Thieme Clinical Companions

Dermatology

W. Sterry
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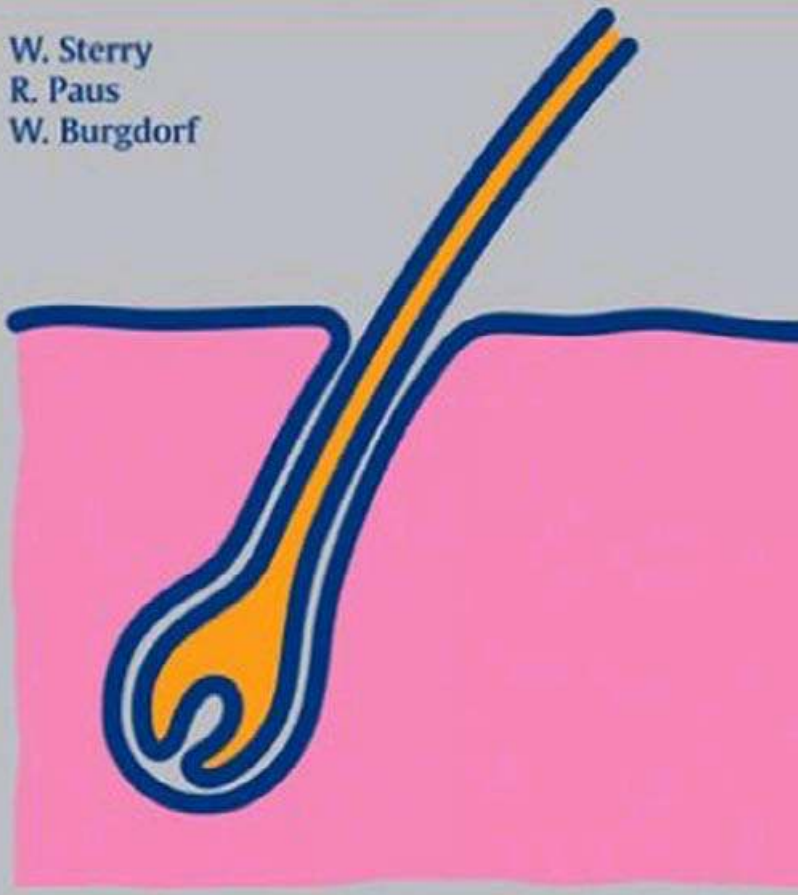

Thieme

Contents

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Dermatology

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Preface

We are happy to present you with our new book *Dermatology* in the *Thieme Clinical Companions* series. A similar text has appeared in five German editions since 1987 and been highly successful. The goal of this book is to present everything one needs to diagnose and treat most cutaneous diseases in a compact, "one-stop" resource, carefully edited by three experienced dermatologists. The therapeutic options represent best practice internationally and reflect the diversified experience of three dermatologists, one of whom trained and worked in the USA for 20 years.

The contents have been extensively reviewed with the help of a number of colleagues listed on the title page. Some of them have provided additional input for the English version, including Drs. Peter von den Driesch, Bertold Rzany, Christiane Voit, and Margitta Worm. In addition, Dr. Maja Hoffmann helped with the differential diagnostic considerations in the last chapter. We would especially like to thank Dr. Gerd Wolf, who provided constructive criticism and detailed information on topical therapy.

Mr. Stephan Konnry at Thieme International guided the writing and production of this text. He was helped by Dr. Cliff Bergman and Dr. Christiane Brill-Schmid. We thank all three individuals for their cooperative spirit and valuable input.

We hope that you will enjoy reading this *Clinical Companion* as an introduction to dermatology and, moreover, that you find it helpful, if not indispensable, in your clinical training and practice. We are eager to hear from you, with complaints, constructive suggestions, or even praise.

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1 Introduction to Skin Biology

1.1 Overview

The skin is not only the largest organ of your body, but also the heaviest: it has a surface of 1.5–2 m^2 and contributes $^1/_7$ to $^1/_6$ of body weight. The skin provides a fascinating "theater of life" in which—in contrast to all other organs—you can directly watch, dissect, and manipulate key principles of biology and pathology *in action*, and where the environment and an individual's way of life leave unmistakable traces for those who know how to read them.

Subjecting the skin to a professional examination, therefore, can reveal many invaluable clues about your patient's general well-being; internal disease; social, cultural, and eating habits; psychological disturbances; and occupation. All this provides medically very useful information, even when dermatology is not your main field of interest.

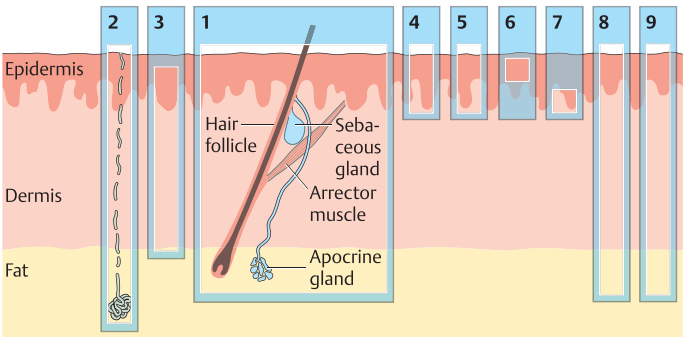


Fig. 1.**0** · Overview of skin, providing orientation for Figs. 1.**1–9**.

1.2 Functional Anatomy

The skin has many more crucial functions than we realize in daily life. It is therefore is not surprising that the loss of as little as 20% of your skin can condemn you to death. Architecturally, our skin is a constantly remodeled, intricately perfused and innervated three-layered structure (*epidermis, dermis, subcutis*). Specialized skin "appendages" protrude from the skin (*hair, nails*) or are embedded in it (*sweat and sebaceous glands*). Two special structures—*hair follicles* and *mammary glands* (derived from epidermis)—mark us as mammals. Figure 1.**0** provides an overview of the parts of the skin that are illustrated in the subsequent figures. Figures 1.**1**, 1.**2** are photomicrographs showing normal skin from a hair-bearing region and from the thickened palmar skin with sweat glands. Figure 1.**3** provides a three-dimensional view, showing how the epidermis and dermis interdigitate.

These basic skin layers are complemented and joined by three dense networks that link our skin to the rest of our body: *lymphatic system*, *blood vessels*, and *cutaneous nerves*. These networks provide proper nutrition, oxygen supply, and removal of toxic

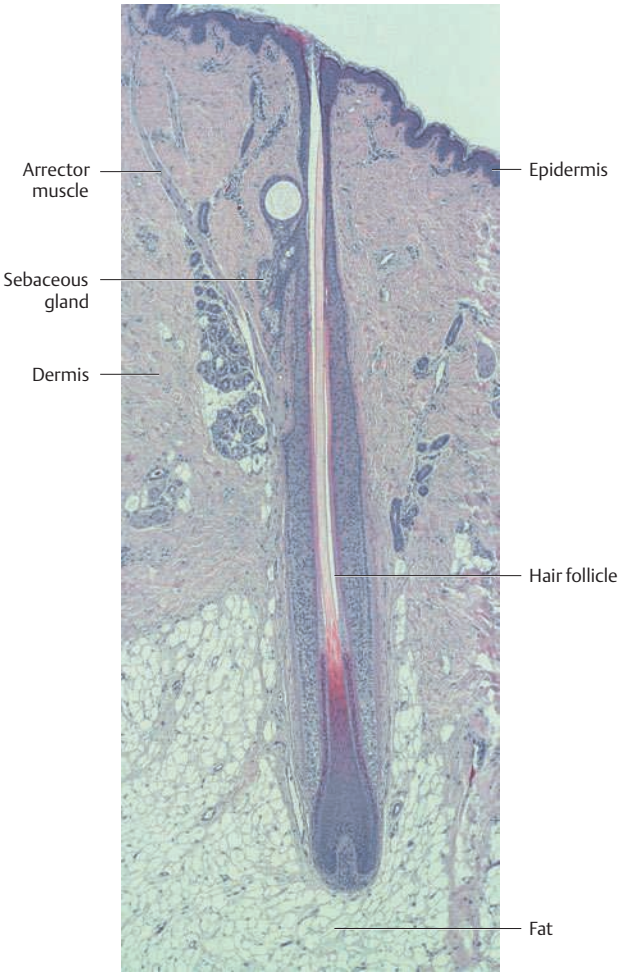


Fig. 1.**1** · Normal skin from hair-bearing area. Hematoxylin and eosin (H&E) stain.

products from our skin, and are vital for fluid balance, skin sensation, and proper skin immune responses. They also integrate the skin into very complex neuro-endocrine-immune networks essential for the organism's survival.

All organisms must have an outer covering that interacts with the environment, helping them to survive multiple exogenous threats while maintaining their structural integrity, be it the cell membrane of an amoeba or the skin of a human. Potential

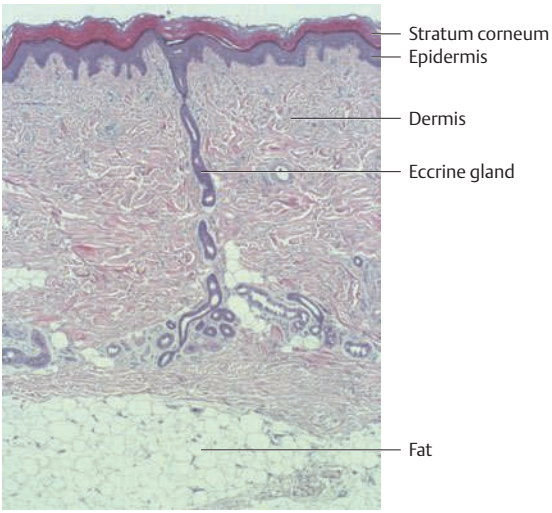


Fig. 1.**2** · Normal skin from palm. H&E stain.

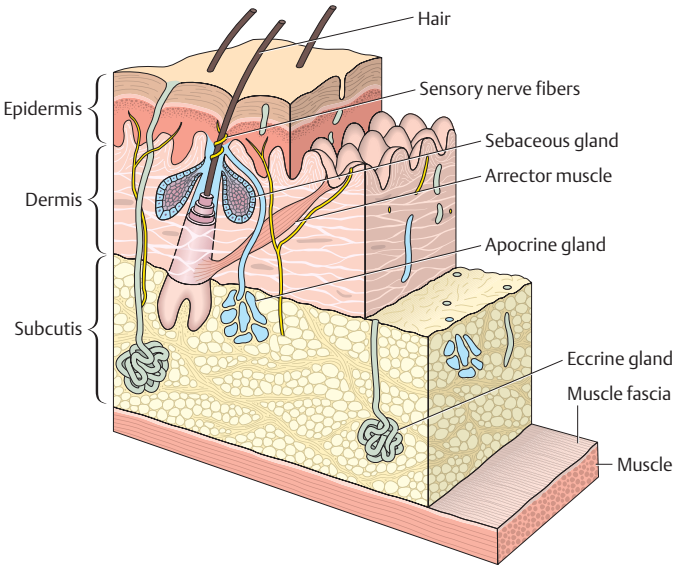


Fig. 1.**3** · Three-dimensional diagram of skin. Note how epidermis and dermis interdigitate.

dangers include UV radiation and free radicals which can damage DNA and cell membranes, dessication, overheating, mechanical trauma, infectious agents, toxins, and chemical irritants.

At the same time, this outer barrier must be flexible enough to allow for growth and movement of the organism it protects. In addition, it must also execute vitally important sensory functions by registering environmental signals (by the generation of pain and itch signals) so the organism can adequately respond to them (e.g. by flight reaction, shifting balance and position, striking out at an attacking force, or scratching away an unwelcome skin guest). This barrier also is vital for safeguarding the organism against the deadly loss or overaccumulation of heat and fluid. The skin is also the body's largest water storage site ($^1/_3$ of your total fluid is contained in the skin), and constitutes your major energy reserve (skin fat provides up to 40 days of energy reserve).

The gel-like, collagen-rich dermis, which underlies, supports, and nourishes the epidermis, is densely vascularized by two very extensive, interconnected, and well-innervated vascular networks: one at the border to the epidermis (*papillary plexus*), and one at the border of the subcutaneous fat (*reticular plexus*). These are complemented by a system of lymphatic vessels, whose inherited malformation or acquired malfunctioning results in massive skin edema due to an imbalance between fluid influx and efflux.

This very extensive skin perfusion system harbors about $^1/_4$ of your circulating blood (more than your brain!), and the total length of skin capillaries has been estimated as 240 km. This guarantees ample access of erythrocytes, nutrients, humoral blood components, and immune cells to the skin. This perfusion system is also critical for thermoregulation, since vasodilatation or vasoconstriction in a large area of skin rapidly alters skin and body temperature. Thermoregulation and fluid balance are further facilitated and optimized by about 2.5 million specialized sweat glands, derived from epidermal invaginations, most of which are located in the skin of the palms, soles, axillae, and scalp. Under extreme circumstances, their activity can generate a loss of up to 5 liters of fluid per day.

The sensory function of the skin is refined and sensitive. Our skin can discriminate differences in weight of as little as 0.005 g, react to temperatures between – 18 °C and +44 °C, and send nerve impulses (action potentials) with a velocity of 2 m/s to the spinal cord and brain. This results from a dense network of interconnected free nerve fibers and specialized sensory receptors that populate the epidermis, most densely in the most touch-sensitive skin regions. This constantly remodeled neural network is generated by neurons located amazingly far away from the skin, for example in the dorsal root ganglia. These neurons feed skin-derived signals into the sensory cortex, where some individual skin regions (such as lips, fingers, tongue, genitalia) are heavily over-represented. Hair shafts with their generous neural supply serve as particularly sensitive touch receptors; just try slightly moving a hair and notice how you can record the lightest touch. Free nerve endings, specialized tactile organelles, intraepithelial Merkel cells and a plethora of receptors sensitive to pressure, heat, cold, and vibration complement the sensory armamentarium of the skin.

Finally, our integument serves as a crucial instrument of social and sexual communication, generates tools of defense, movement, and attack (hair, nails, claws, hoofs), and operates as an excretory organ: the skin removes unwanted substances by packaging them into dead cells (squames = corneocytes, hair shaft cells = trichocytes) which are then shed, and by excreting noxious agents with sweat and sebum.

1.3 Epidermis

The epidermis, a very thin but tough cornified (i. e. keratinized) avascular outer layer, provides the skin's direct interface with the environment (Fig. 1.**4**). It is composed primarily of keratinocytes along with smaller populations of two other resident cells—melanocytes and Merkel cells. In addition, there are migratory cells moving in and out of the skin, serving as outposts of the immune system (Langerhans cells, intraepidermal T cells) (Fig. 1.**5**, Table 1.**1**). When necessary, as during a bacterial infection, a rapid influx of (aggressive) neutrophils into the epidermis is triggered by the keratinocytes, thus producing pustules, and—not uncommonly—undesired neutrophil-induced tissue destruction alongside that of the insulting infectious agents.

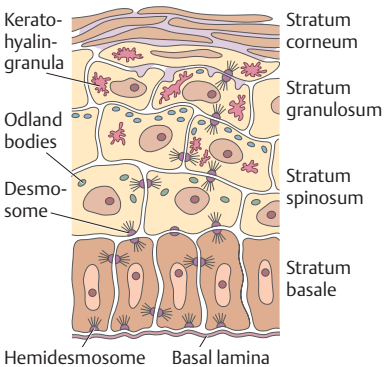


Fig. 1.**4** · Layers of epidermis.

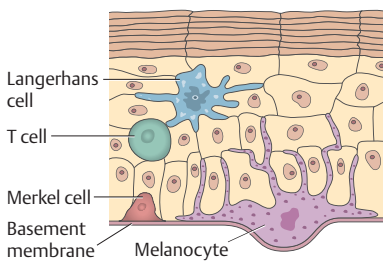


Fig. 1.**5** · Cells of epidermis.

The outermost layer of the epidermis is the *stratum corneum*. It is made up of terminally differentiated, dead keratinocytes (corneocytes). These are perfectly sculpted, flattened hexagons whose complex geometric shape allows for optimal packing. Corneocytes are nonvital epithelial cells that have lost and digested their nucleus, and are loaded with keratin filaments in an amorphous protein matrix, which is held together by the cornified envelope. They are glued together like bricks in a wall by a mortar rich in lipids (ceramides, cholesterol, free fatty acids). According to one estimate, a normal person sheds 50–60 billion corneocytes per day, supposedly adding up to a total annual loss of 4 kg; this amount is dramatically up-regulated in hyper-

proliferative skin diseases such as psoriasis. Many of these shed corneocytes end up as the "house dust" that settles in your home and work environments.

The stratum corneum is a semipermeable, hydrophobic layer that not only repels microorganisms, water, and chemicals, but also shields the layers of dividing keratinocytes deeper in the epidermis (basal cells) from UV light damage. It is covered with an acidic protective film generated by sweat, sebum, and decomposition products of the rich residential microflora which keeps the skin surface moist and smooth, and hinders the growth of pathogenic microorganisms. Additional defense against infection is provided by antimicrobial peptides (e.g. human β-defensins) that are generated by epidermal keratinocytes and stored in the stratum corneum. Thus, even in the absence of the key cellular protagonists of adaptive immunity (T cells, Langerhans cells), a healthy stratum corneum and its protective acidic film (pH 5.7) provide a tough penetration barrier to potential invaders, along with very effective innate immunity.

The process of terminal differentiation of epidermal keratinocytes originates in the basal layer of the epidermis, and ultimately in a pool of epithelial stem cells located in the bottom of the so-called *rete ridges*. The actual thickness of the epidermis varies widely, from 0.05 mm on the eyelid to 1.5 mm on the sole. Epidermal thickness is the net result of a carefully controlled equilibrium between keratinocyte proliferation in the basal layer, keratinocyte terminal differentiation in the stratum spinosum and granulosum, programmed epidermal cell death (keratinocyte apoptosis), and corneocyte shedding from the stratum corneum. Inherited or acquired deviations from the normal in any of these four parameters greatly disturb epidermal homeostasis and lead to scaling, thickening (lichenification), thinning (atrophy), or tumor formation (viral warts).

There are several types of cell junctions in the epidermis. Each plays an important pathophysiologic role in holding the cells together and allowing them to communicate.

- Desmosomes: many different proteins are involved in the complex structure. Among the most important are the desmogleins (Fig. 1.**6**). Antibodies against desmosomal proteins cause pemphigus (p. 229), while staphylococcal scalded skin syndrome (p. 75) with massive loss of epidermis is caused by a bacterial toxin damaging a desmoglein.
- Adherent junctions: connect actin filaments and help with signaling as well as adherence.
- Gap junctions: formed by connexins; create connecting pores which allow rapid transport of materials or signals between two cells; defects can cause deafness and skin diseases.

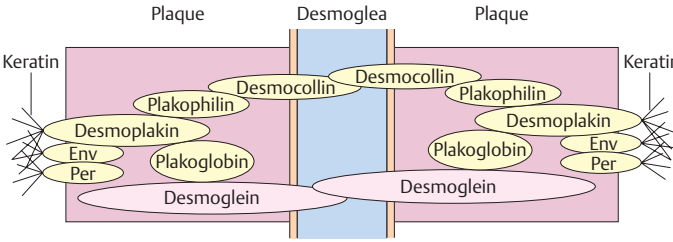


Fig. 1.**6** · Desmosome, showing complex way in which two keratinocytes are held together. Env = envoplakin; Per = periplakin (Image courtesy of Michael Hertl MD, Marburg, Germany).

Roughly one in ten cells in the basal layer of the epidermis is a melanocyte. These cells, derived from the neural crest, produce melanin, package it in organelles (*melanosomes*) and transfer it via long dendrites to epidermal and hair follicle keratinocytes so as to give color to the epidermis and hair. In both structures, melanin not only protects the skin against UV damage and serves as a free-radical scavenger, but also sends important social, psychological, and sexual communication signals to other members of the community. These are so important in human society that an entire industry caters to the modification of hair colors and to a lesser extent skin colors. Apocrine glands complement the social communication activities of the skin by sending invisible olfactory signals (pheromones) that, often only subconsciously, register as "very attractive" or "deeply repulsive." Never underestimate the profound impact a skin disorder can have on an individual's normal functioning in society and self-esteem, even if the disorder appears only trivial to you.

1.4 Hair

In most of our mammalian ancestors, the protective functions of the epidermis were further enhanced by a widespread, dense hair coat. These heavily melanized keratin fibers—being rigid and extremely resistant to wear and tear—provide additional protection against UV light and chemical damage, trauma, and attack; impede the access of airborne insects to the skin; and provide dramatically enhanced properties for skin insulation and thermoregulation (the latter so efficiently that we transform the hair shafts of other mammals into wool sweaters, or even wear fur coats). Furthermore, hair shafts disperse sebum, sweat, and odors over the skin surface, and transport cellular debris and resident parasites out of the follicular canal.

All of these functions of hair are still valid in humans today. The approximately 100 000 scalp hair follicles predominantly serve decorative and communicative functions. Our scalp and beard hairs send widely visible, immediately registered optical signals of social, sexual, cultural, psychological, or even political content to our fellow humans. Not surprisingly, therefore, sudden hair loss or excessive hair growth in cosmetically sensitive skin regions is often a catastrophic event, as the affected individual's psychological equilibrium, self-esteem, and well-functioning in society can be deeply threatened. Though this is often overlooked and underestimated, a similar argument can be made for abnormal nail growth and overactive sweat glands; discolored and misshapen nails, a sweaty shirt, and wet palms all send unwelcome signals and cause distress.

Moreover, we have recently come to understand that the pilosebaceous units that are distributed very irregularly and in strikingly different variants (e.g. vellus, terminal, pubic hair) throughout our entire integument—with very few notable exceptions such as palms and soles—not only tirelessly generate important epithelial skin products (hair shafts, sebum), but also are formidable endocrine factories. The most productive and versatile epithelial stem cells of skin also reside in a special region of the hair follicle's outer root sheath, the *bulge*. The entire epidermis can be regenerated from this source alone. In hair-bearing skin, the numerous hair follicles actually serve as the "bone marrow of the skin," from whose stem cell population skin regeneration (including skin repigmentation) begins. While epithelial stem cells in the epidermis and the hair follicle are the irreplaceable source of epidermal renewal and hair follicle cycling, they and their direct progeny also are subject to malignant degeneration—basal cell carcinomas are usually derived from follicle elements. Remarkably, most recent evidence suggests that the hair follicle epithelium even harbors stem cells derived from the neural crest, from which both neurons and melanocytes can be

generated experimentally, while mesenchymal stem cells have been identified in the connective tissue sheath of the hair follicle.

1.5 Basement Membrane Zone

The ridge structure of the avascular epidermis is mirrored by and intertwined with a ridge-like counterpart (*papillary dermis*) in the underlying, much thicker, highly flexible and extremely elastic support layer, the dermis. This central layer of the skin bestows the remarkable mixture of structural firmness and flexibility that is so characteristic of mammalian skin, and is the chief component of leather used in clothes, shoes, and handbags. Together with the basement membrane that links epidermis and dermis, rete ridges and dermal papillae ensure good cohesion of the upper two skin layers, even under conditions of extreme stretch and shear.

The basement membrane zone (BMZ) has a surprisingly intricate architecture (Fig. 1.**7**). It is jointly generated by epidermal keratinocytes and dermal fibroblasts, and consists of extracellular matrix (type IV and type VII collagen, laminins, nidogen, glycosaminoglycans) and hemidesmosomal components (integrins, bullous pemphigoid antigens, plectin), various adhesion molecules, and a bewilderingly complex array of structural and signaling interactions between an ever-growing number of molecular players. This complexity may result from the fact that the BMZ serves as a very efficient attachment system for the epidermis, while still allowing it full access to nutrients, oxygen, antibodies, complement, and trafficking immune cells arriving via the dermis. Invading microorganisms (and topically applied therapeutic substances) must pass through the BMZ, while noxious products of epidermal metabolism and excess intraepidermal fluid must be removed into the circulation.

Thus, the BMZ represents an entire system of dermoepidermal anchorage, skin flexibility, and elasticity, as well as epithelial–mesenchymal communication and trafficking. Not surprisingly, it is in this dynamic, constantly remodeled dermoepidermal interface where most inflammatory skin diseases manifest themselves, and where defects in individual BMZ components result in a large array of therapy-resistant genodermatoses.

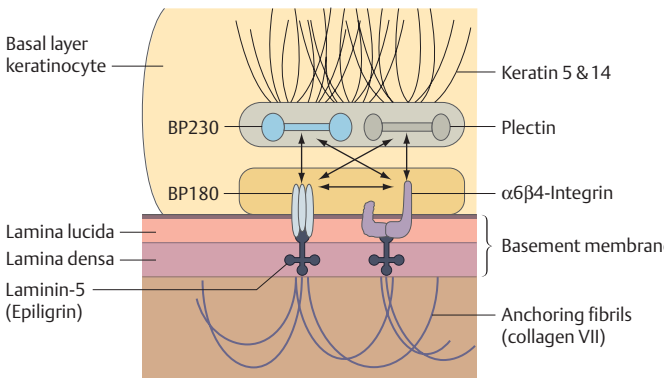


Fig. 1.**7** · Basement membrane zone with hemidesmosome and extracellular matrix components (Image courtesy of Michael Hertl MD, Marburg, Germany).

1.6 Dermis

The adjacent dermis that underlies the BMZ is best viewed as a densely populated, well-hydrated, and exquisitely perfused mucopolysaccharide gel with added elastic properties (due to a network of interwoven elastic fibers, which degenerates with increasing sun damage and age), in which many interacting, different cell populations are suspended. Dermal fibroblasts are the key resident cells of the dermis. The location of the mesenchymal stem cells from which these fibroblasts originate is unclear. One likely possibility is the hair follicle connective tissue sheath, whose fibroblast populations may be quite important during cutaneous wound healing, as they may serve as a cell pool for the formation of granulation tissue.

The dermis harbors a rich network of nerves with free nerve endings in the epidermis, a generous network around hair follicles and specialized receptors (Fig. 1.**8**). In addition, the eccrine glands course through the dermis, before emptying sweat onto the epidermal surface. Finally there are complex networks of vessels (Fig. 1.**9**).

Fibroblasts are complemented by migratory immune cells, including the relatively sessile mast cells (preferentially located around skin nerves, blood vessels, and hair follicles), professional phagocytes (macrophages, also called histiocytes) and dermal dendrocytes (most of which may represent a subpopulation of Langerhans cells). These cells form yet another important line of defense against invading microorganisms, where innate and adaptive immunity meet. Mast cells and macrophages are also intimately involved in regulating fibroblast functions and thus fully participate in dermal remodeling under physiological and pathological conditions.

The abundant supply of resident dermal mast cells and macrophages offers additional, immediately operative, innate immune defenses once an infectious agent has trespassed the epidermal defenses, an insect bite has injected undesired material straight into the dermis, or skin trauma has torn an open pathway into the epidermal

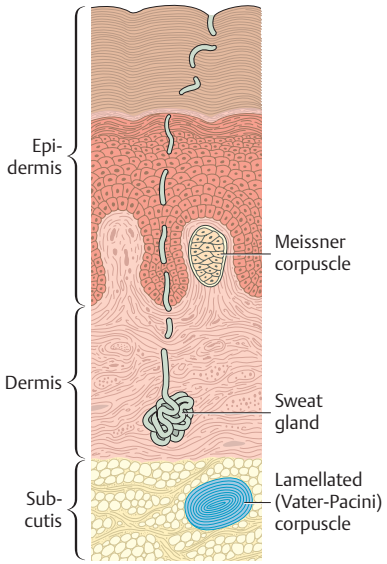


Fig. 1.**8** · Specialized nerve receptors in the skin, shown along with an eccrine sweat gland.

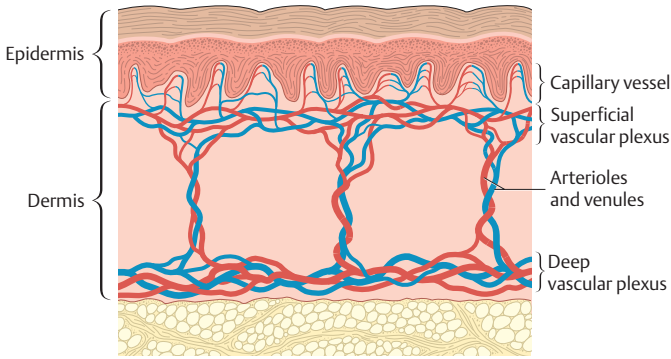


Fig. 1.**9** · Vascular network of the skin.

immune defenses, suddenly exposing the much less well-defended dermis and subcutis to a hostile environment. These dermal mast cells and macrophages secrete a wide array of compounds that very rapidly up-regulate defensive (yet, often enough, also autodestructive) immune responses geared to contain and locally restrain invading infectious agents until the protagonists of specific immunity (Langerhans cells, T cells, and possibly dermal dendrocytes) have been called into action and have become fully operative, and/or until additional innate immune defenses (neutrophils, eosinophils) have been attracted from the skin vasculature.

Recent research shows, however, that the historical distinction between "innate" and "acquired" immunity, in real life and especially in the skin, is much more blurred than our love for simplistic categorization has led us to believe, and that both arms of the skin's immune system are intricately interwoven during essentially all major immune responses our skin can launch. A newly emerging related concept is that of the *dermal microvascular unit*, which consists of intimate and multidirectional interactions between endothelial cells, fibroblasts, smooth muscle cells, perivascular mast cells, and dermal dendrocytes with immune cells that exit from the cutaneous vasculature. This dermal microvascular unit is responsible for far more than the supply of oxygen and nutrients to the skin; it deeply influences immune cell trafficking, vessel tone, and many other aspects of normal skin function. It is here where many inflammatory skin diseases run through critical stages of their pathogenesis, and may be therapeutically targeted most effectively.

1.7 Subcutis

If you are not obese or anorectic, about 10% of your body weight is contributed by the third, deepest and usually thickest layer of your skin—the *subcutis* or subcutaneous fat. The predominant cells of the subcutis are *adipocytes*, highly specialized mesenchymal cells turned into a storage site for fat. The subcutis provides thermal insulation, serves as a crucial energy store, and acts as an important shock absorber for underlying organs and structures. This highly vascularized tissue is also a veritable hormone factory, where most steroid hormones can be metabolized or synthesized, and numerous neurohormones and neuropeptides are generated. Adipocytes also

regulate food uptake, general energy metabolism, and resistance or sensitivity to insulin, primarily by the secretion of leptin and adipokines.

1.8 Neuroendocrine-immune Networking

These secretory activities of adipocytes lead us to one of the most fascinating aspects of skin biology: the full integration of our integument into the neural, immune, and endocrine networks that transcend and unite all of our individual organ systems and whose cooperation and coordination ultimately guarantee both our own survival as individuals and that of the human species.

How critical this level of full skin integration is for the entire organism has already been alluded to above, when we discussed the importance of skin as an organ of thermoregulation; sensation; energy, electrolyte and fluid balance; defense against infection; and social communication. Conversely, the skin cannot exist without adequate perfusion, nutrition, and oxygenation. We have learned that all this is largely accomplished by means of intricate vascular and neural networks that connect our skin to rest of the organism and serve as high-velocity, high-capacity conduits for oxygen, nutrients, toxins, mediators of anaphylaxis, neuropeptides, neurotransmitters, action potentials, immune cells, humoral immune components, antigens, hormones, eicosanoids, growth factors, cytokines, and excess fluid (among other things).

But our skin engages in more than networking via conduit systems. It also dispatches individual cells to distant organs, where they elicit responses in other defined cell populations, which then migrate into the skin to execute their characteristic functions. This is exactly what happens when allergic eczema develops in response to environmental antigens, or other type IV immune responses are launched (for example, against infectious agents): intraepidermal Langerhans cells take up, process, and present the antigen in question, and travel via skin lymphatics to the nearest regional lymph node, where they have the highest chances of encountering a T lymphocyte with just the right T-cell receptor that recognizes the antigenic peptide presented by the Langerhans cell's MHC class II molecule. If this most efficient of all antigen-presenting cells finds such a lymphocyte with a cognate T-cell receptor, and appropriate T-cell activation signals are provided (including so-called co-stimulatory ones), that T-cell proliferates, leaves the lymph node and eventually finds its way into the epidermal region that had dispatched Langerhans cells to call for help.

Similar trafficking and recruitment loops have been postulated for T-cell responses to skin tumor antigens, and numerous inflammatory skin diseases or inflammatory skin reactions are based on this basic immunocutaneous loop.

Over the past two decades, it has become clear that keratinocytes not only sport innate immune defenses of their own and are the site from whose midst the above loop originates: they also in crucial secretory activities that orchestrate cutaneous inflammation in response to, for example, allergens, irritants, microorganisms, and damage by UV radiation. By secreting a wide spectrum of agents from proinflammatory (TNF α, IL-1, chemokines, IFN-γ) to anti-inflammatory/tolerogenic (IL-10, TGFβ1, or IL-1RA) the skin epithelium thus profoundly influences whether a potent inflammatory response is triggered or suppressed, and which type of immune response is favored (e.g. type I or type IV). Other protagonists of the skin immune system, such as mast cells and macrophages, contribute to these long-neglected "unspecific" but important immunomodulatory controls that regulate immune responses within and far beyond the skin. Thus the skin has become appreciated as a central player even in systemic immunity, not just a passive battleground for the activities of T and B cells, as it had long been considered.

To complicate things further, immune responses in the skin and elsewhere in the body are also influenced by a plethora of additional, intracutaneously released or generated compounds that are not generally considered as primary immunomodulators. This includes the release of neuropeptides and neurotransmitters from skin nerve endings during neurogenic inflammation as well as the long unsuspected, yet powerful, endocrine and neuroendocrine activities of the skin. We now know that the skin, and most notably its pilosebaceous units, are active in the synthesis and metabolism of key steroid hormones such as androgens, estrogens, and vitamin D_3 derivatives. Moreover, they also generate hormones such as corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), β-endorphin, cortisol, prolactin, and melatonin, and many other signaling molecules traditionally associated with extracutaneous functions of the nervous, hemopoietic, hepatobiliary and/or endocrine systems. Numerous cell populations in the skin are now known to also express functional, cognate receptors to all these secreted (neuro-) endocrine signals. This makes it much less of a mystery why psycho-emotional stress and hormonal changes can trigger so many skin diseases, change their course, or modulate their response to therapy.

To give one final example, it is now clear that the skin is an abundant source for nerve growth factors (neurotrophins). These are generated in quantity by the skin epithelium, not only in order to guide its own innervation during skin development and hair follicle cycling, but also to regulate its own growth, regeneration, and death in an autocrine and paracrine manner as well as to modulate the skin immune system (especially mast cell functions) and skin repair.

Thus, whatever happens in the skin immediately becomes part of wider neuroendocrine–immune networks, which can affect far-distant regions of our body and systemic response patterns. Conversely, numerous extracutaneous events, for better or worse, tightly link our integument via the above networks into what happens elsewhere. Moreover, the skin itself locally produces and uses classical signals of endocrine, neuroendocrine, neural, and immune communication to regulate its own growth, death, differentiation, repair, and/or metabolic activities.

1.9 Outlook

At the end of this brief introduction to the fascinating universe of skin biology, reflect a little longer on what we really know about the functions of our skin.

It is important to remember that we have come to understand these functions gradually, step by step, largely by observing what happens when normal skin functions are compromised or lost, are never fully acquired in the first place, or are overactive. For example:

- The skin's crucial role as a defense against infection system and an immune organ becomes evident in viral, bacterial, and fungal skin infections, as well as in allergic and autoimmune skin diseases.
- The skin's metabolic importance is demonstrated by the dire consequences of vitamin D deficiency due to inadequate sun exposure.
- The development of skin carcinoma as a result of excessive sun exposure or defective DNA damage repair systems highlights the role of the skin in protection against UV radiation.
- Vitiligo, albinism, and hair loss illustrate the consequences of changes in our social communication image.
- Chronic pruritus and peripheral neuropathy in diabetic patients point us to the sensory functions of skin.

- Skin ulcers, xerosis, excessive scaling, and disorders of keratinization such as the ichthyoses remind us of the crucial barrier function of our integument.

Yet, if our concepts of skin functions are essentially based on a "damage assessment strategy," we are likely to have missed many additional functions whose failure or absence does not cause easily apparent skin alterations. We still need to better comprehend the functional significance of the neuroendocrine–immune networking of the skin. Thus, the quest for understanding the full complexity of skin functions and skin physiology has only just begun.

And this is where *you* come in: When you use this book as your personal assistant to help you diagnose and treat defined skin diseases, do not miss the great opportunity that presents itself when you carefully look at, and reflect upon, the signals that the skin of your patient is trying to send you.

Remember: This is biology talking to you—just listen!

Table 1.1 · **Cellular protagonists in the skin**

Cell	Location	Function	Comments
Keratinocytes	Epidermis Hair follicle Nail apparatus	Barrier, UV protection, antimicrobial defense, secretion of enzymes and regulatory molecules, major endocrine and metabolic activity	Terminally differentiate into nonvital hexagonal corneocytes; epithelial stem cells located in bulge region of the hair follicle outer root sheath and epidermal rete ridges
Sebocytes	Dermis; usually associated with hair follicle ("pilosebaceous unit")	Sebum production, secretion of enzymes, regulatory molecules, major endocrine and metabolic activity	Derived from hair follicle keratinocytes; sebum production by holocrine secretion of sebocytes
Apocrine gland cells	Subcutis; usually associated with hair follicle ("folliculosebaceous-apocrine unit")	Production of apocrine sweat and pheromones	Derived from hair follicle keratinocytes, neural control: adrenergic; sweat production by "decapitation secretion"
Eccrine gland cells	Subcutis	Thermoregulation, excretion via eccrine sweat; many medications eliminated via sweat	Derived from epidermal keratinocytes; deeply coiled glands analogous to glomeruli in some ways
Myocytes	Arrector pili muscle, blood vessel smooth muscle	Contraction	Regulates blood flow, causes "goose bumps" by pulling hair erect
Granulocytes	Skin vasculature	Natural immunity	Neutrophils, basophils, eosinophils in normal, uninflamed skin almost exclusively in the blood vessel lumen
Vascular endothelial cells	Blood vessels	Formation, regeneration of blood vessels, perfusion	Interact with immune cells to further local immune response

Continued Table 1.1 ▸

Table 1.1 · Continued

Cell	Location	Function	Comments
Lymphatic endothelial cells	Lymph vessels	Intracutaneous fluid balance, passageway for immunocyte trafficking and antigen transport, nutrition, removal of metabolic and other skin products	Dermal endothelial cells are an integral component of the dermal microvascular unit, where trafficking immune cells interact with endothelial cells, fibroblasts, smooth muscle cells, and perifollicular mast cells, macrophages and dermal dendrocytes
Erythrocytes	Skin vasculature	Oxygenation	In normal, uninflamed skin exclusively in the blood vessel lumen; amount and oxygenation status of erythrocytes in the papillary plexus is a key determinant of skin color
Merkel cells	Epidermis, hair follicle	Mechanosensory cell, (modulation of epithelial growth? neurosecretory functions?)	Origin disputed: epithelial or neural crest-derived?
Melanocytes	Epidermis, hair follicle	Protection from damage by UV light and reactive oxygen species; hair shaft pigmentation; other secretory activities	Neural crest-derived, dendritic cells that produce melanin and transfer it to keratinocytes and hair follicle cells
T lymphocytes	All skin compartments (but mainly epidermis and distal hair follicle epithelium)	Antimicrobial defense, tumor immunosurveillance, regulation of inflammatory responses	Invisible in routine histology of normal epidermis; preferred residence in epidermis (= epidermotropism) and distal hair follicle epithelium with dendritic morphology; traffic between epidermis, regional lymph node/spleen and circulation
Langerhans cells	Epidermis (dermis, distal hair follicle epithelium)	Chief antigen-presenting cell of the skin	Dendritic morphology; emigrate from epidermis to regional lymph node for antigen/allergen presentation to T cells; one dermal subpopulation of Langerhans cell-like cells is called dermal dendrocytes

Table 1.1 · Continued

Cell	Location	Function	Comments
Mast cells	Dermis, subcutis; preferential location around skin nerves, blood vessels and hair follicles	Major component of natural immunity: rapid defense against bacterial and parasitic infection; possibly involved in wound healing, angiogenesis, hair growth control	Mast cell degranulation leads to urticaria and angioedema; key role in neurogenic inflammation; "central switchboard" of inflammation and tissue remodeling
Neurons	Neuronal cell body of sensory neurons located in dorsal root ganglion or trigeminal ganglion; only axons project into the skin	Sensation, "trophic" functions, immunomodulation (e.g. neurogenic inflammation via induction of mast cell degranulation)	Intracutaneous nerve fibers have multiple different functions beyond sensation; autonomic fibers regulate blood vessel tone and sweat production
Glial cells (Schwann cells)	Sheath myelinated intracutaneous nerve fibers	Maintenance and modulation of nerve fiber function; release of "trophic" signals (nerve growth factors)	Important role during axonal regeneration during wound healing; rich sources of neurotrophins
Fibroblasts	Dermis, connective tissue sheath and dermal papilla of hair follicle	Secretion, organization, digestion, and remodeling of extracellular matrix (collagen and elastic fibers); generation and remodeling of basement membranes (together with epithelial cells)	Specialized fibroblasts of the hair follicle retain inductive/morphogenetic properties throughout life and dictate hair follicle size and growth activity; hair follicle connective tissue sheath contains mesenchymal stem cells, important for wound healing
Adipocytes	Subcutis	Thermal insulation, physical cushion/buffer function and energy store by fat accumulation; secretion of regulatory molecules, major endocrine and metabolic activity	Organized in well-vascularized fat lobules, separated by thin septae, which connect the subcutis to the underlying muscle fascia
Macrophages	Dermis, subcutis	Key phagocytes of the skin; regulate fibroblast functions	Also termed histiocytes; multiple macrophages coalesce to form multinucleated giant cells e.g. in foreign body, sarcoid, or tuberculoid granulomata

2 Dermatologic Diagnosis

2.1 Components of the Dermatologic Evaluation

The diagnosis of skin diseases is not as difficult as it initially seems, so do not let yourself be intimidated. The keys to successful diagnosis are systemic and complete skin examination, an understanding of anatomy and physiology of the skin, and the use of basic dermatologic terminology.

- **Description of skin findings** (p. 7): Dermatology is a visual specialty. The careful morphologic description of cutaneous changes is at the center of dermatologic diagnosis. This skill must be learned, as it often leads to the correct diagnosis in itself, and cannot be replaced by laboratory examinations or other investigative procedures.
- **Simple clinical tests** (p. 22): One of the joys of dermatology is relative freedom from tracking down complex laboratory and imaging reports. On the other hand, a number of simple procedures carried out by dermatologists can rapidly indicate the correct diagnosis.
- **History** (p. 24): Although a dermatologic diagnosis can often be made without taking a history, relevant information should be collected to aid in the differential diagnostic process, to be aware of other medical conditions the patient is confronting, and to be aware of any medications the patient is taking.

2.2 Description of Skin Findings

The following tips will help improve your skills in diagnosing skin lesions:

- **Develop a logical and systemic approach to skin examination**: Approaching each patient in the same way, carefully examining the skin, and documenting your findings in a reproducible, legible fashion is the most reliable way to make correct diagnoses.
- **Try to examine the skin in a room with daylight.**
- **Examine the entire skin surface during the first dermatologic examination.** This should include:
  - Palms and soles, ears, submammary, interdigital, axillary, inguinal, genital, and perianal skin.
  - Adjacent mucosa including lips, mouth, conjunctivae, nasal mucosa, and in some instances anus.
  - Skin appendages (hair and nails) as well as scalp.
  - Screening for malignant melanoma (p. 396) and other skin malignancies (p. 419).
  - Assessment of general skin appearance (color, texture, dryness, hydration, odor).
  - Evidence for exposure to sunlight, nicotine, other noxious agents.
- **Match objective evidence to subjective complaints**; a patient who denies itch but has numerous excoriations may have an underlying psychosocial problem.
- A **total skin examination** should always be offered, although some patients may not consent. In the case of widespread rashes, it is mandatory. Consider this scenario—a patient presents with a skin problem on the hands and you fail to check the feet, where a fungal infection is obvious; you have made the entire diagnostic process slower.

- **Look with your fingers**. Many lesions, especially actinic keratoses, can be more easily felt or palpated than seen. Palpation also helps to determine the depth and consistency of a lesion, which may aid in the differential diagnosis.
- **Determine the anatomic location of the lesion:**
  - Is it epidermal, dermal or subcutaneous?
  - Are the skin appendages, blood vessels, or nerves involved?
- **Determine the primary symptom:** This often simplifies the diagnostic process.
- **Become skilled in using simple diagnostic aids:** The use of some of the procedures outlined below should be almost automatic. For example, if a rash is scaly, most dermatologists almost routinely do a potassium hydroxide (KOH) examination for fungi.

2.3 Primary and Secondary Lesions

Lesion morphology is the code language of dermatology. Using a surprisingly limited number of names for lesions and then a somewhat more complex series of modifiers, it is possible to describe everything one sees on the skin. Primary lesions (Table 2.**1**) are the basic elements of skin morphology; they can undergo a variety of changes to become secondary lesions (Table 2.**2**).

- Figure 2.**1** shows the primary and secondary lesions, while Figure 2.**2** demonstrates how the border of a lesion can vary.

Table 2.1 · **Primary lesions**

Lesion	Description
Flat; not palpable	
Macule	Localized change in color of the skin: "A blind man cannot find a macule." Possible colors and their common causes: *Red:* Hyperemia (erythema), telangiectases (small dilated vessels), leakage of blood (purpura, petechiae, ecchymosis, suggillation) *Blue:* Cyanosis, hematoma (black eye), dermal melanin *Brown:* Dermal and epidermal melanin, hemosiderin *White:* Anemia, vasoconstriction, loss of melanin *Yellow:* Carotenoids, bile, solar elastosis *Gray-black:* Epidermal melanin, heavy metals, tar, dithranol, foreign bodies Decorative tattoos can have many colors
Raised; palpable	
Papule	< 5 mm in diameter, caused by increased thickness in epidermis, dermis, or both
Nodule	> 5 mm
Plaque	Large flat slightly raised lesion, always > 5 mm
Vesicle	< 5 mm, filled with clear fluid (p. 702)
Bulla	> 5 mm, filled with clear fluid (p. 704)
Pustule	Lesion filled with pus
Hive (urtica)	Transient papule or plaque caused by dermal edema (p. 706)

Table 2.2 · Secondary lesions

Lesion	Description
Pustule	Pustules can be both primary, or develop secondarily from vesicles and bulla
Scale	Scales are visible aggregates of corneocytes, varying in size and color
Crust	Dried serum or exudate, often admixed with scale
Erosion	Superficial defect involving only epidermis
Excoriation	Defect extending into dermis, caused by scratching
Ulcer	Chronic defect extending into dermis or subcutaneous defect, which develops as a result of tissue necrosis and heals poorly
Scar	May be raised, flat (rarely) or atrophic; result of healing of skin defect
Cyst	Space lined by epithelium and usually filled with products of lining cells (keratin, sebum, mucin)
Necrosis	Dead tissue

2.4 Additional Descriptive Terms

Modifiers Used to Describe Lesions

- **Color:** Both name of color and its nature (uniform, irregular, patchy).
- **Form:** Configuration, border, and surface:
  - *Circinate:* arched or rounded border.
  - *Annular:* circular or ring-shaped.
  - *Discoid*, *nummular:* disk or coin-shaped.
  - *Serpiginous:* winding, twisting (snake-like).
  - *Iris* or *cockade* (target-like).
  - and many more, including *oval*, *finger-shaped*, *leaf-like*, *swirled*, or *starry*.
- **Border:** Sharp (well-circumscribed) or vague (blurred).
- **Surface:** Smooth, rough, warty, vegetating, glistening, dull.
- **Consistency:** Soft, doughy, hard, fluctuant, lobed, knotty, moveable, fixed, attached to …

Patterns of Distribution

- **Linear:** Following a line.
- **Lines of Blaschko:** Following embryologic skin lines (Fig. 2.**3**).
- **Reticular:** Net-like.
- **Grouped**.
- **Herpetiform:** Arranged in clusters, grape-like.
- **Zosteriform:** Following a dermatome (p. 62).
- **Discrete:** Solitary.
- **Confluent:** Blending together.
- **Chessboard pattern:** Arranged in rectangular patterns.
- **Disseminated:** Randomly distributed.

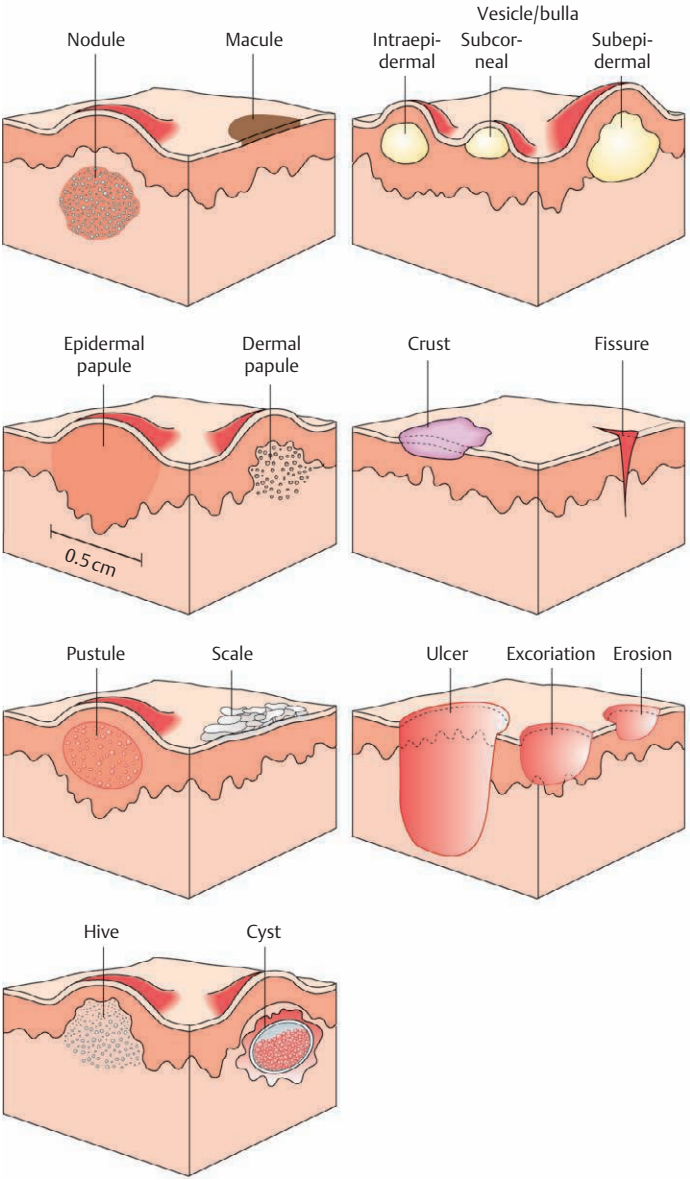


Fig. 2.1 · Primary and secondary lesions.

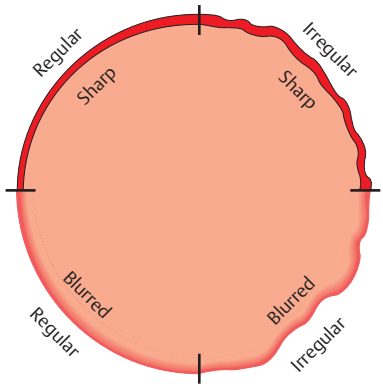


Fig. 2.**2** · Borders of lesions (after Steigleder).

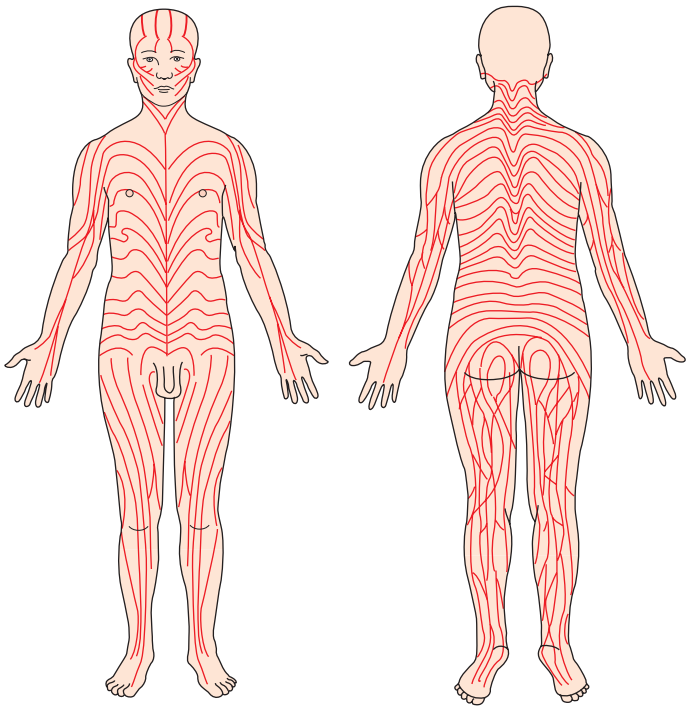


Fig. 2.**3** · Lines of Blaschko.

Distribution Over the Skin Surface

- **Degree of spread:** Localized, regional, generalized (widespread), universal.
- **Limited to certain areas** (such as palms and soles or scalp).
- **Specific patterns** (p. 709): Symmetrical, asymmetrical, light-exposed skin, light-protected skin, intertriginous areas, seborrheic areas, pressure points, sites of predilection.

Relation to the Skin Appendages

- Each lesion **centered about a hair**, producing a distinctive pattern.
- **Interfollicular:** Not involving hairs.
- **Palmoplantar:** Limited to palms and soles, thus not connected with hairs.
- Favoring regions with large concentrations of **sebaceous glands or sweat glands**.

Description of Complex Findings

Note: The following terms are frequently used in dermatologic descriptions but are not traditionally considered primary or secondary lesions.

- **Atrophy:** Loss of substance of the skin.
- **Ecchymosis:** Large area of extravasation of erythrocytes.
- **Enanthem:** Abrupt appearance of mucosal lesions, similar to exanthem.
- **Erythema:** Redness of the skin (p. 707).
- **Erythroderma:** Diffuse redness of the entire skin, usually associating with scaling.
- **Exanthem:** Abrupt appearance of diffuse or generalized similar skin lesions (usually represents viral infection or drug reaction).
- **Lichenification:** Response of skin to chronic rubbing, leading to thickening with accentuated markings.
- **Livedo:** Blue-red discoloration of skin due to passive congestion of vessels, often with net-like pattern.
- **Petechiae:** Tiny areas of extravasation of erythrocytes, usually pinhead-size.
- **Poikiloderma:** Combination of telangiectases, atrophy and pigmentary changes (p. 706).
- **Purpura:** General term for extravasation of erythrocytes into the skin.
- **Rhagade or fissure:** Linear split or defect, extending into dermis and often originating from an orifice.
- **Sclerosis:** Hardening and thickening of skin, so that it is less freely moveable, often associated with contraction so that involved area lies below level of normal skin.
- **Sinus:** Tract lined with epithelium, often discharging secretions.
- **Suggillation:** Synonym for ecchymosis, also used for bruise or contusion.
- **Telangiectases:** Small, irreversibly dilated blood vessels (p. 706).

Description of General Skin Condition, Vascular Status, and Associated Findings

- **General terms:** Xerotic (dry), seborrheic (oily), ichthyotic (scaly), actinic damage, atrophic, thickened, abnormal texture, hyper-, hypo- or anhidrotic.
- **Vascular status:** Cyanotic, pale, cold, warm, edematous, with varicosities, necrotic.
- **Nature of wound healing:**
  - Central or peripheral healing, with scarring or atrophy.
  - Pigmentary changes, erosion or ulcer, crust, or scale.
- **Dynamics of lesion:** All lesions in same stage or lesions in different stages.
- **Associated findings:** Lymphadenopathy, fever, malaise, as examples.

Simple Clinical Tests

These tests can be done during the initial examination.

- **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.
- **Pull off scales or deposits:** Easily removed, firmly attached.
- ***Note:*** Scales mean epidermal involvement. Always remove scales or crusts; they may be "hiding" an underlying tumor.
- **Tug on hairs:** Easily breakable, readily removed, hair bulb visible.
- **Insert probe:** Can be used to explore sinus tract; used in the past to analyze tubercular lesions, which were relatively insensitive to such pressure.
- **Provocation tests:** Manipulate lesions by rubbing, pressing, applying heat or cold, having patient exercise.
- **Look for specific clinical signs:** Dermographism, pathergy (p. 257), Nikolski phenomenon (p. 230), Darier sign (p. 466).

2.5 Tools of the Trade

Spatula

- **Tongue blade:** Used to remove crusts and scales, test for dermographism, and examine mouth.
- **Glass spatula:** Used for diascopy. By pressing on the skin hard enough to exclude blood flow, one can eliminate purely vascular lesions and better appreciate dermal changes, such as the "apple jelly" color of many granulomatous infiltrates (tuberculosis, sarcoidosis).

Hand Lens

A hand lens or *loupe* is an essential instrument for anyone examining the skin. It allows a better view and easier appreciation of finer details.

Dermatoscopy

- **Synonyms:** Epiluminescence microscopy, dermoscopy.
- **Definition:** Method of observing superficial layers of skin using 10–100× magnification with oil immersion. Both hand-held and computer-assisted instruments are available.
- **Uses:**
  - *Differential diagnosis of pigmented skin lesions:* Separating melanocytic lesions from vascular lesions, basal cell carcinomas, dermatofibromas and others.
  - *Differential diagnosis of melanoma:* Using the dermatoscope, one can better distinguish between dysplastic or atypical melanocytic nevi and melanomas, increasing the diagnosis accuracy to around 90%. This approach is especially useful in patients with multiple atypical lesions and those at high risk of developing melanoma.
  - *Detailed examination of the skin:*
    - Proximal nail fold to look for abnormal vessels in connective tissue disorders.
    - Wickham striae as sign of lichen planus.

  - Cauliflower surface with thrombotic capillary loops suggests verrucae.
  - Scabies burrows (hang glider sign).
  - On the scalp, cadaver hairs and exclamation point hairs suggest alopecia areata, loss of follicular openings indicates scarring alopecia, and follicular hyperkeratoses point towards lichen planus.

► **Procedure:**
- Apply appropriate oil (olive, peanut, immersion) or sonographic gel to the skin to improve the optic interface between skin and dermatoscope lens, which is gently pressed onto the skin.

Caution: When the skin surface is not relatively flat, dermatoscopy is less effective. This applies to nodular tumors and on mucosal surfaces. In curved areas, as between the digits, a smaller lens is available with some instruments.

► **Instruments:**
- *Dermatoscope:* 10× magnification, using achromatic lens and halogen or diode light source.
- *Stereomicroscope:* Allows 40–100× magnification.
- *Digital image processing:* When the optical system is connected to a computer, digital images can be processed and stored. Such a system allows rapid retrieval for later comparison and eliminates all the problems associated with storing many clinical slides. In addition, most systems have a computer-assisted analysis system, helping to distinguish between melanocytic nevi and melanomas. The main disadvantage is their high cost.

Wood's Light Examination

► **Definition:** UV radiation from a mercury-vapor source is passed through a nickel oxide filter, producing light at a wave length of about 365 nm.

► **Uses:**
- *Dermatophyte infection: Microsporum* species that infect hairs impart a green fluorescence. Wood's light can be used for screening or for control of therapy.

Caution: Both sebum and salicylic acid preparations may have blue-green fluorescence; also the scales do not fluoresce, just infected hairs. In addition, *Trichophyton* infections do not fluoresce.

- *Favus: Trichophyton schoenleinii* imparts a green fluorescence.
- *Erythrasma:* Coral red fluorescence.
- *Trichomycosis axillaris:* Orange fluorescence.
- *Tinea versicolor:* Orange fluorescence.
- *Pseudomonas:* Green fluorescence.
- *Porphyrin:* Red fluorescence of skin and teeth in some porphyrias; fluorescence of urine in others.
- *Pigment abnormalities:* Hypopigmentation can be distinguished from depigmentation, vitiligo more readily seen, ash leaf macules in tuberous sclerosis and café-au-lait macules in neurofibromatosis more easily found.
- *Tetracycline:* Can be identified in teeth, keratin plugs.
- *Contact allergens:* Some allergens fluoresce and can be found on the skin or in cosmetics; examples include halogenated salicylanilides and furocoumarins.
- *Mineral oil:* Remains in hair follicles and can be seen after washing (as in oil acne).
- *Miscellaneous:* Topical medications or protective creams can be labeled with fluorescent marker, allowing control of usage patterns.

Search for Parasites

- **Scabies:** Dermatoscopy can be very useful, showing the classic "hang glider" sign when the female is found at the end of the burrow. Another approach is to searched carefully for an intact burrow, cover it with immersion oil, unroof it carefully with a large-bore needle or fine scalpel blade, and search for mites and eggs under low magnification.
- **Lice:** Look carefully for moving objects on the hairs, adjacent skin and, in the case of pediculosis corporis, on the seams of the clothing. Pick them up with tweezers and fix to a slide with adhesive tape or xylol and then examine. In the same ways, nits can be separated from hair casts.

Other Diagnostic Procedures

Other tests and examinations are discussed as relevant under specialized topics such as diseases of hair, mycology, phlebology, and andrology.

2.6 History

Principles

The history is not as crucial to dermatologic diagnosis as it is in most other specialties, but it often provides valuable clues and should be taken carefully when the physical examination has not provided a diagnosis.
When allergic reactions, infections, exogenous damage, drug reactions, or cutaneous manifestations of systemic diseases are being considered, the history often is the only way to obtain the diagnosis. In addition, it is often essential in planning therapy.

Procedure

The most useful approach is to concentrate on a few **key questions**, which can be expanded upon depending on the clinical situation. The patient's answers also provide the framework for additional questions. Questioning should be direct, but not aggressive; preserving the doctor–patient relationship is more important than any single question.

- *When exactly did the skin changes start?*
- ***Caution:*** Patients often gives misleading answers as they either have not noticed the early stages of their diseases or have ignored them.
- *Where exactly did the skin changes start?*
- ***Caution:*** The first changes may have developed at a site where the patient could not easily observe them.
- *Are the lesions symptomatic?* (Do they burn, itch, feel tight, warm, cold?)
- ***Caution:*** Symptoms such as itching or pain may turn out to be misleading. Do not ignore the possibility of scabies just because the patient says the lesions do not itch.
- *How did the lesions spread?*
- *How did the individual lesions first look and how have they changed?*
- ***Caution:*** Patients often have a different understanding of morphologic terms than do physicians. Be sure to ask what is really meant by terms such as "pimple," "boil," "eczema,"or "sore."

- *What do you think started the problem? What makes it worse?*
- Ask what the patient was doing when the problem started. Some diseases are typically made worse by cold, exercise, or the like. Often the patient may provide valuable clues, but just as often their assessment of etiology or causality is very misleading—remain skeptical, without showing it.
- *How have you treated it so far?*
- Frequent washing or the use of a tincture may explain why an exanthem is very dry; use of an ointment in the groin may clarify the development of macerated lesions.

If the answer is still unclear, then take a complete medical, social and family history, as well as a detailed medication history.

Additional helpful questions include:

- *Have you ever had anything similar to this before?*
- *What was the diagnosis then?*
- *Do you have any skin problems elsewhere* (mouth, feet, nails, scalp, genital region, perianal region, groin, axillae, ears)?
- *What has been the influence of external factors* (sun, work, eating, drinking, cosmetics, stress, medications) or internal factors (menses, pregnancy, nursing, illnesses)?
- *What are the associated signs and symptoms?*
- *How do you feel otherwise* (malaise, fever, weight loss, night sweats)?
- *What medications are you taking?* Be sure to ask about tranquilizers, sleeping pills, vitamins, headache preparations, laxatives, appetite control pills and natural products. Patients often do not consider one or more of these categories as medications, and fail to report them.
- Lifestyle—drugs, alcohol, smoking, stress.
- Sexual practices, last time you had sex (when relevant).
- *Any systemic signs or symptoms before skin disease started* (prodrome)?
- *Any other illnesses?* Be sure to ask about cardiovascular, renal, hepatic, thyroid, rheumatologic diseases, HIV, diabetes mellitus.
- *Personal or family history of atopic dermatitis, hay fever or asthma?* Other allergies?
- Ethnic background.
- Foreign travel, especially to tropical regions.
- *How much does the skin disease influence daily function* (quality of life assessment)?
- Psychosocial situation—job, family, relationships, handicaps.

2.7 Histologic Diagnosis

Principles

- **Indications** for a histologic examination include:
  - All excised tumors and pigmented lesions.
  - Differential diagnostic questions.
  - Help with difficult or unclear diagnoses.
  - *Legal or cautionary reasons:* Sometimes, even though the diagnosis is clear, histologic proof is wise before embarking on potentially dangerous therapy.
- The choice of an **appropriate site and lesions**, the **care** with which the biopsy is taken, the **method** of fixation and processing, and the provision of **all relevant clinical data** all contribute greatly to the utility of a skin biopsy.

- **Importance of additional information:** The histological diagnosis of **tumors** can usually be made without a history, but is much easier and effective when historical data is available. In the case of **inflammatory dermatoses**, very few have a pathognomonic histological picture, so that the quality of the additional information almost directly correlates with the quality of the histological diagnosis.

Taking the Biopsy

- The biopsy must be large and deep enough.
- Avoid squeezing (crush artifact) by trying to pop out or lift out without a forceps.
- Place immediately in fixative; do not let the biopsy dry out.
- Intact lesions should be biopsied; ruptured blisters or excoriated papules provide little information.
- Punch biopsies should just include lesional skin, since they cannot be oriented during processing (Fig. 2.**4**). Punch biopsies in hair-bearing areas should be parallel to the direction of hair shafts (Fig. 2.**5**).
- If you are considering atrophy or cutaneous tissue changes, then an elliptical biopsy from the edge of the lesion including perilesional skin is helpful for orientation and comparison (Fig. 2.**6**).
- Only very small pieces of tissue ($< 1\,mm^3$) are needed for electron microscopy.

Fixation

- **Light microscopy:**
  - *Solution:* Standard is 10% buffered formaldehyde; when specimens are mailed, usually 4% is employed. Minimum fixation period is 24 hours.
  - Be sure there is enough solution; the ideal proportion is at least 10 times as much solution as tissue.
  - Formaldehyde solution is not well suited for molecular biological investigations.

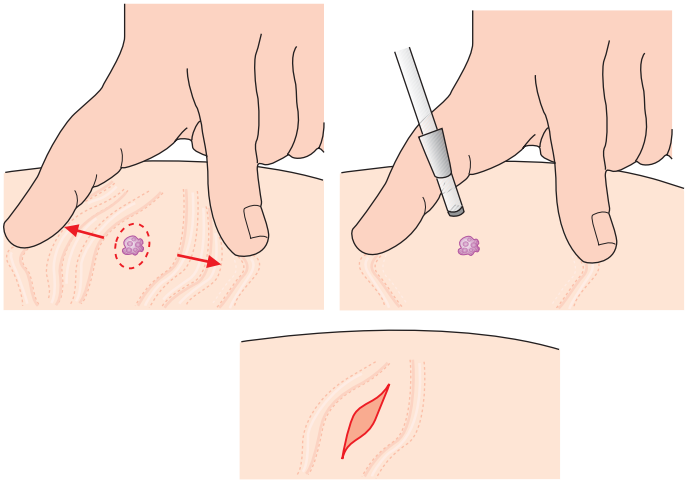


Fig. 2.**4** · **Punch biopsy.** Tension applied perpendicular to the skin tension lines will produce a more easily closed biopsy site.

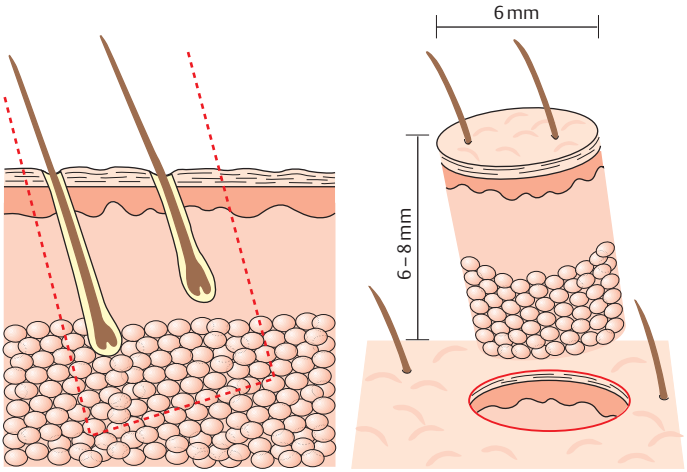


Fig. 2.**5** · **Scalp biopsy.** Angle of incision should be parallel to the hair shafts.

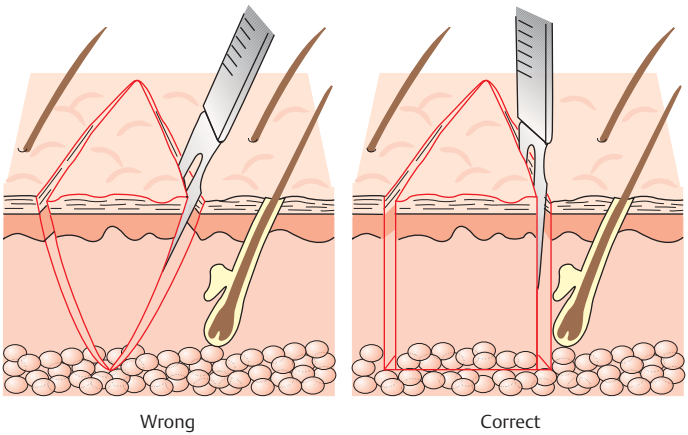


Fig. 2.**6** · **Spindle-shaped excision.** The incision should be perpendicular to the skin surface, insuring a broad-based biopsy with an adequate sampling of the subcutaneous fat.

► **Immunofluorescence, immunohistochemical staining, and molecular biological studies:**
- Check with the responsible laboratory for appropriate fixative. For immunofluorescence studies, special transport medium or freezing is usually chosen.
- Frozen sections should be placed in a special plastic tube (perhaps filled with 0.9% NaCl solution), closed and immediately frozen in liquid nitrogen.

- Immunohistochemical staining and in-situ hybridization can usually be done on formalin-fixed, paraffin-embedded tissue.

