percentage of infected patients.

- **Clinical features:**
  - Lichenoid red-brown papules on cheeks, extensor surfaces of extremities and buttocks. Resolve spontaneous over a few days; in rare cases, more persistent. Usually nonpruritic.
  - Associated signs and symptoms vary with causative virus.
- **Diagnostic approach:** Clinical diagnosis; search for HBsAg, but not necessary to do extensive viral epidemiology.
- **Differential diagnosis:** Easy clinical diagnosis in young children; in older children and adults, consider lichen planus, lichen nitidus and lichenoid drug eruption.
- **Therapy:** Symptomatic.

Papular Purpuric Gloves and Socks Syndrome

- Caused by many different viruses; most commonly B19, HHV-6. Patients present with edema and purpura of the palms and soles; occasional spread to dorsal surfaces of hands and feet or onto limbs. Many have enanthem and about 10% have lymphadenopathy. Self-limited, clearing in 1–2 weeks; only supportive care is needed.

Unilateral Laterothoracic Exanthem

- **Synonym:** Asymmetric periflexural exanthem of childhood.
- Peculiar eruption usually starting in one axilla and spreading centrifugally. Cause unknown. Features macules, papules and lacy spreading rings. Eventually thorax is then involved and then dissemination may occur to other half of body. Other signs and symptoms minimal. Resolves over 1–2 weeks. Symptomatic treatment.

Child Abuse

- Dermatologists have a responsibility not to overlook signs of possible child abuse, and at the same time not to misdiagnosis dermatologic conditions as child abuse. Neither task is easy.
- In many health systems, specially trained nurses and physicians are available to help evaluate such cases in order to insure that no abused child is overlooked, but that at the same time the rights and feelings of parents are respected. In most instances physicians are legally required to report suspected child abuse.

Caution: Every dermatologist must be informed about the local legal and social aspects of referral for potential child abuse.

- It is usually wisest to say to the parents something like, "This seems to be a difficult type of case, not responding as we had expected; we would like to have one of our special nurses examine your child." Confrontation during the physical examination is almost always a social disaster and sometimes a legal one.
- **Clinical features:** Any difficult-to-explain clinical finding in a child raises the question of abuse. Examples include:
  - Bruises or hematomas that seem excessive or recurrent, or follow lines that suggest use of a belt for whipping.
  - Anogenital warts, tears, fissures, or bruises, gaping anus.
  - Blisters and ulcers not fitting pattern for childhood bullous diseases.
  - Uniform skin lesions about the diameter of a cigarette.
  - Burns with peculiar patterns, suggesting body part was dipped or held in hot water.

  Caution: Recurrent appearances in the emergency room with bruises, trauma, or unexplained findings are an absolute danger sign.

- The reverse side of the coin is conditions that can mimic child abuse (Table 39.**2**). Accusing parents of child abuse when they are innocent may also have catastrophic effects. There are several reports in the medical literature of "epidemics " of child abuse in communities caused by overzealous physicians or nurses misinterpreting harmless findings.

Table 39.2 · **Diseases that can mimic child abuse**

Clinical finding	Possible abuse
Hematomas following accident, especially in children with hematologic disorders	Beating
Dermatitis artefacta	Beating, burning, cutting
Ehlers–Danlos syndrome (hematomas, scars, fragile skin)	Beating
Epidermolysis bullosa (fragile skin)	Burns, scalds
Lichen sclerosus (perianal subtle hemorrhage)	Sexual abuse
Epidermal nevus in anogenital region	Viral warts following sexual abuse
Localized pemphigoid in anogenital region (ulcers, erosions)	Sexual abuse
Mongolian spot (blue-gray dermal pigmentation)	Trauma
Phytophotodermatitis	Burns, scalds, whipping
Bleomycin hyperpigmentation (hyperpigmented bizarre streaks)	Whipping
Staphylococcal scalded skin syndrome	Burns, scalds
Pityriasis lichenoides et varioliformis acuta	Cigarette trauma
Genital psoriasis	Sexual abuse
Striae distensae	Whipping
Diaper dermatitis	Inadequate care, sexual abuse
Crohn disease (gaping anus)	Sexual abuse

39.3 Geriatric Dermatology

Overview

- There are two major types of cutaneous aging:
  - *Instrinsic aging:* Natural changes: "ticking of biological clock".
  - *Extrinsic aging:* Major extrinsic factor is UV irradiation; effects of chronic UV exposure include increased risk of cutaneous malignancy, as well as many other changes.
    - ***Note:*** The easiest way to form visual image of extrinsic versus intrinsic aging is to compare the skin of the forearm to the skin of the buttocks in an elderly individual.
  - As both life expectancy and UV exposure increase, the number of aging-related cutaneous disorders has increased and will continue to do so.

- **Intrinsic aging (functional changes):** Epidermal atrophy, decreased cell turnover leading to reduced wound repair, fewer Langerhans cells and generally impaired immune response, decreased sensation, drier skin (less sebum and epidermal lipids), decreased hairs, less vitamin D production, less sweating (impaired thermoregulation) and less vascular reactivity.
- **Extrinsic aging (UV-induced changes):** DNA and mitochondrial damage leading to basal cell carcinomas, actinic keratoses squamous cell carcinomas and malignant melanomas; induction of matrix metalloproteinases (solar elastosis); accelerated cell death; vascular changes.
- **Clinical features**
  - Skin is generally drier, less turgid, often with fine scaling.
  - Excessive washing or inadequate lubrication leads to increased scaling, dryness and pruritus; main factors are altered epidermal lipids and sebum, as well as changes in sweating.
  - *Changes in hair:*
    - *Both sexes:* Graying of hair (canities) and reduced density of genital and axillary hairs.
      - ***Note:*** The temporal bone acquired its name because it typically underlies the first site where gray hairs appear (tempora is the plural of the Latin tempus = time).
    - *Women:* Increased moustache or beard hairs, as well as androgenic alopecia.
    - *Men:* Most have some degree of androgenic alopecia; increased hair growth in ears, nostrils, eyebrows.
  - *Nails* grow more slowly, become dry and brittle, often develop longitudinal ridges and on the feet may become thickened and dystrophic, either with or without accompanying onychomycosis.
  - *Light-exposed skin* features wrinkles, deep furrows (especially on nape), focal hyper- and hypopigmentation, telangiectases, senile purpura (hemorrhages on forearms secondary to weakened vessels), stellate pseudoscars (white irregular patches on forearms). Likelihood of malignancies depends on skin type and amount of UV exposure; almost every patient in Western countries has a few actinic keratoses. A peculiar finding is periorbital comedones (Favre–Racouchot disease).
  - Seborrheic keratoses are an almost normal finding, most commonly on the trunk.
- **Skin care:**
  - Nondrying soaps or synthetic detergents should be used; skin should be promptly lubricated after bath or shower. Many older patients require help to do this.
  - Extremely dry skin benefits from use of lotions or creams containing urea or lactic acid. Just as in children, the greater sensitivity of elderly skin may lead to burning after application.
  - Topical retinoids and hydroxy acids seem to be the most effective simple approaches to arresting or partially reversing photodamage. They should be combined with adequate sun protection.
- **Common dermatoses in elderly people:**
  - *Scalp:* Seborrheic dermatitis; in those with bald heads—actinic keratoses, basal cell carcinoma, squamous cell carcinoma.
  - *Face:* Angular stomatitis (perlèche) from improperly fitting dentures or drooling, actinic cheilitis, rosacea, rhinophyma, xanthelasma, seborrheic keratoses, keratoacanthoma, basal cell carcinoma, squamous cell carcinoma, lentigo maligna melanoma.

- *Trunk:* Seborrheic keratoses, candidiasis, tinea corporis, senile angiomas, basal cell carcinoma (superficial type), Bowen disease, Paget disease, superficial spreading melanoma, nodular melanoma, lymphoma.
- *Extremities:* Squamous cell carcinoma, basal cell carcinoma, Bowen disease, extramammary Paget disease, superficial spreading melanoma, acral-lentiginous melanoma, nodular melanoma, lymphoma.
- *Anogenital region:* Candidiasis, erythroplasia (mucosal squamous cell carcinoma in situ), lichen sclerosus, extramammary Paget disease, Bowen disease, plasma cell balanitis or mucositis.
- *Entire body:* Erythroderma, large-patch parapsoriasis, lymphoma, zoster, paraneoplastic markers.
- Treatment is covered in the respective chapters.

40 Psychodermatology

Overview

► **Definition:** Psychodermatology concerns itself with the psychological causes of skin diseases and the patient's psychological adjustments to having skin diseases. Skin diseases can be completely somatic (seborrheic keratosis), somatic but with marked effect on psyche (malignant melanoma), somatic but with apparent emotional triggers (atopic dermatitis), or completely psychological (delusions of parasitosis).

The skin has long been considered a "mirror of the soul". We become red with anger or pale with fear. Our language also supports this connection; someone who annoys you "gets under your skin."

The skin, and especially the skin appendages, are richly innervated. Melanocytes, Merkel cells, and cutaneous nerves all arise from the neuroectoderm. Modern advances in psychoneuroimmunology have shed light on the fascinating interactions between the psyche, nervous system, endocrine organs, and immune system. For example:

- The immune system is innervated.
- Hematopoietic cells and neurons share certain receptors for neuropeptides and neurotransmitters.
- Lymphocytes can secrete many neuropeptides and other neuroendocrine factors.
- Cells of the immune system and nervous system can produce and react to the same cytokines.

There are two classic ways in which the nervous system and immune system communicate:

- Neuroendocrine peptides (growth hormone, prolactin, ACTH, β-endorphin, others) are secreted by the pituitary gland, which is controlled by factors secreted by the hypothalamus.
- The autonomic and sensory nervous systems interact directly with the immune system.

Many cutaneous cells (keratinocytes, melanocytes, fibroblasts, sebocytes) produce a variety of neurohormones, neurotransmitters, neuropeptides, and neurotrophins (nerve growth factor and others). In addition, they may express the corresponding receptors, a feature formerly considered to be limited to endocrine and neural cells.

The organs of the lymphoid system have sympathetic and cholinergic innervation. Sympathetic nerve endings are in close contact with antigen-presenting cells, T cells, and even B cells. Direct connections between cutaneous nerve endings and Langerhans cells or mast cells have also been shown. One can therefore postulate mechanisms for the neural and thus psychic control of the immune response in disorders such as atopic dermatitis. The old designation of neurodermatitis becomes modern once more, although we do not advocate switching names again.

Every pruritic dermatitis can become worse with stress. There are numerous possible mechanisms, including the central release of endorphins, which have analgesic and euphoric actions but also cause pruritus. Peripheral nerve endings may be triggered by stress to release various neuropeptides that cause mast cell degranulation and the release of histamine and other mediators as well as inflammatory infiltrates. The interactions between pruritus and stress can thus evolve into a vicious cycle.

Psychosomatic Dermatoses

Examples of dermatoses in which it is extremely difficult to separate the physical and emotional comments include atopic dermatitis, chronic urticaria, psoriasis, idiopathic pruritus, prurigo simplex, lichen simplex chronicus, acne excoriée, and stress-induced telogen effluvium. The exact neurophysiologic mechanisms influencing these disorders remain a subject of discussion and research.
The mainstay of therapy should be appropriate topical and systemic treatment. Without question, psychotropic medications, psychological therapy (behavior therapy, relaxation therapy) and even psychodynamic approaches (group therapy, individual therapy) can be useful supplements, as can training of patients and parents in how to best cope with the disease.

Body Dysmorphic Disorder

- **Synonym:** Dysmorphophobia.
- **Definition:** Mental disorder in which a person of normal appearance is preoccupied with an imagined defect in appearance, or overconcerned about a minor abnormality.
- **Epidemiology:** Estimated that 1% of population and 10% of dermatologic practice suffer from this disorder; typical patients are young, unhappy, worried women.
- **Pathogenesis:** These patients display features both of obsessive-compulsive behavior (frequently checking mirror) and of delusional thinking (firmly convinced of an abnormality).
- **Clinical features:** Typical complaints include:
  - Facial burning, unclean skin, too many vessels, burning, other defects that are not visible to anyone else.
  - Scalp or tongue burning.
  - Anogenital problems (pruritus, discharge, fear of venereal diseases or HIV).
- **Diagnostic approach:** Absolutely essential to exclude underlying diseases, but at the same time not reinforce disease perception by endless testing. Requires tremendous skill as physician to walk this line.
- **Therapy:**
  - Establish confidence, assure patient that you take the problem seriously.
  - Consider referral to psychologist or psychiatrist; this is almost always refused.
  - Neurotropic agents can be helpful:
    - Selective serotonin re-uptake inhibitors (SSRI) are preferred for obsessive-compulsive problems.
    - Antipsychotic agents are required for those with delusional behavior.

  Caution: We deliberately avoid recommending medications or dosages. Any physician who feels they want to employ psychotropic medications for dermatologic patients is ethically obliged to obtain special training and expertise in the use of these agents.

Delusions of Parasitosis

- **Synonyms:** Monosymptomatic hypochondrial psychosis, delusional disorder—somatic type.
- **Definition:** Psychiatric disorder in which patients are firmly convinced they have a parasitic infestation.
- **Epidemiology:** Uncommon disease, usually involves middle-aged or older women, often from higher socio-economic groups. In younger patients, male:female ratio is equal and there is often history of substance abuse.

- **Pathogenesis:** These patients are not psychotic, because their psychosis centers around just one point; other mental functions are surprisingly normal. Some speak of an *encapsulated psychosis.*
- **Clinical features:**
  - The patients typically present with widespread excoriations, a long history, and often carrying a small bottle or box. In the box they have meticulously saved all the "parasites" harvested from their skin, but microscopic examination of the contents reveals only threads, scales, and dirt. They may complain of *formication* (sensation of arthropods crawling on their skin, biting and stinging them). Most have been diagnosed several times as having scabies and treated with scabicides.
  - Two other monosymptomatic hypochondrial psychoses may occasionally be seen by dermatologists:
    - *Delusions of bromhidrosis (unpleasant body odor):* Patients exude a normal body odor but they are convinced they smell so bad that no one can bear to be in their presence.
    - *Delusions of facial asymmetry:* Patients are convinced their face is distorted, usually presenting with a mirror to demonstrate the asymmetry explicitly. Careful morphometric studies actually show that every face is asymmetrical, but this is no consolation to the patient.
  - A final fascinating aspect is the frequency with which family members come to share the delusion—known as *folie à deux.* The "deux" is not always accurate, as sometimes many individuals are involved.
- **Diagnostic approach:**
  - Exclude all causes of pruritus that have not been already investigated.
  - Force yourself to examine the contents of the box or bottle again.
- **Therapy:**
  - Unless scabies is identified, resist the temptation to try a scabicide one more time, just in case.
  - Topical antipruritics.
  - Antipsychotic medication is the only thing that helps. The most effective agent is pimozide, approved for Tourette syndrome. We have found it useful to explain to the patient that we know they do not have Tourette syndrome (thank goodness) but for a peculiar reason unknown to all, they seem to require the same medication. Pimozide is not easy to use and newer antipsychotics will likely replace it. Once again, training and experience in using psychotropic medications is required.

Dermatitis Artefacta

- **Definition:** Psychocutaneous disorder in which the patient inflicts cutaneous damage to satisfy underlying need.
- **Epidemiology:** Rare disease, almost limited to women, and often those with connection to health care field.
- **Pathogenesis:** Most patients have borderline personality disorder and there is no clear social explanation for their behavior. In some instances, the skin damage is a reaction to stress that they cannot otherwise manage.
- **Clinical features:**
  - Lesions are highly variable, but typically difficult to assign to an established dermatosis, absent from areas patient cannot reach (mid-back), common on forearms, face, and breasts, and more likely to be on contralateral side from dominant hand. They may appear as erosions, ulcers, burns, hemorrhagic lesions, or abscesses.

- Typical measures include applying irritating chemicals, injecting urine, feces, milk, or the like, or excessive painful manipulation. Cigarette burns are favorite trick; always be suspicious of lesions roughly the diameter of a cigarette. Self-induced ulcers are typically highly irregular. Another classic feature is a failure to respond to therapy.

► **Diagnostic approach:** Once again, one must may every effort to exclude nonartifactual disease, such as vasculitis, pyoderma gangrenosum, hematologic disorders, or immune defects. Cultures from abscesses revealing mixed pathogenic organisms often suggests artifactual disease.

► **Differential diagnosis:** There are several other psychodermatological considerations:

- *Malingering:* Patient induces lesions intentionally for a conscious benefit, such as creating the suspicion of an occupational injury.
- *Munchausen syndrome:* An extreme example of a factious disorder in which the patient intentionally simulates signs and symptoms of disease for the purpose of obtaining treatment, but without any apparent motive.
- *Munchausen syndrome by proxy:* Occurs when someone else induces lesions in another so that the second party receives unnecessary diagnostic and therapeutic attention. In Munchausen by proxy, skin lesions are more common because it is easier to show the physician something on the other person.

► **Therapy:**

- Occlusive bandages or dressing will give the lesions a chance to heal and help confirm the working diagnosis.
- It is not usually helpful to confront the patient at first.
- If underlying psychiatric disorder is present (depression, generalized anxiety), treatment may help. Antipsychotic drugs are occasionally helpful.

Other Artifactual Diseases

There are a number of other diseases in which self-manipulation is clearly responsible, but where there is little evidence of accompanying emotional problems and the disease is usually controllable with antipruritic measures. Examples discussed elsewhere in this book include:

► Prurigo simplex subacuta (p. 329).
► Prurigo nodularis (p. 330).
► Lichen simplex chronicus (p. 330).
► Lip dermatitis from repeated biting, licking (p. 489).
► Trichotillomania; other forms of hair and nail manipulation (p. 506).

41 Topical Therapy

41.1 Overview

The skilled use of topical agents is what distinguishes a dermatologist from other physicians. An old truism is that a dermatologist can usually achieve more by choosing the best vehicle than can a non-dermatologist by using active ingredients in the wrong vehicle. Most of the advances in modern topical agents have been achieved by dermatologists working with industrial partners.

Topical Pharmacokinetics

- **Diffusion:** The movement of molecules along concentration gradient via random motion. For a topically applied agent to enter the skin, it must diffuse between the vehicle and the stratum corneum.
- **Adsorption:** The attachment of topically applied substances to the skin.
- **Absorption:** The uptake and storage of topically applied substances in the skin.
- Both adsorption and absorption are dependent on many factors, including:
  - *Location* (for example, number of hair follicles present).
  - *Age of patient:* Absorption much greater in neonates.
  - *Condition of skin:* Intact stratum corneum has maximum barrier function; as stratum corneum is abnormal or damaged, uptake of lipophilic agents is dramatically increased.
  - *Environmental factors:* Humidity, temperature.
  - *Choice of vehicle.*
- **Resorption:** The uptake of topically applied substances with transfer to blood vessels or lymphatics. In the case of most dermatologic agents, resorption is not desirable. For example, the less systemic uptake of corticosteroids, the better. On the other hand, in transdermal delivery systems (usually patches, sometimes ointments), resorption is the goal (estrogen, clonidine, nitroglycerin, scopolamine, and analgesic patches; nitroglycerin ointment).
- **Metabolism:** Cutaneous agents can be metabolized in the skin or resorbed and then metabolized in the liver. The skin contains all the relevant enzymes needed to metabolize foreign materials including oxygenases, hydrolases, transferases, and esterases; their activity is 1–5% of the corresponding liver enzymes. For example, benzoyl peroxide is almost 100% converted to benzoic acid in the skin.

Topical Agents

A topical medication consist of one or more active ingredients combined with a vehicle. The vehicle contains a base to which have been added preservatives, emulsifiers, fragrances, and other products. Water is present in almost every product.

Note: Ideally, a product should contain only one active ingredient. Occasionally two or three are present, but such products should be considered exceptions.

- **Vehicle:**
  - The vehicle is very important in determining the pharmacokinetics. For example, the active ingredient must be more soluble in the outer layer of the stratum corneum than in the vehicle, or diffusion will not start. Many tricks are used to insure maximum penetration, including adding agents that alter the stratum corneum (urea), or creating carrier structures (microsomes).
  - The following vehicles are recognized in the European prescribing regulations:
    - Hydrophobic (lipophilic) ointments.

- Absorption ointments: Water-in-oil (W/O) or oil-in-water (O/W) mixtures capable of taking up water.
- Hydrophilic ointments: Polyethylene glycol (macrogol) ointments.
- Hydrophobic creams (W/O creams).
- Hydrophilic creams (O/W creams).

Note: An aqueous liniment is an O/W emulsion with a high water content and is easily washed off. This is in sharp contrast to the older lay definition of a liniment as an almost oily liquid applied to the skin.

- Ambiphilic creams: Features of both O/W and W/O creams.
- O/W lotions.
- Hydrophobic gels.
- Hydrophilic gels.
- Shake lotions.
- Hard pastes.
- Soft pastes.
- Liquid pastes.

Note: In lay terms, an ointment is greasy, a cream rubs in, a gel is clear or translucent, and a paste or shake lotion contains a nondissolved powder.

- The most widely used ointment and cream bases in Germany are listed in Table 41.**1**. They are based on the *Neues Rezeptur Formularium* (NRF), the *Deutsches Arzneibuch* (DAB) 2004 edition and the *Deutscher Arzneimittel Codex* (DAC) 2004 edition.

Table 41.1 · Common ointment vehicles

	% Composition
Wool wax alcohol ointment DAB (Unguentum alcoholum lanae) (W/O absorption ointment with wool wax alcohol)	
Wool wax alcohol	6.0
Cetearyl alcohol	0.5
White petrolatum	93.5
Aqueous wool wax alcohol ointment DAB (Unguentum alcoholum lanae aquosum) (Hydrophobic or W/O cream)	
Wool wax alcohol ointment	50.0
Water	50.0
Hydrophobic Basiscreme DAC (NRF 11.104.) (Hydrophobic cream, W/O cream without wool wax)	
Triglycerol diisostearate	3.0
Isopropyl palmitate	2.4
Hydrophobic Basisgel DAC	24.6
Potassium sorbate	0.14
Water-free citric acid	0.07
Magnesium sulfate heptahydrate	0.5
Glycerol 85%	5.0
Water	64.29

Table 41.1 · Continued

	% Composition
Cooling ointment DAB (Unguentum leniens) (W/O cream without emulsifiers)	
Yellow wax	7.0
Cetyl palmitate	8.0
Peanut oil	60.0
Water	25.0
Basiscreme DAC (Ambiphilic cream)	
Glycerol monostearate	4.0
Cetyl alcohol	6.0
Mid-chain triglyceride	7.5
White petrolatum	22.5
Macrogol-1000 glycerol monostearate	7.0
Propylene glycol	10.0
Water	40.0
Hydrophilic ointment (Unguentum emulsificans) DAB (O/W absorption ointment, capable of taking up water)	
Emulsifying cetearyl alcohol (Type A)*	30.0
Thick paraffin	35.0
White petrolatum	35.0
Aqueous hydrophilic ointment (Unguentum emulsificans aquosum) DAB (Hydrophilic O/W cream—anionic)	
Hydrophilic ointment DAB	30.0
Water	70.0
Nonionic hydrophilic cream DAB (Unguentum emulsificans nonionicum aquosum) (Hydrophilic, O/W cream—nonionic)	
Polysorbate 60	5.0
Cetearyl alcohol	10.0
Glycerol 85%	10.0
White petrolatum	25.0
Water	50.0

* Mixture of cetearyl alcohol and godium cetearylsulfate

► **Preservatives and emulsifiers:**

- *Preservatives* are essential to prolong shelf life and to reduce the rate with which products decay when used. Common preservatives include sorbic acid, potassium sorbate, parabens, propylene glycol, and occasionally benzoic acid or sodium benzoate.
- *Emulsifiers* are used creative mixtures containing two immiscible substances. One substance is distributed in small globules throughout the other. The emulsifiers currently approved in Germany are shown in Table 41.**2**.

Table 41.2 · **Common emulsifiers**

Oil/water	Emulsifying cetearyl alcohol (type A)*
	Macrogol** sorbitan monostearate
	Macrogol** cetearyl ether 100
	Macrogol**-8-stearate
	Macrogol**-1000 monocetylether (Cetomacrogol 1000)
Water/oil	Wool wax and wool wax alcohols
	Triglycerol diisostearate
	Glycerol monostearate
	Sorbitan monostearate

* Mixture of cetearyl alcohol and sodium cetearylsulfate
** Macrogol is also known as polyethylene glycol

► An overview of the use of topical agents is presented in Table 41.**3**. It is based on the German formularies, but will still be useful to those working in other systems as a rough guideline.

Note: As one moves down chart, the cooling, drying and anti-inflammatory action decreases, while the lubrication and water retention increases!

Table 41.3 · **Use of dermatologic vehicles in different stages of diseases**

Vehicle	Examples	Stage of disease	Effect
Wet dressing		Acute	Cooling, debridement
Powder		Acute	Cooling, absorption
Shake lotion		Acute	Cooling, drying, anti-inflammatory
Non-stabilized	Lotio alba aquosa DAC or skin-colored (NRF 11.22.) Lotio alba spirituosa (NRF 11.3.) or skin-colored		
Stabilized	Emulsified zinc oxide shake lotion (NRF 11.49.) Aqueous zinc oxide paste FH Z.3		

Table 41.3 · **Continued**

Vehicle	Examples	Stage of disease	Effect
Hydrophilic paste	Hydrophilic zinc oxide paste 40% with ammonium bitumi-nosulfonate 5% (NRF 11.108.) Zinc oxide shake lotion 25% (NRF 11.109.) Emulsified zinc oxide shake lotion (NRF 11.49.)	Acute	Cooling, drying, anti-inflammatory
Solutions	Aqueous Alcoholic	Acute	Cooling, drying, anti-inflammatory
Hydrogels		Acute	Anti-inflammatory
Non-ionic	Hydroxyethyl cellulose gel DAB		
Anionic	Sodium carmellose gel DAB Aqueous carbomer gel DAB 2-propanol carbomer gel DAB		
O/W lotion		Subacute	Anti-inflammatory
Non-ionic	Hydrophilic emulsion base (NRF S. 25.) Cetomacrogol lotion FN		
Anionic	Tegin lotion		
O/W cream			
Nonionic	Aqueous liniment SR DAC (NRF 11.93.) Nonionic hydrophilic cream DAB Nonionic hydrophilic cream SR DAC (NRF S. 26.) Nonionic aqueous liniment DAC (NRF 11.92.)	Subacute	Anti-inflammatory
Anionic	Unguentum emulsificans aquosum DAB Anionic hydrophilic cream SR DAC (NRF S. 27.)		
Ambiphilic cream	Basiscreme DAC		Anti-inflammatory
Pseudo W/O cream	Cooling ointment DAB		Anti-inflammatory
O/W absorbent ointment			
Nonionic	Unguentum Cordes		
Anionic	Unguentum emulsificans DAB		

Continued Table 41.3 ▶

Table 41.3 · Continued

Vehicle	Examples	Stage of disease	Effect
W/O creams			
With wool wax	Unguentum alcoholum lanae aquosum DAB Eucerin cum aqua Lanolin DAB	Subacute	Anti-inflammatory
Without wool wax	Hydrophobic Basiscreme DAC (NRF 11.104.) Cremor sorbitansequioleati Cremor vaselini MB 59		
W/O absorbent ointments		Chronic	Lubrication, retains moisture
With wool wax	Unguentum alcoholum lanae DAB		
Without wool wax	Unguentum sorbitansequioleati Emulsifying ophthalmic ointment (NRF 15.20.)		
Lipophilic pastes			Lubrication, retains moisture
Hard	Zinc paste DAB (2 phase paste) Zinc oxide-starch absorption ointment ZL (2 phase paste)		
Soft	Soft zinc oxide paste DAB (2 phase paste)		
Liquid	Oleum zinci (NRF 11.20.)		
Carbohydrate and lipo gels	White petrolatum Ph. Eur.		Lubrication, retains moisture
	Simple ophthalmic ointment DAC Hydrophobic basis gel DAC (Oleo gel) Lard DAB (Lipo gel)		
Plaster			Activation
Occlusion			

From Wolf G, Süverkrüp R *Rezepturen: Probleme erkennen, lösen, vermeiden*. Deutscher Apotheker Verlag, 2002, pp. 117–172.

Urea

- Urea is a very useful addition. It is hygroscopic (water-binding) and keratolytic, as well as antiproliferative. Furthermore, it almost never causes allergic contact dermatitis. It is irritating and burns upon application, especially with higher concentrations, damaged skin, or in children.
- **Indications:** Urea can be used as a primary active ingredient for dry skin or hyperkeratotic lesions. It is useful for hyperkeratotic atopic dermatitis and psoriasis. In addition, it increases the penetration of corticosteroids and dithranol. In higher concentrations (40%), it can be used to remove dystrophic or onychomycotic nails (p. 697). Because it is nonsensitizing, it is ideal for long-term therapy.

Caution: Use cautiously in acute dermatitis; once healing has started, increase gradually 3% → 5% → 10%. In children, be sure they understand it will burn for a few minutes; if they are too young to understand, use 1–3%.

Salicylic Acid

- Excellent keratolytic agent; used at 2–10% concentration to remove scales in psoriasis and at higher (10–20%) concentrations for palmoplantar keratodermas and other markedly hyperkeratotic lesions. Like urea, it is irritating in acute stages.
- Often combined with dithranol, not only to increase penetration but also to stabilize the product.

Caution: Use with great care in children; absorption can rapidly lead to salicylism.

41.2 Topical Antiviral Therapy

Wart Therapy

Although there are a number of therapeutic approaches, none achieves more than a 50% cure rate. Flexibility is the key.

- **Keratolytics:** Salicylic or lactic acid (in concentrations from 5% to 20%) can be used in plasters, flexible collodion, or solutions:
  - The key to use is regular debridement (sanding, trimming, visits to office) coupled with daily application, ideally with some form of occlusion.
  - Many different mixtures with a variety of other ingredients including trichloracetic acid, oxalic acid, and even 5-fluorouracil are available.

Caution: Many stronger formulations are designed to be applied 1–2 × weekly by physician or nurse. Be sure you know the requirements for solutions you use.

- **Podophyllotoxin:** Antimitotic effect on microtubules; effective for mucosal warts but not cutaneous lesions. The specific commercial product containing purified podophyllotoxin is preferable to the older mixtures of podophyllin resin, which varied highly in contents and efficacy.
- **Topical immunotherapy:** Imiquimod is effective on genital warts but not cutaneous warts because the vehicle does not provide sufficient penetration (see below).
- **Cryotherapy:**
  - Liquid nitrogen is sprayed on the wart or applied with a special sound. If a cotton applicator is used, it must be large (such as a vaginal swab); an ordinary cotton bud does not transfer enough cold.
  - The cold kills the adjacent tissue and induces a blister; it does not kill the virus particles. Usual regimen is freeze for 10 seconds, allow to thaw, and repeat twice.

Note: Initially observe patients frequently after freezing until you develop a feel for how hard you must freeze to induce a blister.
- Freezing can be repeated 1–2 × weekly; once every 2 weeks is not adequate, as too much healing occurs in the interval.
- *Side-effects* include pain on application, painful blisters and erosions, slow healing. Difficult to use around the nails, or in children with multiple lesions.

- **Surgical measures:**
  - Patients often assume that when a wart is surgically removed, the cure rate is much higher than with other methods. This is not the case, leading to disappointed patients and recurrent warts in surgical scars.
  - Many approaches, all under local anesthesia, include curettage and cautery, electrosurgery alone, or scalpel excision.
- **Laser therapy:**
  - Ablation with CO_2 laser.
  - Destruction of feeder vessels with tunable dye laser.
- **Suggestion:** Placebo treatment is rarely indicated in dermatology, but in this special case, it can be endorsed. Warts have a relatively high spontaneous cure rate in children, so the approach has a scientific background. One can employ pure suggestive therapy, painting with fluorescent material and irradiating with Wood's light, or sham radiotherapy. Another possibility is to use a laser at doses so low that there is no tissue effect.
- **Other measures:**
  - Intralesional bleomycin (0.1 mg every 1–4 weeks); best avoided on acral areas.
  - Interferon (IFN)-α-2a or interferon-α-2b: 3 million IU weekly, along with destructive measures.

Imiquimod

- **Mechanism of action:** Stimulation of Toll-like receptor 7 on plasmacytoid dendritic cells and induction of cytokines essential to innate immune response, especially IFN-α, interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF).
- Major indication is condylomata acuminata and other mucosal warts; also promising for actinic keratoses and superficial basal cell carcinomas.
- Condylomata are treated 3 × weekly; medication applied and washed off after 6–10 hours. Erythema of treated areas indicates inflammatory response is being elicited. Treatment should last until lesions have healed, with maximum use for 16 weeks.
- For nonmucosal surfaces, prior handling with keratolytics, occlusion, or more frequent application may be needed.
- Suggested regimens for actinic keratoses and superficial basal cell carcinomas are 3 × weekly for 6 weeks, and then if inflammatory response is good, 2 × weekly for the next 6 weeks.
- Side effects include local irritation, varying depending on tissue and method of application.
- Proprietary products containing imiquimod are relatively expensive.

Acyclovir

- **Mechanism of action:** Inhibition of viral DNA polymerase by insertion of foreign base analogue.
- Topical acyclovir is widely available and frequently employed, but not very effective. It can be tried 5 × daily for 5 days, *starting immediately with first sign of tingling or pain,* in mild cases of recurrent herpes simplex virus infection.

- Side effects include burning, erythema, and rarely allergic contact dermatitis.
- **Note:** Systemic therapy is cheaper, more effective, and without serious side effects.

41.3 Topical Antibiotics

Overview

Topical antibiotics are controversial. At first glance, they appear a wise choice as one achieves effective control of bacteria without systemic risks. There are two excellent reasons *not* to use them:

- Induction of allergic reaction, which then makes systemic use of entire classes of antibiotics impossible.
- Increasing use is one possible factor in development of community-based resistant strains of bacteria.

In addition, there are many other antibacterial agents that can be employed (see next section).

Available Agents

- **Gentamicin:**
  - Optimum effect at pH 7.8; thus, does not combine with other products, especially those with acidic base.
  - Available as 0.1% creams and ointments.
  - Effective against staphylococci, *Proteus*, and *Klebsiella*.
  - *Side effects* include sensitization, ototoxicity, and even nephrotoxicity.
  - If chosen, only for short-term use on small wounds or superficial pyodermas.
- **Oxytetracycline:**
  - Available in 1–3% concentration as ointment, cream, solution, or ophthalmic ointment.
  - Effective against staphylococci, *Propionibacterium acnes*. When combined with polymyxin B, also against Gram-negative species such as *Pseudomonas aeruginosa*, *Proteus*, and *Klebsiella*.
  - Solutions used in acne vulgaris; problems with discoloration of skin.
  - Should not be used on wide areas during pregnancy nor around the nipple in nursing women because of effects on fetal teeth.
  - Terramycin ointment is a mixture of oxytetracycline and polymyxin B.
- **Erythromycin:**
  - Available as 0.5–4% cream, ointment or gel; also can be compounded using erythromycin base.
  - Effective against staphylococci, streptococci, and *Propionibacterium acnes*.
  - Widely used in acne.
  - Use with care during pregnancy or nursing.
  - Zineryt contains both erythromycin and zinc acetate, designed for acne.
- **Fusidic acid:**
  - Available in many forms including cream, ointment, gel, powder, impregnated gauze.
  - Effective against staphylococci, enterococci.
  - Widely used in Europe for wound care, pyoderma, secondarily infected dermatitis, and ulcers.
  - Very low rate of sensitization; rarely employed systemically.
  - **Note:** Probably the antibiotic best suited for topical use, with no apparent disadvantages for short-term use.

- **Metronidazole:**
  - Azole with unique nitro group; long used orally for trichomonas and rosacea; also effective against Gram-negative bacteria (such as in Gram-negative toe web infections and Gram-negative folliculitis).
  - Available as 0.5–1.0% creams and gels, or can be mixed (p. 695) for rosacea.
- **Chloramphenicol:**
  - Widely used for acne in Europe as alcoholic solution.
  - Controversial because of development of allergic contact dermatitis and, in rare but well documented cases, of bone marrow failure and aplastic anemia.

  Note: No longer recommended.

41.4 Dyes and Antiseptics

Overview

Dye solutions have long been a mainstay of dermatologic therapy in Europe, but they never received widespread acceptance in the USA. They have now been removed from some European formularies because of a (largely theoretical) risk of carcinogenesis.

- **Mechanism of action:** Antimycotic, antibacterial, drying, and in some instances anti-inflammatory.
- **Advantages:** Inexpensive, low incidence of allergic contact dermatitis, almost no resistance.
- **Disadvantages:** Stain everything, may inhibit keratinocyte and fibroblast proliferation in ulcers, theoretical risk of carcinogenesis. None has excellent evidence for effectiveness, although many have been used for almost a century.

Available Agents

- **Arning tincture:**
  - Active ingredients are anthrarobin and ammonium bituminosulfonate.

    Caution: Anthrarobin is often not available in pharmaceutical quality.
  - Weakly antimicrobial effect; very drying and somewhat anti-inflammatory.
  - Burns on use but does not stain.
- **Methylrosaniline chloride:**
  - Known in USA as methyl violet; main component of gentian violet, which it has replaced in Europe.
  - Used as 0.5–1.0% solution for candidiasis and intertrigo.
- **Gentian violet:**
  - No longer allowed in Europe; replaced by methylrosaniline chloride.
  - Available in USA; usually employed as 0.5–1.0% aqueous solution for candidiasis and intertrigo.
  - In higher concentrations, under occlusion (such as under foreskin) or in infants, can be irritating and cause necrosis.
- **Eosin:**
  - Available as both alcoholic and aqueous solutions for superficial infections.
- **Castellani paint:**
  - Long favorite for dermatophytosis in intertriginous sites, especially between toes; antimycotic, antibacterial, and drying.

- Also known as *carbolfuchsin topical solution* (USP). Contains basic fuchsin, phenol, resorcinol, acetone, alcohol, and water, as well as chlorocresol in some formularies. Resorcinol and chlorocresol no longer recommended in Europe.
- Replaced by 0.5% fuchsin solution in ethanol (NRF 11.26).

► **Brilliant green:**
- Difficult to manufacture without extensive heavy metal contamination.
- No longer employed in Europe.

Other Antimicrobial Agents

► **Clioquinol (iodochlorhydroxyquin):**
- Best known in USA under its trade name of Vioform.
- Available as 0.5–3.0% cream, ointment, or pastes. Also combined with low-potency corticosteroids (Vioform–HC).
- Popular for secondarily infected atopic dermatitis.
- Can also be compounded (p. 692).
- Inactivated by zinc and other cations; avoid using simultaneously in aqueous vehicle systems.

► **Chinolinol (8-hydroxy chinolin):**
- Close relative of clioquinol.
- Bacteriostatic and fungicidal.
- Widely used as 0.1% solution (NRF 11.127.) for wet dressings in pyoderma. If mixed as cream, care needed as it is inactivated by anionic hydrophilic creams or O/W creams.

► **Octenisept:**
- Combination of octenidine HCl 0.1 g and phenoxyethanol 2.0 g in 100 mL aqueous solution.
- Useful for skin and mucous membrane disinfection.
- Effective against broad range of bacteria, fungi, and viruses.

► **Povidone-iodine:**
- Combination of iodine and the complex polymer povidone (polyvinylpyrrolidone); slowly releases iodine.
- Antibacterial.
- Available in every imaginable form, usually at 10% concentration, including soaps, impregnated sponges for preoperative use, gels, creams, suppositories, and impregnated gauzes.
- Best known in USA as Betadine.
- Used for wound and ulcer care, pyoderma.
- Best avoided in all conditions where iodine is contraindicated (hyperthyroidism, dermatitis herpetiformis); avoid in pregnancy.

► **Silver sulfadiazine:**
- Silver derivative of sulfadiazine, a sulfonamide.
- Broad spectrum of antibacterial action; also effective against yeasts.
- Widely used for burn patients, known colloquially as "burn butter".
- Probably best reserved for acute use, as chronic use may increase risk of sensitization.

  ► ***Note:*** Silver sulfadiazine is a sulfonamide, capable of causing reactions in individuals sensitized to topical or systemic sulfonamides.
- Proprietary products have an excellent moisturizing base, which enhances their efficacy.

► **Potassium permanganate:**
- Dark-violet crystals; dissolves in water have weak antiseptic effect but very strong staining effect—can permanently stain towels and even bathtubs.

- Warn patient that skin and nails will have brown discoloration.
- Irritating if patient exposed to higher concentrations or especially nondissolved crystals.
- Use 1.0% stock solution (NRF 11.82) and dilute to provide concentrations in the range of 1:1000–1:5000.

► **Triclosan:**

- Organochloride compound with wide spectrum of action against Gram-negative and Gram-positive bacteria; also somewhat effective against yeasts and fungi. Can be compounded: hydrophobic triclosan cream 2% (NRF 11.122).
- Used as preservative; also for surgical soaps, in deodorants, and as surface disinfectant in 0.1–0.2% concentration.

Caution: If compounded, the triclosan must be pharmaceutical grade and certified free of dioxins, which can be contaminants in the manufacturing process.

41.5 Topical Antifungal Agents

There is a wide variety of topical antifungal agents, summarized in Table 41.**4**. The biggest family is the imidazoles, with over 20 representatives. Differences between members of the same class are minimal, despite manufacturers' claims to the contrary. Daily application suffices in most instances. There is no truly effective topical agent for onychomycosis, although nail varnishes are now available.

Table 41.4 · **Topical antifungal agents**

Agent	Spectrum		
	Dermatophytes	**Yeasts**	**Molds**
Polyenes			
Amphotericin B		+	
Nystatin		+	
Imidazoles			
Many	+	+	+
Allylamines			
Naftifine	+		
Terbinafine	+		
Hydroxypyridones			
Ciclopirox	+	+	+
Morpholines			
Amorolfin	+		

41.6 Topical Antiparasitic Agents

Permethrin

- **Mechanism of action:** Synthetic pyrethroid; mimics arthropod growth hormone and also interferes with sodium transport.
- **Indications:** Scabies, pediculosis; around the world, varying degrees of resistance; check with local public health authorities for recommended approach if unsure. Usual first-line agent.
- **Contraindications:** Can be used in pregnancy; nursing should be stopped for 3 days application; avoid in infants < 2 months.
- **Use:**
  - *Pediculosis capitis:* Use 1% lotion; apply to washed scalp for 30–45 minutes; rinse. Repeat in 1 week if live lice are found.
  - *Scabies*: Use 5% cream or lotion (2.5% for infants < 12 months); apply to entire body; leave on 12 hours; wash off. One application usually suffices.
- **Side effects:** Can be irritating; rare difficulty breathing or asthma.