► **Electron microscopy:**
- Special fixatives, which usually have a limited shelf life, are required; most often Karnovsky solution is used. Check with the electron microscopy laboratory before doing a biopsy.
- Electron microscopy is only available in larger institutions. It is reserved for special situations such as rapid identification of viruses, assessment of ichthyosis and epidermolysis bullosa, identification of Birbeck granules in Langerhans cell histocytosis, identification of vascular deposits in Fabry disease, and diagnosis of unclear carcinomas and sarcomas. The use of immunohistochemical methods and monoclonal antibodies has greatly reduced the need for electron microscopy.

Submission Slip

The submission slip or form must include the following information:
► **Type of biopsy** (punch, partial excision, total excision, re-excision, tangential (shave) excision, curettage).
► Exact **location** of biopsy.
► For **tumors** that have been completely excised, some system of marking should be employed and a accompanying sketch should provide anatomic details.
► **Important clinical details including:** duration of disease, age and type of lesion biopsied, size and distribution (for widespread disease), previous treatment, associated diseases, and any other relevant clinical data.
► **Clinical diagnosis and reasonable differential diagnostic considerations.**

Staining Methods

► **Routine histopathological examination of skin specimens** is done using formalin-fixed, paraffin-embedded sections stained with hematoxylin and eosin (H&E).
► Two **special stains** are especially suited for the immediate identification of organisms on smears:
- *Methylene blue stain:* Let the smear dry. Place in a dilute solution of methylene blue for 20–30 seconds, then rinse with tap water. Allow to dry. Observe with immersion oil to search for the methylene blue–positive diplococci within neutrophils typical of gonorrhea.
- *Gram stain:* This classic stain allows the rapid separation of Gram-positive (blue–violet) and Gram-negative (red) bacteria. The Gram-positive bacteria retain the initial stain, while the Gram-negative can be decolorized and then stained with a red counterstain. Commercial sets of dyes are used on a fixed smear. Gram-negative diplococci within neutrophils indicate gonorrhea.

► Other special stains are needed to identify a variety of cutaneous structures. The most useful ones are listed in Table 2.**3**.

Immunofluorescence

Principle:
- *Direct immunofluorescence* (DIF) staining labels a variety of antigens, antibodies, complement factors, fibrin, and other structures with fluorescent-labeled antibodies that can then be seen using a special microscope. Most commonly autoantibodies deposited during inflammatory reactions are identified in the

Table 2.3 · Common special stains

Stain	Used to identify:
Hematoxylin-eosin	(Routine)
Alcian blue	Mucin
Congo red	Amyloid
Fite	Mycobacteria
Fontana-Masson	Melanin
Giemsa	Mast cells
Hale (colloidal iron)	Mucin
Masson trichrome	Collagen
Methenamine silver	Fungi, basement membrane
Periodic acid–Schiff (PAS)	Fungi, glycogen, basement membrane
Silver nitrate	Melanin
Toluidine blue	Mucin
Von Kossa	Calcium
Verhoeff–van Gieson	Elastic fibers
Warthin–Starry	Spirochetes

patient's skin, using frozen tissue cut with a cryostat, to which antibodies are applied. DIF can also be used to identify microorganisms.

- *In indirect immunofluorescence* (IIF) the patient's serum is applied to normal skin or foreign issue (monkey esophagus, bladder epithelium, cultured cells). Any circulating antibodies that attach to target structures are then identified by a second application of labeled antibodies directed usually against antibody structures. The titer of serum that produces a positive response can be measured.

► **Uses:** Bullous autoimmune dermatoses, lupus erythematosus, other collagen–vascular disorders, lichen planus, and vasculitis. The diagnostic indications for immunofluorescence examination are shown in Table 2.**4**.

Immunohistochemical Methods

► **Principle:** Antibodies are available to identify a wide variety of antigens in both fresh and formalin-fixed tissue. The antibodies bind in a highly selective manner, often to small epitopes. They can be visualized with a variety of markers including enzymes and fluorescent dyes (Table 2.**5**).

► **Uses:** This technique is critical for the identification and classification of lymphomas as well as for the diagnosis of a wide variety of sarcomas and other tumors. In addition, the nature of inflammatory infiltrates can be assessed.

! ***Caution:*** Tumor cells may fail to express an antigen for their profile changes as they undergo mutations. One should not rely on a single antigen for diagnosis, but use a panel of markers to increase accuracy.

Table 2.4 · Diagnostic guidelines for immunofluorescence

Disease	Target antigen	Biopsy	Findings
Bullous dermatoses			
Pemphigus group			
1 Pemphigus vulgaris (suprabasal blisters)	Desmoglein 1,3 and plakoglobin	*HE:* Border of small fresh blister *DIF:* Perilesional intact skin or mucosa	*DIF:* 1, 3 IgG in intercellular spaces of epidermis, as well as C3, rarely IgM or IgA
2 Pemphigus foliaceus (subcorneal blisters)	Desmoglein 1	*IIF:* Serum	2 Intraepidermal IgG, C3
3 Paraneoplastic pemphigus (suprabasal blisters)	Plakin family: (desmoplakin 1,2, envoplakin, periplakin, plectin); desmogleins; BP-230		*IIF:* 1, 2 In 90%, circulating ABs 3 Wide variety of Abs labeling epidermal cells and basement membrane
Subepidermal blisters			
1 Bullous pemphigoid (also pemphigoid gestationis) (subepidermal blister)	Basement membrane BP-230	*HE:* Border of fresh blister *DIF:* Perilesional intact skin or mucosa; perilesional skin for split skin technique.	*DIF:* 1 Band of IgG and C3 or C3 alone along basement membrane; split skin blister roof
2 Linear IgA dermatosis (subepidermal blister in papillary tips)	BP-180	IIF: Serum; normal skin from triceps region for split skin	2 Linear IgA and also C3 along basement membrane 3 IgG and C3 along basement membrane; split skin blister floor
3 Epidermolysis bullosa acquisita (subepidermal blister)	Collagen VII		*IIF:* 1 In 50–70% circulating IgG against basement membrane; split skin blister roof 2 Negative 3 In 20–50% circulating IgG against basement membrane; split skin blister floor

Table 2.4 · Continued

Disease	Target antigen	Biopsy	Findings
Other bullous lesions			
Dermatitis herpetiformis (*Subepidermal* blisters concentrated in papillary tips)	Transglutaminase, endomysium	*HE:* Lesional skin *DIF:* Perilesional skin *IIF:* Serum	*DIF:* Granular IgA, C3 in papillary tips; rarely linear deposits of IgA
Cicatricial pemphigoid (subepidermal blisters)	BP-180, laminin 5, $\alpha6\beta4$ integrin	*HE:* Lesional skin *DIF:* Perilesional mucosa *IIF:* Serum	*DIF:* Linear IgG and C3 at basement membrane, less often IgA and IgM Split skin: Varies with antigen *IIF:* Usually negative
Connective tissue disorders			
Lupus erythematosus		*HE:* Lesional skin *DIF:* Lesional, ideally non-sun-exposed skin; non-sun-exposed normal skin	Granular IgG, IgM, C3 along basement membrane In chronic cutaneous LE, only involved skin affected; in systemic LE, deposits in normal skin
Dermatomyositis		*HE:* Lesional skin *DIF:* Lesional, ideally non-sun-exposed skin; non-sun-exposed normal skin	Similar to LE, but often negative
Vasculitis			
Leukocytoclastic vasculitis Urticarial vasculitis Other forms of vasculitis		*HE:* Lesional skin *DIF:* Lesional skin; early lesion except for urticarial vasculitis when late lesion must be chosen	IgG, IgA, IgM or C3 around involved vessels; IgA common for Henoch-Schönlein purpura; DIF not required for diagnosis of vasculitis

AB = antibody; DIF = direct immunofluorescence; HE = hematoxylin-eosin; IIF = indirect immunofluorescence; LE, lupus erythematosus.

Table courtesy of Peter von den Driesch and Elke Knußmann-Hartig.

Table 2.5 · Common immunohistochemical stains

Stain	Identifies
Bcl2	Follicular B-cell lymphoma (negative in primary cutaneous follicular center lymphoma)
Bcl6	Follicular B-cell lymphoma
Carcinoembryonic antigen (CEA)	Eccrine, apocrine glands, Paget disease
CD3	T cells (T-cell receptor)
CD8	Cytotoxic T cells
CD10	B-cell and T-cell precursors
CD20	B cells
CD34	Stem cells, dermatofibrosarcoma protuberans
CD35	Follicular dendritic cells
CD45RO	Effector and memory T cells
CD68	Macrophages
CD79a	B cells
CD117	Mast cells
Cytokeratins	Epidermis, appendages, and related tumors
Desmin	Smooth and skeletal muscle
Epithelial membrane antigen (EMA)	Eccrine, apocrine, sebaceous glands and their tumors
Factor VIII	Endothelial cells, vascular tumors
Factor XIIIa	Dermal dendrocytes, dermatofibromas
HMB-45	Melanocytes, more often in melanoma than nevi
Ki-67	Proliferation marker
Leukocyte common antigen (LCA)	Leukocytes
MelanA	Melanocytes, nevi, melanomas
S-100	Melanocytes, neural cells, many others
Smooth muscle actin	Smooth muscle cells and myofibroblasts

2.8 Molecular Diagnostics

- **Principle:** Many new techniques involving molecular biological methods are available for dermatologic diagnosis. These new approaches have increased the sensitivity and specificity of diagnosis, and play a major role in diagnosing infectious diseases, tumors (primarily lymphoma and malignant melanoma), autoimmune disorders, and genodermatoses.

Caution: False-positive results are common; scrupulous attention to detail and use of appropriate controls are essential.

- **In situ hybridization:** A known nucleic acid, single stranded and usually labeled with radioactivity or fluorescence, is applied to prepared cells or histologic sections and annealing occurs in situ; purpose is to analyze the intracellular or intrachromosomal distribution, transcription, or other characteristics of the nucleic

acids. In **fluorescent in situ hybridization (FISH)**, short sequences of DNA are labeled with florescent dyes and then allowed to hybridize to target DNA; useful for identifying specific mutations for which a probe is available.

- **Polymerase chain reaction (PCR)** provides the rapid amplification of specific DNA sequences using primers, leading to the identification of foreign nucleic acids present in very small amounts.
- **Reverse transcriptase PCR (RT-PCR)** demonstrates the transcription of a defined gene by generating cDNA from RNA.
- **Real-time PCR** allows quantification of either DNA or RNA.
- **Detection of immunoglobulin and T-cell receptor rearrangements:** Assessing clonality of B-cell or T-cell proliferation is essential in studying cutaneous lymphomas. PCR is widely used to study both the T-cell receptor (TCR) and IgH, having widely replaced Southern blotting.
- **DNA microarrays** contain many segments of DNA serving as probes mounted on a single chip. Messenger RNA is extracted from the specimen and applied to the chip. The expression of thousands of genes can be analyzed simultaneously, creating patterns of gene activity for various tumors.

2.9 Mycologic Diagnosis

Obtaining Culture Material

- **Dermatophyte infection:**
  - Generous amounts of material should be taken from the edge of the lesion, which is the site where fungi are most likely. The skin can be scraped with a sterile scalpel or curette; hairs should be epilated with a tweezers.
  - A bacterial smear obtained in the usual fashion is useless for diagnosing dermatophytes.
  - Disinfection is not needed if the material is to be cultured on media containing cycloheximide (directed against contaminating molds) and antibiotics (against bacteria). Strong disinfectant measures may destroy the suspected fungus.
- **Onychomycosis:**
  - Remove fine pieces of nail from the subungual area, after first cutting away markedly damaged nails.
  - If a superficial nail infection is suspected, scrape material from the surface of the nail using a scalpel.
- **Candida:**
  - Use bacteriological swabs to culture the mouth, intestinal tract, and vagina. The swabs are rolled over the surface of the culture medium.
  - If infection of the glans penis is suspected, the glans can be pressed directly on a culture plate.

Culture Conditions

- The usual culture medium is Sabouraud glucose agar (with cycloheximide for dermatophytes, without for yeasts) or Kimmig agar; in both instances antibiotics are added to the agar. Culture is at room temperature.
- Yeasts grow within a week and then are subcultured to rice agar for further differentiation (search for chlamydospores and pseudomycelia).
- The further identification of yeasts may require biochemical tests (uptake of sugar or nitrogen, fermentation of sugar). In unclear cases, PCR can be employed to identify the organism's nucleic acid fingerprint.

2.10 Diagnosis of Hair Disorders

Definitions

- **Alopecia:** Visible loss of hair, usually refers to scalp.
- **Color changes:** Canities = gray hair; poliosis = localized white hair.
- **Effluvium:** Increased daily hair loss; normal loss 25–100 hairs daily, so effluvium is loss of > 100 hairs daily.
- **Hair shaft anomaly:** Inherited or acquired structural hair shaft defect.
- **Hirsutism:** Increased hair growth in male pattern in a woman.
- **Hypertrichosis:** Increased hair growth in an area that is not normally rich in hairs.
- **Terminal hair:** Hair reaching into deep dermis or subcutaneous fat, 50–100 m in diameter, rich in pigment with medulla when examined microscopically.
- **Vellus hair:** Finer, more superficial hair, usually < 2 cm in length, < 30 m in diameter, with no pigment and no visible medulla when examined microscopically.

Approach to Alopecia and Effluvium

- **Careful history** (especially important when dealing with hair disorders).
  - *How long have you had hair loss?*
  - *Any associated problems*—nail changes, other skin problems, symptoms (scalp burning, pain pruritus), changes in general health?
  - *Personal history:* Endocrinologic disorders especially thyroid), underlying diseases (connective tissue disorders), operations, accidents, pregnancy and delivery, miscarriages, infections, severe acute illnesses in past year, diets (crash diets in recent months)?
  - *Any treatment? Did it help?*
  - *Allergies? Atopy?*
  - *Medication history:* Hair loss is listed a complication of many medications, but there are only a few medications that often cause the problem. They include chemotherapy agents, beta-blockers, thyroxine in excess dosages, antithyroid agents, and aromatase inhibitors. The list of medications that cause hypertrichosis is also small (p. 515).
  - *Hair problems in the family:* Similar to present illness? Others?

  Caution: Patients generally deny the presence of male/female pattern baldness in their family; ask specifically about individual family members.
  - *Contact with animals:* Source of infection, especially for dermatophyte infections.
  - *Dietary habits:* Low protein or low iron diet? Zinc deficiency (especially in vegetarians and vegans, as zinc is found in meat and cheese)? Amphetamine misuse?
  - *Psychosocial history:* "Stress", anxiety, depression, other problems that could help explain a trichotillomania or overreaction to modest degree of hair loss.
- **Is there a pattern?**
  - *Male or female pattern baldness* (after Hamilton or Ludwig) indicates androgenetic alopecia (p. 500). Mixed patterns are common.
  - *Localized circular alopecia* without inflammation, and often with involvement of eyelashes or eyebrows, indicates alopecia areata (p. 503).
- **How much hair loss has really occurred?** Patients tend to overestimate the degree of hair loss. Try to confirm by looking at photos, such as on driver's license or credit card.

- **Check the hair shafts: RIB rule**.
  - **R***emoved easily*: Think of alopecia areata, dermatophyte infections, anagen effluvium with acute poisoning or chemotherapy, severe systemic infections, telogen effluvium, loose anagen hair syndrome in young girls.
  - **I***rregularly spaced*: Think of scarring alopecia, alopecia areata, traction alopecia.
  - **B***roken hairs*: Think of alopecia areata, artifactual alopecia, dermatophyte infection (*Microsporum*) traction alopecia, hair shaft anomalies.
- **Check the scalp:**
  - *Erythema and scales?* → seborrheic dermatitis, psoriasis, atopic dermatitis, contact dermatitis, dermatophyte infection.
  - *Acneiform lesions?* → acne keloidalis nuchae, folliculitis decalvans.
  - *Papules, nodules, ulcers?* → adnexal tumors, nevus sebaceus, aplasia cutis congenita, basal cell carcinoma, epidermoid cyst, metastasis, sarcoidosis, nodular amyloidosis.
  - *Suggestion of scarring?* (missing follicles, irregular distribution of hairs, epidermal atrophy, sclerosis, telangiectases, pus, erosions, blisters) → chronic cutaneous lupus erythematosus (discoid), lichen planus, localized morphea, alopecia mucinosa, bullous diseases).
  - *Use dermatoscopy:* Cadaver and exclamation point hairs such alopecia areata, irregular distribution or loss of follicular orifices indicates scarring alopecia, follicular keratotic plugs point towards lichen planus.

  Caution: Urgent attention is required to **exclude scarring alopecia** because of the possibility of underlying disease and the likelihood of further scarring if no treatment is undertaken.
- **Total body examination:**
  - Check the distribution of *terminal and vellus hairs* (hypertrichosis, hirsutism, secondary sexual characteristics, alopecia universalis).
  - Check for other clues of associated diseases on the skin or mucosa.
- **Biopsy:** The best approach is to obtain three 6 mm punches from the border sampling areas where the scarring is most recent. Biopsies should be parallel to the adjacent hair shafts. Two biopsies are for routine histology, PAS, and Giemsa—one sectioned longitudinally and the other transversely. The third should be frozen for immunofluorescence and other special tests. Topical and systemic corticosteroids should be stopped for 2–4 weeks before biopsy and all other topical medications stopped for 3 days. Most patients are reluctant to have three biopsies, so compromises are the rule.
- **Laboratory studies:**
  - *Routine blood studies:* Complete blood count (CBC), sed rate, (C-reactive protein (CRP), antinuclear antibodies (ANA), glucose, HbA1c, serum protein electrophoresis, iron, ferritin, thyroid function tests, liver and renal parameters. If the history does not suggest hormonal problems, routine (expensive) hormonal analysis is not useful.
  - *When diffuse non-scarring alopecia is present:* Routine blood studies plus syphilis serology, serum zinc, HIV test; in addition in women, free testosterone, dehydroepiandrosterone sulfate (DHEAS), prolactin (improper drawing procedure may lead to false-positive values: blood should be drawn after patient has been lying down for 10–20 minutes, should be done on an empty stomach before 10 a.m. and with cigarette smoking not allowed beforehand).

Further Diagnostic Possibilities

- **Wood's light (p. 23):** Always use to exclude easily overlooked *Microsporum* infections.
- **Hair count:**
  - This test is easily done by the patient and helps to quantify the effluvium. Most patients dramatically overestimate the numbers of hairs they are losing.
  - The same test can be used to assess therapy and helps convince even skeptical patients.
  - Method:
    - Day 1: Wash the scalp vigorously and brush the hairs.
    - Days 2–4 or 5: Do not wash hair, comb hair once daily each morning, save all the hairs each morning, count them and place in a separate envelope that is dated and numbered.
    - In the office, transfer this data into the patient's record.
- **Diagnosis of hair shaft anomalies:** Made by cutting hairs off close to the scalp with as little tugging or trauma as possible. The hairs can be embedded in a standard medium and covered with a coverslip, then examined with routine and polarization microscopy. In special cases, scanning electron microscopy may be needed.
- **Toxicologic examination:** Often requested by patients, but only rarely helpful and frequently misleading. Many heavy metals and a variety of other substances are deposited in the hair shaft and thus excreted from the body. If poisoning is suspected, 20–30 hairs should be obtained and one should consult with legal medicine experts or law authorities to be sure appropriate tests and ordered and, if criminal poisoning is a possibility, that the chain of evidence is kept intact.

Hair Cycle, Trichogram, and Trichoscan

- **Hair cycle (Fig. 2.7):**
  - On the scalp, each hair bulb spends 2–6 years producing a hair shaft (*anagen* phase), and then rests for 3–5 months (*telogen* phase). The transition from anagen to telogen lasts 2–5 weeks and is known as *catagen.*
    - ***Note:*** Anagen 1000 days; telogen 100 days; catagen 10 days.
  - With increasing age, the duration of the anagen phase decreases. The length of this phase is genetically determined and varies considerably from individual to individual. At the end of telogen, the hair separates itself from the follicle and falls out, either spontaneously with combing or brushing (< 100 hairs/day) or by hair washing (up to 300 hairs). A given hair follicles produces 10–12 hairs over a lifetime.
  - The proximal end of the hair shaft has a distinctive appearance during each phase. Telogen hairs have a club-like appearance that patients frequently fear is the root of the hair. Correcting this misconception alleviates much anxiety.
- **Trichogram:**
  - To be reproducible and useful, a trichogram must be done in a standardized way by an experienced individual. Problems include artifacts induced during removal of hairs, taking too few hairs, and errors in evaluating the hairs because of lack of understanding of the changes during the cycle.
  - The trichogram often has a positive psychological effect, in addition to quantifying the nature of the hair cycle. Patients sense that something is being done. A trichogram is not well-suited for monitoring therapy; the Trichoscan® is far superior for this purpose.

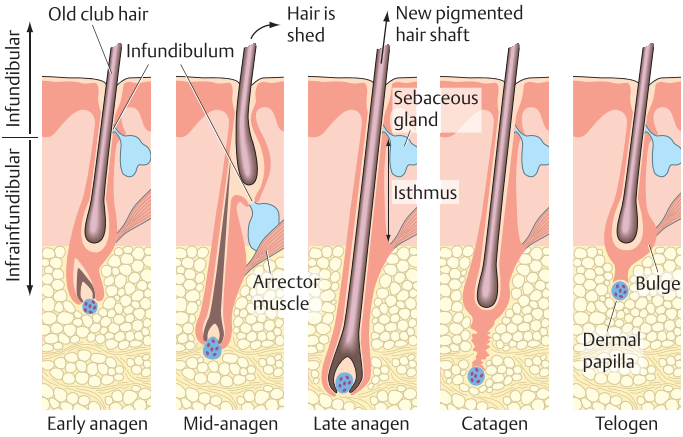


Fig. 2.**7** · Stages of the hair cycle.

- Method for analyzing the hair bulbs to identify in what stage hairs are being lost and thus to distinguish between different types of hair loss (Fig. 2.**8**):
  - *Shortened anagen phase:* Increased number of telogen hairs that can be recognized as bulged hairs without proximal pigment.
  - *Production of defective keratin:* Dysplastic hair bulbs with absent root sheath and proximal hair blub bent like a cane handle.

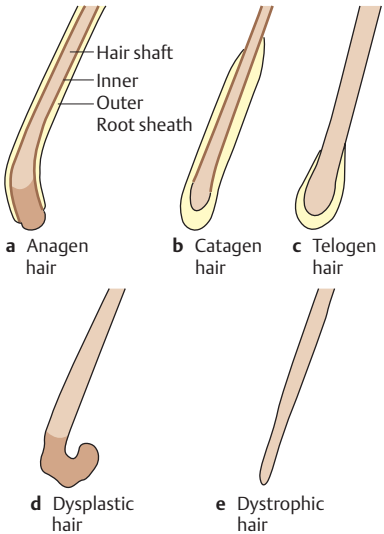


Fig. 2.**8 a–e** · Schematic representation of the hair bulbs during the physiologic hair cycle (**a**, **b**, **c**) as well as pathological findings (**d**, **e**) in trichogram.

  - *Toxic effects on keratin synthesis*: Dystrophic hair bulbs with immature hair shaft.
- Necessary materials:
  - Needle holder (remove spring).
  - Rubber tubing (to cover the gripping surfaces).
  - Slides and coverslips.
  - Mounting solution.
- Method:
  - Wait 5 days after last hair washing.
  - Take hairs from two sites (either frontal and occipital, or from edge of involved area and from uninvolved site).
  - Grasp 60–80 (at a minimum 40) hairs 1 cm from scalp with needle holder and pull them out briskly in the direction of the hair shaft.
  - Fan the hairs on a glass slide, apply mounting solution and coverslip.
  - Evaluate under the microscope.
- Normal values:
  - Anagen hairs 80–95%.
  - Catagen hairs 0–5%.
  - Telogen hairs up to 20%.
  - Dysplastic hairs 20–30% (in children with fine hair, up to 50%).
  - Dystrophic hairs up to 2%.
  - Hair density on scalp: 250–450 hairs/cm^2.
  - Hair growth rate: 1 cm/month or 0.3 mm/day.
- Frequent mistakes:
  - Hair washing or aggressive combing before procedure reduces number of telogen hairs.
  - Poor epilation technique, such as removing too slowly or in the wrong direction, leads to increased number of dysplastic, pseudodystrophic, and broken hairs, as well as leaving more firmly adherent anagen hairs behind, making the trichogram results unreliable.
  - Confusing dysplastic and dystrophic hairs. Dystrophic hairs never have the fishhook or cane form of dysplastic hairs.

► **Trichoscan:**

- The Trichoscan is a recently-developed phototrichogram system that uses digital photography and an elegant computer program to provide objective measurements of hair density and hair follicle activity (anagen/telogen ratio). It is ideally suited to following these parameters during therapy. It offers many advantages over a trichogram including speed, painlessness, reproducibility, and ease of archiving.
- *Method:* On day 0, a small area of the scalp is shaved—about 1.8 cm^2—at a site about 2 cm behind the anterior hairline. This site can be easily covered by most patients. After 3 days, the area is dyed with a special dye, in order to make it easier to distinguish hair follicles showing regrowth from those without activity. Then a digital image is made at 20× magnification. The software then analyses the picture, measuring hair density and anagen/telogen ratio, as the anagen hairs are identified as having grown 0.3 mm/day.

3 Other Diagnostic Methods

3.1 Phlebologic Diagnosis

History, Inspection, and Palpation

► The **phlebologic history** searches for both predisposing factors and current problems. The most important points are shown in Table 3.**1**.

Table 3.1 · **Phlebologic history and interpretation**

History	Interpretation
Nature of pain: burning, lancinating, radiating	No correlation between nature of pain and phlebologic problem; often caused by orthopedic or neurologic problems
Calf cramps	Not common with varicose veins; more likely to reflect arterial disease, hypothyroidism, hypokalemia, osteoporosis, or spondylarthritis; often no cause found
History of fracture or injury to leg, especially with prolonged disuse.	Risk for phlebothrombosis; carefully exclude post-thrombotic syndrome
Family history of venous diseases, age of onset	Family history and early onset suggest disease is likely to be progressive and severe
Stationary job (standing/sitting)	Increased risk for varicose veins
History of thrombosis	Distinguish carefully between phlebitis and phlebothrombosis; patients often confuse the two
Allergies	Patients with chronic venous insufficiency at increased risk for allergic contact dermatitis
Heavy legs, tendency to swelling, warmth, pruritus	Unspecific complaints, but often associated with chronic venous insufficiency

► **Inspection:**
- The patient should be examined while standing.
- In thin patients, varicosities are easily visualized. Incompetent perforating veins are seen as a compressible, protruding nodule (blow-out vein).
- *Cutaneous manifestations of chronic venous insufficiency include:* Edema, corona phlebectatica paraplantaris (prominent small veins at edge of foot), starburst veins, dilated small veins (venectasia), pigmentary changes, stasis dermatitis, dermatosclerosis (hypodermatitis), atrophie blanche, and ulceration (stasis ulcer). These features correlate with the severity of the venous stasis.
- Stages of chronic venous insufficiency (I–III) are based on Widmer's classification (p. 555).
- Simply the location of a leg ulcer allows one to make an intelligent guess at the cause (Fig. 3.**1**).

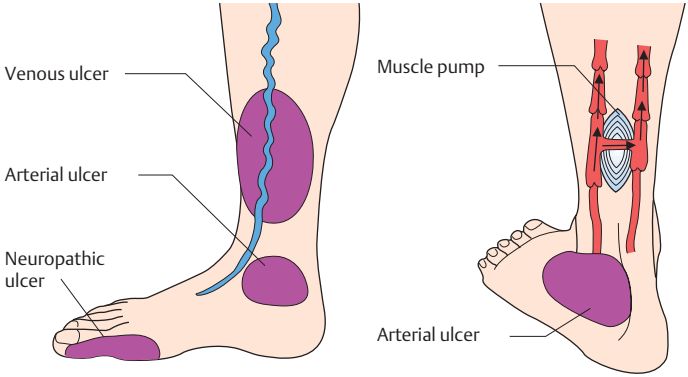


Fig. 3.1 · Location of leg ulcers.

► **Palpation:**
- Palpation allows one to readily recognize edema, induration, and perforating veins. When incompetent perforating veins are palpated, a buttonhole defect in the fascia can often be detected; sometimes it is tender.
- When the proximal great saphenous vein is palpated in the groin, one can detect an incompetent saphenofemoral junction valve as the patient coughs. Sometimes there is a permanent thrill if there is enough backflow.

Further Diagnostic Procedures

New diagnostic procedures such as Doppler ultrasonography and duplex ultrasonography have greatly reduced the important of phlebography. Functional testing with devices such as light reflection rheography, digital photoplethysmography, and venous occlusion plethysmography are less often employed. Clinical functional tests such as the Trendelenburg tests are of little more than historical interest.

Doppler Ultrasonography

► **Principle:**
- Doppler ultrasonography is based on the observation by Doppler that an apparent change in frequency of waves results when the transmitter and receiver are in motion relative to one another. Shifts in frequency of emitted ultrasonic waves and their echoes are influenced by reflection of the blood flow. The change in frequency allows one to determine the direction of flow and measure the velocity.
- Usually 4 MHz and 8 MHz devices are used to assess peripheral vessels. At these frequencies, shifts are audible. The 4 MHz unit is used for deep vessels, the 8 MHz for superficial vessels.

▶ ***Note:*** With increasing frequency, resolution improves but depth of penetration decreases.

- *Indications:* Doppler ultrasonography is most useful for identifying nonfunctioning valves in both superficial and deep veins, as well as for assessing arterial flow. In most instances, it is not sensitive enough to diagnosis a thrombosis; one exception is detection of pelvic vein thrombosis.

► **Method:**
- *Subfascial system:* The patient lies on his back. First, the common femoral artery is identified in the groin. It should have a triphasic flow profile (peak–dip–peak). Then the receiver is placed over the various veins; the sound of the flow varies with breathing. When the Valsalva maneuver is performed, valvular incompetence can be identified by an audible reflux. The main causes of valvular insufficiency include previous phlebothrombosis, marked varicosities with secondary changes in deeper veins, and congenital absence of valves.
- The *popliteal space* is examined in the same way with the patient lying on their abdomen. The Valsalva maneuver is replaced by proximal and distal manual compression and distal decompression. The tibial arteries and veins are assessed in the same way.
- *Epifascial system:*
  - Reflux in the great and small saphenous veins is checked with the patient standing after distal compression. The extent of reflux is used to classify the degree of varicosities using the Hach scale (I–IV) (p. 554).
  - Incompetent perforating veins are best located with duplex ultrasonography. They can be identified with Doppler ultrasonography by applying a proximal tourniquet and then listening for distal reflux.

Duplex Ultrasonography

► **Principle:** Doppler ultrasonography is combined with conventional B-mode ultrasonography to show flow of blood within a vessel. The intravascular flow is color coded; colors differ depending on flow towards or away from the sound. Frequencies of 5.0–14.0 MHz are used.

► **Indications:** This technique allows one to also assess the nature of the vessel wall, the severity of a valvular defect, degree of recanalization, amount of collateral flow, and the speed of the reflux flow. Arterial narrowing and occlusion can also be assessed Perforating veins and the variable location of the junction of the small saphenous vein with the popliteal vein can be more accurately identified and marked on the skin (duplex mapping).

Compression Ultrasonography

► **Indications:** The main use is to detect phlebothrombosis. Doppler ultrasonography is only useful for pelvic vein thrombosis (loss of the breathing-modulated flow of the common femoral vein). Otherwise, compression ultrasonography is standard.

► **Principle:** The veins are compressed with the scanner, using B-mode ultrasonography. Compression should be slight; in the case of a thrombus, compression is more difficult. The sensitivity and specificity of this approach are over 95%, thus just as good as phlebography. The latter is reserved for cases where compression ultrasonography is unclear or cannot be performed.

Light Reflection Rheography and Photoplethysmography

► **Principle:** Light reflection rheography (LRR) and photoplethysmography (PPG) are indirect methods of measuring the return transport capacity of the venous system. The measurements are made with a measuring head that is fastened 10 cm above the medial malleolus. The head contains three sources of infrared light and one receiver. Light directed into the skin is reflected by local blood flow in the skin and redirected towards the receiver where they are captured by a photo element which then transmits electrical impulses that are recorded (Fig. 3.**2**).

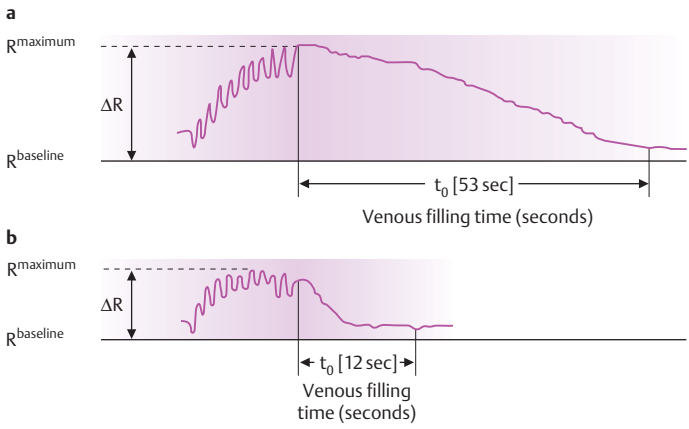


Fig. 3.2 a,b · LRR/PPG curves. **a** In a normal adult. **b** In a patient with venous insufficiency.

- **Indications:**
  - Estimation of the effectiveness of operations to remove incompetent saphenous veins or perforating veins.
  - Quantitate pumping capacity of calf muscles.
  - Although the method is simple and easily performed, it gives limited information that can only be used in conjunction with Doppler and duplex ultrasonography results.
- **Procedure:** First the calf muscles are used by performed dorsal flexion of the foot 10°. This reduces the degree of filling of the subpapillary veins. Then when the patient is still, the veins refill.
- **Interpretation:** The resulting curves allow one to determine two parameters:
  - *R-difference* (R), which reflects the difference in filling of the veins.
  - *Refilling time* (t_0):the time needed for the veins to refill. In normal individuals, this is around 25 seconds. A reduced refilling time results with deep or epifascial reflux, but also with perforator vein reflux alone.
- **Therapeutic consequences:** If the refilling time is shortened, surgery or sclerosing injections might lead to improvement both in this parameter and in venous stasis. Using a tourniquet, the great saphenous vein or an incompetent perforating vein can be compressed and then the refilling time measured again. If the refilling time is increased, then the chronic venous insufficiency is at least partially correctable and treatment is appropriate.

Plethysmography

- **Principle:** Plethysmography measures volume changes and thus arterial flow. Rapid volume changes in a limb can only be caused by changes in amount of blood.
- **Indication:** Diagnosis of leg and pelvic thromboses; monitoring of thrombosis therapy.
- **Other uses:** Demonstrating venous flow obstruction, measuring pump function of calf muscles, measuring the capillary filtration rate.

Strain-gauge Plethysmography

- **Principle:** Mercury in rubber tubes changes its resistance as the tubes are stretched. The strain-gauge tubes are placed around the extremity. Changes in circumference are reflected in changes in electric current, which can be recorded.
- **Example:**
  - *Demonstration of obstructed venous return:* The leg is held at 45° with the knee joint flexed at 170°. The speed of the venous flow from the calf and foot is measured after compression has been applied and released.
  - A strain-gauge tube is placed around the calf. A cuff with 80–85 mm Hg pressure is placed around the thigh.
  - *Venous capacity:* The plethysmograph measures at minute intervals the increasing venous volume (= vein capacity in mL/100 mL).
  - *Venous drainage:* The pressure cuff is released suddenly. The rate of drop in venous volume over 2 minutes is measured to reflect the degree of venous resistance (vein draining in mL/100 mL per minute).
- **Interpretation:**
  - If there is an obstruction to venous flow proximal to the measuring device, venous capacity and venous drainage are reduced.
  - Venous drainage values < 30 mL/100 mL per minute are abnormal.

  Caution: Dermatosclerosis or edema can also cause low values.
- **Reliability:** Leg vein thrombosis can be diagnosed with 90% accuracy when the veins are completely blocked and relatively high. The procedure is less helpful for calf and thigh thrombosis and in the postthrombotic syndrome.

Phlebodynamometry

- **Principle:** The venous pressure in the leg is measured directly.
- **Indications:** The main indication is in clarifying a postthrombotic syndrome, to see if surgical invention might be helpful. In addition, it offers the best way of quantifying the functional venous capacity.
- **Method:** A dorsal foot vein is cannulated with a butterfly needle. Then the venous pressure is measured with the patient standing using either a manometer or electronic device. The normal pressure varies with the height of the patient (distance from heart to foot vein). After the baseline pressure is established, the patient does 15 toe stands. Then the procedure is repeated with a tourniquet occluding the vein that is being considered for removal.
- **Interpretation:** Normally the pressure drops by 50%. The time for refilling is comparable to that with light reflection plethysmography. Less drop in pressure or a slower refilling time suggest postthrombotic syndrome. In the extreme situation, the pressure rises with exercise, indicating marked obstruction. If the parameters improve after the tourniquet is applied, then the compromised vein should be removed.

3.2 Allergy Testing

Patch Testing and Photopatch Testing

- **Principle:** In order to prove type IV contact sensitization, the potential allergen is applied to the skin under occlusion in a nontoxic concentration for 24–48 hours. In sensitized individuals, a localized dermatitic reaction occurs. In photopatch testing, the allergens are applied in parallel, and one set is irradiated.

- **Indications:**
  - Allergic contact dermatitis (high sensitivity).
  - Photoallergic or phototoxic reactions following UV light exposure.
  - Fixed drug reaction (testing at site of reaction).
  - Protein contact urticaria.
  - Drug reactions and vasculitis (additional readings at 20 minutes and 6 hours, low sensitivity, use is controversial).
- **Procedure:**
  - The test substances are applied to a 50 μL aluminum chamber or a patch (hence the name), which is attached to hypoallergenic tape.
  - The allergens are usually diluted with white petrolatum or water; less often alcohol, olive oil, isopropyl myristate or acetone may be used.
  - As a negative control, white petrolatum is usually chosen.
  - The tape and aluminum chamber are firmly attached to the skin with additional wide strips of tape.
  - The patches are applied to the upper $^1/_3$ of the back, or in special circumstances the triceps area.
- **Interpretation (Table 3.2):**
  - The test substances are removed after 48 hours (some recommend 24 hours but we prefer 48 hours). After waiting 30 minutes to let local irritation subside, the reaction is read. The site is checked again after 72 hours and in some instances after 96 hours (in photopatch testing and if reactions are unclear).
  - Sometimes it is wise to re-examine the site after several days, as some reactions, such as those to metals and corticosteroids, are notorious for appearing late.
  - If contact urticaria is suspected, the site should be read after 20 minutes. These substances should be applied separately from the regular patches, as once the tape has been pulled off, even if it is re-applied, occlusion is compromised.
- **Side effects:**
  - *Exaggerated dermatitis reaction:* Some patients with severe allergic contact dermatitis may experience a flare following patch testing. Treatment with topical corticosteroids usually suffices.
  - Severe reactions, especially photopatch test reactions, can lead to postinflammatory *hyperpigmentation* that may be disturbing to the patient.
  - Sensitization to a test substance occurs only very rarely.

Table 3.2 · **Interpretation of patch tests**

Symbol	Appearance	Interpretation
–	No reaction	Negative
?	Only erythema, no infiltrate	Allergic, irritant, or unclear
±	Few follicular papules	Allergic, irritant, or unclear
+	Erythema, infiltrate, discrete papules	Allergic reaction (1+)
++	Erythema, infiltrate, papules, vesicles	Allergic reaction (2+)
+++	Erythema, infiltrate, confluent vesicles	Allergic reaction (3+)
ir	Pressure changes, blisters, irritation from tape outside area of application	Irritant reaction
nt		Not tested

- *Anaphylactic shock:* In rare cases, exposure to a patch test allergen may cause anaphylaxis in a very sensitive individual. The risk is greatest with antibiotics. If the patient gives a history of a type I reaction, then patch testing should be done with care, with resuscitation equipment available.
- *Angry back syndrome:* Patients with active dermatitis often react to multiple allergens producing numerous false-positive reactions. After the dermatitis and the patch test reactions have calmed down, the patient should be re-tested for clinically relevant allergens. Any patient with more than seven positive reactions to non-cross-reacting allergens should be suspected of having angry back syndrome.
- *False-negative reactions:* Sometimes patients are truly allergic to a substance but patch testing fails to reproduce the clinical setting. For example, an individual may be sensitive to preservatives in eye drops, but may not react to the same material on the thicker skin of the back. The test area can be made more sensitive by repeated tape stripping, or a more sensitive site such as the temple can be chosen.

Note: Patch testing should only be done when there is a reasonable clinical suspicion of allergic contact dermatitis. Since the allergen concentration is chosen so that some normal individuals react to the patch, a small number of false-positive reactions are built into the system. Thus every positive reaction should be viewed for its clinical relevance. Simply issuing an "allergy pass" listing all positive patch tests helps neither the patient nor future treating physicians.

Patch Test Series

- **Standard test series:** In Germany, the standard series is continually under modification but currently consists of 29 allergens that enable the identification of most common causes of allergic contact dermatitis. The current collection is shown in Table 3.**3**.

Photopatch Testing

- **Indication:** To confirm photoallergic reaction.
- **Method:** The standard series of photoallergens is applied in duplicate. After 24 hours, one set is removed and the area irradiated with 5–10 J/cm^2 or half the minimal erythema dose of UVA. Both sides are read after another 24, 48 and 72 hours.
- **Interpretation:** The same system is used as for regular patch testing. When the nonirradiated site is normal and the irradiated site shows a reaction, a photoallergic reaction has been shown.

Rub, Scratch, Prick, and Intracutaneous Testing

- **Indications:**
  - *Acute allergic reaction* (type I reaction): Drug reactions, urticaria, food allergies, allergic rhinitis, allergic conjunctivitis, allergic asthma.
  - Some instances of *delayed allergic reactions*, such as vasculitis and purpura, although the utility of this procedure is controversial.
- **Methods:**
  - *Rub test:* The allergen is applied to the intact skin on the forearm. This is the least sensitive test for type I allergies, suited for very sensitive patients (those with severe reactions) and when testing native allergens.

Table 3.3 · Standard patch test series of the German Contact Allergy Group

No.	Substance	Concentration	Vehicle	24 h	48 h	72 h	96 h
1	Potassium dichromate	0.5%	WP				
2	*p*-Phenylene diamine	1.0%	WP				
3	Thiuram mix	1.0%	WP				
4	Neomycin sulfate	20.0%	WP				
5	Cobalt (II) chloride 6 H_2O	1.0%	WP				
6	Benzocaine (ethyl aminobenzoate)	5.0%	WP				
7	Nickel (II) sulfate 6 H_2O	5.0%	WP				
8	Colophony resin	20.0%	WP				
9	N-isopropyl-N′-phenyl-*p*-phenylene diamine	0.1%	WP				
10	Wool wax alcohol	30.0%	WP				
11	Mercapto mix without MBT	1.0%	WP				
12	Epoxide resin	1.0%	WP				
13	Balsam of Peru	25.0%	WP				
14	*p*-tert-Butyl phenol formaldehyde resin	1.0%	WP				
15	Formaldehyde	1.0%	Water				
16	Fragrance mix	8.0%	WP				
17	Mercury (II) amide chloride	1.0%	WP				
18	Turpentine	10.0%	WP				
19	(Chlor)-methylisothiazolinone (MCI/MI)	100 ppm	Water				
20	Paraben mix	16.0%	WP				
21	Cetyl stearyl alcohol	20.0%	WP				
22	Zinc diethyldithiocarbamate	1.0%	WP				
23	Dibromodicyanobutane + 2-phenoxyethanol	1.0%	WP				
24	Propolis	10.0%	WP				
25	Bufexamac	5.0%	WP				
26	Compositae mix	6.0%	WP				
27	Mercaptobenzothiazole (MBT)	2.0%	WP				
28	Lyral	5.0%	WP				
29	Dispersion mix blue 126/106	1.0%	WP				

WP = white petrolatum.

- *Scratch test:*
  - The skin of the forearm is scratched with a lancet, so that only the stratum corneum is damaged; no bleeding should occur. The allergen is applied as a solution.
  - Histamine (1 mg/mL) solution and normal saline are used as controls.
- *Prick test:*
  - About 3 μL of allergen in solution is applied to the skin of the forearm. Then the skin is pricked with a lancet or needle. The same controls are used as for scratch test.
- The prick test is better than the scratch test, as it is more sensitive and more reproducible. The scratch test is reserved for native allergens that are hard to dissolve, such as some foods and medications. The "prick in prick" test can also be used, where the lancet is first stuck into the allergen (for example, a nut) and then into the skin.
- *Intracutaneous test:* 0.02–0.05 mL of an antigen solution is injected superficially in the skin using a tuberculin syringe. The same controls are used as above.

► **Interpretation:** All these skin tests are read at 20 minutes, and if a delayed reaction is suspected, again after 6 and 24 hours.

- *20 minute reaction:* The allergen site is compared with the positive wheal from histamine and the negative wheal from the control. There is no standardized method of reading. We recommend measuring the wheal and the peripheral erythema; for example, $^{5}/_{12}$ means a 5 mm wheal with the erythematous ring measuring 12 mm. Positive reactions must be more than 50% of the size of the histamine wheal.
- *6 hour reaction:* The wheal and the erythema are once again measured.

Choosing the Right Test

► **The gold standard is the prick test.** The widest array of well-tested commercial allergens are designed for this procedure. The sensitivity of the test for inhalation allergens is high. In contrast, for food allergens, especially fruits and vegetables, the sensitivity is low. Thus, it is often necessary to use the foods themselves for testing. Since native allergens can lead to severe reactions, it is wise to do rub or scratch tests before doing prick tests.

► **The most sensitive in-vivo allergic test is the intracutaneous test.** Here the risk of a severe allergic reaction is the highest, and special sterile allergen solutions are required. Thus intracutaneous testing is reserved for special situations such as titrating the reaction in insect toxin allergies.

Provocation Tests

► **Indications:** If the skin tests are contradictory or do not fit with the history, the relevant allergen can be administered as a form of challenge, using a variety of routes.

! ***Caution:*** All provocation tests are potentially dangerous and must be done in a setting where resuscitation measures are readily available.

► **Methods:**

- *Conjunctival provocation:*
  - *Principle:* The antigen is prepared in a sterile 0.09% NaCl solution. One drop is placed in the conjunctival sac.
  - *Reactions:* After about 2 minutes, the conjunctiva becomes reddened. The solution can also be irritating, so a control should be applied to the other eye.

- *Nasal provocation:*
  - *Principle:* The allergen extract is blown into the nose with a vaporizer.
  - *Reactions:* After about 10 minutes, sometime much sooner, the patient begins to experience sneezing, rhinorrhea, tearing and in severe reactions headache and bronchospasm.
  - *Interpretation:* The reduced nasal airflow or increased resistance can be quantified with a rhinomanometer. The identification of eosinophils in the nasal secretions also helps quantify the reaction.
- Bronchial provocation:
  - *Principle:* The allergen extract is inhaled.
  - *Reactions:* Bronchospasm.
  - *Interpretation:* Pulmonary function testing is used before and after exposure. A positive test is proven when the FEV_1 drops to $< 80\%$ of original value.
- *Oral provocation:*
  - *Principle:* Suspected medications or foods are given in capsules or concealed in foods with a intense covering taste; in Germany, blackcurrant juice is often used. Start with $^1/_{10}$–$^1/_{100}$ of the usual "dose." A placebo should be employed.
  - *Reactions:* Recurrence of the signs and symptoms described in the history, involving the skin, lungs, gastrointestinal tract, or other organs.
  - *Interpretation:* The gold standard for challenging patients with historically documented food allergies is double-blind placebo-controlled testing. Many patients are children; in this instance, the parents must also be blinded.

Factors Influencing Test Results

- **Site of testing:** Different areas of the skin react differently to challenge. For example, the upper back is more reactive than the lower back. The difference has been estimated as threefold. The back is also more sensitive than the forearm; under the same conditions, a wheal on the upper back will be twice as large as one on the forearm. The most sensitive area on the arm is the antecubital fossa. The ulnar aspect is more reactive than the radial.
- When testing with type I allergens there is a risk of a systemic anaphylactic reaction. This is especially true with tests for food allergens and insect toxins. In such instances, it is wiser to test on the forearm, as reactivity is lower and a tourniquet can be applied to reduce systemic spread, if needed.
- **Influence of medications:** Many medications can influence allergy testing, as shown in Table 3.**4**.

Serologic Tests

Identification of IgE

- **Principle:** The radio-allergosorbent test (RAST) identifies IgE antibodies directed against specific allergens.
- **Indications:** In-vitro diagnosis is a useful addition to the history and in-vivo tests. The sensitivity is comparable to prick tests and is also dependent on the quality of the allergen preparations.
- **Interpretation:**
  - IgE values measured with ELISA, FAST, or radiochemical methods.
  - Results are given in semi-quantitative fashion: RAST class 0 (negative); RAST classes 1–4 (positive).
  - In the CAP test, the RAST class 4 is divided into CAP classes 4–6. CAP 1–3 correspond to RAST 1–3. The CAP test employs a different system of binding the antigen to a test surface.

Table 3.4 · Influence of medications on test reactions

Medication	Prick, scratch, intracutaneous tests	Patch tests	Provocation tests	Photopatch tests
Antihistamines				
Topical	↓ ↓ ↓	(↓)	0	(↓)
Systemic	↓ ↓ ↓	(↓)	↓	(↓)
Corticosteroids				
Topical	(↓)	↓ ↓ ↓	↓ ↓ ↓ [b]	↓ ↓ ↓
Systemic	↓ ↓	↓ ↓ ↓	↓ ↓	↓ ↓
B-mimetics	0	0	↓ ↓ ↓ [b]	0
Theophylline	0	0	↓ ↓ [b]	0
Indomethacin (NSAIDs)	0	0	0	↓
Cromoglycates	0	0	↓ ↓ ↓ [a,b]	0
Tranquilizers, antidepressants	↓	0	(↓)	0

a, conjunctival provocation; b, bronchial provocation.

Special Procedures

When a false-negative IgE test is suspected, the **basophil release test** can be employed. Basophils are challenged with the allergen and their release of histamine or leukotrienes quantified. In this way, bound IgE is also studied.

There are also many other tests including macrophage and leukocyte migration inhibition assays, as well as the lymphocyte transformation test (employed in some centers to study drug reactions). All of these tests are expensive and are not recommended for routine allergy testing. They should not be used to prove an allergy, either in a medical or medicolegal sense.

3.3 Light Testing

- **Indications:** Light testing (phototesting) is indicated whenever a skin disease is suspected of being caused by or aggravated by light. Phototesting is also used to determine the appropriate doses before starting UV therapy and to determine how light-sensitive an individual is.
- **Skin types:** An appreciation of the different skin types and their relative sensitivity to UV irradiation is essential before contemplating phototesting. Fitzpatrick and colleagues first described these types in Boston, based on 30 minutes sun exposure at mid-day in summer (Table 3.**5**).

Minimal Erythema Dose (MED)

- **Definition:** The amount of UV required to induce erythema in an irradiated site. The faintest erythema extending to the margins of the irradiated field is taken as a positive result (Table 3.**6**).

Table 3.5 · Skin types (after Fitzpatrick)

Skin type	Erythema	Pigment
I	Always	Never
II	Always	Sometimes
III	Sometimes	Always
IV	Never (Mediterraneans)	Always
V	Never (Asians, Indians)	Independent of sun exposure
VI	Never (Blacks)	Independent of sun exposure

Caution: Types V and VI can also develop sunburn after extreme exposures and darken.

Table 3.6 · Interpretation of light testing

Grade	Clinical Findings
0	No erythema
+/–	Recognizable but irregular erythema
+	Uniform faint erythema (used for MED)
++	Prominent erythema without edema
+++	Intense erythema with edema and pain
++++	Intense erythema and edema, marked pain, sometimes blister formation

► **Method:**
- The determination of the MED is done separately for UVA and UVB. The testing should be done with the same device with which therapy is planned, or at least with a device that emits the same quality of irradiation.
- Testing is carried out on previously nonirradiated skin, usually the buttocks. One can either use a plate with five holes, each about 1 cm^2, transmitting varying degrees of UV, or with a system where a light-impermeable shield has a number of small apertures that can be opened manually to increase the dose of light in a stepwise manner.
- UVB testing is read after 24 hours.
- For UVA testing, the MED is not applicable. Either immediate pigment darkening (IPD) can be assessed right after exposure or minimal tanning dose (MTD) can be determined after 24 hours.

Photo Provocation Testing

► **Principle:** Some skin diseases (lupus erythematosus, polymorphous light eruption) can be reproduced by exposure to repetitive UV light. In some instances, this is diagnostically useful when the clinical picture is unclear and other tests have failed to answer the question. In rare cares, provocation testing is done with visible light, as in some cases of light-induced urticaria.

► **Method:**
- The provocation fields should be 5 × 5 cm.
- *Visible light* (400–800 nm): exposure for 10 minutes, reading immediately and after 30 minutes.

- *UVA* (320–400 nm): exposure on four consecutive days: skin type I–II 60 J/cm^2, skin type III–IV 100 J/cm^2. Reading immediately, after 24 hours, and then after last exposure, readings also at 48 and 72 hours as well as 1 week (delayed reactions common in lupus erythematosus).
- *UVB* (280–320 nm): provocation testing rarely needed.

Caution: There is a marked risk of sunburn.

- When a photoallergic or phototoxic reaction is suspected, caused either by ingested or topically applied agents, phototesting can be combined with exposure to agent to confirm the relation.

Minimal Phototoxic Dose (MPD)

► **Definition:** The MPD is the minimal UVA dosage that, combined with a standardized psoralen dosage, causes a barely visible uniform erythema. The MPD is used to assess the patient's sensitivity before starting PUVA therapy.

► **Method:**

- The patient receives a standardized, weight-adjusted dose of psoralen (p. 607). The same test area is used as for MED.
- For skin types I and II, doses of 0.5, 1.0, 2.0, 4.0, and 6.0 J/cm^2 are administered; for skin types III and IV, 1.5, 3.0, 6.0, 7.5 and 9.0 J/cm^2.
- The reaction is read after 72 hours, when a PUVA reaction is maximal. Thus it is ideal to irradiate on Friday and read on Monday.

► **Interpretation:** The light dose needed for a ± finding (Table 3.**6**) is the MPD.

3.4 Ultrasonography

Ultrasonography is discussed above in detail for phlebologic diagnosis, but it also has other uses in dermatology.

High-Frequency Cutaneous Ultrasonography

► **Principle:** A 20 MHz transducer with integrated gel stand-off pad and color coding is used.

► **Indications:** Measuring thickness of tumors before surgery, monitoring skin thickness, especially for scleroderma but also for psoriasis and in a variety of experimental settings.

Lymph Node and Soft Tissue Ultrasonography

Principle: A 7.5–14 MHz transducer is used with integrated water bath, along with color-coded duplex ultrasonography and power mode to show the perfusion pattern (central–peripheral).

Indications:

- Absolutely essential in the follow-up of malignant melanoma and other malignant skin tumors where there is a risk of nodal involvement, as the sensitivity is increased by at least 30%.
- Combined with fine needle aspiration to diagnosis melanoma metastases.
- Used preoperatively to assess the location of a tumor in relation to nerves, vessels, and other soft tissue structures.

Characteristic echo patterns:

- *Melanoma metastasis:* Echo-poor to echo-free, balloon-shaped structure with dorsal signal enhancement, especially when quickly growing hemorrhagic-necrotic metastases (length/width index < 2) are depicted.

- *Reactive lymph nodes:* Oval structure with echo-rich center and echo-poor periphery. When inflamed, echo-poor area increased (length/width index >2).
- *Lymphoma:* Large echo-poor structures, often irregular and confluent, with eccentric echo-rich centers, and typical branching of vasculature.
- *Other metastases:* Usually echo-poor, noncompressible structures with irregular vascular pattern.
- *Hematoma:* Early lesions are echo-poor structures with dorsal signal enhancement; later heterogenous, diffuse echo-rich interior structures as sign of organization.
- *Seroma/lymphatic cyst:* Well-circumscribed, echo-poor compressible structure with dorsal signal enhancement; later appearance of internal echo-rich structures suggesting septae.
- *Lipoma:* Circumscribed subcutaneous structure, varying from echo-poor to echo-rich, depending on degree of fibrosis, but with a sharp border.
- *Abscess:* Poorly circumscribed, echo-poor, compressible structure.

Caution: All space-occupying lesions should be re-examined after 4 weeks. If they are progressing, then either fine needle biopsy or excision should follow.

Note: Prospective studies have shown that the early identification of melanoma metastases with ultrasonography leads to a significant increase in the overall survival.

4 Viral Diseases

4.1 Overview (Table 4.1)

Table 4.1 · Overview of relevant dermatologic viral diseases and their causative agents

Virus group	Disease
Poxvirus	
Variola virus	Smallpox
Vaccinia virus	Vaccinia and related diseases
Cowpox/cat pox virus	Cowpox, cat pox
Paravaccinia virus	Milker's nodule
Parapoxvirus ovis (PPOV)	Orf (ecthyma contagiosum)
Molluscum contagiosum virus	Molluscum contagiosum
Herpesvirus	
Herpes simplex virus (HSV-1, HSV-2)	Herpes simplex
Varicella-zoster virus (VZV)	Varicella (chickenpox), zoster
Human cytomegalovirus (CMV)	Severe infections in immunosuppressed patients, neonates; Gianotti–Crosti syndrome
Epstein–Barr virus	Infectious mononucleosis (often with ampicillin/amoxicillin rash); Gianotti–Crosti syndrome
Human herpesvirus 6	Exanthem subitum
Human herpesvirus 8	Kaposi sarcoma
Picornavirus	
Coxsackieviruses	Hand-foot-and-mouth disease; herpangina; various exanthems
ECHO viruses	Various exanthems
Paramyxovirus	
Measles virus	Measles
Mumps virus	Mumps

Continued Table 4.1 ▶

Table 4.1 · Continued

Virus group	Disease
Togavirus	
Rubella virus	Rubella (German measles)
Hepadnavirus	
Hepatitis B virus	Gianotti–Crosti syndrome
Flavivirus	
Hepatitis C virus	Co-factor in several disorders including porphyria cutanea tarda, cryoglobulinemia, and in some countries lichen planus
Parvoviruses	
Parvovirus B19	Erythema infectiosum
Papillomavirus	
Human papillomaviruses (HPV)	Warts, condylomata, cervical carcinoma
Retroviruses	
HIV-1, HIV-2	HIV/AIDS
HTLV-1	Adult T-cell leukemia lymphoma

Note: The common childhood exanthems are considered under Dermatoses in Childhood (p. 571).

4.2 Poxvirus Infections

Introduction

- **Virology:** Poxviruses are complex DNA viruses and the largest viruses.
- **Primary hosts:** Humans, monkeys, cows, sheep, cats.
- **Major groups:**
  - Orthopoxviruses (smallpox, vaccinia, cowpox, monkeypox).
  - Parapoxviruses (milker's nodule, orf).
  - Miscellaneous (molluscum contagiosum).

Smallpox (Variola vera)

- **Definition:** Acute viral infection, highly contagious, with marked mortality.
- **Epidemiology:** Smallpox was declared extinct in the early 1980s by the World Health Organization. Since then, because of the discontinuation of vaccination and the lack of natural exposure, the overall resistance has become greatly reduced.

Laboratory accidents, spontaneous mutations in animal pox viruses, and acts of terrorism are all potential pathways for the reintroduction of this feared infection.

- **Clinical features:**
  - Sudden onset of fever, chills, malaise and arthralgias.
  - Rapid development of exanthem; initially macules, then blisters, pustules, and finally crusts and scars.
  - All lesions are always in the same stage (synchronous development).
  - Black pox refers to hemorrhagic lesions in the skin and mucosa, as well as in internal organs; frequently fatal.
- **Diagnostic approach:** History, identification of virus with electron microscopy (negative staining), viral culture, serology.
- **Differential diagnosis:** Chickenpox, cowpox, monkeypox, severe acute acne, meningococcal septicemia, acute generalized exanthematous pustulosis (pustular drug eruption).
- **Therapy:** Isolation of suspected cases, contact Centers for Disease Control or local public health officials; vaccinia immune globulin, semicarbazone derivatives, and symptomatic measures (topical antiseptics, supportive care).
- **Immunization:** Vaccines are available. Individuals with a high risk of exposure from terrorist activity (soldiers, emergency room workers) have been immunized in some countries; many developed countries have large stores of vaccines for use should smallpox break out.
- **Immunity:** Survivors are immune for many years.

Vaccinia

- **Definition:** Cutaneous complication of smallpox vaccination.
- **Epidemiology:** Since vaccination is used so little today, few problems are seen. Vaccinia is a relative of the smallpox viruses whose exact origins are unknown. It elicits a much milder disease but with cross-immunity.
- **Clinical features:**
  - A*utoinoculation:* Vaccina virus transferred from vaccination site to other regions; grouped ulcerated or necrotic papules with erythematous base.
  - *Transinoculation:* Virus is transferred to other individuals; appears similar to a vaccination reaction.
  - *Eczema vaccinatum:* Severe widespread cutaneous disease following transfer of vaccinia virus to patients with atopic dermatitis, or less often, vaccination of affected patients. Widespread umbilicated pustules; lethality as high as 30%.
- **Diagnostic approach:** Identify virus (see smallpox).
- **Differential diagnosis:** Smallpox, eczema herpeticatum.
- **Therapy:** Vaccinia immune globulin, supportive care.

Cowpox and Cat Pox

- **Definition:** Infection following accidental transfer of cowpox/cat pox virus to humans.
- **Epidemiology:** Transfer from infected cows (farmers) or cats (pet owners); much more common in cats, despite the name.
- **Clinical features:** Crusted papules at inoculation site with fever and malaise; rarely disseminated pustular or hemorrhagic disease, but then life-threatening.
- **Diagnostic approach:** Identification of virus (see smallpox).
- **Therapy:** Supportive care.

Milker's Nodule

- **Definition:** Paravaccinia virus infection spread from cows to dairy farmers or veterinarians.
- **Epidemiology:** The infected cows (less often sheep or goats) have harmless warty growths on their udders (false pox); in contrast, cowpox causes mild clinical problems in the bovine hosts.
- **Clinical features:** Firm, dome-shaped nodules, several centimeters in diameter with an erythematous periphery, usually on the hands. They may trigger erythema multiforme or lymphangitis. Heal without scarring over weeks.
- **Diagnostic approach:** History, histology, identification of virus (not required).
- **Therapy:** Topical antiseptics. Lesions resolve spontaneously. If desired, cryotherapy or shave excision under local anesthesia can be employed.

Orf (Ecthyma Contagiosum)

- **Definition:** Parapoxvirus ovis infection spread from sheep or goats to contact persons.
- **Epidemiology:** The infected animals have a stomatitis, so infection requires contact other than milking. With sheep, those nursing the young lambs are at risk, as are the shepherds caring for sick animals.
- **Clinical features:** Identical to milker's nodule (Fig. 4.**1**).
- **Diagnostic approach:** History, histology, identification of virus (not required).
- **Therapy:** Supportive measures, see milker's nodule.

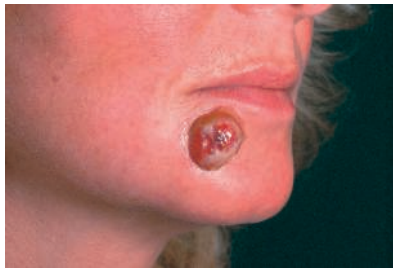
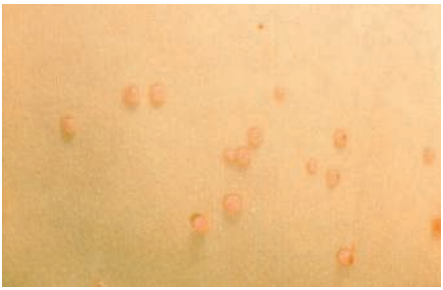


Fig. 4.**1** · Orf.

Molluscum Contagiosum

- **Definition:** Multiple umbilicated papules or nodules caused by molluscum contagiosum virus; mollusca contagiosa (pl.).
- **Epidemiology:** Predisposing factors include atopic dermatitis, immune defects, immunosuppression, HIV/AIDS. Most patients are children.
- **Clinical features:**
  - Incubation period days to several months. Skin-colored, 1–5 mm umbilicated papules, often arranged in groups or linear fashion (Köbner phenomenon after autoinoculation) (Fig. 4.**2 a**).
  - Sites of predilection include face, neck, eyelids, axillae in children; genital region in adults; disseminated in atopic dermatitis or HIV/AIDS.
  - In patients with HIV/AIDS, giant molluscum contagiosum are possible, reaching 3–5 cm in size.



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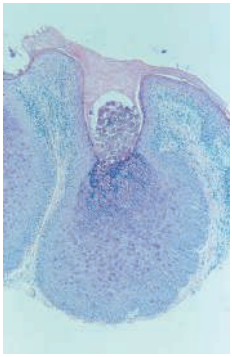

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Fig. 4.2 · **a** Mollusca contagiosa. **b** Histology of molluscum contagiosum, showing numerous inclusion bodies.

- **Diagnostic approach:** Clinical picture, histology (colorful giant molluscum bodies) (Fig. 4.2 **b**).
- **Therapy:**
  - Solitary lesions can be destroyed with curettage or a sharp tweezers; usually anesthesia is not needed but topical EMLA is useful in children (apply, occlude, wait 30–35 minutes).
  - Application of salicylic acid plasters is another approach.
  - Widespread disease, especially in children, may rarely require general anesthesia and then curettage of all lesions.
  - Always warn patient or parent to be alert for appearance of new lesions, as some may not be clinically apparent during treatment.

Caution: Mollusca contagiosa are contagious, and this point must be addressed. Infected children should avoid contact with other children with atopic dermatitis or immunosuppression. They should also avoid contact sports and shared wash clothes or towels.

4.3 Herpesvirus Infections

Herpes Simplex Virus Infections

- **Definition:** Diseases caused by infections with herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2).
- **Pathogenesis:**
  - *Initial infection:* HSV enters via small defects in skin or mucosa and starts to replicate locally; then spreads via axons to sensory ganglia where further replication occurs. Through centrifugal spread via other nerves, affects wider areas. After resolution of the primary infection, the virus remains latent in the sensory ganglia.
  - *Recurrent infection:* Reactivation of virus by various stimuli (UV light, fever) as well as local or systemic immunosuppression leads to seeding of the virus into area served by the sensory ganglia and thus to local recurrences.

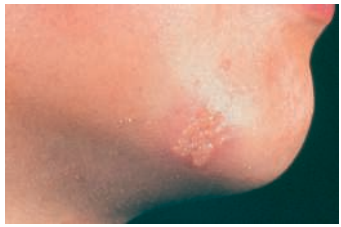
► **Epidemiology:** Almost everyone suffers from HSV-1 infection; the first infection is silent in 90%, non-specific in 9%, and clinically manifest in only 1%. Infection occurs in childhood. HSV-2 appears after start of sexual activity and affects 25–50% of population. Both viruses can be shed when patient is asymptomatic, easing transmission.

► **Clinical features:**

- *Common findings:*
  - Incubation period 6–8 days.
  - Both HSV types can cause oral and genital infections; their clinical presentations are identical. In the genital area, the recurrence rate for HSV-2 infections is 10× greater than for HSV-1, while with orofacial infections, HSV-1 has a significantly higher recurrence rate.

► **Orofacial HSV infections:**

- *Initial infection:* Herpetic gingivostomatitis. Usually in infants; extensive erosions with hemorrhagic crusts on lips and oral mucosa; difficulty feeding, foul smelling breath, systemic signs and symptoms.
- *Recurrences:*
  - Small grouped blisters on erythematous base, rapidly become pustules and then eroded; often painful with dysesthesias and neuralgias.
  - Common sites: lips (*herpes labialis),* chin (Fig. 4.**3 a**), cheeks, periorbital region (Fig. 4.**3 b**).
- *Eczema herpeticatum:* Patients with atopic dermatitis (p. 190) can develop extensive orofacial HSV infections which disseminate, especially favoring areas of active dermatitis (Fig. 4.**3 c**). Neck is most common site.



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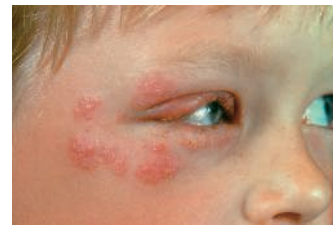

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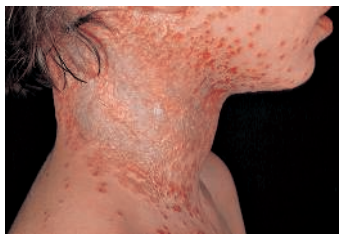

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Fig. 4.**3** · Herpes simplex. **a** Grouped vesicles on chin. **b** Multiple periorbital lesions. **c** Eczema herpeticum: disseminated HSV infection in atopic dermatitis.

► **Periungual HSV infection:** *Herpetic whitlow.* Most often affects doctors, dentists, and health personal; sharp reduction since more extensive use of gloves because of HIV. Periungual erythema, pain, and then vesicles.

! ***Caution:*** Do not mistake for bacterial or candidal infection. No incision and drainage. Check for regional lymphadenopathy.

- **Genital HSV infections:**
  - *Initial infection:*
    - Disseminated, rapidly eroded vesicles leading to small painful superficial ulcers as well as bilateral lymphadenopathy.
    - Burning or pain on urination common.
    - Cervix involved in 80% of women.
    - Systemic signs and symptoms; malaise, fever, headache.
    - Healing after 2–3 weeks.
  - *Recurrences:* Grouped blisters or pustules on erythematous base (Fig. 4.**4**). Women often have minimal symptoms. In 80% of patients: HSV-2. Differential diagnosis includes all genital ulcers (see STD, p. 134).
  - *Uncommon sites:* buttocks or upper thigh; anal or rectal involvement more painful with paresthesias, retention of urine or stool, impotence.

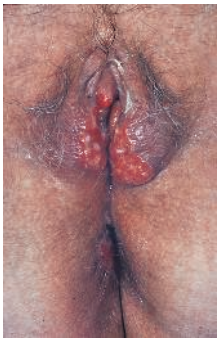


Fig. 4.**4** · Chronic ulcerative genital HSV infection in immunodeficient patient (chronic lymphocytic leukemia).

- **Herpes gladiatorum**: Wrestling or other close contact sports (rugby : scrum pox) are ideal for transfer of HSV between team members, usually HSV-1 spread when beard is rubbed on trunk or neck of opponent. Widespread lesions in areas of body contact.
- **HSV encephalitis:** HSV is most common cause of viral encephalitis in adults. 95% HSV-1. Often no associated skin or mucosal lesions. Favors temporal lobes and limbic system. Quick diagnosis via MRI (sometimes brain biopsy) and aggressive antiviral therapy; mortality around 80%.
- **Neonatal HSV infections:**
  - HSV-2 (and increasingly HSV-1) in birth canal with direct transfer to newborn and potential for HSV sepsis.
  - Genital HSV recurrences in women are asymptomatic in 70% of cases, making diagnosis most difficult.
  - Course of HSV in newborns tends to be severe because of incomplete immune response. Sepsis, encephalitis; 30% have no skin findings. If mother has genital herpes, cesarean section and antiviral therapy for newborn.
- **Herpetic keratitis:** Infection of cornea with HSV leading to erosions or ulcers. Often heals with scars, reducing visual acuity. Immediate ophthalmologic consultation at the slightest suspicion.
- **Postherpetic erythema multiforme:** Over 95% of patients with recurrent erythema multiforme have recurrent HSV as trigger (p. 281).

► **Diagnostic approach:**
- Clinical findings usually so typical that laboratory investigations not needed.
- *Most rapid approach:* Tzanck smear searching for multinucleated giant cells (Fig. 4.**5**).
- *Other possibilities:*
  - Identification of virus: immunofluorescent staining of smear with monoclonal antibodies, PCR, electron microscopy, culture.
  - Serology (ELISA): most useful for epidemiological studies.

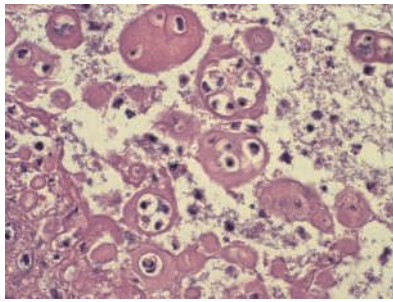


Fig. 4.**5** · Herpes simplex, multinucleated giant cells.

► **Differential diagnosis:** Deciding between HSV and early zoster can be difficult, but zoster should be unilateral and not recurrent. HSV also develops more rapidly following immunosuppression than does VZV.
► **Therapy:**
- *Systemic treatment* with acyclovir, valaciclovir, or famciclovir.
- P*rophylaxis for recurrences:* If patient has more than six recurrences yearly, consider acyclovir 400 mg p.o. b.i.d. or valaciclovir 1000 mg p.o. daily. Use for 1 year; then vacation to check for improvement. Often used for many years. Same regimen can be employed for recurrent erythema multiforme.
- *Drying measures:* Zinc oxide lotion, calamine lotion.
- HSV vaccines are in development; most promising for HSV-2 in women.
- *Neonatal HSV:* Specific hyperimmune globulin and i.v. acyclovir.

Varicella (Chickenpox)

► **Definition:** Initial infection with varicella-zoster virus (VZV).
► **Clinical features:**
- Highly infectious childhood disease; in 30% clinically nonapparent.
- Incubation period 2–3 weeks.
- Typically starts with red maculae on trunk, oral mucosa and scalp, which rapidly become vesicular and pustular; later crusts (Fig. 4.**6**). As new lesions continue to appear, the rash is asynchronous with lesions in all stages and varying sizes present at once (in contrast to the synchronic rash of smallpox and eczema herpeticatum); "star map" appearance. Intensely pruritic. Palms and soles always spared.
- *Characteristic lesion:* 1–2 cm oval erythematous macule with central blister.
- Scalp involvement is very common and leads to nuchal lymphadenopathy.
- Scratching often leads to secondary infections and then scars.

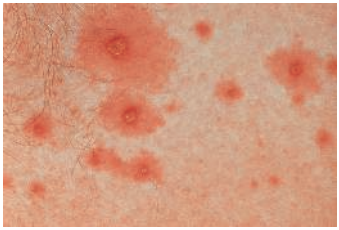


Fig. 4.**6** · Varicella (chickenpox).

- Children are usually not very ill, but adults often have systemic symptoms and even pneumonia.

► **Diagnostic approach:** Usually clinical; Tzanck smear, immunofluorescent staining of smear with monoclonal antibodies.

► **Therapy:** Drying lotions, antihistamines for itch, antibiotics (topical or systemic) for secondary infections. Systemic acyclovir is rarely used, but slightly reduces course of disease and may allow children to return to school or kindergarten sooner.

► **Immunization:** Varicella vaccine is a routine part of childhood immunizations.

► **Varicella in pregnancy:**

- *1st and 2nd trimesters:* in 25–50% of cases transplacental transfer of VZV to fetus with risk of varicella embryopathy syndrome.

! ***Caution:*** Cooperate closely with gynecologist and pediatrician.

- *3rd trimester:* Congenital varicella with poor prognosis.
- *Therapy:* Pregnant patients with varicella should receive both varicella-zoster immune globulin and antiviral therapy (acyclovir).

Zoster (Herpes Zoster, Shingles)

► **Definition:** Segmental (dermatomal) painful skin disease caused by reactivation of VZV.

► **Epidemiology:** 10–20% of seropositive adults develop clinically apparent zoster. Peak age 50–70; in younger patients think of HIV and iatrogenic immunosuppression.

► **Pathogenesis:** Following the initial varicella infection, VZV persists life-long in the sensory ganglia of the spinal chord and cranial nerves. When reactivated, it follows the associated nerves into the skin; thus both the peripheral nerve and the skin of its dermatome involved (Fig. 4.**7**).

► ***Note:*** When patients know that the disease starts in a nerve, they seem to accept the dysesthesias and pain better.

► **Clinical features:**

- *Prodromal phase:* dysesthesias or pain in distribution of the affected nerve without visible skin changes; may last up to 7 days. Typically burning or lancinating pain.
- *Eruption* of grouped vesicles and then pustules on an erythematous base (Fig. 4.**8 a**), occasionally hemorrhagic or necrotic; also lasts about 7 days. Always respects the midline, and only few lesions are outside the involved dermatome and its two immediate neighbors (Fig. 4.**8 b**). More widespread disease suggests immunosuppression.
- *Healing* with drying, crusting, and usually some scarring; also 7 days.

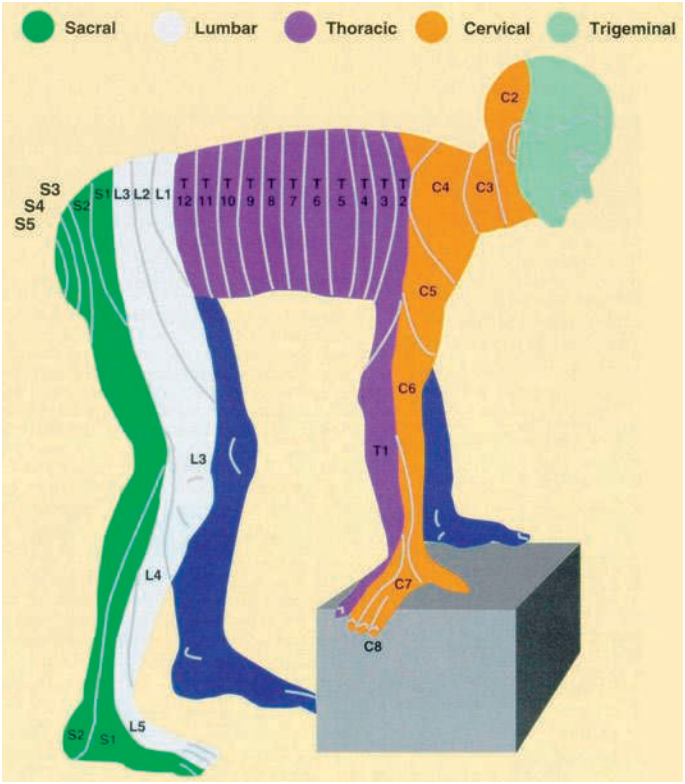
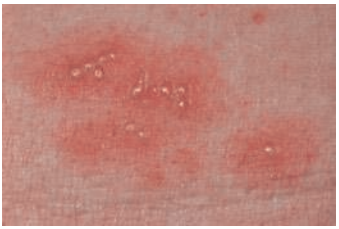


Fig. 4.**7** · Dermatomes.

► **Complications:**

- *Ocular involvement:* When 1st branch of trigeminal nerve (opthalmic nerve) is involved (Fig. 4.**8 c**), 50% have ocular involvement, including keratitis, corneal erosions, conjunctivitis, iridocyclitis, secondary glaucoma, optic neuritis, impairment of muscles (double vision), facial paralysis. Vesicles on the tip of the nose (Hutchinson sign) indicate nasociliary nerve involvement and greater likelihood of eye involvement.

  Caution: Always consult the ophthalmologist.
- *Otic involvement:* Involvement of inner ear when 8th cranial nerve is affected, leading to reduced hearing, vertigo, and zoster lesions of tympanic membrane and outer ear canal.
- *Ramsay Hunt syndrome*: Involvement of both 7th and 8th cranial nerves, leading to facial paralysis, hearing loss, vertigo, and zoster lesions of tympanic membrane and outer ear canal.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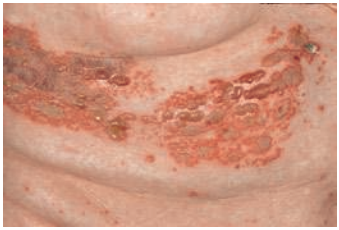
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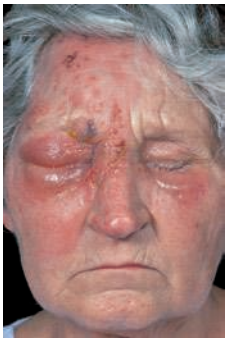
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Fig. 4.**8** · Zoster. **a** Early zoster with grouped vesicles on an erythematous base. **b** More severe zoster, clearly showing dermatomal limitation. **c** Zoster involving the first branch of the trigeminal nerve, with lid edema.

- Affected sacral ganglia can lead to retention of urine or stool.
- *Generalized zoster*: Usually in immunosuppressed patients, resembles varicella but starts in a dermatome before disseminating.

Note: The clinical picture is more synchronous and uniform than in varicella.

- *Uncommon variants:* Zoster pneumonitis, encephalitis, nephritis, cystitis, and cholecystitis.
- *Postherpetic neuralgia*: Pain in the involved dermatome that lasts more than 6 weeks; the most dreaded complication of zoster.
- *Zoster in pregnancy:* No serious problems.

► **Diagnostic approach:** Clinical features, Tzanck smear, if questions exist, then immunofluorescent staining of smear with monoclonal antibodies. With trigeminal nerve involvement or any signs and symptoms of eye involvement, always get ophthalmologic consultation.

► **Differential diagnosis** (p. 704): HSV infection; in such a case, the immunofluorescent examination of a smear can readily separate VZV from HSV.

► **Therapy:**

- *Acute zoster:*
  - Drying measures (zinc oxide lotion, calamine lotion).
  - In the case of severe infections or immunosuppressed patients, antiviral therapy is recommended (Table 4.**2**). Ideally should be started within 48 hours of presence of vesicles; most patients come to physician's attention much later.
- *Postherpetic neuralgia*: Pain therapy is associated with a wide variety of side effects. Inexperienced physicians should work closely with a special pain clinic or physician.

Table 4.2 · Approved antiviral agents for zoster

Agent	Dose	Duration
Acyclovir i.v.[a]	Adults, infants < 3 months, children > 12 years: 5 mg/kg q. 8 hours Children 3 months–12 years: 250 mg/m² q. 8 hours	At least 5 days
Acyclovir p.o.	Adults 800 mg 5× daily	5–7 days
Brivudin[b]	Adults 125 mg daily in single dose	7 days; 10 days for severe cases
Famciclovir	Adults 250 mg t.i.d.	7 days
Valaciclovir	Adults 1000 mg q. 8 hours	7 days

a On the basis of our clinical experience, a dose of 5–10 mg/kg for adults or 250–500 mg/m² is recommended. Treatment should last 5–7 days. Immunosuppressed patients should receive the maximum dose for 10 days. Patients with severe disease should be treated with i.v. medication.
b Interactions with other drugs are common; check the manufacturer's recommendations.

- *Stage 1:* NSAIDs or similar agents (acetaminophen 1.5–4.0 g daily or ibuprofen 600–2400 mg daily).
- *Stage 2:* Add weak opiate analgesics such as tramadol 200–400 mg daily or codeine 120 mg daily; perhaps as combination products.
- *Stage 3:* Add strong central-acting opiate such as buprenorphine 0.6–1.6 mg daily or morphine 30–360 mg daily.
- When the pains are very neuralgic, consider adding carbamazepine 400–1200 mg daily to Stage 1 agents. Other possibilities include antidepressants (clomipramine 50–100 mg daily) or antipsychotic agents (methotrimeprazine 20–150 mg daily).
- Further possibilities include sympathetic nerve blockade, transcutaneous electric stimulation, and neurosurgical destruction of responsible pain pathways or centers.

Epstein-Barr Virus Infection

- **Causative agent:** Epstein–Barr virus (EBV) (human herpesvirus 4).
- **Pathogenesis:** EBV infects B cells and epithelial cells of the oro- and nasopharynx; capable of immortalizing cells and thus an effective carcinogen.
- **Clinical features:**
  - Most common disease is infectious mononucleosis, result of acute EBV infection. Patients have a pharyngitis and are often treated with ampicillin or amoxicillin. They then develop a characteristic morbilliform drug exanthem. Other less common acute findings include mucosal ulcerations and facial edema.
  - In small children. EBV is one of the triggers of Gianotti–Crosti syndrome (p. 574).
  - EBV is responsible together with HPV for oral hairy leukoplakia in HIV/AIDS patients (p. 161). In addition, usually found in CNS and primary effusion lymphomas in this patient group.
  - EBV is an important factor in both Burkitt lymphoma and nasopharyngeal carcinoma (primarily in East Asia); other co-carcinogens are likely to be involved.
- **Diagnostic approach:** Serology, peripheral smear.
- **Therapy:** Symptomatic therapy; antiviral agents are only minimally helpful.

Cytomegalovirus Infection

- **Causative agent:** Human cytomegalovirus (HCMV) (human herpesvirus 5); virus is so named because it induces megalocytes (large cells) in cell cultures. HCMV is preferred term because there are many animal CMVs.
- **Epidemiology:** HCMV is a common virus; 40–60% of adults show serologic evidence of infection, with higher numbers in sexually active individuals.
- **Clinical features:**
  - Acute HCMV is usually asymptomatic but can mimic infectious mononucleosis and also have acute exanthem.
  - Cutaneous manifestations of HCMV infections appear almost exclusive in immunocompromised patients (HIV/AIDS, posttransplantation, hematologic malignancies) or in newborns.
  - Most important problem is HCMV retinitis in HIV/AIDS patients; prevalence dramatically reduced by HAART.
  - Anogenital ulcerations are common in both HIV/AIDS patients (mistaken for severe HSV infection) and in immunosuppressed infants (overlooked as severe diaper dermatitis).
  - Systemic infections in infants can lead to sepsis and extramedullary hematopoiesis with cutaneous nodules: blueberry muffin baby.

  Note: TORCH syndrome refers to transplacental infection with **t**oxoplasmosis, **o**ther agents, **r**ubella, **c**ytomegalovirus and **h**erpes simplex; mothers are often healthy but newborns critically ill; congenital leukemia, Langerhans cell histiocytosis, neuroblastoma, and mastocytomas can also appear similar.
- **Diagnostic approach:** Identification of virus with PCR, sometimes nuclear inclusions (owl eye cells) in skin biopsy.
- **Therapy:** For persistent cutaneous infections, valaciclovir, ganciclovir, cidofovir, or foscarnet can be employed.

4.4 Picornavirus Infections

Hand-Foot-and-Mouth Disease

- **Causative agents:** Coxsackievirus A (types 5, 9, 10, 16) and B (types 2 and 5), as well as enterovirus 71.
- **Epidemiology:** Usually children are affected; more common in summer.
- **Clinical features:**
  - Incubation period 5–8 days.
  - *Typical triad:*
    - Ulcerative stomatitis, especially on hard palate (lips, tonsils, and pharynx spared).
    - Small papules or papulovesicles on the hands and feet, including palms and soles.
    - Less often diffuse exanthem.
  - Patients generally well; no serious complications.
- **Diagnostic approach:** Clinical findings; if questions, virus can be identified in oral rinsing; serological tests also available.
- **Differential diagnosis:** Often confused with herpes simplex but pattern is different and patient well. Oral lesions alone resemble herpangina and aphthae.
- **Therapy:** None needed; symptomatic mouth rinses.

Herpangina

- **Causative agents:** Coxsackievirus A (types 1–6, 8, 10 and 22); also some coxsackievirus B and ECHO viruses.
- **Epidemiology:** Usually children are affected; more common in summer.
- **Clinical features:**
  - Incubation period 3–4 days.
  - Patients are ill with sudden fever (up to 40.5 °C), malaise, headache, myalgias, sore throat. Lasts around 4 days.
  - *Oral lesions:* Characteristic tiny (1–2 mm) ulcerations on hard palate; rapidly ulcerate; often linear. Heal within a week.
- **Diagnostic approach:** Clinical findings; virus can be isolated from pharynx or stool; complement-fixing antibodies appear after 2 weeks.
- **Differential diagnosis:** Do not confuse with primary herpetic gingivostomatitis; patients are ill but oral findings much more discrete.
- **Therapy:** Supportive care; mouth rinses, antipyretics.

4.5 Cutaneous Manifestations of Hepatitis Virus Infections

Hepatitis B Infection

- **Causative agent:** Hepatitis B virus (HBV) is a hepadnavirus.
- **Epidemiology:** HBV is transferred parenterally (blood or blood products, contaminated instruments, injecting drug abusers), sexually (about 50%) or perinatally.
- **Dermatoses associated with HBV infection:**
  - Gianotti–Crosti syndrome.
  - Lichen planus.
  - Mixed cryoglobulinemia.
  - Erythema nodosum.
  - Pyoderma gangrenosum.
  - Polyarteritis nodosa.
  - Urticaria.
  - Leukocytoclastic vasculitis.
  - Serum sickness–like prodrome with urticaria, angioedema, arthritis, proteinuria, or hematuria.
  - Dermatomyositis-like syndrome.

Hepatitis C Infection

- **Causative agent:** Hepatitis C virus (HCV) is a flavivirus (RNA virus).
- **Epidemiology:** HCV is transferred parenterally in most cases; high prevalence in injecting drug abusers. Less often transferred by sexual intercourse or perinatally. Rarely causes jaundice, so infection often overlooked.
- **Dermatoses associated with HCV infection:**
  - B-cell lymphoma (lymphoplasmacytic lymphoma, Waldenström macroglobulinemia) associated with mixed cryoglobulinemia.
  - Leukocytoclastic vasculitis.
  - Polyarteritis nodosa.
  - Porphyria cutanea tarda.

- Lichen planus.
- Urticaria.

Caution: Many dermatoses formerly associated with HBV infection have turned out to be more often or exclusively associated with HCV. Thus, both of these lists should be viewed as working formulations.

4.6 Human Papillomaviruses

Introduction

► **Causative agent:** Human papillomaviruses (HPV) are a group of closely related DNA viruses. Over 100 subtypes have been identified, with differential epithelial preferences (skin vs. mucosa) and different clinical patterns (Table 4.**3**).

Table 4.3 · **Human papillomaviruses (HPV) and associated diseases**

Disease	HPV types	Oncogenicity
Plantar warts	1, 2, 4, 60, 63	0
Common, filiform, and plantar mosaic warts	1, 2, 3, 4, 7, 54	0
Plane warts, sometimes epidermodysplasia verruciformis	3, 10, 28 less often 2, 26–29,41	++
Macular and slightly raised lesions in epidermodysplasia verruciformis	5, 8, 14, 17, 20, 38	+++
Squamous cell carcinomas in immunosuppressed patients	5, 8, 38	+++
Condylomata acuminata	6, 11 less often 16, 18, 31, 33	+
Bowenoid papulosis	16, 18	+++
Bowen disease (especially genital)	16, 18	+++
Carcinoma of the cervix	16 (60%), 18 (20%) rarely 11, 31, 33, 35	+++
Butchers' warts	7	?
Focal epithelial hyperplasia (Heck disease)	13, 32	?

+, low risk; ++, intermediate risk, +++, high risk.

► **Epidemiology:** 5–20% of all 15–49 year-old individuals have some form of HPV infection; children are very commonly infected. HPV-induced lesions can be transferred from site to site on host (finger to mouth) or from individual to individual (condylomata acuminata).

► **Oncogenic potential:** The demonstration that HPV 16 and 18 are the causative agents for human cervical carcinoma has had a great impact on the diagnosis and management of genital HPV infections in patients and their partners.

Common Warts

- **Synonym:** Verrucae vulgares.
- **Definition:** Hyperplastic tumors induced by HPV.
- **Clinical features:**
  - Hyperkeratotic papillomatous tumors, usually 2–6 mm in diameter. Characteristic findings are loss of skin markings and intralesional hemorrhagic dots or streaks (Fig. 4.**9 a**).
  - Most common sites are acral—hands, feet. On fingers, frequently periungual (Fig. 4.**9 b**).

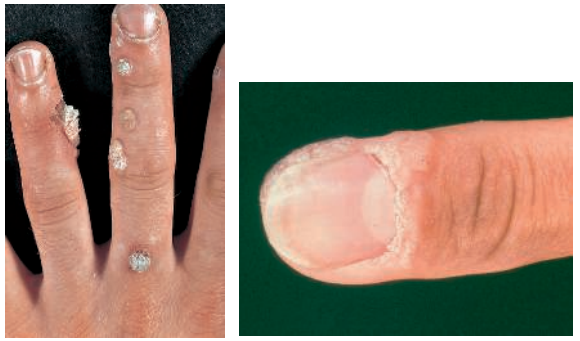


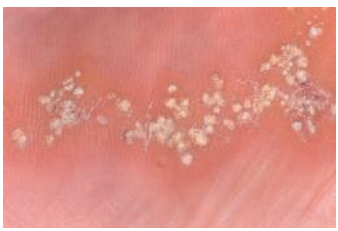
Fig. 4.**9** · Common warts. **a** Common warts of hands with obvious papillomatous features. **b** Common periungual warts.

- **Diagnostic approach:** Clinical findings (punctate bleeding when pared), histology; identification of HPV type only essential for genital lesions with infected female or partner.
- **Differential diagnosis:** In children, molluscum contagiosum. In adults, actinic keratosis, seborrheic keratosis, stucco keratosis, keratoacanthoma.
- **Therapy:**
  - ***Cave:*** Do no harm! Most common warts, especially in children, resolve spontaneously. Procedures that are extremely painful or cause scarring should therefore be avoided.
  - All forms of therapy have at least a 50% recurrence rate.
  - Small, not extremely hyperkeratotic lesions can be treated with cryotherapy; usually two freeze–spray cycles employed: repeated weekly.
  - Application of salicylic acid plasters (every 2–3 days) or flexible gels (daily) followed by paring or curettage (1–2 × weekly by physician or aide).
  - As the number of warts increases, the more painful the treatment becomes and the success rate drops.
  - Laser destruction of individual resistant or painful lesions (especially periungual) may be useful.
  - In resistant cases, imiquimod with aggressive removal of scale and occlusion (see condylomata acuminata below).

Plantar Warts

- **Synonym:** Verrucae plantares.
- **Definition:** Usually solitary endophytic, often painful, tumors of soles (and palms).
- **Clinical features:**
  - Irregular papule with central loss of skin markings; usually at sites of mechanical pressure. Overlying reactive hyperkeratosis. Usually tender or painful (Fig. 4.**10 a**).
  - May become quite large and, when therapy-resistant, may evolve into verrucous squamous cell carcinoma (epithelioma cuniculatum).
  - Mosaic warts, caused by different HPV types, are diffuse sheets of small, relatively flat warts with lacy or mosaic pattern (Fig. 4.**10 b**).
- **Diagnostic approach:** Punctate hemorrhage, loss of skin lines, tenderness.
- **Differential diagnosis:** Clavus or corn is also located at site of pressure, usually over boney prominence; central plug but no punctate hemorrhage. Callus is reactive hyperkeratosis; larger more irregular lesion without central core or punctate hemorrhage.
- **Therapy:**
  - Conservative approach with salicylic acid plaster or flexible gel, or simply occlusive tape (duct tape), followed by curettage or trimming; may require many treatments.
  - Cryotherapy less effective than on other surfaces because of difficulty in raising a blister.
  - *Resistant cases:* Laser destruction with CO_2 (risk of painful scars) or dye laser, or photodynamic therapy.
  - Imiquimod can be used postoperatively, but is not effective as primary treatment because of the thickened stratum corneum.
  - Controlling hyperhidrosis (p. 528) may be a useful adjunct.

a



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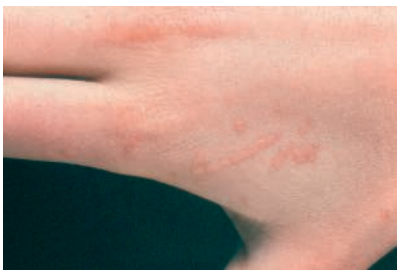


c

Fig. 4.**10** · Plantar warts. **a** Solitary. **b** Mosaic. **c** Plane warts.

Plane Warts

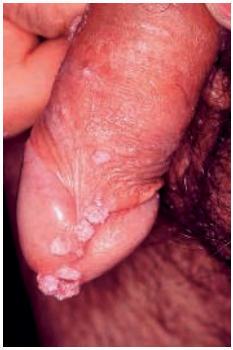
- **Synonym:** Verrucae planae.
- **Definition:** Small HPV-induced papules (plane as in flat, not as in plain or common).
- **Clinical features:**
  - 1–2 mm, skin-colored subtle papules, often not recognized as warts by patient (Fig. 4.**10 c**).
  - Most common sites are face and hands.
  - Frequently spread by autoinoculation, especially on face of men (less often legs of women) by shaving.
  - Most patients are children or young adults. Plane warts in older patients raise the question of immunosuppression.
- **Diagnostic approach:** Clinical findings, histology; HPV typing rarely needed.
- **Differential diagnosis:** On face, syringomas, xanthelasma; on chest, papular granuloma annulare and eruptive vellus hair cysts.
- **Therapy:** Therapy can easily cause lesions to spread; so "slow and gentle" are the magic words! Try imiquimod, topical retinoids, light cryotherapy, laser destruction.

Condylomata Acuminata

- **Synonym:** Genital warts.
- **Definition:** Sexually transmitted HPV infection of genital and perianal transition mucosa; most common STD.
- **Pathogenesis:** Most commonly caused by HPV 6 and 11 which are not oncogenic. Important to exclude infection with HPV 16 and 18 which are oncogenic. In affected women, HPV analysis of Pap smear may supplement cytology to assess risk.
- **Clinical features:**
  - Incubation period 4 weeks–6 months.
  - Tiny white papules which rapidly both spread and enlarge. Larger lesions often macerated. May be genital (Fig. 4.**11 a**) or perianal (Fig. 4.**11 b**).
  - *Infections in children:* Vertical transmission in utero or during birth can lead to infections which may appear with considerable time delay. Laryngeal papillomatosis is caused by HPV in infant's larynx.

  Caution: Always think of potential sexual abuse when a child presents with condylomata acuminata. In boys, lesions usually perianal; in girls, more often vulvar or urethral.
- **Diagnostic approach:** Always examine sexual partner(s) and exclude other STDs. Painting with 5% acetic acid will unmask discrete lesions by turning them white. Be sure affected women have cervical examination. If lesions are recalcitrant, consider HPV typing.
- **Differential diagnosis:** Table 36.**3** (p. 548) discusses differential diagnosis of genital warts. Condylomata lata (secondary syphilis) sound similar, but are large broad-based moist lesions.
- **Therapy:**
  - Application of podophyllotoxin 0.5% solution by patient using various regimens (for example, b.i.d. for 4 days, then 3 days of rest; repeat as needed until clear). In some countries, 5–20% tincture of podophyllin is used; it must be applied by physician 1–2× weekly until clear.

  Caution: The podophyllin tincture is more irritating and should not be applied to the urethra, internally, or during pregnancy. It also contains mutagenic and carcinogenic compounds and is, in our opinion, best avoided.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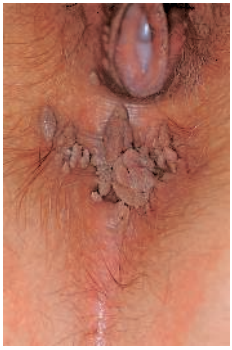
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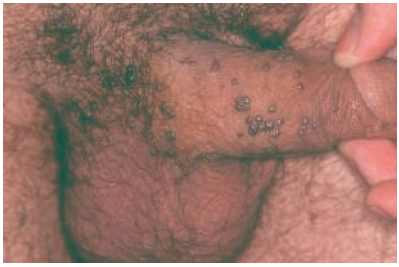


Fig. 4.**11** · Condylomata acuminata. **a** Perianal. **b** Penile. **c** Bowenoid papulosis.

- Application of 50–85% trichloracetic acid tincture weekly; can be used during pregnancy.
- Cryotherapy (not anal or urethral).
- Imiquimod cream daily for 6 weeks; decrease frequency if irritating.
- Destruction with electrocautery, curettage, or laser.

Caution: Fumes are infectious and must be properly evacuated; masking is essential, to avoid any chance of inhalation.

- Adjuvant therapy with IFN-α (intralesional or systemic) may improve response in immunocompetent patients but has not been proven to reduce recurrence rate; expensive and associated with systemic side effects.
- *Adjuvant measures:*
  - Always refer patients with perianal disease for proctologic examination. Most have anal disease which serves as source of re-infection and in homosexuals as favored site of transmission.
  - Correct predisposing factors (maceration, intertrigo, vaginal discharge, phimosis, immunosuppression, sources of mechanical damage).
  - With widespread penile disease, circumcision is sometimes required.

Bowenoid Papulosis

► **Definition:** Genital carcinoma in situ, histologically resembles Bowen disease (p. 418) but may regress.

► **Pathogenesis:** Bowenoid papulosis was originally described as a pseudomalignancy, because the tendency of individual lesions to regress; HPV studies have shown it is early carcinoma in situ. Typically affects young patients.

- **Clinical features:** Multifocal pigmented macules or papules on the genital skin and mucosa; often involve perineum or penile shaft (Fig. 4.**11 c**).
- **Diagnostic approach:** Histological diagnosis; should be followed by HPV typing, evaluation of cervix and rectum, and partner check.
- **Differential diagnosis:** Closely resemble seborrheic keratosis, but these are not expected on genital skin.
- **Therapy:** Same as for condylomata acuminata; larger lesions can be excised.

Epidermodysplasia Verruciformis (EDV)

- **Synonym:** Lewandowsky–Lutz disease.
- **Definition:** Rare chronic HPV infection with specific autosomal recessive immune defect (MIM code 226400). Two different mutations in *EVER1* and *EVER2* genes on chromosome 17q25 which code for membrane proteins of the endoplasmic reticulum.
- **Pathogenesis:** Patients are infected by a series of different HPV types, some of which are carcinogenic.
- **Clinical features:** In childhood patients develop multiple warts and large flat lesions resembling tinea versicolor, with no tendency to spontaneous regression. Later Bowen disease and squamous cell carcinoma develop, primarily in sun-exposed skin.
- **Diagnostic approach:** Clinical findings; HPV typing and genetic studies essential.
- **Differential diagnosis:** Widespread warts in immunosuppressed individuals, such as posttransplantation or HIV/AIDS.
- **Therapy:** All the measures discussed above can be tried; careful monitoring and compulsive use of sunscreens; both imiquimod and topical 5-FU may be helpful; systemic retinoids for prophylaxis. Carcinomas treated in standard fashion.

5 Bacterial Diseases

5.1 Introduction

Some common cutaneous bacterial diseases are listed in Table 5.**1**.

Table 5.1 · **Common cutaneous bacterial diseases**

Group	Bacteria	Diseases
Staphylococcia	*Staphylococcus aureus* *Staphylococcus epidermidis*	Folliculitis, furuncle, furunculosis, carbuncle, impetigo, cellulitis, paronychia, toxin-mediated diseases (staphylococcal scalded skin syndrome)
Streptococci[a]	*Streptococcus pyogenes* (group A, β-hemolytic) *Streptococcus viridans*	Erysipelas, impetigo (less often), scarlet fever, ecthyma, lymphangitis, necrotizing fasciitis, purpura fulminans
Corynebacteria	*Corynebacterium minutissimum* *Corynebacterium tenuis* *Corynebacterium diphtheriae*	Erythrasma Trichomycosis axillaris Cutaneous diphtheria
Borrelia	*Borrelia burgdorferi*	Lyme borreliosis including erythema migrans, lymphadenosis cutis benigna, acrodermatitis chronica atrophicans
Treponemes	*Treponema pallidum* *Treponema pertenue* *Treponema carateum*	Syphilis Yaws Pinta
Mycobacteria	*Mycobacterium lepra* *Mycobacterium tuberculosis* *Mycobacterium bovis* *Mycobacterium avium-intracellulare* *Mycobacterium marinum* *Mycobacterium buruli*	Leprosy Tuberculosis Tuberculosis Chronic infections in HIV/AIDS Swimming pool granuloma Buruli ulcer
Actinomycetales	*Actinomyces israelii*	Actinomycosis
	Nocardia brasiliensis	Nocardiosis
Gram-negative bacteria		Gram-negative folliculitis, gram-negative toe web infection, mixed infections, pyoderma in immunosuppressed patients
	Haemophilus ducreyi *Haemophilus influenzae*	Chancroid Facial cellulitis in childhood
	Pseudomonas aeruginosa	Nail fold infections, toe web infections, sepsis
	Klebsiella pneumoniae	Mixed infections

Continued Table 5.1 ▶

Table 5.1 · Continued

Group	Bacteria	Diseases
Gram-negative bacteria (Continued)	*Salmonella typhi*	Typhoid fever
	Escherichia coli	Mixed infections
	Yersinia enterocolitica *Yersinia pestis*	Yersiniosis, erythema nodosum Plague
Chlamydia	*Chlamydia trachomatis*	Lymphogranuloma venereum
Neisseria	*Neisseria gonorrhoeae* *Neisseria meningitidis*	Gonorrhea Meningococcal meningitis, pneumonia

a Infections with staphylococci and streptococci are usually referred to as pyodermas.

5.2 Gram-positive Bacteria: Staphylococci

- Staphylococci can be divided into two clinically relevant groups:
  - Coagulase-positive staphylococci (*Staphylococcus aureus*) producing both invasive and toxin-mediated infections.
  - Coagulase-negative staphylococci (*Staphylococcus epidermidis*), causing variety of hospital infections.

Folliculitis

- **Definition:** Hair follicle infection or irritation. The most common forms are caused by invasive staphylococci, but other bacteria, viruses, and fungi may also be responsible. Yet other forms (eosinophilic folliculitis in HIV/AIDS) are noninfectious. Mechanical irritation is also a factor, such prolonged sitting (*truck driver folliculitis*) or tight clothes (*blue jean folliculitis*); exposure to cutting oils is another factor.

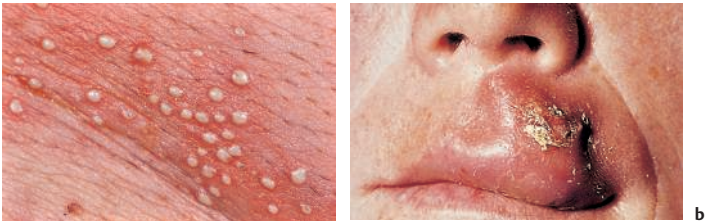
Superficial Folliculitis

- **Synonyms:** Bockhart impetigo.
- **Clinical features:**
  - Tiny pustules with erythematous border localized in superficial aspect (infundibulum) of follicle (Fig.5.**1 a**).
  - *Localization:* In children, usually scalp; in adults, trunk, buttocks, thighs, beard area.
- **Therapy:** Topical antiseptics or antibiotics (fusidic acid or erythromycin). If lack of response, systemic antibiotics (penicillinase-resistant penicillins or first-generation cephalosporin for 7–10 days).

Furuncle

- **Clinical features:**
  - Deep follicular infection that starts as firm red nodule which rapidly becomes painful and then, after a few days, fluctuant (Fig. 5.**1 b**). Heals with scarring over weeks. In some individuals, chronic-recurrent.
  - *Localization:* Neck, face, axillae, groin, upper back.

! Caution: There is a risk of sepsis in immunosuppressed patients.



a b

Fig. 5.1 · **a** Superficial folliculitis. **b** Furuncle on upper lip with massive edema.

- **Therapy:** (p. 675).
  - Avoid manipulation; topical antiseptics, systemic antibiotics (penicillinase-resistant penicillin or first-generation cephalosporin for 7–10 days).
  - *Solitary furuncle:* Systemic antibiotics; incision and drainage after several days when fluctuant.
  - *Recurrent furuncles* (furunculosis): Systemic antibiotics (often clindamycin 300 mg q.i.d. for 7–10 days), search for predisposing factors (diabetes mellitus, immunosuppression, perineal or nasal carriage of *Staphylococcus aureus*—see below, careful skin hygiene.

Carbuncle

- Large indurated plaque resulting from confluence of multiple furuncles; same treatment as for furuncles.

Bullous Impetigo

- **Epidemiology:** In Germany most impetigo is caused by streptococci; in the USA, most caused by staphylococci. Bullous lesions suggest staphylococcal origin, but lack of blister is not diagnostically helpful.
- **Pathogenesis:** Staphylococci in phage group II produce a toxin, exfoliatin, coded by the phage virus, which is capable of splitting the epidermis in the stratum granulosum (acting on desmoglein 3). This action produces large superficial blisters or more diffuse superficial skin loss.
- **Clinical features:**
  - Most patients are neonates (neonatal pustulosis) infants, or small children.
  - Sudden appearance of small blisters that rapidly enlarge; little associated erythema. Soon form yellow crusts.
- **Diagnostic approach:** Bacterial culture; see if siblings have similar lesions.
- **Therapy:**
  - Topical antiseptics or fusidic acid.
  - Systemic antibiotics (penicillinase-resistant penicillins or first-generation cephalosporins) may slightly speed course of healing.

Staphylococcal Scalded Skin Syndrome (SSSS)

- **Definition:** Widespread superficial skin loss caused by exfoliation.
- **Clinical features:**
  - Most patients are newborns or small infants.

- Rapid onset (sometimes with prodrome) of diffuse erythema and fever. After 12 hours, Nikolski phenomenon positive—stratum corneum can be pushed over underlying layers.
- Problems with temperature and fluid control because of widespread skin loss.

► **Diagnostic approach:** The organism usually cannot be cultured from the skin, but often from pharynx or other sites. Biopsy with frozen section.

► **Differential diagnosis:** In SSSS, the skin biopsy shows a very superficial epidermal split, whereas in toxic epidermal necrolysis, there is full-thickness epidermal necrosis.

► **Therapy:**
- Topical antiseptics or fusidic acid.
- Place on bed covered with nonadherent sheeting.
- Attention to fluid replacement, electrolytes, temperature control.
- Systemic antibiotics (penicillinase-resistant penicillins or first-generation cephalosporins; as soon as possible, culture and sensitivity-directed choice of agents).
- Search for staphylococcal carrier among parents or especially nursing personnel in case of nursery epidemics.

Caution: Systemic corticosteroids are not effective in SSSS and should be avoided.

► **Prognosis:** Rapid healing with therapy; less than 5% mortality.

Staphylococcal Scarlet Fever

► Exanthem resembling scarlet fever produced by exfoliation. In contrast to true streptococcal scarlet fever (p. 573), pharyngitis, strawberry tongue, and oral lesions are all absent. Treatment same as for bullous impetigo.

Staphylococcal Sepsis

► **Pathogenesis:** *Staphylococcus aureus* is a common cause of community-acquired sepsis, whereas *Staphylococcus epidermidis* is the major cause of Gram-positive nosocomial sepsis. Major causes are intravenous access lines, dialysis lines, CNS shunts, artificial joints.

► **Clinical features:** Skin findings include pustules, subcutaneous abscesses, areas of purpura with pus.

Note: Skin findings may be the first clue to a life-threatening infection.

► **Diagnostic approach:** Blood culture.

► **Therapy:**
- Systemic antibiotics; choice of agent directed by local hospital patterns as well as culture and sensitivity.
- Remove offending line or medical device.

Staphylococcal Carriage

► **Clinical features:** About 20% of individuals carry *Staphylococcus aureus* in their nares, a lesser number in the perineum. Up to 60% may transiently be carriers. The bacteria at these sites serve as a source for recurrent furunculosis, for other endogenous infections and for wound infections (with inadequate handwashing by patients or medical personnel).

► **Therapy:**
- Meticulous attention to handwashing and other personal hygiene.
- Disinfectant soaps and shampoos, used daily.

- Mupirocin ointment applied b.i.d. for 5 days, and then twice weekly, is the most effective prophylactic measure.
- Various systemic antibiotic regimens, using agents such as clindamycin and clofazimine, can be tried in consultation with infectious disease consultants.

Methicillin-resistant Staphylococcus aureus

- With increasing and sometimes inappropriate use of antibiotics, methicillin-resistant *Staphylococcus aureus* (MRSA) has become a major problem in hospitals, accounting for 20–30% of hospital infections. Community-based MRSA is also becoming more common. In the ambulatory setting, dermatologic patients have relatively high carrier rates, presumably because of dermatitis with barrier defects aiding colonization. Nursing home inhabitants are more likely to bring MRSA to the hospital than to take it home. Hospital staphylococcal infections can be endogenous or exogenous, in which case the hands of medical personnel are the usual culprits for transfer from one patient to another.
- Patients with MRSA must be isolated immediately; the single most important measure is to stop the spread of MSRA to other patients and to avoid a chronic "colonization" of the medical care facility. If MSRA is identified in cultures from outpatients, they should not be admitted unless absolutely essential. The usual antibiotic agent is vancomycin, although, disturbingly, reports of resistance to this antibiotic are also appearing.

5.3 Gram-positive Bacteria: Streptococci

There are many schemes for classifying streptococci. *Streptococcus* pyogenes (group A, β-hemolytic streptococci) account for 90% of infections. *Streptococcus viridans* (α-hemolytic streptococci) and *Streptococcus pneumoniae* are other important members of the group.

Impetigo

- **Definition:** Superficial skin infection.
- **Epidemiology:** Most patients are children. Infections usually in late summer and fall; more common under poor hygienic conditions.
- **Pathogenesis:** In Europe most impetigo is caused by group A streptococci (*Streptococcus pyogenes*), as well as by mixed infections with *Staphylococcus aureus*.
- ***Note:*** It is impossible to distinguish between staphylococcal and streptococcal impetigo on clinical examination. Furthermore, many infections are mixed.
- **Clinical features:** Crusts that develop from tiny blisters and superficial pustules. Usually on face or hands (Fig. 5.**2**).

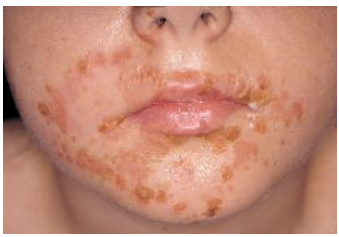


Fig. 5.**2** · Impetigo with honey-colored crusts.

- **Complications:** Glomerulonephritis is very common; rheumatic fever almost unheard of.
- **Diagnostic approach:** Culture usually reveals mixed infection. Antistreptolysin (ASL) and antistreptodornase-B (ADB) titers elevated. Check urine status at start of therapy and after 6 weeks.
- **Therapy:** Topical therapy with disinfectants or fusidic acid ointment is satisfactory for mild cases. Crusts should be removed with disinfectant soaps. Systemic antibiotics, usually penicillin, may speed healing and will reduce spread to contacts.

Note: Avoid contact with other children, as well as shared washclothes and towels.

Ecthyma

- **Definition:** Ulcerative infection usually caused by group A streptococci.
- **Epidemiology:** Patients often show immunosuppression, inadequate nutrition, poor hygiene (homeless, drug abusers). Also common in tourists following visits to the tropics.
- **Clinical features:** Punched-out ulcers, usually on legs, presumably at sites of minor trauma (Fig. 5.**3**). Typically 0.5–3.0 cm with peripheral erythema. Healing is slow and with scarring.
- **Diagnostic approach:** Culture and sensitivity.
- **Therapy:**
  - Address predisposing factors; compression therapy may be needed.
  - Topical disinfectants or fusidic acid ointment; in difficult cases, mupirocin ointment.
  - Culture-directed systemic antibiotics.

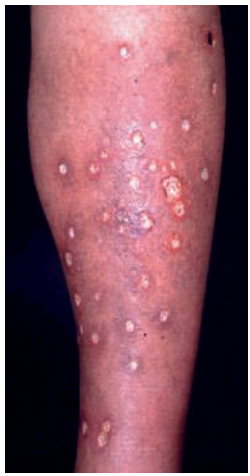


Fig. 5.**3** · Ecthymata.

Erysipelas

- **Definition:** Acute superficial cellulitis involving dermal lymphatics; caused by group A streptococci.

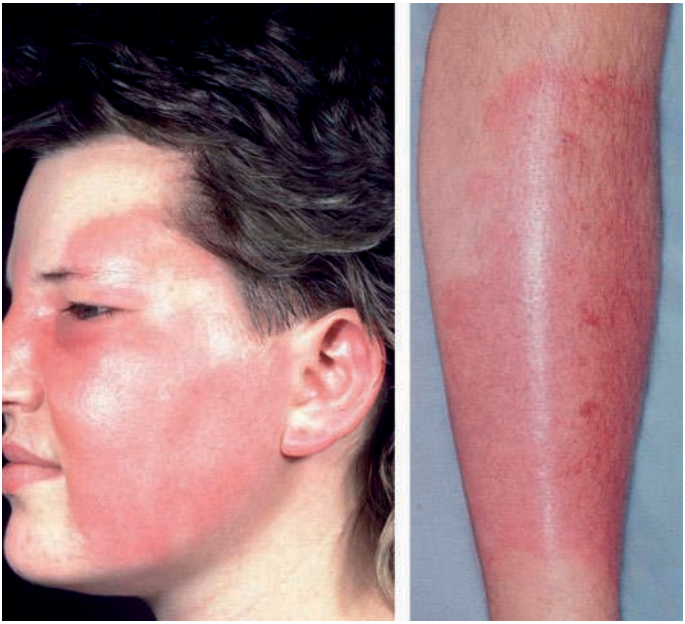


Fig. 5.**4** · **Erysipelas. a** Facial. **b** On the leg.

- **Pathogenesis:** There is usually a portal for entry. On the face, it is often herpes simplex; on the legs, interdigital tinea with maceration. The streptococci come from nasal or perineal carriage, or from respiratory tract infections.
- **Clinical features:**
  - Bright red, sharply demarcated, rapidly spreading erythematous patch. On the face, usually symmetrical involving the cheeks (Fig. 5.**4 a**). On the legs, unilateral with associated swelling (Fig. 5.**4 b**).
  - Fever, chills, malaise.
- **Complications:**
  - Recurrent infections lead to lymphatic damage and then lymphedema. Facial: swollen lip or lid edema; leg: *elephantiasis nostra*.
  - Glomerulonephritis.

  Caution: In immunosuppressed patients, there is a risk of sepsis, necrotizing fasciitis, or shock if treatment is not prompt.
- **Diagnostic approach:** Lesion very difficult to culture; can attempt aspirates from edge. Elevated white blood cell count, sed rate and C-reactive protein; ASL and ADB titers raised.
- **Therapy:** (p. 675).
  - High-dose penicillin i. v.; raise limb; cool compresses.
  - Later attempt to address portal of entry; consider compression, prophylactic antibiotics.

Cellulitis

- **Definition:** Deep infection involving dermis and subcutaneous fat, and often extending to muscles or bones.
- ***Note:*** In English, erysipelas refers only to superficial streptococcal disease, but in German it also includes superficial forms of cellulitis.
- **Pathogenesis:** Staphylococci and streptococci are the most common causes, but many other organisms may be involved including *Clostridium* (gas gangrene), *Haemophilus influenzae* (facial cellulitis), Gram-negative bacteria, and often mixed infections. Often a history of trauma or impaired circulation.
- **Clinical features:** Localized deep erythematous process usually associated with systemic signs and symptoms.
- **Therapy:**
  - Culture-directed systemic antibiotic therapy.
  - Incision and drainage may also be needed.

Necrotizing Fasciitis

- **Synonyms:** Necrotizing or gangrenous erysipelas.
- **Definition:** Fulminating infection of the subcutaneous fat and muscle.
- **Pathogenesis:** Usually caused by group A streptococci; less often by MRSA or Gram-negative bacteria.
- **Clinical features:** Usually involves legs. Often cutaneous lesion is entry portal. Starts with erythema, edema, and warmth. After 2–3 days red-blue color, blisters, and widespread dermal necrosis with vessel thrombosis. Spreads to involve the deep fascia and muscles, producing compartment syndrome (Fig. 5.**5**). The toxic bacterial products and necrotic debris trigger a massive destructive inflammatory reaction.

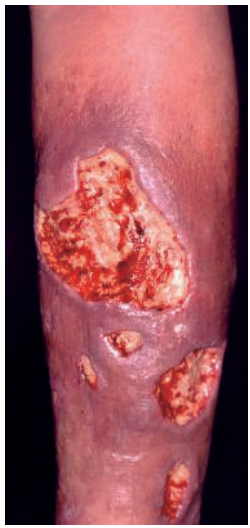


Fig. 5.**5** · Necrotizing fasciitis.

- **Diagnostic approach:** Clinical features, imaging, sonography to exclude deep vein thrombosis; ADB titer rises out of proportion to ASL titer.
- **Therapy:** Immediate generous débridement, even with just clinical suspicion, as diagnosis is notoriously difficult. Adequate drainage. Initially high-dose penicillin G (30 million IU daily) i.v. or broad spectrum coverage, switching to culture and sensitivity-directed agents as soon as possible (p. 675).

Perianal Streptococcal Dermatitis

- **Epidemiology:** Persistent perianal infection by group A β-hemolytic streptococci. Usually in children, especially boys.
- **Pathogenesis:** Patients usually have the same bacteria in their pharynx although they are asymptomatic. Presumed hand transfer. No explanation for perianal location.
- **Clinical features:** Children may complain of pain on defecation, or pruritus. Often subtle erythematous band around anus.
- **Diagnostic approach:** Culture; warn laboratory that streptococci are expected, otherwise they will only look for enteric organisms.
- **Differential diagnosis:** Psoriasis, candidiasis, pinworms, inflammatory bowel disease, child abuse.

Subacute Bacterial Endocarditis

- **Pathogenesis:** α-Hemolytic streptococci account for 60% of cases, staphylococci 20%; Gram-negative bacteria and fungi 10%; other rare causes, especially in immunosuppressed patients; in 10% no organism is cultured.
- **Clinical features:**
  - The cutaneous findings may be the first clue to the life-threatening cardiac infection.
  - Petechiae present on extremities, upper thorax, conjunctivae, gums.
  - *Subungual splitter hemorrhages:* Small red streaks seen subungually at distal end of nail. Can also be produced by chronic trauma (manual laborers).
  - *Janeway spots:* Small hemorrhagic macules on palms and digits.
  - *Osler nodes:* Small 2–3 mm tender erythematous papules on tips of digits, less often more centrally; represent septic microemboli.

Purpura Fulminans

- **Definition:** Life-threatening special form of disseminated intravascular coagulopathy (DIC).
- **Epidemiology:** Most cases follow a streptococcal infection such as scarlet fever; some may appear during the recovery period; on occasion, other infectious triggers.
- **Clinical features:**
  - Skin findings include massive ecchymoses with irregular borders, almost always starting on the legs. The intravascular thromboses lead rapidly to gangrene.
  - Patients are critically ill with fever, shock, anemia, and tachycardia. Consumptive coagulopathy leads to dramatic reduction in platelets.
- **Diagnostic approach:** CBC, platelet count, coagulation parameters.
- **Differential diagnosis:** Waterhouse–Friderichsen syndrome (meningococcal sepsis) is similar, but lesions are more widespread and CNS findings prominent.
- **Therapy:** Intensive care, high-dose penicillin, anticoagulation, perhaps high-dose corticosteroids.
- **Prognosis:** High mortality rate.

Therapy of Streptococcal Infections

- **Principles:**
  - Culture and sensitivity for serious manifestations.
  - Antibiotic of choice is penicillin G; in case of penicillin allergy, rely on local sensitivity guidelines.
  - If mixed infection with staphylococci is suspected, then penicillinase-resistant penicillin, perhaps combined with ampicillin.
  - Therapy for at least 10 days.
- **Mild infections (impetigo, scarlet fever, mild erysipelas):**
  - Procaine penicillin (penicillin G) 600,000 IU i.m. 1–2× daily.
  - Penicillin V 250 mg p.o. 4–6× daily.
  - If mixed staphylococcal infection is suspected, dicloxacillin 500–1000 mg p.o. q8 h.
  - *Penicillin allergy:* Erythromycin 500 mg p.o. q.i.d. or clindamycin 150–300 mg p.o. t.i.d.
- **Severe infections (widespread erysipelas, necrotizing fasciitis):**
  - Hospital admission, culture and sensitivity, infectious disease consultation.
  - Penicillin G 10 million IU i.v. q. 8 hours.
  - If mixed staphylococcal infection is suspected, nafcillin 500–1000 mg i.v. q4–6 h (infusion over 1 hour to avoid irritation) or flucloxacillin 1 g i.v. q. 8 hours.
  - If penicillin allergy suspected, cephalothin 500–1000 mg i.v. q4–6 h or cefazolin 500–1000 mg i.v. q6–8 h.
  - If penicillin allergy certain, vancomycin 1.0–1.5 g i.v. daily.
- **Anticoagulation:** All patients receive low-dosage heparin (500 IU fractionated heparin subq. daily) while in hospital.
- **Chronic recurrent erysipelas:** After finishing the therapy for an acute flare, then long-term prophylaxis with benzathine penicillin 1.2 million IU i.m. monthly for 6 months. Alternative regimens include erythromycin 1.0 g p.o. daily and/or co-trimoxazole 800 mg b.i.d. for 5 days every 4–6 weeks.
- **Follow-up:** Because of the risk of cardiac and renal complications, the patient should be followed for at least 6 weeks. If the ASL level remains elevated or the urine sediment is abnormal, treatment should be continued until the values normalizes or nephrology consultation obtained. Follow-up electrocardiogram at 6 weeks. Always look for signs of subacute bacterial endocarditis.

Toxin-mediated Syndromes

- Both staphylococci and streptococci secrete a wide variety of toxins. Hallmark features are:
  - Distant infection (such as streptococcal pharyngitis) causes cutaneous findings (scarlet fever). The bacteria are usually not found in the skin.
  - Often actual infection is mild or limited, but secondary effects of toxins are severe. Often the toxins act as superantigens and trigger a cytokine storm.
- Table 5.**2** summarizes the toxin-mediated reactions, some of which are discussed in more detail above. Kawasaki disease (p. 256) may be a superantigen-mediated disorder.

Table 5.2 · Toxin-mediated reactions

Bacteria	Toxin	Disease
Streptococcus pyogenes	Pyrogenic toxins	Scarlet fever
		Streptococcal toxic shock syndrome
Staphylococcus aureus	TSST-1	Toxic shock syndrome
	Exfoliatins	Bullous impetigo
		Staphylococcal scalded skin syndrome
		Staphylococcal scarlet fever
		Recalcitrant erythematous desquamating disorder (REDD syndrome)

5.4 Gram-positive Bacteria: Corynebacteria

Erythrasma

- **Definition:** Common superficial bacterial infection of intertriginous areas caused by *Corynebacterium minutissimum*.
- **Clinical features:** Red-brown superficial patches with fine scale, often overlooked by patients, located in intertriginous areas (groin, axillae (Fig. 5.**6**), interdigital).

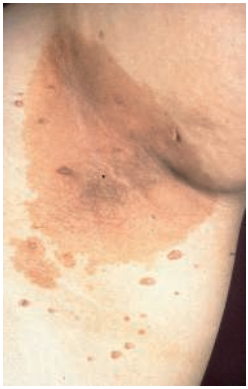


Fig. 5.**6** · Erythrasma.

- **Diagnostic approach:** Clinical suspicion, coral-red fluorescence on Wood's light examination. Microscopy is difficult; culture is impossible.
- **Differential diagnosis:**
  - *Tinea inguinalis:* Patches more infiltrated and with active border.
  - *Candidiasis:* Patches more macerated, with satellite pustules.
  - *Interdigital:* Tinea pedis, Gram-negative toe web infection.
- **Therapy:** Topical erythromycin solution or cream; topical imidazoles; meticulous hygiene. If resistant, then erythromycin 250 mg p.o. q.i.d. for 5–7 days.

Trichomycosis Axillaris

- **Definition:** Axillary hair infection with *Corynebacterium tenuis*.
- **Clinical features:** The axillary hairs are coated by tiny bacterial colonies (Fig. 5.**7**); their orange-brown color (secreted by the corynebacteria) suggests that the hairs have been dusted with a colored powdered sugar. Unpleasant odor. Pigment also found on underwear.
- **Diagnostic approach:** Clinical appearance, unpleasant odor, coral-red fluorescence in Wood's light examination; microscopic examination.
- **Differential diagnosis:** Both nits (p. 126) and hair casts (p. 513) can be excluded on microscopic examination.
- **Therapy:** Shaving of axillary hairs, deodorants, antibacterial soaps, disinfectant solutions.

Fig. 5.**7** · Trichomycosis axillaris.

Cutaneous Diphtheria

- **Definition:** Primary cutaneous infection with *Corynebacterium diphtheriae*.
- **Epidemiology:** Cutaneous diphtheria is common in the tropics; usually children are infected. Introduction via tourists is possible. In the USA, pockets of endemicity among homeless people, especially in Seattle, Washington.
- **Clinical features:** Initial blisters, then necrosis and development of shaggy, dirty ulcer that is slow to heal. Initially no generalized symptoms.
- **Complications:** Risk of nasal or pharyngeal diphtheria, production of toxins and then neurological and cardiac complications.
- **Diagnostic approach:** Skin or throat culture, immune status.
- **Therapy:** Penicillin G 1.2 million IU i. m. daily for 3 weeks or erythromycin 500 mg p. o. 3–4× daily for 3 weeks. If there is any suspicion of classic respiratory tract diphtheria, then also antitoxin and infectious disease consultation.

5.5 Gram-negative Bacterial Infections

Acute Meningococcal Sepsis

- **Definition:** Life-threatening infection caused by *Neisseria meningitidis*.
- **Clinical features:**
  - General signs and symptoms include headache, neck stiffness, nausea, vomiting, myalgias.
  - *Skin findings:*
    - Multiple tiny petechiae, usually on limbs, palms, soles; sometimes mucosa.
    - Larger areas of hemorrhage and necrosis are poor prognostic signs.
  - *Waterhouse–Friderichsen syndrome:* Maximal variant with disseminated intravascular coagulation and adrenal infarcts. Usually in small children.
- **Diagnostic approach:** Immediate spinal puncture and blood cultures; intra- and extracellular paired diplococci in CSF.
- **Differential diagnosis:**
  - *Neisseria meningitidis* causes about 50% of bacterial meningitis in adolescents and 30% in adults; consult infectious disease textbooks for other common organisms.
  - The main cutaneous differential considerations are purpura fulminans (usually from streptococci) in severe cases, as well as subacute bacterial endocarditis, leukocytoclastic vasculitis, and viral exanthems for milder forms.
- **Therapy:** Isolate patient on suspicion of meningococcal meningitis. Infectious disease consult. For uncomplicated cases, ceftriaxone 2.0 g b.i.d. and ampicillin 2.0 g q.i.d. for 2 weeks. For complicated cases (ENT infection, trauma, nosocomial infection), contact public health officials. Tracking of contacts; prophylaxis with rifampicin or ciprofloxacin.

Chronic Meningococcal Sepsis

- **Definition:** Frequently overlooked chronic *Neisseria meningitidis* infection involving skin and joints.
- **Epidemiology:** Uncommon, but occurs in epidemics in university dormitories, army basic training camps.
- **Clinical features:**
  - Slow onset of variety of signs and symptoms including fever, headache, myalgias, arthralgias. Recurrent bouts of fever.
  - Skin changes often located near affected joints. Tiny papules or pustules, petechiae, sometimes hemorrhage, less often erythema nodosum.
- **Diagnostic approach:** Blood culture, skin biopsy.
- **Differential diagnosis:** Similar to disseminated gonococcal disease, but more chronic.
- **Therapy:** Same as for acute meningococcal sepsis; some recommend shorter duration.

Pseudomonas Infections

Pseudomonas aeruginosa causes a wide variety of cutaneous infections, ranging from harmless to life-threatening.

Pseudomonas Paronychia

- **Definition:** Infection of nail apparatus with *Pseudomonas aeruginosa*.
- **Clinical features:** Patients usually have prolonged exposure of hands to water and lack an intact cuticle. Painful erythematous swelling of nail fold with green-gray discoloration of nail.

- **Diagnostic approach:** Wood's light examination as *Pseudomonas aeruginosa* produces a green fluorescent pigment; bacterial and fungal cultures.
- **Differential diagnosis:** All forms of paronychia, especially candidal.
- **Therapy:**
  - Drying measures, topical antiseptics, acetic acid (vinegar soaks, followed by blow drying).
  - Correct predisposing factors.
  - If mixed infection with *Candida albicans*, also treat with imidazole solution or systemic fluconazole.
  - In rare circumstances, systemic antibiotic therapy; check with public health for patterns of resistance of organism.

Gram-negative Toe Web Infection

- **Definition:** Acute infection of the interdigital spaces of the feet; most common cause is *Pseudomonas aeruginosa*, but other Gram-negative organisms can be found, often in combination.
- **Clinical features:** Weeping, macerated, foul-smelling interdigital infection, usually associated with hyperhidrosis and occlusion. Major problem among US soldiers in Viet Nam. Often chronic tinea pedis survives as portal of entry.
- **Diagnostic approach:** Bacterial and fungal cultures; KOH examination.
- **Therapy:**
  - Drying measures; topical disinfectants; treat fungal infection with topical or systemic imidazoles.
  - Quinolones (ciprofloxacin) are probably best agent; follow culture results. Cotrimoxazole also effective, but increasing Gram-negative resistance.

Hot Tub Folliculitis

- Recurrent folliculitis caused by *Pseudomonas aeruginosa*; hot tubs become colonized by the bacteria and users then develop superficial, usually follicular infections. Little risk of severe disease.

Wound and Burn Infections

- **Clinical features:** *Pseudomonas aeruginosa* is a common colonizer of burns and extensive wounds, imparting a green color and sweet-sour smell to the exudate.
- **Diagnostic approach:** Culture and sensitivity; the wounds can be screened with Wood's light, as the green bacterial pigment fluoresces.
- **Therapy:** Most patients have superficial infections which can be treated with wet dressings using disinfectants.

Caution: Risk of pseudomonas sepsis, especially in patients with diabetes mellitus or immunosuppression.

Pseudomonas Sepsis

- **Definition:** Life-threatening infection with *Pseudomonas aeruginosa*, which can sometimes be diagnosed early on the basis of skin findings.
- **Epidemiology:** Predisposing factors include immunosuppression, diabetes mellitus, malignant tumors, and long-term antibiotic therapy.
- **Clinical features:**
  - Initially hemorrhagic vesicles and blisters, solitary or grouped, and widespread. Tendency towards ulceration in flexural areas. Also widespread hemorrhagic lesions. Known as *ecthyma gangrenosum*.
  - Advances to subcutaneous abscesses and cellulitis gangrenosa, which resembles decubital ulceration but not localized at sites of pressure.

- **Diagnostic approach:** Suspect in acutely ill patient with risk factors and cutaneous hemorrhage or ulceration; Gram stain of smear; tissue for culture and histology.
- **Differential diagnosis:** Almost any organism can cause sepsis in immunosuppressed patients. Possibilities include meningococcal sepsis and purpura fulminans.
- **Therapy:** Broad-spectrum antibiotic coverage based on culture and sensitivity results; initial therapy with tobramycin, perhaps combined with broad-spectrum penicillins or cephalosporins.

Caution: Tobramycin is ototoxic and nephrotoxic. Do not mix aminoglycosides with penicillin in the same bottle, as the aminoglycosides are inactivated.

Haemophilus influenzae Infections

- **Clinical features:** Invasive *Haemophilus influenzae* infections used to be most common in infants, causing most meningitis in this age group, as well as cellulitis and other infections. The cellulitis typically follows upper airway infections; it is usually facial. The availability of immunization has dramatically reduced this problem. Noninvasive (noncapsulated) *Haemophilus influenzae* causes community-based pneumonia in adolescents and adults, as well as less serious airway infections.
- **Diagnostic approach:** Culture of nose or pharynx.
- **Therapy:** Broad-spectrum antibiotics, such as second-generation cephalosporins, amoxicillin/clavulanic acid; alternatives include co-trimoxazole or ciprofloxacin.

Salmonella Infections

- **Definition:** *Salmonella typhi* and the related paratyphi cause systemic infections including typhoid fever, whereas the other forms of salmonella cause primarily gastroenteritis.
- **Epidemiology:** 60% of *Salmonella typhi* infections have skin findings; with other species, fewer and less specific changes.
- **Clinical features:**
  - Severe illness with fever, chills, respiratory symptoms and hepatomegaly. Enteritis may be present at start, but usually resolved before patient becomes so ill.
  - *Typhoid roseola or rose spots:* Subtle grouped 2–3 mm pink papules that blanch with diascopy; almost always on abdomen, appearing later in course of disease. Resolve with hyperpigmentation; new lesions can continue to appear.
  - Other skin findings include ulcerative vulvitis or proctitis, hemorrhagic exanthems, erythema nodosum.
- **Diagnostic approach:** Stool culture.
- **Therapy:** Ciprofloxacin 500 mg b.i.d. or ceftriaxone 2 g i.v. daily for 10–14 days.

Gram-negative Pyoderma

- **Definition:** Therapy-resistant pyodermas often occurring after visits to the tropics, following long-term antibiotic therapy, or in immunosuppressed patients.
- **Epidemiology:** Culture results confusing, as both staphylococci and streptococci may be isolated, as well as a spectrum of aerobic and anaerobic Gram-negative bacteria. Host immune response may also be exaggerated.
- **Clinical features:** There are several clinical patterns:
  - *Tropical ulcers:* Punched-out, dirty ulcers following a visit to the tropics.
  - *Chancriform pyoderma:* Aggressive widely undermined ulcers, often genital, confused with pyoderma gangrenosum (p. 251).

- *Blastomycotic pyoderma:* Same as chancriform pyoderma but with epithelial reaction resembling lesions of blastomycosis.
- *Noma:* Destructive orofacial ulceration seen in malnourished children in poor countries; may represent an extreme variant on this theme.

► **Diagnostic approach:** Culture of smear and tissue biopsy under aerobic and anaerobic conditions.
► **Differential diagnosis:** Ecthyma is similar but by definition only caused by streptococci. Overlaps exist.
► **Therapy:** Culture and sensitivity-directed choice of agents; often metronidazole 400 mg t.i.d. combined with ciprofloxacin.

Bartonella Infections

► Bartonella are small Gram-negative bacteria that are difficult to culture and classify. They overlap with Rickettsiae. The main organisms are:
- *Bartonella henselae:* Causes cat scratch fever, a zoonotic infection considered below.
- *Bartonella quintana:* Responsible for *trench fever*, a louse-transmitted disease but with humans as the reservoir; a major problem in World War I.
- *Bartonella bacilliformis*: Found in the Andes and transmitted by sandflies. Causes an acute infection (*Oroya fever*) and chronic self-healing verrucous vascular tumors (*verruga peruana*).

Bacillary Angiomatosis

► **Definition:** Chronic infection with *Bartonella henselae* or *Bartonella quintana* resulting in vasculogenesis; usually in patients with HIV/AIDS.
► **Clinical features:** Erythematous papules and plaques, often on face, which rapidly increase in number and coalesce. May also involve liver (peliosis), spleen, and bone marrow (common cause of osteomyelitis in HIV/AIDS).
► **Diagnostic approach:** Skin biopsy shows large numbers of bacteria positive on Warthin–Starry stain; confirmation with PCR.
► **Differential diagnosis:** Kaposi sarcoma, atypical mycobacterial infection, vast range of other possibilities in immunosuppressed patients.
► **Therapy:** Long-term erythromycin 500 mg q.i.d. or other macrolides; local destructive measures such as CO_2 laser or cryotherapy.

5.6 Miscellaneous Bacterial Infections

In this section we consider unusual infections, special clinical settings, and infections at selected sites.

Hidradenitis

► Hidradenitis or infections of the sweat glands are surprisingly uncommon; presumably the flushing action of sweating reduces the risk of infection. An acute abscess in an area rich in sweat hairs is difficult to define clinically; in the axillae, for example, most lesions are folliculitis or acne inversa. Chronic hidradenitis suppurativa is a misnomer; it is almost always acne inversa, involving hair follicles.
► Eccrine sweat ducts may be occluded; this is known as *miliaria*. Typical causes are high external temperatures, increased sweating, and occlusive clothing or bedding. Miliaria are common in newborns, as they adjust to a drier environment. Most miliaria are clear (*miliaria crystallina*), but when inflammation occurs, the

term *miliaria rubra* is applied. Such lesions look like a bacterial infection, but usually are not.

- A similar process occurs with *neutrophilic eccrine hidradenitis.* Eccrine sweat is responsible for eliminating many chemotherapeutic agents. Sometimes the sweat glands are damaged by these chemicals, producing a sterile pustular response. Similar lesions may occur on the palms and soles of children, perhaps representing a deep miliaria variant.

Ocular Infections

The lids and periocular region are predisposed to several bacterial infections that are similar in appearance:

- **Hordeolum:** Acute usually staphylococcal infection of glands of eyelid; also known as *stye.*
  - *External hordeolum* involves margin of lid and may effect glands of Zeis (modified sebaceous glands) or glands of Moll (modified apocrine glands).
  - *Internal hordeolum* involves Meibomian glands (modified sebaceous glands in the deeper tarsal plate). Can only be identified when conjunctiva is everted; often associated with edema or cellulitis.
- **Chalazion:** Chronic granulomatous inflammation of Meibomian gland; usually presents as painless, sometimes cystic nodule, in upper lid.
- **Blepharitis:** Inflammation of lid margin; most common cause is seborrheic dermatitis; always look for signs of erythema and scaling in other typical sites (hair line, behind ears). *Rosacea* (p. 535) may also cause blepharitis with dryness and pain. When staphylococci cause blepharitis, there is almost always associated conjunctivitis. Also look for nits and consider allergic contact dermatitis to ophthalmologic products.