Lindane

- **Synonym:** Gamma benzene hexachloride.
- **Mechanism of action:** Penetrates chitin exoskeleton; potent neurotoxin.
- **Indications:** Scabies, pediculosis; around the world, varying degrees of resistance; check with local public health authorities for recommended approach if unsure.
- **Contraindications:** Best avoided in pregnancy, nursing and infants < 2 years of age.
- **Use in scabies:**
  - Available as lotions and shampoos. Tend to be irritating and drying, especially if overused. Absorption (infants, damaged skin) can lead to neurotoxicity.
  - *Adults:* Apply lindane lotion each evening for three consecutive evenings (or for two consecutive evenings and then again in 1 week); wash off in morning. Wash bedding, clothes; treat all close contacts (sexual partners, children).
  - *Children 3–10 years:* Apply lotion to entire body for two consecutive days for 2 hours; wash off.
  - *Children < 3 years:*
    - Consider alternative agent.
    - Apply lotion to half of body for 2 hours; wash off; repeat on each side twice (total of 4 days of treatment).
- **Use in pediculosis:**
  - Use shampoo for 5 minutes or lotion for 12 hours. Wash off. Repeat in 1 week if viable organisms seen. Problems with resistance.

Malathion

- **Mechanism of action:** Organophosphorus insecticide; inhibits cholinesterase, blocking nerve transmission.
- **Indications:** Pediculosis; only agent without significant resistance; *not effective in scabies.*
- **Contraindications:** Occasional contact dermatitis; quite toxic if ingested.
- **Available** as 0.5% lotion.
- **Use:** Apply for 8–12 hours; rinse; repeat in 1 week if live lice are still present.

Benzyl benzoate

- **Mechanism of action:** One of the active substances in balsam of Peru; damages chitin exoskeleton.
- **Indications:** Second line treatment for scabies, pediculosis. Approved for careful use in pregnancy.
- **Available** as 25% solution or lotion in Europe; in USA has to be compounded as 25% lotion.
- **Use:** Apply nightly for three nights in scabies; apply 1–2 × for pediculosis.

Other Agents

- **Crotamiton:** Relatively ineffective agent against scabies and lice. Can be used during pregnancy or nursing. Apply daily for 3–5 days; leave on for 24 hours; wash and re-apply. Has some intrinsic antipruritic effect.
- **6–10% precipitated sulfur in petrolatum:** Old, messy, relatively ineffective treatment for scabies; advantage is that it is 100% safe in pregnancy and infancy; apply b.i.d. for 7–14 days.
- Many **natural pyrethrins** are available for the treatment of pediculosis. They tend to be irritating..

41.7 Topical Corticosteroids

Pharmacology

Corticosteroids are 21-C steroids synthesized by the adrenal cortex gland in response to ACTH, or less often angiotensin II. They are divided into *glucocorticoids*, which influence carbohydrate, fat and protein metabolism, and *mineralocorticoids*, which regulate electrolyte and water balance. Glucocorticoids are used almost exclusively in dermatology.

- The *resorption* of topical corticosteroids is very dependent on the site of application. Resorption is 1% on the forearm, 4% on the scalp, 7% on the forehead, and 36% on the scrotum. Resorption is also greater in infants and children. Both urea and DMSO can enhance resorption up to 4-fold. The influence of salicylic acid is controversial. Occlusion clearly enhances resorption.
- If corticosteroids are applied over a long period of time, *tachyphylaxis* develops; in this instance, the effectiveness of the corticosteroid drops considerably. Thus application once or at most twice daily is recommended.
- Corticosteroids accelerate *gluconeogenesis* (synthesis of glucose from amino acids) and thus have proteolytic and anti-insulin effects. Their main effects have a delayed onset, as they primarily depend on altered protein synthesis, but direct membrane effects also occur.
- They are used in dermatology for their *anti-inflammatory*, *immunosuppressive*, and *antiproliferative* actions.

Note: Therapy with topical corticosteroids is always symptomatic, never curative.

Indications and Contraindications

- **Indications:**
  - *Topical:* Allergic and irritant contact dermatitis, atopic dermatitis, other forms of dermatitis, psoriasis, cutaneous lupus erythematosus, lichen planus, sarcoidosis.

- *Intralesional:* Granuloma annulare, alopecia areata, hypertrophic scars and keloids, less often psoriasis and discoid or hypertrophic lupus erythematosus.
- *Systemic:* Wide range of uses including bullous autoimmune diseases, collagen-vascular disorders, severe forms of dermatitis and others.

► **Contraindications:** Bacterial, viral, or fungal infections, wounds, ulcers, atrophy. Many relative contraindications depending on strength of corticosteroid, site of application, and age of patient; for example, high-potency corticosteroids are never applied to the scrotum of boys.

► **Side effects:**

- Sufficient high-potency topical corticosteroids can be absorbed to cause Cushing syndrome. This is especially true in infants. Conversely, if high-potency agents are abruptly stopped, there may be sufficient suppression of the pituitary–adrenal axis to cause an Addisonian crisis.
- Local effects include atrophy, striae, telangiectases, purpura (vessel fragility), hypertrichosis, infections, and perioral dermatitis.

Use

In Europe corticosteroids are divided into four classes, on the basis of increasing potency from I (least potent) to IV (most potent). The standard American classification is into seven groups ranging from 1 (most potent) to 7 (least potent). Representative members of the European group are shown in Table 41.**5**. Most are available from more than one pharmaceutical firm, and many have become generic. Many class I agents are available over the counter.

► **Available agents:**

- It is impossible to remember all the available agents. Pick one to two agents in each group and use them.
- Choose an agent available in multiple forms, such as ointment, emollient cream, and gel. In Europe, many manufacturers make the nonmedicated vehicle available for maintenance therapy. Such products have a high degree of patient acceptance.
- Some agents can be compounded, as indicated in Table 41.**5**. Assuming a reliable pharmacy is available, considerable cost savings can be achieved by compounding 500 mg or 1 kg jars. Since preservatives are less effective in compounded products, patients should be instructed to work out of a smaller container and remove material from the large jar only with a sterile instrument.
- Choice of vehicle is incredibly important. In most instances, potency ranges are as follows: ointment > gel > cream > lotion.
- Do not follow the percentages. Notice that the highest percentage concentration (2%) is used in the weakest agent, hydrocortisone. Patients invariably read the label and may be annoyed when they receive a lower concentration. Always explain this point.
- The fourth-generation or soft corticosteroids are group II agents, indicated in italics in Table 41.**5**, which are prodrugs. The 21-ester bond is split in the skin, so the drugs are inactivated before entering the circulation. They have extremely favorable risk:benefit ratios and are widely used in pediatric dermatology.
- Maximum effect can be achieved by intralesional injection (usually triamcinolone acetonide (1–5 mg/mL). Although problems with particle size have been resolved, injection around the eye is usually avoided because of fear of retinal artery embolization.
- Another effective approach is to use a corticosteroid-impregnated tape, containing flurandrenolide 4 μg/cm^2.

Table 41.5 · Classes of topical corticosteroids

Class	Agent	Concentration (%)
I (weak)	Dexamethasone	0.1
	Fluocortinbutylester	0.75
	Hydrocortisone[a]	0.5–2.0
	Hydrocortisone acetate[a]	1.0
	Prednisolone[a]	0.4
II (medium)	Betamethasone valerate	0.05
	Clobetasone butyrate	0.5
	Flumethasone pivalate	0.2
	Fluocinolone acetonide	0.25
	Fluprednidene acetate	0.1–0.5
	Hydrocortisone aceponate[b]	0.1
	Hydrocortisone buteprate[b]	0.1
	Hydrocortisone butyrate[b]	0.1
	Methylprednisolone aceponate[b]	0.1
	Prednicarbate[b]	0.25
	Triamcinolone acetonide[a]	0.25–0.5
III (strong)	Betamethasone diproprionate	0.05
	Betamethasone valerate	0.5
	Amcinonide	0.1
	Desoximetasone	0.25
	Diflucortolone valerate	0.1
	Fluocinolone acetonide	0.2
	Fluocinonide	0.5
	Halcinonide	0.1
IV (very strong)	Clobetasol propionate[a]	0.05
	Diflucortolone valerate	0.3

a Can be compounded.
b Fourth-generation corticosteroids.

- Many compound products are available, containing corticosteroids combined with antibiotics or antifungal agents. They may be helpful in very acutely inflamed dermatitis or tinea, but in general it is wiser to use two separate agents at different times, separated by at least 2 hours, to achieve maximum benefit from both the corticosteroid and the antimicrobial agent.

► **Helpful hints:**

- Choose strength of corticosteroid based on pathogenesis of disease; hyperproliferative disorders require class III or IV agents.
- Watch for tachyphylaxis; application more than b.i.d. is almost never correct.

- Use with care on face and in intertriginous areas; exceed class II only with definite indications (localized bullous pemphigoid, nonresponsive chronic cutaneous lupus erythematosus).
- Never go above class II in children.
- Avoid using corticosteroids in infectious processes (pyoderma, tinea) unless the underlying disease is being simultaneously treated.
- Always think about steroid-sparing approaches (phototherapy, tar, retinoids, vitamin D analogues, calcineurin inhibitors, dithranol, urea).

41.8 Calcineurin Inhibitors

Overview

► **Definition:** Immunomodulatory substances (*tacrolimus* and *pimecrolimus*) that have been used for years in transplantation medicine but are also available as topical agents for atopic dermatitis and other inflammatory dermatoses.

► **Mechanism of action:**
- Preferential immunosuppressive action on T cells, Langerhans cells, and mast cells; potent and prolonged antipruritic effect.
- Both substances bind to a cytosol receptor (macrophilin-12) forming complexes that inhibit calcineurin. Calcineurin dephosphylates NFAT (**n**uclear **f**actor of **a**ctivated **T** cells), a cytosol transcription factor. If the dephosphorylation is blocked, NFAT cannot reach the nucleus and the transcription of inflammatory cytokines is blocked.
- Tacrolimus and pimecrolimus both also cause mast cell degranulation, perhaps via release of neuropeptides from cutaneous nerves. Consequently there is burning on application at onset of therapy but with rapid accommodation; this is more of a problem for tacrolimus than for pimecrolimus.
- They also interact directly with cutaneous nerve fibers to have additional antipruritic effects.

► **Side effects:**
- Initial burning on application; resolves rapidly.
- In contrast to corticosteroids, no cutaneous atrophy.
- Theoretical risk of reduced immunosurveillance and increased cutaneous tumors; long-term studies in progress to test hypothesis.
- A warning in 2005 from the FDA regarding increased risk of UV-induced cutaneous neoplasms and lymphomas is not supported by data and has been denounced in Europe.

► ***Note:*** Both agents are very expensive, which has been the main limiting factor in their acceptance and use.

Tacrolimus

► **Synonym:** FK506.

► Isolated from the bacterium *Streptomyces tsukubaensis*.

► **Indications:**
- Moderate to severe atopic dermatitis; officially approved for adults and children > 2 years of age but can be used in infants.
- Also employed in other dermatoses such as lichen planus, lichen sclerosus, graft-versus-host disease, scrotal dermatitis, chronic hand dermatitis, renal pruritus, different forms of prurigo, inverse psoriasis, rosacea.

- **Contraindications:**
  - Sensitivity to tacrolimus.
  - Do not use in florid viral infections; can make disorders such as eczema herpeticatum persist.
  - Avoid in Netherton syndrome (p. 195); abnormal barrier leads to excess absorption and toxicity.
  - Do not use in pregnancy or during nursing.
  - Do not combine with UV light because of theoretical increased tumor risk.
- **Cross-reactions:** None known. Theoretical problem with immunizations, which should be delayed for 14–28 days after discontinuation of tacrolimus.
- **Use:** Apply b.i.d. to involved areas as long as inflamed or pruritic. Long-term intermittent use up to 12 months is unproblematic. If no response after 6 weeks, re-examine indications and options.
- **Side effects:** Initially burning on application in > 10%; less often erythema, pruritus, folliculitis. Rarely bacterial and viral infections. Disulfiram effect: adult patients who use tacrolimus on face and drink alcohol may experience painful flushing and erythema.

Pimecrolimus

- Semi-synthetic ascomycin derivative.
- **Indications:**
  - Mild to moderate atopic dermatitis. Officially approved for children > 2 years of age but can be used safely in infancy.
  - Other uses as under tacrolimus.
- **Contraindications:**
  - Sensitivity to pimecrolimus.
  - Other contraindications as for tacrolimus.
- **Cross-reactions:** Same as tacrolimus.
- **Use:** Apply b.i.d. to involved areas as long as inflamed or pruritic. Long-term intermittent use up to 12 months is unproblematic. If no response after 6 weeks, re-examine indications and options.
- **Side effects:** Initially burning on application but less common than with tacrolimus, thus making pimecrolimus a better choice in infants and small children who cannot be warned about burning. Other problems as with tacrolimus.

41.9 Vitamin D Analogues

Overview

Cholecalciferol (vitamin D_3) is synthesized from 7-dehydrocholesterol in the skin under the influence of UV light and then converted in the liver to 25-hydroxycholecalciferol. The most potent form is the renal product 1,25-dihydroxycholecalciferol (calcitriol). In some settings, this potent molecule is also synthesized in the skin.

- **Mechanism of action:**
  - Mobilizes calcium from bone and increases reabsorption of calcium and phosphorus in kidney.
  - In the skin, blocks proliferation and enhances differentiation. Also increases expression of corticosteroid receptors, and has immunomodulatory role.

- **Available agents:** All three have similar spectrum of action; the analogues are used more than calcitriol itself:
  - *Calcitriol:* Chemical structure 1,25-dihydroxycholecalciferol (1,25-dihydroxy vitamin D_3).
  - *Calcipotriol:* Analog of vitamin D_3.
  - *Tacalcitol:* Analog of vitamin D_3.
- **Indications:**
  - Mild to moderate psoriasis, including facial psoriasis.
  - HIV/AIDS-associated psoriasis.
  - Under investigation for some disorders of keratinization.
- **Contraindications:**
  - Pustular psoriasis.
  - Severe renal or hepatic disease; abnormal calcium metabolism.
  - Pregnancy or nursing.
  - Not officially approved for children.
- **Use:**
  - *Calcipotriol:*
    - Apply to maximum of 30% of body surface.
    - Use < 15 g daily.
  - *Tacalcitol:*
    - Apply to maximum of 10% of body surface.
    - Use < 5 g daily.
  - *Both:*
    - Apply daily or b.i.d.; as long as totals observed, can be used long-term.
    - Can be combined with UVB, PUVA, or dithranol.
    - Less than 1% of single dose is absorbed.
    - Monitor serum calcium levels prior to and during treatment; likelihood of abnormalities minimal with analogues.
- **Side effects:** Irritating on application; limits use in flexures, intertriginous areas.

41.10 Retinoids

Tretinoin

- **Synonym:** Vitamin A acid, all-trans retinoic acid.
- **Mechanism of action:** Binds to nuclear vitamin A receptors and modifies gene expression. Direct effects including altering keratinization, especially in follicle, reducing sebum production, and antiproliferative action.
- **Indications:** Acne vulgaris—since the primary lesion in all types of acne is a comedo, and tretinoin is the most effective agent against comedones, it is useful for almost all acne patients. Also effective for prophylaxis and treatment of sun-damaged skin. Less dramatic effects in disorders of keratinization including some forms of ichthyosis, Darier disease.
- **Contraindications:** Although absorption is minimal, best avoided during pregnancy to avoid potential medico-legal problems.
  - ***Caution:*** All retinoids are potent teratogens and should be avoided in pregnancy.
- Many different forms available.
  - ***Note:*** The vehicle plays a very important role in determining the strength and thus imitating effect of tretinoin. For example, 0.025% gel tends to be stronger than 0.5% cream.

- Special formulations include:
  - Oily base for photo-aged skin.
  - Delayed-release system to reduce irritation.

► **Use:**
- Apply sparingly and avoid periorbital region; use only in evening (because of photosensitizing effect).
- Explain to patient that tretinoin is irritating, and that they will look worse after 1–2 weeks as comedones are highlighted.

► ***Note:*** The therapeutic goal is best achieved when mild irritation of the skin is induced.

- Start with low concentration and apply every other night. As tolerance increases, apply nightly and then increase concentration if minimal erythema is not obtained.
- If treated sun-damaged skin, use very low concentration, do not attempt to increase. Many patients do well on twice weekly application.
- Either benzoyl peroxide or a topical antibiotic (usually erythromycin) can be used in the morning.
- Insist patients use sunscreen regularly.

► **Side effects:** Initial irritation, drying, photosensitivity. If too irritating, postinflammatory hypo- and hyperpigmentation.

Other Topical Retinoids

► **Adapalene:**
- Less irritating than tretinoin; used in same way.

► **Isotretinoin:**
- 13-cis retinoic acid.
- Less irritating than tretinoin; used in same way.

► **Tazarotene:**
- Retinoid prodrug with affinity for multiple retinoid receptors.
- Primarily indicated for mild to moderate psoriasis; often chosen for palmoplantar psoriasis and then by analogy for palmoplantar keratoderma and chronic hyperkeratotic hand dermatitis.
- Also effective in treating photodamage.

41.11 Other Topical Agents

Coal Tars

► **Overview:** Coal tar has a long history of use in dermatology. Today it has unfortunately fallen into disrepute because of theoretical concerns about carcinogenesis, which are not supported by 100 years of clinical experience.

► **Mechanism of action:** Tars are antipruritic, anti-inflammatory, antiproliferative, and photosensitizing.

► **Available agents:** There is no uniform single "coal tar." Each batch is obtained by the destructive distillation of bituminous coals, so there are striking variations in composition, which includes oils of varying weights as well as residues (pitch). For compounding, two products are available:
- Pix lithanthracis (DAB6).
- Liquor carbonis detergens (LCD), an alcoholic extract of coal tar.

- Many finished products are also available, including tar gels, creams, ointments, shampoos, and bath additives. The compounded products have two advantages: they are less expensive, and it is easy to gradually increase the concentration of tar. The list of possible compounding instructions is endless; use the local standard or consult with an experienced pharmacist.
- **Indications:** Psoriasis (usually in combination with UV light—Goeckerman regimen—or dithranol), seborrheic dermatitis, any chronic dermatitis.
- **Contraindications:** Acute dermatitis, exudative or pustular psoriasis.
- **Use:** Apply 1–2 × daily; when combined with phototherapy, be alert to phototoxicity. Remissions induced by tar therapy tend to be longer-lasting than those with corticosteroids. Thus, in general, start with corticosteroids and then simultaneously taper corticosteroids and introduce tars in increasing concentrations.
  - ***Note:*** Tars are very messy and difficult for patients to use at home. Thus, with the shift away from inpatient care of psoriasis, a very effective agent has fallen into relative neglect.

Other Tars

- **Shale tar:** Two major products:
  - Ammonium bituminosulfonate is sulfur-rich.
  - Ammonium sulfobitol is sulfur-poor.
- Less irritating than coal tar; used in 2–5% concentration for chronic dermatoses. Best known form is ichthyol.
- **Wood tars:** Many different wood tars are available. They are not photosensitizing, but more allergenic. Examples include:
  - Oil of cade (juniper tar, pix juniperi).
  - Pine tar (pix liquida).
  - Beech (pix fagi).
  - Birch (pix betulina).
- All have modest anti-inflammatory activity and can be used in mild chronic dermatitis. Many have become more popular in recent years as interest natural medicine has increased in Europe; main effect has been increase in allergic contact dermatitis.

Dithranol

- **Synonyms:** Anthralin, cignolin.
- **Mechanism of action:** Dithranol is antiproliferative, but the exact mechanisms are unknown. Radical form is responsible both for effect and discoloration. Maximum concentration in skin achieved 60–300 minutes after application. Metabolized in the skin and excreted in inactive form by kidneys.
- **Indications:** Psoriasis; irritant in alopecia areata.
- **Contraindications:** Exudative or pustular psoriasis; use sparingly in intertriginous areas.
- **Available agents:** Standard compounding recipes available for dithranol in washable or nonwashable ointments, usually combined with salicylic acid; most useful because concentration can be best manipulated (p. 693). Commercial ointments and creams available in a wide range of concentrations. Once again, the standard product is very messy and difficult to use at home.
- **Use:**
  - *Long-term therapy:* Start with 0.1–0.25% dithranol ointment, increasing through the concentrations 0.5–1.0–2.0–3.0–5.0%, each time waiting until the irritant reaction (dithranol dermatitis) has resolved. The dithranol is applied once daily.

- *Ingram regimen:* Combination of dithranol, coal tar, and UV light.
- *Minute therapy:* Higher concentrations of dithranol (1–5%) applied for short periods of time (10–60 minutes); then washed off. Applied once daily. Can be used at home; the commercial cream form is especially useful. More often employed for alopecia areata or very localized psoriasis.

► **Side effects:**
- *Dithranol dermatitis:* Almost invariable; not controlled by corticosteroids or NSAIDs; must be used as "intrinsic monitor".
- *Dithranol pigmentation:* The skin, bedding, and clothes all acquire a purple-brown color. Commercial prewash stain removers are usually effective.
- *Dithranol pseudoleukoderma:* When surrounding skin turns brown and psoriatic lesions resolve, they appear hypopigmented.
- Allergic contact dermatitis rare.

Benzoyl Peroxide

► **Mechanism of action:** Releases H_2O_2; has marked antibacterial effect, lesser effects on comedones and sebum production.
► **Indications:** Acne, especially inflammatory forms.
► **Contraindications:** Should not be combined with phototherapy.
► **Available agents:** Hundreds of commercial products available, ranging from 2.5% to 10% concentration in gel (alcohol or water-based), cream, emulsion, and wash forms.
► **Use:** Apply 1–2 × daily; easily combined with topical retinoids; topical or systemic antibiotics. On face 2.5–5.0% is sufficient; on back, can try 10% or wash. Pay attention to vehicle; patients with acne and dry skin do better with water-based products.
► **Side effects:** Often irritating, rarely (<2%) causes allergic contact dermatitis; bleaches hairs and may cause hypopigmentation in dark-skinned patients.

41.12 Sunscreens

Overview

► **Endogenous UV protection:** Melanin, hairs, reactive thickening of stratum corneum (light-induced callus), antioxidants, DNA repair mechanisms.
► **Broad spectrum filters:**
- Many new organic filter or blocking molecules have been recently approved and will reach the market soon.
- Two agents—*drometrizole trisiloxane* and *bis-ethylhexyloxyphenol methoxyphenyl triazine*—are widely effective against UVA and UVB; others have markedly improved UVA coverage.

► **UVB filters:**
- Para-aminobenzoic acid (PABA): First widely used agent, but today not often found because of allergic contact dermatitis and burning around eyes.
- PABA esters (pentyl-*p*-dimethyl aminobenzoate [Padimate] or *p*-dimethyl aminobenzoate.

Caution: Patients sensitive to para-compounds (sulfonamides, parabens) can have marked photoallergic reactions.

- Cinnamates.
- Salicylates.
- Phenylbenzimidazole sulfonic acid.

- **UVA filters:**
  - Benzophenones.
  - Avobenzone, which is widely used and undergoes photodegradation to form potent allergens.
- **Blockers:**
  - Titanium dioxide.
  - Zinc oxide.
  - Micronized or silicone-coated particles are equally effective; popular because they do not appear as white pastes on the skin.
- **Other protection:** Special UV-protective clothing is available and is a very good choice for children or those requiring maximum protection.

Sun Protection Factor

- Describes the degree of protection offered by a sunscreen.
- In simple terms, if someone can stay in noonday sun for 20 minutes without sunscreen before getting red and 300 minutes with a sunscreen, then the SPF is 15.
- The real world is more complicated:
  - European, Australian and American standards for UVB SPF.
  - No accepted in-vivo UVA SPF method.
  - Water resistance and persistence of sunscreen also must be assessed.
  - Measurements are made with a defined fairly generous application of sunscreen/cm^2. Many studies have shown that the average patient applies far less.
  - Much skepticism over incredibly high ratings; SPF 60 is not 4 × as effective as SPF 15. Some movement to stop at SPF 30.

Use

- **Indications:** Protection from sunburn, reduction of chronic UV exposure with photoaging and carcinogenesis; maximum protection for those with photoallergic, phototoxic, or intrinsic photosensitivity disorders.
- ***Note:*** Although the effectiveness of long-term sunscreens in ameliorating chronic photodamage and carcinogenesis has not been proven (because of the long time and many patients required), there is no reason to think that it will not be helpful. Arguments of opponents center around:
  - *Reduced vitamin D production:* Elderly people should perhaps not use maximum sun protection or take vitamin D supplements.
  - *Increased risk because individuals then increase their sun exposure:* Can only be corrected by public education campaigns.
- **Side effects:** Many patients become sensitized to sunscreen components; thus PABA is rarely used any more; such patients can use blocking agents.

41.13 Phototherapy

Check before Starting Phototherapy

- Rule out dermatoses caused or worsened by light.
- Be sure patient is not taking photosensitizing or immunosuppressive medications.
- Obtain written informed consent.
- Require protective eye covers and genital shielding.
- Apply topical agents following phototherapy; some enhance effects (tars, ointments); others decrease them (vitamin D analogues).

UVB Phototherapy

- **Overview:**
  - Available sources includes:
    - *Broad spectrum:* 280–320 nm.
    - *Selective UVB phototherapy (SUP):* 305–325 nm.
    - *Narrow band:* 311 nm (TL 01).
    - *Excimer laser:* 308 nm.
  - Narrow band has replaced regular UVB in most settings because of increased effectiveness and decreased amount of erythema-inducing irradiation.
- **Indications:**
  - Major indication is psoriasis; most effective wavelengths center around 311 nm (304–314 nm).
  - Atopic dermatitis, pruritus (especially renal pruritus), pityriasis lichenoides et varioliformis acuta, pityriasis lichenoides chronica.
  - Hardening in polymorphous light eruption.
  - Simulation of repigmentation in vitiligo.
- **Contraindications:** Photosensitivity, reduced minimal erythema dose (MED) for UVB.
- **Use:**
  - Determine MED (p. 49); if not determined, then based on skin test and previous experience with specific light source.
  - *Psoriasis:* Start with 70% of MED; increase each time by 10–30%. Administer 3–5 × weekly; maximum reaction at 24 hours so easy to observe. Usually complete remission achieved in 4–6 weeks.
  - *Atopic dermatitis:* Use as adjunct in patients who tolerate light well; start with 70% of MED.
  - *Polymorphous light eruption:* Start 4–6 weeks before spring or planned vacation; start with 70% of MED, increase by 10–20% until mild erythema is induced; then drop back slightly and slowly increase again.
  - *Vitiligo:* Narrow band UVB; start with very low dose (0.1–0–2 J/cm^2) and increase up to 1 J/cm^2 over months.
- **Combinations:**
  - With UVA for hardening in polymorphous light eruption or in pruritus.
  - With salt water baths (27% table salt solution or equivalent in tub for 15 minutes); excoriated lesions may burn.
  - With psoralens (PUVB): sometimes tried in vitiligo, but no well-controlled studies.

UVA Phototherapy

- **Overview:**
  - Available sources include:.
    - Broad spectrum conventional: 320–400 nm.
    - UVA1: 340–400 nm.
  - UVA light is often touted as noncarcinogenic, but this is not true. It does not cause the erythema and sunburn associated with UVB, but instead penetrates more deeply and elicits a different sort of tan. UVA requires much longer exposure periods to have a biologic effect. Most sources also produce visible and infrared light; cold UVA uses filters to eliminate the infrared component.
- **Indications:** Acute atopic dermatitis, morphea, pruritus, perhaps urticaria pigmentosa.
- **Contraindications:** Photosensitivity; most drug-induced photosensitivity occurs with UVA.

► **Use:**
- *Broad spectrum:* 2–12 J/cm^2.
- *UVA1:* Low dose 10–30 J/cm^2; medium, 40–70 J/cm^2; high 80–139 J/cm^2.

41.14 Photochemotherapy

Overview

► The elegant combination of psoralens and UVA (PUVA), as developed in the mid-1970s by the Harvard group of Parrish, Fitzpatrick, and Pathak, is one of the greatest success stories in dermatologic therapy.
► The psoralen molecules intercalate between strands of DNA and are then activated by UVA light. They have a broad spectrum of action, interfering with DNA synthesis but also altering many aspects of immune response. Neither the psoralens nor the UVA alone has any effects (in the doses used).
► The small long-term risk of carcinogenesis is probably related to both DNA damage and immunosuppression.

Oral PUVA Therapy

► **Indications:** Psoriasis, pustular psoriasis, lichen planus (especially exanthematous forms), mycosis fungoides, other low-grade cutaneous T-cell lymphomas, urticaria pigmentosa, graft-versus-host disease, severe hand and foot dermatitis, vitiligo, polymorphous light eruption (hardening), solar urticaria (hardening), chronic actinic dermatitis (hardening).
► **Contraindications:** Severe renal or hepatic disease, pregnancy, nursing, lupus erythematosus, DNA repair defects (such as xeroderma pigmentosum).
► **Pretreatment evaluation:**
- *History:*
  - Photosensitivity, excessive solar damage, photodermatoses (lupus erythematosus, porphyria cutanea tarda); ingestion of photosensitizing medications.
  - Epilepsy (medications, risk of seizure during treatment).
  - In case of psoriasis, previous treatment with methotrexate, radiation therapy or arsenic; all increase risk of carcinogenesis.
  - Renal or hepatic disease.
  - Pregnancy, nursing; desire for future children.
- *Laboratory:*
  - Complete blood count.
  - Renal and hepatic function.
  - Ophthalmologic examination; prescription of sunglasses with maximum UV protection.
- Determination of minimal phototoxicity dose (MPD) (p. 51).

! ***Caution:*** Never start therapy before you have all of the above documented and a signed informed consent.

► **Use:**
- Administer 0.6 mg/kg of 8-methoxsalen (8-methoxypsoralen) (in USA usually 0.4 mg/kg of Oxsoralen ultra); round off using the standard 10 mg tablets.
- After 2 hours, administer broad spectrum UVA light. Treat 4 × weekly (M–T–Th–F).
- Start with 70% of MPD; increase the dose gradually assessing erythema on non-involved skin. Never increase dose 2 days in a row.

Caution: PUVA erythema first develops after 72 hours.

- If MPD is not available, then:
  - *Skin type I/II:* 0.5 J/cm^2; increase by 0.3 J/cm^2 every 3 days until erythema appears.
  - *Skin type III/IV:* 1.0 J/cm^2; increase by 0.5 J/cm^2 every 3 days until erythema appears.
- Patient remains photosensitive for 12 hours; must wear special sunglasses, sunscreen, and avoid exposure.
- Psoralens were initially combined with natural sun exposure, first as "suntan pills" and later to treat vitiligo. This approach may be an option in areas where easy access to UVA phototherapy units is limited, but it is very difficult to control because of the variability in sun exposure.

► **Side effects:**

- *Acute:* Sunburn, gastrointestinal distress.
- *Chronic:* Photodamaged skin, PUVA lentigines, actinic keratoses, squamous cell carcinomas, basal cell carcinomas and malignant melanomas.

Caution: The increase in the already high background risk of developing a malignant melanoma is minimal, but every PUVA patient must be monitored lifelong to insure early identification.

Topical PUVA Therapy

► **Overview:** Many "tricks" have been developed to avoid the systemic ingestion of psoralens with resultant ocular risk and photosensitivity. Possibilities include limited degree of UVA exposure (hand and foot PUVA) and applying the psoralens topically (bath, shower, or cream PUVA). Topically applied psoralens lose their effects after 2–3 hours. Can be used in pregnancy. No need for sunglasses after treatment.

Caution: Extremely low concentrations of topical psoralens are required. In the USA, the initial commercial product was far too concentrated and difficult to use. It is no longer available.

► **Indications:** Same as for oral PUVA.

► **Contraindications:** Many fewer, as process is limited to lesional skin.

► **Cream PUVA:**

- Methoxsalen 0.006% cream in unguentum cordes or other bases.
- Store at 4 °C.
- Apply for 1 hour before irradiation; some use with plastic foil occlusion.

► **Bath PUVA:**

- Require special facilities with bath or shower for PUVA; special plastic sheeting in tub can reduce amount of psoralens required.
- Final concentration is around 1 mg methoxsalen to 1 liter water.
- After 15 minutes, immediate irradiation.
- Dosage: Treat 4 × weekly; onset of erythema is goal. Start with 30% of MPD and increase rapidly to reach erythema threshold. If MPD is not available, then:
  - *Skin type I/II:* 0.3 J/cm^2; increase by 0.2 J/cm^2 every 3 days until erythema appears.
  - *Skin type III/IV:* 0.5 J/cm^2; increase by 0.3 J/cm^2 every 3 days until erythema appears.
  - When erythema appears, no increase in dosage.

41.15 Photodynamic Therapy

Overview

- Photodynamic therapy (PDT) is a special form of photochemotherapy. Special photosensitizers are employed which concentrate in tumors or inflamed tissue and then can be activated with concentrated light sources whose emission spectrum corresponds to the activation spectrum of the sensitizer.
- The usual sensitizer is α-aminolevulinic acid (ALA), one of the intermediates in porphyrin metabolism. A form of "local iatrogenic porphyria" is induced in the target tissue.
- More ALA is taken up by tumor cells than by normal surrounding skin. Irradiation with 630 nm bright red light (LEDs) leads to destruction of tumor cells and endothelial damage in feeder vessels.

Method

- **Indications:** Actinic keratosis, supercoil basal cell carcinoma, superficial squamous cell carcinoma, Bowen disease, isolated superficial cutaneous lymphoma; perhaps condylomata acuminata and psoriasis. Only effective for superficial lesions.
  Caution: Diagnosis must be confirmed histologically before commencing PDT.
- **Light source:**
  - *Monochromatic source:* Pumped rhodamine dye laser (628 nm) or gold vapor laser (628 nm).
  - *Polychromatic source:* Slide projector with 250–500 watt lamp and filter; xenon lamp with filter.
- **Use:**
  - Apply 10–20% ALA cream or methylaminolevulinate for 4 hours under occlusion and protected from light.
  - Apply light for 15–20 minutes.
  - Repeat in 2–3 months.
  - When dealing with multiple actinic keratoses, the ALA can be used to highlight the lesions, which are then treated.
  - Painful: Systemic analgesics and lidocaine/prilocaine (EMLA) may be needed for irradiation. Heals with necrosis and crusting.

41.16 Balneotherapy

- **Overview:** Baths are a very effective way of treating a large area quickly. They are expensive, because of requirements for personal facilities. Bathing or balneotherapy has long occupied a major role in German dermatology, driven primarily by the emphasis on inpatient care and spa visits paid for by health insurance.
- **Cleansing baths:** Baths are incorporated into therapy plans to remove crusts, scales, and residual medications. A variety of tensides can be added. Additionally, 3–5% sodium chloride or sodium bicarbonate may be useful for loosening scales in psoriasis or ichthyosis.

Anti-inflammatory Baths

- **Acute exudative or infected dermatitis:**
  - Adding bolus alba (white clay powder) 250 g/tub has a soothing effect.

- Tannins or synthetic equivalents are useful for their astringent properties. Useful for local baths or wet dressings for intertrigo, as well as hand and foot dermatitis. Tannosynt is best known product in Europe; difficult to find in USA.

► **Chronic skin disorders:**
- Useful for chronic dermatitis, psoriasis, lichen planus, prurigo simplex chronica.
- Most useful choice is coal tar baths; photosensitizing can be used for advantage in psoriasis.
- Polidocanol can be added for antipruritic effect.

Disinfectant Baths

► Chinolinol 0.1% in bath water is antibacterial and antifungal. Low sensitizing potential. Binds to emulsifiers and metal salts with resultant inactivation.
► Potassium permanganate baths have a similar effect but permanently discolor bathtubs. Usual concentration 1:5000 (several crystals completely dissolved in full tub). Should be used alone, as inactivated by many substances.

Oil Baths

► Oil baths are the most effective to re-lubricate dry skin in atopic dermatitis or psoriasis.
► Three approaches:
- Miscible oils are spread through the bath and leave some residues on skin.
- Nonmiscible oils remain on the bath surface and coat the body on exit.
- Both can also be applied to wet skin immediately after bathing.

► Many different oils employed.
► **Cleopatra's bath:** 1 glass of milk with 1 teaspoon each of olive oil and honey; shaken thoroughly; added to bath.
▶ ***Note:*** All baths are drying if the skin is not lubricated at the end. Many people with dry skin enjoy soaking in the tub or taking long hot showers, but fail to re-lubricate their skin and end up with more dryness and pruritus.

41.17 Aesthetic Dermatology

Overview

Dermatologic therapy has always sought to produce both medicinal and aesthetic results. Today there are so many options that a subspecialty of aesthetic dermatology is in the process of establishing itself. It includes the use of appropriate tested cosmetics, instruction in maintenance approaches following therapy, and correction of skin conditions that are primarily aesthetic in nature but may also have medical or psychological aspects.

Botulinum A Toxin

► **Mechanism of action:**
- Botulinum toxin is made by *Clostridium botulinum* as an exotoxin, which blocks the release of acetylcholine and thus inhibits neuromuscular transmission and causes muscle paralysis. There are seven types; type A is the most effective and has the longest duration of action.
- The molecule is relatively unstable, with two subunits bound by a disulfide bond that is easily split.

- Effects first appear after 1–3 days with maximum effect reached at 2 weeks. Average duration of effect 3–6 months. Muscles then become re-innervated.
- The strength of botulinum A toxin is given in biological units based on the effect in mice.

► **Indications:** Botulinum A toxin was initially developing for strabismus; paralyzing the ocular muscles was far more effective and safer than corrective surgery. It also is effective for hyperhidrosis, providing several months of relief for axillary or palmar excessive sweating. The main dermatologic indication is correction of facial wrinkles. The following features must be considered:

- *Type of wrinkle:* Only those caused by muscles of facial expression (mimic wrinkles) are amenable to correction.
- *Consider expectations of patient:* Those with reasonable expectations will be happiest; those with few wrinkles, or perception disorders, will be disappointed.

► **Informed consent:**

- Some products such as Dysport and Botox (now widely used as generic name) are not at present approved for cosmetic usage. Patient must be aware of this.
- Inform patients about other ways to treat wrinkles.
- Counsel regarding the side effects discussed below.
- Patient must agree to pay; insurance plans do not cover cosmetic procedures.
- Take photographs before treatment, and then as needed.

► **Contraindications:**

- *Absolute:* Rare diseases with decreased muscle activity such as myasthenia gravis or Eaton–Lambert syndrome; simultaneous use of macrolide or aminoglycoside antibiotics; pregnancy or nursing; infection in area of injection, psychiatric problems.
- *Relative:* Coagulopathy or therapeutic anticoagulation.

► **Use:**

- Define injection points.
- Draw up botulinum A toxin.

! *Caution:* The commercially available products have different concentrations, different degrees of activity, and different methods of dilution. They are not interchangeable.

- Disinfect area and let dry completely, to avoid denaturing botulinum A toxin.
- Inject target muscle with 30 or 32 gauge needle.
- Cool.

► **Side effects:** Hematoma, pain on injection, burning, pressure sensation, headache, numbness, swelling, undesired muscle paralysis, ptosis of the eyelid when treating the glabellar area, ptosis of the eyebrows when treating the forehead, allergic reaction to individual components.

► **Specific sites:**

- *Glabellar wrinkles:*
  - Very suitable.
  - Always inject 1 cm from orbital rim.
  - 3–5 injection points.
  - *Specific side effects:* Hematomas, headache, paralysis of levator muscle; if ptosis occurs, can use apraclonidine eye drops; 1–3 drops daily stimulates Müller muscle and elevates upper lid.
- *Forehead wrinkles:*
  - Suitable.
  - Always inject in the middle of the forehead.
  - 4–6 injection points.
  - *Specific side effects:* Drooping or elevation of eyebrows.

- *Periorbital wrinkles:*
  - Suitable.
  - Always inject 1 cm lateral to orbital rim.
  - 2–3 injection points.
  - *Specific side effects:* If the lateral rectus muscle is paralyzed, then diplopia (very rare).
- *Perioral and neck wrinkles:* Only for experienced operators.

Soft Tissue Augmentation

► **Overview:** Wrinkles can also be corrected by injection permanent or nonpermanent fillers. Permanent fillers, such as silicone or polymethyl acrylates, have the great disadvantage that not only the effect but also the side effects, such as a foreign body reaction, are persistent. In addition, some filler material may shift in the skin. For this reason, nonpermanent fillers have assumed a predominant role. All fillers should be used with the same precautions and documentation as botulinum A toxin.

► **Hyaluronic acid:**
- Hyaluronic acid (HA) is a polysaccharide of *N*-acetyl glucosamine and glucuronic acid. It is present in many tissues and accounts for about 50% of the ground substance of normal skin.
- Both linked and unlinked HA preparations are available. The linked products have larger molecules and persist longer. Both glutaraldehyde and butanediol diglycide ether (BDDE) are using for linking. HA is broken down to H_2O and CO_2 over 3–8 months.
- *Indications:* Wrinkles, lip augmentation, scars.
- *Contraindications:* Pregnancy, nursing, active autoimmune diseases, use of aspirin; some forms derived from rooster combs cannot be used in patients with eggwhite allergy.
- **Use:**
  - Topical anesthesia.
  - Inject with 27–30 gauge needle with either drop technique or tunnel technique. Larger areas such as cheeks are most easily enhanced using tunnel technique.
  - *Side effects:* Hematoma, erythema, edema, pain, granuloma formation, infection.

► **Poly–L-lactic acid:**
- Combination of polylactate microspheres, mannitol, and carboxymethylcellulose.
- Suited for larger defects such as deeper wrinkles and lipoatrophy.
- Use similar to HA. Granuloma formation more common.

► **Bovine collagen:**
- Several collagens are available. Cross-linked collagen will persist longer. All are derived from cattle in an isolated herd to eliminate risk of prion disease.
- Test injection 0.1 mL intradermal on arm recommended because some patients have allergic reactions to animal proteins. Positive reaction consists of erythema or swelling that persists 6 hours after injection. About 1–3 % of those not reacting to skin test will react to collagen.
- Uses similar to HA.
- Several forms of human-derived collagen are now available in various stages of development. See specialized texts.