Infections of the Fingers

In addition to bacterial and candidal paronychia, there are deeper bacterial infections of the digits requiring prompt attention. They are discussed in conjunction with diseases of the nails (p. 520).

5.7 Zoonotic Infections

- **Definition:** Infections transmissible from animals to humans under natural conditions.

Anthrax

- **Epidemiology:** *Bacillus anthracis* is a Gram-positive rod that forms spores which can live in the soil for decades. Anthrax occurs in a variety of wild and domestic animals; it has traditionally been a disease of veterinarians, farmers, and those in the leather and fur industries. Today feared as a biological weapon; a notorious incident was the sending of anthrax spores via the mail in the USA in 2002.
- **Clinical features:** Two major types of anthrax:
  - *Cutaneous anthrax:* Spores enter the skin through a minor injury, producing red papules that become edematous, then vesicular, and ulcerate; later a firm dark eschar develops and heals with little scarring. Although the lesion is called a malignant pustule, pus is uncommon. Surprisingly asymptomatic. May have associated lymphadenopathy (ulceroglandular form); if untreated, can lead to sepsis.

- *Pulmonary anthrax:* Spores are inhaled; initially flu-like symptoms with fever, as well as widened mediastinum (necrotizing mediastinitis) on radiograph, then fulminant course with death in 1–2 days. Intestinal anthrax is rare, but may develop when spores are ingested; also usually fatal.

► **Diagnostic approach:** History, bacteriologic studies, determine sensitivity to penicillin.
► **Differential diagnosis:** Furuncle (painful), orf, milker's nodule, tularemia, plague.
► **Therapy:** Treatment of choice is ciprofloxacin 500 mg p.o. b.i.d. or doxycycline 100 mg p.o. b.i.d. for mild disease below the neck. If severe, marked edema, or facial, then i.v. use of the same agents is recommended. If the bacillus is sensitive to penicillin, then a switch to amoxicillin or high-dose i.v. penicillin is appropriate. Intravenous corticosteroids may be needed for edema.
► ***Note:*** Treatment does not influence the skin lesions. It must be continued for 60 days to offer effective prophylaxis against pulmonary anthrax.
► **Prophylaxis:** Either ciprofloxacin or doxycycline can be used following possible exposure.
► **Immunization:** Two vaccines are available, but they are short-acting and of questionable efficacy. US military immunizes all soldiers.
► **Prognosis:** Pulmonary anthrax is almost always fatal; most cutaneous anthrax can be treated.

Erysipeloid

► **Epidemiology:** *Erysipelothrix rhusiopathiae* is a Gram-positive rod that infects a variety of animals including pigs, saltwater fish, and poultry. Risk groups include butchers and fishermen. Infections more common in summer.
► **Clinical features:** Incubation period 2–8 days. Livid or red plaque with central healing, usually on finger or hand. Usually mild course; rarely joint involvement, or in immunosuppressed patients sepsis or endocarditis.
► **Diagnostic approach:** History, culture usually from biopsy material.
► **Differential diagnosis:** Despite name, not easily confused with erysipelas. *Seal finger* is clinically similar, but occurs following contact with seals, as it is caused by a marine mycoplasma. *Vibrio vulnificus* is found is shallow or marshy seawater; injuries handling crabs or lobsters may produce such lesions, especially in immunosuppressed patients.
► **Therapy:** Penicillin G 1.2 million IU i.m. daily or b.i.d. for 10 days. With penicillin allergy, erythromycin or tetracycline.

Rickettsial Diseases

► **Definition:** Rickettsia are small Gram-negative bacteria, with cell walls, that multiple only within host cells Examples are listed in Table 5.**3**.
► **Epidemiology:** Rickettsia live within the gut of arthropods and are transferred to humans by bites. Often the natural host is a rodent; the human is an incidental host. Geographic and hygienic factors play a major role, as demonstrated by outbreaks of epidemic typhus during wars and following natural disasters. After an infection, there is long-standing immunity.
► **Clinical features:**

- Headache, nausea, chills, and high fever 1–3 weeks after bite. Typical is a necrotic papule at the site of bite (eschar). Rocky Mountain spotted fever (RMSF) may have lymphadenopathy; typically absent in typhus.
- Soon after the fever, macular to maculopapular exanthems appear on the trunk; they may become hemorrhagic. In RMSF, first lesions are on palms and soles. Epidemic typhus may also have a thrombotic vasculitis.

Table 5.3 · Rickettsia

Organism	Disease	Vector
Rickettsia rickettsii	Rocky Mountain spotted fever	Ticks
Rickettsia prowazekii	Endemic typhus	Lice
Rickettsia typhi	Epidemic typhus	Lice, fleas
Rickettsia conorii	Mediterranean tick bite fever	Ticks
Rickettsia akari	Rickettsial pox	Mites

- **Diagnostic approach:** The classic Weil–Felix test is first positive after 2 weeks and does not help identify the species of rickettsia. Microimmunofluorescence or immunoblot tests are usually used; the same immunofluorescence antibodies can be applied to skin biopsies.
- **Differential diagnosis:** Exanthems are not clinically specific; history and presence of eschar help.
- **Therapy:** Doxycycline 100 mg b.i.d. for 5–7 days for mild disease; severely ill patients should be hospitalized for i.v. medications. Many different alternatives; consult infectious diseases books.
- **Prophylaxis:** Doxycycline 100–200 mg in single dose sometimes employed after tick bite in endemic region, but little supporting data. Aggressive control of vectors.

Tularemia

- **Definition:** *Francisella tularensis* is a Gram-negative rod present in a variety of small mammals in Europe and primarily North America.
- **Epidemiology:** Spread is usually via direct contact, such as in hunters, but spread by vectors is also possible.
- **Clinical features:** Four clinical forms:
  - *Ulceroglandular form:* Most common, often in hunters who skin rabbits. Organisms enter skin, cause small pustules after 2–10 days, rapid advance to dirty ulcers. Regional lymphadenopathy. Less than 5% fatality.
  - *Oculoglandular form:* Similar, but entry via conjunctiva.
  - *Pulmonary form:* Direct lung infection.
  - *Typhoidal form:* Fever without local findings.
- **Diagnostic approach:** Usually clinical diagnosis; immunofluorescence antibodies available for tissue detection, as usual stains difficult; lymph nodes have typical histology (zonal necrosis); serology takes several weeks to become positive.
- **Therapy:** Streptomycin 1–2 g i.m. daily for 7–14 days or gentamicin 5 mg/kg i.v. daily; numerous alternatives; see infectious disease texts.

Cat Scratch Fever

- **Definition:** Self-limiting infection with *Bartonella henselae*, a small Gram-negative rod.
- **Epidemiology:** Most patients are children or adolescents; transmission is via cat scratch or other contact.

- **Clinical features:**
  - Incubation period 3–14 days.
  - Primary lesion at site of scratch; papule that evolves into pustule and then nodule; usually on hand or arm, resolves over 1–2 months; only occurs in 50% of patients.
  - Regional lymphadenopathy, usually unilateral, often fluctuant and painful, resolves after 1–2 months.
  - Systemic signs and symptoms including fever, chills, malaise, myalgias, arthralgias; both erythema multiforme and erythema nodosum may be seen. Rare complications include retinitis, encephalitis, and Parinaud syndrome (sterile conjunctivitis plus unilateral lymphadenopathy).
- **Diagnostic approach:** Very difficult, causative organism confirmed in past decade; usually a clinical decision confirmed by PCR.
- **Differential diagnosis:** Tularemia, sarcoidosis, tuberculosis.
- **Therapy:** Often no therapy needed, but azithromycin 250 mg p.o. daily appears to be agent of choice.

Animal Bites

Bites account for about 1% of emergency room visits in the USA. All patients should be assessed for the risk of rabies and need for tetanus immunization. Bites from different sources have different features:

- **Dog bites:** Most injuries are from crushing or chewing; risk of infection is greatest on distal extremities. Only about 20% become infected. Common organisms include staphylococci, streptococci, *Pasteurella multocida*, and a number of pathogens unique to canines, including *Capnocytophaga canimorsus* (which may cause sepsis in splenectomized individuals). Usually treated with amoxicillin/clavulanic acid. Nonfacial or older wounds generally not closed.
- **Cat bites:** Felines are more likely to inflict puncture wounds; deeper structures more easily reached than by dog bites. At least 50% of bites become infected. *Pasteurella multocida* is most common cause; amoxicillin/clavulanic acid once again appropriate.
- **Exotic bites:** Always check Internet to see what is known; for example, swans transmit *Pseudomonas aeruginosa*; there was an epidemic of monkeypox in USA transmitted by pet ground squirrels.
- **Human bites:** The worst bite of all. The "inadvertent" bite when a clenched fist contacts the teeth (in other words, a punch) often leads to tendon and joint infections in the aggressor. Most infections are mixed, with anaerobic species usually admixed. Amoxicillin/clavulanic acid is usually appropriate; hand injuries should be referred promptly to hand surgeon.

5.8 Borreliosis

- **Synonyms:** Lyme borreliosis or Lyme disease.
- **Definition:** Infection with *Borrelia burgdorferi*, transferred by ticks. Stage I and stage II represent early disease; stage III, late (Fig. 5.**8**).
- **Epidemiology:** *Borrelia burgdorferi* is a spirochete; three different species have been identified:
  - *Borrelia burgdorferi sensu stricto.*
  - *Borrelia garinii.*
  - *Borrelia afzelii.*

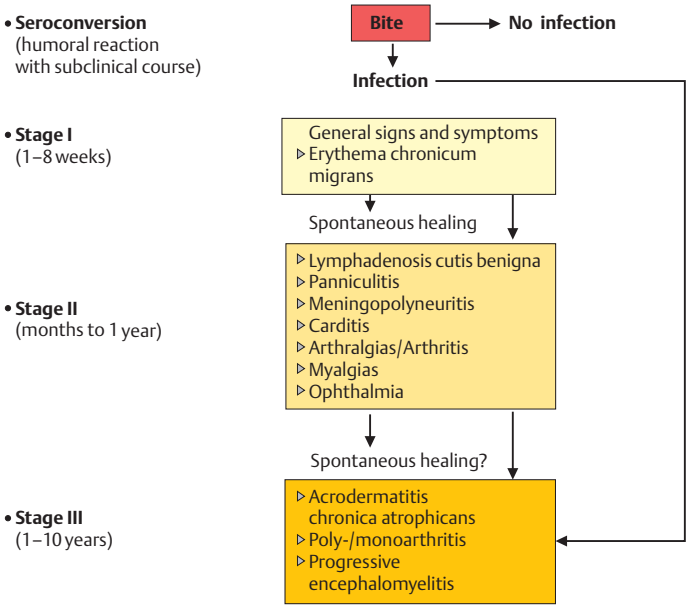
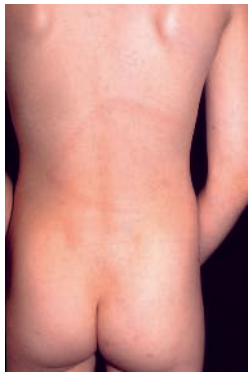


Fig. 5.**8** · Stages of borrelial infection (after Orfanos and Garbe).

- All three are found in Europe, but only *Borrelia burgdorferi sensu stricto* is found in USA. *Borrelia afzelii* is more likely to cause neurologic disease and acrodermatitis chronica atrophicans, perhaps explaining the paucity of these problems in the USA. The initial cases of borrelial arthritis were described along the Lyme River in Connecticut, leading to the name Lyme disease.
- The natural hosts are ticks; in endemic areas, over 90% may be infected. The main vectors are *Ixodes ricinus* (Western Europe), *Ixodes scapularis* (Eastern USA), and *Ixodes pacificus* (Western USA). Both adult ticks and small nymphs transfer the bacteria by bites; in 50% of cases not noticed as the bites are painless. The risk of infection is estimated at 1–5/100 bites, depending on how endemic the disease is. Transmission in the first 36 hours is rare, as the organism must be activated in the tick following attachment. Antibodies are developed, but provide no protection against reinfection (p. 679).
- **Clinical features:**
  - *Stage I:*
    - Incubation period 1–8 weeks.
    - *Erythema chronicum migrans* (ECM): Red papule develops on trunk or limb at site of bite. Slowly a spreading annular erythema evolves as the papule fades (Fig. 5.**9 a**). Often pruritic. Variants include multiple lesions and complex intersecting lesions.
    - Associated headache, malaise, or joint pain. Resolution after about 10 weeks with or without treatment.

Note: A small red border around a tick bite should not be equated with erythema chronicum migrans.
- Differential diagnostic considerations for annular lesions (p. 711).

- *Stage II:*
  - Incubation period 2–12 months.
  - *Lymphadenosis cutis benigna:*
  - Early edematous stage with lymphocytic infiltrate, usually on ear lobe (Fig. 5.**9 b**), nipple, or cheek (children); evolves into solid red-brown tumor with smooth surface, 1–2 cm large over months to a year.
  - Microscopically benign proliferation of B cells with follicles; most common type of lymphocytoma (p. 471).
  - Neurologic manifestations include meningoencephalitis, lymphocytic meningoradiculitis (*Bannwarth syndrome*), radicular pains, peripheral paresis (facial nerve palsy and others); pleocytosis of CSF.
  - Cardiac features include myocarditis with atrioventricular block, pericarditis, pancarditis.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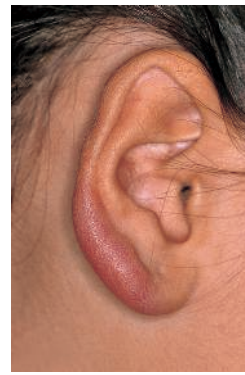
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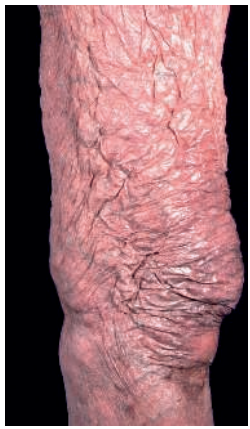
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Fig. 5.**9** · **a** Erythema chronicum migrans. **b** Lymphadenosis cutis benigna (lymphocytoma). **c** Acrodermatitis chronica atrophicans.

  - Rheumatologic manifestations include arthralgias, myalgias, oligoarthritis (often knee), more common in USA.
  - Other findings include lymphadenopathy, inflammatory ocular disease, renal involvement.
- *Stage III:*
  - *Acrodermatitis chronica atrophicans:* Most dramatic change with development of very atrophic skin (*cigarette paper skin)* over the distal extremities (ankles, knees, Fig. 5.**9 c**). Initially puffy vague erythema which over years becomes atrophic with loss of subcutaneous fat so that underlying vessels can be easily visualized.
  - *Juxtaarticular nodules:* Fibrous proliferations over the elbows and knees; when the lesion is linear extending down the forearm, known as *ulnar streak*.
  - Some cases of lymphadenosis cutis benigna may evolve into cutaneous marginal zone B-cell lymphoma, which sometimes responds to antiborrelial therapy.
  - Systemic features include peripheral neuropathies, encephalomyelitis, chronic arthritis.

► **Diagnostic approach:**

- Dermatologic, neurologic, rheumatologic, and cardiologic evaluation, depending on stage and clinical features.
- Serological studies include ELISA and Western blot demonstration of antibodies; in stage I 20–50% (usually IgM); stage II 70–90% (initially IgM, then IgG); stage III 100%.

  Caution: False-positive IgM titers arise in syphilis, some malignancies, autoimmune diseases, and acute Epstein–Barr virus infection. IgG titer alone does not prove active infection.
- Other signs of infection: complement ↓, sed rate ↑, C-reactive protein ↑.
- Active neuroborreliosis diagnosed on basis of CSF pleocytosis with increased lymphocytes and intrathecal antibody product (CSF/serum quotient).
- Histology for lymphocytoma, acrodermatitis chronica atrophicans.

► **Therapy:**

- Stage-adjusted therapy as shown in Table 5.**4**. Adequate therapy is essential to avoid the complications associated with later stages; on the other hand, therapy should not be administered on a prophylactic basis or when the diagnosis is not certain.

Table 5.4 · **Treatment of cutaneous borreliosis**

Stage I	Stage II	Stage III
Doxycycline 100 mg p. o. b.i.d. for 14–21 days	Doxycycline 100 mg p. o. b.i.d. for 21 days or ceftriaxone 2 g i. v. daily for 14 days	Ceftriaxone 2 g i. v. daily for 14 days
Alternatives: Tetracycline, ampicillin, oral cephalosporins	Alternative: Penicillin G 5–10 million IU i. v. t.i.d. for 21 days	Alternative: Penicillin G 5–10 million IU i. v. t.i.d. for 21 days
Children/pregnancy: Ampicillin, amoxicillin, erythromycin	Children/pregnancy: Ampicillin, amoxicillin, erythromycin	

Caution: It is especially important to avoid treating patients with positive IgG titers for borrelial antibodies and vague symptoms for chronic borreliosis.
- If titers remain elevated and clinical findings persists, re-treatment with ceftriaxone i.v. should be considered.

► **Prophylaxis:**
- Avoid exposure in endemic areas; avoid woods as much as possible, use insect repellents; check carefully for ticks 1–2 × daily.
- Removal of tick in first 24 hours is the single most important measure.

5.9 Mycobacterial Infections: Tuberculosis

Overview

► **Causative agent:** Mycobacteria are small, nonmotile, slightly curved acid-fast rods. *Mycobacterium tuberculosis* causes >95% of human tuberculosis; *Mycobacterium bovis* is responsible for the rest.

► **Epidemiology:**
- Only 10% of individuals with normal immune status who are infected with *Mycobacterium tuberculosis* develop active tuberculosis.
- Factors that decrease host resistance include:
  - Malnutrition, immunosuppression, malignancies, other major illnesses.
  - *Age:* Children <3 years of age have a more severe course; 3–12 year-olds almost always have spontaneous healing. Later, resistance drops with increasing age.
  - *Pulmonary silicosis:* Increased risk for tuberculosis; always ask in history.
- Today in Europe drug abusers, patients with HIV/AIDS, lymphoma, leukemia, and iatrogenic immunosuppression are all at great risk for tuberculosis. In some situations, such as prisoners in some parts of Eastern Europe, the problem is epidemic.
- Immigration of patients from countries where tuberculosis is endemic is another factor in the surge of cases in developed countries.
- *Mycobacterium bovis* has become uncommon as cattle tuberculosis has almost been eliminated in most developed countries.

► **Resistance:**
- The number of strains resistant to single agents or to multiple drugs is continuing to increase. Factors include inappropriate single drug therapy and inadequate duration of therapy, both leading to selection of resistant strains. Strict combination regimens, perhaps administered under direct observation, are considered the only effective public health measure.

Note: Patients with HIV/AIDS and multidrug resistant *Mycobacterium tuberculosis* are currently the major sources of infection.

► **Diagnostic approach:**
- *Microscopic examination:* Staining with Ziehl–Neelsen stain or auramine fluorescence staining can be used to examine tissue sections or bodily fluids. Rapid, but only sensitive when large numbers of organisms are present ($10^3 - 10^4$/mL).
- *Culture:* Both species grow slowly on special media (Löwenstein–Jensen) under anaerobic conditions. Initial growth takes 3–10 weeks, followed by differentiation and determination of drug sensitivity, lasting total of 2–3 months. BACTEC method with radiometric measurement of metabolites takes 7–10 days.

- *Other possibilities:* PCR for *Mycobacterium tuberculosis* DNA in skin biopsies; this technique has become important because it is so difficult to culture the organisms in skin.

► **Pathogenesis.**

- *Primary infection:*
  - The usual site of infection is the lungs following droplet spread. A nonspecific leukocyte-rich inflammatory response develops, known as a *tubercle.* From there the bacteria move to regional lymph nodes (*primary complex* or *Ghon complex*). Then the bloodstream is invaded, so that the mycobacteria can be spread throughout the body.
  - After 2–4 weeks a specific cell-mediated immunity develops and the host is usually able to bring the infection under control. Healing occurs with fibrosis and calcification.
- *Endogenous reactivation:* Organisms that have been spread about the body during the primary infection can survive in different organs for years. If the host immune response diminishes, then the bacteria can once again cause active disease. If the resistance is modest, the disease will remain localized; with sharp diminution in resistance, disseminated disease occurs.
- *Secondary infection:* Secondary infections are uncommon with specific immunity and good resistance, but they can occur.

Clinical Forms of Cutaneous Tuberculosis

The clinical expressions of cutaneous tuberculosis all reflect an interplay between the virulence of the bacteria and the variations in host resistance and previous exposure. There is a bewildering list of names; we have picked just a few examples. All are rare today, but may increase in prevalence if the current increasing trend in pulmonary tuberculosis continues.

Primary Cutaneous Tuberculosis (Inoculation Tuberculosis)

► **Definition:** Lesion resulting from direct introduction of *Mycobacterium tuberculosis* or *Mycobacterium bovis* into skin of previously unexposed host.
► **Epidemiology:** Uncommon; most patients are children.
► **Clinical features:** At first small papules develop at inoculation site; they expand into a painless ulcer several centimeters across: *primary lesion* (analogous to tubercle in lung). Then after 3–8 weeks, regional lymphadenopathy appears: *primary complex* (analogous to Ghon complex). Healing within a year, usually with scarring.
► **Diagnostic approach:** Culture and biopsy.
► **Therapy:** Systemic therapy; (p. 100).

Tuberculosis Cutis Miliaris Disseminata

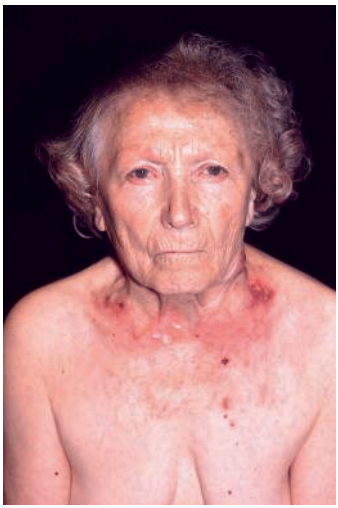
► **Clinical features:** Hematogenous dissemination in infants or immunosuppressed individuals; many skin lesions, as well as systemic lesions, and a very poor prognosis.

Tuberculosis Mucosae et Cutis Ulcerosa

► **Synonym:** Orificial tuberculosis.
► **Clinical features:** Patients with a high load of *Mycobacterium tuberculosis* and poor resistance develop mucosal lesions, usually ragged, painful oral ulcers. Prognosis is dismal.
► **Therapy:** Systemic therapy; (p. 100).

Tuberculosis Cutis Colliquativa

- **Synonyms:** Scrofuloderma.
- **Definition:** Subcutaneous tuberculosis with development of cold abscesses and spread to skin.
- **Epidemiology:** Patients are usually young children or elderly people.
- **Pathogenesis:**
  - *Scrofuloderma:* Spread of subcutaneous tuberculosis into subcutaneous fat and then skin from infected lymph node, bone, or other tissue.
  - *Tuberculous gumma:* Hematogenous spread of mycobacteria with multiple liquefying cold abscesses that break though to the skin.
- **Clinical features:**
  - Usually the lymph nodes of the neck and submandibular region are involved. They are infected from the primary pulmonary tuberculosis or directly infected from the tonsils (in the past when milk infected with *Mycobacterium bovis* was ingested).
  - Initially indolent blue-red nodules (cold abscesses) that enlarge and break down. The ulcers are bizarre, undermined, and tend to form fistulas (Fig. 5.**10 a**). Healing occurs after years, with typical strands of scarring.
  - Hematogenous lesions involve the trunk and extremities, often with simultaneous lesions in bones (fingers, sternum, ribs).
- **Diagnostic approach:** Histology of edge shows typical tubercles; culture or PCR of discharged materials.
- **Differential diagnosis:** Syphilitic gumma, deep fungal infections, acne conglobata, acne inversa.
- **Therapy:** Systemic therapy (p. 100).



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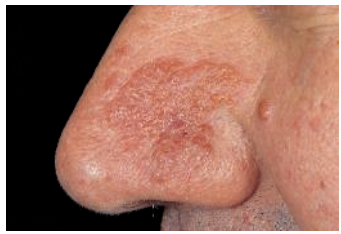

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Fig. 5.**10** · **a** Tuberculosis cutis colliquativa. **b** Lupus vulgaris.

Lupus vulgaris

- **Definition:** Chronic dermal infection with *Mycobacterium tuberculosis* or *Mycobacterium bovis*.
- **Epidemiology:** Most patients are elderly; women are affected twice as often as men. Most common form of cutaneous tuberculosis in Europe.
- **Pathogenesis:** Lupus vulgaris is usually the result of endogenous reactivation; the mycobacteria reach the dermis by direct spread from lymph nodes, or by hematogenous or lymphatic spread.
- **Clinical features:**
  - Large red-brown atrophic patches or plaques with telangiectases (Fig. 5.**10 b**). Sites of predilection include face (especially nose and ears), breasts, and thighs. Crusts, ulceration, and destruction of adjacent tissue (cartilage of ear or nose) lead to mutilation.
  - Classic lesion is the *lupus nodule,* 2–3 mm slightly elevated papule at periphery. On diascopy, characteristic "apple jelly" color surrounded by pale border. When one presses on a lupus nodule with a sound, one can break through with little pain: *sound phenomenon.* The histologic equivalent of a lupus nodule is a tubercle.
  - 40–50% of patients have tuberculosis in other organs. Pulmonary tuberculosis is 10-fold as common as in general population. Other sites include lymph nodes, mucosa, joints, bones.
- **Diagnostic approach:**
  - Biopsy; very few organisms present so PCR more useful than Ziehl–Neelsen stain. Microscopic picture reveals granulomas with classic three-zone pattern of tuberculosis: central necrosis, band of epithelioid macrophages and Langhans giant cells, rim of lymphocytes.
  - Culture and sensitivity.
  - Complete examination to identify tuberculosis elsewhere and search for signs of impaired immune response.
- **Therapy:** Systemic therapy; (p. 100).

Tuberculosis Cutis Verrucosa

- **Definition:** Exogenous reinfection in individual with intact specific immune response; very uncommon.
- **Pathogenesis:** Two sources of infection:
  - *Infected human material:* Injuries during autopsies or other medical services, known as *prosector's wart*.
  - *Infected cows:* Now very rare, but used to be common in slaughterhouse workers and butchers.
- **Clinical features:** Solitary verrucous papule or nodule, no lupus nodules, central clearing.
- **Diagnostic approach:** Biopsy, PCR; organisms otherwise hard to identify.
- **Differential diagnosis:** Butcher's warts are usually multiple; erysipeloid is more inflammatory; atypical mycobacterial infection (swimming pool granuloma).
- **Therapy:** Systemic therapy; (p. 100).

Tuberculids

- **Definition:** In the past tuberculid was defined as a reaction to *Mycobacterium tuberculosis* without direct infection; it included many diseases with granulomatous histology but no connection to tuberculosis, such as rosacea. As tuberculosis became more rare, it became clear that the connections were tenuous. Examples include:

- *Tuberculids with some evidence of relationship to* Mycobacterium tuberculosis: Lichen scrofulosorum, papulonecrotic tuberculid, erythema induratum.
- *Tuberculids unlikely to be infection-related:* Lupus miliaris disseminatus faciei, rosacea-like tuberculid, acneiform tuberculid.

Therapy

► **Overview:** The World Health Organization has issued very specific guidelines for treating tuberculosis (Table 5.**5**). The goals are to effectively arrest the disease in the patient, to decrease transmission, and to avoid selecting drug-resistant strains. Treatment plans all have two phases: an initial phase (more aggressive daily therapy; usually for 2 months) and a continuation phase (less aggressive, often 3× weekly, for 4–6 months). Crucial points are:
- Use of multiple agents, often in combination to avoid resistance.
- Direct observation of patients where possible.
- Minimum of 3× weekly dosing; otherwise peaks and troughs not adequate.

Table 5.5 · **WHO essential drugs for tuberculosis**

	Drug	Dosage (mg/kg)
	Daily	**3 × weekly**
Isoniazid	5	10
Rifampicin	10	10
Pyrazinamide	25	35
Streptomycin	15	15
Ethambutol	15	30
Thiacetazone[a]	2.5	2.5

a Not recommended when ethambutol is available.

► **Treatment of cutaneous disease:** There are few guidelines addressing the treatment of extrapulmonary tuberculosis, since from a public health point of view most patients require treatment for their pulmonary disease. Rifampicin appears to be the single most important agent. A typical regimen for lupus vulgaris or other primarily cutaneous tuberculosis might include:
- *Phase I:* isoniazid + rifampicin + ethambutol or pyrazinamide, all daily for 2–3 months.
- *Phase II:* Same drugs as above, but only 3× weekly for 4–6 months; ethambutol can be eliminated or dose lowered.
- *Alternative:* isoniazid 300 mg daily + rifampicin 600 mg daily for 6 months.
- Immunosuppressed patients should be treated longer. Four-agent scheme with streptomycin may be indicated.
- Follow-up after 6 and 12 months.

5.10 Mycobacterial Infections: Leprosy

Overview

- **Definition:** Chronic infection with *Mycobacteria lepra*.
- **Epidemiology:**
  - Found primarily in tropical and subtropical countries.
  - 2–3 million individuals are infected worldwide, most in the Indian subcontinent.
  - Has disappeared or been eliminated in temperate countries, but cases continue to be introduced by immigration from countries with endemic disease.
  - Aggressive public health measures have dramatically reduced the incidence, but strains resistance to dapsone and rifampicin have started to appear.
  - Infection usually occurs in childhood. The incubation period is 2–10 years; most patients develop adequate immunity so that relatively few patients develop clinical findings. Chronic exposure also appears essential; tourists almost never acquire leprosy, although longer-term visitors occasionally become infected.
- **Pathogenesis:** Just as with tuberculosis, leprosy reflects an interplay between the immune status of the patient and the virulence of the mycobacteria. Didactically useful to think of two poles (Table 5.**6**), although many patients lie somewhere between these extremes.

Table 5.6 · **Comparison of the two poles of leprosy**

Form	Tuberculoid	Lepromatous
Resistance	High	Low
Number of organisms	Low	High
Clinical symmetry	Asymmetrical	Symmetrical
Lesion border	Sharp	Vague
Histology	Granulomas	Diffuse infiltrates

- **Clinical features:**
  - *Indeterminate leprosy:* The initial cutaneous manifestations of leprosy are subtle and not specific. Initially erythematous patch, which in darker-skinned individuals appears pale; most cases resolve, some advance into more severe disease. Differential diagnostic considerations include vitiligo, nevus anemicus, nevus depigmentosus, postinflammatory hypopigmentation, pityriasis alba, tinea versicolor.
  - *Tuberculoid leprosy:*
    - *Skin findings:* One or multiple erythematous or scaly, well-circumscribed macules or patches; usually hypo- or anesthetic (Fig. 5.**11a**). Differential diagnostic considerations include lupus vulgaris, chronic cutaneous lupus erythematosus (discoid), tinea corporis.
    - All patients have nerve involvement. Inflammation of Schwann cells leads to thickening of peripheral nerves.
    - Course generally benign.
  - *Borderline leprosy:* More lesions, more widespread and less sharply defined than in tuberculoid form. Usually symmetrical on trunk but may be asymmetric on face. Less likely to have scale. Nerve involvement less prominent.

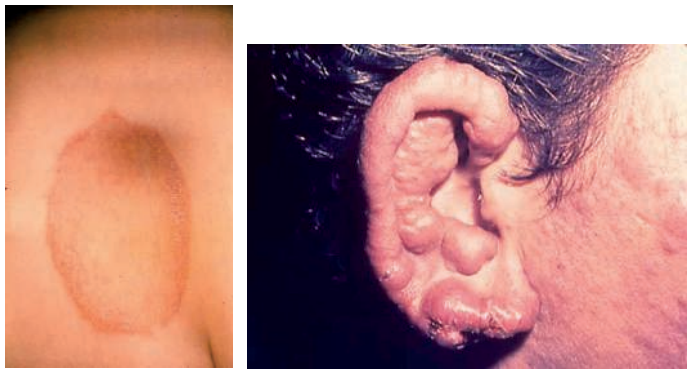


Fig. 5.**11** · **Leprosy. a** Tuberculoid. **b** Lepromatous (Images courtesy of Juan J. Ochoa MD, Chihuahua, Mexico).

- *Lepromatous leprosy:*
  - Papular and nodular lesions symmetrically distributed. Often start on nose and ears, later involve hands, arms, buttocks (Fig. 5.**11b**). Facial lesions can be markedly swollen (*leonine facies*) with loss of eyebrows (*Lucio sign*). In Mexico and Central America, *leprosy bonita* (pretty leprosy) refers to the initial loss of wrinkling in some patients with diffuse disease. Glossitis may occur. Later, destruction of the nasal cartilage with mutilation.
  - Nasal secretions rich in organisms.
  - Complications include orchitis, facial mutilation, neurotrophic ulcers, flexion contractures of hands, foot drop.
  - Differential diagnostic considerations include myxedema, neurofibromatosis, post-kala-azar dermal leishmaniasis.

► **Diagnostic approach:**

- Skin biopsy; histological examination; Ziehl–Neelsen works well in lepromatous leprosy. For paucibacillary forms, PCR is available, but has not been as effective as hoped.
- Nasal smear or scraping from tissue fluid from ear in lepromatous leprosy reveals numerous organisms on Ziehl–Neelsen stain.
- Neurological examination (anesthetic patches, enlarged nerves).
- *Lepromin test (Mitsuda test):* Injection of an extract from lepromatous tissue; positive response is development of nodule after 3–4 weeks in tuberculoid leprosy.
- False-positive serological tests for syphilis in lepromatous leprosy.

► **Therapy:**

- Many different agents available for treating leprosy. Current WHO recommendations:
  - *Tuberculoid leprosy:* Dapsone 100 mg daily and rifampicin 600 mg monthly for 6–9 months.
  - *Single lesion (tuberculoid or indeterminate):* Dapsone 600 mg, ofloxacin 400 mg, and minocycline 100 mg as single dose.
  - *Lepromatous leprosy:* Dapsone 100 mg daily; clofazimine 150 mg, and rifampicin 600 mg monthly for 12–18 months.

Note: After the first dose, patients are no longer infectious to others.
- In case of questions or poor response, always consult responsible public health officials.

Leprosy Reactions

- **Definition:** Acute inflammation that appears suddenly during treatment.
- **Clinical features:**
  - *Type I reaction (reversal reaction):*
    - Increase in cell-mediated (type IV) immunity with flaring of nerve or skin involvement.
    - Therapy: systemic corticosteroids (prednisone 20–60 mg daily).
  - *Type II reaction (vasculitic reaction):*
    - Increased in circulating immune complexes with vasculitis.
  - *Two clinical forms:*
    - *Erythema nodosum leprosum*: Erythematous nodules on legs and arms (in contrast to true erythema nodosum).
    - *Lucio phenomenon*: Necrotizing small vessel vasculitis.
- **Therapy:** Thalidomide 100–200 mg daily.

5.11 Atypical Mycobacterial Infections

Swimming Pool Granuloma

- **Definition:** Infection with *Mycobacterium marinum*.
- **Pathogenesis:** *Mycobacterium marinum* is an aquatic species that causes tuberculosis-like disease in fish. It can enter the skin following injuries in swimming pools, natural bodies of water, or home aquariums.
- **Clinical features:**
  - Incubation period 3 weeks.
  - Site of entry minor injuries on hands, knees.
  - Usually verrucous papules or nodules (Fig. 5.**12**); sometimes associated with sporotrichoid lymphangitic spread (p. 713).
  - Spontaneous healing over years.
- **Diagnostic approach:** Culture from homogenized skin biopsy, at 31–33 °C. Always warn laboratory when diagnosis is suspected. Photochromogen that grows out in 7–10 days.
- **Differential diagnosis:** Common wart, tuberculosis cutis verrucosa, squamous cell carcinoma; if lymphangitic, sporotrichosis.

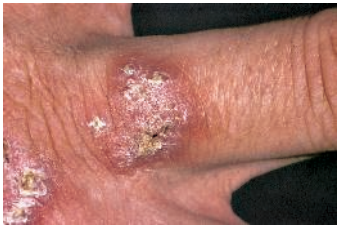


Fig. 5.**12** · Swimming pool granuloma.

- **Therapy:**
  - Small lesions can be excised.
  - Doxycycline 100 mg b.i.d. for 8–12 weeks.
  - Local heat application (hand warmer or similar device).
  - If not responsive, then rifampicin 150 mg t.i.d. and ethambutol 400 mg t.i.d. until clinically responsive, following culture and sensitivity studies.

Buruli Ulcer

- **Epidemiology:** Infection with *Mycobacterium buruli*, which is found primarily in tropical Africa and Australia. Associated with moist environments.
- **Pathogenesis:** *Mycobacterium buruli* is the only mycobacterium that produces a highly tissue-destructive toxin.
- **Clinical features:** Initially subcutaneous nodules develop at the site of injury or inoculation, usually on limbs. These progress rapidly to large undermined ulcers extending down to the fascia, which are surprisingly asymptomatic considering their size and depth. Healing with scarring occurs spontaneously after years.
- **Therapy:**
  - Surgical debridement and then skin grafting.
  - Supplemental heat therapy (infrared radiation).
  - Rifampicin perhaps in combination with co-trimoxazole or clarithromycin appears to be the most effective agent.

Mycobacterium avium-intracellulare

- Group of slow-growing bacteria that are ubiquitous, so that avoidance is impossible.
- Rare cause of primary inoculation or pulmonary lesions in healthy individuals.
- Prior to HAART, major problem in HIV/AIDS affecting at least 40 % of patients with disseminated infection contributing to wasting syndrome. Today, more likely to cause localized disease such as soft tissue abscesses or lymphadenitis (p. 160).
- Therapy is complex; multiple agents are always required for long periods of time. The standard regimen is clarithromycin (or azithromcin), ethambutol and rifabutin for at least six months.

5.12 Actinomycosis

- **Definition:** Chronic, slowly spreading infection with *Actinomyces israelii*, an anaerobic, Gram-positive bacterium.
- **Pathogenesis:** *Actinomyces israelii* is part of the normal flora of the mouth, airways, and gastrointestinal tract. Infections are endogenous, following tissue injury which favors anaerobic growth. Patients are not infectious. Secondary mixed infections, especially with *Actinobacillus actinomycetemcomitans*, are common.
- **Clinical features:** Three classic forms:
  - *Cervicofacial:* Most common form (> 50%); usually follow dental work or periapical inflammation; induration of chin or neck with sinus tracts and drainage of pus; no lymphadenopathy.
  - *Thoracic:* Pulmonary lesions often with drainage to overlying skin; usually follow aspiration.
  - *Gastrointestinal:* Chronic inflammation and drainage, following infection (appendicitis) or bowel injury. A possible variant is pelvic actinomycosis, associated with use of an intrauterine contraceptive device.

- **Diagnostic approach:** Histology, direct identification of yellow granules (*sulfur bodies* = clumps of bacteria) in discharge, anaerobic culture.
- **Therapy:**
  - Surgical excision of injected areas with antibiotic coverage.
  - Treatment of choice for cervicofacial form is amoxicillin 30 mg/clavulanic acid 3 mg/kg t.i.d. for 2 weeks.
  - The standard treatment of high-dose penicillin G (10–20 million IU i.v. daily for 4–6 weeks) fails to consider the many secondary bacteria and is not as effective.
  - In case of penicillin allergy, then clindamycin or tetracyclines.
  - For gastrointestinal and thoracic forms, infectious disease consultation. Choice of regimen dictated by nature of secondary infection.

5.13 Nocardiosis

- **Definition:** Infection caused by *Nocardia asteroides* or *Nocardia brasiliensis*, Gram-positive filamentous bacteria.
- **Pathogenesis:** *Nocardia* are found in soil and plants material worldwide. More likely to cause disease in immunosuppressed individuals.
- **Clinical features:**
  - *Nocardia asteroides* causes pulmonary disease and brain abscesses in those with reduced resistance.
  - *Nocardia asteroides* and *Nocardia brasiliensis* can cause cutaneous disease following inoculation, producing local abscesses or a sporotrichoid pattern.
  - *Nocardia brasiliensis* is one of the common causes of mycetomas (p. 118).
- **Diagnostic approach:** Slow-growing and difficult to culture; always warn laboratory that *Nocardia* are being considered so they can employ correct approach.
- **Differential diagnosis:** Sporotrichoid pattern (p. 713).
- **Therapy:** Co-trimoxazole for at least 6 weeks; longer in immunosuppressed patients.

6 Fungal Diseases

6.1 Nomenclature

Classification

The most useful clinical classification of fungi is:
- Dermatophytes.
- Molds.
- Yeasts.
- Subcutaneous mycoses.
- Systemic or deep mycoses.

6.2 Dermatophytes

Overview

Dermatophytes (Table 6.**1**) live as parasites in tissue containing keratin. They can be divided into:
- *Anthropophilic:* found in humans.
- *Zoophilic:* found in animals.
- *Geophilic:* found in soil.
- **Clinical picture:** Determined by the nature of the dermatophyte, by the tissue it invades, and by the degree of host response. Infections with dermatophytes are usually called *tinea*; for further description, the anatomical site is added, such as tinea capitis for scalp disease. The clinical infection usually starts from an inoculation site and spreads peripherally; thus annular lesions with an active border. In nonmedical jargon, the diagnosis is often "*ringworm*".
- Most common cause of fungal infections in Europe is *Trichophyton rubrum*.
- ***Note:*** Zoophilic and geophilic infections always elicit a more intense immune response and thus appear more aggressive.
- **Id reactions:** The immune response to dermatophyte infections can also cause disease at distant sites where no fungi are present. Most typical picture is dyshidrotic dermatitis.
- **Diagnostic approach:**
  - *Taking specimen:* Disinfect site first to reduce contamination. Use a sterile instrument (scalpel blade, curette, scissors) to obtain tissue from border zone between normal and involved tissue (where concentration of organisms is usually highest).
  - *Microscopic examination:* Hyphae or spores are identified after dissolving the keratin in a 10–15% solution of potassium hydroxide (*KOH examination).* Dyes (chlorazol black E) or fluorochromes (for fluorescent microscopy) can be added. Examination is made at 200–400×.
  - *Culture:* Many standard culture media are available; usually two cultures are made, one on a media containing cycloheximide (for dermatophytes) and one without (yeasts and molds). Hairs can be placed directly on the culture media; fragments from the underside of the nail should be used.

Table 6.1 · Important dermatophytes

Species	Host	Clinical features	Frequency
Trichophyton			
Trichophyton rubrum	Humans	Tinea pedis, tinea manuum, tinea corporis, onychomycosis	Common
Trichophyton mentagrophytes			
var. *interdigitale*	Humans	Tinea corporis, tinea faciei, tinea barbae, tinea capitis	Common; often in children
var. *granulosum*	Mice, guinea pigs		
Trichophyton erinacei	Hedgehogs	Tinea corporis, tinea manuum	Rare
Trichophyton verrucosum	Cows, horses	Tinea corporis, tinea barbae, tinea capitis (often kerion)	Common
Trichophyton violaceum	Humans	Tinea capitis, tinea barbae, tinea corporis	Common in Mediterranean region
Trichophyton tonsurans	Humans	Tinea capitis (black dot), tinea corporis	Common in North and Central America
Trichophyton schoenleinii	Humans	Tinea capitis (favus), onychomycosis	Uncommon; endemic areas
Epidermophyton			
Epidermophyton floccosum	Humans	Tinea inguinalis, tinea pedis, tinea corporis; almost never hair or nail disease	Uncommon
Microsporon			
Microsporon canis	Dogs, cats	Tinea capitis, tinea corporis	Common
Microsporon gypseum	Soil	Tinea capitis, tinea corporis	Common
Microsporon audouinii	Humans	Tinea capitis	Common (uncommon in North America)

Note: Wood's light examination is useful for *Microsporon* species and *Trichophyton schoenleinii*; a negative Wood's light examination does not exclude a fungal infection.

- **Therapy:** The standard therapy includes both topical (p. 594) and systemic agents (p. 622). All are covered in detail elsewhere and only alluded to under the different disease forms in this chapter.

Tinea Corporis

- **Definition:** Dermatophyte infection of the skin of the trunk and extremities, excluding the palms, soles, and inguinal region.

- **Pathogenesis:** Wide variety of dermatophytes can be responsible.
- **Clinical features:** Round or polycyclic circumscribed scaly areas with central clearing. Variable degree of inflammation, in some instances with pustule formation, depending on nature of dermatophyte and host response.
- **Differential diagnosis:** Psoriasis, lichen simplex chronicus, nummular dermatitis, pityriasis rosea, tinea versicolor, parapsoriasis, mycosis fungoides.
- **Therapy:** Topical antifungal agents b.i.d. for 1 month; for more widespread disease, following culture confirmation, systemic agents.

Tinea Capitis

- **Definition:** Infection of the scalp by dermatophytes with hair shaft involvement.
- **Pathogenesis:** Various clinical forms develop, based on host response and nature of hair involvement. Most common causes in USA are *Trichophyton tonsurans* and *Microsporon canis* (very infectious).
- **Clinical features:**
  - *Ectothrix infection:* Spores coat outer surface of hair. Areas of hair loss with stubble of varying size (Fig. 6.**1 a**). Hairs may fluoresce green under Wood's light. Scarring rare. Epidemic tinea capitis is the most common form of ectothrix; caused by *Microsporon canis*, *Microsporon audouinii*, or *Microsporon gypseum*. Responsible for epidemics among schoolchildren. Usually multiple round areas of hair loss; inflammation varies (marked with *Microsporon canis*, while *Microsporon audouinii* produces fine scales with little erythema). Wood's light examination may be positive.
  - *Endothrix infection:* Spores grow into the hair shaft, making it more breakable. Thus, hairs usually end at skin surface, leaving black dots (*Trichophyton ton-*

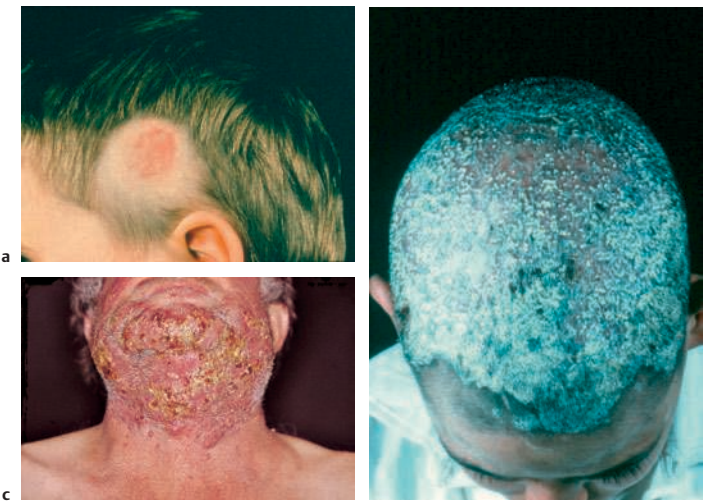


Fig. 6.**1** · **a** Tinea capitis. **b** Favus. **c** Tinea barbae with marked inflammation, caused by *Trichophyton verrucosum* in a farmer.

surans or *Trichophyton violaceum*). Differential diagnosis includes chronic cutaneous lupus erythematosus (discoid), pseudopelade.
- *Kerion*: Intense inflammatory reaction to zoophilic fungus in previously unexposed host, such as young farmers with first exposure to milking cattle; usually *Trichophyton verrucosum* or *Trichophyton mentagrophytes*. Painful inflammatory plaque or nodule with pus draining from follicular openings and honey-yellow crusts (kerion is Greek for honeycomb). Heals with scarring (Fig. 6.**1 b**).
- *Favus*: Infection with *Trichophyton schoenleinii*; relatively common in Middle East, South Africa, and Greenland, otherwise rare. Foul smell (mouse urine). Marked inflammation, large (1–2 cm) adherent crusts that may cover entire scalp, heal with scarring (scarring alopecia). Same clinical picture rarely produced by *Trichophyton violaceum* or *Microsporon gypseum*.

► **Therapy:** Topical therapy ineffective; systemic antifungal agents for 1–2 months, until culture is negative. Only griseofulvin officially approved for children, but others all safe and effective. In case of kerion with secondary infection, add systemic antibiotics based on culture and sensitivity.

Tinea Barbae

► **Definition:** Dermatophyte infection in beard region of men.
► **Pathogenesis:** Similar to kerion; *Trichophyton verrucosum* or *Trichophyton mentagrophytes*.
► **Clinical features:** Patients usually farmers with close animal contact. Develop erythematous plaques with follicular pustules, drainage and crusts (Fig. 6.**1 c**). Surprisingly painless. Heals with scarring.
► **Differential diagnosis:** Staphylococcal infection with multiple furuncles (*sycosis barbae)*; usually painful.
► **Therapy:** Topical therapy ineffective; systemic antifungal agents for 1–2 months.

Tinea Faciei

► **Definition:** Facial dermatophyte infection.
► **Pathogenesis:** Usual cause is sleeping with a pet with zoophilic infection. Infection may be transmitted by close personal contact or spread from other sites to face. Extensive tinea faciei may be sign of immunosuppression.
► **Clinical features:** Erythematous, often scaly patches; often not annular because of facial configuration. Pruritic; may worsen with light exposure.
► **Differential diagnosis:**
- *Chronic cutaneous lupus erythematosus (discoid):* Slower to develop and more persistent; prominent follicles, may be painful.
- *Psoriasis*, *impetigo*, less often *rosacea*, *polymorphous light eruption*.

► **Therapy:** Topical antifungal agents for mild disease; otherwise systemic agents.

Tinea Pedis

► **Definition:** Dermatophyte infection of feet and toes.
► **Synonym:** Athlete's foot.
► **Epidemiology:** Most common fungal infection; 30–50% of adults affected.
► **Pathogenesis:** Most common agents are *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. Infections favored by poor hygiene, increased sweating, occlusive footwear; perhaps by impaired peripheral circulation. Swimming pools, community showers, and saunas are likely sources of infection.

► **Clinical features:** Pattern varies greatly with causative dermatophyte:
- *Hyperkeratotic type:* Also known as moccasin type; diffuse fine scale (Fig. 6.**2 a**), rarely symptomatic, often overlooked or mistaken for palmoplantar keratoderma. First noticed with nail involvement. Usually caused by *Trichophyton rubrum*.
- *Chronic interdigital type:* Typically involves space between more lateral toes; macerated epidermis is white and fissured (Fig. 6.**2 b**). May spread to soles, but rarely to top of foot. Usually caused by *Trichophyton mentagrophytes* var. interdigitale.
- *Dyshidrotic type:* Recurrent attacks of pruritic vesicles and pustules, identical to dyshidrotic dermatitis. Same principle as fungal id reaction, but organisms (usually *Trichophyton mentagrophytes* var. *interdigitale*) can be found.

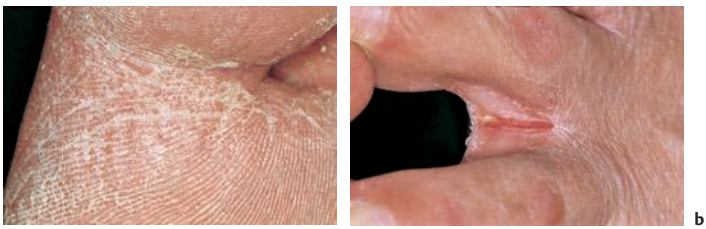


Fig. 6.**2** · Tinea pedis. **a** With fine scale. **b** Interdigital, with fissures.

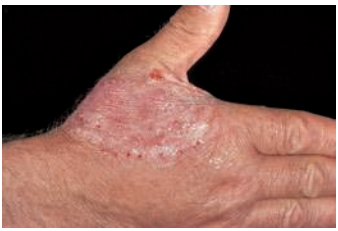
► **Complications:** Gram-negative toe web infections, entry site for erysipelas, predisposing factor for postcoronary bypass cellulitis.
► **Differential diagnosis:**
- *Candida infection:* May also produced macerated appearance, but rare.
- *Gram-negative toe web infection:* usually associated with tinea pedis, search for both.
- *Juvenile plantar dermatosis:* Bilateral, symmetrical, associated with atopy.
- *Dyshidrotic dermatitis.*
- *Palmoplantar pustulosis.*
- *Allergic contact dermatitis.*

► **Therapy:**
- Topical antifungal agents; in severe cases, systemic antifungal agents for 1–3 months.
- Treatment of associated onychomycosis and continued prophylactic use of topical agents are essential to reduce the relapse rate.
- In the case of macerated forms, keep area dry, wear absorbent socks, use sandals in summer.
- Shoes should be disinfected with antifungal sprays to reduce likelihood of reinfection.

► ***Note:*** Tinea pedis is very common and very difficult to eradicate. It can be viewed as a parasite that is simply too well adapted to the host. The older the patient, the less the likelihood of cure.

Tinea manuum

- **Definition:** Dermatophyte infection of the palms.
- **Pathogenesis:** Causative agents include *Trichophyton rubrum*, *Trichophyton mentagrophytes* var. *interdigitale*, less often *Trichophyton violaceum* and *Trichophyton erinacei*. Either primarily inoculation (handling hedgehogs or infected farm animals) or secondary to tinea pedis.
- **Clinical features:** Most often dry hyperkeratotic form (Fig. 6.**3a**); then always check the feet; peculiar but not so rare variant is *"one hand, two feet disease"*. If caused by zoophilic fungus, more localized and inflamed.
- **Differential diagnosis:** Hand dermatitis in all its variants.
- **Therapy:** Topical antifungal agents usually inadequate; systemic therapy required.



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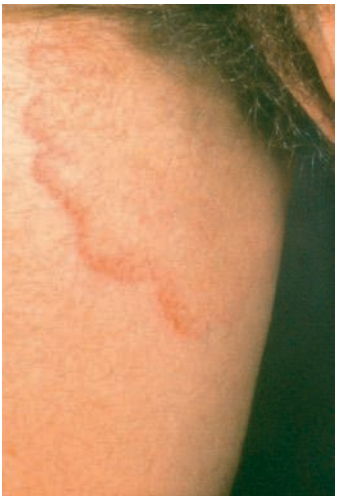

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Fig. 6.**3** · **a** Tinea manuum. **b** Tinea inguinalis.

Tinea Inguinalis

- **Synonym:** Sometimes incorrectly called *tinea cruris* (but cruris refers to lower leg in Latin); eczema marginatum.
- **Definition:** Dermatophyte infection in groin or genital region.
- **Pathogenesis:** Most common causative agents are *Epidermophyton floccosum* and *Trichophyton rubrum*; often associated with tinea pedis or onychomycosis. Old saying, "Put on your socks before your underwear" to avoid spread. More common in men.
- **Clinical features:** Pruritic circumscribed patches with sharp border favoring the medial thigh; may extend to buttocks or perianal region; rarely involves scrotum (Fig. 6.**3b**).

- **Differential diagnosis:** Candidiasis (more common in women, satellite lesions), erythrasma (Wood's light positive), inverse psoriasis (look for psoriasis elsewhere), contact dermatitis, Hailey-Hailey disease. Intertrigo is a superficial irritation which arises when skin folds touch each other, as in the groin, under the breasts or in abdominal folds. It is most often seen with obesity. The occlusion and retention of moisture leads to maceration which may predispose to any of the diseases lists above. We view intertrigo more as a description than as a disease entity.
- **Therapy:** Topical antifungal agents usually sufficient. Drying measures (absorbent powders, astringent solutions, blow dry area after washing, then apply medication).

Note: Check for associated onychomycosis or tinea pedis, which would require systemic antifungal agents.

Onychomycosis

- **Definition:** Infection of nail fold and nail plate with dermatophytes (*Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*) as well as molds (*Hendersonula toruloidea*, *Scopulariopsis brevicaulis*), and yeasts (*Candida albicans*, other *Candida* species). Refers only to a dermatophytic nail infection.
- Covered under Diseases of the Nails (p. 522).

6.3 Yeasts

Overview

- **Pathogenesis:**
  - Almost all pathogenic human yeasts are from the genus *Candida*. The major species is *Candida albicans* types 1 and 2 (formerly known as *Candida stellatoidea*). *Candida albicans* is part of the normal flora of the mouth, gastrointestinal tract, and vagina; it is present in limited numbers, waxing and waning. It is not normally found on the skin or in the respiratory tract. The potentially pathogenic yeasts are shown in Table 6.**2**. The old terms *Monilia* and moniliasis are incorrect and should be avoided.

Table 6.2 · **Yeast species**

Species	Diseases
Candida albicans	Cutaneous candidiasis, esophagitis, vulvovaginitis, endocarditis, and many more
Candida krusei	Cutaneous candidiasis, esophagitis, endocarditis, vaginitis
Candida parapsilosis	Endocarditis, paronychia, otitis externa
Candida pseudotropicalis	Vulvovaginal candidiasis
Candida tropicalis	Onychomycosis, vaginitis, meningitis, respiratory infections
Torulopsis glabrata (*Candida glabrata*)	Part of normal flora but in immunosuppressed patients may cause life-threatening systemic disease including fungemia and meningitis

- Skin and mucosal infections are caused by candidal mycelia; systemic candidiasis is usually caused by blastospores (budding yeasts).
- The host–organism interplay with *Candida albicans* is very complex and poorly understood; experts disagree on the significance of the yeast in the stool, for example. Some feel that gastrointestinal candidal colonization or quantitative increases in yeasts may be associated with diseases such as atopic dermatitis or urticaria. Treatment with nonabsorbable oral anticandidal agents such as nystatin occasionally produces improvement, but we remain skeptical.
- Patients with very specific immune defects tend to have extremely persistent infections (*mucocutaneous candidiasis*).

► **Epidemiology:**
- *Candida albicans* causes disease in young, old, or immunosuppressed individuals; exceptions are vulvovaginitis and balanitis, which affect patients with intact immunity.
- Over 90% of infections are caused by *Candida albicans,* but other species cannot be overlooked; often difficult to identify and typically more resistant to therapy.

▶ ***Note:*** *Candida* infections are often a sign of immunosuppression (diabetes mellitus, HIV/AIDS, long-term antibiotic therapy, hematologic malignancies). Patients with recurrent or refractory disease should be evaluated for such risk factors.

► **Clinical features:** *Candida albicans* infections are known as candidiasis; usually involve the skin or mucous membranes but can be systemic in immunosuppressed patients (Table 6.**2**). Rich clinical spectrum: intertriginous and anogenital candidiasis, onychomycosis, paronychia, oral candidiasis in many forms, intestinal candidiasis, systemic candidiasis, mucocutaneous candidiasis.

► **Therapy:**
- *Polyene antifungal agents* such as nystatin, amphotericin B, and natamycin are old standbys but still effective; they form complexes with ergosterol in the plasma membrane and thus inhibit growth. Nystatin is not absorbed and thus often used for treating oral and intestinal infections.
- *Imidazoles*, both topical and systemic, are also highly effective. They are available as lozenges for oral and gastrointestinal disease, as well as for vaginal use.

▶ ***Note:*** It is critical to correct the predisposing factors, ranging from occlusion and maceration to weight loss, control of diabetes, or avoidance of long-term antibiotic usage.

Oral Candidiasis

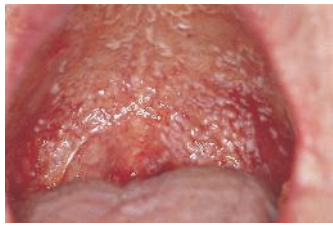
► **Clinical features:** A variety of clinical forms that vary greatly in appearance:
- *Acute pseudomembranous candidiasis (thrush):* The classic form, known to every mother; thick, cottage-cheese-like plaques that can be easily scraped off, revealing an erythematous base (Fig. 6.**4 a**). Most common in infants. Common sites include buccal mucosa, tongue, palate.
- *Acute atrophic candidiasis:* Often painful, flat erythematous areas; typically involves tongue and is secondary to long-term antibiotic usage.
- *Chronic hyperplastic candidiasis:* Thick persistent white plaques, usually in men; not easily removed. Differential diagnosis: other forms of leukoplakia (p. 490).
- *Chronic atrophic candidiasis:* Most often affects denture wearers; atrophic dusky erythematous area confined to area under denture; often confused with allergic or irritant reaction.

- *Angular cheilitis (perlèche):* Painful rhagades at corner of mouth; predisposing factors: drooling (infants and elderly), eating disorders (malnutrition and forced vomiting), poorly fitting dentures. Often combined infection with *Candida albicans* and bacteria.
- *Median rhomboid glossitis:* Erythematous rhomboid patch without papillae on the midline of the dorsal surface of the tongue at the transition from middle to the posterior portion; long thought to represent an embryologic fusion defect, but now considered another form of candidiasis.

► **Therapy:**

- Nystatin or imidazole lozenges t.i.d.–q.i.d. for 5–10 days; easier to use than direct application of medications.
- In the case of angular stomatitis, protective imidazole pastes are helpful.
- In resistant cases, consider 10 days of oral nystatin to reduce bowel load.

Note: Correct the predisposing factors.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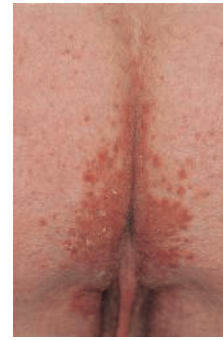
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Fig. 6.**4** · Candidal infection. **a** Of oral mucosa with easily removed white coating. **b** Intertriginous, with typical satellite lesions.

Intertriginous Candidal Infections

► **Clinical features:**

- Any moist intertriginous area can be infected; examples include submammary, inguinal, perianal, and occasionally axillary disease. Lesions typically macerated with fissures and satellite lesions, often pustules (Fig. 6.**4b**).
- In addition, candidal vulvovaginitis and balanitis are common.
- Most diaper dermatitis is irritant, but then rapidly colonized by *Candida albicans*; the presence of satellite lesions is a good clue to this. Problem worse when topical corticosteroids are applied. *Granuloma gluteale infantum* refers to reactive red-brown inflammatory nodules that develop in this setting.

- **Therapy:** Drying measures usually suffice. Dye solutions are effective and economical but messy. In Europe, methylrosaniline chloride and eosin solutions (p. 592) are still used. Topical nystatin or imidazole products are also widely used. Oral nystatin is also safe. For vulvovaginitis, vaginal suppositories usually highly effective; if not or with recurrent disease, then oral imidazoles (usually fluconazole) is recommended.

Chronic Mucocutaneous Candidiasis

- **Definition:** Heterogenous group of congenital immune defects featuring severe and persistent candidal infections.
- **Clinical features:** The classification of chronic mucocutaneous candidiasis (CMC) is shown in Table 6.**3**. Patients have persistent cutaneous, mucosal, and nail infections, usually with *Candida albicans*. Some forms are associated with endocrinologic disturbances.

Table 6.3 **· Forms of chronic mucocutaneous candidiasis (CMC)**

CMC type	Inheritance	MIM code	Onset
Familial CMC with endocrine disturbances	AR	212050	Childhood
	AD	114580	Childhood
Familial CMC with hypothyroidism	AD		Childhood
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECD)	AR	240300	Childhood
Chronic localized candidiasis	Unknown		Childhood
Candidiasis with hyper-IgE syndrome	AR	24370	Childhood
CMC with thymoma	Unknown		Adult
Familial chronic nail candidiasis with ICAM-1 deficiency	AR	607644	Childhood
CMC with chronic keratitis	Unknown		Adult
Chronic oral candidiasis	Unknown		Adult

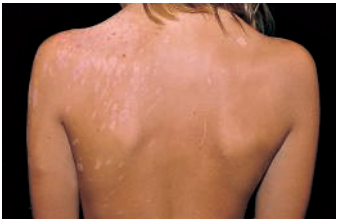
AD = autosomal dominant; AR = autosomal recessive.

- **Diagnostic approach:** Persistence, age of onset, and associated features usually lead to diagnosis; exact immunologic evaluation and in some instances, genetic evaluation.
- **Therapy:** Fluconazole has become the standard therapy; usually 200–800 mg daily. Higher doses needed when *Torulopsis glabrata* identified. In resistant cases, voriconazole (200–400 mg daily) is promising.

Tinea Versicolor

- **Synonym:** Pityriasis versicolor.
- ***Note:*** The European term *pityriasis versicolor* is preferable as this disorder is not a dermatophyte infection and therefore not a "*tinea*.".
- **Definition:** Common superficial yeast infection causing hypo- or hyperpigmentation.

- **Pathogenesis:** Causative agent is *Malassezia furfur*, which is the pathogenic form of the commensal cutaneous yeasts *Pityrosporon ovale* and *Pityrosporon orbiculare*. Because the causative agent is part of the normal flora, it is impossible to eradicate and thus recurrences are common. Mechanisms of pigmentary change are unclear; darkening is a result of hyperkeratosis, but lightening may reflect an umbrella effect as well as a direct effect on melanocytes.
- **Clinical features:**
  - Typical sites are the upper chest and back; much less often the neck, upper arms, and face. The scalp is the most abundant reservoir of *Pityrosporon*.
  - In fair-skinned individuals, the lesions are typically hyperpigmented, tan 1–3 cm oval patches, often confluent. When scraped lightly, they are very scaly; a good diagnostic clue, as few other disorders release so much scale. After tanning or in dark-skinned individuals, the lesions tend to be light. Versicolor refers to the variable colors (Fig. 6.**5 a,b**).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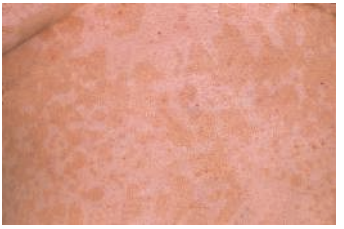
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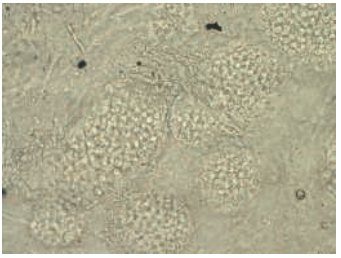
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Fig. 6.**5** · Tinea versicolor. **a** Hypopigmented form. **b** Hyperpigmented form. **c** KOH examination showing hyphae and spores (spaghetti and meatballs).

- **Diagnostic approach:** KOH examination reveals hyphae and spores (spaghetti and meatballs, Fig. 6.**5 c**). Another approach is stripping with clear adhesive tape, staining with methylene blue for 5 seconds, rinsing, and examining under the microscope. Culture not possible.
- **Differential diagnosis:**
  - *Hypopigmented lesions:* Vitiligo, pityriasis alba.
  - *Hyperpigmented lesions:* Ephelides, lentigines, café-au-lait macules.
  - *Erythematous lesions:* Tinea corporis, pityriasis rosea, secondary syphilis, seborrheic dermatitis.
- **Therapy:**
  - Standard approach is to use either imidazole shampoo (ketoconazole) or selenium sulfide shampoo. Scalp and entire body surface to the groin should be lathered up and then rinsed after a few minutes. Initially, the treatment daily for 7–10 days.

Caution: Always treat the scalp; it is the major reservoir for the yeasts.

- Recurrences are common; patients can simply use the medicated shampoo 1–2× weekly indefinitely.
- In stubborn cases, a short course of itraconazole or fluconazole can be employed; some recommend 1 tablet weekly for prophylaxis.

6.4 Subcutaneous Mycoses

The subcutaneous mycoses are not a biological family, but a group of clinical problems all caused by direct inoculation of the organism into the skin and subcutaneous tissue. They are more common in tropical and subtropical regions, presumably because of both enhanced growth of fungi in the soil and on plants and increased likelihood of injury (going barefoot, less protective clothing).

Sporotrichosis

- **Definition:** Subcutaneous and occasionally systemic mycosis caused by *Sporothrix schenckii*.
- **Epidemiology:** Although *Sporothrix schenckii* is found worldwide, sporotrichosis is primarily seen in North and Central America; famous epidemic among South African miners.
- **Pathogenesis:** The fungus is inoculated through injuries, usually from wood or plants; a classic injury is from a rose thorn.
- **Clinical features:**
  - *Localized sporotrichosis:* Verrucous papules and plaques develop following inoculation. Then spread with firm subcutaneous nodules appearing along the path of lymphatic drainage. In the USA, diseases that spread in this fashion (nocardiosis, atypical mycobacterial infections, plaque, and many others) are referred to as *sporotrichoid* (p. 713).
  - *Superficial ulcerated sporotrichosis:* In this form, many spores are inoculated by abrasion. The classic setting is a gardener or farmer carrying bales of sphagnum moss that rub on his abdomen.
  - *Systemic sporotrichosis:* Rare; involves lungs, muscles, bones, and even CNS.
- **Diagnostic approach:** Occasionally cigar-shaped yeasts can be seen on biopsy with periodic acid–Schiff (Pas) stain; *Sporothrix schenckii* is dimorphic; culture at 25 °C reveals a mold and at 37 °C, a yeast.
- **Therapy:**
  - Itraconazole 400–600 mg p. o. daily for 6–8 weeks. With systemic involvement, amphotericin B also is a possibility.
  - Localized lesions can be treated with either cryotherapy or hyperthermia to speed healing.

Chromomycosis

- **Synonym:** Chromoblastomycosis, verrucous dermatitis.
- **Definition:** Chronic infection, usually involving foot or leg, following inoculation injury with soil-borne fungi.
- **Epidemiology:** Most common in rural areas of tropical and subtropical countries.
- **Causative agents:** Many dematiaceous fungi including *Phialophora verrucosa*, *Fonsecaea pedrosoi*, *Fonsecaea compactum*, *Cladosporium carrionii*, *Rhinocladiella aquaspersa*.

- **Clinical features:** Over weeks to months, verrucous nodules and plaques develop at the site of injury (*mossy foot*). Sporotrichoid spread along lymphatics is possible, but systemic spread rare.
- **Diagnostic approach:**
  - Histology reveals subcutaneous granulomas containing small (5–15 μm) brown bodies that divide by equatorial splitting, not budding. They have many names: copper pennies, sclerotic bodies, Medlar bodies.
  - *Culture:* Slow-growing dark filamentous colonies at 20–25 °C; speciation based on microscopic findings.
- **Differential diagnosis:** Chromomycosis and mycetoma often confused.
- ***Note:*** Chromomycosis grows outwards (raised verrucous lesions) whereas mycetoma grows inwards (sinus tracts).
- **Therapy:**
  - Small lesions should be excised.
  - Systemic antifungal therapy is difficult; itraconazole and voriconazole are least toxic; flucytosine may be more effective but quite toxic. Systemic amphotericin B is not recommended; intralesional may be effective but is extremely painful.
  - Cryotherapy and hyperthermia may also be of supplemental value.

Mycetoma

- **Synonym:** Madura foot (from the Indian state of Madura).
- **Definition:** Chronic soft tissue infection caused by a wide variety of fungi and bacteria; placed under fungal infections for convenience.
- **Pathogenesis:** The list of causative agents is long. All cause disease in the same way—they are inoculated into the skin via an injury and then proliferate in the subcutaneous tissue, extending to fascia, muscles, and bones. Two types:
  - *Eumycetoma:* Caused by fungi in the genera *Aspergillus*, *Exophiala*, *Madurella*, *Pseudallescheria*, and others.
  - *Actinomycetoma:* Caused by bacteria in the genera *Actinomadura*, *Actinomyces*, *Nocardia*, and *Streptomyces*.
- **Clinical features:** Initial finding is a soft tissue swelling, usually involving the foot. The process develops to involve deeper structures but also to form abscesses and draining sinuses with discharge of colored granules (colonies of organisms).
- **Diagnostic approach:** The granules have different colors (white, yellow, black), which give clues to the organisms; microscopic examination and culture needed to confirm diagnosis.
- **Differential diagnosis:** Chromomycosis with verrucous exophytic lesions.
- **Therapy:** Culture-directed antibiotic or antifungal therapy, the latter usually with amphotericin B. The bacterial forms are relatively therapy-responsive; the eumycetomas are often so resistant that amputation is the most reasonable approach.

6.5 Systemic Mycoses

Overview

- **Pathogenesis:** The systemic mycoses are caused by dimorphic fungi that live as a yeast or a mold, depending on environmental conditions. They often cause asymptomatic infections in healthy individuals, but are frequently more aggressive in weakened individuals. Risk factors include HIV/AIDS, cancer chemotherapy, solid organ transplantation, and long-term intensive care treatment. Depending on

what organisms are locally common, a variety of prophylactic regimens are employed in high-risk patients.

- **Epidemiology:** In Europe the two most common infections are cryptococcosis and aspergillosis. To avoid diagnostic errors, it is important to know where the various deep fungal infections are common.
- **Diagnostic approach:** In all causes, histologic examination of skin lesions can reveal the causative organisms. Final confirmation is made via culture. Infectious diseases texts should be consulted for more advanced diagnostic techniques including serological studies.
- **Therapy:** Systemic therapy is always required.

Cryptococcosis

- **Epidemiology:** Found worldwide; first described in Berlin, Germany.
- **Pathogenesis:** *Cryptococcus neoformans* is presumably spread from bird droppings. Initial infection via the lungs; dissemination seen only in immunosuppressed individuals.
- **Clinical features:**
  - Cutaneous fadings are uncommon; they reflect dissemination and indicate a critically ill patient. In HIV/AIDS, the disseminated papules closely resemble molluscum contagiosum.
  - Cryptococcal meningitis is the most feared complication. Renal and bone disease is also common, but less catastrophic.
- **Therapy:** Previous mainstays of therapy were amphotericin B and flucytosine. Fluconazole appears effective for meningitis; voriconazole also shows promise.

Aspergillosis

- **Pathogenesis:** The usual pathogen is *Aspergillus fumigatus,* although occasionally other species are isolated. All have a worldwide distribution. The usual home of aspergillus is the lungs, where it may cause a fungal ball (*aspergilloma*) or allergic reaction. Invasive pulmonary disease is usually the starting point in immunosuppressed patients. Local inoculation, usually with *Aspergillus flavus,* may occur in burn patients or leukemia patients (via contaminated tape or at venous access sites).
- **Clinical features:**
  - Locally destructive skin disease following inoculation, with red-violet color, central necrosis, and ulceration. Other forms of local disease may involve ear or eye.
  - As part of disseminated disease, septic emboli blocking vessels, causing necrosis and eschar formation.
  - Main clinical risk in disseminated disease is aspergillus meningitis, which is almost always fatal; endocarditis is a problem in cardiac transplantation.
- **Therapy:** Many agents available including voriconazole, caspofungin, and combinations of the standard agents, amphotericin B, flucytosine, and itraconazole. Regimen depends on immune status and organ pattern.

Blastomycosis

- **Epidemiology:** *Blastomyces dermatitidis* is a soil fungus, found primarily in the central USA.
- **Pathogenesis:** Initial infection is pulmonary and usually asymptomatic. The organism can later cause pulmonary cavitation or spread to involve most often bone or prostate, as well as skin. The causes of reactivation are poorly understood; blastomycosis is not a problem in HIV/AIDS.

- **Clinical features:** The cutaneous lesions are typically verrucous, slowly spreading nodules or plaques (Fig. 6.**6**). They are almost always the result of dissemination, not local inoculation. They may be confused with a basal cell carcinoma, tuberculosis cutis verrucosa, or halogenoderma.
- **Therapy:** Itraconazole is usually the treatment of choice; in severe cases, amphotericin B may be employed.

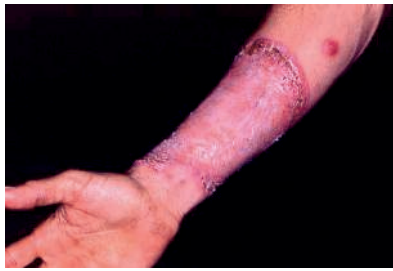


Fig. 6.**6** · Blastomycosis (Image courtesy of Robert H. Schosser MD, Greenville, North Carolina, USA).

Histoplasmosis

- **Epidemiology:** *Histoplasma capsulatum* var. *capsulatum* is also most common in the central USA, but also found in South America, Asia, Australia, and Africa. *Histoplasma capsulatum* var. *duboisii* causes African histoplasmosis.
- **Pathogenesis:** Primary infection is in the lungs. Reactivation occurs after many years, causing chronic pulmonary disease. An aggressive course may be seen in children or in HIV/AIDS with widespread involvement.
- **Clinical features:**
  - Skin involvement is uncommon in disseminated disease; less than 10% have papules or nodules following hematogenous seeding. Oral infiltrates and ulcers are more common.
  - Major systemic problems are hepatosplenomegaly, bone marrow infiltrates with pancytopenia, endocarditis, and meningitis.
  - In African histoplasmosis, cutaneous nodules and abscesses are common; they can be excised.
- **Therapy:** Itraconazole or ketoconazole are used for non-life-threatening cases. In immunosuppressed patients, initial control must be obtained with amphotericin B. In HIV/AIDS, once the infection is under control, then lifelong prophylaxis with itraconazole.

Other Uncommon Fungal Infections

Other uncommon infections are listed in Table 6.**4**.

Table 6.4 · Other uncommon fungal infections

Disease	Causative agent	Comments	Treatment
Superficial infections			
Tinea nigra	*Exophiala werneckii*	Dark patch on sole; mistaken for pigmented lesion	Topical antifungal agents, perhaps with keratolytics or curettage
Piedra alba	*Trichosporon beigelii*	Black nodules attached to hairs; usually scalp; common in Gulf States of USA	Shaving; imidazole or ciclopirox olamine lotions
Piedra nigra	*Piedraia hortae*	White nodules attached to hairs; usually pubic or axillary; common in Asia, South Pacific	Shaving; imidazole or ciclopirox olamine lotions
Tinea imbricata (tokelau)	*Trichophyton concentricum*	Disease of Pacific islands; large concentric scaly rings; so common that initially diagnosed as genodermatosis	Systemic antifungal agents
Subcutaneous infections			
Zygomycosis (mucormycosis)	Fungi of the Zygomycetes class (*Mucor*, *Rhizomucor*, *Rhizopus*, and others)	Immunosuppressed or diabetic patients; cutaneous inoculation or sinus infections which can extend to the CNS	Amphotericin B plus debridement
Subcutaneous zygomycosis	*Basidiobolus ranarum*	Subcutaneous granulomas in non-immunosuppressed children; Indonesia, India and Africa.	Amphotericin B
Lôbo disease (keloidal blastomycosis)	*Loboa loboi*	Keloidal or verrucous plaques; Central and Northern South America; no systemic disease	Excision
Deep infections			
Coccidioidomycosis	*Coccidioides immitis*	Deserts of southwestern USA, northern Mexico. Usually pulmonary disease; often presents with erythema nodosum. Disseminated lesions resemble molluscum contagiosum. Severe problem in HIV/AIDS and pregnancy	Fluconazole, amphotericin B for life-threatening disease
Paracoccidioidomycosis (South American blastomycosis)	*Paracoccidioides brasiliensis*	Usually pulmonary disease; skin findings include crusted periorificial nodules resembling leishmaniasis	Itraconazole, fluconazole, or amphotericin B

7 Other Infectious Diseases

7.1 Leishmaniasis

Overview

- **Epidemiology:** An estimated 10 million people around the world have leishmaniasis, with 400 000 new infections yearly. Although leishmania have a worldwide distribution, absent only in Australia, there are pockets where various forms of the disease are endemic. In Europe, increasing tourism in the Mediterranean basin and Middle East has made cutaneous leishmaniasis one of the more common exotic diseases. Recent military actions in the Middle East mean that many Western soldiers and civilian employees are at risk of acquiring leishmaniasis.
- **Pathogenesis:** Leishmania are flagellate protozoans; there are approximate 30 species, a good number of which are pathogenic. The species are identified on the basis of geographic distribution and disease forms. A simplified scheme (Table 7.**1**) recognizes four complexes of species, each responsible for a clinical symptom complex. This scheme is an oversimplification; current references should be sought by those few who require more information on speciation of protozoans.
- A wide variety of mammals, in most cases rodents, are the natural hosts. Infected patients with widespread or systemic disease are another source of infection. All forms are transferred by sandflies (*Phlebotomus* in Old Word, *Lutzomyia* in New World). Individuals who are infected develop a lifelong immunity, but this may be of limited utility as it is restricted to a given species or even subspecies.
- **Diagnostic approach:** Clinical features, smear or scraping, biopsy. Microscopic examination reveals intense lymphocytic infiltrate; Giemsa stain may make it easier to find the intracellular parasites (2–5 μm). Speciation is based on the polymerase chain reaction (PCR).

Table 7.1 · **Leishmania complexes**

Complex	Disease
Leishmania tropica	Old World cutaneous leishmaniasis
Leishmania mexicana	New World cutaneous leishmaniasis
Leishmania viannia (brasiliensis)	New World cutaneous and mucocutaneous leishmaniasis
Leishmania donovani	Visceral leishmaniasis

Old World Cutaneous Leishmaniasis

- **Synonyms:** Hundreds of synonyms reflecting the many cities in the Middle East where one can become infected: Baghdad boil, Aleppo boil, Jericho boil, or simply Oriental boil.
- **Definition:** Cutaneous infection with *Leishmania tropica* complex.
- **Epidemiology:** Found in Mediterranean basin, Middle East, and sub-Saharan highlands.
- **Pathogenesis:** The normal host for *Leishmania tropica* is rodents, as well as infected humans in endemic areas. Sandflies are low-flying (3 meters) nocturnal in-

sects; tourists living in the upper stories of hotels are at much less risk than those on the ground floor. After inoculation, the organisms undergo a complex life cycle in humans.

Note: The incubation period is extremely variable, ranging from a few days to several years; the average is 2–4 weeks.

- **Acute cutaneous leishmaniasis:**
  - Following the bite, a papule develops, then rapidly enlarges and breaks down in the center. The ulcer usually has a rolled border and may become secondarily infected (Fig. 7.**1**).
  - The lesion heals over about a year, leaving a distinctive depressed hyperpigmented scar.

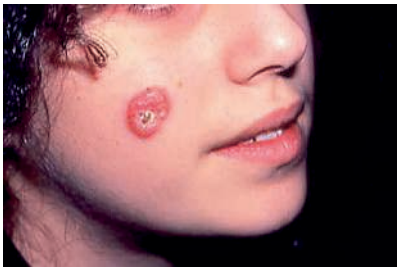


Fig. 7.**1** · Cutaneous leishmaniasis in American college student recently returned from visit to the Middle East.

  - Typical sites are exposed areas such as the cheeks and arms.
  - In some classifications three types are recognized, each with different vectors and causative species:
    - *Dry or urban:* Classic form with single lesion as described above (*Leishmania tropica*).
    - *Wet or rural:* More acute infection with multiple lesions (*Leishmania major*).
    - *Ethiopian:* More chronic and less severe (*Leishmania aethiopica*) but may lead to diffuse cutaneous leishmaniasis.

  Note: Always suspect leishmaniasis when confronted with a facial nodule or ulcer in someone who has lived in or visited the endemic areas. It is frequently confused with lymphoma.

- **Leishmaniasis recidivans:** A form of either wet or dry leishmaniasis, characterized by chronic course, central healing, and development of serpiginous lupoid nodules at the periphery.
- **Diffuse cutaneous leishmaniasis:** Rare form in patients who are relatively anergic and develop disseminated disease, with both local and hematogenous spread to produce nodular lesions resembling lepromatous leprosy, as well as mucosal disease. Also called *anergic cutaneous leishmaniasis.* Caused by *Leishmania aethiopica* and several New World species.
- **Differential diagnosis:** Infected bites and stings, bacterial pyoderma, subcutaneous fungal infections, basal cell carcinoma, squamous cell carcinoma. Leishmaniasis recidivans resembles lupus vulgaris; diffuse cutaneous leishmaniasis is similar to lepromatous leprosy.
- **Therapy:**
  - Spontaneous healing is the rule, so often no therapy is needed for acute cutaneous leishmaniasis.

- Standard treatment is intralesional injection of sodium stibogluconate (Pentosan) diluted 1:3 with a local anesthetic; 1–2 × weekly for 2–4 weeks.
- Cryotherapy or surgical excision of small lesions is also appropriate.
- Recent literature suggests using ketoconazole, itraconazole, or allopurinol.
- Topical paromomycin 15% with 10% urea can be applied b.i.d. for 3 weeks.
- Leishmaniasis recidivans and diffuse cutaneous leishmaniasis require systemic therapy (see below).

New World Cutaneous Leishmaniasis

- **Definition:** Cutaneous infection with *Leishmania mexicana* or *Leishmania viannia* complexes.
- **Clinical features:** The clinical spectrum of New World cutaneous leishmaniasis is wide. In general, the lesions are more likely to be multiple, ulcerative, destructive, and chronic than their Old World counterparts. A number of colorful terms have been applied:
  - *Chiclero ulcer:* Destruction of the ear cartilage in forest workers (chicleros harvest chicle, a ingredient in chewing gum).
  - *Uta:* Variant in Andean highlands; limited number of lesions.
- Members of the *Leishmania viannia* complex cause both persistent ulcerative cutaneous disease and mucocutaneous leishmaniasis. Several species can cause diffuse cutaneous leishmaniasis (see above).
- **Diagnostic approach:** See above.
- **Differential diagnosis:** Depending on the clinical form, lepromatous leprosy and yaws may also come into consideration, as well as the diseases discussed under Old World cutaneous leishmaniasis.
- **Therapy:** Systemic therapy is indicated because of the likelihood of multifocal or chronic disease and the risk of both mucocutaneous (for many species) and diffuse cutaneous disease. The mainstay of therapy is systemic pentavalent antimony compounds—either sodium stibogluconate or meglumine antimonite. Liposomal amphotericin B and pentamidine are also effective. Public health officials should be consulted for exact therapeutic guidance; speciation of the leishmania may be important in choosing the agent.

Mucocutaneous Leishmaniasis

- **Synonym:** Espundia.
- **Definition:** Infection with *Leishmania viannia* complex.
- **Epidemiology:** Most common in the jungles of Brazil and Peru. Most common species in the complex is *Leishmania brasiliensis*.
- **Clinical features:** Following facial infection, the leishmania spreads via blood vessels or lymphatics to the nasopharyngeal mucosa. After an interval of months or years, the feared destructive process starts, usually in the nasal septum, but spreading to involve lips, palate, pharynx, and even larynx.
- **Differential diagnosis:** Paracoccidioidomycosis, lepromatous leprosy, and destructive carcinomas.
- **Therapy:** Systemic therapy is always required (see above).

Visceral Leishmaniasis

- **Synonyms:** Black fever, Dumdum fever, kala-azar.
- **Definition:** Infection with *Leishmania donovani* complex.
- **Epidemiology:** Primarily seen in India and the Sudan, but also occurs in South America, China, other parts of Africa, even the Mediterranean basin.

- **Clinical features:** A completely different disease than the other forms. Patients have disseminated disease with leishmania in their reticuloendothelial system (liver, spleen, bone marrow, lymph nodes); they suffer from fever, chills, malaise, and anemia; over a period of time their skin acquires a gray shade. Untreated, generally fatal in 1–2 years.
- **Complications:** Those patient who survive may develop *post-kala-azar dermal leishmaniasis*; this happens to about 20% of patients in India, but is rare in other regions. Years after successful treatment or spontaneous cure, they acquire hypopigmented or erythematous facial (and sometimes truncal) macules that progress to papules and nodules. Clinical picture resembles lepromatous leprosy.
- **Diagnostic approach:** The protozoan can be found in the bone marrow or lymph nodes. Serological diagnosis is possible, but often false-negative in immunosuppressed patients. In the unfortunate with both visceral leishmaniasis and HIV/AIDS, the organisms are seen in the buffy coat. In post-kala-azar dermal leishmaniasis, skin biopsy is diagnostic.
- **Differential diagnosis:** Consider hematologic malignancies, subacute infections (such as brucellosis, malaria, tuberculosis), and other diseases associated with hepatosplenomegaly.
- **Therapy:** Liposomal amphotericin B is the treatment of choice. Antimony compounds are used for post-kala-azar dermal leishmaniasis.

7.2 Other Protozoan Infections

There are surprisingly few other protozoan diseases with cutaneous manifestations (Table 7.**2**).

Table 7.2 · **Protozoan infections with cutaneous manifestations**

Disease	Organism	Comments
Amebiasis	*Entamoeba histolytica*	Patients with hepatic or intestinal disease develop ulcers, either perianal, or via direct extension to overlying skin; jagged painful ulcers with undermined borders
Chagas disease	*Trypanosoma cruzi*	Transmitted by reduviid bugs. Site of bite is chagoma; periorbital edema known as Romaña sign; later cardiac, gastrointestinal, and CNS disease
Toxoplasmosis	*Toxoplasma gondii*	One cause of TORCH syndrome (p. 65)
Trichomoniasis	*Trichomonas vaginalis*	Sexually transmitted disease; vaginal burning and discharge; urethritis and ascending infections
Trypanosomiasis (African sleeping sickness)	*Trypanosoma brucei*	Only skin change is nodule at site of tsetse fly bite; primary problem CNS disease

7.3 Pediculosis

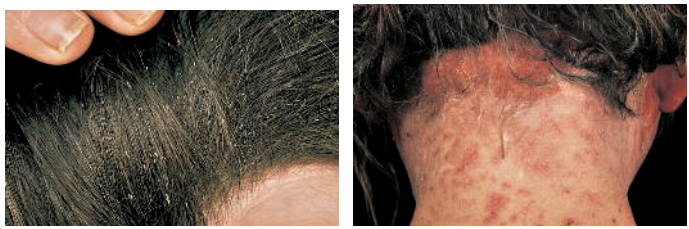
Overview

- **Definition:** Lice (*Pediculus* spp.) are blood-sucking, wingless, ectoparasitic insects that infest their victims for long periods of time with a high degree of host specificity.
- **Disease transmission:** Lice transmit a number of important diseases:
  - Epidemic typhus (*Rickettsia prowazekii*).
  - Relapsing fever (*Borrelia recurrentis*).
  - Trench fever (*Bartonella quintana*).

Pediculosis Capitis

- **Synonym:** Head lice.
- **Definition:** Infestation with *Pediculus humanus capitis*.
- **Epidemiology:** Often seen in epidemics among kindergarten and grade school children; also common in homeless people.
- **Pathogenesis:** Lice live on the scalp and suck blood there. They firmly attach their eggs (nits) to the hair shaft just at the skin surface.
- **Clinical features:** Pruritic eruption on back of scalp and nape (Fig. 7.**2 a,b**); often with excoriations and secondary infections (lice dermatitis). The hairs may become matted from repeated scratching (*plica polonica*).

Note: Always think of pediculosis capitis when confronted with dermatitis of the nape.



a **b**

Fig. 7.**2** · **Pediculosis capitis. a** With multiple nits on hairs. **b** With typical nuchal dermatitis.

- **Diagnostic approach:** Look for nits on the hair shafts, as well as for lice on the scalp.
- **Differential diagnosis:** Hair casts look similar to nits, but form an encompassing cylinder whereas the nits are attached at an angle. *Piedra* is much less common and consist of clumps of bacteria or fungi.
- **Therapy:**
  - Resistance of head lice to pediculicides has become a problem. Check for local resistance pattern.
  - All agents should be applied twice, 7–14 days apart. Recommendations vary regarding length of application, including overnight use, but all appear effective when used for 10–30 minutes and rinsed.
  - Malathion 0.5% lotion is most effective, but there is resistance in France and the UK.

- Pyrethrins and the synthetic permethrin have fair action and a reasonable resistance profile.
- Lindane (gamma benzene hexachloride) is still widely used, but relatively ineffective for this indication and with marked resistance.
- The nits are always a problem; many schools have rules banning children returning as long as nits are present. Best solutions following treatment are soaking with vinegar and water (50:50) and using a fine-toothed nit comb.

Pediculosis Corporis

- **Definition:** Infestation with *Pediculus humanus corporis*.
- **Epidemiology:** Pediculosis corporis is primarily a disease of the unwashed. It is common in homeless people and during wars (trench fever) and other disasters.
- **Pathogenesis:** The lice feed on the body, but live in the clothing and tend to lay their eggs along the seams.
- **Clinical features:** Presents with marked pruritus, lack of personal hygiene, and secondarily infected, excoriated dermatitis on trunk (*vagabond skin*).
- ***Note:*** Look for the lice and nits on the clothing, not on the skin.
- **Differential diagnosis:** All pruritic dermatoses, especially scabies.
- **Therapy:**
  - Disinfection of clothing and bedding (boiling, hot ironing, fumigation).
  - Attempt to change living conditions.
  - Same pediculicides as for *Pediculus humanus capitis* can be used, but less important.
  - In mass epidemics, usually insecticidal dusting powders employed.

Pediculosis Pubis

- **Definition:** Infestation with *Phthirus pubis*.
- **Epidemiology:** Usually transmitted by sexual contacts.
- **Clinical features:** Patients usually identify moving lice on their pubic hairs (*crabs*). Also complain of pruritus. Nits usually on pubic hair, but occasionally elsewhere (axillary or body hairs; eyelashes, eyebrows). The feeding sites turn into distinctive blue-gray hemorrhagic macules (*maculae ceruleae* or *taches bleuâtres*).
- **Diagnostic approach:** Identification of lice or nits.
- **Therapy:**
  - Permethrin cream or shampoo or lindane lotion or shampoo applied for 10 minutes; repeat in 1 week.
  - Ivermectin p.o. is also effective for resistant cases (see scabies).

7.4 Scabies

- **Definition**: Intensely pruritic infestation with the mite *Sarcoptes scabiei*.
- **Epidemiology:** Worldwide distribution. In some areas, such as certain Caribbean islands, it is endemic with virtually everyone infested. In the past, it typically appeared in cycles (*seven year itch*), but this is no longer the case. In recent years, epidemics in homes for the elderly have become a problem.
- **Pathogenesis:** *Sarcoptes scabiei* is a mite that lives only on humans. It does not transfer any diseases. Transfer is by close personal contact, such as mother–child, siblings, or sexual partners. Female mites burrow in the epidermis just below the stratum corneum, depositing eggs and feces as they move along. The first infestation remains asymptomatic for a period of weeks, until an immune response

develops and pruritus results. Upon re-infestation, the symptoms appear in a matter of days.

► **Clinical features:**

- *Burrows:* Fine slightly raised, sometimes erythematous, irregular lines with a terminal swelling where the female mite can be found. Typical sites (Fig. 7.**3**) include interdigital spaces, sides of the hands and feet, flexural surface of the wrist, anterior axillary line, penis, nipples (Fig. 7.**4a,b**).
- *Intense pruritus*: Few skin diseases itch as much as scabies; usually worst at night.
- *Dermatitis*: Immune reaction (type IV) to mites leads to both pruritus and diffuse exanthem. Typical sites are thighs, buttocks, trunk.
- *Variations:*
  - *Pyoderma:* Pruritus leads to excoriations and erosions which become secondarily infected. In some areas, there is a vicious cycle of scabies → impetigo → glomerulonephritis.
  - *Scabies incognita:* Patients with meticulous personal hygiene (*scabies of the cleanly*) or those using topical corticosteroids may completely mask the findings of scabies, complaining only of pruritus.
  - *Nodular scabies:* Persistent papules usually in infants, favoring the groin, axillae, and genitalia. Occasionally seen in adults once again genitalia most

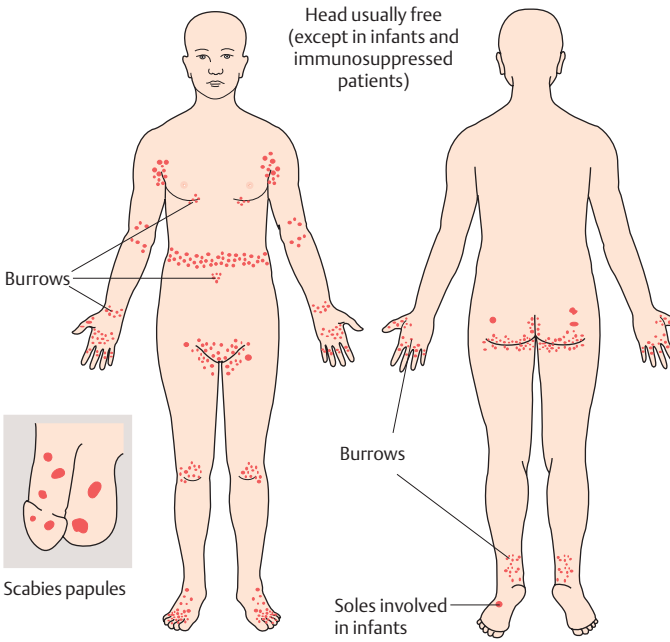


Fig. 7.**3** · Sites of predilection for scabies.

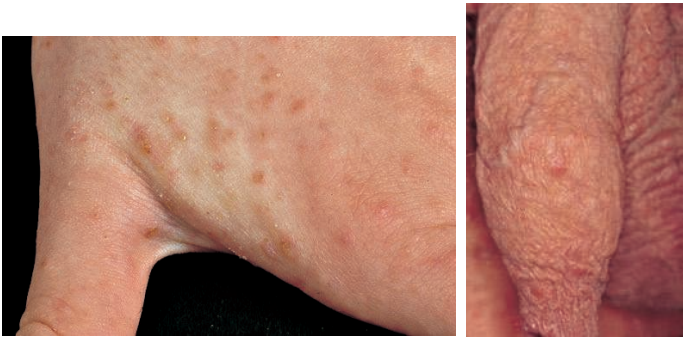


Fig. 7.4 · **Scabies. a** With burrows and inflammatory papules in interdigital spaces. **b** Burrow on penis.

common. On biopsy, lymphocytic infiltrate. Remain for months after elimination of all mites; blamed on "antigen persistence".
  - *Crusted scabies (Norwegian scabies):* Massive scabies infestation with crusted hyperkeratotic, psoriasiform lesions, as well as subungual lesions. Seen in debilitated patients, sometimes in Down syndrome; increasingly common in HIV/AIDS patients.
  - *Animal scabies:* There are over 40 different forms of animal scabies, including those involving cats, dogs, and birds. These mites cannot reproduce on humans. They tend to bite at sites of contact (hands, arms, face if sleeping with pet), cause pruritus without any incubation period, and then die.

► **Complications:** Acarophobia: fear of persistent infection following cure; major psychological problem (p. 580).

► **Diagnostic approach:** Identification of mite; look at ends of burrows (dermatoscopy can help; *hang glider sign*); unroof with fine scalpel and examine under microscope.

► ***Note:*** Suspect scabies in any unexplained pruritic disease which is worse at night or also present in family members or other contacts.

► **Differential diagnosis:** All pruritic diseases; the issue is always to include scabies in the differential diagnosis.

► **Therapy:**
- Permethrin 5% cream has the best safety record and the least reports of resistance. It should be viewed as the agent of choice. Apply at night, wash in morning; repeat after 1 week.
- Lindane lotion is the worldwide standard, but not as effective as permethrin. It should be used in the same way.

  Caution: Lindane should not be used in pregnancy or in infants. It is potentially neurotoxic and there are several alternatives.
- A warm bath prior to application will increase the efficacy of treatment; remember that with eroded areas, absorption is increased.
- Bedding and clothing should be washed in hot cycle of washing machine; under normal conditions no other precautions are needed.
- For resistant cases, epidemics or crusted scabies, ivermectin 150–400 μg/kg p.o. administered on days 1 and 14 is highly effective.

7.5 Other Epizoonoses

Arthropod Assault Reaction

- **Definition:** Pruritic nodule resulting from bite or sting of arthropod.
- **Epidemiology:** Knowledge of local factors and seasonal variation is required to accurately guess at source of arthropod assault.
- **Pathogenesis:** The term "insect bite" reaction is an oversimplification, as many arthropods, both insects and arachnids (spiders, ticks, mites, and scorpions), can inflict injury. Bites are inflicted by the mouth parts, while stings are administered by other body parts, such as the tail stinger of a scorpion. The resulting lymphocytic infiltrate, often rich in eosinophils, may be the result of retained body parts, injected toxins, or injected microbes (as in borreliosis, p. 92).
- **Clinical features:** Typically there are one or more erythematous papules or nodules. They are on exposed skin, often grouped, and sometimes stopping at a point where clothing causes constriction, such as a sock or belt line. The diagnosis of arthropod assault is an awkward one; patients often say something like "It can't be a sting or bite, I would never come to the doctor for that." Some convincing talk is usually required. There may be unique patterns such as bullous reactions (more common in infants, immunosuppressed, especially patients with chronic lymphocytic leukemia).
- **Histology:** The microscopic picture is a mixed lymphocytic infiltrate, usually with eosinophils. In the case of tick bites, the mouth parts will sometimes be retained, easing the diagnosis.
- **Diagnostic approach:** If the pattern is common in your area, then the clinical diagnosis usually suffices. Biopsy may be helpful in puzzling cases.
- **Differential diagnosis:** Insect bite reactions were formerly called pseudolymphomas. We do not like this term and have avoided it. The classic well-accepted examples of an insect bite reaction are nodular scabies and the reaction surrounding molluscum contagiosum, but any bite or sting can induce a persistent nodule. Lymphadenosis cutis benigna in borreliosis occurs later and not necessarily at a bite site, but has a similar histologic pattern. Another cause of erythematous nodules with a dense lymphocytic infiltrate (and mucin) is lupus tumidus. Finally, many low-grade B-cell lymphomas were formerly identified as pseudolymphoma.
- **Therapy:** Topical or intralesional corticosteroids; on rare occasions, excision.
- **Prophylaxis:** Avoiding outdoor activity. The best insect repellents are those containing diethyltoluamide (DEET). When extensive exposure is anticipated, choose the product with the highest DEET concentration.

Cimicosis

- **Synonym:** Bedbug bites.
- **Pathogenesis:** *Cimex lectularius* or bedbug is 0.5 cm flattened bug that lives in furniture or crevices in the bedroom, is active at night, and feeds on humans by obtaining blood. Bedbugs are uncommon in both Germany and the USA, but can be seen; often patients return from vacations with bites.
- **Clinical features:** Bedbug bites are painless, but soon itch intensely and are quite persistent. They often follow a line and are grouped (breakfast, lunch, and dinner).
- **Diagnostic approach:** History of night-time bites, linear arrangement.
- **Therapy:** Symptomatic measures (antipruritic agents or topical corticosteroids, systemic antihistamines); call the exterminator.

Pulicosis

- **Synonym:** Flea bites.
- **Pathogenesis:** Fleas are 1–3 mm insects capable of jumping quite far; they have limited host specificity and often transfer from household pets or other animals to humans.
- Human pathogens include:
  - *Pulex irritans:* Human flea; relatively uncommon.
  - *Ctenocephalides felis* or *C. canis*: Cat and dog fleas; common.
  - *Xenopsylla cheopis:* Rat flea, worldwide distribution; transmit endemic typhus and plaque.
  - *Ceratophyllus gallinae:* Chicken flea; common.
- **Clinical features:** Multiple tiny pruritic papules, often with central hemorrhagic punctum. Surprisingly, often one family member will be extensively involved, and the others spared or minimally affected.
- ***Note:*** A typical feature of flea bites is that when a new bite occurs, the older lesions also begin to itch again.
- **Diagnostic approach:** Clinical features and appropriate exposure.
- **Therapy:** Symptomatic therapy; veterinary examination of suspected domestic animals.

Trombiculiasis

- **Epidemiology:** Trombiculidae mites are scattered around the world. They are sometimes known as *harvest mites* because they so often infect grains, but they are also seen in gardens and forested areas. They are indiscriminate, attacking birds, mammals, and humans. In East Asia they transmit *Rickettsia tsutsugamushi*, the causative agent of scrub typhus.
- **Pathology:** The most common agent in Europe is *Trombicula autumnalis*. Larval forms of the mites, known as chiggers, attach themselves to passers-by and then use enzymes to create a hole in the epidermis through which they can receive nutrients. The chemicals they employ cause intense pruritus.
- **Clinical features:** Intensely pruritic small red papules on exposed areas; typically on the legs just above the sock line or on the trunk just above the belt line.
- **Diagnostic approach:** History, clinical findings.
- **Therapy:** Symptomatic therapy with topical corticosteroids or antipruritic agents. The best approach is regular use of insect repellents.

7.6 Worms

There are many worm infestations that cause tremendous public health problems in developing countries. They are seldom seen in developed countries, except among tourists. In almost all cases, elevated eosinophil levels are seen, so any patient with unexplained hypereosinophilia, perhaps associated with pruritus or urticaria, should be checked for the presence of parasitic worms.

Cutaneous Larva Migrans

- **Synonym:** Creeping eruption.
- **Definition:** Infestation of human skin by larva that are unable to complete their life cycle in the skin.

- **Epidemiology:** The most common cause of cutaneous larva migrans is infestation by the dog and cat hookworm, *Ancylostoma braziliense*. Tourists to the Caribbean islands are a high-risk group.
- **Pathogenesis:** The larval worms are deposited in moist soil via stool. They enter their accidental host via the skin, and wander about creating complex burrowing patterns. Many other worms also migrate through the skin. They include the animal parasites *Ancylostoma caninum* (dog hookworm), *Uncinaria stenocephala* (pig hookworm), and *Gnathostoma spinigerum* (fish nematode), as well as the human parasites *Necator americanus* (human hookworm) and *Strongyloides stercoralis.* The human parasites enter via the skin but rapidly get to their target organs. In the case of *Strongyloides stercoralis*, if the larva mature rapidly in the bowel, they can penetrate the perianal skin causing *larva currens.*
- **Clinical features:** After a few hours, the entry site begins to itch and a red papule develops. After a few days, the larva begins to migrate in the skin, creating bizarre erythematous curved lines.
- **Diagnostic approach:** Classic clinical picture.
- **Therapy:**
  - The nonhuman worms will die after a few months, but few patients are willing to wait.
  - Cryotherapy is often endorsed, but the worms can live for at least 5 minutes at −25 °C, so it is probably not efficacious.
  - Topical thiabendazole is the treatment of choice. No commercial product is available but it can be easily compounded (p. 699). Apply t.i.d. for 1 week, or apply 1× daily under plastic wrap (Saran, cling-film) occlusion for 1 week.
  - If not responsive, then systemic therapy with thiabendazole 500 mg b.i.d. for 3–4 days, albendazole 400 mg daily for 3 days, mebendazole 100 mg b.i.d. for 3 days, or ivermectin 200 μg/kg in single dose, which can be repeated weekly for 2 weeks.

Other Diseases Caused by Worms

- **Myiasis:** Many different fly larvae (*maggots*) can invade human flesh. Usually they need an entry site, such as a chronic ulcer or wound. Most maggots only eat necrotic debris, although some attack healthy tissue. Specially bred sterile maggots are used in wound débridement. Some maggots may migrate below the skin surface (*myiasis migrans*). Individual maggots must be extracted or excised; many tricks are recommended to ease the process, such as covering the entry tunnel with oil or attaching a piece of bacon to attract the parasites.
- **Enterobiasis:**
  - Worldwide infection caused by *Enterobius vermicularis*, the pinworm. Most common in young children; frequently brought home from day nurseries or kindergarten.
  - Life cycle is simple; eggs are ingested; after developing in gut, female wanders out of anus at night and lays eggs on perianal skin. If not treated, cycle repeats itself every 4–6 weeks following reingestion of eggs.
  - Main complaint is pruritus ani, worse at night. Complications include chronic urticaria, vulvovaginitis (direct spread), and a fertile ground for human papillomavirus and molluscum contagiosum infections.
  - Diagnosis made by clear adhesive tape stripping of perianal region. Stool examination also positive.
  - Always consider when confronted by perianal pruritus or dermatitis in children.
  - Treatment includes pyrantel pamoate (10 mg/kg), mebendazole 100 mg or albendazole 400 mg in single dose; perhaps repeated in 2 weeks.

- **Onchocerciasis:**
  - Caused by *Onchocerca volvulus* and transmitted by *Simulium* flies. The main endemic areas are in equatorial Africa and Yemen, as well as foci in Central and South America.
  - The larvae (microfilariae) migrate through the skin, causing pruritus and itching, as well as frequent postinflammatory hypopigmentation. Some patients have very few organisms but an intense edematous inflammatory reaction (*sowda*in Yemen, *coastal erysipelas* in the Americas).
  - The mature female and her much smaller partner coiled together in a subcutaneous nodule (*onchocercoma*); she releases many new microfilariae.
  - The main problem with onchocerciasis is involvement of the eyes (*river blindness*). The microfilariae wander through the eyes and trigger a destructive inflammatory response.
  - Diagnosis is based on identifying the organisms in the eye or in skin snips. Serologic studies are also available.
  - The treatment of choice is ivermectin 150 μg/kg in a single dose. In endemic areas, an extensive World Health Organization campaign is underway to completely eliminate onchocerciasis. Here the entire population receives a single dose of ivermectin once yearly, as only microfilariae are killed and one must wait for the adult worms to die.
- **Schistosomiasis:**
  - Schistosomiasis is a major public health problem in the world. Infections with several different *Schistosoma* flukes cause chronic bladder and bowel disease, including bladder cancer. The distribution includes Africa, Middle East, Asia, and Central America.
  - The eggs are excreted via urine or stool into water; snails serve as intermediate hosts. The free-swimming cercariae are the form that then re-enter humans.
  - The migrating cercariae cause a pruritic dermatitis. A few weeks later a severe allergic reaction occurs (*Katayama fever*). Then later, as the female releases eggs, some may wind up in the skin where they cause a granulomatous dermatitis. The must common sites are the anogenital and periumbilical regions.
  - The diagnosis is based on finding eggs in the urine or stool, as well as on serological tests. Eggs can also be found in skin biopsy from granulomatous lesions.
  - Praziquantel is the treatment of choice; either 40 mg/kg in a single dose or 20 mg/kg q8 h × 3. Programs with population-based use of praziquantel, as well as attention to sanitation measures, are under way.
  - *Swimmer's itch:* There are many non-human flukes involving, for example, water birds. When humans swim in shallow infested water, the cercariae may penetrate their skin, causing pruritic red papules and nodules. The animal parasites cannot complete their life cycle in humans, so there is no risk of internal involvement. This problem is common in both North America and Europe. Treatment is symptomatic.

8 Sexually Transmitted Diseases

8.1 Overview

- **Terminology:** The term *sexually transmitted disease* (STD) is being replaced in some circles by *sexually transmitted infection (STI)*. We see little advantage in the change. The older term *venereal disease* refers in a more limited way to diseases such as gonorrhea that are almost exclusively transferred by sexual contact, whereas STDs include diseases that are also acquired by nonsexual means. The most common STDs are shown in Table 8.**1**.

Table 8.1 · **Common sexually transmitted diseases**

Classic venereal diseases (covered in this chapter)	Other sexually transmitted infections
Syphilis	HIV/AIDS
Gonorrhea	Candidal balanitis and vulvovaginitis
Chlamydia infections	Condylomata acuminata
Chancroid	Herpes genitalis
Lymphogranuloma venereum	Cytomegalovirus
Granuloma inguinale	Hepatitis B and hepatitis C
Bacterial vaginosis	Pediculosis pubis
	Scabies

- **Public health considerations:** Every country has public health regulations of varying degrees of complexity, indicating which infectious diseases (both STDS and other infections such as tuberculosis deemed to be community threats) must be reported, who must report them (treating physician, laboratory), and how patient confidentiality is to be treated. The AIDS epidemic has put entirely new constraints on the system; in Germany, the reporting of cases of HIV infection is entirely anonymous.
- **Tracking contacts:** Only if public health authorities have the name of the patient can they assist the practicing physician in identifying and treating contacts of the patient, thereby interrupting the chain of transmission. The treating physician's rule is to win the patient's confidence so that this effort is as successful as possible.
- **Treatment guidelines:** There are many well-known guidelines for the treatment of STDs. We have used those of the Germany STD Society, published in 2001.

8.2 Syphilis

Overview

- **Synonym:** Lues.
- **Definition:** Chronic infection caused by *Treponema pallidum* and almost exclusively transferred by sexual intercourse. The early stages are primarily cutaneous and mucocutaneous; after decades, untreated syphilis affects the cardiovascular and nervous systems.
- **Epidemiology:** The epidemiology of syphilis would fill a book in itself. After the advent of penicillin, many predicted the demise of syphilis, but in the past two decades it has made a discouraging resurgence, fuelled by the increasing incidence of HIV/AIDS and the breakdown of many social systems in the former Soviet Union.
- **Pathogenesis:** *Treponema pallidum* is a spirochete 6–20 μm long and 0.1–0.2 μm wide with 10–20 spirals. The generation time is long, > 30 hours; this plays an important role in therapy. The organism is very sensitive and scarcely survives in the environment. Transmission is by close tissue contact with entry through minor points of injury.

Clinical Classification

The stages of syphilis are shown in Table 8.**2**.

- **Early syphilis:** All disease manifestations and the subsequent latent period during the first 2 years after the infection:
  - *Primary syphilis:* About 3–8 weeks after the primary infection, inflammation arises at the site of inoculation and the regional lymph nodes.
  - *Secondary syphilis:* Around 9 weeks (between 6 and 12 weeks) after the infection, bacteremia, generalized exanthem, systemic signs and symptoms, and production of antibodies. Rarely, this stage may be prolonged by inadequate antiobiotic therapy.
  - *Latent syphilis*: Symptom-free period following secondary syphilis; only recognized by positive serological tests. Can be caused by subcurative antibiotic dosages, often given for other infections, when syphilis is overlooked.

  ▶ ***Note:*** Be careful not to confuse latent syphilis, which is untreated or improperly treated syphilis, with positive seroreactions in appropriately treated patients.
- **Late syphilis:** Syphilis occurring more than 2 years after primary infection. Granulomatous inflammation with few organisms and marked cellular immune response, which causes most of the trouble. Organs most often involved include skin, bones, cardiovascular system, and CNS.
- **Congenital syphilis**: Also known as *syphilis connata.* Follows transplacental transmission of *Treponema pallidum.*

Table 8.2 · **Stages of syphilis**

Stage	Time after infection (years)	Disease
Early syphilis	0–2	Primary syphilis Secondary syphilis Latent syphilis (seropositive)
Late syphilis	> 2	Tertiary syphilis Quaternary syphilis Latent syphilis (seronegative)

Primary Syphilis

► **Clinical features:**

- Dark red nodule develops at site of entry about 3 weeks after contact; it becomes eroded and then ulcerated.
- *Chancre (ulcus durum):* Firm, 1 cm, circumscribed ulcer; base is ham-colored while periphery is more red (Fig. 8.**1**). On palpation, firm, compared to button or small coin. The size of ulcers varies greatly (larger when herpes genitalis is entry site). Heals spontaneously over 3–8 weeks.

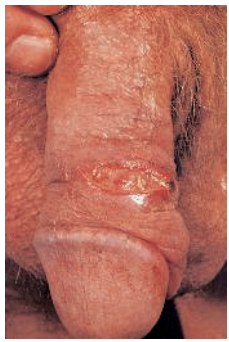


Fig. 8.**1** · Primary syphilis: chancre.

- **Location:**

Note: Any location is possible.

  - *Men:* Prepuce, glans, sulcus, less often shaft. In homosexuals, perianal region or rectum.
  - *Women:* Vagina or cervix (often overlooked), labia majora or minora, clitoris, posterior commissure, perianal region, rectum.
  - *Extragenital lesions:* Lips, tongue, palate, finger.
- Most chancres are asymptomatic; about 50% are either overlooked or not clinically appreciable. Rectal and anal lesions more likely to be painful. Occasionally chancre coupled with marked edema of foreskin and secondary phimosis. Sometimes with mixed infections, inflammation is so extreme that the foreskin must be split to avoid penile gangrene.
- *Regional lymphadenopathy:* Appears 1–2 weeks after chancre; usually unilateral; 1–2 cm firm, nontender lymph nodes without inflammation of overlying skin.

► **Diagnostic approach:**

- *Darkfield examination: Treponema pallidum* cannot be seen with usual stains such as Gram stain; darkfield microscopy is the most convenient way to identify the organism.
  - Clear secretions from the ulcer are needed.
  - *Treponema pallidum* shows three characteristic motions: rotation on the long axis, sharp folds, and minimal motion forward and backwards.
  - Secretions can be dried on a slide which is then studied with the fluorescent treponemal antibody (FTA) technique; can be mailed to referral laboratory.
  - Lesions that are usually positive include chancres, early congenital syphilis, condylomata lata, and other secondary lesions where secretions can be extracted.

- Darkfield of limited utility for mucosal lesions as there are many normal spirochetes in the mouth.

- *Obtaining secretions:* Considerable mechanical irritation and pressure is needed to obtain clear lymphatic fluid for a darkfield examination.
  - Cotton gauze soaked in physiological saline is used to rub ulcer (painful!) until clear fluid appears.
  - Pick up fluid with coverslip; apply to one drop of physiologic saline on glass slide.
- *Serologic testing:* FTA-IgM is positive 2 weeks after initial infection. If clinical suspicion exists, but the darkfield and serology are negative, the patient should be rechecked in 1–2 months.

► **Differential diagnosis:**

- *Herpes genitalis:* Usually multiple erosions and painful lymphadenopathy.
- *Traumatic ulcers:* Painful and not firm or button-like.
- *Chancroid:* Painful, soft, undermined ulcer.
- *Lymphogranuloma venereum:* Little or no ulceration, but fluctuant lymphadenopathy.
- *Erythroplasia of Queyrat (mucosal squamous cell carcinoma in situ):* Chronic, histology decisive.
- *Plasma cell balanitis of Zoon:* Chronic, histology decisive.
- *Fixed drug eruption:* Erosion, no ulcer; no lymphadenopathy; usually helpful drug history.

Secondary Syphilis

► **Clinical features:**

- There are an incredible number of exanthems and enanthems associated with secondary syphilis. Syphilis was formerly known as the great imitator. The rashes in secondary syphilis are known as syphilids. All reflect local inflammation caused by *Treponema pallidum* during its bacteremic phase. The role of circulating immune complexes is unclear.

  ► ***Note:*** The rashes of secondary syphilis usually do not itch and are only rarely bullous; anything else is possible.
- *Macular syphilid:* The most common finding, initially pale irregular pink macules (*syphilitic roseola*) typically on side of chest, later spreading to involve trunk, palms, and soles with typical red-brown color (Fig. 8.**2 a**). Marked individual variation. Nonpruritic, nonscaling, blanchable with diascopy.
- *Variations:*
  - *Papular syphili*d: Sometimes firm red-brown papules evolve in varying numbers. Multiple small papules known as *lenticular syphilid* (Fig. 8.**2 b**).
  - *Annular or circinate syphilid:* Spread of papules with central clearing and peripheral growth.
  - *Corymbose syphilid:* Many small papules surrounding a single larger lesion.
  - *Corona venerea:* Papules along anterior hair line.
  - *Palmoplantar syphilid:* Papules on palms and soles with red-brown color and scale (*clavi syphilitici*) (Fig. 8.**2 c**).

    ► ***Note:*** Always suspect syphilis when confronted with an acute palmoplantar rash.
  - *Lichen syphiliticus:* Tiny follicular papules, resembling milia; rare and occurs late.
  - In immunosuppressed patients, especially HIV/AIDS, larger lesions may be ulcerated (*malignant syphilid*, Fig. 8.**2 d**) or crusted (*rupial syphilis*).

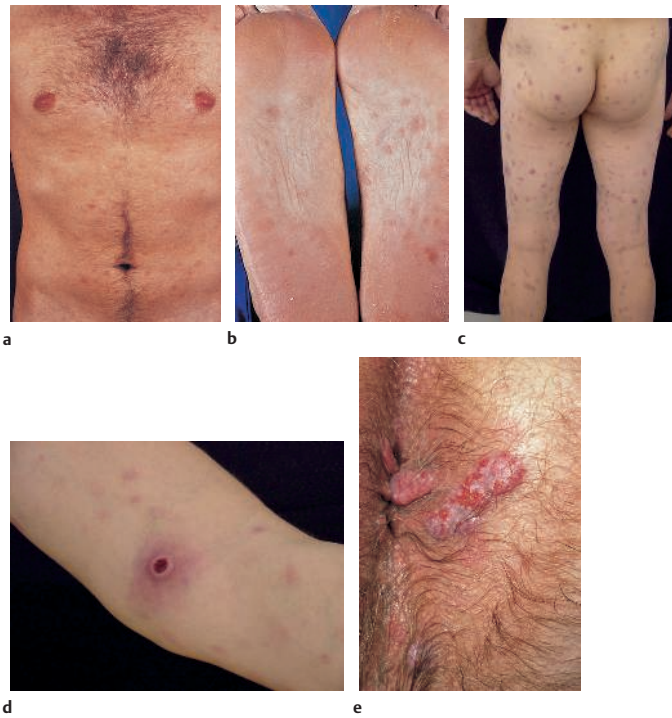


Fig. 8.**2** · **Secondary syphilis. a** Maculopapular exanthema. **b** Syphilis on soles. **c** Papular exanthem. **d** Ulcerated nodule. **e** Condylomata lata.

  - *Syphilitic leukoderma:* Any of the secondary lesions can heal with postinflammatory hypopigmentation; most common on the nape; usually resolves.
  - *Condylomata lata:* Eroded genital papules teeming with spirochetes (Fig. 8.**2 e**). Sometimes similar lesions inter digitally.
  - *Syphilitic alopecia:* Moth-eaten hair loss; usually numerous small, poorly circumscribed areas of incomplete hair loss (never complete loss as in alopecia areata).
- *Mucosal changes:*
  - *Mucous plaques:* Small papules on oral mucosa, which rapidly become eroded.
  - *Opaline plaques:* Later stage with glossy gray membranous covering.
  - *Plaques fouée:* Dark red plaques on tongue.
  - *Syphilitic angina:* Involvement of tonsils by spirochetes with swelling and dusky erythema; usually unilateral. In German, known as specific angina (because in the early days of dermatology, everything that was not syphilis was not specific).

- *Other systemic changes:*
  - *Generalized lymphadenopathy:* Most regular feature—painless firm lymphadenopathy involving antecubital, axillary, nuchal, preauricular, and other nodes. In the famous *syphilitic handshake*, the physician slid his hand up the arm to palpate the patient's antecubital nodes; sometimes known as the father-in-law check.
  - *Liver:* Acute hepatitis.
  - *Kidneys:* Acute glomerulonephritis with deposition of immunoglobulins and complement.
  - *Spleen:* Enlarged in almost 100% of cases.
  - *CNS:* Meningitis or meningoencephalitis; 25% have CSF abnormalities. Perhaps more common in HIV/AIDS.
- *Musculoskeletal abnormalities:*
  - *Periostitis:* Most commonly involves bones close to skin surface; typical sites tibia, sternum, and medial end of clavicle; pain worse at night.
  - Polyarthritis (immune complex disease).
  - Tenosynovitis.

► **Diagnostic approach:** Serology (100% positive; one has only to think of the possible diagnosis); dark field of eroded lesions.

► **Prognosis:** Even in the absence of treatment, all lesions resolve and many patients never develop further manifestations.

Latent Syphilis

► **Definition:** Seropositive latent syphilis is the phase following the resolution of secondary syphilis where the patient looks and feels normal but has a positive serology.

► **Diagnostic approach:**
- If the FTA-IgM test is positive in an asymptomatic patient, a complete examination is needed.
- The following steps are essential:
  - CSF examination and neurological evaluation.
  - Assessment of aorta (ultrasonography or imaging techniques).
  - Ophthalmologic consultation.

Tertiary Syphilis

► **Cutaneous manifestations:** Sometimes referred to as late benign syphilis, as these changes are much less serious and much more responsive to therapy than the other late manifestations.
- *Tuberous syphilid:*
  - Grouped red-brown papules and nodules (1–2 cm) that clear centrally and expand peripherally over years. Often annular or curved pattern (*tuberoserpiginous syphilid*).
  - Can occur anywhere, but more often on upper arms, back, or face.
- *Gumma:*
  - Firm 1–3 cm subcutaneous nodules that are painless and usually solitary, but frequently ulcerate discharging a rubbery (gum-like) substance.
  - Typical sites include palate (perforation), nose (collapse causing *saddle nose,* scalp, and face. May also involve liver, bone, or testes.

► **Musculoskeletal disease:**
- *Periosteitis:* Continuation of process starting in secondary syphilis.
- *Osteolysis* sometimes progressing to sclerosis of the entire marrow cavity: *ivory bones.*

- *Gummata* involving bone.
- *Juxtaarticular nodes:* Gummata that tend not to liquefy.

► **Cardiovascular disease:**
- About 10% of untreated patients develop cardiovascular syphilis.
- *Treponema pallidum* involves the vaso vasorum (vessels nurturing the aorta) and leads to aneurysm formation and aortic insufficiency.
- Diagnosis is based on standard ultrasonography and imaging procedures to measure aorta and then monitor changes.

Note: 80% of patients with syphilitic aortic disease die from this problem, despite both antibiotic therapy and surgery.

► **CNS disease:** In late syphilis, most neurological symptoms are caused by chronic vessel inflammation. Spontaneous resolution can occur during the tertiary inflammatory phase, but not in the quaternary phase.
- *Asymptomatic neurosyphilis:* CNS involvement is only detected by examination of CSF; no signs or symptoms.
- *Meningovascular neurosyphilis:* Main finding in meningeal inflammation, usually with prominent headache. Also numerous CNS thromboses cause a variety of neurological and psychiatric symptoms. Gummata may also caused focal defects.
- Diagnosis based on CSF examination for cells and protein, serology (blood and CSF) and neurologic examination.

Quaternary Syphilis

The most devastating complications of syphilis are the late parenchymal problems, which are not generally reversible.

► **General paresis:**
- Formerly known as general paresis (or paralysis) of the insane; before the advent of antibiotic therapy, syphilitic patients kept mental institutions filled.
- About 2% of untreated patients advance to this stage; onset of signs and symptoms is 20–25 years after initial infection. Primary damage is to the gray matter of the anterior lobes, causing a wide spectrum of neurological and psychiatric disease.

► **Tabes dorsalis:** About as common as general paresis. Changes involve the dorsal roots and posterior columns of spinal cord. Divided into three stages:
- *Anesthetic stage:* Hypesthesia especially on the feet leads to neurotropic ulcers *(mal perforant);* lancinating abdominal and extremity pain, and paralysis of ocular nerves. *Argyll Robertson pupil* describes a pupil that is miotic and responds to accommodation effort but not to light.

Note: Pupil abnormalities must be present for the diagnosis of tabes dorsalis.
- *Ataxic stage:* Uncoordinated movements with typical locomotion (*slap walk*) and positive *Romberg sign* (unable to stand steady with eyes closed).
- *Pseudoparetic stage:* Patient also develops signs and symptoms of paresis.

► **Diagnostic approach:** Same as for tertiary neurosyphilis.

Congenital Syphilis

► **Definition:** Syphilis in utero from mother to fetus. Two subtypes:
- *Early congenital syphilis* (*syphilis connata praecox*): Lesions occur during the first 2 years of life (analogous to primary syphilis).
- *Late congenital syphilis* (*syphilis connata tarda*): Lesions occur after 2 years of life (analogous to secondary syphilis).

► **Pathogenesis:** The degree of fetal damage depends on the time of infection in the mother (Table 8.**3**) and, more importantly, on whether or not she is treated promptly and appropriately.

Table 8.3 · **Relationship between time of untreated maternal infection and manifestations of congenital syphilis**

Time of maternal infection	Consequences for fetus
Before pregnancy	
>2 years (late syphilis)	Little risk
<2 years (early syphilis)	Intrauterine death or early congenital syphilis
During pregnancy	
1st half	Intrauterine death or early congenital syphilis
2nd half	Mild congenital syphilis, or child is normal at birth but develops late congenital syphilis (and mother, secondary syphilis)

► **Early congenital syphilis:**
- The fetus's immature immune response allows syphilis to run a rapid and damaging course. Prognosis is especially poor if signs and symptoms are present at birth.
- Clinical findings include:
  - *Present at birth:* Low birth weight, abnormally large placenta, hepatosplenomegaly, blisters and erosions mainly on palms and soles (*pemphigus syphiliticus*), osteomyelitis—mortality rate 50%.
  - *Developing in first months in untreated infants: Snuffles* (chronic runny nose, often bloody), periorificial rhagades, pemphigus syphiliticus may also appear here in delayed fashion, periosteitis and osteochondritis involving mainly long bones with so much pain that infants do not move limbs (*Parrot pseudoparalysis*), CNS disease (50%), glomerulonephritis with nephrotic syndrome.

► **Late congenital syphilis:**
- Resembles late syphilis, but cardiac involvement is uncommon.
- Clinical findings include:
  - *Interstitial keratitis:* Affects about 10%, usually bilateral; appears at age 10–30. Initially iritis, then corneal neovascularization and clouding. Treatment is topical corticosteroids, not antibiotics, which cause a flare; sometimes corneal transplantation needed.
  - Salt and pepper retina.
  - *Sensory deafness:* Develops at 10–20 years of age in 10–30%; usually bilateral.
  - *Neurosyphilis:* Late onset but affects 30–50%.
  - *Cutaneous findings:* Analogous to late syphilis (gummata and tuberous lesions).

► **Stigmata:** Clinical lesions that develop secondary to congenital syphilis, even after treatment. One or more is almost always present. Findings include:
- Saddle nose (75%).
- Frontal bossing (hot cross bun or buttocks skull).

- Maxillary hypoplasia (85%).
- *Higouménaki sign:* Thickening of medial end of clavicle.
- Saber shins.
- *Clutton joints:* Effusions into large joints.
- Gothic palate (high arched palate): 75%.
- Periorificial furrowed scars (*Parrot lines*).
- Dental changes:
  - *Hutchison incisors:* Incisors shaped like tip of a screwdriver, often notched; 65%.
  - *Mulberry molars:* First molars with complex surface; 65%.

  ▶ ***Note:*** The *Hutchinson triad* consists of Hutchison incisors, sensory deafness, and interstitial keratitis.

Serologic Diagnosis of Syphilis

Overview

There are a number of serologic tests for syphilis. They are used to make the diagnosis, to confirm the effectiveness of therapy, and to monitor patients for recurrence. An overview of the available tests and their use is given in Table 8.**4**. Two screening tests and two confirmatory tests suffice for almost all circumstances; not all the tests listed in the table are described in detail. There are two basic categories of tests:

- **Nontreponemal tests:** Identify antibodies against phospholipids such as lecithin or cardiolipin.
- **Treponemal tests:** Identify antibodies against *Treponema pallidum*.

The former are cheaper and more sensitive; the latter, more specific.

Table 8.4 · **Serologic tests for syphilis**

Screening test	TPHA test VDRL test RPR card test IgG-ELISA test
Confirmatory test	FTA-ABS test VDRL titers
Need for therapy	IgM-FTA-ABS test 19S-IgM-FTA-ABS test IgM-ELISA Cardiolipin test
Follow-up	Cardiolipin test VDRL test 19S-IgM-FTA-ABS test IgM-ELISA test

Treponema pallidum Hemagglutination Test (TPHA Test)

- **Basis:** Sheep erythrocytes coated with *Treponema pallidum* antigens are incubated with patient serum; if antibodies are present, the red cells agglutinate.
- **Indications:** Screening.
- **Evaluation:** Highly specific; false positive under 0.1%; becomes positive in third week and remains positive for life of patient.
- **Advantages:** Easy to do.
- **Disadvantages:** Standardized reagents not available so reproducibility varies; expensive.

Venereal Disease Research Laboratory Test (VDRL Test)

- **Basis:** Flocculation test. Nonspecific antibodies that react with both *Treponema pallidum* cell wall phospholipids and cardiolipin are identified. The patient's serum is mixed in a colloidal solution of cholesterol, lecithin, and cardiolipin. If antibodies are present, a precipitate occurs. The serum is diluted and the level at which a reaction still occurs (for example 1:64) is noted. After treatment, the titer will drop over months.
- **Indications:** Screening and monitoring of therapy.
- **Evaluation:** Highly sensitive nontreponemal test, 100% positive in secondary syphilis.
- **Advantages:** Cheap, reproducible, worldwide usage, ability to titrate makes it quantitative.
- **Disadvantages:** 10–20% false-positive results; a positive VDRL test must always be confirmed.
- **False-positive reactions:** Diabetes mellitus, cirrhosis, autoimmune diseases (lupus erythematosus, systemic sclerosis, rheumatoid arthritis), pregnancy, viral diseases (HIV, measles, mumps, even herpes genitalis), advanced systemic malignancies, multiple blood transfusions, advanced age, i.v. drug abuse.

Fluorescent Treponema pallidum Antibody Absorption Test (FTA–ABS Test)

- **Basis:** A slide is coated with *Treponema pallidum*. Patient's serum is absorbed with nonpathogenic treponemes and then applied to slide. Antibodies bound to *Treponema pallidum* are identified with immunofluorescence.
- **Indications:** Confirmatory.
- **Evaluation:** Becomes positive in fourth week and remains so forever.
- **Advantages:** Very sensitive and specific.
- **Disadvantages:** Standardized reagents not available so reproducibility varies.

IgM–FTA–ABS Test

- **Basis:** Same as FTA–ABS test, but only labeled anti-IgM antibodies are used to determine if patient has IgM antibodies against *Treponema pallidum*.
- **Indications:**
  - *Early diagnosis:* IgM antibodies are the first to be produced; they can be found at 2 weeks, before a chancre appears.
  - *Assessing disease activity:* IgM production continues as long as living *Treponema pallidum* are present in body, so one can determine if latent phase is present or not.
  - *Evaluating therapy:* The IgM–FTA–ABS test usually turns negative 1 month after therapy; always within 1 year.
  - *Diagnosis of congenital syphilis:* IgM cannot cross the placenta, so if the infant has IgM antibodies, *Treponema pallidum* has crossed the placenta.
  - *Recognition of second infection:* Increase in IgM antibodies coupled with VDRL titer increase suggests second infection without clinical signs.
- **Advantages:** Very sensitive and specific.
- **False-positive reactions:** Rheumatoid factor is an IgM antibody whose Fc portion is directed against IgG. If the patient has a positive rheumatoid factor and treated syphilis, then persistent IgG antibodies will bind to treponemes on the slide; rheumatoid factor molecules bind to them and are identified by the labeled anti-IgM.

19S–IgM–FTA–ABS Test

- **Basis:** If a patient has a large amount of IgG antibodies against *Treponema pallidum* and only a small amount of IgM, then the IgG can block the test treponemes on the

slide, giving a false-negative test for IgM. To correct this, the 19S fraction of serum where IgM is found is separated out and only this portion used for testing.
- **Indications:** Negative IgM–FTA–ABS test but appropriate history.

Evaluation of Serologic Tests
- **Confirmation of infection with *Treponema pallidum*:** Two positive tests with *Treponema pallidum*-specific tests. Blood should be re-drawn for the confirmatory testing. An endemic treponematosis must be excluded.
- **Assessing degree of activity:** IgM–FTA–ABS becomes negative when *Treponema pallidum* has been eliminated. VDRL titer > 1:64 also suggests active disease.
- **Second infection:** New appearance of IgM antibodies, and rapid increase in VDRL titer by 2 dilutions or more.

CSF Serologic Diagnosis
- **Absolute indications:**
  - Confirmed and treated early syphilis with delayed drop in titer (IgM still present 1 year after therapy).
  - Confirmed early or late syphilis (treated or not) and development of neuropsychiatric signs and symptoms.
  - Patient with newly discovered positive serology, no previous documentation, and neuropsychiatric signs and symptoms.
  - Follow-up examination after positive CSF examination, 1 year after therapy.
  - HIV infection.
- **Relative indications:**
  - Any early syphilis except primary syphilis.
  - Latent syphilis without suitable history and documentation.
- **Technique:** The CSF tests are analogous to the blood tests. At the same time, the CSF is analyzed in routine fashion for cells and protein.

Therapy

- **Overview:**
  - The therapeutic recommendations of the German STD organization are shown in Table 8.**5**.
  - Therapy first after diagnosis is completely confirmed (identification of *Treponema pallidum* or confirmatory serological testing).
  - Syphilis is a reportable disease in most countries.
  - HIV serology.
  - Examination of sexual partners; then treatment or follow-up.
  - No sexual contacts until treatment is completed.
- **Penicillin therapy:**
  - Penicillin G remains the treatment of choice; still no evidence of resistant *Treponema pallidum*.
  - Therapeutic serum, level of 0.03 IU/mL must be maintained for 7 days. Because of the serious nature of tertiary syphilis, it is generally recommended to treat for 2–3 weeks.
  - Intramuscular injections are preferred to oral therapy, because of both unreliable patients and unreliable absorption.
  - ***Note:*** Do not combine with bacteriostatic agents; penicillin interferes with cell wall production and is only effective against growing spirochetes.
  - *Complications:* Allergic reactions common; each patient must be asked about penicillin allergy and emergency equipment must be available.
  - *Penicillin allergy:* Doxycycline is the usual choice; if tetracyclines cannot be used, then erythromycin may be employed.

Table 8.5 · Treatment of syphilis

	Agent	Dose	Duration
Early syphilis			
Standard	Benzathine penicillin	2.4 million IU i.m. (1.2 million IU in each buttock)	Single dose
Alternatives			
	Doxycycline	100 mg b.i.d. p.o.	14 days
	Erythromycin	500 mg q.i.d. p.o.	14 days
Late syphilis			
Standard	Benzathine penicillin	2.4 million IU i.m.	Days 1,8,15
Alternatives	Procaine-benzylpenicillin	1.2 million i.m. daily[a]	21 days
	Doxycycline	200 mg b.i.d. p.o.	28 days
	Erythromycin	2.0 g i.v. daily	21 days
Neurosyphilis	Penicillin G	5 million IU 6x daily	14–21 days
Congenital syphilis	Penicillin G	50,000 IU/kg i.v. × 2 50,000 IU/kg i.v. × 3	Days 1–7[b] Days 8–10

a Procaine-benzylpenicillin 0.9 million IU and benzylpenicillin 0.3 million IU.
b Days of life.

- **Treatment during pregnancy:**
  - Penicillin is employed exactly as in nonpregnant patients.
  - In the case of penicillin allergy, use erythromycin. Since erythromycin crosses the placenta poorly, the infant should be treated with penicillin after birth.
- **HIV infection:** Always check CSF if the time of initial infection cannot be precisely identified (frequent second infections) or is more than 1 year in the past. If this cannot be clarified, then treat as neurosyphilis for at least 14 days.

8.3 Endemic Treponematoses

The endemic treponematoses are important both because they infect large numbers of people and because they cause false-positive reactions for syphilis; even the *Treponema pallidum* specific tests cannot help separate the diseases. The diseases go through stages parallel to syphilis, but with significant differences in organ involvement.

Yaws

- **Synonym:** Frambesia.
- **Definition:** Endemic treponematosis caused by *Treponema pertenue*.
- **Epidemiology:** Previously widespread in equatorial Africa and South America; today, small endemic areas in South America, occasional cases in Africa. Transmitted by close contact during childhood.

- **Clinical features:**
  - *Incubation period:* 3–6 weeks.
  - *Primary stage:* Verruciform nodule at site of inoculation; mother yaws, which resembles a raspberry (framboise in French); heals spontaneously.
  - *Secondary stage:* Disseminated cutaneous lesions, sometimes worse in occluded or moist areas. Palmoplantar fissuring and keratoses known as *crab yaws*. Bone pain common, especially in tibia.
  - *Tertiary stage:* Gummata develop but no CNS or cardiovascular disease.
- **Diagnostic approach:** Same as for syphilis.
- **Therapy:** Benzathine penicillin 2.4 million IU once.

Pinta

- **Definition:** Endemic treponematosis caused by *Treponema carateum*.
- **Epidemiology:** Limited to remote areas of southern Mexico, Central America, and northern South America. Transfer by direct contact.
- **Clinical features:**
  - *Incubation period:* 3–6 weeks.
  - *Primary stage:* Smooth papule, usually on extremity. Sometimes grouped papules, persists for months.
  - *Secondary stage:* Disseminated papules (*pintids*), often appear before primary lesions is resolved. Resolve with hypopigmentation. May continue to appear for years.
  - *Tertiary stage:* No bone, CNS, or cardiovascular disease.
- **Diagnostic approach:** Same as for syphilis.
- **Therapy:** Benzathine penicillin 2.4 million IU once. Totally depigmented lesions not influenced.

Endemic Syphilis

- **Definition:** Endemic treponematosis caused by *Treponema pallidum* var. *endemicus*.
- **Epidemiology:** Occurs mainly in dry regions of Middle East and North Africa; previously endemic in Bosnia but eradicated by mass treatment program in 1960s. Spread by direct contact and perhaps drinking vessels.
- **Clinical features:** Primary lesion usually oral and overlooked. Secondary lesions include mucous patches and bony lesions. Tertiary disease consists primarily of gummata and bony changes; CNS or cardiovascular disease extremely rare.
- **Diagnostic approach:** Same as for syphilis.
- **Therapy:** Benzathine penicillin 2.4 million IU once.

8.4 Gonorrhea

Overview

- **Definition:** Common sexually-transmitted infection caused by *Neisseria gonorrhoeae*, affecting mucosa and transitional epithelium; typically leading to urethritis in men and to an often asymptomatic cervicitis in women.
- **Epidemiology:**
  - Peak ages: 18–25; more than 50% are under 25 years of age.
  - Always sexually transmitted except for blennorrhea in newborns and some cases of vulvovaginitis in prepubertal girls.