Chemical Peeling

- **Definition:** Use of toxic exfoliative substances to remove skin. Depth of removal depends on agent, concentration, body location, length of exposure, and degree of occlusion, as well as status of skin and previous treatments.
- **Available agents:**
  - α-*Hydroxy acids (AHA)* and derivatives (glycolic acid, lactic acid, citric acid):
    - Most originally obtained from fruits and thus known as fruit acids.
    - Multiple effects, primarily reduce keratinocyte adhesion and induce fibroblast activity.
  - β-*Hydroxy acids*; *salicylic acid:* Very superficial peel, removing stratum corneum.
  - *Trichloracetic acid (TCA):* Mainstay of peeling; denatures tissue; not absorbed.
  - *Retinoids* (p. 601).
- **Levels of peeling:** Three levels usually considered:
  - *Superficial peel:*
    - Removal of outer part of epidermis.
    - Mild procedure; sometimes called soft peel or lunch peel. Little toxicity; rapid, but short-term improvement. Can be used anywhere on body.
    - Agents include AHA 20–40%, and TCA 10%.
    - Can be done by nurses or other auxiliary personnel.
    - Indications include dry skin, superficial keratoses, photoaging, mild acne, hyperpigmentation, melasma.
    - Side effects minimal but include erythema, pigmentary disturbances, triggering of recurrent herpes simplex virus infections.
  - *Medium peel:*
    - Removes entire epidermis and impinges on papillary dermis.
    - Agents include AHA 50–70% and TCA 35%.
    - Usually done by physician.
    - Indications include acne scars, actinic keratoses, plane warts, melasma, tiny wrinkles, photoaging. Should not be used in Type IV–V skin.
    - Side effects include persistent erythema, pigmentary disturbances and scarring.
    - *Deep peel:*
    - Reaches to reticular dermis.
    - Agents include TCA 50% (or pretreatment plus 30%) and phenol.
    - Usually done under general anesthesia, always by physician.
    - Indications include deeper wrinkles, photoaging, thicker keratoses or lentigines.
    - Same problems as with medium peel but scarring more liking; when phenol is used, risk of cardiac arrhythmias.
- **Procedure:**
  - Explanation, informed consent, photos, as for botulinum A toxin.
  - Pretreatment for 2–4 weeks with AHA 8–15%.
  - Clean skin, then apply peeling agent either with brush or sponge or with gloved hand. Apply with constant pressure.
  - Start with lowest usual concentration, leave on for 2 minutes, neutralize if applicable and cool.
  - Re-emphasize need for sunscreens.

Bleaching

- **Available agents:**
  - *Azelaic acid:* Blocks tyrosinase to cause depigmentation (also keratolytic and antibacterial). Usual concentration 15%.
  - *Hydroquinone:* Most widely used bleach; blocks oxidation from tyrosine to dopa. Used in 2–4% concentration in variety of "lightening creams." Higher concentrations, available especially in Africa and Asia, carry risk of exogenous ochronosis and hyperpigmentation.
  - *Monobenzyl ether of hydroquinone:* Highly effective, causing irreversible pigmentation, also at sites distant to application. Only used to complete depigmentation in widespread vitiligo.
  - *Kojic acid:* Tyrosinase inhibitor obtained from malted rice; used at around 2% concentration.

  Note: All attempts at bleaching must be combined with regular use of a sunscreen.

Cosmetic Care

In Germany many dermatology clinics have a cosmetician who is involved in treatment of acne and rosacea patients. In some instances, the health insurance pays for the treatment.

- **Acne treatment:**
  - *Superficial treatment:* Mild debridement with abrasive soaps or scrubs; similar to what patient can accomplish at home.

    Note: Not everyone is convinced that abrasive scrubs or treatments are helpful. They feel good, but cause follicular irritation and may worsen acne in some patients. In addition, they reinforce the erroneous connection between unclean skin and acne.
  - *Acne surgery:* Comedones are incised and expressed; produces short-term improvement but studies have shown that lesions refill over 1–2 weeks.
- **Rosacea:** Sobye suggested a pattern of massage to move lymphatic fluid in parts of the face that move relatively little with facial expression. Effectiveness minimal, but may be useful adjunct. Massage is directed centrally, involving forehead, temples, nose, and lateral cheeks. Patients best taught to do procedure themselves at home (up to 3 × daily).

Camouflage

Special make-up is one of the most overlooked tools in the dermatologic trade. In Europe, advice is often given in the clinic or practice. In the USA, patients are referred to the cosmetic company. Diseases such as vitiligo and vascular malformations can often be covered more effectively than treated. In addition, skilful use of make-up, such as using a green base to reduce erythema, helps many erythematous and vascular processes.

Fine Needle Electrosurgery

Fine needles at a low (1–3 A) setting can be used to selectively destroy telangiectases or carry out epilation. In recent years, both tasks have been replaced to a large extent by lasers, which are more effective and far quicker.

Sclerotherapy

Small telangiectases, especially starburst telangiectases, can be treated by injection with variety of sclerosing agents, as discussed under phlebology (p. 555).

42 Systemic Therapy

42.1 Antiviral Therapy

Acyclovir

- **Mechanism of action:** Blocks viral DNA polymerase. Herpes virus thymidine kinase selectively phosphorylates acyclovir (a guanosine analog), which is then incorporated into viral DNA and blocks synthesis.
- **Indications:** Infections with herpes simplex virus (HSV) 1 and 2, acute varicella infection; herpes zoster; cytomegalovirus prophylaxis following solid organ and bone marrow transplantation; widely used for prophylaxis for recurrent herpes simplex virus infections.
- **Contraindications:** Carefully chosen during pregnancy and nursing; small risk of fetal malformations outweighed by risks from maternal varicella and perhaps maternal primary herpes simplex virus with viremia.
- **Dosage:**
  - *Immunocompetent patients:* 200–800 mg p.o. 5× daily or 5 mg/kg i.v. t.i.d. (200 mg for herpes simplex, 800 mg for herpes zoster).
  - *Immunosuppressed patients:* 10 mg/kg t.i.d.
  - Adjust dosage in patients with renal insufficiency.
  - Prophylaxis for herpes simplex: 200 mg p.o. b.i.d.–t.i.d.

  Caution: Cimetidine and probenecid slow the excretion of acyclovir.
- **Side effects*: Seizures, headache, dizziness,** glomerulonephritis, acute renal failure.

Valacyclovir

- **Mechanism of action:** Prodrug of acyclovir; converted in first pass through gastrointestinal tract and liver to acyclovir.
- **Indications:** Infections with HSV-1 and -2; herpes zoster; prophylaxis for recurrent HSV infections. Probably better for zoster than acyclovir. Not approved in immunosuppressed patients.
- **Contraindications:** Pregnancy and nursing; wiser to use acyclovir, which has more safety data.
- **Dosage:**
  - *Infections:* 1000 mg p.o t.i.d. for 7–10 days for zoster, acute HSV.
  - *Prophylaxis:* 1000 mg p.o. b.i.d.
- **Side effects:** See acyclovir.

Brivudin

- **Mechanism of action:** Blocks viral DNA synthesis by interacting with deoxythymidine kinase and DNA polymerase.
- **Indications:** Infections with varicella-zoster virus and HSV-1, especially severe mucocutaneous forms.
- **Contraindications:** Pregnancy and nursing; cannot be used with systemic 5-fluorouracil or other analogues.
- **Dosage:** Adults: 125 mg p.o. q.i.d.

* Side effects printed in boldface are potentially fatal.

- **Side effects:** Gastrointestinal distress, headache, elevated liver enzymes, rare cutaneous drug reactions.

Famciclovir

- **Mechanism of action:** Prodrug of penciclovir; good gastrointestinal absorption, converted in first pass through gastrointestinal tract and liver to active form, which also interferes with DNA polymerase.
- **Indications:** Herpes zoster—as effective as valacyclovir but considerably more expensive; also approved for acute HSV infections.
- **Contraindications:** Pregnancy and nursing.
- **Dosage:**
  - *Zoster:* 250 mg p.o. t.i.d.
  - *Recurrent herpes genitalis:* 125 mg p.o. b.i.d.
- **Side effects:** Headaches, diarrhea, nausea; sometimes confusion in elderly patients.

42.2 Dapsone

- **Synonym:** Diaminodiphenylsulfone, DDS, DADPS.
- **Mechanism of action:** Unclear; competitive antagonist of PABA interfering with normal synthesis of folic acid by bacteria; also seems to have antineutrophil action; metabolizes to aminohydroxyldiphenylsulfone, which is responsible for methemoglobulinemia and hemolysis. Excreted via kidneys (90%) with a half-life of 2–4 days.
- **Indications:**
  - Leprosy, dermatitis herpetiformis, prophylaxis for *Pneumocystis carinii*.
  - Employed for many other dermatologic disorders including pyoderma gangrenosum, autoimmune bullous diseases, bullous LE, granuloma faciale, erythema elevatum et diutinum and leukocytoclastic vasculitis.
- **Contraindications:** Severe cardiovascular disease, marked renal insufficiency, pregnancy, sulfonamide allergy.
- **Drug interactions:** See Table 42.**9**.
- **Precautions:**
  - *Before therapy:*
    - Complete blood count (CBC) and hemoglobin (Hgb).
    - Determine glucose-6-phosphate dehydrogenase (G6PD). Patients with relative deficiency have more hemolysis; common among blacks, Asians.
  - *During first 3 months of therapy:*
    - Weekly, then biweekly, CBC, Hgb, and methemoglobin.
  - *Later:*
    - CBC, Hgb and methemoglobin every 2–3 months; liver functions and renal status every 6 months.
- **Dosage:** Start with 50–100 mg daily and observe response; can increase to 150 or maximal 200 mg daily; many patients with dermatitis herpetiformis do fine on 50 mg daily or q.o.d.
- ***Caution:*** With impaired renal function, divide dose by two. If creatine clearance is < 15 mL/minute, do not use.
- **Side effects:**
  - *Methemoglobinemia:* Everyone gets it, but few have problems. Cyanosis can appear with values as low as 3%. Symptoms usually appear with levels $> 10\%$.
  - *Hemolysis:* Usually starts with 50 mg daily, dose-dependent. At 150 mg daily, a drop in Hgb of 2 g/dl is expected. Usually reversed to some degree by increased

production. Patients with limited cardiovascular or marrow reserve may not tolerate this stress.
- Agranulocytosis, aplastic anemia.
- Nephrotic syndrome, renal papillary necrosis.
- *Peripheral motor neuropathy:* Occurs after long-term use; more common in those with G6PD defects.
- *Sulfone syndrome:* Flu-like illness with malaise, exanthem, hepatitis, lymphadenopathy and eosinophilia. Usually resolves when dapsone stopped.

► **Alternatives:** Sulfapyridine 1.5–2.0 g daily is reasonable substitute in dermatitis herpetiformis.

42.3 Antifungal Agents

Griseofulvin

► **Mechanism of action:** Griseofulvin is incorporated into newly synthesized keratin, so it must be taken for a long time—up to 18 months in the case of toe nails. Its half-life is around 24 hours; micronized forms are better absorbed and distributed. It interferes with microtubule formation.
► **Indications:** Dermatophyte infections; griseofulvin is not effective against yeasts and molds. Organism should be cultured before starting therapy.
► **Contraindications:** Liver disease, porphyria, LE, pregnancy.
► **Drug interactions:** Griseofulvin is metabolized in the liver and interacts with many agents (Table 42.**9**) including:
- Impairs action of coumarin.
- Reduces effectiveness of oral contraceptives.
- Cross-reactions with penicillin possible.

► **Dosage:** Griseofulvin is still the only agent approved for tinea capitis in children; it has been replaced in most of its other uses by the more effective imidazoles.
- Children 10 mg/kg daily; adults 500–100 mg p.o. daily.
- If no response, dose can be doubled after 2 weeks.

► **Side effects:**
- Hepatic toxicity, gastrointestinal bleeding, leukopenia, granulocytopenia.
- Check CBC before therapy and after 2–3 weeks.
- Exanthems, urticaria, photosensitivity.
- May trigger acute intermittent porphyria or systemic lupus erythematosus.

Itraconazole

► **Mechanism of action:** Inhibits cytochrome P450-dependent synthesis of ergosterol, a key component of fungal cell walls.
► **Indications:** Effective against dermatophytes, molds, and many yeasts. Excellent against *Candida albicans* and *Candida krusei*; moderately effective against other *Candida* species.
- Cutaneous mycoses, including onychomycoses.
- Mycoses in HIV/AIDS.
- Mucocutaneous and systemic candidiasis.
- Recurrent vaginal candidiasis.
- Aspergillosis.
- Soft tissue mycotic infections.

► **Contraindications:** Pregnancy; contraception until 4 weeks after end of therapy.
► **Drug interactions:** Inhibits cytochrome P450; many interactions (Table 42.**9**); enhances coumarin, oral hypoglycemic agents, theophylline, and phenytoin.

- **Dosage:**
  - *Cutaneous mycoses:* 100–200 mg p.o. daily for 2–4 weeks.
  - *Onychomycosis:* Interval therapy; 200 mg p.o. b.i.d. for 7 days; repeat in weeks 4 and 7.
  - *Vaginal candidiasis:* 200 mg p.o. twice in one day.
  - Longer-term, higher-dose therapy in HIV, soft tissue, and systemic mycoses.
- **Side effects:** Only common effect is nausea.

Fluconazole

- **Mechanism of action:** Inhibits cytochrome P450-dependent synthesis of ergosterol, a key component of fungal cell walls.
- **Indications:** Effective against dermatophytes and yeasts; not molds. Effectiveness reduced against *Trichophyton mentagrophytes*, *Candida glabrata*, and *Candida guilliermondii*.
  - Useful for candidiasis in almost all settings from acute vaginal to HIV/AIDS to chronic mucocutaneous candidiasis.
  - Dermatophyte infections, including onychomycoses.
- **Contraindications:** Severe liver disease, pregnancy and nursing; contraception until 7 days after completing therapy.
- **Drug interactions:** Inhibits cytochrome P450; many interactions (Table 42.**9**). Enhances coumarin, midazolam, oral hypoglycemic agents, phenytoin, tacrolimus, theophylline.
- **Dosage:**
  - *Vaginal candidiasis:* Single dose of 150 mg.
  - *Systemic candidiasis:* 200–800 mg p.o. daily (depending on organism) in adults; can be used in children if no suitable alternative: 3–6 mg/kg p.o. daily.
  - *Dermatophytes:*
    - Adults: 50 mg p.o. daily.
    - Children: 1–2 mg/kg p.o. daily; higher dose for zoophilic fungi.
  - *Onychomycosis:* 150 mg weekly in single dose, for 3–6 months (fingernails) or 6–12 months (toenails).
- **Side effects:**
  - Seizures, leukopenia, thrombocytopenia.
  - **Hepatic injury—**monitor liver enzymes.
  - **Toxic epidermal necrolysis;** be very cautious about continuing in patients developing an exanthema.

Terbinafine

- **Mechanism of action:** Inhibits sterol biosynthesis by blocking squalene peroxidase causing accumulation of squalene and cell death.
- **Indications:** Primarily dermatophytes.
- **Contraindications:** Renal or hepatic disease.
- **Dosage:** Cutaneous disease 250 mg daily p.o. for 2–4 weeks; onychomycosis 250 mg daily p.o. for 6–12 weeks or interval therapy.
- **Side effects:** No common serious side effects; elevated liver enzymes, disturbed taste; rare toxic epidermal necrolysis.

42.4 Antihistamines

- **Mechanism of action:** Antihistamines share structural similarities with histamine and block its actions by competing for receptor sites. There are two main types of histamine receptors, H1 and H2. Both are found in the skin, and H2

receptors are also found in the gut. H2 blockers decrease gastric section and are used for peptic ulcer disease. H3 receptors are limited to the CNS. In most instances, classic H1 antihistamines are adequate for cutaneous disease; in some instances combined H1 –H2 blockage is more effective.

► **Indications:** Urticaria, anaphylaxis, allergic rhinitis, allergic conjunctivitis. Antihistamines are not as effective in atopic dermatitis as in other manifestations of atopy. They are also frequently employed for other forms of dermatitis, pruritus, and prurigo, but when itch is not histamine-mediated their effectiveness is comparable to that of a sedating placebo.

Table 42.1 · **Classification and use of antihistamines**

Class	Agent[a]	Dose	Sedating	Comments
Ethanolamine	Diphenhydramine	25–50 mg q4–6 h	+++	
	Clemastine	1–2 mg b.i.d.	+	
Ethylenediamine	Tripelennamine	25–50 mg q4–6 h	++	
Piperazine	Hydroxyzine	10–50 mg q6–8 h; 50 mg HS	++	Physical urticarias, nighttime use
Alkylamine	Chlorpheniramine	2–4 mg q4–6 h	+	
Phenothiazine	Promethazine	12.5 mg t.i.d.–q.i.d.; 25 mg HS	+++	Nighttime use
Piperidine	Cyproheptadine	4 mg q4–6 h	+	Cold urticaria, nighttime use; antiserotonin activity
Nonsedating H1	Azelastine	2 mg b.i.d.	–	
	Cetirizine	10 mg daily or b.i.d.	–	
	Levocetirizine	5 mg daily or b.i.d.	–	
	Ebastine	10 mg daily or b.i.d.	–	
	Fexofenadine	60 mg b.i.d. or 60–180 mg daily	–	Not metabolized in liver
	Loratadine	10 mg daily	–	Long half-life
	Desloratadine	5 mg daily	–	Long half-life; not metabolized in liver
	Mizolastine	10 mg daily	–	
Thioguanidine	Cimetidine	300 mg q.i.d.	–	For skin diseases, used with H1 blocker; also immunomodulatory and antiandrogenic
Tricyclic antidepressant	Doxepin	10–20 mg q.i.d.	++	H1, H2 blocker: cardiac side effects

a For the older classes, only a single well-known example is cited

- **Contraindications:** Generally best avoided during pregnancy; more information on older antihistamines. Clemastine generally recommended in Germany. Few are approved for children < 2 years of age; dimethindene is available in Germany for infants > 1 month.
- **Dosage:** It is best to start at a low dose of antihistamines and gradually increase. It may also be wise to use two different antihistamines from different chemical classes to maximize effect. The nonsedating H1 antihistamines, which poorly cross the blood–brain barrier, have been a tremendous advance and have replaced many of the older sedating H1 blockers. On the other hand, in some instances the sedating action is desirable and an older agent serves better. There are also phenothiazines (promethazine) and tricyclic antidepressants (doxepin) with significant antihistamine effects. The antihistamines are summarized in Table 42.**1**.
- **Side effects:**
  - ***Note:*** Acquaint yourself with the specific side effects and their likelihood in the antihistamines you routinely prescribe.
  - Sedation is only a problem with the older agents. However, one is legally mandated to warn the patient about driving, operating heavy equipment, or doing anything requiring alertness when an antihistamine is prescribed, even a nonsedating one.
  - Terfenadine, one of the first nonsedating antihistamines, is no longer available in the USA because of its propensity to cause **life-threatening cardiac arrhythmias.** This problem was made worse by its interaction with macrolide antibiotics and imidazole antifungals.
  - None of the other nonsedating antihistamines has the same high risk, but patients with preexisting cardiac disease, especially rhythm disturbances, should be evaluated carefully.
  - Many are metabolized by the cytochrome P450 enzymes, so that multiple drug interactions are possible (Table 42.**9**).
  - Anticholinergic effects, including urinary retention, dry mouth, even predisposition to heat stroke (decreased sweating).
  - ***Note:*** Many of the antihistamines, especially doxepin and diphenhydramine, are effective topically. Unfortunately they are potent sensitizers and thus probably best avoided, as sensitized patients may then be allergic to systemic antihistamines, which are often administered in an emergency setting.

Other Antiallergic Agents

- **Cromolyn:**
  - Mast cell stabilizer; poorly absorbed; primarily used for asthma, allergic rhinitis, and allergic conjunctivitis in the form of inhalers, nose drops, and eye drops.
  - Available as pill with indication for use in systemic mastocytosis; absorption minimal, but helps stabilize gastrointestinal mast cells.
- **Ketotifen:**
  - H1 receptor antagonist and mast cell stabilizer.
  - Useful in allergic asthma and as eye drops in allergic conjunctivitis.
  - Treatment of choice for pruritus associated with neurofibromatosis.

42.5 Antimalarials

- **Mechanism of action:** Stabilize membranes, especially lysosomes; downregulate expression of MHC molecules; hinder neutrophil and eosinophil migration and function; interact with complement system; inhibit prostaglandin synthesis; many other undoubtedly important immunological interactions.
- **Indications:** The antimalarials were discovered to be effective against lupus erythematosus, as American soldiers receiving malaria prophylaxis during World War II noted improvement in their disease. They are now used for this indication as well as rheumatoid arthritis, polymorphous light eruption, and sarcoidosis. In much lower dosages, they are employed in porphyria cutanea tarda. Our comments apply only to their use in dermatology, not to their worldwide use against *Plasmodium*.
- **Contraindications:** Pregnancy, nursing, G6PD deficiency, simultaneous use of hepatotoxic agents or monoamine oxidase (MAO) inhibitors, myasthenia gravis, hematopoietic diseases.
- **Drug interactions:** Increase levels of digoxin.
- **Precautions:**
  - Ophthalmologic examination before starting therapy and then every 6–12 months.
  - CBC, liver, and kidney parameters before starting therapy; check CBC after 1 month and all parameters at 6 months.
- **Available agents:**
  - Chloroquine (CQ) 250 mg.
  - Hydroxychloroquine (HCQ) 200 mg.

  Note: 250 mg CQ is roughly equal to 400 mg HCQ. Each agent has found favor in different countries.
- **Dosage:** Usually either 200–400 mg HCQ or 250 mg CQ as required. When treating porphyria cutanea tarda, the usual dosage is 125 mg CQ 2–3 × weekly.

  Note: Full dosages of CQ or HCQ can be fatal in porphyria cutanea tarda (p. 312).
- **Side effects:**
  - Agranulocytosis, blood dyscrasia, hemolytic anemia.
  - – Irreversible retinal damage: The risk of retinopathy is generally accepted to be less with HCQ than with CQ, but the key is careful monitoring, not choice of agent. One study suggested safe ranges of < 4.0 mg/kg daily of CQ or < 6.5 mg/kg daily of HCQ. Conflicting data on total cumulative dose. Similar retinal changes can be seen in systemic LE and macular atrophy.

    Note: Deposits can be seen in the retina with a split lamp. They are reversible, but the visible damage is not.
  - – Seizures, EKG abnormalities.
  - Anorexia, nausea, vomiting (common).
  - Pigmentary changes including blue-gray discoloration of hairs especially in redheads; blue discoloration of tibia, palate, face, nail bed.
  - Lichenoid and urticarial exanthems; rarely toxic epidermal necrolysis.
  - General wisdom is that antimalarials make psoriasis worse, but this was not supported by experience during the Viet Nam War, and there are studies showing effectiveness of HCQ in psoriatic arthritis.

Quinacrine

Quinacrine (Atabrine) 100 mg has been used in the past as a back-up agent when CQ and HCQ are not tolerated. It is no longer easily obtained and it used primarily as a local irritant injection for pneumothorax or nonsurgical female sterilization. It causes a yellow skin discoloration but not a retinopathy.

42.6 Retinoids

Mechanism of Action

Retinoids modulation the differentiation and keratinization of keratinocytes, alter fibroblast activity and modulate the T-cell response. They lead to desquamation and epidermal thinning, and can block tumor promotion in epithelial tumors.

Indications and Contradictions

► **Indications:**
- *Isotretinoin:*
  - Acne and rosacea; far and away most important indication for systemic retinoids.
  - Chemopreventive agent in xeroderma pigmentosum and nevoid basal cell carcinoma syndrome to reduce number of new tumors, not to treat existing lesions.
- *Acitretin:* Psoriasis (especially erythrodermic, pustular and arthritic forms), Darier disease, pityriasis rubra pilaris, lichen planus, disorders or keratinization, chronic cutaneous lupus erythematosus, epidermodysplasia verruciformis, and multiple keratoacanthomas.
- *Bexarotene:* Used for cutaneous T-cell lymphomas.
- *Tretinoin:* Used topically in acne but systemically only for acute promyelocytic leukemia to induce differentiation of neoplastic cells; not further discussed here.

► **Contraindications:**
- Women of childbearing age.

! ***Caution:*** The retinoids are potent teratogens. They can be taken by women of childbearing age only with effective contraception, ideally employing two methods. Female patients must sign informed written consent; in many countries, manufacturer offers pretreatment gynecologic consultation and assistance in follow-up. Patient should have negative pregnancy test and normal period before starting therapy.

- Patient should have severe disease, not responsive to other measures.
- Pregnancy and nursing.
- Abnormal liver function, disorders of lipid metabolism, severe diabetes mellitus.

► **Precautions:**
- Pregnancy test before starting treatment.
- Baseline liver function tests, cholesterol and triglycerides; monitor monthly for 3–4 months and then every 3 months.

► **Drug interactions:**
- Vitamin A (exaggerates effect).
- Tetracycline (pseudotumor cerebri).
- Methotrexate (hepatotoxicity).
- Alcohol (hepatotoxicity, cumulative effect on triglycerides).
- See also Table 42.**9**.

Dosage

► **Isotretinoin:**
- Severe acne including acne conglobata.
  - 0.2–0.5 mg/kg daily for 4–10 months with a desired total dose of 120 mg/kg.
  - May start with 0.7–1.0 mg/kg daily for first 2–3 months.

- Therapy-resistant less severe acne: 0.2 mg/kg daily for 4–6 months.
- Rosacea, Gram-negative folliculitis, severe sebaceous hyperplasia: No firm guidelines, but usually 0.2–0.5 mg/kg daily for 2–6 months; effects less dramatic and less permanent than with acne.

► **Acitretin:**
- Psoriasis: 0.3–1.0 mg/kg daily for 2–4 months; often combined with phototherapy.
- Other inflammatory dermatoses (pityriasis rubra pilaris, lichen planus, hyperkeratotic hand dermatitis, Reiter syndrome, pustular disorders); dosages similar to psoriasis.
- Genodermatoses: Generally lower doses, 0.2–0.4 mg/kg daily.

► ***Note:*** When treating disorders of keratinization, treatment must be continued for months to years. Whenever it is stopped, the disease can be expected to recur. Tricks include higher initial dosages to gain control, then lower maintenance dosages, and therapy-free intervals.

► **Bexarotene:**
- Dosage: 300 mg/m^2 daily; adjusted to 200 mg/m^2 and then 100 mg/m^2 depending on tolerability and effectiveness.
- Used for advanced stages of cutaneous T-cell lymphoma.
- Response rate 50%; exact indications remain to be determined.

Side Effects

► **Teratogenicity:** Single most troublesome side effect. Responsible for numerous medico-legal problems in USA. Well-defined embryopathy. Women must not only practice meticulous contraception while taking medication but must continue for at least 1 month after stopping isotretinoin and 2 years after stopping acitretin.

► **Mucosal disease:** The problem is dryness, which effects every patient—cheilitis, conjunctivitis, dry eyes, dry nose with nosebleeds, dry mouth. The effects are reversible and can usually be controlled with lubrication, artificial tears, and artificial saliva.

► **Skin:** Dry skin, alopecia, and brittle nails are all common. The dry skin is desirable in acne patients, but less so in those with papulo-squamous or keratinization disorders.

► **Depression:** Ongoing controversy over the role of isotretinoin in depression and suicidal ideation in teenagers.

► **Liver function:** Abnormal liver function tests common but rarely clinically significant in teenagers. In adults, careful monitoring required.

► **Lipid metabolism:** Elevated triglycerides and cholesterol are the rule, not the exception. Once again, in teenagers, rarely necessary to stop or alter therapy. In adults or those requiring long-term therapy, major problem with risk of pancreatitis and acerbated cardiovascular disease.

► **Skeletal problems:**
- *Arthralgias* and *myalgias* are common.

► ***Note:*** Do not treat teenage athletes during their active season. The effects are sufficient to interfere with performance.
- *Hyperostosis:* Children treated for longer periods of time, as is the case in disorders of keratinization, are at risk to develop **d**iffuse **i**diopathetic **s**keletal **h**yperostosis (DISH syndrome) involving the spine.
- *Calcification:* Tendons and ligaments, especially of distal legs, may be calcified.

► **Others:**
- Pseudotumor cerebri.
- Impaired night vision.
- Hyperthyroidism (bexarotene).

42.7 Corticosteroids

- **Mechanism of action:** Corticosteroids are secreted in a circadian fashion with maximum production in the early morning. For this reason, they should be prescribed in a single morning dose to minimize adrenal suppression or in divided doses to maximize immunosuppressive effects in emergency situations.
- A relatively low dose (prednisolone 10 mg daily) over a period of weeks is sufficient to induce adrenal suppression, so systemic corticosteroids must always be tapered. There is no clear benefit to administering ACTH instead of corticosteroids.
- The physiologic and pharmacologic actions of corticosteroids help explain the side effects and include:
  - *Gluconeogenesis*, leading to diabetes mellitus and a catabolic state with osteoporosis (hip fractures) and muscle atrophy.
  - *Fat mobilization*, leading to redistribution of body fat (moon facies, buffalo hump).
  - Increased numbers of neutrophils, decreased numbers of lymphocytes with suppression of T and B cell activity, leading to increased risk of infections, but providing the *profound immunosuppressive effects*.
  - Increased numbers of erythrocytes and thrombocytes leading to *thrombotic state*.
  - Multiple *anti-inflammatory mechanisms* with reduced wound healing, striae as side effects.
  - *Hypocalcemia* worsening osteoporosis.
  - *Mineralocorticoid effects* of sodium retention and potassium excretion leading to fluid retention, weight gain, and hypertension. Glucocorticoids are about 1:1000 as potent as aldosterone, but at higher dose, clinically significant.
- **Available agents:** Only a limited number of agents is needed; almost every dermatologic condition that requires systemic corticosteroids can be managed with prednisolone. a selected list of glucocorticoids, referred to throughout this book as corticosteroids, is shown in Table 42.**2**.
- **Indications:** The indications for systemic corticosteroids are lengthy. They are summarized, along with the dosage and administration guidelines, in Table 42.**3**.

Table 42.2 · **Systemic corticosteroids**

Agent	Relative potency	Cushing dosage (mg/day)	Comments
Hydrocortisone	1	30	Used for replacement therapy
Prednisolone	4	8	Standard agent
Prednisone	4	8	Converted to prednisolone; interchangeable
Methylprednisolone	5	6	Available i. v. form pulse therapy
Triamcinolone	5	6	Often used intralesionally; in past also i. m. for prolonged effect but no longer so employed. No mineralocorticoid effect
Dexamethasone	30	1	More rapid action; used in shock, cerebral edema, brain metastases

Table 42.3 · Indications for systemic corticosteroids

Regimen	Indications	Comments
Short-term, medium dose	Severe allergic contact dermatitis (poison ivy)	More effective than topical corticosteroids
	Drug reactions	Often used; little data
	Erythema nodosum	Rule out infections first
	Erythema multiforme	Works fine even if HSV present
	Hemangioma	
	Lichen planus (exanthematous form)	Treat for 6–8 weeks
	Leukocytoclastic vasculitis	Often responds to short course
	Sweet syndrome	May require 3–4 weeks
High dose or pulse	Alopecia areata Angioedema	Pulse Single dose
	Jarisch–Herxheimer reaction	Single dose
	Lupus erythematosus	Pulse therapy for CNS disease, severe renal disease, vasculitis
	Pressure urticaria	Sometimes hard to control without bursts
	Pyoderma gangrenosum	May require long-term low dose until healed
Long-term	Autoimmune bullous diseases	May require treatment for months–years
	Connective tissue diseases	May require treatment for months–years
	Sézary syndrome	Modest doses, but long-term
	Vasculitis	Depends on type; usually long-term

- **Contraindications:** Severe infections, osteoporosis, gastrointestinal ulcers, myopathies, psychosis, glaucoma, recurrent thrombosis. In every case, the contraindications are relative and must be weighed against the possible benefits, but also documented and discussed with patient.
- **Drug interactions:** Long list of interactions, including:
  - *Antidiabetics:* Increased blood sugars.
  - *Barbiturates, carbamazepine:* Increased corticosteroid levels.
  - *Estrogens:* Enhanced corticosteroid effects.
  - *Isoniazid:* Reduced levels of isoniazid.
  - *Phenytoin:* Reduced levels of corticosteroids.
  - *Rifampin:* Reduced levels of corticosteroids.
  - See also Table 42.**9**.

- **Dosage:** There are a number of general principles to follow in using systemic corticosteroids:
  - In dermatologic diseases, corticosteroids are never curative; they only provide symptomatic relief.
  - The longer they are used and the higher the dose, the greater the certainty of side effects.
  - **Note:** It is wise to have a treatment strategy before starting corticosteroids, as their use is a slippery slope. It is often quite difficult to discontinue therapy, and then one is overwhelmed by the negative effects.
  - *Short-term medium-dose regimens:*
  - Prednisolone 40–60 mg p.o daily for 1–2 weeks as needed.
  - **Note:** Develop your favorite regimen and always use the same one: this makes answering questions easier. One possibility is 60 mg daily for 4 days, 40 mg daily for 4 days, 20 mg daily for 4 days, and stop.
  - *Short-term high-dose and pulse regimens:*
    - Prednisolone 80–120 mg p.o daily.
    - Methylprednisolone 500 mg i.v. q12 h for 3–5 days.
  - *Long-term therapy:*
    - Prednisolone, starting at dosages of 80–120 mg to obtain disease control and then tapering as soon as possible, switching to q.o.d. regimens and using steroid-sparing agents to minimize size effects.
    - Goal is prednisolone 10 mg p.o. in morning; even at this level, both osteoporosis and Cushing syndrome possible.
    - If embarking on long-term therapy, document bone density and institute osteoporosis prophylaxis. Typical regimen includes calcium (1.0–1.5 g daily, depending on diet, vitamin D (400 IU daily), and often bisphosphonates (alendronate 5 mg daily), as well as weight-bearing exercise.
    - Exclude inactive tuberculosis.
- **Caution:** Three common dermatologic diseases require special mention:
  - *Atopic dermatitis:* Rapid response to corticosteroids, but equally rapid flare when stopped. Better never to use.
  - *Lupus erythematosus:* There are no cutaneous indications for systemic corticosteroids; save this agent for severe systemic problems.
  - *Psoriasis:* Best to avoid because of limited effectiveness and inevitable flare when corticosteroids are tapered. Withdrawal may lead to pustular psoriasis in patients who have previously not had this form.
- **Side effects:** Most of the side effects have been alluded to under the mechanisms of action. They include:
  - *Osteoporosis:* After 6 months, 50% have osteoporosis; incidence of hip fractures varies from 4–25% depending on duration and patient group.
  - *Hypertension:* Careful monitoring, routine care.
  - *Diabetes mellitus:* Monitor those at risk for diabetes mellitus and carefully control those with the disease.
  - Be alert for accompanying *infections.*
  - Most other side effects fall under *Cushing syndrome* (p. 318).

42.8 Immunosuppressive Agents

Because of the many side effects of long-term corticosteroid therapy, and because of the failure of some conditions to respond to corticosteroids, a wide number of other immunosuppressive agents are employed.

Azathioprine

- **Mechanism of action:** Purine antagonist that interferes with NK, T, and B cells.
- **Indications:** The steroid-sparing agent of choice in LE, dermatomyositis, and overlap syndromes, as well as in transplantation medicine. Also useful in many forms of vasculitis, Behçet syndrome, pyoderma gangrenosum, and chronic actinic dermatitis.
- **Contraindications:** Pregnancy, liver disease, bone marrow damage, active infections.
- **Drug interactions:** Allopurinol increases toxicity of azathioprine.
- **Precautions:** Thiopurine methyltransferase (TPMT) levels should be measured before starting therapy; individuals with low activity (genetic polymorphism) will experience greater immunosuppression.
- Monitor CBC, hemoglobin, platelets; if neutrophils drop below 3000/μL.
- **Dosage:** 1–3 mg/kg p.o. daily (3–5 mg/kg in transplantation medicine). If no response, increase dose cautiously but remember that response to azathioprine is slow. Some patients once under control do amazingly well on q.o.d. doses.
- **Side effects:**
  - Leukopenia, thrombocytopenia, pancytopenia.
  - Pancreatitis.
  - Nausea, vomiting, toxic hepatitis, arthralgias, stomatitis.
  - Long-term risk of increased cutaneous malignancies.

Chlorambucil

- **Mechanism of action:** Alkylating agent that interferes with DNA synthesis.
- **Indications:** Best established combined with corticosteroids in pemphigus vulgaris, mycosis fungoides, and Sézary syndrome; widely used in hematologic oncology.
- **Contraindications:** Pregnancy, bone marrow damage, acute infections.
- **Drug interactions:** Phenylbutazone, phenobarbital, vitamin A increase toxicity.
- **Precautions:** Men should avoid fathering a child for 6 months after conclusion of therapy; sperm storage recommended in oncology patients.
- **Dosage:** No established dose in dermatologic disease; in Winkelmann regimen for Sézary syndrome usual dosage is 4 mg daily, increase to 6 or 8 mg possible, with close monitoring of CBC and platelets.
- **Side effects:**
  - Bone marrow suppression.
  - Gastrointestinal toxicity rare.
  - Mucositis, peripheral neuropathy.
  - Rare but serious toxic hepatitis and pulmonary fibrosis.
  - Reproductive side effects (azoospermia with >400 mg).

Cyclophosphamide

- **Mechanism of action:** Alkylating agent, blocks DNA and RNA.
- **Indications:** Steroid-sparing agent in pemphigus vulgaris; also used in LE, vasculitis, Wegener granulomatosis, pyoderma gangrenosum, Behçet syndrome. Widely used in oncologic therapy, especially for hematologic malignancies.
- **Contraindications:** Pregnancy, reduced bone marrow function.
- **Drug interactions:**
  - *Allopurinol:* Increases cyclophosphamide toxicity.
  - *Digoxin:* Reduced absorption of digoxin tablets.
  - *Succinylcholine:* Neuromuscular blockade prolonged.
  - *Warfarin:* Decreased effectiveness.

- **Dosage:**
  - *Routine therapy:* 1–3 mg/kg p.o. daily.
  - *Pulse therapy:*
    - *Oral:* 15 mg/kg in single dose; once monthly.
    - *Intravenous:* 500 mg 1.0 g/m^2 once monthly; hydrate aggressively beforehand to reduce bladder toxicity and administer mesna.
- **Side effects:**
  - Cardiotoxicity, hepatotoxicity.
  - Myelosuppression, thrombocytopenia, leukopenia, pancytopenia.
  - Nausea, vomiting, diarrhea.
  - Hemorrhagic cystitis (< 5% except with pulse therapy).
  - Sterility, azoospermia, amenorrhea.
  - Alopecia.

Cyclosporine

- **Mechanism of action:** Cyclosporine inhibits helper T-cell function by blocking interleukin (IL)-2 function; also blocks other lymphokine release including IL-1, IL-3, IL-8, tumor necrosis factor (TNF) α and INF-γ.
- **Indications:** Standard for many years in transplantation medicine. In dermatology used in severe therapy-resistant psoriasis, severe or erythrodermic atopic dermatitis, severe hand dermatitis, pyoderma gangrenosum, and autoimmune diseases.
- **Contraindications:** Underlying malignancy, hypertension, renal disease; pregnancy; active infection.
- **Drug interactions:** Many interactions that require close attention:
  - *Methotrexate:* Increases toxicity of both agents.
  - *Aminoglycosides*, *amphotericin B*, *co-trimoxazole*, *NSAIDS*, *sulfonamides:* Increase nephrotoxicity.
  - *Amiodarone, anabolic steroids*, *chloroquine*, *imidazoles*, *macrolides*, *oral contraceptives*, *retinoids*: Increase cyclosporine levels.
  - *Calcium channel blockers:* Diltiazem and verapamil increase cyclosporine levels; others do not.
  - *Carbamazepine*, *co-trimoxazole*, *phenytoin*, *rifampicin*, *sulfonamides:* Reduce cyclosporine levels.
  - *Digitalis:* Cyclosporine raises levels.
  - *HMG-CoA reductase inhibitors:* Risk of myopathy.
- **Precautions:**
  - Before starting therapy, obtain CBC, creatinine, BUN, uric acid, bilirubin, liver function tests, potassium and lipids; check urine.
  - Every 2 weeks, check blood pressure, renal status, uric acid, and potassium.
  - Prompt attention to infections.
- **Dosage:**
  - 2.5–5.0 mg/kg p.o. daily. Usually start at 2.5 mg/kg; work up if no response within 2 weeks; be prepared to taper down.
  - Dosage reductions required:
    - If *creatinine* exceeds pretreatment or normal value by 30%.
    - If *potassium* exceeds normal values.
    - If *bilirubin or liver enzymes* exceed pretreatment or normal values by 200%.
    - *and* the increase persists for 2 weeks, then reduce cyclosporine dose by 25%. If not normalized within 2 weeks, must stop drug.
    - If diastolic blood pressure > 95 mm Hg, reduce dose or stop. Treat hypertension with nifedipine, which does not interact with cyclosporine.

- **Side effects:**
  - Renal failure.
  - Leukopenia.
  - Hypertension (50–90%).
  - Headache, tremors.
  - Gingival hyperplasia, oral candidiasis.
  - Hirsutism.

  Caution: Patients should avoid UV radiation because of increased risk of cutaneous malignancies. Cyclosporine should not be combined with phototherapy.

Methotrexate

- **Mechanism of action:** Folic acid antagonist.
- **Indications:** Severe psoriasis, psoriatic arthritis, bullous pemphigoid.
- **Contraindications:**
  - *Absolute:* Pregnancy, gastrointestinal ulcer, hepatic cirrhosis.
  - *Relative:*
    - Renal or hepatic dysfunction, hepatitis, alcoholism.
    - Anemia, leukopenia, thrombocytopenia.
    - Desire for children.
    - Severe infections.

  Caution: Both men and women should practice contraception for 12 months after taking methotrexate.
- **Drug interactions:**
  - *Binding resins:* Reduce methotrexate levels.
  - *Co-trimoxazole*, *NSAIDS*, *omeprazole*, *penicillin*, *probenecid*, *salicylates:* Increase methotrexate levels.
  - *Cyclosporine:* Increase toxicity of both agents.
  - *Phenytoin:* Reduce levels of phenytoin.
- **Precautions:**
  - Avoid alcohol and salicylates when on methotrexate; use NSAIDS with caution.
  - Increase fluid intake.
  - Monitor liver status; risk of hepatic fibrosis.

  Note: Changes in routine liver function tests are a poor predictor of the development of hepatic fibrosis.
    - Serum procollagen III aminopeptide (PIIINP) levels are the most sensitive indicator of hepatic fibrosis; if they remain normal, liver biopsy is not needed.
    - Other centers employ sonographic evaluation of liver every 6 months.

  Caution: Consult with hepatologist regarding liver biopsy if PIIINP increases, sonographic picture changes or once total dose >1.5 g. Adjust strategy to national guidelines.
  - *Other laboratory tests.*
    - *Before treatment:* CBC, hemoglobin, leukocytes, thrombocytes; renal function; chest radiograph.
    - *During treatment:*
    - CBC, leukocytes, thrombocytes weekly at first, then monthly. If leukocyte count $<3000/\mu L$ or platelet count $<100\,000/\mu L$, withhold therapy.
    - Renal function every 3 months.
- **Dosage:**
  - *Oral:*
    - 7.5–25 mg p.o. once weekly.
    - *Weinstein regimen:* 2.5–7.5 mg q12 h $\times$ 3; repeat weekly.
  - *Parenteral:* 10–25 mg i.m. or i.v. once weekly.