- After intercourse with an infected women, 35% of men become infected. In the reverse setting, 60–90% of women become infected after contact with an infected man.
- Most men develop signs and symptoms within 3–4 days. Asymptomatic infections, often persistent and usually in women, are a significant reservoir.
- Development of resistant strains is a worldwide problem.

► **Pathogenesis:**
- *Neisseria gonorrhoeae* is a Gram-negative diplococcus (paired coccus), typically coffee-bean shaped; also known as *gonococcus*.
- Initially mucosal surfaces are infected: urethra, rectum, endocervix, pharynx, conjunctiva. Later, there may be regional complications and systemic spread.
- Gonococci have a variety of variable surface antigens. The most important are the thread-like pili that help the bacteria anchor to epithelial cells or even sperm. The main subunit, pilin, has antigenic variation that makes development of an immunization an as yet unmet challenge.

Local Infections

► **Genital gonorrhea in men:**
- *Urethritis:* Incubation period 3–4 days. In 70–85%, dysuria and pus-laden discharge, which cannot be clinically separated from other urethritides. 15–30% asymptomatic. Without treatment, resolution in days to weeks.
- *Regional complications:* Acute epididymitis, chronic prostatitis.

► **Differential diagnosis:** Nongonococcal urethritis.

► **Genital gonorrhea in women:**
- *Urethritis:* Incubation period 5–8 days. Often overlooked or misdiagnosed as cystitis; 80% of cases asymptomatic.
- *Cervicitis:* Also usually asymptomatic, mild cloudy discharge and erythematous ostium.
- *Regional complications:*
  - *Salpingitis:* Gonococci attach to sperm and can infect the fallopian tubes; more common around menses.
  - *Peritonitis:* Most common site for peritoneal infection after exiting tubes is perihepatic *(Fitz-Hugh–Curtis syndrome*). May cause adhesions.
  - *Pelvic inflammatory disease:* Infection involving fallopian tubes, ovaries, and peritoneum; *Neisseria gonorrhoeae* is common cause. Leads to chronic abdominal pain, dyspareunia, infertility, and tubal pregnancy.
  - *Vulvovaginitis in children:* The vagina is more sensitive and easily infected in prepubertal girls. Thus *Neisseria gonorrhoeae* can cause a purulent vulvovaginitis, which is usually the result of sexual abuse. Differential diagnostic considerations include other bacterial infections (often spread from perianal region, herpes simplex, foreign bodies, irritating bubble baths).

  ❓ ***Caution:*** Always consider sexual abuse when confronted with vaginal discharge in a prepubertal girl. Culture for gonococci.

► **Gonococcal blennorrhea:**
- Infection occurs by direct spread of bacteria during passage through birth canal; less often in adults by direct contact.
- Erythema and swelling of the lids, conjunctivitis, and pus-laden discharge. Risk of corneal ulceration.
- Uncommon because of prophylaxis (see therapy).

► **Anorectal gonorrhea:**
- Present in 40–50% of women with cervical or urethral gonorrhea; higher percentage of male homosexuals.

- Often overlooked clinically; usually asymptomatic (85%) or mistaken for normal discharge.

► **Pharyngeal gonorrhea:**
- Disease of women and male homosexuals; not clinically distinctive.
- Asymptomatic in 90% of cases; otherwise mistaken for "sore throat".

Disseminated Gonococcal Infection (Gonococcal Sepsis)

► **Epidemiology:** Disseminated gonococcal infection (DGI) is rare, occurring in 1–3% of infections. At greatest risk are menstruating females who are asymptomatic carriers.

► **Pathogenesis:** Strains of *Neisseria gonorrhoeae* that cause DGI are usually exquisitely penicillin-sensitive.

► **Clinical features:**
- *DGI triad:*
  - Polyarthralgia without arthritis.
  - Tenosynovitis.
  - *Dermatitis:* Tiny tender grey pustules on erythematous base, often over joints; histologically, septic vasculitis.
  - Patients usually have systemic signs and symptoms: fever, chills, malaise.
- *Gonococcal arthritis:* At start, polyarthritis (knee, ankle, hand); later monoarthritis (almost always knee); diagnosis based on isolating *Neisseria gonorrhoeae* in joint aspirate.
- Other rare systemic findings include endocarditis (EKG abnormalities) and meningitis.

Diagnostic Approach

► *Direct smear:* Urethral or cervical smear with Gram or methylene blue stain (p. 28).

► *Indirect identification:* Dried smear (can be mailed) labeled with immunoassay (Gonozyme); not suited for pharyngeal or rectal smears.

► *Culture:*
- Take material with Dacron or calcium alginate-tipped applicator or platinum loop.
- Can culture urethra, cervix, rectum, or pharynx. Also first-catch urine sediment following centrifugation.
- Plate immediately on selective medium (Thayer–Martin) at 37 °C with CO_2 enrichment; commercial products include TransGrow. Transport media available but less desirable.
- The colonies appear after 24–36 hours; they stain dark with dimethyl-*para*-phenylene diamine (*oxidation reaction*). Positive microscopy and oxidation reaction together are more than 99% accurate.
- Simple test available for β-lactamase formation using chromogenic cephalosporin (Cefinase).

Therapy

► **Overview:**
- Important factors include increased numbers of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) strains in different parts of the world, as well as multiresistant strains.

! *Caution:* Be aware of local resistance patterns and of where your patient's infection was acquired.

- Frequent chlamydial coinfection (25–50%); many countries recommend always adding antichlamydial therapy to any regimen for gonorrhea.

► **Uncomplicated urethral gonorrhea:**
- *Intramuscular:* Spectinomycin 2.0 g or ceftriaxone 250 mg, each as single dose.
- *Oral:* Cefixime 400 mg, ciprofloxacin 500 mg, ofloxacin 400 mg, or azithromycin 1.0 g, each as single dose.
- Azithromycin also covers chlamydial infection; otherwise add either doxycycline 100 mg b.i.d. for 7 days or azithromycin 1.0 g in a single dose.

► **Pharyngeal gonorrhea:** Intramuscular ceftriaxone is preferred but oral quinolones are acceptable (dosages as above).

► **Anal gonorrhea:** Intramuscular therapy is preferred.

► **Complicated/disseminated gonorrhea:**
- Ceftriaxone 1–2 g i.m. or i.v. 1 × daily for 7 days (b.i.d. if meningitis or endocarditis).
- Cefotaxime 1.2 g i.v. t.i.d. for 7 days.
- Alternatives for β-lactam allergy:
  - Spectinomycin 2 g i.m. b.i.d. for 7 days.
  - Erythromycin 500 mg i.v. q.i.d. for 7 days.
- If epididymitis is present, add prednisolone 30 mg daily and NSAIDs.

► **Mixed infections:** Because of the high likelihood of coexistent chlamydial or anaerobic infections, most regimens for pelvic inflammatory disease offer broader coverage. Examples include:
- Second-generation cephalosporin and metronidazole or doxycycline.
- Clindamycin and gentamicin.

► **Pregnancy:** Erythromycin 500 mg i.v. q.i.d. for 7 days.

► **Blennorrhea:**
- *Adults:* Ceftriaxone 1 g i.m. (single dose usually suffices).
- *Infants:* Ceftriaxone 25–50 mg/kg i.v. or i.m. (single dose usually suffices).
- Rinse eyes with physiological saline.
- Children:
  - Ceftriaxone 25–50 mg/kg i.v. or i.m. 1x daily for 7 days (10–14 days if signs and symptoms persist).
  - Cefotaxime 25 mg/kg i.v. or i.m b.i.d. for 7–14 days.
  - If > 50 kg, adult dose.

► **Additional measures:**
- Always treat sexual partners; risk of overlooked gonorrhea is high. If treatment not possible, then culture and follow-up.
- Rule out accompanying syphilis or HIV infection.
- Follow-up culture 4–7 days after therapy.
- Rectal culture on all women with gonorrhea.
- Rectal and pharyngeal cultures on all homosexual men with gonorrhea.
- *Recurrent gonorrhea:* Culture and treat all sexual partners (no exceptions), rectal and pharyngeal cultures.

8.5 Other Sexually Transmitted Diseases

Chlamydial Infections

► **Epidemiology:** *Chlamydia trachomatis* (serotypes D–K) is a common cause of STD and the most usual cause of nongonococcal urethritis.

► **Clinical features:**
- *Men:*
  - *Urethritis*: Incubation period 1–3 weeks. Discharge (often minimal) and dysuria. In smear, > 5 WBC per oil immersion field without gonococci. Without treatment, spontaneous resolution but recurrences possible. In 25–50% of cases, accompanying gonorrhea.
  - *Epididymitis*: Usually unilateral; swelling and induration of testes; very painful with fever. Usually accompanied by urethritis. Smear as above.
  - *Reiter syndrome* (p. 275): Urethritis, arthritis, conjunctivitis, psoriasiform skin changes; chlamydia are established trigger (along with bowel flora).
  - *Proctitis:* Usually male homosexuals; rectal pain, discharge, diarrhea; negative gonococcal culture; neutrophils in rectal smear.
- *Women:*
  - *Cervicitis:* Usual site, pus-laden or watery vaginal discharge with cervical erosions.
  - *Salpingitis (PID):* Most common cause of acute infection.
  - *Urethritis:* Dysuria, without hematuria or urge; often associated with cervicitis.
- *Children:*
  - *Pneumonia*: Acquired in birth canal, often with permanent lung damage.
  - *Conjunctivitis:* Common, but long-term sequelae rare.

► **Diagnostic approach:**
- Smear and methylene blue stain; > 4 WBC/oil immersion field and no gonococci; fluorescent-labeled monoclonal antibodies (Micro Trac) also available.
- *Method of choice:* PCR or ligase chain reaction (LCR) of cervical smear (women) or first urine (men); almost 100% specificity and over 80% sensitivity; two products available (PCR—Amplicor; LCR—LCx); both easily transported; also can be used for ejaculate or conjunctival discharge.
- Cultures and serologic procedures not necessary for routine practice.

► **Therapy:**
- Doxycycline 100 mg b.i.d. for 7 days or azithromycin 1 g in single dose.
- *Alternatives:* Tetracycline 500 mg q.i.d. for 7 days, erythromycin 500 mg b.i.d. for 14 days, erythromycin 500 mg q.i.d. for 7 days, or ofloxacin 300 mg b.i.d. for 7 days.
- In pregnancy, erythromycin.
- With chronic disease, longer courses (10–14 days).
- *Epididymitis*: Hospitalize, prednisolone 30 mg daily and NSAIDS.
- *PID:* Hospitalize, treat with minocycline and ciprofloxacin.
- Always treat partner.

Chancroid

► **Synonym:** Ulcus molle.

► **Definition:** Acute STD with painful genital ulcers and lymphadenopathy caused by *Haemophilus ducreyi*.

► **Epidemiology:** Endemic in many parts of Africa, South-east Asia and Central America, where it is one of the most common STDs. Focal endemic areas in USA; most recently in Jackson, Mississippi. In Europe, usually in tourists. Male:female ratio 5:1.

► **Pathogenesis:** *Haemophilus ducreyi* is a Gram-negative, thermolabile anaerobic rod. Transmission is almost always by sexual intercourse.

► **Clinical features:**
- *Incubation period:* 3–5 days (very variable, range 1–35 days).
- *Ulcer:*
  - Starts as small red papule that rapidly becomes pustular and then ulcerates (2–3 days). Sometimes several papules. Ulcers jagged, undermined and painful; mirror image (kissing) ulcers common.
  - Painful, especially when splashed with urine.
  - *Location:* Men: glans penis, inner aspect of foreskin, frenulum. Women: labia, perianal region, cervix.
- *Lymphadenopathy:* Acute painful, usually unilateral; develops in 50% after 1–2 weeks. Typically forms abscesses that rupture forming fistulas.
- *Course:* Spontaneous healing after 4–6 weeks in men, many months in women.

► **Diagnostic approach:**
- Clinical features (painful soft ulcer); smear (Gram-negative rods grouped like a "school of fish"; both relatively inaccurate.
- Culture requires special media and methods; check with local lab. In best hands, 75% sensitivity. Ideally PCR confirmation.

► **Differential diagnosis:**
- *Primary herpes simplex*: 50% also have lymphadenopathy; starts with blisters; often systemic signs and symptoms that are not seen with chancroid.
- *Syphilitic chancre*: Firm ulcer; lymphadenopathy never fluctuant or draining.
- ***Caution:*** Always rule out mixed infection. Test for syphilis and HIV.
- *Lymphogranuloma venereum*: Ulcer smaller, often overlooked; lymphadenopathy occurs after ulcer is healed; bilateral and nontender.
- *Other possibilities:* Granuloma inguinale, chancriform pyoderma, traumatic ulcer.

► **Therapy:**
- Azithromycin 1 g p.o. single dose.
- Ceftriaxone 250 mg i.m. single dose.
- Erythromycin 500 mg p.o. q.i.d. ×7 days (preferred in HIV infections).
- Ciprofloxacin 500 mg p.o. b.i.d. ×3 days.
- Pregnancy: Erythromycin or ceftriaxone.
- Examine and treat partners.

Lymphogranuloma Venereum

► **Synonym:** Durand–Nicolas–Favre disease.

► **Definition:** STD caused by *Chlamydia trachomatis* serovars L1–L3 with acute lymphadenopathy and late fibrosis.

► **Epidemiology:** Lymphogranuloma venereum (LGV) is becoming less common in its endemic regions in Latin America, Africa, India, and South-east Asia. Foci in some European port cities (Amsterdam, Hamburg), as well as in Houston, Texas and some other southern areas of USA. Recently an upsurge in homosexual men with primarily diarrhea and proctitis.

► **Pathogenesis:** *Chlamydia trachomatis* is an obligate intracellular pathogen, which is transferred in this setting almost exclusively by sexual contact.

► **Clinical features:**
- *Incubation period:* 3–30 days (usually 10–14 days).
- *Genital infection:*
  - Primary lesion is 5–8 mm painless erosion, usually overlooked, which heals over days.

Fig. 8.**3** · Lymphogranuloma venereum with massive lymphadenopathy (Image courtesy of Peter J. Kohl MD, Berlin, Germany).

  - Lymphadenopathy is prominent, bilateral, and both above and below inguinal ligament (*crease sign*, Fig. 8.**3**). The enlarged nodes become adherent and often rupture with fistula formation. Without treatment, healing occurs in 2–3 months.
  - Late complications include destruction of lymphatics with elephantiasis of the penis, scrotum, or vulva, accompanied by fistulas.
- *Rectal infection:* More common in women and homosexual men. Bloody discharge with pain; late complications include fistulas, structures, and elephantiasis (*esthiomène*).
- *Oral infection:* Enlarged cervical nodes, later axillary and thoracic nodes involved; differential diagnosis is lymphoma.
- *Systemic symptoms:* During the acute phase, patient usually ill with fever, headache, myalgias; may even get aseptic meningitis or hepatitis. Skin findings include erythema nodosum, exanthems, and photosensitivity.

► **Diagnostic approach:**
- Most reliable approach is serology to identify 4-fold increase in antichlamydial titers. Not serovar specific.
- Direct identification of organisms in smear with fluorescent-labeled monoclonal antibodies.
- Culture on McCoy cell line followed by identification with labeled antibodies.
- PCR possible but also not serovar specific.
- Lymph nodes show microabscesses with granulomatous inflammation and epithelioid giant cells.

► **Differential diagnosis:** Syphilis, herpes genitalis, granuloma inguinale, chancroid, acne inversa, other causes of anal and rectal inflammation and fistula formation (e.g., Crohn disease).

► **Therapy:**
- Doxycycline 100 mg b.i.d. for 21 days or tetracycline 500 mg q.i.d. for 21 days.
- Alternatives include erythromycin 500 mg q.i.d. for 21 days or sulfamethoxazole/trimethoprim 800/160 mg b.i.d. for 21 days.
- Erythromycin is preferred in pregnancy.
- Partners should be treated.
- Late complications require surgical management.

Granuloma Inguinale

► **Synonym:** Donovanosis.

► **Definition:** Chronic granulomatous destructive STD caused by *Calymmatobacterium granulomatis*.

- **Epidemiology:** Main endemic areas are India and New Guinea; occasionally seen in other tropical areas and imported into Western countries. Men are more often infected than women.
- **Pathogenesis:** *Calymmatobacterium granulomatis* is a Gram-negative intracellular rod, transmitted almost exclusively by sexual intercourse.
- **Clinical features:**
  - *Incubation period:* 1–12 weeks.
  - Initial lesion is papule in anogenital region that rapidly ulcerates with juicy red granulation tissue (Fig. 8.**4**). Spreads locally or by auto-inoculation.
  - Sites include penis, labia, and perianal region.
  - Complications include deep ulcers, massive scarring causing pseudo-lymphadenopathy, lymphedema and elephantiasis. Chronic lesions are at risk of development of squamous cell carcinoma. Rare hematogenous spread.
  - Spontaneous healing may occur, but often persistent and destructive infection.

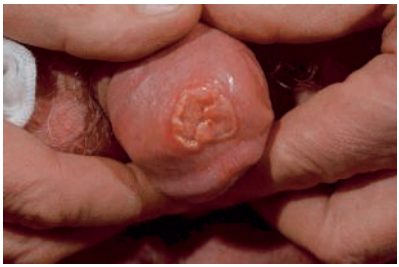


Fig. 8.**4** · Granuloma inguinale (Image courtesy of Peter J. Kohl MD, Berlin, Germany).

- **Diagnostic approach:**
  - No reliable, sensitive method.
  - Direct identification of *Calymmatobacterium granulomatis* in crush preparation of curetted tissue; classic finding is *safety pin sign*—bipolar staining bacteria within macrophages.
  - Histology shows granulomas in which the organisms can sometimes be identified with Giemsa or silver stains.
  - Culture very difficult; can be tried on McCoy cell lines.
- **Differential diagnosis:** Lymphogranuloma venereum, chancriform pyoderma, pyoderma gangrenosum; late stages, verrucous squamous cell carcinoma, acne inversa.
- **Therapy:**
  - Many alternatives available: azithromycin 1 g weekly for 3 weeks; erythromycin 500 mg q.i.d. for 21 days, norfloxacin 400 mg b.i.d. for 21 days, ciprofloxacin 750 mg b.i.d. for 21 days, doxycycline 100 mg b.i.d. for 21 days or sulfamethoxazole/trimethoprim 800/160 mg b.i.d. for 21 days.
  - Erythromycin or azithromycin used in pregnancy.
  - Treat patterns.

Additional Sexually Transmitted Diseases

Nongonococcal Urethritis (NGU)

- **Definition:** Commonly used but less than ideal term for infectious urethritis not caused by *Neisseria gonorrhoeae*.

- **Pathogenesis:** The most common causes are:
  - *Chlamydia trachomatis*, serovars D–K (40–60%).
  - *Ureaplasma urealyticum* and other mycoplasma (30–40%).
  - *Trichomonas vaginalis* (1–2%).
  - Herpes simplex virus, *Candida albicans* (very rare).
- **Clinical features:** Burning and pain on urination. Gonococcal urethritis has a much more purulent discharge than the others, but clinical identification is impossible. Mixed infections are common.
- **Diagnostic approach:**
  - *Examination of urine sediment:* > 4 WBC per high power field.
  - Direct examination and culture for *Neisseria gonorrhoeae*.
  - Identification of chlamydia.
  - Not necessary to search for other causes on initial encounter.
- **Therapy:** See chlamydial infections (p. 149).

Bacterial Vaginosis

- **Definition:** Vaginal inflammation caused by increased concentration of anaerobic bacteria in vaginal flora (dysbacteriosis—alternation in normal balance, rather than true infection).
- **Pathogenesis:** Most common organism identified is *Gardnerella vaginalis*, small Gram-negative cocci.
- **Clinical features:** Thin, gray, vaginal discharge with classic fishy odor; little inflammation.
- **Diagnostic approach:** Examination of discharge: fishy odor enhanced when KOH is added (*whiff test*), pH > 4.5, *clue cells* (vaginal epithelial cells coated with cocci).
- **Therapy:**
  - Metronidazole 500 mg bid for 7 days (or 1 g daily for 7 days).
  - In pregnancy or when metronidazole is otherwise contraindicated: ampicillin 500 mg q.i.d. for 7 days.
  - Rapid response, but also check for other infections. Sometimes necessary to remove intrauterine device.

9 HIV Infection and AIDS

9.1 Overview

Definition

- **HIV infection:** Epidemic infection with the human immunodeficiency virus HIV-1 or HIV-2.
- **AIDS:** *Acquired immunodeficiency syndrome*—advanced stage of HIV infection which is defined by the presence of AIDS-defining illnesses and reduction in CD4 cells (CD4+ T cells).

Causative Agent

- HIV-1 and HIV-2 are retroviruses in the lentivirus group. They are single-stranded RNA viruses employing reverse transcriptase with an affinity for CD4 cells which exert cytopathic and cytolytic effects.
- In the course of the infection, new mutations in HIV appear. Causes are the extremely high spontaneous mutation rate associated with reverse transcriptase copying and the selection pressure from antiretroviral agents.

Epidemiology

- HIV-1 began to spread in the 1970s. It presumably arose from monkey retroviruses in Africa, with initial human infections occurring in Africa, the Caribbean, and the USA.
- Groups with high seropositivity for HIV-1 include:
  - Male homosexuals with multiple partners (initial major risk group).
  - Intravenous drug abusers.
  - Recipients of HIV+ blood or organs (now very low risk; but in early days of epidemic, devastating affect on hemophiliacs).
  - Sexual contacts of HIV+ individuals.
  - Infants born to HIV+ women.
- HIV-2 started in West Africa in the 1980s and spread to India in the 1990s; does not play a role in Western Europe or USA.
- AIDS has switched from a disease of male homosexuals in Western countries to a devastating disease of heterosexuals in sub-Saharan Africa, India, South-east Asia, and now appears to be established in China.
- At the end of 2004, around 40 million people worldwide were infected with HIV, with 5 million new infections yearly. There were 3 million deaths from AIDS in 2004.
- **Methods of transmission:**
  - *Sexual intercourse:* Most common; men more likely to infect women than vice versa; male homosexuals still a risk group.
  - *Perinatal:* During birth or in the perinatal period by nursing; tremendous problem in developing countries.
  - *Blood inoculation:* Shared needles among drug abusers; improper sterilization of needles; injuries to health care workers and laboratory personnel (usually needle stick; other routes unlikely).
  - *Transfusions:* Risk of receiving HIV-infected blood very small when proper screening procedures used.

- *Organ transplantation:* Risk also very small.
- *Saliva:* Controversial; risk extremely low, if any.
- *No transmission* by close personal contact or insects.

Centers for Disease Control (CDC) Staging

HIV infection is divided into three clinical categories (A, B, C) and three levels of CD4 cells (Table 9.**1**). Once the infection has reached a given stage, there is no upgrading, even in the face of clinical improvement or increasing CD4 counts.

- **Category A:** Documented HIV infection but none of the conditions listed in B or C:
  - Asymptomatic HIV infection.
  - Persistent generalized lymphadenopathy (lasting > 3 months in at least two extrainguinal locations).
  - Acute primary HIV infection: resembles infectious mononucleosis with lymphadenopathy, fever, malaise, and a truncal exanthem (Fig. 9.**1**).
- **Category B:** Documented HIV infection; accompanying illnesses which are not AIDS-defining (category C) but suggest immunodeficiency:
  - Bacillary angiomatosis.
  - Candidiasis, oropharyngeal (thrush).
  - Candidiasis, vulvovaginal; persistent, frequent or poorly responsive to therapy.
  - Cervical dysplasia or carcinoma in situ.
  - Constitutional symptoms (fever > 38.5 °C or diarrhea for > 1 month).
  - Zoster involving multiple dermatomes or recurrent.
  - Idiopathic thrombocytopenic purpura.
  - Listeriosis.
  - Pelvic inflammatory disease, especially with complications.
  - Oral hairy leukoplakia.
  - Peripheral neuropathy.
- **Category C:** Documented HIV infection; AIDS-defining illness.
  - Candidiasis of bronchi, trachea, or lungs.
  - Candidiasis, esophageal.
  - Cervical carcinoma, invasive.
  - Coccidioidomycosis, disseminated or extrapulmonary.
  - Cryptococcosis, extrapulmonary.
  - Cryptosporidiosis, chronic (> 1 month).

Table 9.1 · **CDC classification of HIV infections**

CD4 category	Clinical category		
	A	**B**	**C**
	Asymptomatic, acute HIV infection, persistent lymphadenopathy	Neither A nor C	AIDS-defining illness
1 (CD4 > 500/l)	A1	B1	C1
2 (CD4 200–500/l)	A2	B2	C2
3 (CD4 < 200/l)	A3	B3	C3

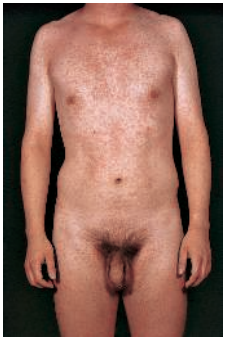


Fig. 9.**1** · Exanthem with acute HIV infection.

- Cytomegalovirus (CMV) infection (other than liver, spleen, or lymph nodes).
- CMV retinitis (with loss of vision).
- Encephalopathy, HIV-related.
- Herpes simplex virus infection: chronic (> 1 month) ulcers or herpetic bronchitis, pneumonia, or esophagitis.
- Histoplasmosis, chronic (> 1 month).disseminated or extrapulmonary.
- Isosporiasis, chronic (> 1 month).
- Kaposi sarcoma.
- Lymphoma (Burkitt lymphoma, primary effusion lymphoma, or CNS lymphoma, as well as others).
- *Mycobacterium avium-intracellulare* or *Mycobacterium kansasii* infections, disseminated or extrapulmonary.
- *Mycobacterium tuberculosis*, any site.
- *Mycobacterium*, other or unidentified species, disseminated or extrapulmonary.
- *Pneumocystis carinii* pneumonia (main signs and symptoms: dry cough, dyspnea, fever).
- Pneumonia, recurrent.
- Progressive multifocal leukoencephalopathy (JC virus).
- Salmonella septicemia, recurrent.
- Toxoplasmosis of brain (main signs and symptoms: focal neurologic findings, headache, loss of consciousness, seizures, fever).
- Wasting syndrome (HIV cachexia).

► Patients in subcategories A3, B3, and C3 meet the immunologic criteria for AIDS; those in C1, C2, and C3 meet the clinical criteria.

9.2 Cutaneous Manifestations

Overview

The possibility of HIV infection should be suggested by the appearance of skin diseases in atypical age groups, with atypical localization or morphology and with a prolonged or severe course. Figure 9.**2** correlates the various cutaneous manifestations with the stage of HIV/AIDS when they usually appear. Possible differential diagnoses are listed in Table 9.**2**.

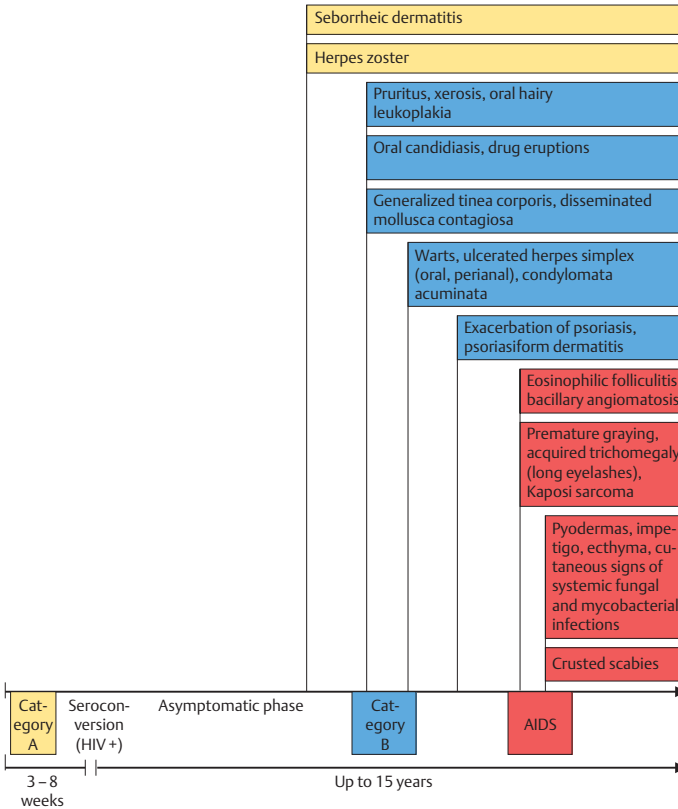


Fig. 9.**2** · Skin and mucous membrane changes in HIV infection.

Infections

► **Fungal infections:**
- Candida infections of the oral mucosa; appearance in adult life without explanation or with ulceration—think of HIV.
- Heartburn in an HIV-positive patient is candidal esophagitis until proven otherwise.
- Severe seborrheic dermatitis; *Malassezia* species play a role in immunodeficient patients (p. 276).
- Onychomycosis (Fig. 9.**3 a**), tinea pedis or disseminated tinea corporis.
- Cutaneous cryptococcosis (nodules resembling molluscum contagiosum).

► **Bacterial infections:**
- Acneiform exanthems triggered by *Staphylococcus aureus* (superficial folliculitis) or *Malassezia* species; occasional no causative agent is found.

Table 9.2 · Differential diagnosis of skin changes in HIV infections

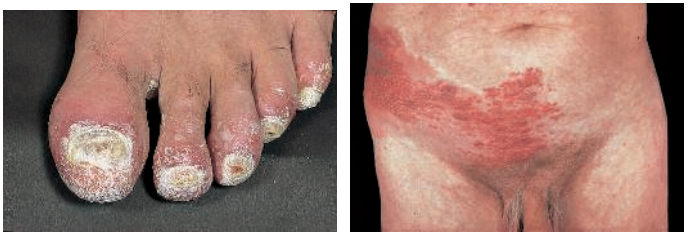
Type of lesion	Possible diagnoses
Papules, nodules	
Any site	Common warts, plane warts, bacillary angiomatosis, nodular scabies, disseminated deep fungal infections (coccidioidomycosis, cryptococcosis, histoplasmosis), Kaposi sarcoma, basal cell carcinoma, squamous cell carcinoma
Facial	Mollusca contagiosa, common warts, plane warts, disseminated deep fungal infections, Kaposi sarcoma, bacillary angiomatosis, basal cell carcinoma, squamous cell carcinoma
Anogenital	Mollusca contagiosa, condylomata acuminata, squamous cell carcinoma in situ or invasive, nodular scabies, Kaposi sarcoma
Crusted	Impetigo, ecthyma (caused by mycobacteria or gram-positive bacteria), ecthyma-like infections with varicella-zoster virus (painful), persistent herpes simplex virus infections, especially perianal with ulcers, disseminated deep fungal infections, Kaposi sarcoma, basal cell carcinoma, squamous cell carcinoma
Vesicles, bullae, pustules	
Grouped	HSV or VZV infections; all rules are off—recurrent, crusted, chronic, disseminated, atypical
Multiple	Bullous impetigo, erythema multiforme/toxic epidermal necrolysis, Reiter syndrome, pustular psoriasis, eosinophilic folliculitis, ecthyma gangrenosum, infectious endocarditis
Erosions, ulcers	
Any site	HSV, VZV, CMV, ecthyma, nocardiosis, mycobacterial infection, fixed drug eruption, basal cell carcinoma, squamous cell carcinoma
Anogenital	HSV, CMV, foscarnet-induced ulcers, squamous cell carcinoma
Acneiform	Acne, rosacea, perioral dermatitis, eosinophilic folliculitis, papular eruption of AIDS, rarely disseminated deep fungal infections
Folliculitis	*Staphylococcus aureus*, *Candida albicans*, *Malassezia* species, eosinophilic folliculitis, papular eruption of AIDS
Erythematosquamous	Psoriasis, severe seborrheic dermatitis, Reiter syndrome, tinea corporis, xerosis
Acute exanthem	Primary HIV infection, other infectious exanthems (childhood exanthems may recur), drug eruptions (very common)

Continued Table 9.2 ▶

Table 9.2 · Continued

Type of lesion	Possible diagnoses
Purpura	Idiopathic thrombocytopenic purpura, leukocytoclastic vasculitis, infectious endocarditis, drug eruptions
Pruritus	Xerosis, atopic dermatitis, scabies, eosinophilic folliculitis, papular eruption of AIDS, drug reaction
Nail and nailbed lesions	Tinea unguium (often white, superficial), candidal paronychia and onychomycosis, herpetic and *Staphylococcus aureus* whitlows, marked psoriatic changes (pits, onycholysis, subungual debris), yellow nail syndrome, zidovudine hyperpigmentation, ingrown nails and paronychia from protease inhibitors
Drug reactions	Exanthems (almost 100% for sulfamethoxazole/trimethoprim, for example), often severe; nail discoloration from zidovudine, ingrown nails and paronychia from protease inhibitors, lipodystrophy from protease inhibitors

Modified from Johnson RA, Dover JS. Cutaneous manifestations of human immunodeficiency virus disease, Table 215–4, in Fitzpatrick TB et al. (eds) *Dermatology in General Medicine,* 4th edition, New York, McGraw-Hill, 1993.)



a **b**

Fig. 9.3 · **a** Massive onychomycosis in HIV infection. **b** Severe herpes zoster in HIV infection.

- Pyoderma, ecthyma.
- Mycobacterial infections: *Mycobacterium avium-intracellulare*.
- Bacillary angiomatosis (caused by *Bartonella*; differential diagnosis Kaposi sarcoma, pyogenic granuloma).
- Exanthems associated with variety of infections.
- All STDs are more common (syphilis, chancroid, herpes genitalis).

► **Viral infections:**

- Ulcerated persistent (usually perianal) herpes simplex.
- Zoster; appearing at young age, often recurrent (Fig. 9.**3 b**).
- Condylomata acuminata; recurrent, therapy-resistant, widespread).
- Common and plane warts; widespread, therapy-resistant.
- Mollusca contagiosa; numerous, occasionally giant.
- Kaposi sarcoma (see below).
- Oral hairy leukoplakia (see below).

Other Skin Diseases Associated with HIV/AIDS

- Xerosis, acquired ichthyosis, pruritus.
- Psoriasis, Reiter syndrome; overlaps with severe seborrheic dermatitis.
- Pityriasis rubra pilaris.
- Anal dermatitis.
- Eosinophilic folliculitis, papular dermatitis of AIDS (perhaps identical).
- Increased number of drug reactions.
- Alopecia.
- Elongated eye lashes (acquired trichomegaly).
- Nail changes include yellow nail syndrome, leukonychia, splitter hemorrhages; linear hyperpigmentation secondary to antiretroviral therapy.
- Vasculitis, such as polyarteritis nodosa or leukocytoclastic vasculitis.
- Telangiectases, cherry angiomas.
- Scabies, often crusted scabies.
- Idiopathic thrombocytopenic purpura.
- Aphthae.

Kaposi Sarcoma

- Kaposi sarcoma (p. 460) is a vascular tumor caused by human herpesvirus 8, probably infecting lymphatic vessels. It classically affects elderly men in Europe, but affects children in Africa and is seen with both HIV infection and iatrogenic immunosuppression. Although the skin is most often involved, Kaposi sarcoma can affect the gastrointestinal tract and other internal organs.
- Typical lesions are red-brown macules or papules, usually initially following skin lines; lesions may wax and wane as CD cell count varies. Later nodules and ulcerated plaques. Oral involvement is particularly common in HIV/AIDS.
  - ***Note:*** If Kaposi sarcoma is identified in a young patient, or occurs on the face or in the mouth, always think of HIV/AIDS.

Oral Hairy Leukoplakia

- One of the most sensitive clinical signs for HIV/AIDS, and a poor prognostic sign.
- Fine filamentous strands are found on the lateral edges of the tongue. They are asymptomatic but firmly adherent and not easily removed with a tongue blade or toothbrush.
- The primary cause is Epstein–Barr virus, but the lesions frequently contain human papillomavirus (thought to be a co-factor) and are colonized by *Candida albicans*.
- Usually improves or resolves with highly active antiretroviral therapy (HAART); specific systemic antiviral therapy is not warranted. Topical retinoids may produce improvement.

9.3 Extracutaneous Manifestations

Almost every organ can be involved in HIV/AIDS; extensive knowledge of all possible manifestations is required to manage such patients. Common and troublesome complications include pulmonary infections, retinal CMV infection with risk of sudden blindness, neurological and psychiatric problems, chronic diarrhea, several unusual lymphomas, and a broad spectrum of drug side effects including life-threatening toxic epidermal necrolysis.

Diagnostic Approach

- **History:**
  - *Travel:* Southeast Asia, Africa.
  - *Sexual practices:* Homo-, bi-, heterosexual; number of partners; unprotected sexual intercourse; contact with prostitute, members of risk groups or individuals known to have HIV/AIDS.
  - *Sexually transmitted infections:* Syphilis, gonorrhea, others.
  - *Other infectious diseases:* Hepatitis B, hepatitis C, zoster, candidiasis, tuberculosis, histoplasmosis, coccidioidomycosis.
  - History of intravenous drug use, blood transfusions or other blood product replacement, organ transplantation, injuries with contact with infectious materials (health care workers).
  - Other diseases with intrinsic or iatrogenic immunosuppression.
- **Clinical examination:**
  - Inspection of entire skin surface and accessible mucosa.
  - Close search for skin infections that are common in HIV/AIDS.
  - Evaluation of lymph nodes with documentation.
  - Weight.
  - Auscultation and percussion of lungs.
  - Palpation of abdomen (liver, spleen, other masses).
  - Neurological status.
  - Retinal examination (CMV retinitis).
- **Laboratory:**
  - CD4 absolute count and CD4/CD8 ratio.
  - CBC.
  - Hepatic and renal function tests.
  - *Serology:* Antibodies against hepatitis A, B, and C, syphilis, toxoplasmosis, CMV, Epstein–Barr virus.

Diagnosis of HIV

- **Legal aspects:** HIV testing can only be done with the written permission of the patient. The physician must counsel patient, obtain written permission, and document this in the chart. In Germany, if the permission is not granted, the physician can refuse to treat nonemergency problems.
- The results of the testing are absolutely confidential. Positive tests are reported for national statistical purposes using a code that insures anonymity. The confidentiality can legally be broken to protect others at risk of HIV/AIDS, such as sexual partners or a health care worker exposed to patient's blood or serum.
- **Technical aspects:** ELISA test is used for screening; confirmation with Western blot. Two different blood specimens (*not two different tests*) must be positive before the patient is considered HIV-positive.
- **Meaning of a positive test:**
  - An HIV infection is present; this does not equate to AIDS.
  - HIV is in the patient's cells and can be transferred to others. Blood, organs and sperm are infectious and should not be "transferred".
  - Pregnant patients can transfer HIV to their offspring.
  - The prognosis of an HIV infection cannot be stated at the time of first diagnosis; there are too many variables.
- **Meaning of a negative test:**
  - The possibility of an HIV infection acquired in the past 3–6 months is not excluded.

- If risk-taking behavior has occurred in the past 3 months, the test must be repeated in 6–12 weeks.
- More sensitive tests searching for HIV RNA in the blood or lymphatic system can greatly reduce the chances of a false-negative test.

► **Further testing:**

- *Viral load*: Quantification of HIV load. Several techniques are used: RNA–PCR, branched DNA signal amplification assay (b-DNA-SA) or nucleic acid sequence based amplification (NASBA). In order to allow the viral load tests to be compared, results are expressed in copies/mL.
- *HIV resistance analysis (genotypic):* Should be carried out before switching retroviral therapy when a patient shows clear signs of viral replication while under treatment. The value of such testing before starting therapy is disputed, but there is at least 10% primary resistance among new infections in Europe.

Therapy

Caution: The treatment of HIV infection with retroviral agents is one of the most rapidly changing and complex areas of medicine. Physicians should be familiar with the most recent national or international therapeutic guidelines.

► **Therapeutic principles:**

- Current therapeutic recommendations are available from many Internet sources including www.aidsinfo.nih.gov, www.cdc.gov.hiv/treatment, www.aids.org, www.aidsnews.org. The World Health Organization site (www.who.int/hiv/en) contains extensive statistics and news, but little on therapeutic issues.
- Only physicians with extensive experience should manage patients receiving antiretroviral therapy.
- The success of the various HAART regimens means that many patients with newly diagnosed HIV infections will not die from their disease. In each individual case, one of the determining factors for life or death is the skill with which the antiretroviral drugs are administered.
- The first regimen prescribed should be highly active and contain multiple agents. The quicker the viral load is reduced, the longer the treatment is likely to be effective. Multiple agents are required to minimize the development of resistant strains.
- More than 20 agents are approved worldwide for antiretroviral therapy, so the number of possible regimens is almost unlimited. In each case, individual decisions should be based on methods of administration, side effects and cross-reactions, as well as associated diseases.
- Advice on therapeutic problems, such as a lack of response or drug interactions, should be obtained from an expert.
- Lymphocyte subpopulations and HIV load should be measured every 3 months. Routine blood work including CBC, liver, and kidney function should be checked every 4–6 weeks initially, and then less often as indicated.
- In the case of therapy failure, resistance analysis should be carried out. If protease inhibitors are employed, their blood levels should be measured.

► **Therapeutic agents:** Three classes of therapeutic agents are available (Table 9.**3**):

- *Fusion inhibitors* block the entry of HIV into cells.
- *Reverse transcriptase inhibitors* (RTI) block the translation of viral RNA into DNA. Three subcategories are available: nucleoside analogs (NRTI) and one nucleotide analog (NtRTI), and nonnucleoside inhibitors (NNRTI).
- *Protease inhibitors* (PI) block the maturation and discharge of new viral particles.

Table 9.3 · Antiretroviral therapy

Drug types	Drugs available in Germany in 2004
Reverse transcriptase inhibitors	
Nucleoside analogues (NRTI)	Zidovudine, stavudine, didanosine, emtricitabine, lamivudine, abacavir, zalcitabine
	Combinations: Zidovudine + lamivudine, zidovudine + lamivudine + abacavir
Nucleotide analog (NtRTI)	Tenofovir
Nonnucleotide reverse transcriptase inhibitors (NNRTI)	Nevirapine, efavirenz, delavirdine
Protease inhibitors	Saquinavir, indinavir, ritonavir, atazanavir, saquinavir, nelfinavir, amprenavir, fosamprenavir
	Combination: Lopinavir + ritonavir
Fusion inhibitor	T20

► **Indications:**
- The optimal time for the initiation of antiretroviral therapy has not yet been decided. The tendency is to treating as soon as the diagnosis is made, but most recent guidelines should be followed.
- Patients in stage A1 are the source of controversy. Patients with a reduced CD4 cell count or manifestations of disease are generally treated. In A1 patients, both the CD4 cell count and viral load are weighed in determining the need for therapy.

► **Therapeutic approach:**
- Treatment is usually started with 2 NRTI combined with a NNRTI or a PI.
- An effective response is indicated by a 10–100-fold reduction in the viral load in the first 2–4 weeks. A less rapid drop suggests suboptimal therapy. After 3 months, the viral load should be below measurable levels.
- Opportunistic infections are treated as indicated by infectious disease guidelines and consultation. The use of HAART has reduced the need for prophylaxis, but after the occurrence of an infection, prophylactic measures should be reviewed.

► **Treatment of Kaposi sarcoma:**
- *Cosmetically or functionally disturbing stable lesions*: Excision, cryotherapy, intralesional injection of vinblastine (0.2 mg/mL), ionizing radiation (single dose 800 cGy or fractionated up to 1300 cGy).
- *Disseminated nonpulmonary disease with CD4 cell count* $> 200\,\mu L$: HAART plus IFN-α (9 million IU subq. daily for 12 weeks, then 3× weekly for 6–9 months).
- *Disseminated progressive disease with CD4 cell count* $< 200\,\mu L$: HAART plus liposomal doxorubicin 20 mg/m^2 i. v. over 30–60 minutes every 2–3 weeks.

Prevention

► No efforts should be spared in AIDS prevention. Education of all at-risk groups, widespread availability of condoms, consideration of needle exchange programs

for drug abusers, and screening of prostitutes are all measures which have reduced the transmission of HIV. The politics of their implementation is a major social issue in many countries.

- Although there are many programs devoted to developing an HIV vaccine, no effective productive is currently available.

Occupational Injury with Possible HIV Exposure

- **Needle stick injuries**, both working directly with a patient and transferring blood in a laboratory, are capable of transmitting HIV to a health care worker.
- **Every patient and their bodily products** should be regarded as potentially carrying HIV (*universal precautions*).
- **If an injury with contamination occurs**, let the wound bleed freely if possible and then disinfect.
- **Prophylactic medications:**
  - Always take the first round of medications; then one can carefully consider all the options, assess the patient, and check the latest guidelines.
  - Inquire as to patient's HIV and hepatitis status; draw blood for confirmatory testing.
  - Usual recommendation is two NRTIs and two PI, often available as combination products. Check latest guidelines.
  - In pregnancy, there is insufficient data on PI and efavirenz is contraindicated.
  - Report the incident *without fail* to occupational health authorities.
  - The risk of acquiring hepatitis B and hepatitis C from a needle stick injury or other contact is considerably greater than that of acquiring HIV. Do not overlook this possibility.
    - All health care workers should be immunized against hepatitis B; if this is not the case and the patient is positive, then both active and passive immunization in the first 48 hours is recommended.
    - No immediate treatment for hepatitis C is recommended; exposed individual should be followed; those who do not develop clinical hepatitis but harbor the virus are at high risk of being carriers and should be treated with ribavirin and IFN-α.

10 Allergic Diseases

10.1 Basic Mechanisms

Allergy

- **Definition:** An acquired exaggerated or potentially harmful immune response to harmless exogenous substances, known as *allergens*. The immune reaction has two phases—the *sensitization phase* and the *effector phase*. During sensitization, the body acquires the ability to recognize an antigen as an allergen. Once this ability is present, subsequent exposures can lead to an allergic reaction—the effector phase.
- **Gell and Coombs classification:** Gell and Coombs identified four forms of "allergic reactions" with different immune mechanisms for tissue injury:
  - *Type I reaction (immediate hypersensitivity):* A type I reaction occurs within seconds to minutes after exposure when allergen combines with IgE on mast cells and causes degranulation and release of mediators. Typical reactions include urticaria, allergic rhinitis, conjunctivitis, or extrinsic asthma, and anaphylactic reactions. After about 6 hours, the late phase of the acute reaction can kick in; this may explain both the delayed appearance of urticaria or asthma and the lesion morphology in atopic dermatitis.
  - *Type II reaction (antibody-mediated hypersensitivity reactions)*: Antibodies recognize allergens bound to cell surfaces. Included in this group are complement-dependent lysis, antibody-dependent cell-mediated cytotoxicity, and phagocytosis induced by opsonizing antibodies. Reactions occur 6–12 hours after exposure. Typical clinical reactions include some forms of hemolytic anemia and many drug reactions.
  - *Type III reaction (immune complex–mediated hypersensitivity reactions)*: Here circulating immune complexes activate the complement cascade; reactions occur after 6–12 hours and include serum sickness, some forms of vasculitis, and many aspects of lupus erythematosus.
  - *Type IV (cell-mediated or delayed hypersensitivity reaction)*: This reaction appears first after 24 hours or longer; sensitized T cells either release mediators or steer T-cell cytotoxicity; examples include allergic contact dermatitis, tuberculosis, rejection of allografts, and graft-versus-host disease.

  Note: In any immune reaction, one must distinguish between the highly specific reactions between antigens (allergens) and T-cell receptors or immunoglobulin chains on B-cells, and all the nonspecific responses that accompany this interaction. In addition, most allergic disorders exhibit several mechanisms contributing to the inflammatory response.

Pseudoallergy

- **Definition:** Hypersensitivity reactions to exogenous substances that clinically mimic allergic reactions but are not mediated by specific immunologic sensitization.
- **Pathogenesis:** Although the mechanisms are poorly understood, they may include direct release of mediators, other intrinsic pharmacologic properties, and perhaps unexplained host response mechanisms. Common examples include release of histamines by certain pharmacologic agents or food components, as well as aspirin intolerance.

► **Diagnostic approach:** The diagnosis of pseudoallergy is always difficult, as there are no reliable skin or blood tests. In almost all cases, elimination followed by provocation challenge is required to confirm the suspected diagnosis.

10.2 Urticaria

Definition

► **Urticaria** (hives) is a group of inflammatory disorders characterized by wheal and flare type skin reactions (urtica, erythema) and pruritus resulting from the release of histamine and other mediators by activated skin mast cells. Similar reactions in the subcutaneous tissue or mucosa feature primarily swelling and are known as *angioedema*.

Note: *Urticaria* refers to a disease, *urtica* (wheal, hive) to its primary lesion.

Pathogenesis

► Urticaria symptoms are mast cell–dependent and their induction requires mast cell activation (degranulation) by specific or nonspecific triggers. Mast cells are key effector cells in the immune response. Specific triggers of mast cell degranulation include stimulation of mast cell surface IgE by selected allergens or drugs as well as physical stimuli (cold, friction, pressure) in physical urticaria disorders. Nonspecific triggers such as stress are relevant to all urticaria disorders. In addition, modulators of mast cell activation and/or degranulation (ambient temperature, alcoholic drinks, fever, emotions, hyperthyroidism, and other endocrine factors) can modify the induction of symptoms and the course of urticaria.

Clinical Features

► The basic lesion in urticaria is a hive or wheal (Fig. 10.**1 a,b**). Wheals vary greatly in size and configuration but have three unifying features:
- Central swelling surrounded by reflex erythema.

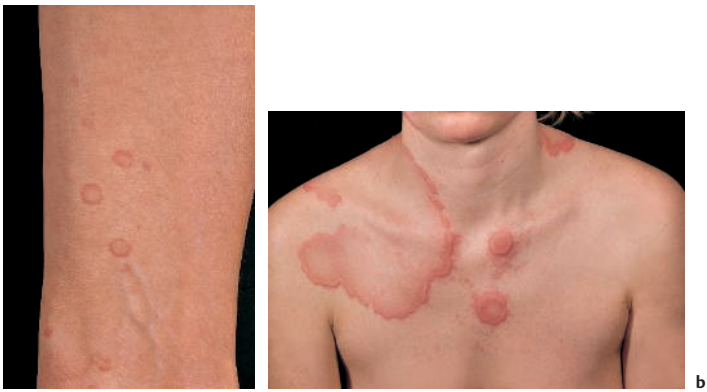


Fig. 10.**1** · Urticaria. **a** Typical lesions. **b** Giant lesions.

- Marked pruritus.
- Transitory nature with individual lesions lasting 1–24 hours.

Note: The time course of urticaria is essential to describing and investigating the disease:

- *Acute urticaria* lasts < 6 weeks; individual lesions are short-lived but the patient has urticaria daily for up to 6 weeks.
- *Chronic urticaria* lasts > 6 weeks.
- In general, patients with acute urticaria are evaluated with history alone and then treated; those with chronic urticaria are extensively investigated searching for a treatable underlying cause.

► The released mediators may cause associated signs and symptoms such as diarrhea, tachycardia, or respiratory problems, but they are not usually of major clinical significance.

Histology

► The key features are dilated upper dermal vessels with marked tissue edema. Depending on the duration of the lesion, a mixed perivascular infiltrate can be seen, as well as eosinophils. Urticaria is biopsied only to exclude vasculitis, bullous pemphigoid, and other urticarial lesions, as the diagnosis can best be made clinically.

Classification

► Urticaria is classified on the basis of both course and triggers (Table 10.**1**). The categories are not mutually exclusive, as physical urticaria can be chronic.

Table 10.1 · **Classification of urticaria**

Group	Subgroup
Idiopathic urticaria	Acute urticaria (< 6 weeks)
	Chronic urticaria (> 6 weeks)
Physical urticaria	Dermographism (urticaria factitia)
	Cold contact urticaria
	Solar urticaria
	Delayed pressure urticaria
	Heat contact urticaria
	Vibratory urticaria/angioedema
Other urticaria disorders	Cholinergic urticaria
	Contact urticaria
	Aquagenic urticaria
	Exercise induced urticaria/anaphylaxis
	Associated disorders

Differential Diagnosis

► The main differential diagnostic consideration is deciding which form of urticaria is present. Urticarial drug reactions must also be excluded, as well as serum sickness, early lesions of bullous pemphigoid (especially when dealing with elderly

patients), and arthropod assaults (often difficult to determine if lesions are multiple bites and stings, or a few bites and secondary urticaria). The lesions of bullous pemphigoid clinically resemble urticaria but are highly inflammatory with numerous eosinophils and sometimes histologically show early subepidermal blister formation.

Note: Some disorders that carry the name urticaria are not "urticaria disorders." For example, "Urticaria pigmentosa" is a form of cutaneous mastocytosis and "urticarial vasculitis" is a vasculitis, as is "familial cold urticaria."

Idiopathic Urticaria

- Most common group of urticaria disorders. Up to 25% of individuals develop idiopathic urticaria at one time in their life. In almost all cases remission occurs within 6 weeks (acute urticaria); in some patients symptoms persist (chronic urticaria), usually for months to years. Urticaria develops spontaneously (out of the blue) and usually cannot be induced.

Acute Urticaria

- **Pathogenesis:** The underlying cause remains unknown in most cases. The most common triggers include food components, drugs (NSAIDs), infections, and infestations.
- **Diagnostic approach:** No routine testing recommended, unless the history strongly indicates a need.
- **Therapy:** Nonsedating antihistamines are the mainstay of therapy; sedating agents can be used in the evening if desired. A short course of prednisolone (50 mg p.o. daily × 3 days) may be helpful, but controlled studies are lacking. Topical treatment is not effective; if patient insists, a topical anesthetic (polidocanol) or distractor (menthol cream or lotion) may be tried (p. 674).

Chronic Urticaria

- **Pathogenesis:** The three most common underlying causes (Table 10.**2**) of chronic urticaria are:
  - Autoreactivity or expression of circulating mast cell secretagogues including autoantibodies (autoimmune urticaria).
  - Chronic infections.
  - Intolerance to food components.
- Note that all of the factors listed in Table 10.**2** can also induce acute urticaria. They are emphasized here because patients with chronic urticaria are more likely to be subjected to detailed investigations.
- **Diagnostic approach:**
  - *History:* Establish clinical course; associated angioedema; ask specifically about possible triggers including stress, drugs (analgesics, penicillin, laxatives, oral contraceptives), food components (preservatives, food colorings, foods rich in histamine), and any relation to certain eating situations (certain restaurants); exclude physical triggers (often overlooked by patients, especially when delayed); family history of urticaria or angioedema.
  - *Laboratory:* Guided by history, test for underlying causes such as autoreactivity (autologous serum skin test, thyroid function and autoantibodies, antinuclear antibodies); screen for chronic infections (sed rate, aspartate aminotransferase [AST], *Helicobacter pylori* testing, stool for ova and parasites); exclude dental and ENT inflammatory foci.

Table 10.2 · Possible causes of chronic urticaria

Type	Cause	Eliciting factor[a]	Pathomechanism (MC activating signal)
Autoreactivity	Autoreactivity	Unknown	Circulating MC secretagogues
	Autoimmunity	Unknown	Anti-$Fc_{\varepsilon}RI$-AAb, anti-IgE-AAb
	Others	Unknown	Unknown
Chronic infection	Chronic infection	Unknown	Unknown[b]
Intolerance	Intolerance	Foods, drugs, others	Unknown
	Pseudoallergy	Pseudoallergens	Unknown[c]
	Others	Others	Unknown
Other causes	Type I allergy	Allergens	IgE and antigen via $Fc_{\varepsilon}RI$
	Internal disease	Unknown	Gammopathy
	Others	Unknown	Unknown
Idiopathic	Unknown	Unknown	Unknown

AAb = autoantibody; CU = chronic urticaria; MC = mast cell.
a Specific eliciting factors only; unspecific eliciting factors (e.g. stress) impact on disease activity of all CU subtypes.
b Potential candidates include: (1) pathogen-derived signals (e.g. toxins, LPS); (2) pathogen–host interaction (e.g. immune complexes, pathogen specific IgE); (3) host-derived signals (e.g. complement, neuropeptides).
c Potential mechanisms include activation by neuropeptides and/or complement of MCs that exhibit pseudoallergen-mediated reduction of activation thresholds.

- *Test for intolerance to food components:*
  - Pseudoallergen-free diet for 3 weeks.
  - Oral provocation testing in patients who have benefited from pseudoallergen-free diet. Requires hospitalization. Provocation tests are carried out either using capsules containing small amounts of suspected agents or foods that contain potentially relevant components such as those listed in Table 10.**3**.
- Exclude less common causes such as allergies (specific IgE, prick testing) and underlying internal diseases (systemic lupus erythematosus).

Table 10.3 · Possible food allergens

Dyes	Quinoline yellow, yellow-orange S, azorubin, amaranth, erythrosine, Ponceau 4R, patent blue, indigo carmine, brilliant black, ferric oxide red, cochineal, tartrazine
Preservatives	Sorbic acid, sodium benzoate, sodium metabisulfite, sodium nitrate
Antioxidants	Butyl hydroxyanisole (BHA), propyl gallate, butyl hydroxytoluol (BHT), tocopherol
Taste enhancers	Monosodium glutamate
Natural substances	Salicylic acid, biogenic amines, *p*-hydroxy benzoic acid esters, fragrances

► **Therapy:** The only real treatment is to find the underlying trigger. Nonsedating H1 antihistamines are first-line treatment; consider dosing them higher than recommended, alternating two or more agents and adding H2 antihistamines. Ketotifen and doxepin are also occasionally effective. Immunosuppressive drugs such as cyclosporine A and corticosteroids should not be chosen for long-term use because of unavoidable severe side effects.

Physical Urticaria

Physical urticarias are conditions in which one specific physical trigger is required to induce urticaria symptoms. Two or more forms of physical urticaria may be present in one patient, and patients with chronic idiopathic urticaria may also have physical urticaria. In some patients a combination of two or more physical triggers may be required to induce urticaria.

► **Dermographism:**
- *Definition:* The development of urticarial lesions when the skin is stroked or written on (Fig. 10.**2**); caused by shearing pressure applied to the skin, but the mechanisms of mast cell activation are unclear.
- *Diagnostic approach:* Write on the skin, using a tongue blade or reverse end of a pen. Standard is a 10 cm line. The reaction is read after 5–10 minutes and in 4–6 hours, as late reactions occasionally occur.
- *Therapy:* Nonsedating antihistamines; sometimes higher dosages are needed.

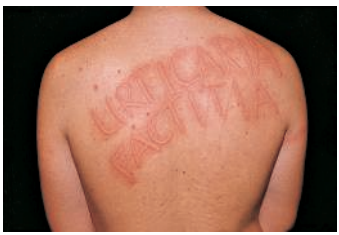


Fig. 10.**2** · Urticaria factitia, as written on the patient's back, is a synonym for dermographism.

► **Cold urticaria:**
- Hives are triggered by varying degrees of cold exposure. In some patients, only a slight drop in room temperature is sufficient; others require contact with ice cubes.
- *Diagnostic approach:* Apply 4 °C (ice cube, TEMPTest) for 5 minutes, reading after 10 minutes and after 2 hours if delayed reaction suspected Some forms can only be triggered by cold water bath or cold breeze; if available, place patient in cold chamber at 4 °C.
- Determine the threshold for cold urticaria (small glasses filled with water or TEMPTest at 4 °C, 8 °C, 12 °C, and 16 °C, applied consecutively starting with warmest to inner aspect of forearm for 5 minutes.

! ***Caution:*** Only carry out extensive cold testing when resuscitation facilities are available.

- *Laboratory:* Cold agglutinins, cryoglobulins, cryofibrinogen, borrelial serology.
- *Differential diagnosis*: Familial cold urticaria is a rare type of periodic fever inherited in an autosomal dominant manner featuring arthralgias, fevers, and vasculitis; intensely pruritic erythematous macules and sometimes hives are seen.

- *Therapy:*
  - Warn the patient about sudden exposure to cold (swimming, ice cream/cold drinks, cold i.v. infusions); jumping into a cool pool or lake can be fatal.
  - Oral antibiotics for 3 weeks (penicillin V 500 mg q.i.d. or doxycycline 100 mg b.i.d.) has about a 40% cure rate. The mechanism is unclear.
  - Careful conditioning with cold baths or showers may help, but must be continued indefinitely.
  - Nonsedating antihistamines; sometimes higher dosages are needed.

► **Solar urticaria:**
- Rarely, various wavelengths of UV or visible light may trigger urticaria. The cause remains unidentified in most cases.
- *Diagnostic approach:* Incremental increase in light (p. 49), using both UV light and visible light of various wavelengths.
- *Therapy:* Light avoidance or protection; light conditioning, nonsedating antihistamines; sometimes higher dosages are needed.

► **Other types:** Less frequent forms of physical urticaria include delayed pressure urticaria, heat contact urticaria, and vibratory urticaria/angioedema, which are diagnosed on the basis of provocation tests using the specific physical trigger (i.e. pressure, heat, vibration). As in other physical urticarias, the underlying mechanisms remain largely unknown, which limits therapeutic options to conditioning and nonsedating antihistamines.

Other Forms of Urticaria

This group includes urticarias that can be induced by triggers other than physical stimuli.

► **Cholinergic urticaria:**
- Triggered by an increase in body temperature (exercise, emotional stress, passive heat exposure).
- Tiny, transient, pruritic urticarial lesions appear promptly with increased temperature.

  ▶ ***Note:*** The skin findings are not typical of hives, so most patients simply describe an itchy rash, in contrast to other forms, where they say "I have hives."
- Cholinergic urticaria is often combined with other forms.
- *Diagnostic approach:* Physical activity (running stairs, stationary bicycle) or warm bath (40 °C); test is only valid when body temperature rises more than 0.5 °C (confirm with electronic thermometer).
- *Therapy.* An antihistamine with a strong cholinergic effect such as cetirizine should be used. Conditioning can be effective.

► **Contact urticaria:**
- Caused by a type I allergy to contact allergens or by an intolerance to substances that come in contact with the skin. Triggers include allergens as well as toxins, pseudoallergens, and mast cell activators (Table 10.**4**).
- *Diagnostic approach:* Prick and patch testing; reading after 20 minutes.

  ▶ ***Note:*** Patch testing for contact urticaria should be done separately from the usual batteries of patch tests. If the other patches are removed after 20 minutes, they may not re-adhere for the desired 24 or 48 hours.
- *Therapy:* Avoidance of the eliciting agent; nonsedating antihistamines.

► **Other forms:** Less frequent types of urticaria conditions include aquagenic urticaria (trigger: skin contact with water) and exercise-induced urticaria/anaphylaxis (trigger: physical exercise). Diagnosis is made with provocation tests. Once again, nonsedating antihistamines are the treatment of choice.

  ▶ ***Note:*** Sometimes antihistamines can be taken 1–2 hours before the anticipated exposure or activity, with good effect.

Table 10.4 · Causes and triggers of contact urticaria

Cause	Common triggers
Allergic reaction (type I allergen)	Plants (latex, cornmeal, pollen, mahogany, teak, roses, wheat flour) Animal proteins (fish, milk, meat, silk; saliva, dander, blood) Vegetables, spices, and fruits (potato peels, pitted fruits, oranges) Medications (bacitracin, cephalosporins, chloramine, chlorhexidine) Industrial materials (ammonia, formaldehyde, acrylic acid)
Nonallergic reaction (toxin, pseudoallergen, mast cell secretagogue)	Food preservatives (e.g. benzoic acid, sorbic acid) Fragrances (cinnamic acid, balsam of Peru) Topical antibiotics (bacitracin, neomycin) Nettles, insect stings, caterpillar hairs, jellyfish

Associated Disorders

- There are several syndromes in which urticaria is a key component:
  - *Muckle–Wells syndrome:* Urticaria, amyloidosis, and deafness, inherited in autosomal dominant manner.
  - *Schnitzler syndrome:* Urticaria plus gammopathy.
  - *Gleich syndrome:* Urticaria, angioedema and eosinophilia.
  - *Wells' syndrome:* Eosinophilic cellulitis with flame figures; sometimes urticaria. Often related to arthropod assault.

10.3 Angioedema

- **Synonyms:** Angioneurotic edema, Quincke edema.
- **Definition:** Angioedema is the deep dermal and subcutaneous equivalent of urticaria, with increased vascular permeability and swelling.
- **Pathogenesis:** Common angioedema is caused by the same spectrum of factors as urticaria. Two common triggers are Hymenoptera stings and angiotensin converting enzyme (ACE) inhibitors. A rare form related to abnormalities in complement metabolism is discussed below. In addition, hereditary vibratory angioedema has been described, as well as rare cases of acquired vibratory angioedema.
- **Clinical features:** Angioedema can present in any site, but typically involves the face and neck. Many patients have massive facial swelling. Involvement of the tongue or of the neck can lead to airway obstruction. In addition, angioedema is far more likely to be accompanied by anaphylaxis than is urticaria. Thus angioedema is a potentially life-threatening situation. Many patients have accompanying urticaria, some do not. Pruritus is uncommon; some patients complain of burning.
- **Differential diagnosis:** Infections (cellulitis), trauma, superior vena cava syndrome, subcutaneous emphysema, Melkersson–Rosenthal syndrome.
- **Therapy:** Most patients are admitted because of the risk of airway obstruction and anaphylaxis. Treatment consists of antihistamines and usually i.v. corticosteroids with consideration for bronchodilators.

Hereditary Angioedema

- **Synonym:** Hereditary angioneurotic edema (HANE).
- **MIM code:** 106100.
- **Definition:** Defect in C1-esterase inhibitor, leading to unchecked complement activation and recurrent subcutaneous and mucosal swelling.
- **Pathogenesis:**
  - *Type I* (85%): reduced plasma C1-esterase levels (< 30% of normal).
  - *Type II* (10%): normal levels of functionally defective inhibitor.
  - *Type III* (5%): inhibitor inactivated by autoantibodies.
  - Excessive bradykinin release is the main cause of the angioedema.
- **Clinical features:** Recurrent swelling primarily in face and extremities. No urticaria. Nonpruritic. Rarely, transient or slight erythema before attack. Laryngeal edema can be life-threatening; gastrointestinal wall swelling is rare cause of acute abdomen.
- **Diagnostic approach:**
  - ***Note:*** It is crucial to establish correct diagnosis in patient and family, because of the possibility of sudden death.
  - Measure C3, C4; C3 normal, C4 not identifiable; can use to monitor. Identify type of esterase defect in cooperation with immunology laboratory.
- **Differential diagnosis:**
  - Urticaria with angioedema, intolerance reactions (foods, drugs), physical angioedema (pressure, vibration).
  - Acquired angioedema with underlying hematologic disorder, usually monoclonal gammopathy (*Caldwell syndrome*) or systemic lupus erythematosus and in capillary leak syndrome.
  - Gleich syndrome (angioedema with urticaria and eosinophilia).
- **Therapy:**
  - *Acute attack*: C1-esterase inhibitor concentrate; if not available, 500–2000 mL fresh or fresh frozen plasma (p. 674).
  - ***Note:*** Systemic corticosteroids, antihistamines, and norepinephrine have no effect.
  - *Prophylaxis:* Androgens (Danazol 200–600 mg daily); adjust based on clinical findings and inhibitor levels. C4 does not need to stabilize.

10.4 Food Allergies

- **Definition:** Immunologic reaction to foodstuff producing signs and symptoms of disease.
- **Clinical features:** Urticaria, anaphylaxis, allergic asthma, intestinal colic, nausea, vomiting, gas, diarrhea, vasculitis, arthralgias, hematogenous contact dermatitis, and oral allergy syndrome (OAS) may all be seen. In some cases atopic dermatitis can be provoked by foodstuffs; careful allergic testing and documentation is required.
- **Diagnostic approach:**
  - *History:*
    - Careful history; have patient keep detailed diary of what they eat.
    - Atopy—history of pollen allergies?
    - Cross-reaction between birch and hazelnut pollen with hazelnuts (filberts), walnuts, and fruits (apples, cherries, kiwi, peaches, and pears).
    - Cross-reaction between mugwort pollen and many spices and herbs (anis, basil, caraway, carrots, celery root, chamomile, chives, coriander, dill, fennel

seeds and leaves, legumes, lemon balm, lovage, paprika, pepper, peppermint, sage, soy, thyme, tumeric).
  - *Protein allergies:* Fish, shellfish (intolerance reactions to intrinsic histamine also possible), chicken eggs (white or yolk), milk (casein, lactalbumin, β-lactoglobulin); when gastrointestinal signs and symptoms present, always think of lactose intolerance.
  - Drug reactions, for example aspirin or penicillin.
- *Skin testing:*
  - Raw foodstuffs in scratch test; standardized allergen extracts (egg white, foodstuffs, spices, preservatives) in prick test, followed by intracutaneous test.
  - If the prick test reaction is as large as the histamine control, strong suggestion of sensitization.
  - If a hematogenous contact dermatitis or cross reaction is suspected in a patient where the history suggests allergic contact dermatitis, then patch testing.
- *IgE levels:* If the history strongly suggests a food allergy, then draw serum for IgE testing before skin testing. Always determine total serum IgE as well as specific IgE levels against suspected substances to be more precise. Basophil degranulation assay is another possibility in this group.
- *Provocation testing:*
  - Goal is to confirm a food reaction (allergic or toxic) following an elimination diet.
  - Foods should be tested in a placebo-controlled, double-blind setting. When testing children, the parents must also be blinded (proven critical in atopic dermatitis). Use results of history, skin testing, and IgE to determine which foods are tested.

  Caution: Provocation testing should be done on in-patients in a facility where resuscitation is immediately available.

► **Differential diagnosis:**
- *Enzyme deficiencies: Lactase* (inherited, secondary), galactokinase, galactose-1-phosphate-uridyltransferase, phenylalanine 4-monooxygenase (*phenylketonuria*).
- *Vasoactive amines:*
  - *Histamine:* Dark fish meat (especially canned mackerel), sauerkraut, sausage, wine.
  - *Tyramine:* Cheese, yeast, herrings.
  - *Phenylethylamine:* Chocolate.
  - *Serotonin:* Bananas.
- *Pseudoallergic reactions:* Occur with both foodstuffs and additives; for example, tartrazine and naturally occurring salicylic acid may elicit reactions.
- *Reactions to impurities:* Foods contaminated with molds, bacteria, or chemicals from processing.

► **Therapy:**
- *Avoidance:* As far as possible.
- *Diet counseling:* Advice regarding hidden allergens, how to maintain balanced diet despite intolerance.
- *Diet manipulation:* In the case of pseudoallergy, elimination diet, followed by re-introduction of new food every 3 days.
- *Allergy emergency set:* Have patients with type I allergies carry an anaphylaxis kit containing an epinephrine autoinjection, solutions of antihistamines, and corticosteroids; issue an allergy pass.