Note: The dermatologic dosages should never be confused with the considerably higher dosages employed in oncology. The lessons learned from rheumatology using low-dose methotrexate for rheumatoid arthritis are valuable; most dermatologists employ < 15 mg weekly of methotrexate and encounter few problems.

- **Side effects:**
  - Bone marrow suppression with leukopenia, thrombocytopenia, pancytopenia, and hemorrhage: Despite the concerns over liver disease, the greatest risk to patients on methotrexate is profound hematologic problems. An antidote is available—leukovorin 12 mg i.m. q6h for 4–6 doses.
  - Hepatotoxicity: See precautions for discussion of monitoring. The duration (> 3 years) and total dose (> 1.5–2.0 g) are key risk factors for hepatic fibrosis. After long-term use, about 10% have hepatic fibrosis and 3% cirrhosis.
  - Pulmonary fibrosis.
  - Gastrointestinal bleeding, anorexia, nausea, vomiting.
  - Renal failure.
  - Seizures.
  - Defective spermatogenesis.
  - Stomatitis, alopecia, reactivation of phototoxic disorders.
  - *Cutaneous ulcerations:*
    - *Superficial:* Erosions and ulcers of psoriatic plaques; heal rapidly when dose is lowered.
    - *Deep:* Develop in damaged skin (stasis dermatitis); very persistent.

Note: Remember, most of these catastrophic side effects occur during oncologic therapy. Nonetheless, the dermatologist cannot afford to ignore them.

Mycophenolate mofetil

- **Mechanism of action:** Inhibits inosine monophosphate dehydrogenase, an essential enzyme in guanidine nucleotide synthesis, in lymphocytes. The enzyme is scarcely influenced in other cells and tissues. Also influences mast cell degranulation and lipoxygenase activity.
- **Indications:**
  - Psoriasis vulgaris, as monotherapy or combined with topical medications.
  - Severe cases of atopic dermatitis, dyshidrotic dermatitis.
  - Widely used in transplantation medicine as steroid-sparing agent; now used in same way in pemphigus vulgaris, bullous pemphigoid, vasculitis, pyoderma gangrenosum, and other corticosteroid-responsive disorders.
- **Contraindications:** Pregnancy, nursing; caution with history of gastrointestinal ulcer or renal disease.
- **Drug interactions:**
  - *Acyclovir, ganciclovir:* Levels of both antivirals and mycophenolate mofetil increased.
  - *Antacids:* Reduced absorption.
  - *Probenecid:* Increases levels of mycophenolate mofetil.
  - *Resins:* Decreased absorption.
  - *Retinoids:* Decreased levels of both agents.

  Note: Routinely combined with cyclosporine in transplant patients; has less bone marrow toxicity than azathioprine and is replacing it in many settings; latter two should not be combined with azathioprine.
- **Precautions:**
  - CBC weekly for 1 month, then tapered to every 2 weeks and then monthly.
  - Hepatic and renal function pretreatment, after 1 month and then every 2–3 months.

- **Dosage:** 500 mg 2–4 × daily.
- **Side effects:**
  - Bone marrow suppression with leukopenia, thrombocytopenia, anemia.
  - Pain, headache.
  - Hypertension.
  - Nausea, vomiting, diarrhea.
  - Increased risk of infections.

42.9 Biologicals

- **Definition:** Biologicals or immunobiologicals are molecules capable of altering the normal cellular immune response; they are usually molecules designed to interrupt pathways of cell signaling, activation and cytokine production.
- **Nomenclature:** The naming of biologicals is initially confusing, but in fact easily understandable. The following terms are used:
  - *mab:* Monoclonal antibody.
  - *cept:* Fusion protein with receptor effect.
  - *mu:* Human antibody.
  - *xi:* Chimeric (mouse-human) antibody.
  - *zu:* Humanized mouse antibody.
  - *li:* Anti-inflammatory.
- For example, Inf-li-xi-mab is an anti-inflammatory, chimeric, monoclonal antibody.

Note: At this time (January 2006), many biologicals are approved and under review for a perplexing range of indications, varying from one regulatory agency to the next. Consult Internet sources for latest information in your country. The biologicals used for psoriasis are considered in detail elsewhere (p. 271).

42.10 Antiemetic Therapy

Overview

Dermatologists in Germany administer chemotherapy for malignant melanoma and other tumors. A crucial part of cancer chemotherapy is antiemetic therapy, as anorexia, nausea, and vomiting are the most common side effects. Drugs such as DTIC and cisplatin induce vomiting in >90% of patients. Vomiting is triggered by 5-hydroxytryptamine (5-HT3) and dopamine receptors in the gastrointestinal tract and CNS (zona postrema).

Antiemetic Agents

- **Antihistamines:** Several categories minimally effective.
- **Dopamine receptor antagonists:** Metoclopramide 10–20 mg q4 h.
- **Serotonin receptor antagonists (5-HT3-RA):** Ondansetron 16–32 mg i. v.; then 8 mg q12 h i. v. or tropisetron 5 mg i. v., then 5 mg i. v. or p. o.
- **Corticosteroids:** Dexamethasone 10–20 mg i. v. before chemotherapy.
- **Phenothiazine:** Triflupromazine 10–30 mg q4 h.
- **Benzodiazepine:** Diazepam 10 mg before starting chemotherapy, then 5 mg daily.
- **Combination regimens:**
  - *Highly emetogenic regimens:* 5-HT3-RA + antihistamines + dexamethasone + diazepam.

- *Delayed vomiting (often from cisplatin):* 5-HT3-RA + dexamethasone.
- *Anticipatory vomiting:* 5-HT3-RA + diazepam.

Caution: Combinations are preferred to maximum dosages. 5-HT3-RA can cause extrapyramidal signs and symptoms. Dexamethasone should not be used in patients receiving immunotherapy.

42.11 Pain Therapy

Overview

The other mainstay of care for tumor patients is adequate pain relief, which is the single greatest factor in increasing qualify of life for these unfortunate people. Basic principles of pain therapy include:

- Always work together with pain center or pain therapy specialists.
- Try to manage with oral agents. Infusion of i. v. agents should be reserved for those who are still uncomfortable with oral therapy.
- Continuous infusion or on-demand infusion are preferred to bolus injection of pain medications.
- Do not be afraid to use the agents in their maximum therapeutic range.
- Adjuvants are effective in increasing the effect of pain drugs (Table 42.**4**).
- Be alert to side effects; opiates always cause constipation, so provide laxatives or stool softeners.
- Pay close attention to potential drug interactions.
- **Dosage:** A modified stepwise therapy scheme is shown in Table 42.**5**.

Caution: The agents and adjuvants used for pain relief have a vast number of drug interactions. Discussion of these exceeds the limits of a dermatology text, but if you are treating pain patients you must inform yourself about this aspect.

Table 42.4 · **Adjuvant pain therapy**

Indication	Agent	Dose
Depression	Tricyclic antidepressant (clomipramine)	25 mg HS, may increase to 25 mg t.i.d. or 75 mg in time release dose
Burning dysesthesia (neuropathy)	Haloperidol	3 × 0.5 – 1.0 mg
Nerve compression, increased CNS pressure	Dexamethasone	4 mg i. v.; can repeat 3–6 × daily
Intermittent, lancinating pain	Carbamazepine	2 × 200 mg daily; maximum 800 mg daily
	Valproic acid	3 × 300 mg daily; maximum 4 × 600 mg
Muscle spasms	Muscle relaxants (Baclofen)	3 × 5 mg; maximum 3 × 25 mg

Table 42.5 · Stepwise approach to pain therapy

Agent	Duration (hours)	Dose (24 hours)
1st stage + adjuvants		
Paracetamol	4	4–6 × 0.5–1.0 g
Ibuprofen	3–4	4–6 × 400–600 mg
Diclofenac	4–8	2–3 × 100 mg
Metamizole	4–6	4–6 × 0.5–1.0 g
2nd stage (+ above and adjuvants)		
Tramadol	4–8	4–6 × 50–100 mg
Codeine	2–3	4–6 × 20–100 mg
Tilidine–naloxone	8–10	2–3 × 100–200 mg
3rd stage (+ above and adjuvants)		
Morphine sulfate drops or suppository	2–4	4–8 × 10–30 mg
Morphine sulfate time-release	12	2–3 × 30–80 mg
Buprenorphine	> 30	2–3 × 0.2–0.4 mg
Fentanyl TTS (transdermal)	48–72	0.6–6.0 mg daily
4th stage		
Peridural or subcutaneous opiates; regional anesthesia		

Modified from WHO guidelines; see also www.painweb.de

42.12 Miscellaneous Agents

Clofazimine

Note: Not readily available in most countries; check with public health authorities.

- **Mechanism of action:** Phenazine dye used in leprosy therapy; has antineutrophil effect, but mechanisms unknown.
- **Indications:** Approved for leprosy and erythema nodosum leprosum; incorporated into some regimens against *Mycobacterium avium-intracellulare*; often tried for Melkersson–Rosenthal syndrome, pyoderma gangrenosum, necrobiosis lipoidica, granuloma annulare, and granuloma facile. Formerly recommended for pustular psoriasis but not effective.
- **Contraindications:** Pregnancy.
- **Dosage:** 100 mg daily–t.i.d.; reduce with clinical response; long-term therapy possible.
- **Side effects:**
  - Nausea and vomiting.
  - *Long-term use:* Eosinophilic enteritis, crystal deposition enteropathy.

- Pink to brown discoloration of skin, tears, urine, sweat, and other bodily fluids; may persist long after therapy is stopped.

Colchicine

- **Mechanism of action:** Inhibits microtubular system, thus interfering with cell division, migration, other neutrophil functions, collagen synthesis, and deposition of amyloid.
- **Indications:** Mainstay of gout therapy. In dermatology used for Behçet syndrome, vasculitis, and amyloid deposition primarily in familial Mediterranean fever.
- **Contraindications:** Pregnancy; established teratogen.
- **Drug interactions:**
  - *Cyclosporine:* Increased levels of cyclosporine.
- **Precautions:** Check CBC, platelets before therapy and then every 2 weeks, later every 1–2 months.
- **Dosage:** Start with 0.5–1.0 mg daily; maximum tolerated dose is 1.5–2.0 mg daily. Try to reduce as soon as possible.
- **Side effects:**
  - Thrombocytopenia, pancytopenia, agranulocytosis, aplastic anemia: Rare and idiosyncratic.
  - Nausea, vomiting, diarrhea: Inevitable, almost everyone at 1.5 mg daily has problems.
  - Azoospermia, myopathy, alopecia.

Cyproterone

- **Mechanism of action:** Antiandrogen.
- **Indications:**
  - *Low-dose with estrogens:* Acne, hirsutism, androgenic alopecia.
  - *Mid-dose:* Severe hyperandrogenism.
  - *High-dose:* Prostate carcinoma; reduction of sexual drive in sexual offenders.
- **Contraindications:** Pregnancy, severe hepatic dysfunction, thromboembolic disease, estrogen-dependent tumors.
- **Dosage:**
  - *Low-dose:* 2 mg cyproterone and 0.035 mg ethinyl estradiol on days 5–25 of menstrual cycle.
  - *Mid-dose:* 2 mg cyproterone and 0.035 mg ethinyl estradiol + 10 mg additional cyproterone on days 5–19.
  - Treatment must be continued for months to years. The mid-dose should be reserved for severe hirsutism.
- **Side effects:** Headache, nausea, vomiting, weight gain, breast tenderness, irregular menses, mood changes, loss of libido.

Note: Not available in USA.

Fumaric Acid Ester

Fumaric acid is the trans isomer of maleic acid. The natural product contains a variety of esters complexed with different salts; a standardized product is available in Germany.

- **Mechanism of action:** Blocks NFκB signaling and thus many aspects of inflammatory reaction; also effects on apoptosis, cytokine production and dendritic cell function.
- **Indications:** Moderate to severe psoriasis.
- **Contraindications:** Pregnancy, severe or chronic gastrointestinal disease.

► **Dosage:** Fumaric acid is available as.
- *Fumaderm initial:* 30 mg dimethyl fumarate, 67 mg ethyl hydrogen calcium fumarate, and small amounts of the zinc and magnesium salts.
- *Fumaderm:* 120 mg dimethyl fumarate, 87 mg ethyl hydrogen calcium fumarate, and small amounts of the zinc and magnesium salts.
- The recommended mode of administration is shown in Table 42.**6**.

Table 42.6 · **Dosage scheme for Fumaderm**

Day	Morning	Noon	Night	Form
1–3	0	0	1	Fumaderm Initial
4–6	1	0	1	Fumaderm Initial
7–9	1	1	1	Fumaderm Initial
10–12	1	1	2	Fumaderm Initial
13–15	2	1	2	Fumaderm Initial
16–18	2	2	2	Fumaderm Initial
19–21	0	0	1	Fumaderm
22–24	1	0	1	Fumaderm
35–27	1	1	1	Fumaderm
28–30	1	1	2	Fumaderm
31–33	2	1	2	Fumaderm
34–36	2	2	2	Fumaderm
Then continue with 2–2–2				

Precautions: Follow laboratory parameters as shown in Table 42.7.

► **Dosage reduction:** Follow laboratory parameters as shown in Table 42.**7**. If the following parameters are obtained, then the dosage should be reduced to previously tolerated level; if problems persist, medication should be stopped.
- WBC $< 4000/\mu L$.
- Lymphocytes $< 500/\mu L$.
- Creatinine $> 30\%$ of initial value.
- Proteinuria.
- Persistent eosinophilia ($> 25\%$ for > 6 weeks).

Table 42.7 · **Laboratory testing in patients receiving fumaric acid esters**

Time	CBC	Liver enzymes	Renal function, urine status
Before therapy	Yes	Yes	Yes
1st month	Every 14 days	Once	Once
2nd month	Every 14 days	Once	Once
3rd month	Every 14 days	Once	Once
4th month (if no problems)	Once	Once	Once

- **Side effects:**
  - To begin with, diarrhea and flushing are common, but they usually resolve with continued therapy.
  - Lymphopenia, leukopenia.
  - Nephrotoxicity with proteinuria.

Thalidomide

- **Mechanism of action:** Another antineutrophil medication with unclear mechanisms; may have anti-TNF effect. Originally used as mild sedative, but turned out to be potent teratogen, producing characteristic limb defects.
- **Indications:** Agent of choice for erythema nodosum leprosum; effective in Behçet syndrome, severe aphthosis, pyoderma gangrenosum, LE (especially hyperkeratotic variants), and prurigo nodularis.
- **Contraindications:** Women of childbearing age must use double contraception; signed, witnessed informed consent. In most countries, not available as prescription drug but through public health officials or the manufacturer.
- **Dosage:** In acute disease, usually start with 300–400 mg daily, but taper rapidly; usual maintenance dosage is 25–100 mg.
  Note: Usually obtained from manufacturer or leprosy treatment centers.
- **Side effects:**
  - Teratogenic, causing limb defects.
  - Peripheral neuropathy (dose-dependent; not always reversible).
  - Nausea, vomiting, dizziness, constipation.

42.13 Drug Interactions

Overview

The more systemic medications one employs, the greater the likelihood of an interaction between the two drugs, increasing or decreasing the effectiveness of one or both. It has been estimated that if a patient is taking more than five medications, the likelihood of a drug interaction is 50%; with more than 10 medications, it approaches 100%.

Alert pharmacists, with computerized records of all medications a patient is receiving, can help greatly to alert the physicians to possible problems. For this reason, every outpatient should be encouraged to use a single pharmacy. As of 2005, patients in Germany receive a slight financial benefit if they do so.

Causes

The major causes of drug interactions are:

- **Cytochrome P-450 (CYP):** A group of enzymes involves in the metabolism of many drugs. When increased amount of CYP are induced, increased active metabolites are available and the drug potency increased. Conversely, when production of CYP is impaired, then the potency is reduced. The most important enzyme is CYP3A; its main interactions are shown in Table 42.**8**.
  - *Inducers* are medications that increase levels of CYP3A, thus leading to increased metabolism and loss of effectiveness of other drugs.
  - *Inhibitors* block CYP3A and thus lead to decreased metabolism and gain in effectiveness.

- The *substrate drugs* are those metabolized primarily by CYP3A, which are thus most influenced. Note that several drugs are both inhibitors and substrates, thus when used they inhibit their own metabolism.

► **Renal resorption:** When several agents compete for renal resorption, variations in amount excreted and thus variations in potency are possible.

► **Impaired gastrointestinal absorption** because of antacids leads to loss in effectiveness, as does competition for bile acids by resins or different agents.

Table 42.8 · **CYP3A substrates, inhibitors, and inducers**
Caution: This table is designed to demonstrate the broad spectrum of CYP3A interactions. Consult more detailed sources when prescribing.

Substrates	Inhibitors	Inducers
Benzodiazepines	*Calcium channel blockers*	*Anticonvulsants*
Calcium channel blockers	Diltiazem	Carbamazepine
Diltiazem	Verapamil	Phenobarbital
Felodipine	*Imidazoles*	Phenytoin
Nifedipine	Itraconazole	*Anti-HIV agents*
Verapamil	Ketoconazole	Some NNRTIs
Immunosuppressive agents	*Macrolides*	*Rifampin (and other rifamycins)*
Cyclosporine	Erythromycin	
Tacrolimus	Clarithromycin	*Others*
Macrolides	*Not azithromycin; thus few interactions*	St. John's wort
Erythromycin		
Clarithromycin	*Protease inhibitors*	
Protease inhibitors	*Others*	
Statins (not all)	Grapefruit juice	
Others	Mifepristone	
Losartan		
Sildenafil		

Based on Table 2 in Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med 2005; 352:2211–21.

Table 42.9 · Drug interactions for systemic dermatologic agents

Caution: This table summarizes the most important drug interactions for the systemic agents discussed in the chapter. It is not intended to be exhaustive, but rather designed to highlight severe or common reactions. The multiple interactions associated with antiemetic and pain therapeutic agents are not listed; they should be sought in specialized books. Always check latest prescribing information for information on drug interactions.

Interaction with	Effect
Antibiotics	
Macrolides (erythromycin, clarithromycin)	Potent inhibitor of CYP3A (Table 42.**8**); always check for all possible interactions before prescribing
Astemizole, terfenadine (**both no longer available**)	Levels ↑ with cardiotoxicity
Carbamazepine	Effectiveness ↑
Coumarin	Effectiveness ↑ ↑
Cyclosporine	Levels ↑
Indinavir, other protease inhibitors	Effectiveness of both ↑
Itraconazole	Effectiveness ↑
Penicillin	Effectiveness ↓ **Note:** Azithromycin only interacts with penicillin
Prednisolone	Effectiveness ↑
Tetracyclines	M = minocycline, D = doxycycline Many agents (antacids, calcium, food, iron, zinc) block absorption with effectiveness ↓
Oral contraceptives	Controversial slight loss of effectiveness
Carbamazepine (D,M)	Antiobiotic ↓
Coumarin (D, m)	Effectiveness ↑
Phenobarbital (D,M)	Antibiotic ↓
Antifungals	
Griseofulvin	
Coumarin	Anticoagulant effect ↓
Oral contraceptives	Menstrual irregularities, increased risk of pregnancy
Penicillin	Cross-reactions possible
Phenobarbital	Griseofulvin ↓
Imidazoles	F = fluconazole, I = itraconazole
Antacids	Absorption ↓; imidazoles down ↓
Astemizole	QT prolongation, arrhythmias (no longer available)
Benzodiazepines	Sedation ↑

Table 42.9 · Continued

Interaction with:	Effect
Antifungals (Continued)	
Calcium channel blockers (I)	Effectiveness ↑
Carbamazepine	Imidazoles ↓
Cimetidine (F)	Fluconazole ↓
Cisapride	Levels of cisapride ↑, dysrhythmias
Corticosteroids	Effectiveness ↑
Coumarin	Anticoagulant effect ↑
Cyclosporine	Effectiveness ↑
Digoxin	Effectiveness ↑
Estradiol (F)	Effectiveness ↓
Food	Absorption ↑; imidazoles ↑
HMG-CoA reductase inhibitors (I)	Effectiveness ↑; myopathy, rhabdomyolysis
H2-blockers	Itraconazole absorption ↓ but metabolism also ↓; effect variable
Isoniazid (I)	Itraconazole ↓
Omeprazole	Effectiveness ↓
Oral hypoglycemic agents	Antidiabetic effect ↑
Phenobarbital	Itraconazole ↓
Phenytoin	Itraconazole level ↓
Rifampicin	Itraconazole level ↓
Tacrolimus	Effectiveness ↑
Terfenadine	QT prolongation, arrhythmias (no longer available)
Theophylline	Effectiveness ↑
Terbinafine	
Rifampicin	Terbinafine ↓
Tricyclic antidepressants	Terbinafine ↑
Antihistamines	
Most sedating H1	
CNS depressants	Sedation ↑
Astemizole, terfenadine	(No longer available)
Imidazoles	QT prolongation, arrhythmias
Macrolides	QT prolongation, arrhythmias

Continued Table 42.9 ▶

Table 42.9 · Continued

Interaction with:	Effect
Cyproheptadine	
Serotonin antagonists	Effectiveness ↓ with increased suicide risk
Fexofenadine	
Macrolides	Fexofenadine ↑
Loratadine	
Imidazoles	Levels ↑ but not clinically manifest
Macrolides	Levels ↑ but not clinically manifest
Promethazine	
CNS depressants	Effectiveness ↑
Antiviral agents	
Acyclovir	
Cimetidine	Acyclovir ↑
Probenecid	Acyclovir ↑
Theophylline	Effectiveness ↑
Brivudin	
5-fluorouracil, other fluoropyrimidine	Effectiveness ↑
Azathioprine	
Allopurinol	Azathioprine ↑
Tubocurarine	Effectiveness ↓
Clofazimine	
Cyclosporine	Effectiveness ↑
Chlorambucil	
Phenobarbital	Chlorambucil toxicity ↑
Phenylbutazone	Chlorambucil toxicity ↑
Vitamin A	Chlorambucil toxicity ↑
Chloroquine or hydroxychloroquine	
Ampicillin	Effectiveness ↓
Cimetidine	Chloroquine ↑

Table 42.9 · Continued

Interaction with:	Effect
Chloroquine or hydroxychloroquine (Continued)	
Cyclophosphamide	Cyclophosphamide ↑
Cyclosporine	Effectiveness ↑
Digoxin	Effectiveness ↑
Magnesium salts	Absorption ↓, effectiveness ↓; antacids ↓
Metronidazole	Toxicity (dystonia) ↑
Phenylbutazone	Risk of toxic epidermal necrolysis ↑
Colchicine	
Cyclosporine	Effectiveness ↑
Corticosteroids	
Aminoglutethimide	Corticosteroids ↓
Carbamazepine	Corticosteroids ↓
Cholestyramine	Absorption down, corticosteroids ↓
Estrogens	Corticosteroids ↑
Isoniazid	Effectiveness ↓
Ketoconazole	Corticosteroids ↑
Macrolides	Corticosteroids ↑
Oral hypoglycemic agents	Blood sugar ↑
Phenobarbital	Corticosteroids ↓
Phenytoin	Corticosteroids ↓
Rifampin	Corticosteroids ↓
Salicylates	Excretion ↑, effectiveness ↓
Cyclophosphamide	
Allopurinol	Cyclophosphamide ↑
Coumadin	Effectiveness ↓
Digoxin	absorption ↓, effectiveness ↓
Succinylcholine	Neuromuscular blockade ↑
Cyclosporine	Caution: Long list—monitor carefully.
Aminoglycosides	Nephrotoxicity ↑
Amiodarone	Cyclosporine ↑
Amphotericin B	Nephrotoxicity ↑
Anabolic steroids	Cyclosporine ↑

Continued Table 42.9 ▶

Table 42.9 · Continued

Interaction with:	Effect
Calcium channel blockers	
Diltiazem, verapamil	Cyclosporine ↑
Nifedipine	No interaction
Carbamazepine	Cyclosporine ↓
Chloroquine	Cyclosporine ↑
Co-trimoxazole	Nephrotoxicity ↑, cyclosporine ↓
Digoxin	Effectiveness ↑
HMG-CoA reductase inhibitors	Effectiveness ↑, myopathy, rhabdomyolysis
Imidazoles (all)	Cyclosporine ↑
Macrolides	Cyclosporine ↑
Methotrexate	Both agents ↑, enhanced toxicity
Metoclopramide	Cyclosporine ↑
NSAIDS	Nephrotoxicity ↑
Oral contraceptives	Cyclosporine ↑
Phenytoin	Cyclosporine ↓
Rifampin	Cyclosporine ↓
Sulfonamides	Nephrotoxicity ↑, cyclosporine ↓
Dapsone	
Didanosine	Dapsone ↓
Probenecid	Dapsone ↑
Trimethoprim (co-trimoxazole)	Blocked excretion, both ↑
Methotrexate	
Charcoal, binding resins	Methotrexate ↓
Co-trimoxazole	Methotrexate ↑
Cyclosporine	Both agents ↑, enhanced toxicity
NSAIDs	Methotrexate ↑
Omeprazole	Methotrexate ↑
Penicillin	Methotrexate ↑
Phenytoin	Methotrexate ↑
Probenecid	Methotrexate ↑
Retinoids	Hepatotoxicity ↑ (especially acitretin)
Salicylates	Methotrexate ↑
Sulfonamides	Methotrexate ↑; also folate deficiency ↑

Table 42.9 · Continued

Interaction with:	Effect
Mycophenolate mofetil	
Acyclovir, ganciclovir	Both ↑
Antacids	Mycophenolate mofetil ↓
Binding resins	Mycophenolate mofetil ↓
Probenecid	Mycophenolate mofetil ↑
Retinoids	Both ↓
Retinoids	
Cyclosporine	Retinoids ↑
Methotrexate	Hepatotoxicity ↑ (especially acitretin)
NSAIDs	Retinoids ↑
Phenobarbital	Effectiveness ↑
Phenytoin	Effectiveness ↑
Tetracycline	Also causes pseudotumor cerebri
Vitamin A	Toxicity ↑

43 Radiation Therapy

Overview

Ionizing radiation has long been known to have effects on the skin. The early pioneers, including Pierre Curie, experienced erythema and ulceration after exposure. Many of the advances in radiation therapy were made by dermatologists. Today, a combination of surgical advances, public fear of X-rays, and simple office economics threaten the existence of cutaneous radiation therapy.

Definitions

- **Radiation:** Energy transmitted through space or medium by waves.
- **Ionizing radiation:** High-energy radiation.
- **Dose:** Energy administered to a volume.
- **Rad** (radiation absorbed dose): The absorbed dose of ionizing radiation, resulting from the transfer of 0.01 J of energy to 1 kg kilogram of tissue. Now superseded by Gray.
- **Gray (Gy):** Standard unit; 1 Gy = 100 rad.
- **Dose rate:** Dose per unit time or intensity. The dose rate varies inversely with the square of the source-skin distance (target-skin distance); known as inverse square law.
- **Half-value layer (HVL):** The thickness of a given substance that reduces the intensity of a beam of radiation to $^1/_2$ of its original value (half-value thickness).
  - Both the nature of the absorbing material and the energy of the radiation determine how much diminution occurs.
- **Half-value depth (HVD):** The depth in a given tissue at which $^1/_2$ of the surface dose is administered.

Sources

- **Soft or superficial radiation:** Uses high-energy photons produced by traditional dermatologic X-ray machines with combination of filters; capable of producing HVD of 2.0–5.0 mm.
- **Electron beam:** Uses electrons produce by linear accelerator; electrons lose energy rapidly when penetrating skin; can be applied to entire skin surface.

Indications

Malignant tumors

- The ideal tumor for radiation treatment is a relatively superficial basal cell carcinoma, perhaps in a difficult surgical site in a patient who requires anticoagulation. Common indications include basal cell carcinoma, squamous cell carcinoma, lymphoma, and Kaposi sarcoma.
- Malignant melanoma is not usually irradiated, except for lentigo maligna melanoma in situ.
- Merkel cell carcinoma is best treated with excision and radiation therapy.
- A histological diagnosis should be available before radiation therapy is planned. Often the dermatopathologist can measure the depth of tumor, making more precise treatment possible.
- Radiation therapy may be used for palliative treatment of inoperable tumors.
- Electron beam therapy can be tailored for treated cutaneous malignancies, usually using a surface gel bolus to concentrate the dosage more superficially.

- The main indication for electron beam is total skin electron beam therapy (TSEBT) for mycosis fungoides. In specialized centers, this is an effective first line treatment, which induces relatively long remissions but apparently few cures. Electron beam can also be used in more advanced cutaneous lymphomas, as well as in larger or deep basal cell carcinomas, as a higher dose at depth can be achieved.

Benign conditions

- In the past a wide variety of conditions were treated with radiation therapy, including plantar warts, psoriasis, acne, and hirsutism. In each instance, the treatment was temporarily effective but in most cases overused, leading to radiation dermatitis and secondary tumors.
- Keloids are perhaps the only benign condition that can be considered for radiation therapy today.

Treatment Regimens

- Exact treatment plans should be determined by physicians experienced in radiation therapy. Today the trend is to use fractionated dosages, which provide better sparing of normal tissue.
- Basal cell carcinoma and squamous cell carcinoma are usually treated with around 50 Gy—either 6 Gy × 8 sessions or 12 Gy × 4, or variations in between.
- Lentigo maligna melanoma in situ requires a higher dose, around 100 Gy, often fractioned over 20 sessions.
- Kaposi sarcoma and most lymphomas are much more radiation sensitive; dosage ranges are 20–30 Gy for Kaposi sarcoma and 5–15 Gy for lymphoma, sometimes given in only 1–2 sessions.

Radiation Reactions

- **Skin:** Around 4 Gy is sufficient to cause erythema after 1–2 days. The erythema peaks after a week, then resolves, usually with hyperpigmentation. The clinical picture is often more complex as the patient is being repeatedly exposed. As a general rule, up to 8 Gy are tolerated with complete healing. Above this dose, some degree of chronic radiation dermatitis is expected.
- **Appendages:**
  - 3–4 Gy are sufficient for temporary epilation; 8 Gy can cause permanent loss of hair.
  - Sweat and sebaceous glands are also temporarily inhibited by 4 Gy and may suffer permanent damage at 8 Gy.

  ▶ ***Note:*** These effects explain why ionizing radiation was so popular for acne and hirsutism.
- **Radiation dermatitis:**
  - *Acute radiation reactions* following therapy or accidental exposure (as in Chernobyl) can be classified as follows:
    - *Grade I:* Erythema.
    - *Grade II:* Vesicles, blisters.
    - *Grade III:* Erosions, ulcers, necrosis.
  - *Chronic radiation dermatitis* is the prototype of poikiloderma with telangiectases, hypo- and hyperpigmentation, and atrophy. The tissue also becomes sclerotic and has a tendency to ulcerate and then heal extremely poorly.
- **Secondary tumors:** The latency period is 20–30 years, but then the risk of basal cell carcinoma and squamous cell carcinoma is considerable. The tumors are more difficult to treat in the background of radiation dermatitis, and may be intrinsically more aggressive. There is a linear correlation between dose and risk of tumors; no absolutely safe dose has been established.

- **Treatment:** There is no effective prophylaxis for radiation dermatitis, other than careful selective of exposure parameters to minimize effects. The surrounding skin must be protected with shielding, usually with lead sheeting. The erythematous phase may be helped by topical corticosteroids or a bland ointment. Once chronic radiation dermatitis has developed, the patient should be instructed in how to best protect the area from subsequent trauma and monitored frequently for the development of radiation keratoses (analogous to actinic keratoses) and more aggressive tumors. If radiation keratoses develop, best to excise entire area of radiation damage if feasible; otherwise treat individual lesions as squamous cell carcinoma in situ.

44 Therapy During Pregnancy and Nursing

Overview

Note: The basic rules are simple:

- Prescribe as few medications as possible during pregnancy.
- Always have firm indications.
- Use single agents; not mixtures.
- Check every drug prescribed during pregnancy in a reference source.
- Always try topical agents first; absorption is possible, but guaranteed to be less than systemic.
- Oral administration is preferred to intravenous or intramuscular because then the medication is easier to remove from the body.
- Document carefully.

It is relatively simple to follow these rules because every pregnant women shares the concerns of her physicians. The real problem is before a pregnancy has been identified, which can sometimes take months. The most critical period is 15–60 days after conception, as this is the time frame for organogenesis.

Drug Ratings

The categories used to rate drugs for use in pregnancy are shown in Table 44.**1**.

Caution: The dermatologic agents listed in Table 44.**2** are either D or X and should not be used. There are other D and X agents; this list is not exhaustive.

Table 44.1 · Rating of drugs for use in pregnancy

Category	Explanation
X	Contraindicated. Never use in pregnancy
D	Evidence of risk for fetus; only use in rare circumstances
C	Possible risk; human studies lacking
B	No risk to humans, or no risk in animals and human studies not performed
A	Controlled studies have shown no risk

Table 44.2 · Contraindicated medications

Category D	Category X
Azathioprine	Acitretin
Colchicine	Estrogens
Cyclophosphamide	Danazol
Hydroxyurea	Finasteride
NSAIDs	Flutamide
Potassium iodide	Isotretinoin
Tetracyclines	Methotrexate
	Stanozolol
	Thalidomide

Caution: No medication is 100% safe during pregnancy. No common dermatologic agents are category A. Remember that even without medications, pregnancy is fraught with dangers:

- Spontaneous abortion rate is around 3%, but less than 1% if fetal heart beats are identified in weeks 10–12.
- Spontaneous malformation rate is 2–4%.

Antibiotics

► **Pregnancy:**

- *First choice:*
  - Penicillins, cephalosporins, erythromycin.
  - Cephalosporins are excreted more rapidly and more widely distributed, so dose must be increased.
  - Spiramycin (another macrolide) is treatment of choice for toxoplasmosis during pregnancy.
- *Alternatives:* Clindamycin, lincomycin; sulfonamides (not in third trimester because of risk of jaundice).
- *Relative contraindications:* Metronidazole is best administered as a suppository for trichomoniasis, and not used systemically. Toxic in animal studies and controversial in humans.
- *Absolute contraindications:*
  - Tetracyclines: Increased risk of hepatotoxicity in mother; dental and bony defects in fetus after 15th week.
  - Aminoglycosides: Ototoxic.
  - Chloramphenicol: Gray syndrome (potentially fatal toxic reaction in fetus).
  - Gyrase inhibitors: No enough data.
- *Topical agents:* Neomycin, bacitracin, and fusidic acid have minimal absorption and are safe. In acne therapy, topical erythromycin is safest. Aminoglycosides, chloramphenicol, and tetracyclines are systemically absorbed and should be avoided.

► **Nursing:**

- *First choice*: Penicillins, cephalosporins, erythromycin.
- *Alternatives:* Aminoglycosides and tetracycline with appropriate indications; minimal transfer to fetus.
- *Relative contraindications:* Stop nursing when metronidazole is administered.
- *Absolute contraindications:* Gyrase inhibitors cause irreversible cartilage damage.

Antifungal Agents

► **Pregnancy:** No agent can be recommended.

- *First choice*: Terbinafine is rated B but still should only be used when absolutely necessary.
- *Relative contraindications:* Amphotericin B can be used for life-threatening infections (such as coccidiomycosis).
- *Absolute contraindications:* Griseofulvin and the imidazoles are category C and best avoided.
- *Topical agents:* Imidazoles and nystatin are generally safe.

Caution: Avoid intravaginal use in first trimester and use on other mucosal surfaces, especially if eroded.

- **Nursing:**
  - Avoid imidazoles on breast while nursing.
  - Imidazoles appear in milk, but risk unclear; if appropriate, use oral nystatin instead.

Antihistamines

- **Pregnancy:**
  - All can be used topically, but other reasons to avoid (e.g. allergic contact dermatitis).
  - For systemic use, those with B ratings include clemastine, dimethindene, and chlorpheniramine. All should be avoided close to delivery.
- **Nursing:**
  - Triprolidine, meclizine often recommended; clemastine probably best avoided.

Local Anesthetics

- **Pregnancy:** Local anesthetics enter the circulation and are transferred to the fetus where they can have systemic effects.
  - *First choice:*
    - Esters are preferred to amides, as fetuses have higher esterase activity.
    - Those esters with marked protein binding such as bupivacaine cross the placenta with greater difficulty.

  Note: A small excision need not be deferred in pregnancy; the need for procedures where large amounts of local anesthetics are required should be considered carefully.
- **Nursing:** Prilocaine can cause methemoglobinemia and is best avoided; otherwise no problems for routine use.

Analgesics

- **Pregnancy:**
  - Opiates should only be used with strict indications. Codeine and hydrocodone preferred to morphine. Contraindicated just prior to delivery or if miscarriage is threatened.
  - NSAIDs must be avoided in third trimester because of risk of premature closure of ductus arteriosus; should be used only for strict indications in the first and second trimesters.
- **Nursing:** Transfer to fetus possible; only with strict indications.

Immunosuppressive/Chemotherapy Agents

- **Pregnancy:**
  - Chemotherapy agents should only be used for life-threatening processes, in consultation with obstetricians and oncologists.
  - Cyclosporine is category C; the other common agents are all D or X.
- **Nursing:** Careful indications; cyclosporine is also to be used with care, as it can cause immunosuppression, growth retardation, and perhaps carcinogenesis in infants.

Other Agents

- **Acyclovir:** Very complex; limited studies but widely used in pregnancy despite definite small risks to fetus, because risk of fetal varicella or neonatal herpes considered greater.

- **Benzoyl peroxide:** Safe.
- **Corticosteroids:** Can be used safely both topically and systemically. Possible systemic effect is adrenal suppression, so pediatrician should be alerted at delivery as treatment may be required. No evidence of teratogenicity in humans. During nursing, if dosage is > 40 mg prednisolone daily, then pause for 4 hours after administration.
- **Dithranol:** Category C; used without problems.
- **Lindane:** Best avoided in pregnancy because of recurrent medico-legal controversies; official category B.
- **Permethrin:** First choice during pregnancy for scabies and pediculosis; alternatives include benzyl benzoate (scabies) and pyrethrins (pediculosis).
- **Podophyllin:** Contraindicated; no reliable data.
- **Povidone-iodine:** Contraindicated; risk of fetal hypothyroidism.
- **PUVA:** Contraindicated; insufficient data; bath PUVA assumed safer than systemic PUVA.
- **Retinoids:** Systemic retinoids absolutely contraindicated. Topical retinoids best avoided although used for years in acne without incident; category C, but once again medico-legal status is cloudy.
- **Salicylic acid:** Avoid widespread use in pregnancy because of absorption and transfer to fetus; do not use on breast during nursing.
- **Vitamin D analogues:** Limited data, but appear safe.

45 Operative Dermatology

45.1 Principles of Dermatologic Surgery

Informed Consent

Note: Except for emergencies and very minor procedures, both verbal and written preoperative information should be provided at least 24 hours before surgery. In the case of minors, the discussion must always include a parent or legal guardian.

Information that should be provided includes:

- **General risks:** Anesthesia; wound infection; scarring; nerve, vessel or lymphatic injury.
- **Operation-specific risks:**
  - Structures likely to be damaged.
  - Need for multiple procedures (especially in micrographic surgery).
  - Possible need for skin graft if primary closure is anticipated to be difficult.
  - Grafts or flaps should be diagrammed, showing where donor tissue will be taken or how tissue will be moved.
  - Likelihood of impaired healing and necrosis (especially with flaps and grafts).
  - Risk of recurrence in the case of tumor surgery.
  - Likelihood of scarring, especially if history of keloids or surgery in high-risk location.
  - Risk of thrombosis if immobilization is anticipated.

Note: Although forms are essential and save a great deal of time, it is best to also write a note documenting that everything has been explained. The patient (or parent) should be given a chance to ask questions, given a 24 hour waiting period, and allowed to sign the consent form without pressure. In some countries, a witness is required.

Preoperative Diagnosis

Note: The need for preoperative diagnotic evaluation depends greatly on the extent of the procedure and the general health of the patient. Routine physical examination and laboratory studies are of little benefit, as documented in a study of 20 000 patients scheduled for elective hemorrhoidectomy.

- **Always consider:**
  - *Risk of bleeding:* Always ask about use of aspirin, heparin, or coumarin. If the history suggests a disorder of coagulation, then detailed laboratory investigation including von Willebrand factor, factor Xa, platelets, and hemoglobin. If platelet count is normal, but history suspicious, also do bleeding time as functional test.
  - *Problems with wound healing*: Ask about previous problems; consider role of systemic corticosteroids, diabetes mellitus, polyneuropathy, chronic venous insufficiency, peripheral arterial disease.
  - *Allergies:* Local anesthetics (usually an overdosage or hyperventilation, but always ask); analgesics, antibiotics; others.
  - *Associated diseases;* HIV/AIDS, hepatitis, cardiovascular disease.

Preoperative Disinfection

- Risk of infection varies greatly, depending on vascularity of tissue; rare on scalp and face, common on feet.
- Periorificial operations are always confronted with only a semisterile field, as the mouth or anus always has residual microorganisms.
- Risks of infection increase greatly with extent and duration of procedure. Also influenced by individual factors, especially diabetes mellitus and immunosuppression.
- Usually use Octenisept or 3% peracetic acid ester solution. In special cases:
  - When a flap is be developed, it is best to use a clear solution (such as peracetic acid) so that vascularity of flap can be assessed.
  - Mucosal surfaces can be sterilized with 0.1% benzalkonium chloride solution or Octenisept solution.
- Disinfectant always applied from center to periphery in circular strokes of increasing size.

Preoperative Sedation and Anesthesia

- **Preoperative sedation:**
  - ***Note:*** This can be very useful in anxious patients or children, to expand the range of operations that can be accomplished without intubation anesthesia.
  - In children, midazolam is preferred.
  - In adults: usual choice is benzodiazepines (diazepam or oxazepam); 5–10 mg 30–50 minutes before surgery.
  - ***Caution:*** Both midazolam and benzodiazepines are respiratory depressants.
  - In high-risk patients or when a long operation is anticipated:
    - Insert venous access line.
    - Have oxygen and suction available.
- **Topical anesthetics:**
  - EMLA, a commercial mixture of lidocaine and prilocaine, is the most effective topical anesthetic.
  - Indications include venipuncture sites in children, spinal puncture, preparing a site for injection of local anesthetic, or as sole agent for minor procedures such as removing molluscum contagiosum or skin tags.
  - The ointment is applied 45–60 minutes before the procedure and covered with occlusive foil; self-adhering products are simplest to employ.
  - ***Caution:*** EMLA is a vasoconstrictor, so small vascular lesions may disappear.
- **Cryoanthesthesia:**
  - Highly overrated technique; not suitable for digits or areas where poor wound healing is expected.
  - Suitable for very minor procedures and for preparing for an injection.
  - Use ethyl chloride spray at a distance of 20–30 cm, spraying until skin just turns white. Then proceed immediately.
  - ***Caution:*** Never use liquid nitrogen cryospray for anesthesia. The risk of necrosis is too great.
- **Infiltration anesthesia:**
  - Almost every example of skin surgery can be done with local infiltration anesthesia, including biopsies, simple excisions, flaps, and grafts.
  - Choice of agents is important (Table 45.**1**), as is attention to maximum volume and addition of epinephrine.
  - Prefer lidocaine 1–2% in combination with epinephrine. Maximum dose is 55 mg/kg.

Table 45.1 · Local anesthetic agents

Agent	Onset (m)	Duration (h)	Max dose (with epi)	Max dose (without epi)	Comments
Articaine	1–3	1	600	400	Rapidly metabolized
Lidocaine	1–2	1–2	500	300	Most often used; marked vasodilation
Mepivicaine	1–2	1.5–3	500	300	Long lasting; minimal vasodilation
Prilocaine	1–2	1–3	600	600	Can cause methemoglobinemia; careful in children
Ropivacaine	1–5	2–6	–	200	Long postoperative pain control; used in nerve blocks

From Table 1.1 in Kaufmann R, Podda M, Landes E. *Dermatologische Operationen*. Thieme, Stuttgart, 2005, p. 7. (epi = epinephrine)

- ***Note:*** Standard wisdom is not to use epinephrine when administering local anesthetics to digits, penis, nose or ears, or for nerve blocks. Recent studies indicate that when the circulation to the distal part is normal, epinephrine is a safe useful adjunct.
- Use an 18–21 gauge needle, insert once along line of incision, and inject while withdrawing along course.

► **Nerve block:** Can be used for large procedures, areas that are hard to inject (digits, penis, nose, ear, lips), and supplemented with additional infiltration.

Caution: Nerve blocks are always done using a local anesthetic without epinephrine.

- **Finger block:** Point of injection just distal to metacarpal-phalangeal joint. With continuous back aspiration, inject 1–2 mL of anesthetic on each side of finger while advancing toward the palm. Also inject the dorsal aspect of the finger with 1–2 mL. Numbness within 5–10 minutes.
- **Supraorbital nerve (forehead and nose):** Infiltrate above the eyebrow just medial to the supraorbital notch or foramen.
- **Infraorbital nerve (lower lid and medial cheek):** Infiltrate within the mouth above and posterior to the second upper premolar.
- **Mental nerve:** Infiltrate within mouth just distal to second lower premolar and mental foramen.
- **Penis block:** Inject 2–4 mL lateral to dorsal penis vein bilaterally, with infiltration of both dorsal and ventral sides; the latter must sometimes be extended to frenulum.

Postoperative Dressing

Note:

- The initial wound dressing should be left in place for 48 hours. The risk of contamination is greatest during this period. Later the wound is relatively closed, although without tensile strength.
- For complex flaps, use a transparent dressing so the vitality of the transplanted tissue can be observed without removing the entire dressing.

► **Dry sterile dressing:** Uncomplicated primarily closed wounds without exposed bone, cartilage, or fascia can be closed with a traditional dry dressing. Adhesive wound closures such as Steri-Strips can be used to better approximate the wound

edges if needed. They should be left in place until the wound is stable and removed carefully (or allowed to fall off).

- **Moist sterile dressing:**
  - Preferred for superinfected and moist wounds, especially if a wound contains exposed bone, cartilage, or fascia, requires conditioning or following skin transplantation.
  - Sterile dressings are moistened with Octenisept solution, which does not interfere with granulation tissue. Ideal for use with pinch grafts and split skin grafts on infected wounds.
  - Either physiologic saline or lactated Ringer solution can be used to moisten dressings over exposed bone and cartilage.
- **Dressing materials**: Usually combination of antiseptic ointment (povidone-iodine or fusidic acid), mesh dressing, and sterile bandages or hydrocolloid dressing.

Wound Infections

- **Clinical features:** Pain, erythema and heat—the classic signs.
- **Therapy:**
  - In most instances, suture material must be at least partially removed and wound re-explored. Systemic antibiotics and topical disinfectants are important but not sufficient measures.
  - If the wound contains pus, rinse with 1% H_2O_2 solution or povidone-iodine solution.
  - Carry out culture and sensitivity so that antibiotic therapy can be as specific as possible. Start with locally accepted broad-spectrum coverage.

45.2 Basic Techniques

Scissor Excision, Curettage, Biopsy

- **Anesthesia:**
  - Cryoanesthesia.
  - Lidocaine/prilocaine (EMLA).
  - Infiltration anesthesia.
- **Scissor excision:**
  - *Indications:* Skin tags.
  - *Technique:* Rapid excision using tip, not throat, of scissors.
- **Curettage:**
  - *Indications*: Benign epidermal lesions including seborrheic keratosis, actinic keratosis, wart, molluscum contagiosum.
  - *Technique:*
    - Disinfect; then local anesthetic. Place skin under tension between thumb and forefinger; grasp curette like a pencil and move across the surface of the lesion.
    - With experience, one can feel the difference between lesional tissue and the firmer normal dermis.
    - Curettes are sharp (or should be kept sharp), so be careful and do not exert undo pressure.
    - Bleeding can be controlled with ferric subsulfate (Monsel's) solution (which may discolor), 35% aluminum chloride solution, or 5–10% trichloracetic acid. Some prefer to use mild electrocautery.

- Warts are best treated with curettage combined with electrocautery or laser destruction of base.

► **Punch biopsy (p. 26):**
- *Indications*: Diagnostic biopsy.
- *Technique:*
  - Punches available in 2, 3, 4 and 6 mm sizes; 3 and 4 mm are most practical for routine purposes.
  - Disinfection and local anesthesia.
  - Despite the name "punch," the trick is to place the skin under tension in a direction perpendicular to skin tension lines and then to gently turn the instrument with mild downward pressure until a "pop" is felt, indicating the subcutaneous fat has been reached.
  - Extensive pressure is not needed if the punch is properly sharpened.

▶ ***Note:***
- Punch biopsies are not suited for sampling subcutaneous fat, for which a long thin ellipse is preferred.
- Most punch biopsies can be removed for the skin by pressing down on both sides of the defect so the plug is elevated, cutting the base with a curved iris scissors, and lifting the biopsy out and placing it is formalin solution with the scissors. Forceps are almost never needed.
  ▶ ***Note:*** A crushed biopsy with forceps marks makes interpretation difficult and is a sign of sloppy work.

► **Excisional biopsy:**
- *Indications*: This type of biopsy is designed to sample subcutaneous fat, or sample transition from normal to abnormal skin (needed primarily when defects in collagen or elastin are suspected).
- *Technique:* Disinfection and local anesthesia; long thin ellipse to minimize tension; close with simple sutures.

Excision with Primary Closure

► **Indications:** Almost all benign and malignant lesions.

► **Technique:**
- Disinfection and local anesthesia.
- Excision of ellipse with scalpel, usually # 15 blade. Angle at tip of spindle should be $< 30°$ to avoid the development of dog ears, which then require additional attention.
- Plan the ellipse around the long axis of the lesion. On the face, and in most instances elsewhere, try to place parallel to skin tension lines (Fig. 45.**1**). On the face, pay attention to the aesthetic units (forehead, periorbital region, nasal region, perioral region).
- Benign lesions should be excised with the excision placed just beyond the visible border of the lesion.
- The excision should always extend into subcutaneous fat, making undermining and closure much simpler. Closure is usually with a few dermal stitches to approximate and reduce tension, followed by simple skin closure with single stitches. Larger lesions or those under tension require more extensive subcutaneous or even epifascial undermining.
- Simple deeper lesions, primarily cysts and lipomas, can often be extruded through a small incision in the overlying epidermis. The ellipse should include the central pore in the case of a cyst. The lesion can be carefully mobilized with a blunt curved dissecting scissors. With lipomas, the risk of bleeding at the base is significant, especially with larger lesions or angiolipomas. Electrocautery may be needed if pressure is ineffective.

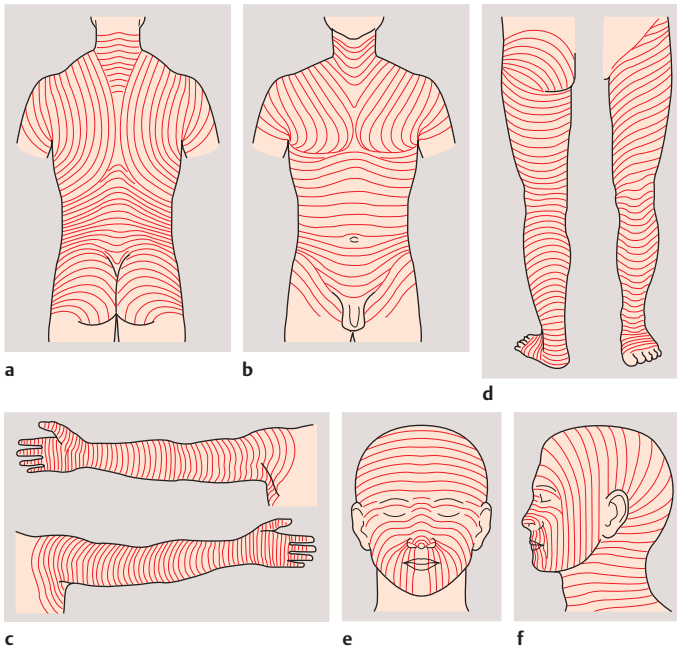


Fig. 45.**1** · Relaxed skin tension lines (modified from Borges and Konz).

Micrographic Surgery

- Indications: Basal cell carcinoma, especially if large, recurrent, or located in problem zone (perinasal, periorbital, periauricular); squamous cell carcinoma, dermatofibrosarcoma protuberans, other sarcomas, lentigo maligna melanoma.
  - ***Note:*** The indications for micrographic surgery remain controversial. Practitioners of the method tend to employ it for all cutaneous malignancies, although evidence-based medicine is just starting to accumulate data to delineate the appropriate usage.
- **Technique:** There are two basic approaches (Figs. 45.**2**, 45.**3**):
  - Tübinger Torte (in Germany) and Mohs' technique (in USA).
  - Both are based on meticulous histologic control of the entire margin of the excision; the Torte accomplishes this by an ingenious sectioning plan taking a small peripheral ring, while Mohs depends on flattening the excision and cutting sections from the entire base.
  - Each requires extensive marking and detailed sketches.
  - In most instances, the dermatologic surgeon also does the microscopic examination. If permanent sections are used, the wound is temporarily covered until the final results are available. If the margin is involved, the procedure is repeated in just that area.

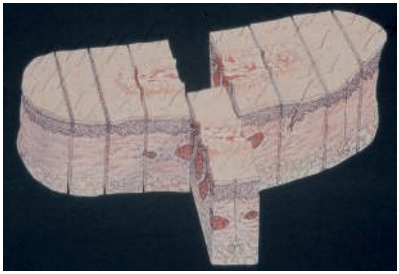


Fig. 45.**2** · Bread loaf technique, showing how easily this standard approach can miss a positive margin.

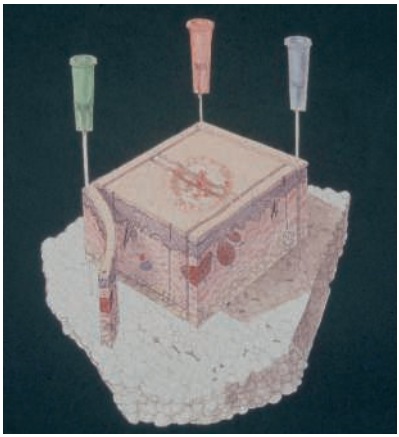


Fig. 45.**3** · Microscopic control of margins.

- Once the entire tumor has been removed and this has been confirmed microscopically, then closure is accomplished, sometimes primarily, but often with a flap or graft.

Note: Micrographic surgery offers the highest cure rates (95–99%) coupled with the maximum sparing of normal tissue.

Suture Technique

► **Sutures:**

- As general rule, atraumatic nonabsorbable sutures are used for skin closure and absorbable sutures for dermal and subcutaneous work.
- *Exceptions:*
  - On the scalp, coarse polyfilament sutures are used to allow rapid closure and tight knots.
  - In the mouth and perianal region, rapidly absorbed polyfilament sutures are used; they dissolve within 14 days, eliminating the need for suture removal.
- Recommendations for various body regions are shown in detail in Table 45.**2**.

Table 45.2 · Recommended suture material for different body regions

Region	Suture material
Face and neck	Subcutaneous: Slowly absorbable monofilament sutures (PDS 4/0 or Serrasynth 4/0) or rapidly absorbable braided sutures (Vicryl 4/0) Skin: Nonabsorbable monofilament sutures (Ethilon 5/0, 6/0)
Scalp	Nonabsorbable braided sutures 2/0, 3/0
Mouth, tongue	Rapidly absorbable braided sutures (Vicryl rapid 3/0, 4/0)
Trunk	Subcutaneous: Slowly absorbable sutures (PDS 2/0 or Serasynth 2/0, 3/0) Skin: Nonabsorbable Prolene 3/0, 4/0
Extremities	Subcutaneous: Slowly absorbable monofilament sutures (PDS 3/0, 4/0 or Serasynth 3/0, 4/0) Skin: Nonabsorbable monofilament sutures (Ethilon 3/0, 4/0)
Hands and feet	Nonabsorbable monofilament sutures (Ethilon 4/0, 5/0)
Anogenital region (mucosa)	Rapidly absorbable braided suture (Vicryl rapid 3/0, 4/0)

- **Suture placement:** General guidelines include:
  - Generous undermining for mobilization to allow placement of subcutaneous sutures under relatively little tension.
  - The subcutaneous knots should point downward, so an inverted suture is required.
  - Low-tension skin sutures are essential for best cosmetic results.
  - On the scalp, more tension is acceptable as necrosis does not occur and the stitches must also produce hemostasis.
  - On the hands and feet, as well as the periorbital region, the approximation should be somewhat less tight.

  Note: Resist the temptation to pull a wound together. It should move easily together and your stitches simply hold it in the new position.
- **Knots:**
  - *Single simple knot:*
    - Easiest knot; gives excellent cosmetic result if under low tension and removed promptly.
    - Should be combined with subcutaneous sutures to ease closure.
  - *Vertical mattress:*
    - The advantage of either the Allgöwer (intracutaneous on one side) or Donati (penetrates skin on both sides) stitches is excellent wound edge approximation. Pressure is better distributed.
    - In difficult areas such as inguinal or axillary regions or when infection is likely, we prefer the Allgöwer mattress to a running subcutaneous suture because if an infection develops, a limited number of sutures can be removed.
  - *Running subcutaneous stitch:*
    - When used by skilled surgeon, provides the best cosmetic results.
    - Reserve for wounds under low tension where infection is unlikely.
  - *Buried corner suture (Zoltan):*
    - Used in Z-plasty, flats and grafts to avoid compromising vascular supply of a tip.

  - Similar to Allgöwer stitch, but the tip is incorporated with a horizontal subcutaneous passage.

- **Ligatures:**
  - Ligatures are designed to stop bleeding from a vessel by "strangulating" it. In ordinary surgery, they can be tied over a clamp.
  - When larger vessels are ligated, as during phlebologic surgery, then the ligature can be passed on a round noncutting needle to insure that the vessel is correctly captured but not damaged. Usually material is polyglactin (Vicryl) 3/0 or 4/0.

  Caution: Avoid tugging or exerting excess pressure when placing ligatures, especially on larger vessels. If the vessel is torn, then two ligatures must be placed in a bloody field—often a hard task.

- **Suture removal:**

  Note: Removal of sutures at the earliest safe moment is the surest way to insure a good cosmetic result and avoid the "railroad track" markings that arise when sutures are left in place too long. The surgeon should establish the date and clearly inform the patient.

  - Rough guidelines are:
    - Face: 4–9 days.
    - Scalp and trunk: 10–14 days.
    - Hands and feet: 7–10 days.

45.3 Closure Techniques

Overview

- An excision must be planned considering the relaxed tension lines, the skin tension of the patient, the orientation of the lesion, and the skills of the surgeon. Thus every procedure is unique; none can be copied exactly out of a book.
- The best method of closure is the one that accomplishes the best functional and aesthetic result in the shortest period of time. Some of the more common methods are shown in Fig. 45.**4**.
- Flaps are usually done with local anesthetic without epinephrine; otherwise it is difficult to notice flap ischemia.
- The surgeon must master both the geometry of flaps as well as a minimally traumatic approach to tissue handling to maximize success. Temporary sutures are a more gentle way to retract tissue during mobilization than skin hooks; forceps should be completely avoided.
- When in doubt, provide wound drainage. On the face, flat drains custom-cut out of sterile surgical gloves are often useful.
- The wound dressing should not exert excessive pressure, because this can threaten a flap. A clear dressing makes it easier to check the vascular status of the flap.
- The exact lines of a flap are usually determined during the operation, with the placement of Burow triangles reserved for the end.
- Sometimes the surgical site must be kept absolutely at rest; for example, with facial surgery a ban on speaking and the provision of liquid diet to avoid chewing are sometimes necessary.
- A satisfactory cosmetic result can only be obtained when the skin sutures are free of tension and loosely tied.

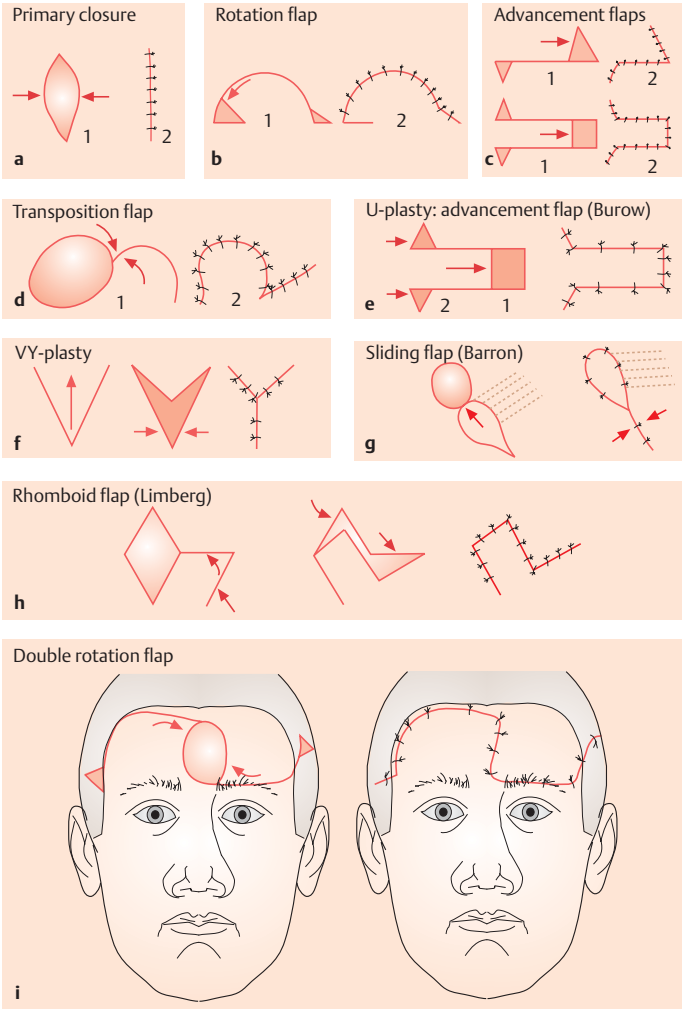
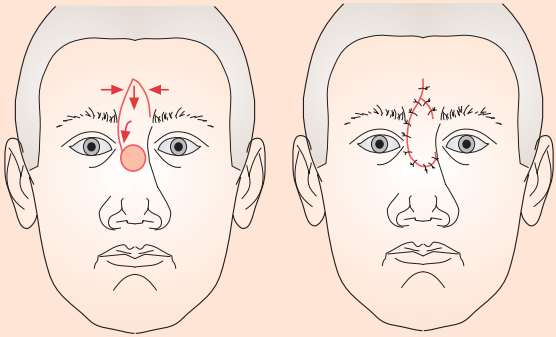


Fig. 45.4 · Methods of wound closure. **a** Primary closure. **b** Rotation flap. **c** Advancement flap. **d** Transposition flap. **e** U-plasty (advancement flap). **f** VY-plasty. **g** Sliding flap. **h** Rhomboid flap. **i** Double rotation flap. **j** Axe flap (rotation flap with back cut). **k** U-plasty (advancement flap). **l** H-plasty.

Axe flap (rotation flap with back cut)



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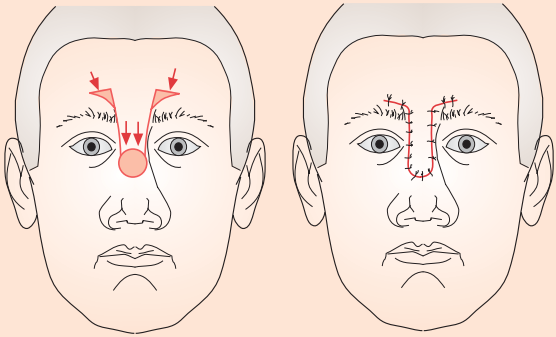
U-plasty (advancement flap)



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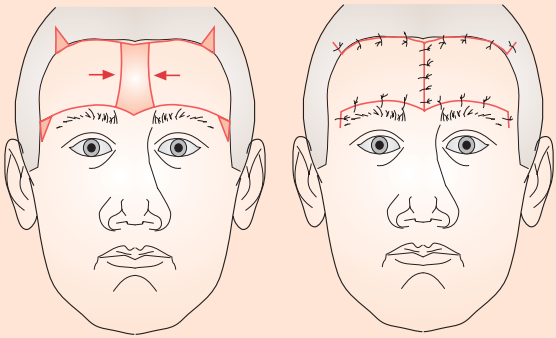
H-plasty



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Simple Excision

- **Indications:** Small lesions, especially when the long axis of the defect follows the skin tension lines.
- **Technique:**
  - Most important is a tension-free skin closure. Subcutaneous or epifascial undermining should be used generously to ensure this.
  - The maximum angle of the tip of the ellipse should be $< 30°$. Otherwise, the excision should be extended or otherwise modified.
  - An inverted dermal suture is ideal for rough closure and reducing tension.

Advancement and Rotation Flaps

- **Indications:** Larger defects; these closures have a broad base so that the vascular supply to the flap is usually stable.
- **Technique (see Fig. 45.4):**
  - Extensive epifascial undermining required to ensure mobility.
  - Always try to design the flap with as broad a base as possible and do not threaten the vascular supply by unnecessary manipulation or force.
  - Aim for a tension-free skin closure.
  - On the forehead and trunk, consider using an *H-plasty* or *double rotation flap.*

Fasciocutaneous and Myocutaneous Flaps

Both these flaps are supplied by arteries and used to cover defects in which bone, cartilage, or fascia is exposed. They are used primarily on the thigh and arm, when the subcutaneous fat and associated vessels are relatively thin; including a fascial flap insures far better vascularization.

- **Indications:**
  - General indication is deeper defects.
  - Decubitus ulcers.
  - Defects on background of radiation dermatitis.
  - Allows prompt closure of defects in functionally important sites.
- **Technique:**
  - *Pectoralis major flap:* Cervical region and cheek.
  - *Gluteus maximus flap:* Sacral, especially for decubital ulcers; can be done bilaterally to close larger ulcers.
  - *Rectus femoris flap and tensor fasciae latae flap:* Lateral aspect of hips, upper thighs.

Grafts

- **Indications:**
  - When closure with a flap appears impossible, or associated with increased operative risk.
  - To correct ectropion.

  Note: The best results are obtained when the donor site is close to the defect and has comparable properties. For example, pre- or retroauricular skin is best suited for facial grafts.
- **Split-thickness graft:**
  - *Technique:*
    - Skin is harvested using a dermatome. Usual sites are lateral thigh, buttocks, and scalp. Desired thickness 0.3–0.8 mm. Cover donor site with inert polyurethane membrane dressing for 5–10 days.
    - Graft is tacked using nonfilament sutures or metal clips.

Caution: When covering chronic venous ulcers, which generally are at risk of infection, sutures should be avoided.
  - Wound is dressed with nonadherent dressing, immobilized, and first re-examined after 5–7 days.
  - If minimal local infection develops, wet dressings soaked in Octenisept solution are useful.
- *Mesh graft:* Cutting the graft with a mesh cutter can provide up to a 6-fold increase in coverage. Mesh grafts are well-suited for leg ulcers and other infected wounds, as they automatically allow for drainage.

► **Full-thickness graft:**
- These grafts consist of epidermis and dermis; they require a well-vascularized wound, but do not shrink, thus producing better cosmetic results than split-thickness grafts.
- *Technique:*
  - Usual donor sites are pre- or postauricular, supraclavicular, medial upper arm, or inguinal region.
  - Donor site is closed primarily.
  - Graft must be completely defatted.
  - Graft is fixed with monofilament sutures, which are left long so that they can be tied over a dressing so that it exerts a gentle pressure immobilizing the graft.
  - Dressing first changed after 5–7 days.

Note: With full-thickness graft, hair follicles are also transferred. This must be anticipated in planning the graft.

► **Composite graft:**
- *Technique:* Usual procedure is to take a piece of ear containing cartilage and use it to correct nasal defect. The graft should be a bit larger than the defect, as shrinkage is inevitable.

Caution: In areas with scarring (previous surgery) or radiation dermatitis, grafts are at greater risk because of reduced vascular supply.

45.4 Other Techniques

Cryotherapy

► **Principle:** Solid tissue freezing using liquid nitrogen (-196 °C) induces tissue necrosis. Patients must be warned about the pain, blister formation, and slow healing.

► **Indications:**
- Routine indications are actinic keratoses and warts. Other lesions that can be treated include hypertrophic scars, keloids, superficial malignancies (early squamous cell carcinoma, Bowen disease, superficial basal cell carcinoma), and leukoplakia (after histological diagnosis), small hemangiomas, Kaposi sarcoma.
- Experienced physicians may use deep cryotherapy with thermoprobe for treating basal cell carcinoma in selected locations in patients who are not good operative risks.

► **Technique:**
- Ordinary treatment involves using a spray unit or contact probe. Length of exposure depends on thickness of lesion. Actinic keratoses can be treated for 5–10 seconds; warts should be frozen until the entire lesion and a tiny peripheral rim appear white. In other lesions, individual adjustment is required.

- Actinic keratoses need only be frozen once; other lesions should be frozen at least twice, allowing for adequate thawing in between.

Note: If cotton-tipped applicators are used, then a generous applicator, such as a vaginal swab, is required. Traditional small applicators (cotton buds) do not transfer enough cold to produce effects.

- When an invasive tumor is treated, a thermoprobe is needed to insure that the base of the tumor is frozen solid to a predefined temperature (usually –25 °C); such procedures should be left for experts in cryotherapy.

Dermabrasion

- **Principle:** Superficial removal of skin using high-speed (> 25 000 rpm) diamond fraise or brush. Irregular features are exchanged for a smoother, flatter scar.
- **Indications:**
  - Rhinophyma, large congenital nevi in first months of life.
  - Uses have become more limited in recent years with increasing emphasis on lasers and chemical peeling. In the past, dermabrasion was widely used for tattoos, but is now replaced entirely by lasers. Severe acne scarring is still an indication, although mild scarring is almost exclusively treated with chemical peels.
  - Extensive actinic keratoses of the scalp may also respond well.
- **Technique:**
  - Usually done under sedation with nerve block or local anesthetic. General anesthesia required for infants with congenital nevi.
  - Preoperative coverage with antibiotics and antiviral agents is necessary for widespread procedures. Prophylaxis against herpes simplex virus is particularly important for whole-face dermabrasions.
  - The skin is stretched taut by the assistant and the fraise moved across the skin at a right angle to its axis of rotation. Only light pressure and a uniform motion are required; otherwise it is easy to penetrate the dermis.
  - Gauze pads dipped in physiologic saline solution are used to remove abraded tissue and provide cooling. They must be kept out of the way of the fraise.

Caution: Extreme caution must be exerted around the mouth and eyes. Skin can be caught on the fraise and rolled away or otherwise damaged.

  - Acne dermabrasions using a wire brush require a special Freon 114 (1,2-dichlorotetrafluoroethane) spray, which is used to harden the skin making the tissue removal easier. Other chlorofluorocarbons and liquid nitrogen are too cold, and produce extensive tissue damage.
  - The usual depth is into the papillary dermis until punctate bleeding points are seen.
- **Postoperative care:**
  - *Small lesions:* Cover with hydrocolloid gels.
  - *Larger areas, such as large nevi:* Cover with nonadherent dressing and gauze soaked in an antiseptic solution.

Circumcision

- **Principle:** The foreskin is excised in a circular fashion. Electrosurgical resection is no longer practiced because of problems with necrosis and scarring.
- **Indications:** Phimosis, following emergency surgery for paraphimosis, lichen sclerosus (often associated with phimosis), chronic balanitis, recurrent condylomata acuminata under foreskin, tumors of foreskin, deviation caused by foreskin.

- **Technique:**
  - Administer penis block using 2% prilocaine and provide additional circular block on ventral surface.
  - Marker clamps at 12, 6 (frenulum), 3, and 9 o'clock positions to insure no torsion is introduced between the inner and outer parts of the foreskin during suturing.
  - Incision of foreskin with scissors and circular resection with immediate adaptation with rapidly absorbed polyfilament sutures (Vicryl 3/0 or 4/0).
  - Watch for frenular artery and use ligature or fine electrocautery. Sometimes useful to reposition frenulum if deviation has been a problem.
  - When treating lichen sclerosus, do not be too aggressive in removing foreskin but leave a bit in case tissue is needed for a foreskin plasty.
- **Postoperative care:**
  - Dressing with antiseptic ointments and solutions.
  - Immobilization for 3 days.
  - Elevation of penis to reduce edema.
- **Medications:**
  - Subcutaneous heparin.
  - Diazepam 10 mg p.o. t.i.d. for prophylaxis against erections.
  - NSAIDs usually suffice for pain.

Liposuction

- **Principle:** Removal of fatty tissue with high-pressure suction devices.
- **Indications:**
  - Extensive lipomas, lipomatosis, lipodystrophy.
  - Aesthetic indications for body remodeling, especially for hips and thighs.
  - To obtain tissue for autologous fat transplantation.
- **Instruments:**
  - Manually manipulated cannulas.
  - *Ultrasonographic liposuction:* Fat broken apart by sound waves; makes rapid removal possible but carries risk of overheating.
  - *Vibration liposuction:* Tip of canula vibrates rapidly, freeing fragments of fat for suction. Minimizes blood loss and trauma.
- **Technique:**
  - The extent of the procedure and the patient's general health determine whether procedure is done on an inpatient or outpatient basis.
  - Area marked with waterproof marker while patient is standing.
  - Tumescence anesthesia is introduced, using the following mixture:
    - 50 mL prilocaine 1%.
    - 3 mL sodium hydrogen carbonate 8.4%.
    - 0.5 mL epinephrine 1:1000.
    - 500 mL lactated Ringer solution.
  - Wait at least 50 minutes for anesthesia to take effect.
  - Regular symmetrical passage of canula through fatty tissue. Always hold opening down (away from skin surface) to avoid creating folds or furrows in remodeled area.
  - Always monitor amounts of fluid and fat removed.
- **Postoperative care:**
  - Large absorbent dressings are applied to capture remaining anesthesia fluid, which will slowly leak out. For this reason, cannula holes are not closed.
  - Use compression garments for 2–3 months.

Note:
- Especially in aesthetic procedures, document the preoperative discussion and subsequent informed consent in detail. Preoperative photographs are essential.
- Warn the patient about the risk of hemorrhage, dysesthesias, edema, irregular skin surface, and asymmetry.
- Emphasize the possible need for reduction plasties to remove excessive skin, depending on age of patient and elasticity of skin.
- Complications include anaphylaxis, thrombosis, embolus, increased or decreased sensation in overlying skin, hemorrhage, necrosis and penetration into body cavities.

Nail Surgery

Note: Nail surgery should only be done by experienced physicians, because of the risk of loss of function with subsequent medico-legal problems.

Nail extraction:
- *Indications*: Ingrown nail, chronic paronychia, exposing nail bed for surgical procedure.
- *Technique*: Finger block plus tourniquet (rubber drain fixed with hemostat). Separate nail from nail bed with nail elevator and then extract with hemostat. Antiseptic ointment and dressing.

Emmert procedure:
- *Indications*: Ingrown nail, chronic lateral nail bed inflammation.
- *Technique*: Nail block and tourniquet. Wedge excision of edge of nail and nail bed down to periosteum; removal of lateral and proximal nail matrix: Use monofilament nonabsorbable Prolene 2/0 or 3/0 with transungual approach to close. Antiseptic ointment and dressing.

45.5 Laser Therapy

Principles

Function:
- LASER =**l**ight **a**mplification by **s**timulated **e**mission of **r**adiation.
- Various media (gases, solids, liquids) can be stimulated to produce coherent (same frequency and wavelength) bundles of high energy light in UV, visible, or infrared range.
- Laser systems are named according to the medium, the method of stimulation, and whether they generate continuous wave (cw) or pulsed energy. There are many variation on pulsing, including Q-switching (QS), and a variety of scanners and shuttering devices.

Mechanism of action:
- Laser radiation is absorbed by chromophores in the skin. Melanin, other skin pigments (carotenoids), hemoglobin, and water are damaged by thermal effects or scattered by pressure waves.
- The depth of penetration is proportional to the wavelength of the laser, so that highly selective sites of action can be chosen. Longer wavelength lasers (red, infrared) provide greater penetration.
- Lasers can be used as a fine destructive "knife" (CO_2 laser), for coagulation (argon, Nd:YAG, copper vapor) and for selective photothermolysis (dye laser, QS-ruby laser).

- The essence of selective photothermolysis is that laser energy is delivered to a chromophore structure at intervals greater than the cooling time for the material, so that the thermolysis is confined to the structure such as a vessel and does not involve adjacent tissue.
- The longer the impulse, the greater the thermal effects. When treating pigmented lesions, the impulse duration should be less than 100 ns.

Laser Safety

- In Europe, lasers are classified as class I–IV based on the intensity of their beam. All dermatologic lasers as class IV. Different safety standards are established for each class of laser.
- Before a laser is put into use, it should be registered both with the facility's and physician's insurance firms and with the local safety regulation officers.
- A qualified technician, often a physicist, should be appointed with responsibility for the technical status of the laser. Regular inspections of the device are required. This is technically independent of routine maintenance.
- Any area where lasers are in use must be marked. The doors should have warning signs or lights and should be locked so that only authorized personnel have access.
- Eyes must be protected. Physicians, nurses. and technicians should wear special laser protective glasses. Patients should have eye shields.
- All surfaces that could be hit by the laser beam should have diffuse-reflecting surfaces.
- Laser plume should be evacuated; viable human papillomavirus (HPV) particles can be found in the smoke plume.

Instruments

- The medically important lasers are summarized in Table 45.**3**.
- **Intense pulsed light source (IPL):**
  - Not a laser, but similar indications.
  - Intense light over a wide range (5550–1200 nm) with pulses of 2–20 ms.
  - Main indications are epilation (larger field size than laser), superficial vascular lesions, and nonablative treatment of skin aging.

Indications

- The indications are shown in Table 45.**4**.
- ***Note:*** Laser therapy is destructive; the diagnosis must always be clinically or (in the case of tumors) histologically established before treatment.

Laser Phototherapy

- **Indications:** Psoriasis, vitiligo, other forms of hypopigmentation.
- **Lasers:** Excimer or IPL.
- **Mechanism of action:** Intense high-dose UVB energy at 308 nm is delivered directly to the psoriatic plaque, sparing the surrounding skin. In the case of vitiligo, the annoying tanning of the adjacent skin is avoided.
- **Side effects:** Burns, just as with UVB therapy.

Vascular Lesions

- **Indications:** Vascular lesions are generally amenable to laser treatment. The choice of laser depends on the size of the vessels, color of lesion, and location. Sometimes longer wavelengths are better, to avoid competitive absorption by melanin and increase depth of penetration.

Table 45.3 · Medically important lasers

Laser	Wavelength (nm)	Continuous wave (cw) power (W)	Pulsed fluence (J/cm²)	Indications
Argon	514 488 + 514	< 1	–	Coagulation of superficial vascular lesions
Frequency–doubled (fd) Nd:YAG (KTP)	532	–	< 20	Coagulation of superficial vascular lesions
Flashlamp pulsed dye laser (FPDL)	500–630	–	< 20	Nevus flammeus at 585nm
Ruby	694	–	Q-switched: < 12 Normal mode: < 60	Q-switched: pigment removal Long–pulsed: epilation
Alexandrite	755	–	Q-switched: < 7 Long pulsed: < 60	Q-switched: pigment removal Long–pulsed: epilation
Nd:YAG-cw	1064	< 100	Q-switched: < 12 Pulsed: < 250 Long pulsed: < 60	cw: coagulation, cutting Q-switched: pigment removal Pulsed: vascular lesions Long pulsed: epilation
Erbium:YAG	2940	–	Pulse energy up to 2 J	Athermal ablation
CO_2	10 600	< 50	Pulse energy up to 1 J	Cutting, ablation
Excimer	308		5 mJ	Psoriasis, vitiligo

- **Mechanism of action:** The major effect is absorption of energy by hemoglobin.
- **Side effects:**
  - Scarring, hypo- and hyperpigmentation.
  - *Pain:* All procedures are painful, roughly in the order dye < argon < copper vapor < Nd:YAG, with the last being most troublesome. Larger lesions must be treated with lidocaine/prilocaine (EMLA) or local infiltration; in infants with hemangiomas, general anesthesia is needed.

Pigmented Lesions

The pigmented lesions can be divided into congenital and acquired lesions, as well as tattoos. A variety of lasers are available.

- **Congenital and acquired lesions:**
  - These lesions contain melanin, which absorbs at a maximum of 520 nm. Examples include nevi of Ota and Ito, as well as lentigines, ephelides, and café-au-lait macule.

Table 45.4 · Indications for different lasers

Laser	Indications
Dye laser	Superficial and deep vascular lesions
	Facial erythema
Argon laser	Superficial vascular lesions
Copper vapor laser	Facial erythema
	Xanthelasma
CO_2 laser	Xanthelasma
	Warts
	Epidermal nevus
	Rhinophyma
	Flat seborrheic keratoses
	Neurofibromas
	Syringomas
Q-switched solid phase lasers	Café-au-lait macule
	Nevus spilus
	Nevus of Ota and Ito
	Ephelides
	Senile lentigines
	Tattoos
Erbium:YAG laser	Senile lentigines
	Flat seborrheic keratoses
	Superficial tumors (trichoepitheliomas, angiofibromas)
	Leukoplakia
	Acne scars
	Skin resurfacing
	Actinic keratoses
Long-pulsed solid lasers, IPL	Epilation
Excimer laser	Psoriasis
	Vitiligo
	Hypopigmentation

- Melanocytic nevi are generally best removed surgically so that material is available for histologic examination.

► **Tattoos:**
- Lasers have replaced dermabrasion and other scarring methods for the removal of tattoos.
- The pigment particles are attacked by a laser chosen to match the absorption of the tattoo color and vaporized so they can be engulfed by macrophages.
- Multiple procedures are usually required.
- Side effects include hypo- and hyperpigmentation, scarring, changes in tattoo color, dermatitis changes, and rarely pyogenic granuloma.

Miscellaneous Lesions

► **Indications:**
- Once the diagnosis has been established, a wide variety of lesions can be ablated with a laser. The list includes warts, condylomata, seborrheic keratoses, actinic keratoses, actinic cheilitis, xanthelasma, multiple adnexal tumors (syringomas, trichoepitheliomas), neurofibromas, and angiofibromas.
- In special cases, malignant tumors may also be destroyed with a laser. Examples include superficial basal cell carcinoma and Kaposi sarcoma, as well as palliative treatment of inoperable or metastatic tumors.

► **Lasers:**
- A *CO_2 laser* is often chosen for ablation; usually used in short-pulsed mode with very short (ns) impulse duration and high energy, often coupled with a scanner device. The tissue is vaporized and coagulated; it can be removed carefully in layers as the level of penetration is only 0.01–0.1 mm.
- An *erbium:YAG laser* is useful for very superficial lesions such as actinic keratoses, in which case it does not have a coagulatory effect.

▶ ***Note:*** When lasers are used for tissue ablation, an effective plume or smoke removal system is needed. The odor can be most unpleasant. In addition, when viral lesions are treated, infectious HPV particles are found in the smoke. Special protective glasses are also required.

Epilation

► **Indications:** Hypertrichosis, hirsutism, cosmetic indications, transsexual changes.

► **Lasers:**
- Long-pulsed solid lasers such as alexandrite, Nd:YAG, or ruby.
- IPL.

► **Mechanism of action:** Destruction of follicle with high-energy light. Only possible for pigmented hairs. Treatment must be repeated several times; at least six sessions required.

▶ ***Note:*** The skin should be cooled to reduce epidermal damage.

Skin Rejuvenation

► **Synonyms:** Laser skin resurfacing, laser skin regeneration.

► **Indications:** Photoaging, solar elastosis, wrinkles; perhaps prophylaxis against actinic keratoses and squamous cell carcinomas on face.

► **Lasers:** CO_2, erbium:YAG for ablative rejuvenation; Nd:YAG with cooling, diode, and erbium glass for nonablative dermal remodeling; pulsed dye laser at low fluence.

► **Mechanism of action:** All have wavelengths that are primarily absorbed by water, sparing melanin and hemoglobin. Superficial ablation is a "laser peeling," or removal of the most superficial layers. Nonablative lasers cause dermal shrinking and thus tighten the skin.

► **Side effects:** Hypo- and hyperpigmentation; scarring (with ablative lasers).

46 Wound Healing

Disturbances in Wound Healing

Both the disease process itself and inappropriate treatment can impair wound healing. Both local and also systemic factors play significant roles.

- **Factors that enhance wound healing:**
  - *General:* Youth, good general condition, good nutritional status.
  - *Local:* Sterile wound, good circulation, maintenance of normal body temperature, tension-free suture repair, elevation or immobilization of wound (not of patient).
- **Factors that retard wound healing:**
  - *General:* Inadequate treatment of underlying disease, advanced age, systemic disorders (metabolic diseases, anemia, arteriosclerosis, malignancy), impaired immunity, malnutrition, vitamin, protein and trace element deficiencies —for example, vitamin C, iron, or zinc), infections, medications (corticosteroids, cytostatic agents), allergies (suture materials, topical medications), bed rest, smoking.
  - *Local:* Infection, necrosis, exudates, foreign bodies, drying out, cold, hematoma, edema, previous damage to tissue (ionizing irradiation, previous surgery, chronic venous insufficiency), neuropathy, focal disturbances in circulation (one artery occluded), tumors (ulcerated basal cell carcinoma does not heal as ulcer), suture repair under tension, wound not immobilized.