- *Symptomatic therapy:*
  - Antihistamines (p. 618).
  - Cromolyn (p. 620) in patients with gastrointestinal signs and symptoms; poor absorption, only helps in 30% of cases.
  - Oral hyposensitization is only suggested in cases of confirmed type I allergy to milk or eggs. The response rate is lower than for pollen allergies. The dosage must be increased daily.
  - If there is a cross-reaction between foodstuffs and classic pollen allergies, hyposensitization against the pollens helps in up to 60% of patients.

10.5 Other Allergic Diseases

► **Overview:** In Germany, most dermatologists are trained in allergy, so they routinely do tests to identify airborne allergens causing allergic rhinitis and allergic conjunctivitis, and then offer hyposensitization in their offices. Some have more complex allergy practices dealing with food allergies and environmental diseases. Allergy testing may also help identify possible causes of drug reactions, as discussed in Chapter 11.

► **Hymenoptera stings:**

- About 5% of the population is allergic to bee, wasp, or hornet venom. Typically, after repeated stings patients develop a more severe reaction with marked local swelling or angioedema; many progress to anaphylaxis. The severity of the reaction is assessed by the history, as shown in Table 10.**5**.
- The diagnosis must be confirmed with skin testing (in a carefully controlled setting) and RAST. Hyposensitization is complex, as discussed below.

► ***Note:*** All patients with hypersensitivity to Hymenoptera venom should be given an emergency kit to carry at all times, containing epinephrine, antihistamines, and corticosteroids.

Table 10.5 · **Classification of Hymenoptera toxin hypersensitivity**

Grade	Signs and symptoms
0	Strong local reaction (> 10 cm, duration > 24 hours)
I	Generalized urticaria, pruritus, nausea
II	Grade I + angioedema, vomiting, diarrhea, dizziness, anxiety
III	Grade II + shortness of breath, stridor, dyspnea, dysarthria, hoarseness, confusion
IV	Grade III + hypotension, collapse, loss of consciousness, incontinence, cyanosis, cardiorespiratory arrest

10.6 Hyposensitization

► **Overview:** An antigen responsible for allergic rhinitis, allergic asthma, or Hymenoptera sensitivity is injected in increasing amounts with the goal of reducing the IgE-mediated hypersensitivity so that on subsequent exposures the patient remains symptom-free or reacts with less severe findings.

- **Mechanism of action:** The effectiveness and specify are well established. The mechanism of action remains unclear. Possibilities including blocking IgG antibodies, auto-anti-idiotype antibodies, an increase in specific suppressor T cells, and reduction of basophil function.
- **Indications and contraindications:**
  - ***Note:*** The indications for hyposensitization are always based on history, skin testing, and RAST.
  - *Indications:*
    - Allergic asthma.
    - Allergic rhinitis.
    - Hymenoptera venom hypersensitivity.
    - *Atopic dermatitis:* Hyposensitization is only worthwhile if disease flares are clearly associated with one or a few seasonal allergens.
  - *Contraindications:*
    - *Absolute:* Use of β-blockers or ACE inhibitors, acute infections, severe chronic inflammatory diseases, chronic pulmonary disease, multiple sclerosis, pregnancy, immune defects.
    - *Relative:* Age < 5 years, immunizations (leave 1–2 week window), malignancy, hyperthyroidism, cardiovascular disease, epilepsy, active tuberculosis, autoimmune diseases.
- **Hyposensitization against inhaled allergens:**
  - *Available agents:* A wide range of allergen extracts is available, in the from of aqueous solutions, semi-depot solutions, depot solutions, or allergoid solutions. The choice of the agent depends on the allergen spectrum.
  - The extracts are available in various concentrations with the proportions 1:10:100. Start with the weakest concentration and depending on tolerability, double the dosage every 7 days. Once 0.8–1.0 mL is reached, advance to the next concentration using 0.1–0.2 mL. The package instructions on increasing the dosage are only rough guidelines. Each hyposensitization program must be individually adjusted, depending on how the patient reacts to the injections.
  - The route of administration is subcutaneous. The physician must administer the injection. At each visit, document if the patient had a local or systemic reaction to the previous injection.
  - ***Caution:*** After each injection, the patient must wait 30 minutes because of the risks of severe anaphylactic reactions, especially with inadvertent intravascular injection.
  - Once the maximum dose is reached, it is then administered every 4–8 weeks.
  - Seasonal allergens can be given until just before the onset of the season and then continued as:
    - *Co-seasonal hyposensitization*: The maximum dose is reduced by two thirds and administered monthly. After the season, the dose is once again increased in weekly increments.
    - *Pre-seasonal hyposensitization*: No injections during the season; start from scratch again in the fall.
  - Total duration of treatment is usually 3 years.
- **Hyposensitization against Hymenoptera venom:** Once again, a wide range of products is available. Usually aqueous solution is used. Most patients are admitted to hospital for rush hyposensitization, which is then continued on an outpatient basis with depot products. The duration of treatment is 3–5 years. Specialized texts or local allergy centers should be consulted for exact details.
- **Anaphylactic reactions:** Hyposensitization can only be carried out in a clinic or practice where emergency resuscitation measures are available and where the physicians and office personnel receive routine training and testing in resuscita-

tion. Treatment of anaphylaxis is discussed in detail (p. 673). The patient must be rapidly assessed and then treated according to Table 47.**1**.

► **Common errors:**

- Inaccurate or incomplete diagnosis.
- Incorrect assess of indications, usually failing to incorporate clinical features and treating based on prick testing or RAST results.
- Choosing the wrong extract.
- Mistakes in advancing dose.
- Terminating injections too soon.

11 Drug Reactions

11.1 Overview

- **Classification:** Drug reactions can be classified in many ways. One useful approach is to separate predictable reactions occurring in normal patients from unpredictable reactions occurring in susceptible patients, as proposed by Patterson and colleagues.
  - *Predictable adverse reactions:*
    - Overdosage (wrong dosage or defect in drug metabolism).
    - Side effects (sleepiness from antihistamines).
    - Indirect effects (antibiotics change normal flora).
    - Drug interactions (alter metabolism of drugs; most commonly the cytochrome P-450 system).
  - *Unpredictable adverse reactions:*
    - Intolerance (normal side effect occurs at low dose).
    - Allergic reaction (drug allergy or hypersensitivity; immunologic reaction to drug; requires previous exposure or cross-reaction).
    - Pseudoallergic reaction (nonimmunologic activation of mast cells).
    - Idiosyncratic reaction (unexplained reaction, not related to mechanism of action, without known or suspected immunologic mechanism).

  Note: Although we will concentrate on cutaneous drug reactions, remember that every organ system can be affected.
- **Epidemiology:** Many drug reactions start with skin findings. Thus, the skin can serve as an early warning for severe, potentially life-threatening reactions. At least 20% of patients hospitalized for 10 days or more develop some form of drug reaction.
  - *Risk factors* for cutaneous drug reactions include:
    - *Patient factors:* age, sex, atopic predisposition, immune status.
    - *Underlying diseases.*
    - *Drug-related:* Dose, route of administration, number of drugs, drug interactions, drug metabolism.
    - *Genetic factors:* Pharmacogenetics is beyond our scope, but every individual has an almost unique array of enzymes that may influence how they react to medications.

  Note: The most common types of drug reactions are macular and maculopapular exanthems (40%), along with urticaria and angioedema (37%). Fixed drug eruption (6%) and erythema multiforme/toxic epidermal necrolysis (5%) are the only other frequently seen patterns; all others account for 0–3%, but may be clinically distinctive.
- **Pathogenesis:** In some instances, a drug reaction can be clearly assigned to an immunologic reaction type, although more often the mechanisms are not understood.
  - *Type I:* Urticaria, angioedema, anaphylaxis.
  - *Type II:* Thrombocytopenic purpura.
  - *Type III:* Leukocytoclastic vasculitis, serum sickness.
  - *Type IV:* Allergic contact dermatitis, some exanthems, photoallergic reactions.
  - The mechanisms for the common maculopapular and erythema multiforme–like drug reactions are unknown, as is the reason why a fixed drug eruption recurs in exactly the same site.
  - Pseudoallergic reactions (analgesics, contrast media, local anesthetics) are also common.

- **Clinical features:** There are two important rules:
  - Almost every drug can cause almost every type of reaction. Clinically, one must learn which reactions are most likely to produce certain findings. The various drug reactions are covered below in detail.
  - 80% of allergic and pseudoallergic drug reactions are caused by β-lactam antibiotics, aspirin, NSAIDs, and sulfonamides.
- **Diagnostic approach:**
  - *History:*
    - The history is the most essential tool in diagnosing a drug reaction. Any exanthem in a hospitalized adult should be suspected of being a drug reaction. Obtain a complete list of all drugs; for in-patients, the chart offers complete documentation. For outpatients, even more effort is required. Ask about over-the-counter medications (laxatives, sleeping pills, herbal medications). Explore previous possible drug reactions and determine whether or not the current medications have been taken previously.
    - Determine the correct time course. If a patient is exposed to a medication for the first time, an allergic reaction cannot occur within the first 4–8 days. Re-exposure, cross-reactions, or pseudoallergic reactions all occur more rapidly, sometimes almost instantaneously (anaphylaxis).
    - *Ask about associated signs and symptoms*, such as fever, chills, diarrhea, or arthralgias.
    - *Does the patient have a known contact allergy to para-compounds?* This could explain a reaction to sulfonamides, oral hypoglycemic agents, thiazide diuretics, local anesthetics of the ester-caine type. Similarly, ethylene diamine sensitivity can explain sensitivity to theophylline and related products.
    - *Have other family members had unusual drug reactions (for example, drug induced-lupus erythematosus)?*
    - *How was the drug administered?* The likelihood of sensitization is topical > oral > intramuscular > intravenous. The best example is previous use of topical antihistamines sensitizing patient to oral agents.
    - *Does the patient have concurrent illnesses?* HIV/AIDS predisposes to sulfamethoxazole/trimethoprim reactions, while infectious mononucleosis is associated with a high incidence of reactions to ampicillin.
  - **Allergy testing:** Patch, prick, scratch, and intracutaneous tests can all be used. In addition, oral exposition may be helpful but must be used carefully.
    - *Prick testing*: Useful when type I reaction has occurred, especially with agents of high molecular weight such as antisera, insulin, vaccines, and latex. Also helpful in evaluating IgE-mediated reactions to β-lactam antibiotics and sometimes other agents.
    - *Patch testing*: Patch testing is essential if allergic contact dermatitis is suspected, but may also be helpful if a drug has caused a dermatitic delayed reaction (type IV). Examples where patch testing has been helpful include chloramphenicol, diethyl barbiturate, ethylene diamine, gentamicin, mafenide, methimazole, neomycin, parabens, paraphenylenediamine, phenacetin, propylphenazone, thimerosal, and sulfamethoxazole/trimethoprim.
    - *Interpretation*: Such tests are read just like any other allergy test. The likelihood of reactions to the test solution or preservatives when employed intracutaneous tests is considerable. Anything other than a clearly positive reaction must be viewed skeptically.
    - *Photopatch testing*: If a photoallergic reaction is suspected (p. 45).
  - *In-vitro diagnosis:* The possibilities for in-vitro diagnosis are limited, even though a rapid method of determining drug sensitivities is a great priority. One

explanation for the difficulties of skin or in-vitro testing is that many drug reactions are elicited by drug metabolites.
  - Specific IgE levels can be measured for penicillin (major determinant), insulin, latex, gold, muscle relaxants, and sulfamethoxazole/trimethoprim. If positive, such tests are helpful, but a negative test does not exclude a reaction.
  - Specific IgG and IgM antibodies may be useful for immune thrombocytopenia and purpura (type II).
  - Coombs test is useful for drug-induced hemolysis, but rarely relevant in dermatologic disorders.
  - Complement activation and immune complex assays may be helpful in evaluating vasculitis and serum sickness (type III).
  - Lymphocyte transformation test has long been endorsed for determining drug sensitivities but is fraught with false-positive results and remains experimental.
- *Discontinuation:* Sometimes the diagnosis is made when the suspected agent is stopped and the skin disorder clears promptly. All drugs that are not essential should be stopped. Essential drugs should be replaced as far as possible with agents of a different chemical class. In some instances, one must treat the drug reaction (for example, urticaria with antihistamines) because the medication is required.
- *Provocation testing:* The patient can be challenged with the drug in question. This approach is potentially dangerous, and should be used only on in-patients and only by experienced physicians. Resuscitation facilities must be available for acute reactions, but the risk of severe chronic reactions is more difficult to estimate. A patient with erythema multiforme who is challenged could develop toxic epidermal necrolysis the next time—a potentially fatal disease with no effective therapy.

Caution: Never simply suggest that the patient try a pill!

► **Special cases:**
- *Penicillin:* This is a common allergen, but often still required in life-threatening situations. For these reasons, the ability to document penicillin allergy has been refined. Care is required, as small amounts of penicillin can elicit severe reactions and penicillin is a potent topical sensitizer. We employ the following stepwise scheme:
  - *IgE*: Specific IgE antibodies against the major allergenic determinants (penicilloyl G [benzylpenicillin], penicilloyl V [phenoxymethylpenicillin]) can be measured.
  - *Prick testing:* Use ampicillin, benzylpenicillin, benzyl penicilloic acid, cephalothin, methicillin, penicillin polylysine, as well as the penicillin taken by patient.
- *Local anesthetics:* There are two major groups of local "caine" anesthetics:
  - The *esters* include benzocaine and procaine; they cross react with *para*-substituted compounds and can lead to severe reactions.
  - The *amides*, including lidocaine, mepivacaine, and bupivacaine, are most widely used, and almost never cause allergic reactions.
  - More likely causes of allergic reactions are preservatives; single-dose vials are available without preservatives.
  - *Pseudoallergies* are more common. Systemic pharmacological effects of either the local anesthetic or epinephrine may be misinterpreted. Exceeding the maximum dose of the local anesthetic can result in cardiotoxicity. Hyperventilation and fainting (vasovagal syncope) are also often interpreted as allergies.

  - *Procedure:* To exclude a rare type I reaction, the recommended test sequence is prick and then intracutaneous testing, followed by a subcutaneous therapeutic dose as an inpatient. Use of physiologic saline controls is required.
  - If no reaction occurs, one can be assured that larger injections will not cause problems either.
- *Contrast media:* Patients who experience an anaphylactic reaction to contrast media have an increased risk of having a reaction on re-exposure. Less ionic solutions lower the risk somewhat. Most reactions are not allergic, so prick testing is usually negative. We still recommend it, to exclude the rare type I reactions. Then one can assume a pseudoallergy and suggest using alternative products that are less like to trigger reactions (although perhaps more expensive), and pretreatment with intravenous corticosteroids and antihistamines.

► **Therapy:** In most instances, discontinuation of the drug, topical antipruritic measures (polidocanol lotion), and systemic antihistamines suffice. The major area of concern is systemic corticosteroids, with recommendations ranging from "always use" to "never use." In our view, prompt administration early in suspected type I reactions is likely to help. Their use is discussed with some of the individual diseases below.

11.2 Common Reactions

Maculopapular Exanthem

► Most common reaction (Fig. 11.**1**); usual referral reads "rule out drug reaction." Main differential diagnostic consideration is viral exanthem or on occasion acute exanthem such as guttae psoriasis or pityriasis rosea.

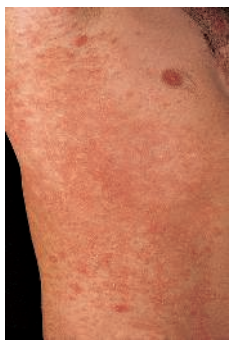


Fig. 11.**1** · Maculopapular reaction to ampicillin.

► **Drugs commonly responsible:** Ampicillin, amoxicillin, aminoglycosides, allopurinol, barbiturates, benzodiazepines, carbamazepine, co-trimoxazole, gold salts, penicillin, phenytoin, piroxicam.

► Patients with allergic contact dermatitis to a topical agent such as an antihistamine may react to the systemic administration of the agent with a widespread erythematous or urticaria-like eruption, known as *hematogenous contact dermatitis*. The extreme variant of this reaction is perhaps the *baboon syndrome*

where patients have prominent flexural and genital erythema mimicking that of mandrils or baboons.

Urticaria (p. 169)

- **Drugs commonly responsible:** Penicillin and related antibiotics, aspirin, captopril, levamisole, NSAIDs, sulfonamides, insulin (Fig. 11.**2**), radiography contrast media.

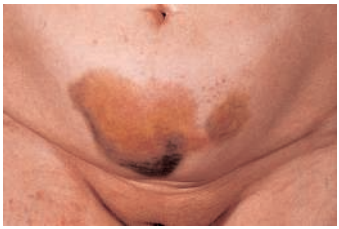


Fig. 11.**2** · Type I insulin allergy with hemorrhagic periphery.

Angioedema (p. 173)

- **Drugs commonly responsible:** ACE inhibitors.

Fixed Drug Eruption

- **Definition:** Cutaneous drug reaction that recurs at exactly the same site with repeated exposure to the agent.
- **Pathogenesis:** A mystery—totally unclear why the reaction remains so localized and recurs at same site.
  - *Drugs commonly responsible:* Ampicillin, aspirin, barbiturates, dapsone, metronidazole, NSAIDS, oral contraceptives, phenolphthalein, phenytoin, quinine, sulfonamides, tetracyclines.
- **Clinical features:** Typically red-brown patch or plaque; occasionally may be bullous (Fig. 11.**3**). Most common sites are genitalia, palms, and soles, as well as mucosa. Lesions typically 5–10 cm in diameter but can be larger; often multiple. Start as edematous papule or plaque; later becomes darker. Frequently resolves with postinflammatory hyperpigmentation. Very uncommon in children.
  - ***Note:*** When confronted with hyperpigmented macule on genitalia, always think of fixed drug eruption.

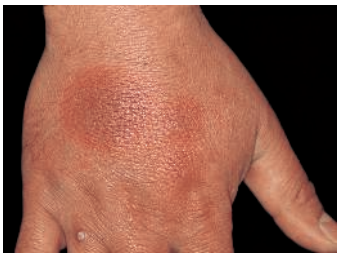


Fig. 11.**3** · Fixed drug reaction caused by barbiturates.

- Controversial variant is *diffuse bullous fixed drug eruption*, which is widespread; should only be diagnosed in patients with documented history of ordinary fixed drug eruption.

► **Diagnostic approach:** Patch testing within the site of the fixed drug eruption is helpful; it may be positive in 50% of cases.
► **Differential diagnosis:** Non-drug-related causes of similar lesions include fruits, tomatoes, UV light, additives and phytotoxins (shitake mushrooms).
► ***Note:*** The only two diseases that frequently come back in the same site are herpes simplex virus and fixed drug eruption.
► **Therapy:** Avoidance of triggering agent; topical corticosteroids may speed resolution.

11.3 Severe Skin Reactions

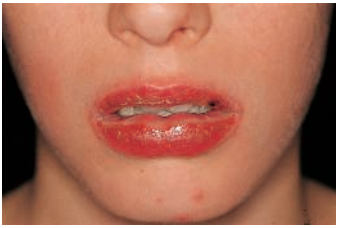
Erythema Multiforme and Erythema Multiforme-like Lesions

► Most erythema multiforme is caused by herpes simplex virus, especially if recurrent (p. 59, 281). The classical clinical findings are iris or target lesions, most often on the distal limbs. Lesions caused by mycoplasma or especially drugs are more often on the trunk and less like to have a target pattern. We prefer the term *erythema multiforme–like* for such lesions, which carry the risk of developing into severe skin reactions as discussed below.

Stevens–Johnson Syndrome (SJS)

► **Definition:** Combination of erythema multiforme with mucosal lesions as well as systemic signs and symptoms.
► **Epidemiology:** < 2/1 000 000 yearly.
► **Clinical features:**
- Patients almost invariably have prodrome with fever, malaise, or arthralgias.
- Abrupt development of erythema multiforme.
- *Mucosal involvement* (Fig. 11.**4 a**):
  - *Mouth* (100%): Erosions, hemorrhage and crusts on lips, and erosions in mouth covered by necrotic white pseudomembrane.
  - *Eyes* (70–90%): Erosive conjunctivitis, can lead to scarring.
  - *Genitalia* (60–70%): Painful erosions.
- When mycoplasma is trigger, pulmonary involvement is possible (20%).

► **Histology:** Identical to erythema multiforme.
► **Diagnostic approach:** Clinical appearance, search for drugs (most common are NSAIDs and antibiotics) and mycoplasma.
► **Differential diagnosis:** Same as erythema multiforme; ocular lesions can be confused with cicatricial pemphigoid.
► **Therapy:**
- Short burst of systemic corticosteroids helpful in many cases but two problems:
  - Exclude or treat underlying infection, which could be worsened by immunosuppression.
  - Some studies suggest corticosteroids not helpful for toxic epidermal necrolysis (see below).
- Routine topical care: disinfectant mouth washes, antibiotic or corticosteroid eye drops (after ophthalmologic consultation).



a

b

Fig. 11.**4** · **a** Stevens–Johnson syndrome, labial lesions. **b** Toxic epidermal necrolysis.

Toxic Epidermal Necrolysis (TEN)

- **Synonym:** Lyell syndrome.
- **Definition:** Severe life-threatening disorder with generalized loss of epidermis and mucosa.
- **Epidemiology:** < 2/1 000 000 yearly.
- **Pathogenesis:** The trigger is always drugs; there is a cytotoxic T-cell reaction with apoptosis of keratinocytes mediated by Fas-Fas ligand.
  - *Responsible drugs include:*
    - *Taken for short period of time:* Sulfamethoxazole/trimethoprim, sulfonamides, aminopenicillins, quinolones, cephalosporins, corticosteroids (surprisingly).
    - *Taken for longer periods of time:* Carbamazepine, phenytoin, phenobarbital, valproic acid, lamotrigine, NSAIDs (especially oxicam types), allopurinol.
- **Classification:** The German Center for Documenting Severe Skin Reactions uses the following grouping: erythema multiforme, SJS (< 10% of body area involved), SJS–TEN overlap (10–30% involvement) and TEN (< 30% involvement) (Table 11.**1**).

Table 11.1 · **Erythema multiforme and severe skin reactions**

Disease	Trigger	% Skin involved	Typical lesions	Location
Erythema multiforme	HSV	< 2	Target lesions	Distal limbs
SJS	Drugs ± HSV	< 10	Mucosal erosions, crusts	Mucosal surfaces
SJS–TEN overlaps	Drugs	10–30	Mucosal lesions, target-like lesions on trunk	Trunk, extremities
TEN	Drugs	> 30	Diffuse erythema ± macules	Entire skin
SSSS	*Staphylococcus aureus* infection with exfoliation	Not defined; usually > 30	Diffuse skin loss	Entire skin

HSV = herpes simplex virus; SJS = Stevens–Johnson syndrome; SSSS = staphylococcal scalded skin syndrome; TEN = toxic epidermal necrolysis.

- **Clinical features:**
  - Prodrome depends on underlying disease and triggering drug.
  - Sudden onset of either diffuse maculae (erythema multiforme–like drug reaction) or diffuse erythema without maculae. Then prompt progression towards widespread erythema and peeling of skin (Fig. 11.**4b**). Skin lies in sheets and folds on the bedding. Extensive mucosal erosions. Possible loss of hair and nails, as well as extensive postinflammatory hypopigmentation.
  - Multiple systemic programs because of fluid and protein loss, difficulties in temperature regulation, fever, leukocytosis, and risk of secondary infections.
  - Fatal in 10–30% of cases.
- **Histology:** Diffuse full-thickness epidermal necrosis with surprisingly little dermal change; stark contrast to staphylococcal scalded skin syndrome, which has only loss of stratum corneum.
- **Diagnostic approach:** Clinical picture, skin biopsy from erythematous noneroded area. Granulocytopenia for more than 5 days is unfavorable sign.
- **Differential diagnosis:** Depending on severity, SJS and overlap syndromes; staphylococcal scalded skin syndrome has different histology and usually affects children; severe burn (history).
- **Therapy:** (p. 674).
  - ***Caution:*** The outlook for TEN is grim and the therapy is controversial. Find out about local guidelines and follow them. The best example is corticosteroids, which are routinely used in some countries and totally contraindicated in others.
  - The mainstay is excellent burn care, ideally in a burn center, with careful attention to electrolyte balance, topical disinfection, and prompt treatment of secondary infections.
  - Systemic corticosteroids, if employed, should be used early to attempt to abort the immunologic reaction. Later in the course, they probably increase risk of infection and slow healing. Dosages in the range of 80–120 mg prednisolone daily have been suggested.
  - Intravenous immunoglobulins are promising and should be employed in severe cases.
  - Ophthalmologic monitoring is essential, as risk of scarring and blindness is significant.

11.4 Uncommon Reactions

- **Acral erythema:** Painful symmetrical erythema of the palms and soles, caused by a number of chemotherapy regimens. Appears days to weeks after treatment. More likely in drugs that are excreted in eccrine sweat with direct toxic effect. Self-limited and not a contraindication to further therapy.
  - *Drugs commonly responsible:* 5-Fluorouracil, doxorubicin, cytarabine, methotrexate.
- **Acneiform lesions:** Papulopustular eruption, usually without comedones, different from acne because of sudden onset and unusual distribution.
  - *Drugs commonly responsible:* Androgens (including danazol, body-building compounds), ACTH, cetuximab (EGFR inhibitor), corticosteroids, oral contraceptives (especially progesterone dominant), cyclosporine, halogenated compounds, lithium (p. 532).
- **Acute generalized exanthematous pustulosis:** Uncommon pustular eruption usually caused by drugs. Typically small nonfollicular pustules on erythematous

background appear suddenly, sometimes associated with fever and neutrophilia. Onset usually abrupt, within 24 hours of drug exposure.
- *Drugs commonly responsible:* Penicillin, macrolide antibiotics.
- Patch testing is positive in up to 80% of cases.

► **Allergic contact dermatitis** (p. 196):
▶ ***Note:*** Don't forget that topical medications can cause allergies.
- *Drugs commonly responsible:* Antihistamines, benzocaine, neomycin, penicillin (so common as to limit topical use), sulfonamides.

► **Bullous reactions** (p. 230):
- *Drugs commonly responsible:* Vancomycin (IgA pemphigus), penicillamine (bullous pemphigoid, pemphigus foliaceus, pemphigus vulgaris).

► **Erythema nodosum** (p. 540):
- *Drugs commonly responsible:* Oral contraceptives, antibiotics, amiodarone, hypoglycemic agents, NSAIDs, sulfonamides.

► **Erythroderma** (p. 282):
- *Drugs commonly responsible:* Barbiturates, captopril, carbamazepine, cimetidine, NSAIDs, furosemide, sulfonamides, thiazides.

► **Hyperpigmentation** (p. 372):
- *Drugs commonly responsible:* ACTH, amiodarone, antimalarials, arsenic, chlorpromazine, estrogens, minocycline, phenytoin, phenothiazine, psoralens (with UV); chemotherapy agents (busulfan, 5-fluorouracil, cyclophosphamide).

► **Hypertrichosis** (p. 515):
- *Drugs commonly responsible:* Androgens, cyclosporine, minoxidil, phenytoin are most common; others include diazoxide, streptomycin, corticosteroids, penicillamine, psoralens.

► **Lichen planus-like eruptions** (p. 286): Many drug eruptions have a lichenoid histologic pattern but few clinically mimic lichen planus.
- *Drugs commonly responsible:* β-Blockers, gold salts, developing solutions for color film.

► **Lupus erythematosus** (p. 212):
- *Drugs commonly responsible:* Hydralazine, procainamide are most common; also isoniazid, minocycline and biologicals.

► **Photoallergic and phototoxic reactions:** There is considerable overlap between these two reactions and the lists of causative agents are often confusing (p. 297).
- *Photoallergic reaction:*
  - *Drugs commonly responsible:* Benzodiazepines, griseofulvin, nalidixic acid, NSAIDs, phenothiazines, sulfonamides, sulfonylureas, thiazides, triacetyldiphenylisatin (laxative).
- *Phototoxic reaction:*
  - *Drugs commonly responsible:* Amiodarone, furosemide, nalidixic acid, NSAIDs (especially piroxicam, carprofen, diclofenac), psoralens, phenothiazines, tetracyclines (especially doxycycline).

► **Psoriasiform eruption:**
- *Drugs commonly responsible:* ACE antagonists, β-blockers, antimalarials, gold, interferons, lithium, some oral contraceptives.

▶ ***Note:*** The clinical question is always if an underlying psoriasis was triggered, if a previously inapparent psoriasis was uncovered, or if the maculopapular eruption simply resembles psoriasis but has no biological connection. There are often medicolegal implications, so all statements should be worded carefully and documented well. Look for evidence of other signs of psoriasis (nails, gluteal cleft, scalp, retroauricular region, joints) and take detailed personal and family history.

- **Purpura** (p. 245): May be divided into thrombocytopenic purpura and nonthrombocytopenic purpura.
  - In *thrombocytopenic purpura*, antibodies may be formed against a complex of the medication and plasma proteins, but then be capable of attacking platelets (innocent bystander theory). Because the patient is thrombocytopenic, involvement of other organs may be seen, such as hematuria, hemoptysis, or gastrointestinal bleeding.
    - *Drugs commonly responsible:* Heparin, co-trimoxazole, gold salts, quinidine, quinine, sulfonamides. Heparin is so widely used that it is responsible for the bulk of clinical thrombocytopenia and thus purpura, with an incidence of around 5%. Type I heparin-induced thrombocytopenia (HIT) occurs with 1–2 days and is not serious, but type II HIT is life threatening with paradoxical thromboses. Use of low molecular weight heparin greatly reduces risk.
  - In *nonthrombocytopenic purpura*, there are overlaps with progressive pigmented purpura (p. 247) and the entire picture is less clear. Excluding heparin, the same group of agents are implicated, with the addition of barbiturates, carbromal, allopurinol (Fig. 11.**5**) meprobamate, and iodides.
- **Serum sickness:** The prototypical type III reaction, a hypersensitivity response to foreign proteins featuring fever, urticaria, arthralgias, edema, and lymphadenopathy. It is caused by deposition of circulating immune complexes in tissue. True serum sickness is rare today because most animal antisera have been replaced but a number of medications can cause a *serum sickness-like reaction.*
  - *Drugs commonly responsible:* Penicillin; less often hydralazine, NSAIDS, *p*-aminosalicylic acid, sulfonamides, thiazides.
- **Vasculitis:** Drugs may be involved in leukocytoclastic vasculitis (p. 247), which also often presents as a purpura (see above).
  - *Drugs commonly responsible:* ACE inhibitors, amiodarone, ampicillin, cimetidine, furosemide, NSAIDs, phenytoin, sulfonamides, thiouracil, and many more.
  - In addition, some forms of ANCA-positive vasculitis are drug-related (p. 255).

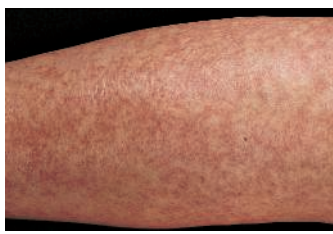


Fig. 11.**5** · Purpuric exanthem caused by allopurinol.

11.5 Drug Pseudoallergies

- **Synonyms:** Drug intolerance reaction, anaphylactoid drug reaction.
- **Definition:** Nonimmunologic reactions such as urticaria, asthma, and anaphylaxis caused by medications.
- **Pathogenesis:** The medications are multiple and not clearly understood. The common denominator is mast cell degranulation with release of histamine and other mediators (Table 11.**2**).

Table 11.2 · Medications causing histamine release

Group	Individual substances
Analgesics	Aspirin, codeine, morphine, papaverine
Antibiotics	Aminoglycosides, neomycin, polymyxin B, vancomycin
Antifungals	Ketoconazole, itraconazole, amphotericin B
Antihypertensives	Hydralazine, tolazoline
Anti-infectives	Pentamidine
Muscle relaxants	Alcuronium, decamethonium, pancuronium, succinylcholine, suxamethonium, tubocurarine
Narcotics	Opiates, thiopental
Contrast media	
Miscellaneous	ACTH, chloroquine, chlorpromazine, local anesthetics, phenylethylamine, phenothiazine, reserpine, tyramine

► **Diagnostic approach:**
- Gradually increasing dosages are given; for example for aspirin, one proceeds with 1, 10, 50, 100, 250, 500 and finally 1000 mg. Most often 100–250 mg is required, but sometimes the 1 mg dose is sufficient to trigger an anaphylactoid reaction. Other medications are tested with analogous dosage schemes.

Caution: Severe acute and delayed reactions are possible, so testing is done on in-patients with resuscitation measures available.

- If a substance is tested and no reaction found, then it can be recommended. The allergy pass should indicate a pseudoallergy and ideally include recommendations for alternative medications.

► **Differential diagnosis:** Includes type I reactions, food intolerance reactions, and toxic reactions caused by overdosage.

12 Dermatitis

The terms *dermatitis* and *eczema* are among the most confusing in dermatology. Dermatitis means "inflammation of the skin," although some object to the term because it seems to omit the vital interplay between epidermis and dermis in cutaneous inflammation. Eczema comes from the Greek ekzein (= boiling) and is used by some to refer to an acute inflammation with vesicles and edema; others, however, are happy with the concept of chronic eczema. We have chosen only to use the term dermatitis, modify it with acute, subacute, or chronic, and regard eczema as a synonym. *Dermatosis* means "condition of the skin" and generally refers to noninflammatory disorders, although there is considerable overlap.

12.1 Atopic Dermatitis

Definitions

- **Atopy:** A familial predisposition to development of allergic asthma, conjunctivitis, rhinitis, and atopic dermatitis.
- **Atopic dermatitis:** In the best tradition of a circular definition, atopic dermatitis is the dermatitis that develops in individuals with atopy. It usually appears in infancy, is chronic and intensely pruritic with varying clinical patterns at different stages of life.

Epidemiology

Some 5–10% of the population of western Europe develop atopic dermatitis. The disease is familial, with apparent polygenic inheritance. A number of suspected gene loci have bene identified. A classic feature is that one family member may have allergic rhinitis and no skin findings, while another has only atopic dermatitis.

Pathogenesis

There appear to be two rather different ways to reach the same disease state:

- **Extrinsic atopic dermatitis syndrome (EADS):**
  - 80%.
  - Elevated total serum IgE.
  - Polyvalent type I sensitization (children against foods, adults against pollens and house dust mites).
  - CD4 cells dominate infiltrate.
- **Intrinsic atopic dermatitis syndrome (IADS):**
  - 20%.
  - No immunologic changes as in EADS.
  - CD8 cells dominate infiltrate.
- **Other features:**
  - Increased cholinergic reactions (white dermatographism, paradoxical sweat response to cholinergic agents).
  - Dry skin with distorted barrier function, perturbations in epidermal lipid composition (overlaps with ichthyosis vulgaris, p. 333).

Clinical Features

The clinical features of atopic dermatitis can be divided into the basic features and the facultative or associated features. There are many diagnostic scoring schemes for atopic dermatitis; if a patient has three major features and three minor features, they are likely to have the disorder.

► **Major features:**
- Pruritus.
- Typical dermatitis (face in children, flexures in adolescents, hands or nape in adults) (Figs. 12.**1**, 12.**2a–c**).
- Chronic or chronic, recurrent course (Fig. 12.**2 d**).
- Positive personal or family history for atopy.

► **Minor features:**
- *Cradle cap* as infant; yellow crusts on scalp.
- *Dry skin* with ichthyosis vulgaris, hyperlinear palms, keratosis pilaris.
- Thick, fine dry hair.
- Elevated serum IgE; IgE-mediated skin reactions.
- Predisposition to skin infections (*Staphylococcus aureus*, herpes simplex virus, human papilloma virus, molluscum contagiosum) because of selective reduced cellular immunity.
- Dermatitis on palms and soles (juvenile plantar dermatosis).
- Nipple dermatitis.
- Cheilitis (dry, inflamed lips, Fig. 12.**2e**).
- Lateral thinning of the eyebrows (Hertoghe sign).
- Double fold of lower lid (Dennie–Morgan fold or line).
- Periorbital hyperpigmentation, obvious facial paleness, or erythema.
- Pityriasis alba.
- White dermatographism.
- Increased pruritus with sweating.
- Diseases flares with emotional changes.
- Unable to tolerate wools or fat solvents.
- Food allergies.

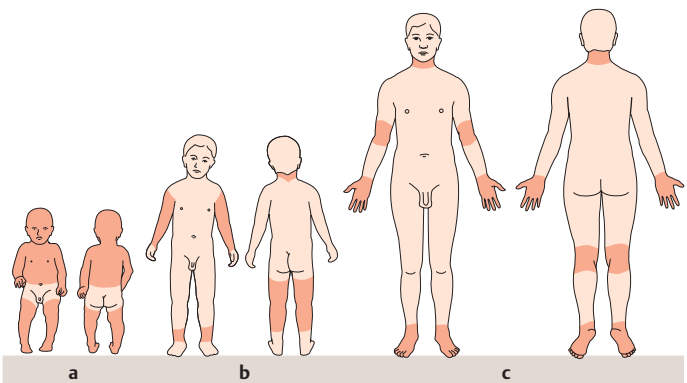


Fig. 12.**1** · **Distribution of lesions of atopic dermatitis over a lifetime. a** Infants. **b** children. **c** Adolescents and adults.

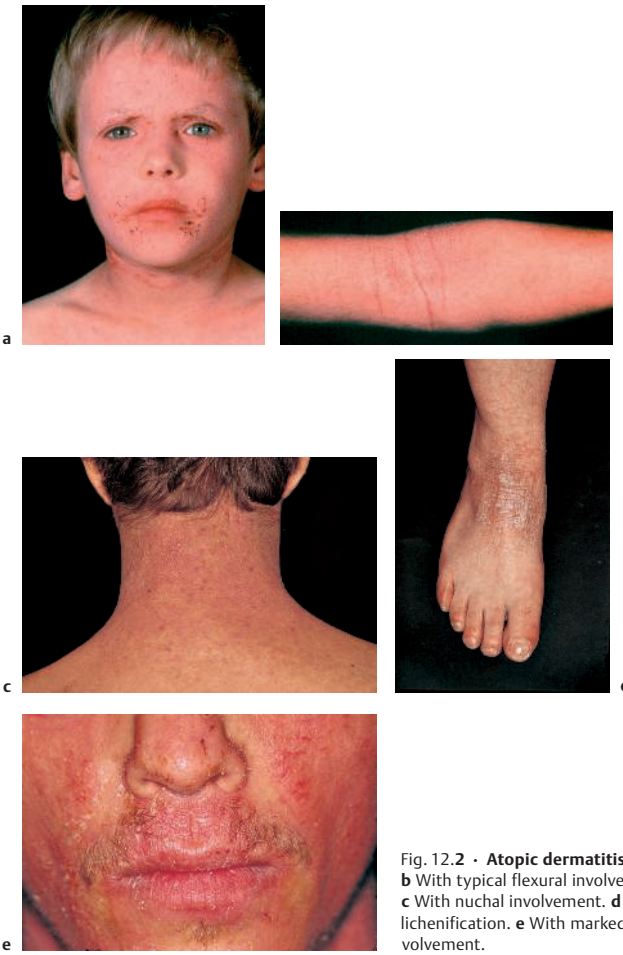


Fig. 12.2 · **Atopic dermatitis. a** Facial. **b** With typical flexural involvement. **c** With nuchal involvement. **d** With lichenification. **e** With marked lip involvement.

- Recurrent conjunctivitis, keratoconus, anterior and/or posterior subcapsular cataracts.
- Absent or reduced corneal or gag reflex.

► **Provocation factors:** Irritants, type I allergens, pseudoallergens (citrus fruits; other foods or food additives), bacterial superantigens, hormones, increased sweating, dry air, emotional stress.

Histology

- **Acute:** Parakeratosis, spongiosis, perivascular infiltrates.
- **Chronic:** Hyperkeratosis, acanthosis, sparse infiltrates.

Diagnostic Approach

- **Routine measures:**.
  - Typical skin changes varying with age of patient.
  - Family and allergy history.
  - Serum IgE level, CBC (looking for elevated eosinophil count).
  - White dermatographism, reduced gag reflex.
  - Eye examination.
- **Special investigations:**
  - Prick testing with common food and inhalant allergens.
  - Allergen-specific IgE determinations.
  - Atopy patch testing. Common aeroallergens are applied and interpret as in a routine patch test.

Differential Diagnosis

- The differential diagnostic considerations vary considerably over the lifetime of the patient and location of the findings. The classic pictures of facial, flexural, or nuchal dermatitis are extremely typical and can be diagnosed at a glance.
- In infants with scalp involvement, seborrheic dermatitis often is identical; often the diagnosis is made later in life as typical findings appear. Atopic dermatitis tends to appear after 6 months of age, whereas seborrheic dermatitis may be present earlier.
- Allergic contact dermatitis should be excluded; even though patients with atopic dermatitis are hard to sensitize, they are exposed to so many creams and ointments that sensitization is not uncommon.
- Adults may present with hand dermatitis (p. 200), eyelid dermatitis, or nuchal dermatitis.

Therapy

Note: No disease is more complicated to treat than atopic dermatitis. It is absolutely essential to work with the patient (and the parents). Listen to their observations; make them a part of the treatment team. This is the easiest way to reduce the emotional aspects of the doctor–patient–parent relationship. For example, do not decide that a patient needs an ointment; instead ask the patient or parent "Do you do better with a cream or ointment—something that rubs in or something that stays a bit greasy?"

- **Topical:**
  - Routine skin care with emollient creams or ointments; if tolerated, with urea as humectant; bath oils.
  - *Topical anti-inflammatory agents:*
    - *Topical immunomodulators* (p. 599): Pimecrolimus (> 6 months); tacrolimus 0.03% > 2 years, 0.1% > 15 years. Use b.i.d. until response, then taper; can combine with corticosteroids.
    - *Corticosteroids* (p. 596): Usually class I–II agents suffice; class III–IV reserved for flares, limited time period. In most instances once daily application is adequate; never more than b.i.d.

  - *Tars:* Available as creams or mixed as ointments; perhaps for chronic lichenified lesions, such as hands; gels are designed for psoriasis and should not be used in atopic dermatitis.
  - *Tannic acid creams or ointments* also useful on hands and feet.
  - *Topical antiseptics*, used for baths and topical therapy; antiseptics (triclosan 1–3% cream) are preferable to antibiotics because of less sensitization.

► **Systemic:**
- *Antihistamines* for severe pruritus; in general, the sedating (older) agents work better; some evidence that cetirizine is anti-inflammatory.
- *Cyclosporine* (p. 628) for severe refractory disease.
- *Unsaturated fatty acids:* Efficacy unclear.
- *Antibiotics* for flares; cover for *Staphylococcus aureus*, which is usually involved.

► **Phototherapy:**
- Helpful in patients who report that they tolerate sunlight well.
- UVA1 is probably best for acute flares; selective UVB phototherapy (SUP) and 311 nm UVB best for chronic disease.

► Other measures:
- *Avoidance of triggers:* Wool clothes, fabric softeners often help, avoid work that requires frequent hand washing.
- If relevant type I allergens are identified, then avoidance: pollens, house dust mites.
- Elimination diet only if type I allergy is proven.
- Pseudoallergen-free diet if clinically suggested.

Caution: The routine use of restricted diets in infants with atopic dermatitis is to be discouraged.

- Psychologic counseling; job counseling.
- Training of parents and children at special centers or clinics.
- Vacation at high altitudes or sea level, especially if pollens appear to play role or disease is sunlight-responsive. House dust mites cannot live above 1500 m, perhaps explaining effectiveness of high altitude vacation.

12.2 Syndromes Associated with Atopic Dermatitis

There are a number of syndromes that are traditionally described as "associated with atopic dermatitis." When one examines the patients closely, they have a chronic dermatitis that may or may not be identical to atopic dermatitis.

Wiskott–Aldrich Syndrome

► **MIM code:** 301000. Gene locus Xp 11.23–11.22. Defect in *WAS* (Wiskott–Aldrich syndrome) gene.

► **Definition:** X-linked recessively inherited disease with triad of immune defects, thrombocytopenia, and atopic dermatitis.

► **Epidemiology:** Incidence of 4/1 000 000 men.

► **Pathogenesis:** WAS is involved in many signal transduction pathways. Major effects are on T-cell activation and actin polymerization (cell migration).

► **Clinical features:**
- *Immune defect*: Decreased humoral immunity against polysaccharides predisposes to recurrent infections with pneumococcus and other bacterial with polysaccharide cell walls; otitis media, pneumonia, meningitis, and sepsis. Later also herpes virus and *Pneumocystis carinii* infections.

- *Thrombocytopenia*: Purpura, prolonged bleeding time, bloody diarrhea. Megakaryocytes in marrow normal.
- *Atopic dermatitis*: Onset in first year, more hemorrhagic than usual disorder; elevated IgE and IgA.
- Most patients die from infections or bleeding in the first 2 years; those who survive are at increased risk of malignancies, especially lymphomas.

► **Differential diagnosis:** Atopic dermatitis, other immune defects.
► **Therapy:** Intravenous immunoglobulin 0.2–0.6 g/kg every 4 weeks; bone marrow transplantation can be curative and also resolves skin problems.

Netherton Syndrome

► **MIM code:** 256500. Mutation in *SPINK5* gene, which encodes the serine protease inhibitor LEKT 1.
► **Clinical features:** Association of atopic dermatitis with keratinization disorders (ichthyosis linearis circumflexa; rarely other forms of ichthyosis) and bamboo hairs (p. 510).

12.3 Contact Dermatitis

► Contact dermatitis is divided into *allergic contact dermatitis* (ACD) and *irritant contact dermatitis* (ICD). These two processes are contrasted in Table 12.**1**. Although the theoretical differences are considerable, the two forms of contact dermatitis are usually grouped together because:
- Often both are present in the same individual.

Table 12.1 · **Major differences between toxic and allergic reactions**

Parameter	Toxic	Allergic
Dose-dependent	Yes	Usually not
Prior exposure required	No	Yes
Percentage exposed with reaction	High	Low
Adaptive immunity involved	No	Yes
Spread to nonexposed sites	No	Yes

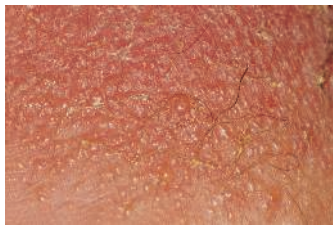
- They can appear clinically quite similar.
- The two diagnoses are not mutually exclusive.

► **Pathogenesis:** In the sensitization phase of ACD, allergens are taken up by Langerhans cells, processed and presented to T cells in the regional lymph node following migration. On re-exposure, the sensitized T cells are activated and trigger cutaneous inflammation at the site of exposure. The clinical reaction occurs 24–72 hours after antigen exposure. In ICD, cytokines are directly released by stimulated or damaged keratinocytes. Damage to the stratum corneum or epidermal lipids is intrinsic part of ICD, but also makes sensitization more likely.
► **Clinical features:** Acute contact dermatitis is pruritic, erythematous, and often vesicular. Subacute lesions may be crusted but still inflamed, while chronic contact dermatitis is dominated by lichenification, hyperkeratosis and rhagades with little sign of inflammation. Except for the distribution patterns, the two variants are identical.

- **Histology:** The microscopic pictures of ACD and ICD are identical. Acute disease will show spongiosis and a lymphocytic infiltrate perivascular infiltrate with dermal edema. More chronic lesions have signs of epidermal reaction including hyperkeratosis, parakeratosis, acanthosis and less infiltrate. ICD with toxic substances such as acids may show direct epidermal damage with necrotic keratinocytes, but this is the exception.

Allergic Contact Dermatitis

- **Definition:** Dermatitis resulting from type IV reaction following exposure to topical substances in sensitized individuals.
- **Epidemiology:** 2–5% of population are affected; much higher in some occupational groups.
- **Clinical features:**
  - The hallmark of ACD is initial confinement to the area of skin that came into contact with an allergen (Fig. 12.**3**). This produces sharply localized, often irregular or unnatural patterns, which can suggest the correct diagnosis.
  - If the allergen is absorbed or taken systemically, lesions may develop at sites that never came into contact with the trigger. The extreme version of this is *hematogenous contact dermatitis* when, for example, a patient sensitized to topical antihistamines takes the same medication systemically. Another variant of this is the *baboon syndrome*.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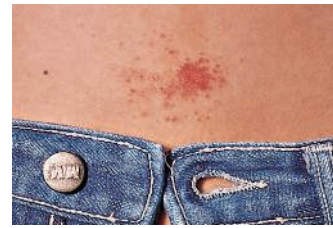
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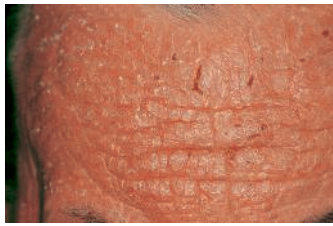
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Fig. 12.**3** · **Contact dermatitis. a** Acute allergic contact dermatitis with vesicles. **b** Allergic contact dermatitis to nickel in jeans button. **c** Subacute contact dermatitis with erythema and scales.

- The localization of ACD often gives clues as to the possible triggering agent (Table 12.**2**).
- The eyelids are very sensitive and often react to products simply transferred their by the hands, rather than being applied intentionally.
- Hand dermatitis is covered separately (p. 200).
- Some occupations have very high prevalence of ACD and often typical allergens, as shown in Table 12.**3**. Occupational skin diseases are also reviewed elsewhere (p. 565).

Table 12.2 · Common sources of allergens listed by body region

Region	Common allergen sources
Scalp	Cosmetics, hair ornaments
Forehead	Hat band, protective masks, airborne plant allergens, hair dyes
Eyelids	Cosmetics, ophthalmologic products, contact lens products, nail polish, airborne plant allergens
Ears	Hearing aids, glass frames, jewelry, ear drops
Oral mucosa	Dentures, other dental materials, chewing gum, toothpaste, foods
Face	Cosmetics, hair dyes, toiletries, shampoos, sun screens, protective masks, airborne plant allergens
Neck	Jewelry, cosmetics, clothing, hair dyes
Axilla	Deodorants and antiperspirants, other toiletries, clothing
Trunk	Clothing, metal zippers and buttons, cosmetics
Genitalia	Toiletries, condoms, spermicides, feminine hygiene products
Arms	Jewelry, cosmetics, clothing
Hands	Occupational exposure, gloves especially latex gloves, skin protective creams, cosmetics, toiletries, jewelry
Legs	Toiletries, cosmetics, stockings, other clothes
Legs in stasis dermatitis	Topical antibiotics, other topical medications
Feet	Shoe material (chromates, rubber, glues), antifungal agents, dyes in socks and stockings
Perianal region	Hemorrhoid medications, disinfectants, other toiletries

Table 12.3 · Common allergens in various occupations

Occupation	Allergens
Baker	Aromas and spices, lemon and almond oils, cinnamon, flour bleaches (ammonium persulphate), preservatives (benzoates), immediate-type allergy to proteins of eggs or flour
Office worker	Copy paper, printer and copy inks, glues, rubber
Electrician	Rubber and rubber-related products, metals, insulation material (colophony), resins (epoxy and formaldehyde)
Hairdresser	Permanents (glycerol monothioglycollate, ammonium thioglycollate), fragrances, dyes (para group, azo dyes), rubber, nickel (often present before entering profession)
Home maker	Foods, spices, rubber, soaps and cleansing supplies (fragrances, preservatives, turpentine) disinfectants, metals (chromates, nickel), cosmetics, immediate-type allergy to natural rubber latex
Gardener	Plant allergens (see text; think of airborne route), rubber, pesticides

Continued Table 12.3 ▶

Table 12.3 · Continued

Occupation	Allergens
Health professional	Rubber, fragrances, disinfectants (formaldehyde, glutaraldehyde, mercury salts), medications, immediate type allergy to natural rubber latex
Farmer	Pesticides, conservatives in greases, airborne plant fragments, feed additives (often photosensitizers), rubber
Construction worker	Chromate and cobalt in cement, concrete hardeners, resins (epoxy and formaldehyde), insulation foam, rubber
Metal worker	Cutting oils, greases, soldering solutions, preservatives, fragrances, glues, rust preventatives, rubber, metals
Textile worker	Resins (formaldehyde), dyes, preservatives, stains, rubber

Table 12.4 · Common allergens in topical medications

Category	Examples
Vehicle	Wool alcohols, cetyl alcohol
Preservative	Parabens, chloroacetamide, Euxyl K 400
Active ingredients	Antibiotics, local anesthetics, antihistamines, sun screens, corticosteroids, NSAIDs, older antifungal agents (not imidazoles)
Fragrances	Many

Tables 12.2–12.4 are based on material in Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC *Dermatology*, Springer Verlag, Berlin, 2000.

- An often overlooked cause of ACD is medication, especially over-the-counter products (Table 12.**4**).
- Rhus dermatitis is the most common cause of ACD in North America. Exposure to poison ivy, poison oak, or poison sumac typically causes a vesicular, often linear, pruritic eruption following outdoor exposure. Although the lesions look toxic, Rhus dermatitis is a true type IV allergy that develops only on repeated exposure to the plants.
  - There are very unusual clinical forms of Rhus dermatitis including eyelid involvement and perianal disease (using the leaves as outdoor toilet paper).
  - Patients with Rhus dermatitis may react to other plant products, such as some leather dyes, laundry marking ink in Asia, some varnishes, and the shell of cashew nuts (not the edible component).

► **Diagnostic approach:**

- *History:*
  - A careful history and a bit of imagination are the keys to diagnosing contact dermatitis. Ask the patient about work and hobbies, and about what materials are likely to reach or be applied to the involved area.
  - Document the history carefully; some cases of contact dermatitis turn out to be work-related, and then documentation is crucial.
  - Onset of problem, occupation, course of disease on weekends or in vacation. Previous therapy. Exposure to common contact allergens such as chemicals, detergents, medications, cleansing products, rubber or latex gloves. Previous skin diseases.

- **Note:** Never forget the likelihood of contact dermatitis as a reaction to a medication (Table 12.**4**). Patients almost never think of this possibility, so you must.
- *Clinical features:* The location and pattern usually suggest the diagnosis of ACD. Always check for disease other than at sites of suspected contact.
- *Patch testing* (p. 43): The diagnosis is always confirmed with patch testing. The usual approach is to use an nationally accepted screening panel first, then specialized panels designed for a specific problem, such as for occupations (dentist), locations (hands), or special ingredients (fragrances or preservatives).
- *Testing with suspected product:* Patch testing with a suspected product is fraught with problems. False-positive reactions are common. Repeated open application test is better; product applied t.i.d. for 2 days to an antecubital fossa.

- **Differential diagnosis:**
  - Main differential diagnostic consideration is ICD.
  - **Note:** Both ACD and ICD can be present at same time, as patients with ICD dermatitis are inclined to develop ACD.
  - *Erysipelas:* At first glance, can appear similar to well-defined erythematous area, but rapidly spreads, is not pruritic, and patient is sick.
  - Atopic dermatitis and nummular dermatitis can be similar.
  - **Note:** Clinical distinction is often difficult, so do patch testing when in doubt.
  - *Tinea:* KOH examination.
  - *Polymorphous light eruption:* Can be confusing when considering sunscreen allergy; otherwise, history clarifies.
- **Therapy:**
  - Acute dermatitis of any sort is best treated with moist compresses and high-potency topical corticosteroid creams. In severe cases, a short burst of systemic corticosteroids, tapered over 7–10 days, is needed.
  - More chronic cases can be treated with lower potency corticosteroids in an ointment base.
  - Bath PUVA may be useful for severe hand and foot dermatitis.
  - Oral cyclosporine is a last gasp measure for therapy-resistant chronic disease.
  - The most important step is *avoidance*. Thus, the allergen or allergens must be exactly identified and the patient carefully counseled as to where the allergen and cross-reacting products can be encountered. Some allergens such as nickel or chromate are very difficult to avoid. In some instances, the patient must give up their occupation—an expensive and bureaucratic process.

Irritant Contact Dermatitis

- **Synonyms:** Toxic-irritant (contact) dermatitis.
- **Clinical features:** The clinical features are remarkably similar to allergic contact dermatitis. ICD never spreads beyond the area of contact, tends to be painful rather than pruritic, and, if the causative agent is strong enough, may form large blisters rather than tiny vesicles. ICD can either be very acute, such as when someone spills acid on their skin, or chronic, resulting from repeated exposures that individually would be harmless. In German, this type of irritant disease is known as *cumulative subtoxic dermatitis*—a most useful concept not easily translated into English. There are three special groups at risk: housewives, infants (diaper dermatitis), and healthcare workers.
  - The prototype of ICD is hand dermatitis (see below).
- **Diagnostic approach:** The diagnosis is made on the basis of history of appropriate exposure. If clinical questions exist or if the ICD is work-related, the patch testing should be carried out to exclude ACD, which can accompany ICD and is more easily avoided.

- **Differential diagnosis:** As for allergic contact dermatitis.
- **Therapy:** The treatment is almost the same as for allergic contact dermatitis. Some tricks for hand dermatitis are discussed in the next section. More extensive blisters with skin loss may require antiseptics.

12.4 Other Forms of Dermatitis

Hand Dermatitis

Hand dermatitis is not a single disease, but it is such a great burden for patients and such a challenge for physicians that we discuss it separately.

- **Epidemiology:**
  - 1–4% of population affected; much higher among people with frequent exposure to moisture or hand washing.
  - 40% of hospital personnel have some degree of hand dermatitis.
  - Women are affected twice as often as men, showing the effect of domestic work.
- **Pathogenesis:**
  - Hand dermatitis is usually the summation of many factors. The hands are our interface with so many substances, whether it be at work or at home, that it is amazing they do not suffer more.
  - *Atopic dermatitis* is an important predisposing factor. Patients with atopy are more likely to develop hand dermatitis, as shown in long-term studies of individuals training to become barbers or hairdressers.
  - *Exogenous factors* include:
    - *Irritants:* Oils, paints, and solvents are typically implicated, but considering the population as a whole, water, soaps, and urine are even more important.
    - Repeated exposure is usually the determining factor.
    - Both allergic contact dermatitis and contact urticaria (common among cooks, caused by raw meats and vegetables) may play role.
- **Clinical features:**
  - Acute hand dermatitis is often vesicular, with tiny deep-seated lesions (Fig. 12.**4**); this form is also known as *dyshidrotic dermatitis* or *pompholyx*. Here the blisters are usually along the sides of the fingers and quite pruritic. We do not consider this process as a separate disease.
  - Severe blisters can lead to shedding of large pieces of the palmar skin.
  - Chronic hand dermatitis is usually hyperkeratotic with fissures, so that the hands are tender and easily hurt by motion or irritating fluids.
- **Diagnostic approach:**
  - The same detailed approach listed under contact dermatitis is required.
  - Do patch testing. Refer to special lists to test certain professions.

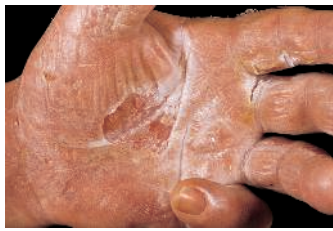


Fig. 12.**4** · Acute hand dermatitis with large blisters and desquamation of sheets.

Table 12.5 · Instructions for patients with hand dermatitis

Only wash your hands when they are dirty; use a mild synthetic detergent and lukewarm water. Dry hands carefully and then lubricate, using either the prescribed medication or hand care product. Also rinse and lubricate your hands after exposure to moisture or wet work.

In many instances you will need gloves. Choose plastic or vinyl gloves, not rubber gloves, as latex is a potent allergen. If possible, wear washable cotton gloves beneath the protective gloves. Try not to wear gloves for more than 20 minutes.

Avoid direct contact with soaps and detergents.

Avoid alcohol, gasoline, solvents, paint thinners and similar products; they are irritating and drying.

Avoid polishes, waxes, and household cleansers.

Wear gloves when you cut, peel, or press fruits or vegetables.

Wear gloves when you wash or treat your hair.

Do not wear a ring when washing your hands. Irritants accumulate beneath a ring. Ideally, you should not wear a ring until your dermatitis is entirely clear. If this is impossible, clean the ring each night with brush and soak it overnight in a mild ammonium solution.

Remember your hands have been injured—comparable to a broken bone. If all the triggering factors are removed, it will take 6 months for your hands to heal. You must follow these recommendations even after you start to feel better.

► **Differential diagnosis:**
- On physical examination, check the backs of the hands; their involvement suggests allergic contact dermatitis. Nail changes indicate chronic disease. Pustules point towards the psoriasis families.
- Foot involvement suggests ACD plays less of a role.
- Present of tinea on feet raises question of fungal id reaction (p. 106).
- Check for other features of atopic dermatitis.

► **Therapy:**

Note: Remember the hands are constantly in contact with other body parts, clothing, and the rest of the environment. It is hard to keep medicine on the hands. Gloves are a two-edged sword; some patients benefit but others find the occlusion worsens their condition.
- Low- to mid-potency corticosteroids in emollient cream or ointment base are best. Most important time to apply is when there is some likelihood they will remain on the skin—such as when watching television!
- Patient counseling is crucial; we provide the instructions shown in Table 12.**5**.
- Use of protective creams may be helpful, especially in the work setting. Having the patient apply fluorescent-labeled protective cream and then examining the hands with a Wood's light can reveal how good a job they are doing of protecting their hands. The same check after a workplace exposure may show if the cream is staying on long enough to be beneficial. Different creams are available for wet and dry work.

Asteatotic Dermatitis

► **Synonyms:** Xerosis, dermatitis sicca.
► **Definition:** Dermatitis secondary to superficial cracks in epidermis as a result of dryness and reduced lipids.

- **Epidemiology:** Common problem, more likely in elderly and those with atopic dermatitis or ichthyosis vulgaris.
- **Pathogenesis:** Exact lipid defects unclear, but older individuals has less of an epidermal lipid accumulation. Typical onset in early winter as central heating is started and room humidity drops. Also seen in compulsive shower takers or those who luxuriate in bubble baths. Acquired ichthyosis (p. 333) is probably a variation on this theme in some cases.
- **Clinical features:** Initially dry skin and pruritus. Sometimes erythematous cracks in skin (French: *eczema craquelé*). Later more diffuse inflammation.
- **Diagnostic approach:** Clinical diagnosis with typical history.
- **Differential diagnosis:** Atopic dermatitis, various forms of ichthyosis, especially acquired ichthyosis.
- **Therapy:** Avoidance of frequent baths or showers; use a synthetic detergent instead of soap; regular lubrication of skin, especially after bathing.

Nummular Dermatitis

- **Synonym:** Microbial dermatitis.
- **Definition:** Sharply circumscribed patches of dermatitis; nummular means "coin-shaped".
- **Epidemiology:** So poorly defined that no reliable numbers available; range in literature 0.1–10%.
- **Pathogenesis:** Probably reflects atopic dermatitis, xerosis, and on the legs stasis dermatitis coupled with hypercolonization by bacteria. More common in those with poor personal hygiene.
- **Clinical features:** 2–5 cm plaques with erythema, papules, vesicles, and crusts (Fig. 12.**5**). Usually pruritic. Most often on extremities; legs in men, arms in women.
- **Histology:** Hyperkeratosis, acanthosis, focal spongiosis and perivascular infiltrates; corresponding to subacute to chronic dermatitis.
- **Diagnostic approach:**
  - Search for other signs of atopic dermatitis or dry skin.
  - Bacterial smear from recalcitrant lesions; also check for staphylococcal carriage in the throat, nares, or anogenital region.
  - Do patch testing; some are allergic or nickel, chromate, or other allergens.
- **Differential diagnosis:** Atopic dermatitis, psoriasis, tinea corporis, impetigo, petaloid seborrheic dermatitis.
- **Therapy:** Topical corticosteroids, perhaps combined with topical antibiotics or tar; if no response, try systemic antibiotics (penicillinase-resistant penicillins or cephalosporins); after healing, maintain lubrication.

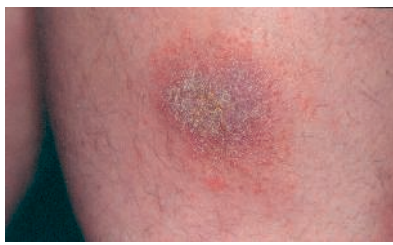


Fig. 12.**5** · Nummular dermatitis.

13 Collagen–Vascular Disorders

13.1 Classification and Overview

The collagen–vascular disorders (connective tissue disorders) are a complex group, without a unifying pathogenesis. All feature arthritis or arthralgias, and most have prominent skin involvement.

- **Lupus erythematosus**.
  - Chronic cutaneus lupus erythematosus.
  - Subacute cutaneous lupus erythematosus.
  - Systemic lupus erythematosus.
  - Drug-induced lupus erythematosus.
  - Antiphospholipid syndrome.
- **Dermatomyositis and polymyositis**.
- **Localized scleroderma**.
  - Morphea.
  - Linear scleroderma.
  - Disabling pansclerotic morphea.
- **Systemic sclerosis**.
- **Pseudoscleroderma**.
  - Eosinophilic fasciitis.
  - *Toxic forms:* Toxic oil syndrome, eosinophilia-myalgia syndrome, polyvinyl-chloride syndrome and others.
  - *Associated with other diseases:* graft-versus-host disease and porphyria cutanea tarda.
- **Mixed collagen–vascular disorders and other overlap syndromes**.
- **Other rheumatologic diseases**.
- **Raynaud syndrome**.

Many collagen–vascular disorders have some form of antinuclear antibodies (ANA), as shown in Table 13.**1**.

Table 13.1 · **Antinuclear antibodies with clinical relevance**

Antigen family	Specific antigen	Antinuclear antibody	Clinical association	Prevalence (%)
DNA	dsDNA	Anti-dsDNA IgG	SLE Sjögren syndrome	45–90 10
	ssDNA	Anti-ssDNA	SLE	50–95
Histone		Anti-histone		
	H1	Anti-H1	SLE	50–80
	H2A and H2B	Anti-H2A, anti-H2B	Drug-induced LE	90
Nucleosomes	Mono nucleosomes	Anti-nucleosome	Early marker for autoimmune disease	

Continued Table 13.1 ▶

Table 13.1 · Continued

Antigen family	Specific antigen	Antinuclear antibody	Clinical association	Prevalence (%)
Low molecular weight RNP	U1 RNP/Sm	Anti-U1 RNP Anti-Sm	Overlap syndromes, SLE, systemic sclerosis, polymyositis, rheumatoid arthritis	90
	RNP-70	Anti-RNP-70	MCTD	
	RNP-A	Anti-RNP-A	SLE	
	Sm-B/B	Anti-Sm-B/B	Highly specific for SLE	20–30
	SS-A 60/Ro60	Anti-SSA60/ anti-Ro60	Sjögren syndrome SLE	70–80 20–60
	SS-A 52 / Ro52	Anti-SSA52/ anti-Ro52	Congenital heart block	95–100
	SS-B / La	Anti-SS-B, anti-La	Neonatal lupus Sjögren syndrome	75 40–90
Other	Jo-1(synthetase)	Anti-Jo-1	Polymyositis, idiopathic pulmonary fibrosis	30–40
	Scl-70 (topoisomerase)	Anti-Scl-70	Systemic sclerosis	30–40
	PM-Scl-100	Anti-PM-Scl-100	Systemic sclerosis, dermatomyositis, rheumatoid arthritis	
	Centromere protein B	Anti-centromere	CREST syndrome Primary biliary cirrhosis	40–80 10–30

13.2 Lupus Erythematosus (LE)

Overview

- **Definition:** A disease featuring autoimmune phenomena that may involve one or multiple organs, frequently has characteristic skin findings, and runs an acute or chronic course.
- **Classification:** The combination of history, clinical findings, and laboratory values can be used to classify LE as follows:
  - *Chronic cutaneous LE*: Almost exclusively skin findings:
    - Discoid LE (DLE).
    - Lupus tumidus.
    - Lupus profundus.
  - *Subacute cutaneous LE (SCLE)*: Predominantly skin findings, mild systemic involvement.
  - *Systemic LE (SLE)*: Primarily systemic involvement.

- **Pathogenesis:**
  - LE is a multifactorial disease with genetic and immunopathologic abnormalities. The release of nuclear antigens because of enhanced apoptosis (FAS-FAS-L) is a key factor.
  - *Important predisposing factors:*
    - *Genetic predisposition:* HLA-B8, -DR2, -DR3, -DQwl, -DRB1; various polymorphisms—TNF-R gene, Fc-γ receptor, CD19 gene.
    - *Complement defects:* C1q, C1r, C1 s, C4, C2 (skin and renal disease).
    - *Exogenous factors:* UV radiation and medications.
    - *Individual factors:* Hormone status, altered immune status.
    - Transplacental transfer of maternal autoantibodies (anti-SSA, anti-SSB) can lead to neonatal LE.
- **Lupus band test:** This test identified the presence of immunoglobulins and complement at the dermoepidermal junction in both normal and lesional skin. Formerly used to classify LE, but now replaced by more sophisticated autoantibody determinations.

Chronic Cutaneous Lupus Erythematosus

- **Definition:** Chronic scarring erythematosquamous lesions primarily in sun-exposed skin. Some groups refer to all chronic cutaneous LE as discoid LE (DLE) but we prefer to reserve the term for a specific type of lesion, which may also be seen in SCLE or SLE.
- **Synonym:** Discoid lupus erythematosus.
- **Epidemiology:** More common in women (2–3:1); usually appears 15–60 years of age.
- **Clinical features:**
  - Erythematous well-circumscribed persistent plaques with follicular hyperkeratoses, telangiectases; heal with scarring, peripheral hyperpigmentation and central hypopigmentation (Fig. 13.**1**). Sometimes tender or hyperesthetic.
  - Sites of predilection include chronic sun-exposed areas: scalp, forehead, cheeks, ears, nose, upper lip, and chin. Usually limited number of lesions; occasionally disseminated.
  - Common causing of scarring alopecia (p. 507), especially in blacks. About 1:250 black women in USA have LE alopecia.
  - Small percentage of patients go on to develop SLE.
- **Histology:** The histologic findings exactly match the clinical: epidermal atrophy with vacuolar degeneration of basal cells, telangiectases, follicular plugs, lymphocytic infiltrate in dermis. Valuable clues are widened periodic acid–Schiff (PAS)-positive basement membrane and deposition of mucin.
- **Diagnostic approach:**
  - Skin biopsy.
  - *Direct immunofluorescence:* Deposits of IgG and C3 along the basement membrane in affected skin in up to 80%, but normal, nonexposed skin always negative.
  - *Laboratory:* Negative or low-titer ANA; sometimes higher titer in disseminated.
  - Exclude SLE.
- **Differential diagnosis:** Tinea faciei (KOH examination), granuloma faciale (brown color, no scarring), psoriasis (silvery scale), lupus vulgaris (diascopy), sarcoidosis (diascopy, no prominent follicles), rosacea (pustules, ears spared). In each case, histology is most helpful.
- *Therapy:*
  - Sun avoidance and high-potency sunscreens (UVA, UVB).
  - Short-term high-potency topical corticosteroids.