Treatment of Underlying Diseases

Note: Treatment of chronic wounds, primarily ulcers, is futile if the underlying disease is not addressed.

- **Chronic venous ulcer:** Compression, mobilization, treat associated varicosities (p. 560).
- **Diabetic foot ulcer:** Reduce pressure, special shoes and foot care, maximize control of blood sugar levels.
- **Decubitus ulcer:** Reduce pressure, special beds or mattresses, partial mobilization.
- **Arterial ulcer:** Endovascular or vessel replacement therapy to restore arterial supply, rheologic therapy.

Rheologic Therapy

Attempts to improve circulation are an essential part of wound healing. If patients have peripheral arterial occlusion, a number of agents may be helpful. They include:

- **Rheologic agents:** Pentoxifylline 400 mg b.i.d.–t.i.d. to decrease blood viscosity; side effects include gastrointestinal problems, retinal bleeding, and leukopenia.
- **Musculotropic vasodilators:** Naftidrofuryl 100–200 mg t.i.d. to dilated vessels; side effects include disorientation and dizziness.
- **Calcium channel blockers:** Nifedipine 10–20 mg daily; diltiazem 120 mg daily. Side effects include edema, dizziness, and cardiovascular problems.
- **Prostaglandins:** Alprostadil i. v. 60 μg in 250 mL 0.9% NaCl solution over 2 hours. Usually given for 14–21 days, or for 7 days every month. Many side effects including edema, increased pain in extremities without adequate circulation, nausea, vomiting, and headache; can ameliorate by slowing rate of administration; pulmonary edema in patients with cardiac failure.

Topical Therapy

Modern wound therapy is adjusted to the severity of the wound, considers economic aspects and incorporates new understanding of the science of wound healing.

- **Cleansing or exudative phase:** Débridement is the key step. There are many possibilities:
  - *Mechanical:* Débride with forceps, scalpel, or curette. Usually can be done with lidocaine/prilocaine (EMLA) anesthesia. Removal of necrotic tissue minimizes risk of infection, allows granulation to develop more luxuriously.
  - *Biosurgery:* Sterile maggots can be used to meticulously groom a wound.
  - *Autolytic:* Interactive dressings (alginates, hydrocolloids, polyurethane foams, hydrogels, activated charcoal, various membranes): All "trap" neutrophils over wound and encourage autolysis of necrotic tissue; painless but time-consuming.
- **Granulation phase:** Clean, well-vascularized wound base develops.
  - Encourage granulation with appropriate dressings (alginates, hydrocolloids, hyaluronic acid) and nonsensitizing agents such as sterile sand or dextrose.
  - Apply wound healing factors such as granulocyte macrophage colony stimulating factor (GM-CSF); platelet-derived growth factor (PDGF); transforming growth factor (TGF) β2, basic fibroblast growth factor (bFGF); or epidermal growth factor (EGF).
  - ***Caution:*** All these biologicals are very expensive and, although promising, their effectiveness has not been overwhelming.
  - Vacuum seal technique (wound is placed under low vacuum pressure with sealed system).
- **Epithelialization phase:** Re-epithelization occurs at this point.
  - Moist wound dressings stimulate re-epithelization. The wound must be protected; good choices include hydrogel and hydropolymer dressings.
  - Pinch, split skin, or keratinocytic culture grafts can be used.
- **Other factors:**
  - Dressing changes should be done under sterile conditions.
  - Wounds can be rinsed with lactated Ringer solution, physiologic saline, or tap water.
  - Antiseptics are preferred to antibiotics because of problems with resistance. Excellent choice is Octenisept solution, which is only minimally cytotoxic. Most useful in exudative phase to reduce bacteria.
  - Antibiotics are generally avoided and should always be chosen carefully on the basis of culture and sensitivity results.
    - *Topical:* Fusidic acid is useful for the usual Gram-positive mixed infections; if MRSA or resistant mixed infections are present, mupirocin.
    - *Systemic:* Ciprofloxacin 500 mg p.o. b.i.d. for 10 days is a good choice for widespread local disease or systemic spread (lymphangiitis).
    - If culture results indicate resistance, then adjust accordingly.

47 Dermatologic Emergencies

Emergency Equipment

- **Emergency set:** Every practice and clinic should have the following immediately available:
  - *Epinephrine* 1:1000 ampoule for subcutaneous use. Dilute 1:10 for i.v. use, giving final concentration of 1:10 000.
  - *Antihistamine*, for example diphenhydramine 50 mg ampoule.
  - *Corticosteroids*, for example hydrocortisone 500 mg or methylprednisolone 125 mg for intravenous use.
  - The set should also include laryngoscope, endotracheal tubes, resuscitator bag, and ideally a defibrillator.

  Note: The above equipment is necessary but not sufficient. All personnel must be trained in resuscitation. Both scheduled practice sessions and surprise drills should be held and documented. The telephone number of the appropriate emergency service should be posted prominently.
- **Prophylactic kit for patient:** Every patient who has had an anaphylactic reaction to Hymenoptera toxin should carry a kit containing an autoinjection device for epinephrine, as well as solutions of antihistamines and corticosteroids.

Anaphylactic Shock

- The most common cause for anaphylaxis in dermatologic patients is hyposensitization. Only those individuals trained in resuscitation should carry out hyposensitization precedures. In high-risk situations, such as testing for venom response, an intravenous line should be placed.
- The administration of the allergen should be stopped if possible; a tourniquet can be placed proximal to the site of inject to stop venous return and the area cooled to slow absorption. The appropriate measures, depending on the severity of the reaction, are shown in Table 47.**1**.

Table 47.1 · **Treatment of anaphylaxis**

Grade	Clinical features	Therapy
I	Pruritus, erythema, edema	Stop exposure Antihistamines i.v. (diphenhydramine 50 mg) Monitor cardiovascular status
II	Early bronchospasm, tachycardia, hypotension, nausea, vomiting	As above, +: Oxygen (nasal tube) Intravenous access with 500 – 1000 ml Ringer solution Corticosteroids i.v. (hydrocortisone 500 mg i.v.) Inhaled bronchodilators for bronchospasm
III	Shock, severe bronchospasm, coma	As above, +: See anaphylactic shock below
IV	Cardiopulmonary arrest	Cardiopulmonary resuscitation

- **Treatment for anaphylactic shock:**
  - Carefully monitor vital signs. Be prepared to intubate or do a tracheotomy.
  - Epinephrine 0.3–0.5 mg (0.3–0.5 mL of 1:1000 solution) subcutaneously; may be repeated at 20 minute intervals. If shock is severe, the epinephrine may be given i.v. but then using 3–5 mL of 1:10 000 solution). Other possible routes are sublingual, inhaled, endotracheal, or via i.v. drip.
  - Further steps should be coordinated with intensive medicine or anesthesia, and follow local guidelines.

Acute Urticaria (p. 169)

Acute urticaria can become an emergency when angioedema or cardiovascular signs and symptoms develop.

- **Mild mucosal swelling:** Admit, i.v. fluids, antihistamines, and corticosteroids.
- **More severe mucosal swelling:** See anaphylaxis above. Admit, subcutaneous epinephrine, corticosteroids, antihistamines; careful monitoring.
- **Bronchospasm:** Beta-agonists (metaproterenol or albuterol as inhalant) or terbutaline 0.25 mg subq.
- **Hereditary angioedema** (p. 174):
  - C1-esterase inhibitor 500–100 IU i.v.; effects seen after 20–30 minutes.
  - Danazol 200–800 mg p.o. can also be given (more effective for prophylaxis).
  - ***Note:*** Corticosteroids, epinephrine, and antihistamines are generally ineffective.
  - Be prepared to intubate or do tracheostomy; often difficult because of swelling.

Toxic Epidermal Necrolysis (TEN) (p. 185)

Caution: TEN has a high mortality rate (25–40%) and should be treated with the same urgency as a severe burn.

- **Diagnosis:**
  - **Skin biopsy with frozen section** (Call the pathologist out at night!): Distinguish between the full-thickness epidermal involvement of TEN and the superficial peeling of staphylococcal scalded skin syndrome (SSSS), which appears quite similar but more often in children. SSSS requires less aggressive therapy.
  - **Drug history:** Almost all TEN is drug-induced; look for high-risk drugs and stop all medications that are not essential.
  - Immediate admission, with consultation with intensive medicine. Room must be warm; be careful in summer with air-conditioned rooms. Patient should be in isolation, with regular monitoring for bacterial infections.
- **Systemic therapy:**
  - Careful attention to fluids and electrolytes.
  - Use of systemic steroids is controversial; follow local guidelines.
  - Local burn unit standards for prophylactic antibiotics.
  - Intravenous immunoglobulins 0.2–0.75 mg/kg daily for 4 days appears to block Fas-mediated keratinocyte death; most promising treatment.
  - Plasmapheresis is another alternative, but less well established than intravenous immunoglobulins.
- **Topical therapy:**
  - Use nonadherent dressings or if widespread denudation, use a burn bed.
  - Remove necrotic skin; puncture blisters.
  - Topical antibiotics such as fusidic acid or silver sulfadiazine.
  - Local anesthetics for oral lesions to facilitate eating.

  Caution: Always get ophthalmologic consultation; there is a risk of erosions and scarring.

Paraphimosis

Phimosis is the condition where the foreskin cannot be contracted back over the glans; it may be congenitally tight or affected by lichen sclerosus, trauma, or infections. In *paraphimosis*, the foreskin becomes partially retracted, edematous, and exerts pressure on the glans, potentially leading to necrosis. In Germany, patients with paraphimosis may present to dermatologists rather than urologists.

- **Initial measures:**
  - Attempt to reduce edema by manual pressure, milking fluid from distal to proximal aspect of penis.
  - Then try the "door bell trick"; hold penis between middle and index fingers and press glans with thumb, aiming to push it back under the foreskin.
  - If unsuccessful, try cold bath (10–15 °C) or multiple needle punctures to allow fluid to drain.
- **Operative approach:**
  - If the foreskin cannot be reduced, then surgical intervention is required to avoid necrosis.
  - The foreskin should be split via a dorsal longitudinal incision and urology consulted. Once the swelling is resolved, circumcision is needed.

Caution: Patients with paraphimosis should always be hospitalized and the nursing staff warned to check frequently until definitive treatment can be provided.

Facial Furuncle/Carbuncle (p. 25)

Caution: There are two major risks—lid edema and cavernous sinus thrombosis.

- **Initial measures:**
  - Admission, bed rest, prohibit talking and chewing.
  - Culture and sensitivity studies.
  - Local disinfectants.
- **Systemic therapy:**
  - Penicillinase-resistant penicillin (dicloxacillin 500–1000 mg t.i.d.–q.i.d. i.v.) or cephalosporins (cephalexin 250–500 mg q.i.d.).
  - Adjust antibiotics based on culture.

Erysipelas (p. 78)

- Patients should be admitted, especially with facial erysipelas.
- High-dose penicillin i.v.; raise limb; cool compresses.
- Later, attempt to address portal of entry; consider compression, prophylactic antibiotics.

Necrotizing Fasciitis (p. 80)

- **Definition:** Severe destruction soft tissue infection caused by mixed infection (type I) or *Streptococcus pyogenes* (type II); recent cases from community-based methicillin-resistant *Staphylococcus aureus*. In addition, bullous erysipelas may evolve into necrotizing fascitis.
- **Initial measures:**
  - Admission, bed rest.
  - Aspiration or incision for culture and sensitivity; exclude clostridial infection with wound smear.
  - Baseline laboratory tests and then follow for leukopenia, hypocalcaemia (fat necrosis), and elevated creatinine (muscle necrosis).

- Surgical consultation.
- Imaging studies (MRI).

► **Surgical management:**
- Extensive debridement.
- Fasciotomy.

! ***Caution:*** Mortality without surgical intervention is 99%; in the best of hands, 30%.

► **Internal therapy:**
- Fluid replacement.
- Broad-spectrum antibiotic coverage following local guidelines; usually includes penicillin, an aminoglycoside and either metronidazole or clindamycin for Gram-negative organisms.
- Adjust antibiotics on the basis of culture and sensitivity.
- Watch for shock.

Deep Vein Thrombosis

► **Diagnosis:** With slightest suspicion, order D-dimer and compression sonography. Doppler ultrasonography and impedance plethysmography are only reliable for pelvic vein thrombosis. If tests are negative, repeat in a few hours or do phlebography.

► **Isolated calf vein thrombosis:** Ambulatory care possible, low molecular weight heparin once daily, compression therapy, and consider for coumarin therapy. Some advise initially monitoring because only 20% of calf vein thromboses extend and risk of emboli is very small. Follow local guidelines.

► **Thigh or pelvic vein thrombosis:** No controversy; complete anticoagulation with heparin and then coumarin.
- Heparin 5000–10000 IU as i.v. bolus; then either by i.v. drip (25–50000 IU daily) or subq. injection (15000 IU b.i.d.).
- Measure activated partial thromboplastin time (aPTT) before starting heparin; aim for value 1.5–2.0× normal value (usually then 50–80 seconds). Monitor b.i.d.
- Simultaneously start coumarin and aim for INR of 2–3.
- Watch for heparin-induced thrombocytopenia and coumarin necrosis.
- Fibrinolytic therapy with urokinase, streptokinase, or tissue plasminogen activator (tPA) may be indicated in selected patients; consult with cardiology.
- Surgical thrombectomy may be indicated in femoroiliac thrombosis less than 1 week old; consult with cardiovascular surgery.

Burns

► **Definition:** Tissue damage caused by thermal energy

► **Clinical features:**
- In most instances, diagnosing a burn is easy but grading it to assess risk and plan treatment can be difficult. The classification of burns is shown in Table 47.**2**.
- Scalds are usually less deep than burns from flames, hot surfaces, or electrical current. Chemical burns vary with agent, but tend to progress over days.
- The other important task is to assess the extent of the burns. It is not always possible to do this immediately. The *Rule of Nines* (Table 47.**3**) is generally employed as shown. One adds the values for areas burned to estimate the percentage of total surface area which is affected. Another rough measure is that the palm of the hand represents 1% of the body surface in all age groups.

Table 47.2 · Severity of burns

Degree		Clinical features	Color	Painful	Depth	Scarring
I	Superficial	Erythema, later peeling	Red	+	Upper epidermis	None
II	Partial thickness	Blisters	Red	+	Epidermis, upper dermis	None; re-epithelializes from adnexal structures
III	Full thickness	Necrosis	White, brown, black	–	Epidermis, dermis, appendages, deeper structures	Scars; grafting required

Table 47.3 · Rule of nines

Region	Newborn	Infant	Child	Adult
Head	21	19	15	9
Chest	16	16	16	18
Back	16	16	16	18
Arm	9.5	9.5	9.5	9
Leg	14	15	17	18
Genitalia	1	1	1	1

► **Therapy:**

Note: The initial management of all burns is cooling; it relieves pain and reduces the extent of damage.

- Children with more than 10% or adults with more than 15% second-degree burns should be admitted. If in doubt, admit.
- All patients should receive analgesics and tetanus immunization as needed.
- Those who are admitted should have an intravenous line, fluid replacement. and be monitored for shock.
- *First-degree burns*: No special care needed; soft dressing; polidocanol ointment or topical corticosteroids.

Note: Topical anesthetics of the benzocaine family are widely sold over the counter for first-degree burns but carry a high risk of sensitization and then allergic contact dermatitis.

- *Second-degree burns:*
  - Débridement.
  - Topical disinfectants or antibiotics and soft dressings.
  - Silver sulfadiazine.
  - Mafenide.
  - Povidone-iodine.
  - Biosynthetic membrane dressings also useful.

- *Third-degree burns:* Specialized burn care, surgical debridement, temporary coverage with skin substitutes; later coverage with skin grafting, cultured keratinocytes, or other bioengineered dressings. Meticulous monitoring for infections. Pressure garments for prophylaxis against keloids.

► **Special cases:**
- *Electrical burns:* Usually deep, often subtle burns—at the sites of entry and exit; watch for myoglobinuria, renal failure, and compartment syndrome.
- *Lightning burns:* Cutaneous injuries may be subtle; sometimes fern figures seen; biggest risks are cardiac conduction defects and neurological problems.

Chemical Burns

► **Clinical features:** Chemical burns result when strong alkali or acid materials are spilled on the skin. The exact nature of the chemical is important in determining the degree and nature of injury.
- *Acid burns* tend to be dry as the liquid immediately kills and fixes the skin, producing superficial, sharply bordered lesions.
- *Alkali burns* are liquefactive, as the bases continue to dissolve the skin causing deeper, more necrotic ulcers.
- In either case, systemic resorption may occur.

► **Therapy:**
- Immediate and extensive rinsing; either with tap water or with antidote solutions if available.
- Balance of management depends on nature of chemical.

► ***Note:*** Hydrofluoric acid burns are particularly destructive; the lesions should be injected with calcium gluconate 10% and mepivacaine solution mixed 1:1. In more extensive burns, i. v. calcium gluconate is required with monitoring by anesthesiology. The calcium salts form harmless calcium fluoride.

Cold Injury

► **Hypothermia:** Diffuse cooling of the body, caused by exposure to cold, snow, cold water; core temperature $< 35\,^{\circ}C$; major medical emergency.

► **Frostbite:** Defined as cold injury caused when skin temperature drops below $0\,^{\circ}C$. Also divided into three classes:
- *First degree:* Blanching, following by re-warming with painful erythema.
- *Second degree:* More extensive, with edema and blisters.
- *Third degree:* Deep tissue damage, with vascular injury and necrosis.

► **Therapy:**

! ***Caution:*** No rubbing; no attempt at re-warming until in hospital.
- Re-warm with total body bath at $40\,^{\circ}C$; hot tap water is usually too warm.
- If less severe, use a lower temperature because of risk of shock.
- Rest of management is just like burn care, except that as necrosis delineates itself, amputation is often needed.
- In second and third degree frostbite, limb remains very sensitive to cold.

► **Immersion foot:**
- *Definition:* Cold damage caused by prolonged exposures at temperature $> 0\,^{\circ}C$; no true freezing.
- Common military injury, also known as *trench foot*.
- Initially painful with erythema, livedo, ulcerations; can progress to gangrene.
- Limb remains very sensitive to cold.

Traumatic Tattoos

- **Clinical features:** Several common causes for particles to be embedded in the skin, including exploding fireworks, accidents using black gunpowder, traumatic road accidents with sand and dirt particles.
  - ***Caution:*** Treatment should be undertaken within 24 hours; otherwise it is very difficult to remove dermal particles.
- **Initial measures:**
  - Ophthalmology consult: Corneal injury?
  - Otorhinolaryngology consult: Ruptured tympanic membrane?
  - Perhaps radiologic evaluation.
- **Removal of particles:**
  - Adequate preoperative analgesia, such as:
    - Ibuprofen 800 mg.
    - Tramadol drops (20 drops = 0.5 mL = 50 mg).
    - Diazepam 10 mg.
    - Topical anesthetic such as EMLA.
  - Topical spray disinfection.
  - Remove larger particles with fine forceps; finer ones with hard toothbrush (perhaps dipped in topical anesthetic).
  - Still deeper particles can be removed with 2 mm biopsy punch.
  - Postoperative therapy with topical retinoids can create additional peeling and discharge of residual particles, as well as helping with healing.
  - Laser therapy for residual hyperpigmentation.
  - ***Note:*** Dermabrasion in this setting has a considerable risk of scarring and is best avoided.

Tick Bite (p. 93)

- ***Note:*** It is far easier to avoid ticks than to risk the difficulties of identification and removal, and the worry. Use insect repellents, ideally with high concentration of DEET; wear long sleeves and trousers in woods, stuff trousers into socks; clothes be can impregnated with insecticide or permethrin.
- **Removal of tick:** Stretch skin tight, and remove tick either with rapid flick of curette or fine forceps, grasping anterior part of tick mouth parts as close to skin surface as possible.
  - ***Caution:*** Trying to suffocate or burn the tick, or squeezing its engorged body, carries the risk of additional regurgitation of infectious material into the skin.
- **Potential infections:** Know what ticks in your area are likely to carry. In Europe, there are two major problems:
  - *Borreliosis:*
    - In endemic areas, 5–50% of ticks may have *Borrelia burgdorferi*. Transfer occurs in 10% of bites, with clinical disease in less than half. Usually tick must be attached for more than 24 hours. Thus daily tick checks in high-risk areas or professions (farmer, forest worker).
    - Only treat if clinical features or serology indicates infection.
    - Prophylactic antibiotics not indicated (although often used).
  - *Tick-borne encephalitis:*
    - Caused by flaviviruses.
    - Endemic areas in Central Europe, including many parts of Germany; more virulent form in Russia.
    - About 1–5% of ticks infected; even with transfer, only 10% of patients symptomatic, so risk very low.

  - Immunization available; should be used by those in endemic areas with frequent exposure.
  - Onset of disease 1–4 weeks after bite; if tick removed in endemic area, refer to primary physician for monitoring.
  - Treatment is symptomatic.
- *Other tick-borne diseases that can be potential emergencies:*
  - Rocky Mountain spotted fever in parts of USA (especially Oklahoma, North Carolina); caused by *Rickettsia rickettsii*. Treatment: doxycycline.
  - Babesiosis or Nantucket fever, caused by *Babesia microti*, a protozoan; particular problem in splenectomized patients. Treatment complex: clindamycin and quinine or other antimalarial agents.
  - Human monocytic ehrlichiosis caused by *Ehrlichia chaffeensis,* primarily in Midwestern USA and also in Europe. Treatment: doxycycline.
  - Human granulocytic ehrlichiosis, caused by *Anaplasma phagocytophila* and *Ehrlichia ewingii*, in USA and Europe. Treatment: doxycycline.

Caution: In endemic areas, ticks may carry more than one pathogen; always consider mixed infections when clinical course of borreliosis is atypical or acute. On Cape Cod and Nantucket Island, ticks may have *Borrelia burgdorferi*, *Babesia microti*, and *Anaplasma phagocytophila.*

Appendix I Common Systemic Medications

Note: The following list includes most of the systemic medications described in this book, for quick reference. Some medications are used in quite different dosages for different dermatologic indications. We have tried to insure uniformity, but if differences are found, always rely on the manufacturers' guidelines and latest prescribing information available online.

Caution: Note that no information has been provided on adjusting dosage for renal impairment. In addition, chemotherapy agents, many analgesics, and psychotropic agents have been omitted. Refer to latest sources for detailed information.

Table I.1 · Common systemic medications

Medication	Use	Dose
Acetaminophen	NSAID	1.5–4.0 g daily
Acitretin	Disorders of keratinization, psoriasis	0.2–1.0 mg/kg p.o. daily (lower doses for disorders of keratinization)
Acyclovir	Herpes simplex Zoster In immunosuppressed	200 mg 5 × p.o. daily 800 mg 5 × p.o. daily 5–10 mg/kg i.v. q8 h
Albendazole	Anthelminthic	400 mg p.o. daily for 1–3 days
Amoxicillin	Antibiotic	500–1000 mg p.o. t.i.d. 1–2 g i.v. q8 h
Amoxicillin + clavulanate	Antibiotic	500 mg amoxicillin/125 mg clavulanic acid 1–2 tab p.o. t.i.d. 1 g amoxicillin/250 mg clavulanic acid i.v. q6–8 h
Amphotericin B	Antifungal	0.25 mg/kg i.v. daily over 4–6 h **Caution:** Liposomal form preferred; complex protocols; see other sources
Ampicillin	Antibiotic	250–500 mg p.o. t.i.d.–q.i.d. 500 mg–3.0 g i.v. q4–6 h
Ampicillin + sulbactam	Antibiotic	1.5–3.0 g i.v. q6 h
Aspirin	Analgesic Anticoagulant	325–650 mg p.o. q4–6h 165 mg p.o. daily
Azathioprine	Immunosuppressive	1–3 mg/kg p.o daily; can use q.o.d.

Continued Table I.1 ▶

Table I.1 · Continued

Medication	Use	Dose
Azelastine	Antihistamine	2 mg p.o. b.i.d.
Azithromycin	Antibiotic	250 mg p.o. daily; 1.0 g as single dose for gonorrhea; 1.0 g as single dose for chancroid
Bexarotene	Retinoid	100–300 mg/m^2 p.o. daily
Brivudin	Herpes zoster	125 mg p.o. daily
Buprenorphine	Central analgesic	0.2–0.4 mg sublingual q6–8 h 0.15–0.3 mg i.v. or i.m. q6–8 h
Calcitonin	Polypeptide hormone	100 IU i.v. or via nasal spray daily ***Note:*** Off-label use for Raynaud syndrome
Carbamazepine	Anticonvulsant, antineuralgic	100–200 mg p.o. b.i.d.; can increase to 1.2 g daily; lower doses for neuralgia; serum level 3–8 mg/L ***Caution:*** High risk of drug reactions!
β-Carotene	Vitamin	75–100 mg daily
Caspofungin	Antifungal	50 mg i.v. daily
Cefazolin	1st generation cephalosporin	500–1000 mg i.v. q6–8 h
Cefixime	2nd generation cephalosporin	200 mg p.o. b.i.d. or 400 mg p.o. daily; 400 mg p.o. in single dose for gonorrhea
Cefotaxime	3rd generation cephalosporin	1–2 g i.v. q8–12 h
Cefotiam	2nd generation cephalosporin	1–2 g i.v. q8–12 h
Ceftriaxone	3rd generation cephalosporin	1–2 g i.v. or i.m. daily or in 2 divided doses; 250 mg i.m. in single dose for gonorrhea
Cefuroxime	2nd generation cephalosporin	0.75–1.5 g i.v. q8–12 h
Cephalexin	1st generation cephalosporin	500 mg p.o. b.i.d.; higher doses for severe infections

Table I.1 · Continued

Medication	Use	Dose
Cephalothin	1st generation cephalosporin	500–1000 mg i.v. q4–6 h; 2.0 g i.m. in single dose for gonorrhea
Cetirizine	Antihistamine	10 mg p.o. daily or b.i.d.
Chlorambucil	Immunosuppressive	0.1–0.2 mg/kg p.o. daily; often 4 mg p.o. daily
Chlormadinone	Anti-androgen	2 mg p.o. daily
Chloroquine	Antimalarial	250 mg daily
Chlorpheniramine	Antihistamine	2–4 mg p.o. q4–6 h
Cidofovir	Antiviral	5 mg/kg i.v. once weekly
Cimetidine	Antihistamine (H2 blocker)	300 mg p.o. q.i.d., 400 mg p.o. b.i.d., or 800 mg p.o. HS; also used i.v.; consult other sources
Ciprofloxacin	Antibiotic	250–500 mg p.o. b.i.d. 200–400 mg i.v. q12 h
Clarithromycin	Antibiotic	250 mg p.o. b.i.d.
Clemastine	Antihistamine	1–2 mg p.o. b.i.d. 1–2 mg i.v. in single dose
Clindamycin	Antiobiotic	150–450 mg p.o. q6–8 h 200–600 mg i.v. q6–8 h
Clofazimine	Antiobiotic	100 mg p.o. daily–t.i.d
Clomipramine	Antidepressant	50–100 mg p.o. daily
Codeine	Analgesic	15–30 mg p.o. 4–6 × daily
Colchicine	Anti gout	0.5–2.0 mg p.o. daily
Co-trimoxazole	Antibiotic	Sulfamethoxazole: 400–800 mg/ trimethoprim 80/160 mg 1 double-strength tab p.o. b.i.d.
Cromolyn	Antiasthmatic; anti-allergic	2 sprays q.i.d.; also available as eye drops, nose drops
Cyclophosphamide	Immunosuppressive	1–3 mg/kg p.o. daily; pulse 7.5–15.0 mg/kg p.o. or 500–1000 mg/m^2 i.v. once monthly

Continued Table I.1 ▶

Table I.1 · **Continued**

Medication	Use	Dose
Cyclosporine	Immunosuppressive	2.5–5 mg/kg p.o.; also available i.v.; serum level 100–300 μg/L
Cyproheptadine	Antihistamine	4 mg p.o. q4–6 h
Cyproterone acetate	Antiandrogen	Usually used with ethinyl estradiol; can also be used to supplement ethinyl estradiol; dose 2.5–5.0 mg p.o. daily
Danazol	Androgen	200–600 mg daily
Dapsone	Immunomodulator	50–100 mg daily; can go to 150 mg; watch for hemolysis, methemoglobinemia
Dimethindene	Antihistamine	1–2 mg p.o. t.i.d. 4 mg i.v. in single dose or b.i.d.
Desloratadine	Antihistamine	5 mg p.o. daily
Dexamethasone	Corticosteroid	0.75–9.0 mg p.o. or i.v. daily in divided doses
Diazepam	Sedative	2–10 mg p.o. t.i.d.–q.i.d. 5–10 mg i.v. t.i.d. 2–20 mg p.o. or rectal in single dose
Diclofenac	NSAID	50 mg p.o. t.i.d.
Dicloxacillin	Antibiotic	0.5–1.0 g p.o. q6–8 h
Diltiazem	Antihypertensive	30 mg p.o. t.i.d.–q.i.d.; wide range upwards
Diphenhydramine	Antihistamine	25–50 mg p.o. q4–6 h
Doxepin	Tricyclic antidepressant, antihistamine	10–20 mg p.o. q.i.d.
Doxycycline	Antibiotic	100 mg p.o. daily; loading dose 200 mg; for acne 50 mg p.o. daily
Ebastine	Antihistamine	10 mg p.o. daily or b.i.d.
Erythromycin	Antibiotic	250–500 mg p.o. t.i.d.–q.i.d.
Ethambutol	Antituberculosis	15–25 mg/kg p.o. daily

Table I.1 · Continued

Medication	Use	Dose
Famciclovir	Antiviral	250 mg p.o. t.i.d.
Flucloxacillin	Antiobiotic	1 g i.v. 3 x daily
Fexofenadine	Antihistamine	60 mg p.o. b.i.d. or 60–180 mg p.o. daily
Fluconazole	Antifungal	50 mg p.o. daily for dermatophytes; 150 mg p.o. weekly for onychomycosis; 200–800 mg p.o. daily for systemic candidiasis
Flucytosine	Antifungal	50–150 mg/kg i.v. daily divided q6 h
Foscarnet	Antiviral	60 mg/kg i.v. over 1 hour q8 h ***Caution:*** Complex regimens; check other sources
Fumaric acid	Antipsoriatic	Detailed dosages (p. 635)
Gentamicin	Antibiotic	2–5 mg/kg i.v. daily in 2 or 3 divided doses
Griseofulvin	Antifungal	500–1000 mg p.o. daily (microsize); 330–375 mg p.o. daily (ultramicrosize); children 10–20 mg/kg p.o. daily
Hydroxychloroquine	Antimalarial	200–400 mg p.o. daily
Hydroxyzine	Antihistamine	10–50 mg p.o. q6–8 h; 50 mg p.o. HS
Ibuprofen	NSAID	200–600 mg p.o. q8–12 h
Indomethacin	NSAID	25–50 mg p.o. q8–12 h
Interferon-α2a and α2b	Immunomodulator	3–10 million IU subq or IM 3× weekly
Isoniazid	Anti-tuberculosis	5 mg/kg p.o. daily
Isotretinoin	Acne	0.5 mg/kg p.o. daily
Itraconazole	Antifungal	100–200 mg p.o. daily; other regimens for onychomycosis
Ivermectin	Anthelminthic	150–400 μg/kg; scabies is treated with 1–2 doses; see literature for anthelminthic therapy

Continued Table I.1 ▶

Table I.1 · **Continued**

Medication	Use	Dose
Ketotifen	Antihistamine	2 mg p.o. b.i.d.
Ketoconazole	Antifungal	200–400 mg p.o. daily
Levocetirizine	Antihistamine	5 mg p.o. daily or b.i.d
Loratadine	Antihistamine	10 mg p.o. daily
Mebendazole	Anthelminthic	Pinworms: 100 mg p.o. in single dose Others: 100 mg p.o. b.i.d. × 3 days
Methotrexate	Immunosuppressive	7.5–25 mg p.o. or i.m. weekly
Methotrimeprazine	Analgesic	10–20 mg i.m. q4–6 h
Methylprednisolone	Corticosteroid	4–48 mg p.o. daily 10–40 mg i.v. as single dose
Metronidazole	Antibiotic Antiprotozoal	500–750 mg p.o. b.i.d. for anaerobic infections 2.0 g in single dose for trichomoniasis
Mizolastine	Antihistamine	10 mg p.o. daily
Morphine	Opiate analgesic	5–30 mg p.o. q4 h PRN 4–15 mg i.v. or i.m. q4 h PRN
Mycophenolate mofetil	Immunosuppressive	1.0–2.0 g p.o. daily
Nafcillin	Antiobiotic	500 mg p.o. q.i.d.; 500–1000 mg i.v. q4–6 h
Naftidrofuryl	Vasodilator	100–200 mg p.o. t.i.d.
Nicotinamide	Vitamin	0.2–1.2 g p.o. daily
Nifedipine	Antihypertensive	5–10 mg p.o. t.i.d.; wide range upwards
Norfloxacin	Antibiotic	400 mg. b.i.d.
Nystatin	Antifungal	2 tab p.o. t.i.d. (1 tablet = 500 000 IU)
Ofloxacin	Antibiotic	400 mg p.o or i.v. q12 h
Omeprazole	Proton pump blocker	20 mg p.o. daily

Table I.1 · Continued

Medication	Use	Dose
Ondansetron	Serotonin antagonist	8 mg p.o. or i.v. 30 minutes before chemotherapy; repeat after 30 and 60 min
Penicillin-Benzathine	Antibiotic	1.2–2.4 million IU i.m. in single dose
Penicillin-G	Antibiotic	400–500 000 IU p.o. q8–12 h 0.5–10 million IU i.v. q4–6 h
Penicillin-V	Antibiotic	125–500 mg p.o. q6 h
Penicillamine	Immunomodulator	250 mg b.i.d.–t.i.d.
Pentoxifylline	Rheologic	400–600 mg p.o. b.i.d.–t.i.d.
Praziquantel	Anthelminthic	40 mg/kg p.o. in single dose or 20 mg/kg p.o. q8 h × 3
Prazosin	Antihypertensive	1–6 mg p.o. daily
Prednisolone	Corticosteroid	5–60 mg p.o. daily Emergencies: 250–1000 mg i.v.
Prednisone	Corticosteroid	5–60 mg p.o. daily
Promethazine	Antihistamine	12.5 mg p.o. t.i.d.–q.i.d.; 25 mg p.o. HS
Pyrantel pamoate	Anthelminthic	10 mg/kg p.o. in single dose
Pyrazinamide	Anti-tuberculosis	1.5–2.0 g p.o daily or 3 × weekly
Quinacrine	Antimalarial	100 mg p.o. daily
Ranitidine	Antihistamine (H2 blocker)	150–300 mg p.o. HS
Rifampicin	Antibiotic	600 mg p.o. 1–2 × daily
Spectinomycin	Antibiotic	2.0 g i.m. in single dose for gonorrhea
Streptomycin	Anti-tuberlosis	1.0 g i.m. daily
Sulfasalazine	Anti-inflammatory	500–1000 mg p.o. b.i.d.; start with lower dose and work up
Terbinafine	Antifungal	250 mg daily; other regimens for onychomycosis

Continued Table I.1 ▶

Table I.1 · Continued

Medication	Use	Dose
Thalidomide	Antileprosy	100–200 mg p.o. q.i.d. **Caution:** Pregnancy precautions, highly variable dosages
Thiabendazole	Anthelmintic	500 mg p.o. b.i.d. for 3–4 days
Tilidine + naloxone	CNS analgesic	50–100 mg p.o. q6–8 h Tablet = 50 mg tilidine + 4 mg naloxone
Tramadol	Analgesic	50–100 mg p.o., i.v. or subq. q6–8 h
Tripelennamine	Antihistamine	25–50 mg p.o. q4–6 h
Tropisetron	Serotonin antagonist	5 mg p.o. or i.v.
Valacyclovir	Herpes simplex Zoster	500–1000 mg p.o. b.i.d. 1000 mg p.o. t.i.d.
Vancomycin	Antiobiotic	500 mg i.v. q6 h
Verapamil	Antihypertensive	80–120 mg p.o. t.i.d.
Voriconazole	Antifungal	200–400 mg p.o. or i.v. daily

Appendix II Favorite Compounding Recipes

Overview

Compounding is no longer as essential to dermatologic practice as it was 50 years ago when every dermatologist had a list of favorite prescriptions (Table II.1). In general, the commercially available products cover the entire spectrum of topical treatment, are more stable than compounded products, and are tested to insure that the active ingredients are delivered to the skin. Nonetheless there are situations where compounding is still very useful. They include:

- Allergies to preservatives or other additives in commercial vehicles.
- Lack of availability of certain combinations of vehicles and active ingredients.
- Lack of flexibility as when dithranol concentration is slowly increased.
- Expense—in many instances, the compounded product is far cheaper.

Practical Approach

- It is best to rely on tested formulations available in a variety of sources such as national formularies. Any changes in such prescriptions should be checked with a pharmacist or colleague experienced in compounding, as even minor changes can influence the effectiveness and stability of the final product. For example, a study in Germany showed that many of the extemporaneously compounded erythromycin solutions were neither stable nor active.
- The effectiveness of the vehicle in dermatologic therapy cannot be underestimated. The choice of the vehicle depends on the acuity and location of the disease, the properties of the skin and chemical nature of the active ingredient.
- It is better to compound from scratch than to add an active ingredient to a commercial product. For example, most corticosteroid creams are fairly finely tuned mixtures; when an antibiotic is added to them, often neither the corticosteroid or the antibiotic is effectively available.
- Compounded products almost always have a shorter shelf life than commercial products. If a large supply is provided, patients should be instructed to transfer the contents stepwise to a smaller jar to minimize the risk of contaminating the main supply.

Caution: Resist the temptation to compound creatively; more than two active ingredients usually means incompatibility or decreased effectiveness.

Table II.1 · Favorite formulations

Name and ingredients[a]	Concentration (%)	Indications
Anal dermatitits paste		
	Vehicle: Hydrocarbon gel	Anal dermatitis
Ammonium bitumino-sulfonate	5.0	
Acid. tannic	2.0	
(Polidocanol)	3.0	
Pasta Zinci DAB	ad 100.0	
Arning tincture (former NRF 11.13.)		
		Antimicrobial; acute dermatitis, especially weeping or super-infected; fissures
Anthrarobin	3.0	
Ammonium bituminosul-fonate	3.0	
Propylene glycol	6.0	
Isopropyl alcohol	40.0	
Ether	ad 100.0	
ASS lotion		
		Postherpetic neuralgia
Acetylsalicylic acid	5.0	
Emulsifying cetearyl alcohol (type A)	2.0	
White clay	10.0	
Titanium dioxide	5.0	
Propylene glycol	15.6	
Water	ad 100.0	
Betamethasone valerate hydrophilic cream (0.025, 0.05 or 0.1%) (NRF 11.37.)		
	Vehicle type: ambiphilic cream	Acute and subacute dermatitis
Bethamethasone-17 valerate	0.025 | 0.05 | 0.1	
Triglyceride (medium chain)	0.5	
Citric acid solution 0.5%	2.5	
Sodium citrate solution 0.5%	2.5	
Basiscreme DAC	ad 100.0	

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Betamethasone valerate hydrophilic emulsion (0.025, 0.05 or 0.1%) (NRF 11.47.)		
	Vehicle type: Non-ionic O/W lotion	Acute scalp dermatitis, mucosal lichen planus
Low-fat easily washable emulsion		
Bethamethasone-17 valerate	0.025 | 0.5 | 0.1	
Hydrophilic skin emulsion (NRF S. 25.)	ad 100.0	
Capsaicin cream (0.025, 0.05, or 0.1%) (NRF 11.125.)		
	Anionic O/W cream	Postherpetic neuralgia, intense pruritus
Ethanolic capsaicin solution 1%	2.5 | 5.0 | 10.0	
Basiscreme DAC	50.0	
Propylene glycol	10.0	
Water	ad 100.0	
Clioquinol cream A		
		Infected acute or subacute dermatitis
Clioquinol	1.0 | 2.0	
Anionic hydrophilic cream SR DAC (NRF S. 27.)	ad 100.0	
Clioquinol cream B		
Clioquinol	2.0	
Hydrous liniment SR DAC (NRF 11.93.)	ad 100.0	
Clioquinol Lotio Cordes		
	Vehicle type: Non-ionic O/W lotion	Herpes simplex, zoster; acute dermatitis
Clioquinol	1.0 | 2.0	
Lotio Cordes	ad 100.0	

Continued Table II.1 ▶

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Clobetasol or betamethasone in white petrolatum		
	Vehicle type: hydrocarbon gel	Short-term therapy of dermatitis; not face; clobetasol class IV; betamethasone class III
Clobetasol-17-proprionate or	0.05	
Betamethasone-17-valerate	0.1	
White petrolatum	ad 100.0	
Dermatitis ointment		
		Chronic dermatitis
Leukichthol[b] or	3.0 – 5.0	
Betamethasone-17-valerate[b]	0.1	
Citric acid solution 0.5%	2.5	
Sodium citrate solution 0.5%	2.5	
Basiscreme DAC	ad 100.0	
Dexamethasone liniment		
	Vehicle type: Anionic O/W cream	Acute and subacute dermatitis
Dexamethasone	0.05	
Hydrous liniment SR DAC (NRF 11.93.)	ad 100.0	
Dithranol–Macrogol[b] ointment (0.25, 0.5, 1 or 2%)(NRF 11.53.)		
		Psoriasis; easily washable; especially suited for scalp
Dithranol	0.25 | 0.5 | 1.0 | 2.0	
Salicylic acid	3.0 | 3.0 | 3.0 | 3.0	
Propylene glycol	24.2 | 24.1 | 24.0 | 23.75	
Macrogol 400	24.2 | 24.1 | 24.0 | 23.75	
Macrogol 1500	24.2 | 24.1 | 24.0 | 23.75	
Macrogol 4000	ad 100.0	

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Eosin alcoholic solution (0.5, 1, or 2%) (NRF 11.94.)		
Eosin dinatrium	0.5 | 1.0 | 2.0	
Ethanol 96%	20.0	
Anhydrous citric acid	0.02 | 0.04 | 0.08	
Water	ad 100.0	
Eosin aqueous solution (0.5, 1 or 2%) (NRF 11.95.)		
Eosin dinatrium	0.5 | 1.0 | 2.0	
Anhydrous citric acid	0.01 | 0.0175 | 0.025	
Water	ad 100.0	
Erythromycin hydrophilic cream (0.5, 1, 2 or 4%) (NRF 11.77.)		
	Caution: Very unstable; never combine erythromycin with other active ingredients.	Acne vulgaris; impetigo and impetiginized dermatitis
Erythromycin base	0.55 | 1.1 | 2.2 | 4.4	
Anhydrous citric acid	0.015 | 0.04 | 0.06 | 0.07	
Propylene glycol	10.0	
Basiscreme DAC	50.0	
Water	ad 100.0	
Erythromycin tincture (0.5, 1, 2 or 4%) (NRF 11.78.)		
		Acne, folliculitis
Erythromycin base	0.55 | 1.1 | 2.2 | 4.4	
Anhydrous citric acid	0.038 | 0.076 | 0.154 | 0.3	
Ethanol 96%	45.0	
Water	ad 100.0 If too dry, also add octyldodecanol q. sat.	
Estrogen scalp tincture for men		
17-β-Estradiol benzoate	0.005	
Isopropyl alcohol 70%	ad 100.0	

Continued Table II.1 ▶

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Estrogen scalp tincture for women		
		Androgenetic alopecia, telogen effluvium in women
17-β-estradiol benzoate	0.015–0.040	
Isopropyl alcohol 70%	ad 100.0 | ad 300.0	
Ichthyol ointment		
	Vehicle type: Hydrocarbon gel or water-absorbent ointment (W/O type)	Psoriasis, chronic dermatitis, prurigo nodularis
Leukichthol	3.0 – 10.0	
White petrolatum or Ungt. alcohol. lanae DAB	ad 100.0	
Keratolytic ointment		
	Vehicle type: water absorbent ointment (O/W type)	Hyperkeratotic lesions
Acid salicyl.	5.0	
Kerasal Basissalbe (ointment)	ad 100.0	Contains 10% urea
Lactic acid cream		
	Vehicle type: O/W cream	Chronic dermatitis
Acid. lact.	1.0	
Sodium lactate 50%	4.0	
Abitima cream	ad 100.0	
Lipid-poor corticosteroid lotion		
	Vehicle type: Non-ionic O/W lotion	Non-comedogenic, cooling corticosteroid lotion
Triamcinolone acetonide	0.025 – 0.1	
Hydrophilic skin emulsion (NRF S. 25.)	ad 100.0	
Lipid-rich corticosteroid Lotion		
	Vehicle type: W/O lotion	For very dry skin; contains 4% urea
Triamcinolone acetonide	0.2	
Excipial U Lipolotio	ad 200.0	

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Menthol lotion		
	Vehicle type: Non-ionic O/W cream paste	Arthropod bites and stings; urticaria
Menthol	0.25	
Zinc oxide shake lotion 25% SR (NRF 11.109.)	ad 100.0	
Methylrosaniline chloride solution (0.1 or 0.5%) (NRF 11.69.)		
	Known in English as methyl violet	Topical antiseptic and antifungal; interdigital dermatophytosis, candidal intertrigo, gram-negative toe web infection
Methylrosaniline chloride ethanol solution 10% (NRF S. 16.)	1.0 | 5.0	
Water	ad 100.0	
Metronidazole hydrophilic cream (1 or 2%) (NRF 11.91.)		
	Vehicle type: Non-ionic O/W cream ▶ ***Note:*** Store 1% cream in refrigerator.	Rosacea
Metronidazole	1.0 | 2.0	
Non-ionic hydrophilic cream SR DAC (NRF S. 26.)	49.0 | 48.0	
Potassium sorbate	0.7	
Anhydrous citric acid	0.035	
Water	ad 100.0	
Minoxidil scalp tincture (2 or 5%)		
	▶ ***Note:*** Minoxidil is dissolved in the mixture of propylene glycol and ethanol with heating; after cooling add water	Androgenetic alopecia
Minoxidil	2.0 | 5.0	
Propylene glycol	15.0	
Water	15.0	
Ethanol 96%	ad 100.0	

Continued Table II.1 ▶

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Nail removal paste 40% urea (NRF 11.30.)		
		Removal of dystrophic or onychomycotic nails
Urea	40.0	
Thick paraffin	15.0	
White petrolatum	20.0	
Bees wax, white	5.0	
Wool wax	20.0	
Nystatin zinc paste		
		Candida intertrigo, angular cheilitis
Nystatin	10 million IU	
Olive oil	5.0	
Zinc paste DAB	ad 100.0	
Rhagade ointment		
		Chronic hand dermatitis
Betamethesone-17-valerate	0.1	
Salicylic acid	5.0	
Leukichthol	20.0	
Ungt. alcohol. lanae DAB	ad 100.0	
Salicylic acid scalp oil (2, 5, or 10%) (NRF 11.44.)		
	▶ ***Note:*** Salicylic acid is hard to keep in solution; thus complex formulations	To loosen scales in psoriasis, severe seborrheic dermatitis.
Salicylic acid	2.0 | 5.0 | 10.0	
Refined castor oil	0 |0 | 45.0	
Thick paraffin	73.0 | 0 | 0	
Octyldodecanol	25.0 | 95.0 | 45.0	
Salicylic acid scalp oil, washable 10% (NFA)		
		Washable scalp oil to loosen scales in psoriasis, severe seborrheic dermatitis
Salicylic acid	10.0	
Ethanol 96%	10.0	

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Salicylic acid scalp oil, washable 10% (NFA)(continued)		
Macrogol-8-stearate	10.0	
Isopropyl myristate	35.0	
Peanut oil	35.0	
Skin care lotion		
	Vehicle type: anionic O/W lotion	Slightly greasy lubricating lotion
Emulsifying cetearyl alcohol (type A)	4.0	
Glycerol monostearate	2.2	
Potassium sorbate	0.14	
Citric acid	0.07	
Triglyceride (medium chain)	5.0	
Peanut oil	5.0	
Water	ad 100.00	
Tar paste, soft		
	Vehicle type: Hydrocarbon gel	Psoriasis, chronic dermatitis, prurigo nodularis
Pix lithanthracis (tar)	5.0	
Soft zinc paste DAB	ad 100.0	
Tar scalp cream		
		Psoriasis, severe seborrheic dermatitis of scalp; can also be used on psoriasis on rest of body
Liquor carbonis detergens	5.0	
Salicylic acid	5.0	
Ungt. emulsificans aquosum	ad 100.0	
Thiabendazole cream		
	Vehicle type: hydrophobic W/O cream	
Thiabendazole	10.0	
Hydrous wool alcohol ointment DAB	ad 100.0	

Continued Table II.1 ▶

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Thiabendazole lipophilic gel 10% (NRF 11.130.)		
	Vehicle type: oleo gel	
Thiabendazole	10.0	
Hydrophobic Basisgel DAC	ad 100.0	
Thiabendazole ointment		
	Vehicle type: hydrophobic ointment	
Thiabendazole	15.0	
(Salicylic acid)	(3.0)	
White petrolatum	ad 100.0	
Thiabendazole solution		
Thiabendazole	2.0	
Water	10.0	
DMSO	ad 100.0	
Thioglycollate epilation cream		
		Removing unwanted hairs; apply, leave on 10 minutes or until hair appears damaged
Emulsifying cetearyl alcohol (Type A)	10.0	
Oleyl oleate	6.0	
Thioglycolic acid solution 80%	6.0	
Calcium hydroxide	8.0	
Calcium carbonate	15.0	
Fragrance	1.0	
Water	ad 100.0	
Urea and lactic acid cream		
	Vehicle type: ambiphilic cream	Ichthyosis vulgaris, long-term care of dermatitis
Urea pura	5.0 – 10.0	
Lactic acid	1.0	
Sodium lactate 50%	4.0	
Basiscreme DAC	ad 100.0	

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Urea lotion		
	Vehicle type: W/O lotion	For very dry skin
Urea	10.0	
Lactic acid	2.0	
Sodium lactate 50%	8.0	
Water	10.0	
Lipoderm lotion	ad 200.0	
Urea ointment		
	Vehicle type: lipogel	Chronic dermatitis
Urea	5.0 | 10.0	
Liquor carbonis detergens	(5.0–10.0)	
Excipial Mandelölsalbe (almond oil ointment)	ad 100.0	
Zinc oxide paste for Unna boot (ex-NRF 11.19.)		
		Gauze wrap impregnated with paste is used to wrap leg when treating chronic venous ulcers, lichen simplex chronicus, artifacts; dries to create a firm, cast-like device
Zinc oxide	10.0	
Glycerol 85%	40.0	
Gelatin	15.0	
Water	ad 100.0	
Zinc oxide paste, antimycotic		
	Vehicle type: W/O cream paste	Intertriginous dermatophyte or candidal infections; inflamed lichen sclerosus
Clotrimazole	1.0	
(Triamcinolone acetonide)	(0.1)	
Zinc oxide	30.0	
Eucerin cum aqua (50% water)	ad 100.0	

Continued Table II.1 ▶

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Zinc oxide paste, aqueous (FH Z.3.)		
	Vehicle type: hydrophilic paste	Acute dermatitis
Zinc oxide	15.0	
Talcum	15.0	
Propylene glycol	15.0	
Bentonite (Veegum)	5.0	
Water	ad 100.0	
Zinc oxide paste, cooling		
	Vehicle type: pseudo-W/O cream paste	Acute dermatitis
Soft zinc paste DAB	50.0	
Ungt. leniens DAB	50.0	
Zinc oxide paste, hard (zinc paste DAB)		
	Vehicle type: hydrocarbon gel	Protective paste; low sensitizing potential; not easily removed
Zinc oxide	25.0	
Corn starch	25.0	
White petrolatum	ad 100.0	
Zinc oxide paste, lipophilic 30% (NRF 11.111.)		
		Protective paste
Zinc oxide	30.0	
Beeswax, white	30.0	
White petrolatum	40.0	
Zinc oxide paste, soft (DAB)		
	Vehicle type: Hydrocarbon gel	Protective paste
Zinc oxide	30.0	
Thick paraffin	40.0	
White petrolatum	20.0	
Beeswax, white	10.0	

Table II.1 · Continued

Name and ingredients[a]	Concentration (%)	Indications
Zinc oxide shake emulsion (NRF 11.49.)		
	Vehicle type: emulsifier-stabilized shake lotion	Acute dermatitis
Emulsifying cetearyl alcohol (Type A)	3.0	
Zinc oxide	18.0	
Talc	18.0	
Glycerol 85%	18.0	
Ethanol 70%	18.0	
Water	ad 100.0	

DAB = Deutsches Arzneibuch, DAC = Deutsches Arzneimittel Codex, NRF = Neues Rezeptur Formularium, FH = Formularium Helveticum, NFA = Neues Formularium Austriacum, SR = Standardrezepturen (former German Democratic Republic).

a Ingredients indicated in parentheses are optional; the remainder is adjusted.

b Use either leukichthol (ammonium bituminosulfonate) without buffer solution or betamethasone with buffer solution.

c Macrogol is also known as polyethylene glycol.

d Mixture of cetearyl alcohol and sodium cetearylsulfate.

Note: We realize most readers will use other formularies and references. We cite these sources because they are standardized and well-established.

Appendix III Dermatologic Differential Diagnosis

How to Use This Chapter

In the tables below, a variety of different approaches to dermatologic differential diagnosis are offered, hopefully making it easier to identify a single disease or a small number of diseases out of the vast number of skin conditions with which we are confronted.

Differential diagnostic possibilities are presented on the basis of the type, shape, color, consistency, and distribution of skin lesions, as well as on common subjective complaints. Sites of predilection and typical patterns of distribution are also listed.

Note: These lists cover topics that we find particularly difficult or interesting. We have made no attempt to include all the primary and secondary lesions or body sites: Many scenarios such as "papules on trunk"are simply too large, covering most of dermatology.

Differential Diagnostic Lists

Vesicles and Bulla

Table III.1 · **Differential diagnosis of vesicles and bullae**

Diagnosis	Clues	See
Acute contact dermatitis (allergic, toxic)	Rapid appearance of poorly circumscribed erythema, papulovesicles, blisters, often weeping areas	p. 195
Acute photodermatitis (allergic, toxic)	Erythema and then blisters minutes to hours after sun exposure	p. 297
Arthropod bite or sting	Tense blister on exposed surface, often other bites nearby; secondary to edema.	p. 130
Bullous pemphigoid	Large tense blisters, often preceded by pruritus or urticarial lesions, elderly patients.	p. 235
Burn	History provides the answer	p. 676
Dermatitis herpetiformis	Intensely pruritic blisters which are usually destroyed by scratching and not seen by physician; knees, elbows, buttocks; patients with gluten-sensitive enteropathy	p. 214
Dyshidrotic dermatitis	Deep-seated small pruritic vesicles on hands and feet, sometimes with fine scale	p. 200

Table III.1 · Continued

Diagnosis	Clues	See
Eczema herpeticatum	Disseminated herpes simplex in atopic patient; worse in areas of dermatitis such as face and neck but can be widespread	p. 58
Epidermolysis bullosa	Easily-induced mechanical blisters on palms and soles, or widespread; present at birth or later (depends on variant)	p. 351
Epidermolysis bullosa acquisita	Often resembles bullous pemphigoid, but has other patterns; can be associated with inflammatory bowel disease	p. 239
Erysipelas	Circumscribed erythema with fever and chills, facial lesions often symmetrical; can evolve to blisters and necrosis; may be bullous when severe	p. 78
Erythema multiforme	Target lesions on extremities, palms and soles; blue-violet center with white intermediate zone and erythematous rim	p. 281
Erythema multiforme-like drug reaction	Lesions similar to erythema multiforme, but usually truncal, iris features less well-developed, often not bullous	p. 282
Fixed drug eruption	Red-brown patch or plaque; history of recurrence in exactly the same site with ingestion of same drug; rarely bullous	p. 182
Friction blister	Large blister with peripheral erythema at site of friction, thus usually palms or soles	
Herpes simplex	Grouped blisters on erythematous base, rapidly become pustular, painful, history of recurrences	p. 57
Impetigo	Honey-colored crusts develop rapidly from blisters and pustules, small children, exposed areas	p. 77
Linear IgA disease of childhood	Blisters grouped in rosette-fashion; often buttocks or facial	p. 240
Lymphangioma	Dilated lymphatics, resembles frog eggs, often congenital, not a true blister	p. 451
Miliaria	Grouped small papules and vesicles on trunk, neck, intertriginous areas; caused by heat, sweating and occlusion	p. 88
Pemphigoid gestationis	Resembles bullous pemphigoid but in 2nd– 3rd trimester; favors abdomen and extremities	p. 238
Pemphigus vulgaris	Fragile blisters, usually presents as erosions with crusting, oral involvement, rarely pruritic.	p. 229
Porphyria cutanea tarda	Fragile skin and blisters backs of hands, hypertrichosis on face	p. 312

Continued Table III.1 ▶

Table III.1 · Continued

Diagnosis	Clues	See
Staphylococcal scalded skin syndrome (SSSS)	Diffuse erythema with superficial peeling, in small children, looks like burn; some lesions may be bullous	p. 75
Stevens–Johnson syndrome	Painful mucosal erosions (mouth, eyes), malaise, fever, sudden appearance; associated with erythema multiforme–like drug reactions.	p. 184
Toxic epidermal necrolysis (TEN)	Diffuse skin loss as maximal variant of erythema multiforme–like drug reaction; drug-induced; patients sick with fever, fluid loss, requires burn care	p. 185
Varicella (chickenpox)	Vesicles on erythematous base, lesions in different stages at same anatomic site, pruritic, mouth and scalp involved, palms and soles free	p. 60
Zoster	Grouped blisters on erythematous base, rapidly become pustular, dermatomal, rarely crosses midline; may be preceded by pain	p. 61

Pustules

Table III.2 · Differential diagnosis of pustules

Diagnosis	Clues	See
Follicular pustules		
Acne	Inflamed papules and pustules along with comedones; face, chest, upper back	p. 530
Acne inversa	Pustules, nodules, sinus tracts and fistulas; axillary or inguinal; not primarily bacterial	p. 531
Demodex infestation	Pustules either associated with rosacea or arising on normal facial skin	p. 536
Dermatophyte infection	Round or polycyclic, slightly scaly lesion with raised border, central clearing; occasionally pustules	p. 106
Folliculitis	Small pustules with erythematous base	p. 74
Furuncle, carbuncle	Tender red nodule with superficial pustule; neck, face, axillae, groin, upper back	p. 74
Malassezia folliculitis	Closely group follicular pustules and inflammation on trunk and back; often in atopic patients	p. 158
Perioral dermatitis	Tiny papules and pustules in perioral region with classic zone of sparing around mouth; also periorbital but can involve entire face	p. 535
Pseudofolliculitis barbae	Ingrown hair adjacent to follicle causes pustule; seen primarily in blacks	

Table III.2 · Continued

Diagnosis	Clues	See
Rosacea	Papules, telangiectases and small pustules; almost exclusively on face; triggered by alcohol, nicotine, spices, heat.	p. 533
Nonfollicular pustules		
Acrodermatitis continua (Hallopeau)	Pustular psoriasis located on fingertips, often with nail involvement	p. 265
Acute generalized exanthematous pustulosis (AGEP)	Large pustules, widespread exanthem, drug reaction with systemic symptoms	p. 186
Behçet syndrome	Recurrent aphthae, genital ulcers; common in Asia and Middle East; rarely pustules, sometimes at site of trauma (pathergy)	p. 256
Candidiasis	Macerated epidermis with crusts, typically pustules at periphery	p. 112
Herpes simplex	Grouped blisters on erythematous base, rapidly become pustular, painful, history of recurrences	p. 57
IgA pemphigus	1–2 cm pustules, often arranged in patterns, truncal (formerly known as Sneddon–Wilkinson disease)	p. 234
Impetiginized dermatitis	Pustules and crusts in area of dermatitis	
Impetigo	Honey-colored crusts develop rapidly from blisters and pustules, small children, exposed areas	p. 77
Palmoplantar pustulosis	Small pustules on palms and soles, often confluent, may be triggered by infections and smoking	p. 265
Pustular psoriasis	Highly variable depending on type; pustules either alone or associated with psoriatic lesions	p. 265
Pyoderma gangrenosum	Large deep rapidly spreading ulcers; heal with cribriform scar; earliest lesion is sterile pustule, also induced by trauma (pathergy)	p. 250
Scabies	Pruritus, burrows, excoriations and secondary pyoderma with pustules	p. 127
Vasculitis	Palpable purpura, pustules, necrosis	p. 247
Zoster	Grouped blisters on erythematous base, rapidly become pustular, dermatomal, rarely crosses midline; may be preceded by pain	p. 61

Hives

Note: The scientific word for a single hive is urtica; the condition with multiple hives is urticaria.

Table III.3 · Differential diagnosis of hives

Diagnosis	Clues	See
Acute exanthem with urticarial features	Virus? Drugs? Multiple small lesions in contrast to classic urticaria with larger lesions	
Angioedema	Acute appearance of subcutaneous facial swelling; laryngeal edema, gastrointestinal problems; rare familial forms (HANE)	p. 173
Arthropod bite or sting	History, involvement of exposed surfaces, lesions often grouped	p. 130
Bullous pemphigoid	Prebullous phase often has pruritus and urticarial lesions; later tense stable large blisters	p. 235
Dermatitis herpetiformis	Intensely pruritic urticarial lesions and blisters which are usually destroyed by scratching and not seen by physician; knees, elbows, buttocks; patients with gluten-sensitive enteropathy	p. 241
Urticaria	Generalized hives, pruritus	p. 167
Urticaria pigmentosa	Red-brown papules and nodules which urticate on manipulation; mast cell proliferation	p. 466
Urticarial vasculitis (and other forms of vasculitis)	Hives persist for more than 24 hours; heal with hyperpigmentation, classic form associated with arthritis	p. 248

Telangiectases

- **Telangiectases** are permanently dilated small vessels.
- **Poikiloderma** refers to the combination of telangiectases, atrophy, and hyper- or hypopigmentation.

Table III.4 · Differential diagnosis of telangiectases

Diagnosis	Clues	See
Basal cell carcinoma	Glassy papules or nodule with prominent peripheral rim rich in telangiectases; often central ulceration	p. 433
Cushing disease	Facial erythema with telangiectases	p. 318
Erythema ab igne	Localized reticular hyperpigmentation and telangiectases caused by local, long-term exposure to heat	p. 383
Generalized essential telangiectasia	Acquired or congenital; widespread telangiectases	p. 452

Table III.4 · Continued

Diagnosis	Clues	See
Genodermatoses with poikiloderma	Bloom syndrome Xeroderma pigmentosum Ataxia-telangiectasia Rothmund–Thomsen syndrome	p. 306 p. 304 p. 453 p. 306
Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome)	Young patients, telangiectases on face, nasal and oral mucosa, frequent nose bleeds, pulmonary arteriovenous fistulas predispose to brain abscesses	p. 452
Necrobiosis lipoidica	Circumscribed atrophic yellow patch, usually on shins, with prominent telangiectases; associated with diabetes mellitus	p. 293
Nevus araneus (spider nevus)	1–2 cm papule with radial telangiectases, usually on face or décolleté, can be sign of liver disease	p. 451
Radiation dermatitis	Poikiloderma following ionizing radiation; history should give answer	p. 615
Starburst veins	Microvaricosities, medial shins and anterior thighs	p. 553
Telangiectases secondary to actinic damage, topical or systemic corticosteroid therapy	Localization and history	
Telangiectases with collagen-vascular disorders (systemic sclerosis—CREST, lupus erythematosus, dermatomyositis)	History, search for other stigmata.	p. 203
Telangiectasia macularis eruptiva perstans (form of mastocytosis)	Red-brown macules with prominent telangiectases, disseminated, urticate when rubbed; other types of mastocytoses less often have telangiectases.	p. 467

Erythema and Flushing

- **Erythema** is a persistent flat red area, usually caused by vasodilation or increased blood flow but without the requirement of visible permanently dilated vessels.
  - *Figurate erythemas* have a pattern, often annular and occasionally migratory.
- Flushing is a transient erythema caused by acute dilation of cutaneous blood vessels.

Table III.5 · Differential diagnosis of erythema and flushing

Diagnosis	Clues	See
Erythema		
Systemic lupus erythematosus	Butterfly rash—symmetric erythema and edema of cheeks, initially transient, later permanent	p. 209

Continued Table III.5 ▶

Table III.5 · Continued

Diagnosis	Clues	See
Annular erythema of Sjögren syndrome	Common in Japanese patients; occasionally in whites	p. 225
Erythema annulare centrifugum	Slowly expanding annular erythema, sometimes with scale	p. 285
Erythema chronicum migrans	Slowly expanding annular erythema without scale; often with central tick bite; sign of borreliosis	p. 93
Erythema gyratum repens	Erythema with scale in "wood grain" pattern, on trunk, paraneoplastic sign	p. 486
Erythema marginatum (rheumaticum)	Transient, rapidly moving erythematous bands in rheumatic fever	p. 224
Erythromelalgia	Painful acute erythema of the digits, often triggered by heat or stress	p. 484
Necrolytic migratory erythema	1–4 cm crusted erythematous patches with central necrotic blisters; marker for pancreatic glucagonoma	p. 486
Palmar erythema	Search for underlying disease (liver disease, hyperthyroidism, rheumatoid arthritis, pregnancy, oral contraceptives, systemic lupus erythematosus, diabetes mellitus, hereditary)	
Rosacea	Erythema often first sign; later papules, telangiectases and small pustules; almost exclusively on face; triggered by alcohol, nicotine, spices, heat	p. 533
"Slapped cheeks"	Erythema of cheeks with nose and mouth free; sign of erythema infectiosum	p. 573
Flushing		
Carcinoid syndrome	Attacks of red-blue discoloration of upper trunk and arms with heat flashes and diarrhea; later pellagra-like changes	p. 320
Drug-induced	Fumaric acid therapy for psoriasis; rarely others (mast cell degranulators, hormones, chemotherapy agents, nicotinic acid, IL-2)	
Mastocytosis	Red-brown macules and papules, sometimes with telangiectases; occasionally flushing	p. 466
Menopause	Hot flashes; history usually obvious	
Pheochromocytoma	Increased blood pressure, tachycardia; attacks for flushing	p. 319
Rosacea	Some patients present with flushing with no other signs; later papules, telangiectases and small pustules; almost exclusively on face; triggered by alcohol, nicotine, spices, heat	p. 533

Distribution of Lesions

Frequently the distribution or localization of a lesion provides an important clue for the correct diagnosis. Figures 50.**1** and 50.**2** provide information on this topic.

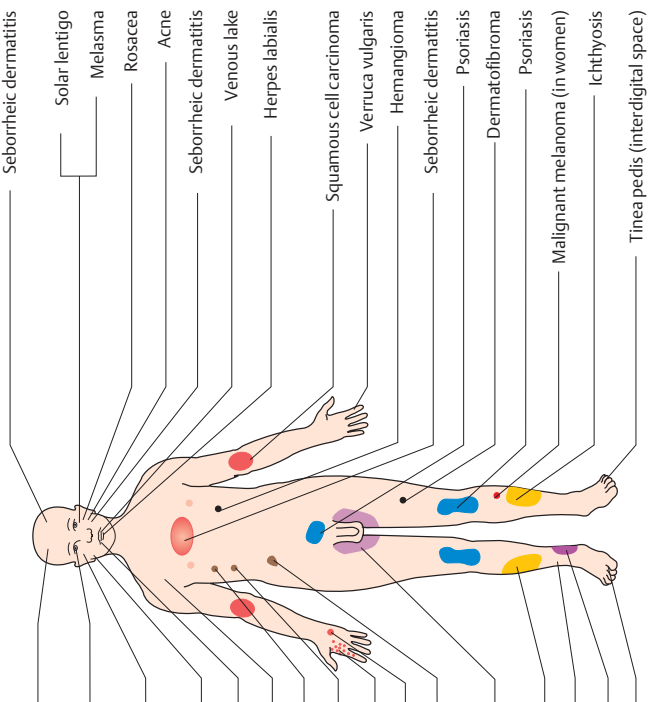

Fig. 50.**1** · **a, b** Homo dermatologicus: typical locations of many common skin diseases.

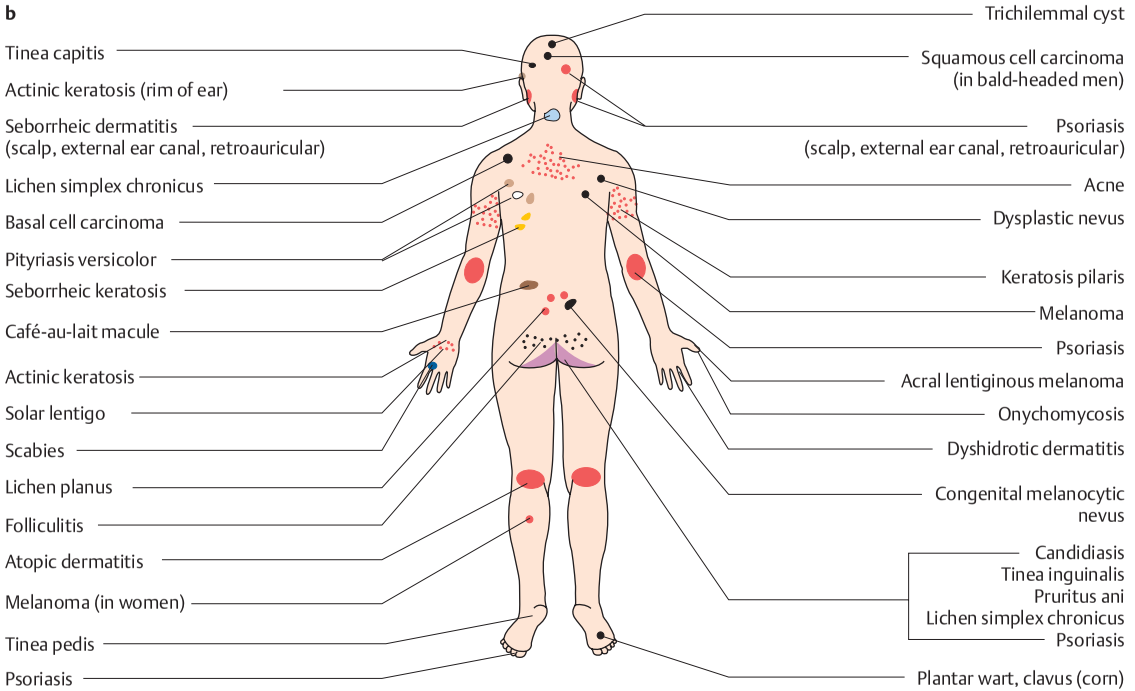

Fig. 50.1 · b

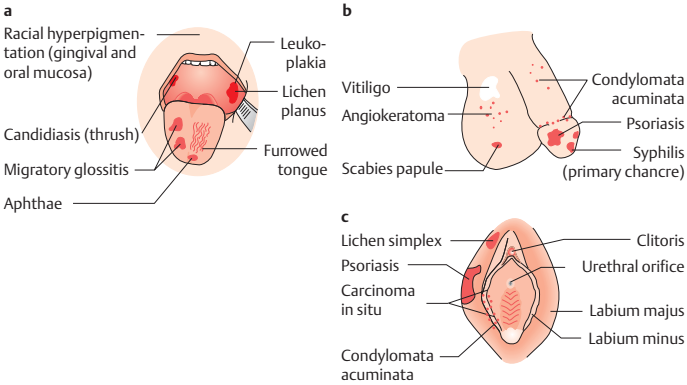

Fig. 50.**2** · **Common diseases. a** Mouth. **b** Male genitalia. **c** Female genitalia.

Special Patterns

Sometimes the pattern of a disease allows a rapid diagnosis or at least allows you to limit the number of possibilities.

Table III.6 · **Special patterns**

Diagnosis	Clues	See
Annular with scale		
Disseminated superficial actinic porokeratosis (DSAP)	1–2 cm plagues, look atrophic but have sharp fine hyperkeratotic border; usually on forearms, shins	p. 343
Erythema annulare centrifugum	Slowly expanding annular erythema, sometimes with scale	p. 285
Erythema chronicum migrans	Slowly expanding annular erythema without scale; often with central tick bite; sign of borreliosis	p. 93
Psoriasis	Silvery scales on erythematous base; favors scalp, gluteal cleft, knees, elbows; rarely annular	p. 262
Reiter syndrome	Annular erosions of glans with white border (circinate balanitis); skin lesions resemble psoriasis; sometimes associated arthritis, urethritis or bowel disease	p. 275
Seborrheic dermatitis	Petaloid variant on chest may be circular or annular	p. 276
Subacute cutaneous lupus erythematosus	Subacute form often psoriasiform or annular	p. 207

Continued Table III.6 ▶

Table III.6 · Continued

Diagnosis	Clues	See
Tinea corporis	Ring with peripheral erythema and scale; central clearing; KOH examination positive	p. 107
Urticaria	Hives can be annular, intersecting, in various stages of regression.	p. 167
Annular without scale		
Granuloma annulare	Grouped small flesh-colored to pink papules producing ring with central clearing; no scale; common on backs of hands and feet; often misdiagnosed as tinea corporis	p. 292
Lichen planus	Rare annular variants; either grouped papules or large plaques with central clearing.	p. 286
Lichen sclerosus	Porcelain white papules or plaques; trunk, genitalia	p. 217
Morphea	Circumscribed sclerotic plaque with violet ring at periphery; maybe quite large	p. 216
Mycosis fungoides	Cutaneous T-cell lymphoma; patches and plaques which are sometimes annular	p. 474
Polycyclic	▶ ***Note:*** All the annular lesions can occasionally evolve into polycyclic patterns	
Erythema gyratum repens	Erythema with scale in "wood grain" pattern, on trunk, paraneoplastic sign	p. 486
Erythema marginatum (rheumaticum)	Transient, rapidly moving erythematous bands in rheumatic fever	p. 224
Iris, target, or cockade		
Cockade nevus	Melanocytic nevus with rings of inflammation (variant of halo nevus)	p. 388
Erythema multiforme	Target lesions on extremities, palms and soles; blue-violet center with white intermediate zone and erythematous rim	p. 281
Erythema multiforme–like drug reaction	Lesions similar to erythema multiforme, but usually truncal, iris features less well-developed, often not bullous.	p. 282
Subacute cutaneous lupus erythematosus	Annular form occasionally has dramatic rings	p. 207
Urticaria	Hives with concentric patterns	p. 167
Dermatoses which follow vessels		
Mondor disease	Phlebitis of large subcutaneous veins of lateral chest	p. 557
Temporal arteritis	Painful, indurated temporal artery; severe headaches, can lead to blindness; giant cells in vessel wall on biopsy	

Table III.6 · Continued

Diagnosis	Clues	See
Thrombophlebitis	Painful subcutaneous cords; if recurrent, exclude pancreatic carcinoma and clotting disorder	p. 557
Varicosities	Usually on legs; look for signs of chronic venous insufficiency	p. 553
Dermatoses which follow lymphatics		
Lymphangiitis	Linear ascending red streak from area of cellulitis or other infection	
Sclerosing lymphangiitis	Nonvenereal, post-traumatic inflammation of penile lymphatics	p. 549
Sporotrichoid infections	Sporotrichosis, nocardiosis, atypical mycobacteria, and others spread from inoculation site via lymphatics, dotting the path of the lymphatic vessel with nodules	
Bizarre or unnatural patterns		
Artifacts	Lesions caused by patient or someone else (spouse, parent)—sometimes for special gain (workman's compensation, sometimes for psychiatric reasons)	p. 581
Contact dermatitis (irritant or allergic)	Erythema, scale, papulovesicles; appropriate history	p. 195
Dermatoses in scars	Sarcoidosis, psoriasis, lichen planus in scars (Koebner phenomenon); years later, squamous cell carcinoma or basal cell carcinoma; hyperpigmentation when ACTH/MSH levels elevated	
Radiation dermatitis	Confined to radiation fields, so often rectangular or unnatural; may ulcerate	p. 615
Trauma	Physical or chemical damage; history tells story—burns, lightening strikes, chemical spills and the like.	
Spared areas		
Arthropod bites or stings	Usually not in areas covered by clothing	p. 130
Excoriations	Area of mid-back which cannot be reached by hands is usually spared	
Papuloerythroderma Ofuji	Confluent papules spare skin folds on abdomen (deck chair sign)	
Perioral dermatitis	Striking spared area directly adjacent to lips—"periperioral" dermatitis is better name	p. 535
Pityriasis rubra pilaris	Diffuse scaly erythema with follicular hyperkeratotic papules; salmon color; palmoplantar keratoderma; nappes claires (areas of sparing)	p. 278
Vasculitis	Often area under pressure—tight socks—relatively spared	p. 247

Painful Tumors and Other Lesions

Only a handful of skin tumors are often painful. They are typically vascular or neural in nature. A limited number of other conditions also frequently present with pain.

▶ ***Note:*** A mnemonic for painful tumors is **ANGEL**: **a**ngiolipoma, **n**eural tumors, **g**lomus tumor, **e**ccrine tumors, **l**eiomyoma.

Table III.7 · **Painful tumors**

Diagnosis	Clues	See
Angiolipoma	Subcutaneous fat tumor with numerous vessels, sometimes thrombi; no clinical clues to separate from other lipomas	p. 447
Neural tumors	Many neural tumors, especially traumatic neuromas, are painful; most common are neurofibroma and neurilemmoma	p. 463
Glomus tumor	Blue-gray nodule Solitary: often painful, frequently subungual Multiple: compressible, not painful	p. 458
Eccrine tumors	Eccrine tumors often contain myoepithelial cells; this may explain their painful nature	p. 426
Leiomyoma	1–2 cm skin-colored to red-brown papules around hair follicles (arms) or plaques on scrotum or nipple; painful when stroked	p. 445

Table III.8 · **Other painful lesions**

Diagnosis	Clues	See
Adiposis dolorosa (Dercum disease)	Multiple painful lipomas in women; rare and controversial	p. 447
Aphthae	Gray mucosal ulcers with erythematous periphery; recurrent; both oral and genital involvement in Behçet syndrome	p. 494
Atrophie blanche	Superficial painful ulcers in chronic venous insufficiency	p. 559
Bullous autoimmune diseases	Mucosal involvement with erosions can be quite painful, interfere with eating	p. 229
Chancroid	Painful dirty genital ulcer with ragged edges	p. 150
Chondrodermatitis nodularis helicis	Painful nodule on helix which is tender and symptomatic when sleeping	
Erysipelas	Circumscribed erythema with fever and chills, facial lesions often symmetrical; can evolve to blisters and necrosis	p. 78
Erythema nodosum	Bruise-like tender deep nodules on shins; never ulcerate; usually sign of acute infection or drug reaction	p. 540
Erythropoietic protoporphyria	Painful burning or urticarial erythema following minor sun exposure	p. 311

Table III.8 · Continued

Diagnosis	Clues	See
Fissures—anal, palmoplantar, lips, retroauricular	Chronic dermatitis, especially periorificial, leads to painful splits and tears	
Herpes simplex	Grouped blisters on erythematous base, rapidly pustular, painful, history of recurrences	p. 57
Lichen planus	Erosions in mouth; look for other signs of lichen planus elsewhere	p. 286
Livedo vasculitis	Net-like vascular patterns, vasculitis, ulcers	p. 258
Pyoderma gangrenosum	Large deep rapidly spreading ulcers; heal with cribriform scar; earliest lesion is sterile pustule, also induced by trauma (pathergy)	p. 250
Stevens–Johnson syndrome	Painful mucosal erosions (mouth, eyes), malaise, fever, sudden appearance; associated with erythema multiforme-like drug reactions	p. 184
Temporal arteritis	Painful, indurated temporal artery; severe headaches, can lead to blindness; giant cells in vessel wall on biopsy	
Ulcers	Most ulcers are painful; exceptions listed in Table III.9	
Zoster	Grouped blisters on erythematous base, rapidly become pustular, dermatomal, rarely crosses midline; may be preceded by pain	p. 61

Painless Ulcers

The occasional painless ulcer should help you narrow down the differential diagnostic considerations.

Table III.9 · Differential diagnosis of painless ulcers

Diagnosis	Clues	See
Neoplastic ulcers	Ulcerated tumors, usually squamous cell carcinoma or basal cell carcinoma	
Neuropathic ulcers	Located overlying bony structures with excessive mechanical load because of loss of warning	
	Peripheral neuropathies (alcohol, drugs)	
	Diabetes mellitus	p. 319
	Leprosy	p. 101
	Syringomyelia	
Venous leg ulcers	Usually surprisingly painless, considering their size and chronicity	p. 560
Chancre	Firm hard, button-like lesion with superficial erosion; usually painless	p. 136

Scalp Lesions

Table III.10 · Differential diagnosis of scalp lesions

Diagnosis	Clues	See
Exudative and erosive lesions		
Langerhans cell histiocytosis	Tiny hemorrhagic papules, tend to erode, may become confluent producing dermatitic plaques and ulcers	p. 467
Pediculosis capitis	Weeping dermatitis of nape; nits on hairs	p. 126
Pemphigus vulgaris	Painful erosions of the mouth, but also scalp and face; other bullous autoimmune diseases may also affect scalp	p. 229
Zoster	Grouped blisters on erythematous base, rapidly become pustular, dermatomal, rarely crosses midline; may be preceded by pain	p. 61
Papules and plaques		
Actinic keratoses	Rough scaly papules, often easier to feel than see, on sun-exposed skin	p. 417
Folliculitis decalvans	Family of non-infectious scalp disorders; all rare; sometimes associated with acne inversa	p. 508
Lichen simplex chronicus	Persistently rubbed plaque with exaggerated skin markings, usually on nape, back of hands or feet; often in atopics	p. 330
Nevus sebaceus	Yellow-orange, usually hairless plaque on scalp or forehead, present at birth	p. 411
Seborrheic keratoses	Hyperkeratotic papules or plaques 0.2–6 cm diameter. Warty to smooth or polished surface, looks like it could be easily peeled off	p. 414
Nodules		
Acne keloidalis nuchae	Keloids on nape in blacks, caused by ingrown hairs	
Basal cell carcinoma	Glassy papules or nodule with prominent peripheral rim rich in telangiectases; often central ulceration	p. 433
Cylindroma (turban tumor)	Solitary or multiple skin-colored to red papules and nodules; when numerous, have been compared to a turban	p. 428
Lipoma	Soft lobular subcutaneous tumor, often on nape; smaller lesions on forehead are deeper (subgaleal lipoma)	p. 447

Table III.10 · Continued

Diagnosis	Clues	See
Nodules (Continued)		
Metastases	Quickly growing dermal or subcutaneous nodules; scalp is favored site for metastases presumably because it is so vascular	
Squamous cell carcinoma	Asymmetrical red scaly or crusted tumor, often with adjacent actinic keratoses	p. 419
Trichilemmal cyst	Firm, marble-like cyst, often multiple, almost exclusively on scalp	p. 408

Alopecia

Alopecia is covered in detail under hair disorders, but reviewed here.

Table III.11 · Differential diagnosis of alopecia

Type of alopecia	Clues	See
Alopecia areata	One or many round areas of complete hair loss; nail changes	p. 503
Anagen effluvium	Follows chemotherapy, poisoning: sudden loss of growing hairs, while resting hairs are retained	p. 499
Androgenic alopecia	Thinning of hair: men frontal and top; women, diffuse on top	p. 500
Scarring alopecia	Many different causes including: Inflammation (lupus erythematosus, lichen planus, sarcoidosis, morphea, bullous dermatoses) Infections (deep dermatophyte infections, furuncles) Folliculitis decalvans, folliculitis capitis abscedens et suffodiens—peculiar scarring inflammatory reactions that appear to be not primarily infectious Tumors (lymphoma, follicular mucinosis, metastases) Physical damage (radiation therapy, scars) Pseudopelade of Brocq—probably end stage of many inflammatory disorders	p. 506
Syphilitic alopecia	Moth-eaten hair loss in secondary syphilis	p. 138
Telogen effluvium	Severe illness, pregnancy, emotional distress may shift hairs into resting cycle; increased hair loss occurs 2–4 months later	p. 498
Tinea capitis	Multiple areas of broken-off hairs and inflammation; primarily in children	p. 108
Trichotillomania	Focal hair loss with breakage and stubble (never as complete as alopecia areata); patients remove hairs themselves	p. 506

Facial Lesions

Table III.12 · Differential diagnosis of facial lesions

Diagnosis	Clues	See
Acneiform follicular lesions		
Acne vulgaris	Inflamed papules and pustules along with comedones	p. 530
Adenoma sebaceum	1–2 mm red-violet smooth papules; chin and nasolabial folds; marker for tuberous sclerosis; early lesions often mistaken for acne	p. 365
Comedones	Early lesions of acne; also sign of solar damage on cheeks of elderly (Favre–Racouchot disease); plugged hair follicles; also known as whiteheads and blackheads	p. 530
Demodex folliculitis	Deep pustules usually with rosacea but can occur on normal skin	p. 536
Gram-negative folliculitis	Pustules, no comedones (except in acne patients); diagnosis made on culture	p. 534
Perioral dermatitis	Tiny papules and pustules in perioral region with classic zone of sparing around mouth; also periorbital but can involve entire face	p. 535
Pseudofolliculitis barbae	Perifollicular pustules and scars from ingrown hairs; on neck primarily in blacks	
Rosacea	Papules, telangiectases and small pustules; almost exclusively on face; triggered by alcohol, nicotine, spices, heat	p. 533
Sebaceous hyperplasia	Yellow 1–4 mm papules with central puncta	p. 429
Scaly lesions		
Actinic keratoses	Rough scaly papules, often easier to feel than see, on sun-exposed skin	p. 417
Atopic dermatitis	Pruritic dermatitis; facial and diffuse in children, flexural in adolescents, acral and excoriated in adults; history of atopic diathesis (asthma, rhinitis, conjunctivitis)	p. 190
Chronic cutaneous lupus erythematosus	Discoid plaques with follicular hyperkeratoses, on sun-exposed skin	p. 205
Contact dermatitis (irritant or allergic)	Erythema, scale, papulovesicles; appropriate history	p. 195

Table III.12 · Continued

Diagnosis	Clues	See
Lichen simplex chronicus	Persistently rubbed plaque with exaggerated skin markings, usually on nape, back of hands or feet; often in atopics	p. 330
Psoriasis	Silvery scales on erythematous base; favors scalp, gluteal cleft, knees, elbows	p. 262
Seborrheic dermatitis	Greasy yellow scales on erythematous base, scalp, hairline, nasolabial folds, eyebrows and external ear	p. 276
Tinea faciei	Inflamed scaly, pruritic patches and plaques; usually in individuals who sleep with pets	p. 109

Lip Swelling

Lip swelling can portend a medical emergency, as it may be the first sign of angioedema with airway obstruction.

Table III.13 · Differential diagnosis of lip swelling

Diagnosis	Clues	See
Angioedema	Acute appearance of subcutaneous facial swelling; laryngeal edema, gastrointestinal problems; rare familial forms (HANE)	p. 173
Contact dermatitis (cheilitis)	Erythema, scale, papulovesicles; appropriate history	p. 195
Erysipelas	Circumscribed erythema with fever and chills, facial lesions often symmetrical; can evolve to blisters and necrosis	p. 78
Furuncle	Painful firm nodule; often starts from hair follicle or sebaceous gland at vermilion border	p. 74
Granulomatous cheilitis	Edematous swelling of upper lip; initially waxes and wanes; later persistent.	p. 489
Melkersson–Rosenthal syndrome	Granulomatous cheilitis plus facial nerve paralysis and fissured tongue	p. 291
Trauma	History	

Other Lip Lesions

Many of the lesions found on the lips are clinically difficult to identify because they are developing on transitional epithelium that is often moist and traumatized.

Table III.14 · Differential diagnosis of lip lesions

Diagnosis	Clues	See
Actinic cheilitis	White discoloration of lower lip, sometimes with erosions or crusts; lip equivalent of actinic keratosis	p. 491
Angular cheilitis (perlèche)	Erythema, rhagades	p. 489
Free sebaceous glands	Tiny yellow papules on lips (Fordyce glands); harmless	p. 429
Herpes simplex	Grouped blisters on erythematous base, rapidly pustular, painful, history of recurrences	p. 57
Impetigo	Honey-colored crusts develop rapidly from blisters and pustules, small children; frequently starts just adjacent to lip.	p. 77
Labial melanotic macules	Tan macules on lips; also occur on genitalia; harmless but often worrisome	p. 376
Lichen planus	White lacy network on lips; intraoral painful erosions; look for other skin findings	p. 286
Lick dermatitis	Erythema and scaling in area reached by tongue or teeth (biting lower lip)	
Mucocele	Submucosal nodule, often with glassy sheen, frequently beneath labial mucosa	p. 410
Other forms of dermatitis	Adult atopics often have lip dermatitis; history for allergic contact dermatitis	
Squamous cell carcinoma	Exaggeration of actinic cheilitis with erosions, crusts and induration ► ***Note:*** Any nonhealing lip erosion should be biopsied to exclude squamous cell carcinoma	p. 419
Venous lake	Blue-gray compressible papule or nodule	p. 451
Wart	Hyperkeratotic papillomatous papules with punctate bleeding; surface usually white on lip	p. 491

Typical Lesions of the Oral Mucosa

On the oral mucosa, almost all lesions are white because of the persistent moisture. In addition, the epithelium is normally parakeratotic in many areas such as the palate. Erosions and ulcerations are common because the epithelium is thin and often traumatized, but usually heals readily.

Table III.15 · Differential diagnosis of oral mucosal lesions

Diagnosis	Clues	See
White lesions		
Candidiasis	Thrush: white plaques that can be rubbed off; other variants are erosive or atrophic	p. 112
Florid oral papillomatosis	HPV-induced papillomatous plaques; variant of verrucous squamous cell carcinoma	p. 421
Leukoplakia	White mucosal patch that will not rub off; many causes—congenital, trauma, HPV, carcinoma—if verrucous or multicolored (speckled leukoplakia), always biopsy	p. 490
Lichen planus	White lacy network on buccal mucosa; white papules on tongue	p. 286
Morsicatio buccarum	Bite lines; white ridges on buccal mucosa where it is traumatized by teeth	
Mucosal warts	White papules; usually in children or immunosuppressed patients; often transferred by chewing from digital warts	p. 491
Nicotine stomatitis (smokers' palate)	Gray-white papules on the palate with a red central puncta; associated with smoking, especially pipes	
White sponge nevus	White-gray, sharply bordered, folded or complex plaques; present at birth	p. 491
Erosions		
Herpetic gingivostomatitis	First infection with herpes simplex virus; usually infants, erosions, hemorrhagic crusts, foul odor, feeding problems	p. 58
Stevens–Johnson syndrome	Painful mucosal erosions (mouth, eyes), malaise, fever, sudden appearance; associated with erythema multiforme-like drug reactions	p. 184
Lichen planus	Painful erosions plus white lacy network on buccal mucosa; white papules on tongue	p. 286
Pemphigus vulgaris, cicatricial pemphigoid	Erosions, crusts on lips; two autoimmune bullous diseases most likely to affect mucosa	
Geographic tongue	Erythematous patches admixed in map-like pattern with more white areas; not true erosions	p. 492

Continued Table III.15 ▶

Table III.15 · Continued

Diagnosis	Clues	See
Erosions (Continued)		
Herpangina	Tiny gray papulovesicular lesions on hard palate; usually in small children; associated with fever and malaise	p. 66
Hand-foot-and-mouth disease	Triad of small oral (mainly palatal) ulcers, papules and vesicles on palms and soles and exanthem; viral symptoms	p. 65
Stomatitis secondary to chemotherapy	Appropriate history; usually widespread and painful erosions; often secondary candidiasis	
Ulcers		
Acute necrotizing ulcerative gingivitis (ANUG)	Mixed bacterial infection, common in immunosuppressed hoists (HIV/AIDS) and in those who neglect oral care	
Extranodal NIC/T-cell lymphoma, nasal type	Old name of lethal midline granuloma says it all; aggressive tumor often with palatal ulcerations	p. 479
Aphthae (major type)	Large necrotic ulcer with white fibrinous coating	p. 494
Behçet disease	Recurrent aphthae, genital ulcers; common in Asia and Middle East	p. 256
Chancre	Hard painless ulcer; when oral, usually on lip or palate; take sexual history when oral ulcer is not readily explained	p. 136
Langerhans cell histiocytosis	Localized version (eosinophilic granuloma) common in mouth; floating (loose) teeth, periodontal ulcerations	p. 467
Squamous cell carcinoma	Ulcerated tumor; smoking and alcohol abuse are risk factors	p. 419
Traumatic ulcer	Burns, electrical burns (chewing on electric cable), chemical burns and trauma all produce similar effects on mucosa; history is the answer	
Wegener granulomatosis	Form of destructive vasculitis; may have gingival erosions or oral ulcers	p. 253

Lesions of the External Ear

Ear lesions may been painful when slept upon, and are frequently manipulated.

Table III.16 · Differential diagnosis of external ear lesions

Diagnosis	Clues	See
Actinic keratosis	Rough scaly papules, often easier to feel than see, on sun-exposed skin	p. 417
Allergic contact dermatitis	Allergy to nickel in jewelry; papulovesicles, erythema.	p. 196
Basal cell carcinoma	Glassy papule or nodule with prominent peripheral rim rich in telangiectases; on ear usually on upper part of helix while chondrodermatitis nodularis helicis is closer to edge of helix	p. 433
Chondrodermatitis nodularis helicis	Painful nodule on helix which is tender and symptomatic when sleeping	
Chronic cutaneous lupus erythematosus	Discoid plaques with follicular hyperkeratoses, which in ear may be mistaken for comedones	p. 205
Comedones	Plugged hair follicles; also known as whiteheads and blackheads; common in acne patients	p. 530
Cutaneous horn	Focal hyperkeratotic horn; always biopsy since any of the above tumors, as well as warts, can be at base	p. 417
Elastotic nodule	Tiny papules on edge of helix; diagnosis usually made on histology; form of solar degeneration. Weathering nodule is same clinically, but shows no elastosis.	
Gouty tophus	White papules and nodules on antihelix; can be large or ulcerated	p. 322
Granuloma annulare	Grouped small flesh-colored to pink papules producing ring with central clearing; no scale	p. 292
Keloid	Excessive scar tissue extending beyond original injury; earlobe following piercing is very common site	p. 441
Keratoacanthoma	Solitary nodule with central crusted plug, rapid growth, usually on sun-exposed skin; variant of squamous cell carcinoma	p. 421
Lymphadenosis cutis benigna	Swollen red plaques; face, especially nose and ear lobes, nipples. Swollen red plaques; face, especially nose and ear lobes, nipples	p. 94
Necrotizing otitis externa	External ear infection with *Pseudomonas aeruginosa*; diabetics and immunosuppressed patients; also known as malignant otitis externa	
Otitis externa	Inflammation of outer ear canal with drainage, which can cause secondary dermatitis; causes include bacteria, rarely fungi (otomycosis), moisture (swimmer's ear) and allergic contact dermatitis to ear drops	

Continued Table III.16 ▶

Table III.16 · Continued

Diagnosis	Clues	See
Psoriasis	Silvery scales on erythematous base; favor scalp, gluteal cleft, knees, elbows; rarely limited to ears	p. 262
Relapsing polychondritis	Tender ears; autoimmune damage to cartilage; also involves nose, airways	
Seborrheic dermatitis	Greasy yellow scales on erythematous base, scalp, hairline, nasolabial folds, eyebrows; sometimes limited to ears	p. 276
Squamous cell carcinoma	Asymmetrical red scaly or crusted tumor, often with adjacent actinic keratoses	p. 419

Lesions of the Palms and Soles

The skin of the palms and soles is markedly thickened, even containing some keratin molecules different than those found at other body sites. Almost every lesion is hyperkeratotic, which is often confusing as reactive hyperkeratotic changes accompany an array of underlying problems.

Table III.17 · Differential diagnosis of lesions of the palms and soles

Diagnosis	Clues	See
Inflammatory-hyperkeratotic palmoplantar lesions		
Dyshidrotic dermatitis	Deep-seated small pruritic vesicles on hands and feet, sometimes with fine scale. Deep-seated small pruritic vesicles on hands and feet, sometimes with fine scale	p. 200
Hyperkeratotic palmoplantar dermatitis	Combination of dermatitis, hyperkeratotic plaques, and rhagades	p. 200
Tinea pedis	Variable patterns—interdigital maceration, dry hyperkeratotic scale, erythematous patches with fine scale, papulovesicular lesions	p. 109
Psoriasis	Silvery scales on erythematous base; favor scalp, gluteal cleft, knees, elbows; may present with palmoplantar disease	p. 262
Lichen planus	Polygonal violet flat-toped papules, lacy white network; on palms and soles, often painful hyperkeratotic lesions	p. 286
Pityriasis rubra pilaris	Diffuse scaly erythema with follicular hyperkeratotic papules; salmon color; Nappes claires (areas of sparing); frequently involves palms and soles	p. 278

Table III.17 · Continued

Diagnosis	Clues	See
Inflammatory-hyperkeratotic palmoplantar lesions (Continued)		
Keratoderma blennorrhagicum	Erythematous palmoplantar macules that become thick and crusted; associated with Reiter disease (reactive arthritis, circinate balanitis, signs of psoriasis)	p. 275
Hereditary palmoplantar keratodermas	Long list of diffuse, punctate, and linear forms of congenital keratoderma; family history. Some appear inflamed; others, verrucous	p. 345
Juvenile plantar dermatitis	Symmetrical erythema and scale of soles in child wearing occlusive footwear; snowmobilers' feet	p. 191
Sézary syndrome	Erythroderma, pruritus, lymphadenopathy, frequent involvement of palms and soles.	p. 477
Palmoplantar pits	True pits are only seen in nevoid basal cell carcinoma syndrome, but all the other lesions are clinically almost identical.	
Punctate keratoderma of palmar creases	Normal variant; more common in blacks; do not treat as warts	p. 347
Nevoid basal cell carcinoma syndrome	Multiple basal cell carcinomas, macrocephaly, medulloblastoma, skeletal anomalies	p. 435
Cowden syndrome	Multiple hamartomas, breast cancer, macrocephaly	p. 366
Darier disease	Tiny palmar hyperkeratoses; 1–2 mm dirty brown papules in seborrheic areas, linear nail streaks, oral cobblestoning	p. 341
"Warts" of the soles		
Arsenical keratoses	Multiple plantar keratoses; other stigmata (pigmentary changes and increased malignancies) and appropriate history	p. 418
Callus (tylosis)	More diffuse reactive hyperkeratosis; also caused by rubbing without underlying bony pressure point.	
Corn (clavus)	Local hyperkeratotic response to pressure; usually underlying bony protuberance; very painful; hard corns are lateral or plantar—soft corns are interdigital.	
Mal perforant	Neurotropic plantar ulcer; early lesions resemble clavi but with central defect	p. 140
Pitted keratolysis	Tiny punched-out lesions in mosaic pattern; more common in athletes, especially swimmers, and those unable to change shoes frequently (infantry soldiers).	

Continued Table III.17 ▶

Table III.17 · Continued

Diagnosis	Clues	See
"Warts" of the soles		
Plantar warts	Only slightly raised keratotic papules on soles; distinct bleeding points; various forms (solitary, mosaic, giant)	p. 69
Syphilitic clavi	Blue-red to red-brown oval scaly 1–2 papules; look for other signs of secondary syphilis	p. 137
Verrucous carcinoma	Chronic, slow-growing HPV-induced squamous cell carcinoma; formerly known on foot as epithelioma cuniculatum; a large chronic wart that fails to respond to treatment deserves a biopsy	p. 421
Papules or plaques on the hands and feet		
Actinic keratoses	Gray-brown discrete papules with adherent scale; often easier to feel than to see	p. 417
Bowen disease	Circumscribed hyperkeratotic plaque with variable scaling: squamous cell carcinoma in situ; often mistaken for dermatitis	p. 418
Chilblain lupus erythematosus	Blue-red plaques and nodules; looks like pernio but more permanent	p. 207
Common warts	Hyperkeratotic papillomatous papules with punctate bleeding	p. 68
Erysipeloid	Uncommon bacterial infection; often on fingers of butchers, farmers, veterinarians; blue-red plaque with minimal systemic symptoms	p. 90
Erythema multiforme	Target lesions on extremities, palms and soles; blue-violet center with white intermediate zone and erythematous rim	p. 281
Granuloma annulare	Grouped small flesh-colored to pink papules producing ring with central clearing; no scale; often misdiagnosed as tinea; back of hands and feet most common sites	p. 292
Lichen planus	Polygonal violet flat-toped papules, lacy white network; most common sites are flexor aspect of wrist and dorsal foot	p. 286
Palmoplantar pustulosis	Deep-seated, sometimes painful pustules, secondary scale; associated with smoking	p. 265
Pernio	Blue-red infiltrates; not painful; develops after long exposure to moderately low temperature	p. 309
Plane warts	Small papules which are often tan; face and backs of hands in children, young adults, spread by scratching with linear streaks	p. 69

Table III.17 · Continued

Diagnosis	Clues	See
Papules or plaques on the hands and feet (Continued)		
Psoriasis	Silvery scales on erythematous base; favor scalp, gluteal cleft, knees, elbows; may present with patches on hands or feet, as well as palmoplantar pustules	p. 262
Pustular palmoplantar lesions	▶ ***Note:*** Palmoplantar pustules are rarely infectious; almost always reactive	
Psoriasis	Palmoplantar pustules usually accompany obvious psoriasis elsewhere; on occasion, only sign of disease—search for other clues	p. 262
Scabies	Burrows especially between digits; intense pruritus worse at night; secondary dermatitis and pyodermas. In infants, feet are common place for burrows; intense pruritus; infants also may have face and scalp disease	p. 127

Lesions of the Shins

Table III.18 · Differential diagnosis of shin lesions

Diagnosis	Clues	See
Cellulitis	Painful soft tissue swelling; extends deeper than erysipelas and often associated with trauma	p. 80
Erysipelas	Circumscribed erythema with fever and chills; can evolve to blisters and necrosis; may be bullous when severe	p. 78
Erythema induratum (Bazin)	Indurated plaques on calves, favor middle-aged women; often ulcerated; sign of tuberculosis	p. 541
Erythema nodosum	Bruise-like tender deep nodules on shins; never ulcerate; usually sign of acute infection or drug reaction	p. 540
Kaposi sarcoma, classic variant	Red-brown to red-blue macules, nodules or plaques; symmetrical on lower legs and feet; usually older men; not HIV-associated	p. 460
Necrobiosis lipoidica	Circumscribed atrophic yellow patch with prominent telangiectases; associated with diabetes mellitus	p. 293
Pernio	Reticular blue-red infiltrates; not painful; develops after long exposure to moderately low temperature	p. 309

Continued Table III.18 ▶

Table III.18 · Continued

Diagnosis	Clues	See
Post-bypass cellulitis	Mild, chronic cellulitis in patients following vein removal for cardiac surgery; entry site invariably chronic interdigital tinea pedis	
Pretibial myxedema	Swollen red plagues on shin, often with overlying peau d'orange change	p. 318
Thrombophlebitis	Painful subcutaneous cords; if recurrent, exclude pancreatic carcinoma and clotting disorder	p. 557

Leg Ulcers

The approach to leg ulcers is also considered under phlebology, as almost all ulcers are related to chronic venous insufficiency (p. 560).

Table III.19 · Differential diagnosis of leg ulcers

Diagnosis	Clues	See
Arterial leg ulcer	More often lateral malleolus or distal; painful; reduced pulses, clammy feet	
Ecthyma	Punched-out ulcer with peripheral erythema, 0.5–3.0 cm; usually streptococcal	p. 78
Hematologic disorders	Sickle cell anemia (in blacks), cryoglobulinemia (check hepatitis serology)	
Iatrogenic ulcers	Sclerotherapy—history	
Livedo vasculitis	Extremely painful ulcers on background of livedo racemosa and atrophie blanche	p. 258
Necrobiosis lipoidica	Circumscribed atrophic yellow patch, usually on shins, with prominent telangiectases; associated with diabetes mellitus; when ulcerated, extremely slow to heal	p. 293
Polyarteritis nodosa	Red-blue 1–2 cm dermal papules, often associated with livedo racemosa; associated with systemic vasculitis or rarely limited to skin	p. 255
Post-traumatic	Burn, trauma, radiation—the answer is in the history. Chronic lesions have risk of malignant degeneration—development of squamous cell carcinoma	
Tropical ulcer	Variety of infectious causes in returning tourists: leishmaniasis and mixed bacterial infections most common	
Ulcerated panniculitis	Red to red-blue subcutaneous nodules with drainage; most common ulcerated form is α1-antitrypsin deficiency (liquefying panniculitis)	

Table III.19 · Continued

Diagnosis	Clues	See
Ulcerated tumor	Any tumor can ulcerate—most common on leg are squamous cell carcinoma and amelanotic melanoma; surprisingly painless.	
Venous leg ulcer	Accounts for over 90% of all leg ulcers. Usually medial malleolus and surprisingly painless; other signs of chronic venous insufficiency	p. 560

Intertrigo

Intertrigo refers to any dermatitis involving opposed skin surfaces and thus by definition is usually flexural, except in obese individuals where rolls of skin rub upon one another. Some consider intertrigo only a sign; we consider it a disease when there is no evidence for infection or underlying disease, but just for friction.

Table III.20 · Differential diagnosis of intertriginous lesions

Diagnosis	Clues	See
Acanthosis nigricans	Velvety dark patches in axilla and groin; paraneoplastic marker in adults; otherwise associated with obesity, diabetes mellitus and lipodystrophy	p. 485
Acne inversa	Inflammatory papules and nodules with fistula formation; axillary, inguinal and perianal	p. 531
Candidiasis	Macerated patches with erosions and peripheral pustules	p. 112
Contact dermatitis (allergic or toxic)	Erythema, scale, papulovesicles; appropriate history	p. 195
Diaper dermatitis	Limited to covered, occluded areas; often combination of candidiasis and irritant dermatitis; increasingly more common in elderly people	p. 199
Erythrasma	Red-brown superficial fine patches in axillae and groin; fluoresce coral red on Wood's light examination	p. 83
Fox–Fordyce disease	Skin-colored axillary papules; intensely pruritic when sweating	p. 529
Hailey–Hailey disease	Weeping plaques with fissures; likened to a dusty road drying out after a rainstorm	p. 342
Inverse psoriasis	Red macerated plaques without characteristic silvery scale; sometimes limited to penis; very difficult to diagnose without other signs of psoriasis	p. 265
Langerhans cell histiocytosis	Tiny hemorrhagic papules, tend to erode, may become confluent producing dermatitic plaques and ulcers	p. 467

Continued Table III.20 ▶

Table III.20 · Continued

Diagnosis	Clues	See
Lichen simplex chronicus	Area of persistent rubbing, exaggerated skin markings; common with vulvar dermatitis	p. 330
Pemphigus vegetans	Variant of pemphigus with red juicy (vegetating) plaques in axilla and groin	p. 232
Skin tags	Small stalked papules; very common in axillae, groin, especially in obese individuals; easily macerated	p. 439
Tinea inguinale	Involves medial thigh, not scrotum or labia; scaly patch with prominent erythematous border	p. 111
Trichomycosis axillaris	Small orange-yellow bacterial colonies attached to axillary, pubic hairs; unpleasant odor	p. 84

Cutaneous Signs of Systemic Disease

One of the fascinating aspects of dermatology is the ability of an experienced practitioner to examine the skin and suggest the possibility of underlying systemic diseases, often with an astounding degree of accuracy. Table III.21 is simply a beginning. The degree of association varies from almost 100% to quite low, but in our opinion, still worth looking at and trying to remember!

Table III.21 · Cutaneous signs of systemic disease

Skin findings	Associated systemic disease	
Acanthosis nigricans	Carcinoma (usually gastrointestinal), insulin-resistance, diabetes mellitus, obesity	p. 485
Acrokeratosis (Bazex)	Carcinoma (often bronchial or gastrointestinal)	
Alopecia areata	Autoimmune diseases (Hashimoto thyroiditis, vitiligo, pernicious anemia, lupus erythematosus)	p. 503
Alopecia, androgenetic in women	Androgen-producing tumors, iron or ferritin deficiency (increased androgen sensitivity), hyperprolactinemia, hyperandrogenism syndromes (polycystic ovary syndrome (Stein–Leventhal)	p. 500
Alopecia, scarring	Lupus erythematosus, systemic sclerosis, metastases, lichen planus, sarcoidosis, amyloidosis, lymphoma	p. 506
Alopecia, loss of axillary and chest hairs	Cirrhosis, endocrine disorders	
Amyloidosis	Multiple myeloma, other gammopathies, chronic infections, autoimmune diseases	p. 322

Table III.21 · Continued

Skin findings	Associated systemic disease	
Anal dermatitis	Hemorrhoids, anal tags, worms, anal polyps, anal fissure, anal fistula, rectal carcinoma, extramammary Paget disease	p. 544
Angiofibromas, multiple	Tuberous sclerosis, MEN1 with risk of Zollinger–Ellison syndrome and other endocrinopathies	p. 365
Angiokeratomas	Fabry disease and other even rarer metabolic disorders	p. 454
Aphthae, oral ulcers	Behçet syndrome, Stevens–Johnson syndrome	p. 256
Arachnodactyly	Marfan syndrome, homocystinuria	p. 356
Bacillary angiomatosis	HIV/AIDS	p. 155
Basal cell carcinomas, multiple	Nevoid basal cell carcinoma syndrome with risk of medulloblastoma and ovarian tumors	p. 435
Beau lines	Severe illness, poisoning, drug reaction dating back several months	p. 525
Bullous skin diseases		
Paraneoplastic pemphigus	Lymphoma, thymoma, sarcoma	p. 234
Epidermolysis bullosa acquisita	Diabetes mellitus, Crohn disease, ulcerative colitis, multiple myeloma, amyloidosis, thyroid disease, tuberculosis	p. 239
Bullous disease of diabetes	Diabetes mellitus	p. 319
Candidiasis	Diabetes mellitus, immunosuppression (HIV, leukemia, lymphoma, chemotherapy, hypothyroidism	p. 112
Chicken skin	Pseudoxanthoma elasticum with cardiac and ocular complications	p. 358
Circinate balanitis	Reiter syndrome with arthritis	p. 275
Clubbed fingers	Chronic pulmonary diseases (carcinoma, COPD, chronic bronchitis, pulmonary fibrosis), subacute bacterial endocarditis, cardiac disease with cyanosis, hyperthyroidism, virtually any chronic disease	p. 526
Cutis verticis gyrata, acquired	Carcinoma (bronchial), mesothelioma, myxedema, amyloidosis	p. 526
Dermatitis herpetiformis	Celiac disease (gluten-sensitive enteropathy)	p. 241
Dermatomyositis (adult form)	Carcinoma (breast, ovarian, uterine, pulmonary, gastric)	p. 213
Ear lobe folds	Correlation with cardiovascular disease	
Effluvium (acute hair loss)	Endocrine diseases, severe illness, pregnancy, malnutrition, chemotherapy, hyperprolactinemia, virilizing tumors, hepatic disease, HIV/AIDS	

Continued Table III.21 ▶

Table III.21 · Continued

Skin findings	Associated systemic disease	
Eosinophilic folliculitis	HIV/AIDS, severe immunosuppression, idiopathic	p. 161
Epidermoid cysts, multiple	Gardner syndrome (colon polyposis, carcinoma)	p. 368
Erythema		
Cheeks	Lupus erythematosus (butterfly rash), Cushing syndrome (full moon face with red cheeks)	
Palmar	Cirrhosis, pregnancy	
Erythema gyratum repens	Underlying malignancy often with ectopic hormone production, rarely idiopathic	p. 486
Erythema marginatum	Rheumatic fever (watch for carditis, arthritis, glomerulonephritis, chorea)	p. 224
Necrolytic migratory erythema	Glucagonoma	p. 486
Erythema nodosum	Infections (tuberculosis, yersiniosis, streptococcal and staphylococcal disease, deep fugal), acute sarcoidosis, Crohn disease, ulcerative colitis, drugs	p. 540
Erythroderma	Sézary syndrome, other malignancies, drug reactions, exacerbation of underlying skin diseases (atopic dermatitis, psoriasis, seborrheic dermatitis, pityriasis rubra pilaris), ichthyoses in infants	p. 282
Eyebrows, lateral thinning	Hypothyroidism, panhypopituitarism, secondary syphilis, poisoning, atopic dermatitis, trichotillomania	
Fibrofolliculomas, multiple	Birt–Hogg–Dubé syndrome with risk of renal carcinoma and spontaneous pneumothorax	p. 367
Fistulas	Tuberculosis, Crohn disease, ulcerative colitis, actinomycosis, osteomyelitis, deep abscesses, malignant tumors, congenital anomalies	
Folliculitis, recurrent	Diabetes mellitus, immunosuppression, HIV/AIDS	p. 319
Flush	Carcinoid syndrome, systemic mastocytosis, pheochromocytoma, carcinoma (gastric, pulmonary, thyroid), drugs	p. 222
Gangrene	Diabetes mellitus, thromboangiitis obliterans, vasculitis, arterial emboli, arteriosclerosis, cryoglobulinemia	

Table III.21 · Continued

Skin findings	Associated systemic disease	
Hyperpigmentation, diffuse	Addison disease (primary or tumor secreting ectopic hormone), Cushing syndrome, malignant melanoma with circulating melanin, hemochromatosis, argyrosis, chrysiasis, pellagra, cirrhosis, malabsorption, some forms of porphyria, chronic renal disease	
Hypertrichosis		p. 513
Localized	Porphyria cutanea tarda (cheeks), under cast (most common cause), other trauma, Becker nevus, faun tail, hair nevus	
Generalized	Drugs (cyclosporine, minoxidil, corticosteroids), acromegaly, anorexia nervosa, mucopolysaccharidoses	
Hypertrichosis lanuginosa acuisita	Carcinoma	p. 486
Hypopigmentation		p. 733
Localized	Vitiligo, poliosis, nevus depigmentosus, nevus anemicus, pinta, leprosy, tuberous sclerosis	
Generalized	Albinism, Chediak–Higashi syndrome, Hermansky–Pudlak syndrome, many other syndromes	
Ichthyosis, acquired	Drugs, carcinoma, lymphoma, sarcoidosis	
Janeway lesion (palmoplantar hemorrhagic macules)	Subacute bacterial endocarditis	p. 81
Kaposi sarcoma	HIV/AIDS, immunosuppression	p. 161
Keratoacanthoma, multiple	Muir–Torre syndrome (carcinomas of colon, lungs, other organs)	p. 369
Koilonychia	Iron deficiency, endocrine disease, polycythemia, hemochromatosis	p. 526
Lentigines, multiple		
Oral, perioral	Peutz–Jeghers syndrome	p. 369
Axillary	Neurofibromatosis (Crowe sign)	p. 362
Diffuse	Carney complex, LEOPARD syndrome	p. 385
Lichen, myxedematous	Gammopathy	p. 320
Scleromyxedema	Gammopathy	p. 320
Lipodystrophy, lipoatrophy	Drugs (protease inhibitors in HIV), complement deficiency, glomerulonephritis, diabetes mellitus, variety of syndromes,	p. 538
Livedo racemosa	Vasculitis (livedo vasculitis, polyarteritis nodosa, thromboangiitis obliterans	p. 258

Continued Table III.21 ▶

Table III.21 · Continued

Skin findings	Associated systemic disease	
Lymphedema	Filariasis, tumor infiltrates, status post-lymph node dissection, retroperitoneal fibrosis, other forms of pelvic instruction, idiopathic (congential and acquired)	p. 450
Mal perforant	Diabetes mellitus, neurosyphilis, syringomyelia, other peripheral neuropathies	p. 140
Milia (especially nonfacial)	Porphyria cutanea tarda, epidermolysis bullosa acquisita	p. 407
Angular cheilitis (perlèche)	Vitamin and mineral deficiencies, diabetes mellitus, candidiasis, improperly fitting dentures, nursing, staphylococcal infections (children)	p. 489
Myxedema		
Pretibial	Usually hyperthyroidism (Graves syndrome)	p. 318
Diffuse	Usually hypothyroidism	p. 318
Nail fold capillaries		
Thickened dilated giant capillary loops	Dermatomyositis, systemic sclerosis	p. 213, 219
Capillary loops twisted and irregular but not thickened or dilated	Systemic lupus erythematosus	p. 209
Neuromas, multiple mucosal	MEN2B syndrome with risk of medullary thyroid carcinoma and pheochromocytoma	p. 367
Onycholysis	Drugs, psoriasis, ischemia, hyperthyroidism	p. 525
Osler nodes (fingertip nodules)	Subacute bacterial endocarditis	p. 81
Palmoplantar keratoderma		
Congenital with leukoplakia	Howel–Evans syndrome with almost 100% risk of esophageal carcinoma	p. 346
Acquired	Weak marker for variety of carcinomas (gastric, pulmonary, esophageal)	p. 345
Panniculitis (especially if above waist or ulcerated)	Carcinoma of pancreas	p. 542
Paronychia, chronic	Diabetes mellitus, hypothyroidism, chronic mucocutaneous candidiasis, drugs (retinoids, protease inhibitors)	p. 520
Poikiloderma	Congenital (many syndromes), graft-versus-host disease, radiation dermatitis, mycosis fungoides, connective tissue disease	p. 360
Polyarteritis nodosa	Hepatitis C (and B)	p. 255
Prurigo nodularis	Chronic renal disease, diabetes mellitus, other causes of pruritus	p. 330

Table III.21 · Continued

Skin findings	Associated systemic disease	
Pruritus ani	Hemorrhoids, anal tags, worms, anal polyps, anal fissure, anal fistula, rectal carcinoma, intestinal candidiasis	p. 545
Psoriasiform lesions (but definitely not psoriasis)	Acrodermatitis enteropathica, acquired zinc deficiency, malnutrition, syphilis (especially under the microscope), early pityriasis rubra pilaris	
Purpura		
Palpable	Palpable purpura = vasculitis. Always biopsy palpable purpura to rule out vasculitis See p. 247 for differential diagnosis	
Nonpalpable	Clotting disturbance (thrombopenia, coagulopathy, disseminated intravascular coagulation), vessel wall defect (scurvy, amyloidosis, lupus erythematosus, erythropoietic protoporphyria) or "leakage" (pigmented purpuras, p. 246)	
Pyoderma gangrenosum	Crohn disease, ulcerative colitis (rarely precedes), IgA gammopathy (almost always precedes), rheumatoid arthritis, Behçet syndrome, leukemia, chronic active hepatitis	p. 250
Raynaud phenomenon	Collagen-vascular disorders (systemic sclerosis, dermatomyositis, lupus erythematosus), hyperviscosity syndrome, arteriosclerosis, thromboangiitis obliterans, thoracic outlet syndrome, neurological disorders; idiopathic is diagnosis of exclusion and waiting	p. 226
Scleredema adultorum	Diabetes mellitus	p. 320
Sclerosis	Systemic sclerosis, dermatomyositis, porphyria cutanea tarda, scleromyxedema, scleredema	p. 222
Spider nevi	Hepatic disease, Osler–Weber–Rendu syndrome	p. 451
Striae	Pregnancy, Cushing syndrome, corticosteroids (systemic, topical or inhaled), body building (anabolic steroids, sudden weight gain), Marfan syndrome	
Sweet syndrome	Various forms of leukemia, especially hairy cell leukemia; also multiple myeloma	p. 249
Telangiectases	Sun-damage, rosacea, CREST syndrome, systemic lupus erythematosus, dermatomyositis, Cushing syndrome (cheeks), telangiectasia macularis eruptiva perstans (mast cell disease), Osler–Weber–Rendu syndrome, essential telangiectasia, carcinoid syndrome, radiation dermatitis, diabetes mellitus (necrobiosis lipoidica), hepatic disease, poikiloderma (see there)	p. 452

Continued Table III.21 ▶

Table III.21 · Continued

Skin findings	Associated systemic disease	
Thrombophlebitis, migratory (not in area of chronic venous insufficiency)	Carcinoma of the pancreas, pancreatitis, mesothelioma	p. 557
Tongue changes		
Hairy tongue	HIV, chronic diseases; usually normal variant	p. 161
Geographic tongue	Psoriasis	p. 492
Fissured tongue	Melkersson–Rosenthal syndrome	p. 492
Macroglossia	Down syndrome, amyloidosis, acromegaly, hypothyroidism	
Glossitis	Vitamin or mineral deficiency, anemia	
Trichilemmomas, multiple	Cowden syndrome with high risk of breast carcinoma, increased risk of thyroid and gastrointestinal carcinomas	p. 366
Vascular malformations	Underlying cerebral, ocular, musculoskeletal or cardiovascular problems (Sturge–Weber syndrome, Klippel–Trenaunay–Weber syndrome)	p. 449
Xanthomas	Exclude elevated cholesterol or triglyceride levels	p. 314
Normolipemic	Apolipoprotein variants, plant sterols, storage disorders, trauma, paraneoplastic markers (diffuse normolipemic plane xanthoma), macrophage disorders (papular xanthoma, xanthoma disseminatum)	p. 315
Xerostomia (dry mouth)	Drugs, Sjögren syndrome, systemic sclerosis, vitamin deficiencies, anemia, uremia, infections with fever	p. 225
Yellow skin	Diabetes mellitus, myxedema	p. 319
With yellow sclerae	Hepatitis (viral, toxic), biliary obstruction	p. 66
Yellow-brown	Hemochromatosis (bronze diabetes)	p. 316

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Quick Check A—Practical tips for the initial examination

Skin findings—Often overlooked points that can be very helpful

- General skin status
- Changes in skin elasticity
- Type of lesion (p. 17)
- Distribution and pattern of lesions
- Linear or bizarre patterns
- Apparent level of skin disease
- Pigmentary changes
- Evolution and healing of lesions
- Köbner phenomenon (p. 352)
- Skin findings on scalp, intertriginous regions, and feet
- Mucosal changes
- Nail changes
- Hair loss or increase (hypertrichosis); types of hairs; changes in color
- Vascular status; peripheral perfusion
- Lymphadenopathy or fever
- Abnormal odor

Simple and immediately employable tests

- ***Note:*** These tests can lead to rapid diagnosis and are cost effective.
- **Palpation:** Consistency, movability, adherence, borders, painful or tender, pulsation? Skin warm/cold, moist/dry? Peripheral pulses?
- **Remove crusts:** Bleeding, base of wound, extent of lesion
- **Express secretions:** Nature, consistency, color, odor, amount
- **Remove scales or crusts:** Easily removed, firmly attached, evidence for underlying tumor
- **Tug on hairs:** Easily breakable, readily removed, hair bulb visible
- **Insert probe :** Can use to explore sinus tract
- **Provocation tests:** Manipulate lesions by rubbing, pressing, applying heat or cold, having patient exercise
- **Look for or induce specific clinical signs:** Dermographism, Auspitz phenomenon, pathergy (p. 257), Nikolsky phenomenon (p. 230), Darier sign (p. 341)
- **Enlarge** with hand loupe or dermatoscope
- **Wood's light examination** (p. 23)
- **KOH examination**
- **Curettage** (p. 654)
- **Punch or tangential biopsy** (p. 655)

Note: See the inside back cover for additional tips.

Quick Check A (continued)—Practical tips for the initial examination

History—Crucial but often overlooked questions

- ***Note:*** Important for the doctor–patient relationship, essential to diagnosis and treatment, help avoid mistakes.
- **Start:** When and where did the skin lesions start? Initial appearance?
- **Symptoms:** Pain, burning, itching?
- **Course:** How have the lesions developed and spread?
- **Treatment:** What has already been tried? Has it helped?
- **Recurrence:** Have you ever had anything like this before?
- **Anywhere else:** Do you have symptoms anywhere else (e.g., mouth, genitalia, feet, toenails)?
- **Associated findings:** Fever, weight loss, chills?
- **Medications:** What do you take, including vitamins, tonics, herbal remedies?
- **Anyone else:** Do any other family members or contact persons have similar skin problems?
- **Atopy and allergy:** Do patient or family members have a positive history of atopic dermatitis, hay fever, asthma, or other allergies?
- **Geography:** Where are you from? Have you traveled in the past 6 months?
- **Quality of life:** How is this disease influencing your life?
- **Psychosocial situation:** Partner, children, job, school, depression?
- **What do you think caused your skin disease?** Always ask; you may learn a lot about the patient and may even get the answer!

Quick Check B—Diagnosis not clear? What next?

Have you considered these diagnoses?

- Artifacts
- Borreliosis
- Bullous dermatoses
- Contact dermatitis to not obvious allergens—sunscreens, corticosteroids, nail polish
- "Dermatitis"—DD: Psoriasis, tinea, atopic dermatitis, seborrheic dermatitis, nummular dermatitis, allergic or irritant contact dermatitis
- Erythema multiforme
- Genodermatoses
- Herpes simplex
- HIV/AIDS associated dermatoses
- Langerhans cell histiocytosis
- Leprosy
- Lupus erythematosus
- Mastocytosis
- Mycosis fungoides
- Nevi of different types
- Normal variations
- Occupational dermatoses
- Paget disease (mammary/extramammary)
- Paraneoplastic markers
- Parapsoriasis
- Polymorphous light eruption
- Porphyria
- Psoriasis—inverse, pustular
- Pyoderma gangrenosum
- Reticulated erythematous mucinosis (REM)
- Sarcoidosis
- Skin signs of internal disease
- Sweet syndrome
- Syphilis
- Tinea versicolor
- Urticarial vasculitis
- Vasculitis

Possible etiologies

- Allergy
- Arthropod assault (insect bite or sting)
- Artifact
- Autoimmune disease
- Bacterial infections (including tuberculosis, leprosy, atypical mycobacteria, *Neisseria gonorrhoeae* and chlamydia)
- Drug reaction
- Endocrine disease
- Foreign body
- Fungi (including subcutaneous and deep infections)
- Genetic defect
- Granulomatous process
- Infestation (scabies)
- Malignancy—cutaneous or underlying
- Metastasis
- Nutritional disorder
- Parasites (including tropical disorders)
- Photosensitivity
- Psychosomatic disorder
- Spirochetes (borreliosis, syphilis)
- Toxic-irritant processes
- Vasculitis
- Viral infections

Have you asked about . . .?

- All important points in history (see Quick Check A)
- Alternative therapies
- Anxiety about skin disease
- Cosmetics
- Depression
- Dietary habits
- Gynecologic signs and symptoms (vaginal discharge, odor)
- Hobbies
- Immunosuppression (iatrogenic, diabetes mellitus, HIV/AIDS)
- Malaise, general wellbeing
- Neurologic, ophthalmologic and ENT signs and symptoms
- Outdoor activities (garden, forest, water)
- Pets

Have you looked for . . .?

- Burrows (scabies)
- Clues from the nails, hair, mouth, teeth, eyes, feet, axillae and anogenital region
- Cryoglobulinemia
- Entry sites (interdigital mycosis)
- Eosinophilia
- Focus of infection (dental abscess, chronic sinusitis)
- Leukocytosis
- Lymphadenopathy
- Malignancy
- Onychomycosis or tinea pedis
- Other skin findings
- Paraproteinemia
- Serologic markers (syphilis, borreliosis, other infections, autoimmune diseases)

Have you already . . .?

- Given up? Don't; there is plenty more to do!
- Carefully listened to patient?
- Consulted experienced colleagues?
- Covered the lesions (Unna boot) to eliminate manipulation?
- Discarded working diagnosis and tried to formulate new differential diagnostic list?
- Done cultures (skin, urine, stool)?
- Exactly described skin disease and thought of disorders it resembles? (often leads to right diagnosis)
- Done exposure test (foods or medications) as part of allergy work-up?
- Reviewed history again? Is it plausible?
- Looked at Quick Check A?
- Observed the lesions over time, with or without therapy?
- Patch testing?
- Had pets examined by veterinarian for ectoparasites?
- Postulated most likely diagnoses?
- Considered predilection sites—which diseases usually appear at the affected sites?
- Talked to referring physician or family doctor?
- Tried to imagine the lesions at other body sites?