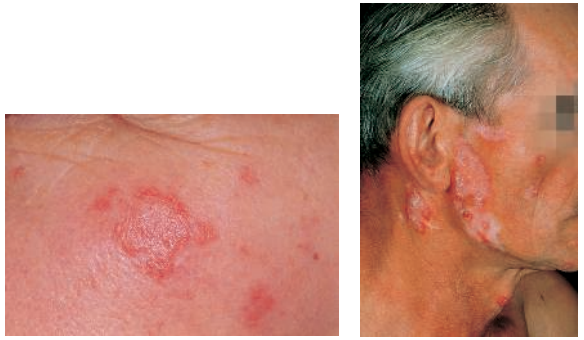


Fig. 13.1 · **Discoid lupus erythematosus. a** Early lesion. **b** Late lesion with scarring.

- Topical immunomodulators (pimecrolimus, tacrolimus) worth trying.
- Cryotherapy or intralesional corticosteroids for stubborn lesions.
- Systemic therapy for widespread, recalcitrant disease:
  - *Antimalarials:* Hydroxychloroquine 200–400 mg daily or chloroquine 250 mg daily; rarely need to go higher for skin findings alone; monitoring by ophthalmologist required every 6–12 months. With response, attempt to stop therapy.
  - Dapsone 50–100 mg daily.
  - Thalidomide 50–200 mg daily; special cases, contraception, watch for neuropathy.
  - Corticosteroids should generally be avoided; if disease is recalcitrant, then perhaps prednisolone 40 mg daily for 5 days a month.

  ▶ ***Note:*** In general, cutaneous lesions are not an indication for systemic corticosteroids in LE.

Other Forms of Chronic Cutaneous Lupus Erythematosus

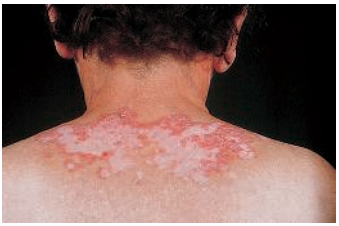
▶ **Lupus tumidus:**
- *Clinical features:* Erythematous papules and nodules on face and upper trunk; very light-sensitive; histology shows rich amount of mucin and abundant dermal lymphocytes.
- *Differential diagnosis:* Lupus tumidus is one of the common causes of benign lymphocytic infiltrates, along with lymphadenosis cutis benigna (borrelial infection), and arthropod bite and sting reactions.
- *Therapy*: As for DLE; intralesional corticosteroids or antimalarials often useful.

▶ **Lupus profundus:**
- *Synonym:* Lupus panniculitis.
- *Definition:* LE with deep inflammation involving subcutaneous tissue.
- *Clinical features:* Firm subcutaneous nodules on face, extremities or trunk; sometimes with overlying changes of DLE, but often with normal epidermis. Heal with sunken, cosmetically disturbing scars.
- About $^1/_3$ of patients develop SLE.
- *Differential diagnosis:* All forms of panniculitis; histology shows lobar panniculitis often rich in plasma cells.
- *Therapy:* Dapsone most effective; also consider antimalarials.

- **Verrucous lupus erythematosus:** Hyperkeratotic plaques, especially on hands and feet; often mistaken for keratoacanthoma, hypertrophic lichen planus, or prurigo nodularis. Patients usually have other clues for LE elsewhere.
- **Chilblain lupus:** Blue-red plaques acral plaques that resemble pernio (p. 309) but are more permanent and patients do not give history of cold exposure; up to $^1/_3$ develop SLE. Systemic therapy usually required.
- **Oral lupus erythematosus:** Typical lesions are palatal erythema or erosions; often overlooked. Rarely presenting feature. Try topical corticosteroids in gel or oral paste; otherwise intralesional corticosteroids or antimalarials.

Subacute Cutaneous Lupus Erythematosus

- **Definition:** Type of LE with widespread photosensitive skin disease, mild systemic involvement, characteristic autoantibody pattern, and good prognosis.
- **Epidemiology:** Women much more often affected (8:1).
- **Clinical features:**
  - Symmetrical widespread nonscarring erythematous patches and plaques with tendency to confluence (*psoriasiform*); usually light-exposed areas such as trunk and arms (Fig. 13.**2 a**). Sometimes *annular* or *target-like* (Fig. 13.**2 b**). Rarely erythema multiforme-like with blisters (*Rowell syndome*).
  - 60% fulfill ACR criteria for SLE; often arthralgias, rarely renal disease.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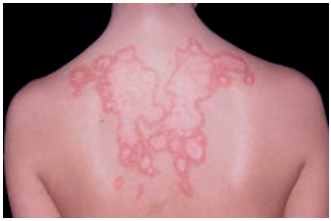
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Fig. 13.**2** · **a** Subacute cutaneous lupus erythematosus. **b** Annular form.

- **Histology:** Interface dermatitis with vacuolar degeneration and superficial dermal infiltrates; epidermal changes and deep infiltrates usually lacking.
- **Diagnostic approach:**
  - Skin biopsy.
  - Deposits of IgG and C3 along the basement membrane in lesional lesion in 50–60%; in normal skin in 10–20%.
  - *Laboratory*: 20–30% have low titer anti-dsDNA antibodies. Often positive for anti-SS-A and anti-SS-B (ANA-negative LE). Occasional complement defects.
- **Differential diagnosis:** The distinctions between discoid and subacute cutaneous LE are shown in Table 13.**2**. Other considerations include psoriasis, tinea corporis, annular erythemas, tinea versicolor, and rarely erythema multiforme.
- **Therapy:** Same as for discoid LE; emphasis on sun avoidance and sun screens. Antimalarials usually necessary, for either skin or arthritis. Also NSAIDs for joint pain.

Table 13.2 · Distinction between discoid and subacute cutaneous LE

Criteria	Discoid LE	Subacute cutaneous LE
Female:male ratio	3:2	8:1
Ethnicity	All	Favors whites
Location		
Head and neck	+	(-)
Trunk	(+)	+
Confluence of lesions	-	+
Follicular keratoses	+	-
Scarring	+	-
Photo-induced	++	++++
Histology		
Hyperkeratosis	+++	+
Epidermal atrophy	++	+
Superficial infiltrate	++	++
Deep infiltrate	++	-
Depots of IgG, C3 at BMZ		
Lesional skin	80%	50%
Normal skin	<10%	25%
ACR criteria	<10%	50–60%
Serology		
ANA	5–30%	80%
Anti SS-A, SS-B	<5%	70%

Neonatal Lupus Erythematosus

- **Pathogenesis:** Mothers with anti-SS-A and anti-SS-B transfer antibodies transplacentally. Anti-SS-A52 cross-reacts with fetal cardiac conduction system antigens.
- **Clinical features:**
  - Mother may be normal (only serological evidence for LE), or have either discoid or subacute cutaneous lesions, or even Sjögren syndrome.
  - Infant has mild lesions of SCLE, often in annular pattern. Lesions are transient and heal without scarring over months. Major problem is congenital heart block, grade I–III, which occurs in 70%.
- **Histology:** Mild interface dermatitis with vacuolar change.
- **Diagnostic approach:**
  - *Laboratory:* Check anti-SS-A, anti-SS-B; rarely anti-U1 RNP positive.

  Caution: Check all infants with congenital heart block, and their mothers, for anti-SS-A and anti-SS-B.
- **Differential diagnosis:** Skin lesions confused with urticaria, annular erythema, and erythema multiforme; all uncommon in infants. Infantile LE starts later in life, has few cardiac manifestations and persistent skin lesions.

► **Therapy:** Skin lesions rarely require therapy. Heart block usually treated with plasmapheresis and dexamethasone (crosses placenta) if recognized during pregnancy; later with a pacemaker.

Systemic Lupus Erythematosus

► **MIM code:** 152700.
► **Epidemiology:** Annual incidence 25/100000; young women most frequently affected.
► **Clinical features:**
- *Cutaneous lesions:*
  - *Butterfly rash:* Classic lesion of SLE; mid-facial circumscribed erythema following sun exposure (Fig.13.**3 a**); initially waxes and wanes; later permanent. 40–50% of patients have cutaneous disease at time of diagnosis.
  - Also may have diffuse erythema of scalp, ears, lips, upper trunk, forearms—sun-exposed areas—but also palmoplantar erythema. Some have transient exanthems, resembling drug eruption or erythema multiforme.
  - *Bullous lesions:* There are two distinct types of bullae:
  - Since LE has marked damage at the basement membrane zone (BMZ), the epidermis may separate. Common under the microscope, but some patients, especially with erythema multiforme lesions or sunburn, have bullae.
  - Some blacks often with LE nephritis have herpetiform blisters, mimicking dermatitis herpetiformis but on face, caused by antibodies to type VII collagen (as in epidermolysis bullosa acquisita). Very responsive to dapsone.
  - *Discoid lesions:* Many patients have hyperkeratotic scarring lesions.
  - Vasculitis may take many forms:
    - Typical leukocytoclastic vasculitis (p. 247).
    - Necrotic infarcted papules on digits, distal extremities; heal with white sunken scars.
    - Peripheral gangrene.
    - Subcutaneous nodules (nodular vasculitis).
    - Livedo racemosa (antiphospholipid syndrome, p. 258).
  - *Alopecia*: Common cause of scarring alopecia secondary to discoid lesions; also diffuse alopecia and association with alopecia areata.
  - *Nail fold changes:* Damaged cuticle with telangiectases (Fig. 13.**3b**). Similar changes in dermatomyositis, systemic sclerosis.
  - *Oral lesions:* Palatal erythema or erosions; less often elsewhere.
- *Systemic lesions:*
  - The American College of Rheumatology (ACR) criteria for the classification of SLE, formerly known as the American Rheumatologic Association (ARA) criteria (Table 13.**3**) illustrate how many organs are typically involved.
  - Most patients have arthritis; major life-threatening complications including renal and CNS disease; standard internal medicine textbooks should be consulted for details.

► **Diagnostic approach:**
- The ACR criteria were designed to identify patients in clinical studies; individuals with four or more criteria were accepted as having SLE. Although they were never intended as diagnostic criteria, they are widely so employed.
- A skin biopsy is useful for diagnosing LE, but not for separating the different types with certainty. Deposits of IgG and C3 along the basement membrane on normal, non–sun-exposed skin suggests SLE but is no longer an accepted criterion.

Table 13.3 · ACR criteria for the classification of SLE

Criterion	Definition
Malar rash	Fixed erythema over malar eminences (butterfly rash) sparing the nasolabial folds
Discoid rash	Lesions with follicular hyperkeratoses, erythema and scale; later atrophic scarring
Photosensitivity	Skin rash as reaction to sunlight
Oral ulcers	Oral or nasopharyngeal ulcerations, usually painless, observed by physician
Arthritis	Nonerosive arthritis involving two or more joints with tenderness, swelling, or effusion
Serositis	Pleuritis or pericarditis, appropriately documented
Renal disease	Persistent proteinuria >0.5 g daily or cellular casts
Neurologic disease	Seizures or psychosis in the absence of any other explanation
Hematologic disorder	Hemolytic anemia with reticulocytosis, or leukopenia $<4000/mm^3$ on 2 occasions, or lymphopenia $<1500/mm^3$ on 2 occasions, or thrombocytopenia $<100\,000/mm^3$ with no other explanation
Immunologic disorder	Anti-ds-DNA, or anti-SM, or anti-phospholipid antibodies (anticardiolipin, lupus anticoagulant, or false-positive syphilis test)
Antinuclear antibody	Positive ANA using immunofluorescence or equivalent assay at any point in course when patient not taking medications known to cause drug-induced lupus

► **Therapy:**

- *Cutaneous lesions:* Sunscreen avoidance and sun screens, topical corticosteroids or immune modulators; antimalarials.

  Caution: With rare exceptions, cutaneous disease should not be taken as an indication for systemic therapy except for antimalarials.
- Table 13.**4** lists the major drugs recommended for SLE, with general indications.
- *Mild systemic diseases:* Arthritis, fever, headache, and other minor systemic complaints respond well to NSAIDs or antimalarials. If corticosteroids are used, the strategy must be to bring a flare under control and then eliminate or use as interval therapy.
- *Urticarial vasculitis:* Dapsone most effective.
- *Moderate systemic disease:* Serositis, pneumonitis, hematologic problems, vasculitis usually require corticosteroids (prednisolone 5–50 mg weekly, rapid taper or switch to interval therapy) and either azathioprine (100–150 mg daily) or methotrexate (7.5–20 mg weekly) for steroid sparing.
- *Severe systemic disease:* Renal, pulmonary, and CNS disease require aggressive therapy.
- High-dose corticosteroids (methylprednisolone pulse therapy 1000 mg daily for 3–5 days, then 1–2 mg/kg daily).
  - Cyclosporine 5 mg/kg daily, especially for membranous nephritis.
  - Mycophenolate mofetil (2 g daily), cyclophosphamide (50–100 mg daily or 500 mg every 4 weeks).

Table 13.4 · Major systemic medications for SLE

Drug	Indications	Comments
Antimalarials	Skin, arthritis, serositis	Eye exam every 6–12 months
NSAIDS	Arthritis, serositis, headache	Watch for GI bleeding, ↓ renal function
Corticosteroids		
Low-dose	Skin, arthritis, constitutional symptoms	Many complications
High-dose	Nephritis, CNS, vasculitis, hematologic problems	Use for control, then taper and add steroid-sparing agents
Azathioprine	Nephritis	Bone marrow, GI toxicity
Cyclophosphamide	Nephritis	Bone marrow toxicity, cystitis
Methotrexate	Arthritis	Hepatic disease
Mycophenolate mofetil	Nephritis	Leukopenia, GI distress
Cyclosporine	Nephritis	Hypertension, renal function

GI = gastrointestinal.

- *Experimental therapies:*
  - Intravenous immunoglobulins used for severe thrombocytopenia, other refractory life-threatening conditions.
  - Plasmapheresis for hyperviscosity syndrome, thrombotic thrombocytopenic purpura.
  - Anti-CD20, -CD40, and -TNF α antibodies.

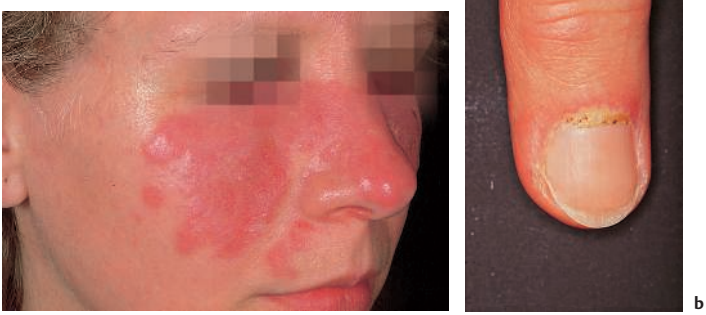

Fig. 13.3 · **Systemic lupus erythematosus. a** Butterfly rash. **b** Nailfold telangiectases.

Drug-induced Lupus Erythematosus

- **Definition:** Clinical syndrome closely resembling LE, induced by various medications, features antihistone antibodies; usually resolves when drugs are stopped.
- **Pathogenesis:** The patients are usually slow acetylators who metabolize drugs slowly. Most of the triggering medications inhibit C4 and thus delay the breakdown of immune complexes. Normal individuals with HLA types associated with LE are at increased risk. Discrepancies between development of ANA and clinical findings of LE.
  - Responsible medications include:
    - *Biologicals:* IFA-α, IFN-γ, anti-TNF (ANAs common, LE rare).
    - *Antihypertensives:* Hydralazine, methyldopa.
    - *Antiarrhythmic agents:* Procainamide, quinidine.
    - *Others:* Minocycline, chlorpromazine, isoniazid.
- **Clinical features:** Similar to SLE, but usually less severe. Most often generalized systemic signs and symptoms; arthritis most common. Procainamide causes serositis and pulmonary disease; renal, CNS, and skin involvement uncommon.
- **Therapy:** Stop medication; manage as SLE but expect remission.
  - ***Note:*** Monitor ANA baseline and every 6 months in patients on biologicals, minocycline for rheumatoid arthritis, hydralazine, or procainamide.

Antiphospholipid Syndrome

- **Synonyms:** Anticardiolipin syndrome, lupus anticoagulant syndrome.
- **MIM code:** 107320.
- **Definition:** Syndrome characterized by livedo racemosa, thromboembolic complications, abortion, and severe, otherwise unexplained headaches. Can be primary or secondary to a variety of diseases.
- **Epidemiology:** Most patients are young women.
- **Pathogenesis:**
  - Antiphospholipid antibodies (aPL) are commonly seen as normal variant in older individuals. Genetic predisposition (HLA-DR4, -DR7, -DRw53). Usual triggers include SLE, chronic infections (usually viral), lymphoma, drugs.
  - aPL appear to recognize phospholipid-binding proteins, not anionic phospholipids as initially thought.
  - Prominent target is β_2-glycoprotein I; after binding with aPL, it triggers activation of T cells, thrombocytes, and endothelial cells.
- **Clinical features:**
  - Arterial emboli, recurrent venous thromboses (CNS, lungs, legs) without other known risk factors in 30%.
  - Abortions, intrauterine death from placental insufficiency.
  - Valvular cardiac disease.
  - *Skin changes:* Livedo racemosa, Raynaud syndrome, persistent acral ulcerations, necrosis and gangrene.
  - *Sneddon syndrome:* Combination of livedo racemosa and CNS thrombotic events.
- **Diagnostic approach:**
  - The diagnosis of antiphospholipid syndrome is complex. Two major, not totally independent groups of antibodies can be identified:
    - Anticardiolipin antibodies (IgG), also responsible for false-positive VDRL titer (p. 143).
    - Lupus anticoagulant antibodies (IgG, IgM) against β_2-glycoprotein and phospholipid components of the prothrombin activator complex.

  - The lupus anticoagulant inhibits the conversion of prothrombin to thrombin; it is found in 5–10% of LE patients (many without other findings of antiphospholipid syndrome).
  - **Note:** Although the lupus anticoagulant is associated with a prolonged partial thromboplastin time, it rarely causes bleeding but instead increases the risk of thromboembolism. The in-vivo defect in clot formation is misleading.
- Most patients have mild thrombocytopenia.
- *Skin biopsy:* May find a thrombus if lucky, but not a useful tool for routine work.
- *Diagnostic criteria* (Sapporo 1998):
  - History of abortion or thrombosis.
  - Presence of antiphospholipid antibodies or lupus anticoagulant.

► **Therapy:**
- Identification of either group of antibodies is not an indication for therapy.
- Treat underlying disease.
- Anticoagulation:
  - Prophylaxis with aspirin 325 mg.
  - After thrombosis, lifelong anticoagulation with coumarin.

13.3 Dermatomyositis and Polymyositis

Overview

► **Definition:** Uncommon group of diseases with loss of muscle strength secondary to autoimmune muscle damage.
- *Polymyositis:* No cutaneous involvement.
- *Dermatomyositis:* Both muscular and cutaneous abnormalities.

► **Epidemiology:** Incidence in children 3/million; in adults 0.5–1.0/100 000; women 1.5–2.0 times more often affected. In adults > 50 years of age, often paraneoplastic.

► **Pathogenesis:** Evidence for immune process is strong, including association with other autoimmune disorders and presence of circulating autoantibodies, both myositis-specific and overlapping. Suspected triggers include viral infections. In the case of polymyositis, the reaction appears primarily cellular with CD8+ cytotoxic T cells damaging muscles. In the case of dermatomyositis, humoral mechanisms appear more important, as complement activation leads to microangiopathy, with muscle necrosis secondary to impaired vascular supply. Invading cells are primarily CD4+. Mechanisms of paraneoplastic dermatomyositis unclear.

► **Classification:**
- *Polymyositis.*
- *Adult dermatomyositis:* Typical onset 40 years of age.
- *Juvenile dermatomyositis:* More acute onset with vasculitis (often leading to gastrointestinal hemorrhage), later calcification, lipodystrophy.
- *Paraneoplastic dermatomyositis:* Later onset, associated with those tumors common in older individuals (breast, head and neck carcinomas).
- *Amyopathic dermatomyositis:* Dermatomyositis with no evidence of muscle involvement over 6 months follow-up.

Clinical Features

► **Muscles:** Pain and then weakness in shoulder and hip girdle muscles. Typical problems include combing hair, getting out of chair, getting up from horizontal position, climbing stairs, or leaving a car. Difficulty swallowing and ptosis or strabismus can also occur. Early disease often associated with fever and malaise.

► **Skin:**
- Skin changes in 80–100% of cases; presenting sign in 25%.
- Periorbital and eyelid edema with violet tint to eyelids; known as *heliotrope lids* (sun-pointing lids); sometimes associated with reduced facial expression (Fig. 13.**4a**).
- Lichenoid papules over the finger joints and knuckles (*Gottron sign*, Fig. 13.**4b**).
- Erythematosus macules and plaques on forehead, chin, shoulders and upper arms (*shawl sign*) or anterior neck and upper chest (*V sign*).
- *Raynaud phenomenon:* Children frequently have distal sclerosis.
- Nail fold telangiectases and atrophy.
- Fissures and ulcers on tips of fingers and toes (*mechanic's hands*).

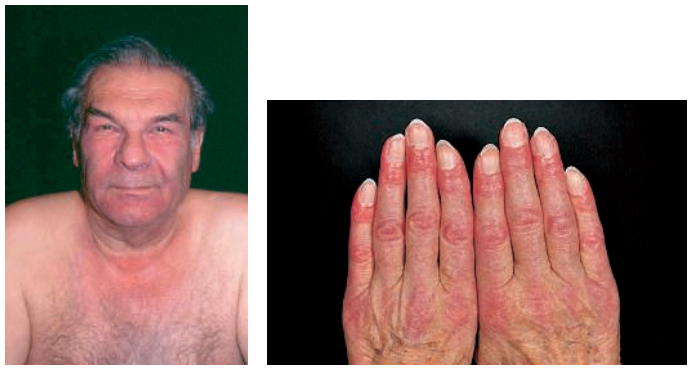

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Fig. 13.**4** · **Dermatomyositis. a** Facial involvement with eyelid swelling. **b** Gottron papules.

► **Arthritis:** Most common at onset of disease; usually peripheral; 25% have morning stiffness.
► **Mucosa:** 10–20% have oral ulcers.
► **Calcinosis:** Distinctive feature of juvenile dermatomyositis; can be very extensive; soft tissue, vessel and muscle calcifications. Often most disturbing sequelae.
► **Lungs:** More common in patients with anti-Jo1; 20% have pulmonary fibrosis.
► **Gastrointestinal tract:** Children have vasculitis and frequent gastrointestinal ulcerations and hemorrhage. In adults, motility problems may occur.
► **Heart:** Asymptomatic EKG changes common; occasionally myocarditis or myopathy.
► **Histology:** The biopsy findings can best be remember as *almost LE*: vacuolar denegation, atrophy, perivascular inflammation, sometimes even a wisp of mucin.

Diagnostic Approach

► **Electromyogram (EMG):** Characteristic changes in affected muscles in 70%.
► **MRI:** Displays inflamed muscles; superior to sonarography or CT.
► **Muscle biopsy:** Most reliable diagnostic text; shows varying stages of necrosis and regeneration with inflammatory infiltrate. In polymyositis, CD8+ cells; in dermatomyositis, CD4+ cells, vasculitis, and perifascicular atrophy (almost diagnostic). Also helps exclude trichinosis.

Caution: Always biopsy muscle that EMG or MRI shows to be affected. Preserve muscle in solution provided by special muscle pathologist and keep under tension with muscle clamp. Otherwise, the procedure is worthless.

- **Laboratory:**
  - Sed rate and C-reactive protein elevated in 50%.
  - Creatine kinase (CK) is best marker; it is elevated at some point in disease. 24-hour urine creatine (*not creatinine—common error*) level > 200 mg is diagnostic. In children and pregnancy, more marked spontaneous variation. Other muscle enzymes can also be measured: AST, ALD, LDH.
  - *Serology:*
    - *Myositis-specific antibodies(MSA)*: Present in < 50%.
    - *Anti-Jo-1 (antisynthetase)*: Present in 20%, correlates with lung disease and Raynaud phenomenon.
    - *Anti-SRP (signal recognition protein):* Acute disease, poor outlook.
    - *Anti-Mi2 (helicase):* Dermatomyositis, good outlook.
    - *Others:* Rheumatoid factor (10%), ANA (20%); no anti-DNA antibodies.
    - *Anti-PM-SCL (anti-PM1):* marker for polymyositis/systemic sclerosis overlap.
  - *Skin biopsy:* Rarely diagnostic.
  - *General evaluation:* Chest radiograph, EKG, echocardiogram pulmonary function.
  - Search for underlying tumor in patients > 50 years of age or with suspicious history.

Note: Do not overlook meticulous pelvic examination. Ovarian carcinoma is one of the more commonly associated tumors.

Differential Diagnosis

- **Other myopathies:** Inclusion body myositis (older, slow onset, 20% dysphagia, biopsy classic); muscular dystrophy (late-onset), neuromuscular atrophy (Charcot–Marie–Tooth disease), myasthenia gravis, thyrotoxic myopathy, Cushing disease, sarcoidosis, alcoholism.
- **Drugs:** Lipid-lowering agents, hydroxyurea, and NSAIDs (rarely) can produce dermatomyositis-like picture.
- **Overlap syndromes:** Polymyositis-systemic sclerosis, eosinophilic fasciitis, SLE. Childhood dermatomyositis often resembles systemic sclerosis, but is much more common.
- **Vasculitis:** May present with muscle weakness.
- **Polymyalgia rheumatica:** Older patients, slow onset, may be associated with temporal arteritis.
- **Trichinosis:** Can exactly mimic dermatomyositis with periorbital edema, nail fold hemorrhages and pain. More painful and usually has hypereosinophilia.

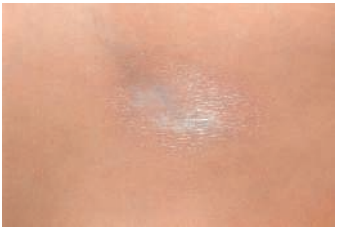
Therapy

- **Corticosteroids:**
  - Start with 20 mg prednisolone b.i.d.; if needed, increase to 40 mg t.i.d. or use pulse therapy. In children with dermatomyositic vasculitis, t.i.d. regimens recommended to suppress disease rapidly.
  - As soon as CK starts to drop, switch to single dose in morning and start tapering in 2 week intervals, checking clinical status and CK before each dose reduction.
  - After several months, switch to alternate-day therapy for its adrenal-sparing role. Often long-term low-dose corticosteroids are needed, but a try at discontinuation is warranted.

- **Second-line agents:**
  - Methotrexate 5–15 mg p.o. or 15–50 mg i.v. weekly or azathioprine 1–3 mg/kg daily; either can be combined with corticosteroids.
  - Cyclophosphamide and cyclosporine are less effective.
- **Intravenous immunoglobulins:** 2 g/kg daily for 2 days; repeat every 4 weeks for 6–12 months; indicated for resistant cases, children with vasculitic component, and in those with steroid-induced diabetes mellitus.
- **Skin:** Antimalarials may help cutaneous lesions, as do topical corticosteroids. Sunscreens essential.
- **Other measures:** Bed rest during flares; physical therapy when stable; absolutely essential to avoid loss of function, especially for children, but if too strenuous, can trigger relapse. Watch for pneumonia—common complication.
- **Paraneoplastic disease:** Appropriate treatment of underlying malignancy; usually combined with or followed by corticosteroids, as recommended by oncologist.

13.4 Morphea

- **Overview:**
  - *Synonyms:* Localized scleroderma, circumscript scleroderma.
  - *Definition:* Cutaneous sclerosis without systemic involvement; several clinical variants.
  - *Epidemiology:* Uncommon disease; female: male 3:1; incidence around 3/100 000 yearly.
  - *Pathogenesis:* Poorly understood. Association with *Borrelia burgdorferi* not substantiated. Circulating autoantibodies support immune role.
- **Clinical features:**
  - *Classic morphea:*
    - Circumscribed sclerotic plaque with ivory center and red-violet periphery (*lilac ring*) (Fig. 13.**5a**). Starts as erythematous patch that slowly spreads. Rarely attached to underlying structures. Usually solitary; 5–20 cm.
    - *Course:* spontaneous or therapy-induced regression occurs.
    - Systemic findings uncommon; rarely malaise or Raynaud phenomenon.
  - *Variants:*
    - *Plaque form*: Larger solitary lesions.
    - *Atrophoderma of Pasini and Pierini:* Superficial erythematous variant of morphea, most common in young girls on trunk, resolves with atrophy and hyperpigmentation but no sclerosis. Clinically sharp vertical drop from normal skin into depressed lesion.
    - *Guttate*: Multiple small, often hypopigmented lesions.
    - *Nodular:* Keloid-like lesions, protuberant.
    - *Linear:* Lesion involving limb, usually leg, in children with bone loss and shortening of limb, as well as loss of function (Fig. 13.**5b**).
    - *Coup de sabre:* Lesion on forehead resembling scar from saber blow; may involve orbit and its content.
    - *Hemifacial atrophy (Parry–Romberg syndome):* Extreme form of linear morphea, distortion of one side of face with alopecia and abnormal pigmentation, sometimes with seizures or trigeminal neuralgia. Deeper involvement than coup de sabre. Some do not recognize it as morphea variant.
    - *Disabling pansclerotic morphea (generalized morphea):* Widespread morphea without systemic involvement. Muscle atrophy, loss of limb function, occasionally fatal.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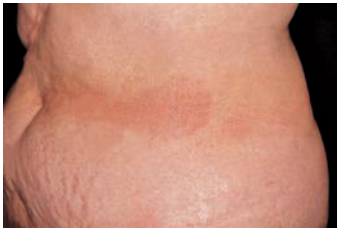
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Fig. 13.5 · **Morphea. a** Annular lesion. **b** Linear lesion.

  - *Lichen sclerosus et atrophicus–like lesions:* Overlap, especially in nongenital lesions (see next section).

- **Histology:** Classic picture of thickened amorphous collagen with entrapment of adnexal structures and fat, occasionally eosinophilic infiltrate. Identical to systemic sclerosis.
- **Diagnostic approach:**
  - Skin biopsy can confirm diagnosis, but not distinguish between morphea and systemic sclerosis. Must rely on clinical findings.
  - ANA and anti-ss-DNA may also be found in linear and widespread morphea.
  - With widespread disease, evaluate joints and esophagus.
- **Differential diagnosis:**
  - Pseudoscleroderma, especially porphyria cutanea tarda and graft-versus-host disease.
  - Drug reaction (bleomycin-induced sclerosis).
- **Therapy:**
  - Solitary lesions with high-potency topical corticosteroids, also under occlusion or intralesional.
  - Bath PUVA or UVA1 (p. 606).
  - Sometimes large plaques respond to penicillin even though the proposed link between *Borrelia burgdorferi* and morphea has been dispelled. Proponents advise repeated courses of i. v. or i. m. penicillin.
  - For widespread or rapidly advancing disease, consider therapy usually reserved for systemic sclerosis.

13.5 Lichen Sclerosus

- **Synonyms:** Lichen sclerosus et atrophicus, lichen albus, white spot disease.
- **Definition:** Dermatosis that presents with either porcelain-white papules and plaques or atrophy and classic histological picture.
- **Epidemiology:** Women more often affected than men; two peaks—prepubertal and later in adult life—but onset at all ages possible.
- **Pathogenesis:** Not totally clear, but IgG antibodies against extracellular matrix protein 1 (EMP1) identified in about 75% of patients.
- **Clinical features:**
  - *Cutaneous lesions*: Typically porcelain-white patches or plaques with an erythematous border. On trunk, very similar to morphea. Sometimes multiple smaller white papules are present (*confetti lesions*, *white spot disease*). Typically

on trunk, especially upper back, as well as flexures. Follicular hyperkeratoses or dilated follicles common; occasionally bullous or hemorrhagic. Asymptomatic.

- *Genital lesions in women:* White atrophic lesions involving vulva, labia minora, clitoris, and introitus (Fig. 13.**6a**). Involvement may spread to perianal region. Typically pruritic; often atrophic, may develop hemorrhage with trauma. Most common in older women (known to gynecologists as *kraurosis vulvae*), but also seen in prepubescent children. Latter sometimes resolves spontaneously, but may persist.

Caution: In young girls, lichen sclerosus with perianal involvement and hemorrhagic areas is frequently mistaken for child abuse.

- *Genital involvement in men*: Lichen sclerosus is a common cause of phimosis, usually not pruritic, and presents with easily damaged white atrophic patches (Fig. 13.**6b**). Often first identified on circumcision specimens; often resolves following procedure. Also known as balanitis xerotica obliterans.
- There is a slight risk of squamous cell carcinoma developing in genital lichen sclerosus, so patients should be monitored.

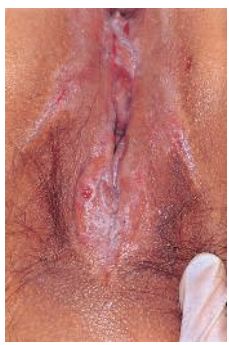
► **Histology:** Epidermal atrophy, follicular plugs, swollen edematous upper dermis with initial band-like infiltrate in upper–mid dermis. Sometimes subepidermal blister with hemorrhage. Older lesions closely resemble morphea. Possible distinction with elastin stain, as lichen sclerosus more likely to show damage.

► **Diagnostic approach:** Clinical examination, biopsy.

► **Differential diagnosis:** On trunk, morphea and vitiligo. Female genitalia: chronic dermatitis, vitiligo, erosive lichen planus, autoimmune bullous diseases. Male genitalia: balanitis in all its variants, idiopathic phimosis, erosive lichen planus.

► **Therapy:**

- *Trunk:* High-potency topical corticosteroids; also try selective UVB phototherapy (SUP) or bath PUVA.
- *Genitalia:* High-potency topical corticosteroids or intralesional corticosteroids (triamcinolone 10 mg/mL diluted 1:3 in lidocaine). Much more effective than topical estrogens or testosterone. Topical immunomodulators (tacrolimus or pimecrolimus).
- In young boys, topical corticosteroids can even reverse phimosis. If phimosis is persistent, then circumcision, perhaps with meatotomy.



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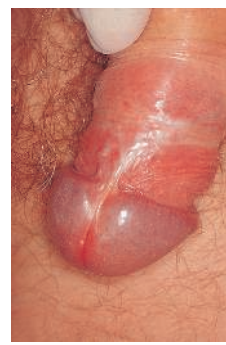

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Fig. 13.**6** · **Lichen sclerosus. a** Extensive involvement of female genitalia. **b** Penile disease with phimosis.

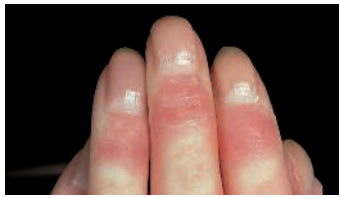
13.6 Systemic Sclerosis

Overview

- **Synonyms:** Systemic scleroderma, progressive systemic sclerosis.
- **Definition:** Multiorgan disease with diffuse sclerosis of connective tissue favoring skin, lungs, gastrointestinal tract and kidneys.
- **Epidemiology:** Incidence 1–2/100 000 yearly; prevalence 20–75/100 000. Peaks between third and fifth decades; increases with age; female:male ratio 5:1, but men have worse prognosis; considerable geographic and ethnic variation.
- **Pathogenesis:**
  - Systemic sclerosis features small-vessel vasculopathy, fibrosis, immune activation.
  - Genetic predisposition (HLA-DR3, -DR5, -DRw6, -DRws52).
  - Current evidence favors vessel damage as the most likely primary event.
  - Autoreactive T cells appear, as in graft-versus-host disease; they may be transferred from fetus to mother during pregnancy (*microchimerism*).
  - Increased production of types I, III, and Iv collagen as well as fibronectin and proteoglycans with deposition in affected connective tissue.
- **Classification:** The German Dermatologic Research classification identifies three forms of systemic sclerosis with progressively worse prognosis:.
  - *Acral systemic sclerosis, type I:* Only involvement of hands and forearms.
  - *Acral systemic sclerosis, type II:* Starts on hands, but spreads to arms and trunk.
  - *Systemic sclerosis, type III:* Starts on trunk, usually severe facial involvement.
  - CREST syndrome can include types I or II. It features **c**alcinosis, **R**aynaud phenomenon, **e**sophageal disease, **s**clerodactyly, **t**elangiectases.

Clinical Features

- **Skin:**
  - *Hands*: Fingers initially puffy and edematous; later sclerodactyly (Fig. 13.**7a**), with loss of finger pads, tightening, reduced motion; painful fingertip ulcers (*rat bite ulcer*); loss of cuticle with telangiectases (*Heuck–Gottron sign*); peripheral calcinosis, often with ulceration of overlying skin and extrusion of calcified debris (*Thibierge–Weissenbach syndrome*).
  - *Face:* Microstomia with tightening of frenulum (Fig. 13.**7b**) (older denture wearers may have trouble inserting and removing dentures); reduced facial expression; prominent telangiectases.
  - Diffuse sclerosis of skin, sometimes restricts respiratory motion (Fig. 13.**7c**).
  - Raynaud phenomenon; often presenting sign.
  - Characteristic *confetti-like hypopigmentation:* focal hypopigmentation with follicular repigmentation; more dramatic in blacks; mistaken for vitiligo as skin often not yet sclerotic.
- **Histology:** Diffuse increase in collagen with loss of vessels and adnexal structures; perivascular infiltrates, sometimes eosinophils and plasma cells; identical to morphea.
- **Systemic findings:**
  - *Gastrointestinal tract:* Sclerosis of lingual frenulum reduces tongue motility; often sicca syndrome; swallowing problems; impaired esophageal motility; with more diffuse involvement, impaired transit and ileus.
  - *Lungs:* Problems both because skin restricts motion and pulmonary fibrosis interferes with oxygen diffusion.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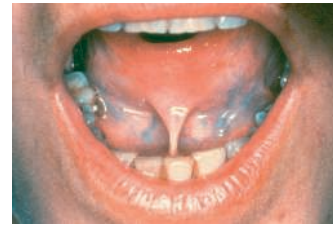
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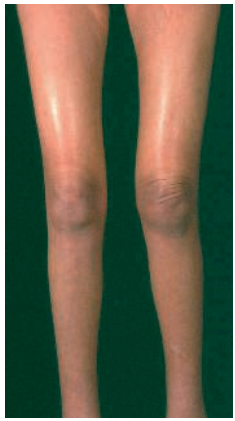
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Fig. 13.7 · **Systemic sclerosis. a** Arachnodactyly. **b** Restriction of frenulum. **c** Diffuse skin thickening and tightness.

- *Kidneys:* Hypertension and progressive renal failure because of nephrosclerosis.
- *Heart:* Subtle and late, but can develop myocardial fibrosis and cor pulmonale. Pericardial effusions common, but usually asymptomatic.
- *Liver:* 15% have associated primary biliary cirrhosis and positive antimitochondrial antibodies.
- *Musculoskeletal:* Many present with arthralgias and muscle pain: later main problem is muscle atrophy. Overlap syndrome with polymyositis (anti-PM-Scl antibodies).
- *Bones:* Acro-osteolysis.
- *Teeth:* Widening of periodontal membrane (useful in radiologic diagnosis, but of little clinical significance).

Diagnostic Approach

- **Skin:** Check for cutaneous involvement and identify most urgent problems.
- **Lungs:** Chest radiograph, pulmonary diffusion studies, bronchoalveolar lavage (to assess inflammatory cells; prognostically useful).
- **Skeleton:** Radiologic documentation of osteolysis, calcification.
- **Gastrointestinal tract:** Esophageal manometry and functional scintigraphy.
- **Heart:** EKG, echocardiogram, cardiac catheterization if cor pulmonale is present.
- **Kidneys:** Renal function, urine status.

- **Laboratory:**
  - Routine tests (CBC, liver function, sed rate, C-reactive protein).
  - *Serology:*
    - More than 90% have positive ANA.
    - Anti-Scl-70 positive in 30–70%; usually with severe course.
    - Rarely (< 5%) anti-RNA polymerase I–II; poor outlook.
    - Anti-centromere antibodies present in type I systemic sclerosis and CREST syndrome.
    - Anti-DM-Scl in overlap syndrome.
    - Rheumatoid factor positive in 30%.

Differential Diagnosis

- **Pseudoscleroderma:** see below.
- **Other collagen–vascular disorders:**
  - Mixed collagen–vascular disorders.
  - Overlap syndromes.
- **Graft-versus-host disease**.
- **Others:** Generalized morphea. Puffy hands can be confused with early stage of acrodermatitis chronica atrophicans.

Therapy

- ***Note:*** Types I and II can usually be treated conservatively, but type III requires immunosuppressive therapy. Each specific problem requires carefully adjusted therapy.
- **Raynaud phenomenon:** See below; same recommendations as for idiopathic disease.
- **Calcification:** Surgery sometimes required; low-dose coumarin may reduce inflammation.
- **Ulcers:** Occlusive dressings and skin equivalents are helpful for distal ulcers.
- **Sclerosis:** Neither penicillamine nor extracorporeal photophoresis has been proven definitely effective. For rapidly progressive disease, immunosuppression often tried.
  - *Immunosuppressive agents:* Systemic corticosteroids (prednisolone 0.5 mg/kg daily), perhaps combined with azathioprine 1–2 mg/kg daily. Methotrexate 20–30 mg weekly, cyclosporine 3–5 mg/kg daily, or cyclophosphamide 2 mg/kg daily or as pulse therapy (500–800 mg once monthly) can be tried; none is overwhelmingly useful.
  - *Aspirin:* Pain relief and inhibition of platelet function.
- **Internal organ involvement:**
  - Angiotensin-converting enzyme (ACE) inhibitors are treatment of choice for renal hypertension.
  - Proton pump inhibitors (omeprazole 20–40 mg daily) indicated for esophageal dysfunction.
  - Pulmonary hypertension treated with i. v. prostacyclin; interstitial lung disease may respond best to cyclophosphamide.
- **Physical therapy:** Infrared light may help increase circulation by raising body temperature; physical therapy can help avoid contractures and retain function.

13.7 Pseudoscleroderma

Although the term "pseudoscleroderma" is not ideal, the concept is sound. There are a number of diseases that mimic morphea or systemic sclerosis, and in many instances appear to have similar causes. They are reviewed in Table 13.**5**.

Table 13.5 · **Causes of pseudoscleroderma**

Disease	Comments	See
Porphyria cutanea tarda	Sclerotic areas, usually on chest, coupled with skin fragility on hands and facial hirsutism	p. 312
Graft-versus-host disease	Chronic stage often features cutaneous sclerosis, usually depigmented	p. 227
Diabetes mellitus	Stiff hand syndrome, sclerodactyly in juveniles	p. 319
POEMS syndrome (Crow-Fukase syndrome)	**P**olyneuropathy, **o**rganomegaly, **e**ndocrinopathy, **m**onoclonal gammopathy (plasma cell dyscrasia), **s**kin changes (sclerosis, glomeruloid hemangiomas)	p. 322
Scleredema	Usually sclerosis of back; extensive mucin; associated with diabetes mellitus	p. 320
Scleromyxedema	Sclerosis associated with gammopathy	p. 320
Nephrogenic fibrosing dermopathy	Resembles scleromyxedema but found as complication of renal dialysis	p. 320
Phenylketonuria	Metabolic disturbance with mental retardation and hypopigmentation; usually detected and managed so sclerosis does not appear	p. 373
Stiff skin syndrome (congenital fascial dystrophy)	Fibrillin mutation leads to sclerodermoid changes, restriction of motion; neurological changes; hypertrichosis	
Carcinoid syndrome	Flushing more typical, but repeated vascular stimulation may lead to sclerosis	
Premature ageing syndromes	Both Werner syndrome and progeria may be confused with scleroderma initially	
Toxin exposure	*Eosinophilia–myalgia syndrome:* Ingestion of contaminated tryptophan led to pulmonary disease, hypereosinophilia, and cutaneous sclerosis *Toxic oil syndrome:* Ingestion of contaminated rapeseed oil caused similar picture	
Drugs	Bleomycin, administered locally or systemically, can cause sclerosis	

Eosinophilic Fasciitis

- **Synonym:** Shulman syndrome.
- **Definition:** Cutaneous induration, often acute onset, with joint contractions, eosinophilia and inflammatory infiltrate in fascia; no systemic involvement except joint contractures.
- **Epidemiology:** Uncommon; age peak 40 years.

- **Pathogenesis:** Unclear; sometimes follows excessive physical activity.
- **Clinical features:**
  - *Skin:* Symmetrical edematous, often painful induration, usually on distal limbs. Rarely associated with morphea.
  - *Musculoskeletal:* Arthralgias, myalgias; reduced range of motion and contractures usually affecting hands, occasionally elbows, shoulders, or other sites.
  - Patients may have malaise, fever, or other systemic complaints.
  - Sometimes associated with hematologic or lymphoproliferative disorders.
- **Histology:** Fascia markedly thickened; inflammatory infiltrate usually rich in eosinophils.
- **Diagnostic approach:**
  - Deep biopsy sampling the fascia; tissue should be preserved in muscle clamp to avoid artifacts.
  - *Laboratory:* Eosinophilia (90%), elevated sed rate (80%), hypergammaglobulinemia (80%), ANA (25%), rheumatoid factor (15%).
  - Borrelial serology to exclude Lyme disease.
- **Differential diagnosis:** Scleredema—not usually on limbs, scleromyxedema, eosinophilia-myalgia syndrome, generalized morphea.
- **Therapy:**
  - Often resolves spontaneously.
  - Prednisolone 60 mg daily; prompt improvement, rapid tapering; good outlook.
  - If poor response, bath PUVA or antimalarials.

13.8 Mixed Collagen–Vascular Disease

- **Synonym:** Sharp syndrome.
- **Definition:** Disease with features of SLE, systemic sclerosis and dermatomyositis, characteristic laboratory findings, and good prognosis.
- **Epidemiology:** Most patients are women; female: male ratio 4:1.
- **Pathogenesis:** Unknown.
- **Clinical features:**
  - Features of all three diseases, but nonetheless combine in a recognizable clinical pattern.
  - Raynaud phenomenon is obligatory; usual presenting sign.
  - Intermittent swelling of hands and feet with distal polymyositis.
  - Often lymphadenopathy.
  - Skin changes combine those of systemic LE with the confetti-like hypopigmentation of systemic sclerosis. Also diffuse nonscarring alopecia.
  - Wide variety of other signs and symptoms including serositis, fever, weight loss, pulmonary fibrosis, esophageal motility disturbances, trigeminal neuralgia. Renal disease uncommon.
- **Diagnostic approach:** Presence of high titer ANA; rarely anti-DNA antibodies; instead high titer anti-ENA (anti-U1-RNP) antibodies.
- **Differential diagnosis:** In addition to the obvious considerations of the three major collagen–vascular disorders, any one of which can appear dominant, one must consider other overlap syndromes such as polymyositis–systemic sclerosis. Usually the antibody pattern determines the answer.
- **Therapy:** Usually systemic corticosteroids are effective, although recurrence with tapering is common. Can be combined with azathioprine or other immunosuppressive agents. Milder cases respond well to antimalarials.

13.9 Other Rheumatoid Diseases

Rheumatic Fever

Streptococcus pyogenes causes several postinfectious immunologic disorders. Rheumatic fever is not associated with impetigo, but acute glomerulonephritis is. Rheumatic fever may be associated with erythema nodosum as well several distinctive cutaneous changes:

- *Erythema marginatum:* Perhaps 10% of patients develop unique rapidly moving, peripherally prominent patches and plaques; quickest of all the annular erythemas (p. 711).
- *Nodules:* Appear in first month of infection; usually along forearm (more distal than in rheumatoid arthritis); resolve spontaneously.

Rheumatoid Arthritis

- **MIM code:** 180300 (but usually not genetic).
- **Definition:** Most common of the autoimmune collagen–vascular disorders; primarily affects joints, with changes in synovial membranes and articular structures, leading to deformity and ankylosis.
- **Pathogenesis:** Viral triggers strongly suspected; possible gene locus at 6p21.3; HLA associations.
- **Clinical features:**
  - *Systemic findings:* multiple—should be reviewed in internal medicine texts.
  - *Skin findings:*
    - Rheumatoid nodules (see below).
    - Granulomatous dermatitis; often linear bands.
    - *Vasculitis:* many different forms possible but usually acral.
    - *Neuropathy:* paresthesias, pain, decreased sweating.
    - *Ulcerations:* sometimes caused by intimal proliferation (cut-onion pattern) without inflammation; also acral.
    - Pyoderma gangrenosum (p. 251).
- **Therapy:** Combination of anti-inflammatory and immunosuppressive therapy for underlying disease, coupled with specific dermatologic approaches.

Rheumatoid Nodule

- **Clinical features:** Common finding in rheumatoid arthritis; up to 2–3 cm nodules appear around elbows and on extensor surface of forearm; overlying skin usually unaffected, but lesions may drain.
- **Histology:** Classic palisading granuloma: macrophages surrounding area of necrobiotic collagen with fibrin. Similar picture in granuloma annulare (p. 292) but with mucin and in necrobiosis lipoidica but with plasma cells (p. 293).
- **Diagnostic approach:** Confirm serological diagnosis of rheumatoid arthritis. Excisional biopsy of small nodule if questions exists.
- **Differential diagnosis:** There are many lesions that appear similar:
  - *Subcutaneous granuloma annulare:* When a child has deep necrobiotic nodules, they do not have rheumatoid arthritis but just granuloma annulare. Also appears on hands in adults.
    - ***Note:*** Consider the whole clinical picture; then there is no overlap between rheumatoid arthritis and granuloma annulare.
  - *Osteoarthritis: Heberden nodes* are cartilaginous and bony enlargements of the distal interphalangeal joints; when proximal, the same lesions are called *Bouchard nodes.* Both are much more common than rheumatoid nodules.

- *Gout:* Tophi are larger, more acral; uric acid answers question.
- Fibrous nodules and ulnar bands in acrodermatitis chronica atrophicans; no necrobiosis on biopsy; other clinical pattern.
- *Rheumatic fever:* 5% of patients may have nodules but they are transient and associated with acute disease; usually on forearms; on biopsy, not necrobiotic.
- *Syphilis:* Subcutaneous nodules can be seen in late syphilis; fibrosis and granulomatous inflammation with plasma cells.

► **Therapy:** Observe or consider excision; then risk of ulcers or sinus tracts.

Juvenile Rheumatoid Arthritis

► The systemic form (least common variant) of juvenile rheumatoid arthritis is known as *Still disease*. Patients are systemically ill with fever spikes coupled with a transient, pale pink, blanching nonpruritic rash. Also marked lymphadenopathy. May go on to have severe vasculitis, consumptive coagulopathy, and macrophage activation syndrome.

Sjögren Syndrome

► **MIM code:** 270150.
► **Definition:** Autoimmune disease with predilection for epithelial surfaces and exocrine glands.
► **Epidemiology:** More common in women; female:male ratio 9:1.
► **Pathogenesis:** Unknown; viral triggers suspected.
► **Classification:** Primary Sjögren syndrome vs. secondary Sjögren syndrome when associated with other defined collagen–vascular disorders (such as systemic sclerosis).
► **Clinical features:** Primarily affects the eyes and mouth; classic findings include dry eyes (reduced tears) and dry mouth (reduced saliva). The oral findings often lead to chronic burning or pain, difficulty swallowing, and caries. Also arthralgias and arthritis. Almost 50-fold increased incidence of B-cell lymphoma; usually MALT type.
- Skin findings are uncommon:
  - Annular erythematous lesions common in Sjögren syndrome among East Asians.
  - Dry skin common but not diagnostically useful.
  - Variety of forms of vasculitis.

► **Diagnostic approach:** Primary Sjögren syndrome can be diagnosed when four of the following six points are present:
- Dry eyes: symptoms.
- Schirmer test.
- Dry mouth: symptoms.
- Reduced saliva production, abnormal sialogram or scintigraphy.
- Abnormal salivary glands on labial biopsy.
- Anti-SS-A/Ro or anti-SS-B/La antibodies.

► **Differential diagnosis:** Postradiation syndrome, HIV/AIDS, hepatitis C infection, lymphoma, sarcoidosis, graft-versus-host disease, and use of anticholinergic drugs should all be excluded, as well as associated collagen–vascular disorders.
► **Therapy:** Artifical tears and salvia; secretagogues; NSAIDs or antimalarials for arthritis; watch for oral candidiasis; management with internist, ophthalmologist, or oral medicine specialist.

13.10 Raynaud Syndrome

Overview

- **Definition:** Vascular spasms of digital arteries with distinct clinical patterns; often associated with autoimmune diseases.
- **Epidemiology:** Female:male ratio > 4:1.
- **Classification:**
  - *Raynaud phenomenon* is the classical clinical triad of ischemia (white), cyanosis (blue), and reactive hyperemia (red) occurring sequentially in a digit.
  - *Primary Raynaud syndrome (Raynaud disease)* is the presence of Raynaud phenomenon for more than 2 years without evidence of an underlying disease.
  - *Secondary Raynaud syndrome:* Same clinical findings, but associated with a variety of disorders:
    - *Collagen–vascular disorders* (especially systemic sclerosis or mixed collagen–vascular disorder, but any of the others is possible).
    - *Exogenous factors:* Vibration (jackhammer operator), repeated hammering (hypothenar hammer syndrome); injuries, postoperative; cold exposure; reflex sympathetic dystrophy (Sudeck atrophy).
    - Gammopathy with hyperviscosity syndrome; polycythemia vera, Waldenström macroglobulinemia.
    - Combination of vasculitis and hyperviscosity: paroxysmal nocturnal hemoglobinuria, cold agglutinin disease, cryoglobulinemia (p. 307), hot-cold hemolysin.
    - Obstructive arterial disease: arteriosclerosis, thromboangiitis obliterans (Buerger disease), thrombosis, thoracic outlet syndrome.
    - Neurological diseases with peripheral manifestations.
    - *Toxins:* Medications (amphetamines, β-blockers, clonidine, oral contraceptives, ergot derivatives—both in medications and in biological products, cytostatic agents (bleomycin, vinca alkaloids); heavy metals, vinyl chloride.
    - *Others:* Paraneoplastic, hypothyroidism.
- **Clinical features:**
  - Triad explained by pathophysiology:
    - *White:* Sudden vasospasm; cold numb fingers (*cadaver digit*).
    - *Blue:* Venous constriction persists even in face of arterial relaxation; cyanosis.
    - *Red:* Restored blood flow, pain, throbbing.
  - Features usually bilateral; typically start in only one digit. After years, may develop persistent finger swelling.
  - Cuticle thickens, proximal nail fold is thinned with telangiectases.
  - Occasionally involvement of toes, nose, or ears.
- **Diagnostic approach:**.
  - Careful history, confirming presence of white–blue–red triad and searching for triggering factors.
  - Clinical and laboratory evaluation to rule out the causes of secondary Raynaud syndrome, including sed rate, ANA, anti-DNA antibodies, anticardiolipin antibodies, β_2-glycoprotein, cold agglutinins, cryoglobulins, serum protein electrophoresis, blood viscosity test.
- **Therapy:** If an underlying disease is found, it should be treated. The Raynaud phenomenon is managed in the same way regardless of cause.
  - ***Note:*** Patients with Raynaud phenomenon must not smoke.
  - Avoidance of cold: Warm gloves, hand warmers.

- Calcium channel blockers are treatment of choice; nifedipine 5 mg t.i.d.; if orthostatic hypotension is problem, try diltiazem 60–120 mg daily or verapamil 240–360 mg daily.
- Other vasodilators such as prazosin also useful, start with 1 mg daily; may increase slowly to as high as 6 mg daily.
- Calcitonin 100 IU i. v. daily for 10–14 days, or calcitonin nasal spray 100 IU 1–3× weekly.
- *Prostaglandins or prostacyclins:* All very expensive; given i. v. either continuously in hospital or daily for 6–8 hours over 5 days:
  - Alprostadil (PGI2).
  - Epoprostenol (prostacyclin).
  - Iloprost trometamol.
- *Topical nitroglycerine paste:* May help to avoid fingertip necrosis.
- *Supplemental measures:* Physical therapy, infrared light, windmilling (swinging hands like windmill to force blood to periphery).

13.11 Graft-Versus-Host Disease (GVHD)

► **Definition:** Disease following bone marrow transplantation or rarely blood transfusion where immunocompetent donor T cells recognize and attack host antigens.

Acute Graft-Versus-Host Disease

► **Epidemiology:** Occurs in 50% of bone marrow transplantation patients.

► **Pathogenesis:** The pathophysiology of GVHD is complex; through a variety of mechanisms donor T cells initiate processes damaging host tissue. GVHD is the greatest threat to the recipient. Even with highly improved matching techniques and many new avenues of immunosuppression, the problem persists. Prophylaxis measures include more refined tissue matching, treating graft material with anti-T-cell serum, specific monoclonal antibodies or mechanical measures to eliminate T cells, and modifying the immunosuppression regimens with immune modulators (cyclosporine, tacrolimus, pimecrolimus).

► **Clinical features:**
- Starts 1–5 weeks after procedure; occurs in 30–60% with a mortality of 10–15%.
- Most commonly affects gastrointestinal tract (diarrhea) and liver (elevated enzymes, decreased function, rarely failure).
- *Skin:*
  - Initially pruritus and tender skin; then macular exanthem favoring flexures, especially axilla.
  - Can progress to widespread skin loss.

► **Histology:** Sick epidermis, atrophy, vacuolar degeneration, apoptosis of keratinocytes; expression of HLA-DR on keratinocytes may precede morphologic changes.

► **Diagnostic approach:** Skin biopsy usually done, but diagnostic only in advanced disease. Early GVHD is very similar to drug reaction microscopically.

► **Differential diagnosis:** The usual clinical question is a drug reaction; many patients have received pre-transplant radiation or chemotherapy, further confusing the issue. When severe, resembles toxic epidermal necrolysis.

► **Therapy:** Mainstay is modifying immunosuppressive regimen, usually increasing corticosteroid dosage, or adding methotrexate.

Chronic Graft-Versus-Host Disease

► **Epidemiology:** Occurs in about 10% of patients; by definition > 100 days after transplantation.

- **Clinical features:**
  - *Skin:* Two basic patterns:
    - Sclerotic lesions, often with hypopigmentation; resembling morphea.
    - Lichenoid exanthem, similar to lichen planus, later more diffuse sclerosis and poikiloderma, with worse prognosis.
  - *Systemic involvement:* includes liver, gastrointestinal tract, and also lungs with bronchiolitis obliterans.
- **Histology:** Either sclerosis or lichenoid infiltrate.
- **Diagnostic approach:** Usually clinically obvious because of past history.
- **Differential diagnosis:** Pseudoscleroderma (p. 222) or lichen planus and lichenoid drug reactions for the skin findings.
- **Therapy:** Immunosuppressive agents that disrupt activation of donor T cells are in wide use. Common choices include cyclosporine, corticosteroids, tacrolimus, mycophenolate mofetil, and T-cell depletion with monoclonal antibodies. Additional possibilities include bath PUVA for the sclerodermoid changes, thalidomide (initially 200–400 mg daily, then reduce to 100 mg daily), extracorporeal photophoresis, high-dose intravenous immunoglobulins, and anticytokine antibodies such as anti-TNFα.

14 Autoimmune Bullous Diseases

14.1 Classification

- **Loss of intraepidermal adhesion:**
- **Pemphigus vulgaris with subtypes:**
  - Classic.
  - Pemphigus vegetans (Neumann type, Hallopeau type).
- **Pemphigus foliaceus with subtypes:**
  - *Classic:*
    - Fogo selvagem (endemic variant).
    - Pemphigus erythematosus (Senear–Usher).
  - Paraneoplastic pemphigus.
  - Drug-induced pemphigus.
  - *IgA pemphigus:*
    - Subcorneal pustular dermatosis (Sneddon–Wilkinson).
    - Intraepidermal neutrophilic dermatosis.
- **Loss of subepidermal adhesion:**
  - *Pemphigoid:*
    - Bullous pemphigoid.
    - Pemphigoid gestationis.
    - Cicatricial pemphigoid.
    - Other variants.
  - *Linear IgA disease:*
    - Chronic bullous disease of childhood.
    - Adult form.
  - Epidermolysis bullosa acquisita.
  - Dermatitis herpetiformis.

14.2 Pemphigus Group

Pemphigus refers to a group of disorders with loss of intraepidermal adhesion because of autoantibodies directed against proteins of the *desmosomal complex* that hold keratinocytes together. The desmosome is a complex structure, with many of its components targets for autoantibodies.

Pemphigus Vulgaris (PV)

- **Definition:** Severe, potentially fatal disease with intraepidermal blister formation on skin and mucosa caused by autoantibodies against desmogleins.
- **Epidemiology:** Incidence 0.1–0.5/100 000 yearly, but higher in some ethnic groups. Most patients middle-aged.
- **Pathogenesis:**
  - Genetic predisposition: HLA-DRQ402, -DQ0505.
  - Patients develop antibodies against desmoglein 3 (Dsg3) and later desmoglein 1 (Dsg1) (see Fig. 1.**6**, p. 6). The bound antibodies activate proteases that damage the desmosome, leading to acantholysis.

- Serum antibody titer usually correlates with severity of disease and course.
  - Occasionally drugs cause pemphigus vulgaris and pemphigus foliaceus. Agents containing sulfhydryl groups (penicillamine, captopril, piroxicam) are more likely to cause pemphigus foliaceus; those without sulfhydryl groups tend to cause pemphigus vulgaris. The latter group includes β-blockers, cephalosporins, penicillin, and rifampicin.
  - ▶ ***Note:*** Drugs from either group can cause either type of pemphigus.

► **Clinical features:**

- Sites of predilection include oral mucosa, scalp, face, mechanically stressed areas, nail fold, intertriginous areas (can present as intertrigo).
- The blisters are not stable, as the epidermis falls apart; therefore, erosions and crusts common (Fig. 14.**1 a,b**).
- Usually has three stages:
  - *Oral involvement:* In 70% of patients, PV starts in the mouth with painful erosions. Other mucosal surfaces can also be involved. Caused by anti-Dsg3 antibodies, as Dsg3 is the main desmoglein in mucosa.
  - Additional localized disease, often on scalp.
  - ▶ ***Note:*** Always check the scalp in patients with unexplained oral erosions.
  - Generalized disease because of development of antibodies against Dsg1 which is present in skin along with Dsg3. Painful, poorly healing crusted erosions and ulcers; blisters hard to find. Pruritus uncommon.

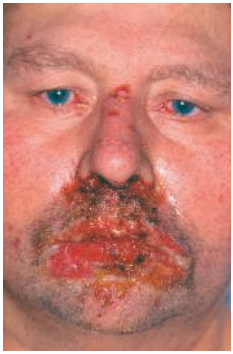
► **Histology:** When a fresh lesion is biopsied (small excision, not punch biopsy), acantholysis is seen (free-floating, rounded keratinocytes) with retention of basal layer keratinocytes (tombstone effect) and mild dermal perivascular infiltrates (Fig. 14.**1 c**).

► **Diagnostic approach:**

- Clinical evaluation; check sites of predilection.
- *Nikolsky sign:*
  - *True Nikolsky sign:* Gentle rubbing allows one to separate upper layer of epidermis from lower, producing blister or erosion—fairly specific for pemphigus.
  - *Pseudo-Nikolsky sign (Asboe–Hansen sign)*: Pressure at edge of blister makes it spread—less specific, seen with many blisters.
- *Histology:* Can be helpful, but often just erosions or nonspecific changes.
- *Direct immunofluorescence:* Perilesional skin shows deposition of IgG (100%), C3 (80%) or IgA (< 20%), as well C1q in early lesions. Antibodies surround the individual keratinocytes.
- *Indirect immunofluorescence:* Using monkey esophagus, 90% of sera show positive reaction; titer can be used to monitor disease course.
- *ELISA:* Can be used to identify anti-Dsg3 with mucosal disease or anti-Dsg1 or anti-Dsg3 with widespread disease.
- Check for associated diseases, especially thymoma and myasthenia gravis.

► **Differential diagnosis:**

- When the skin is involved, the question is usually which autoimmune bullous disease. On rare occasions, bullous impetigo, dyskeratotic acantholytic disorders (Darier disease, Hailey–Hailey disease, Grover disease) can cause problems.
- When only the oral mucosa is involved, the following should be considered:
  - Denture intolerance reactions.
  - *Erosive candidiasis:* Not all oral candidiasis features white plaques (thrush); sometimes atrophy and erosions.
  - *Chronic recurrent aphthae:* Usually smaller lesions with erythematous border but sometimes large, persistent ulcers.



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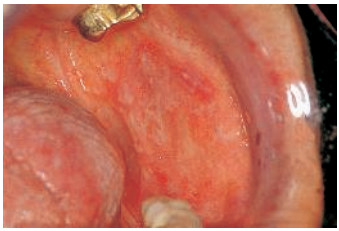

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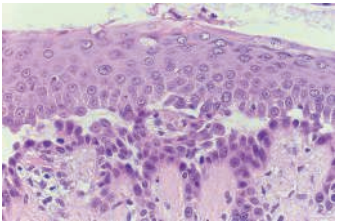


c

Fig. 14.1 · **Pemphigus vulgaris. a** With marked erosions. **b** With oral ulcerations. **c** Histology showing separation just above the basal layer.

  - *Erythema multiforme:* Erosions on lips and mucosa associated with target lesions on skin.
  - *Herpetic gingivostomatitis:* Usually in children.
  - *Erosive lichen planus:* Look for signs of lichen planus elsewhere; if only in mouth, biopsy and direct immunofluorescence often needed.

► **Therapy:**

- Systemic corticosteroids are necessary for long periods of time. The main cause of morbidity and mortality today in patients with pemphigus vulgaris is corticosteroid side-effects. For this reason, corticosteroids are always combined with steroid-sparing agents.
- Patients should be screened for osteoporosis and latent tuberculosis before embarking on long-term corticosteroid therapy. Osteoporosis prophylaxis may be warranted.
- *Combination pulse therapy:* Treatment of choice. Every 3–4 weeks, pulse of prednisolone 1.0 g daily plus single dose of cyclophosphamide 7.5–15.0 mg/kg; in interval cyclophosphamide 1–2 mg/kg daily.
- *Prednisolone-azathioprine therapy:*
  - Start with prednisolone 1.5–2.0 mg/kg and azathioprine 2.5 mg/kg.
  - Goal is to suppress blister formation within 1 week; if this is not achieved; double the prednisolone dose.
  - Once blister formation is suppressed, logarithmic tapering to maintenance dose of prednisolone 8 mg daily and azathioprine 1.5 mg/kg daily.
- *Alternative immunosuppressive agents:* Chlorambucil 0.1–0.2 mg/kg daily; cyclosporine 5.0–7.5 mg/kg daily; mycophenolate mofetil 2.0 g daily.

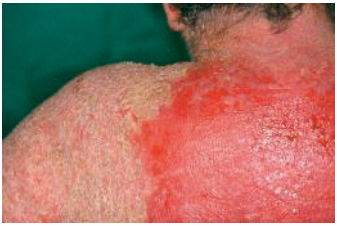
- *Topical measures:* Local anesthetic gels in the mouth before meals may relieve pain and making eating less traumatic; antiseptics and anticandidal measures may also be useful.
- *Therapy-resistant course:* Drastic measures include high-dose intravenous immunoglobulins or column immune absorption of autoantibodies. The immunosuppressive therapy must be continued or a rebound invariably occurs.

Pemphigus Vegetans

- **Definition:** Unusual variant of PV with hyperkeratotic verruciform reaction (vegetans).
- **Clinical features:** Two forms:
  - *Pemphigus vegetans Neumann type:* Originally typical PV, then development of white macerated plaques in involved areas.
  - *Pemphigus vegetans Hallopeau type:* Also known as *pyodermite végétante*, limited to intertriginous areas, starts as pustules that evolve into vegetating lesions.
- **Histology:** Can be tricky; pseudoepitheliomatous hyperplasia and numerous eosinophils; acantholysis can be hard to find.
- **Diagnostic approach:** As for PV.
- **Differential diagnosis:** If mild and localized, can be confused with Hailey–Hailey disease.
- **Therapy:** See PV.

Pemphigus Foliaceus

- **Definition:** Form of pemphigus with superficial blisters caused by autoantibodies against Dsg1.
- **Epidemiology:** All age groups affected; not infrequently children.
- **Pathogenesis:**
  - Autoantibodies against Dsg1, the main desmoglein in the upper epidermis; rarely antibody shift so that they later are formed against Dsg3 and patient develops PV.
  - More often drug-induced than PV. Usual agents have sulfhydryl groups such as captopril, penicillamine, and piroxicam.
  - May be caused by sunburn or as paraneoplastic sign.
- **Clinical features:**
  - Sites of predilection include scalp, face, chest, and back (seborrheic areas) with diffuse scale and erosions (Fig. 14.**2 a**). Can progress to involve large areas (exfoliative erythroderma). Facial rash sometimes butterfly pattern. Oral mucosa usually spared (Dsg1 is scarcely expressed in oral epithelia).
  - Individual lesions are slowly developing slack blisters that rupture easily, forming erosions and red-brown crusts.
  - Several clinical variants discussed below.
- **Histology:** Blister forms in stratum corneum or stratum granulosum; acantholysis rarely seen; usually just a denuded epithelium and sparse dermal perivascular inflammation (Fig. 14.**2 b**).
- **Diagnostic approach:**
  - Clinical appearance.
  - Skin biopsy often not helpful.
  - *Direct* and *indirect immunofluorescence* show superficial deposition of IgG.
  - *ELISA* reveals IgG antibodies against Dgs1.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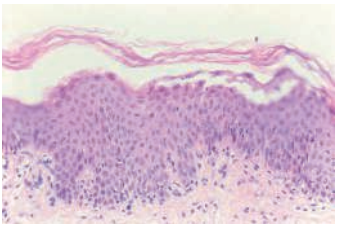
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Fig. 14.2 · **Pemphigus foliaceus. a** With diffuse, superficial erosions. **b** Histology showing subcorneal separation.

- *Medication history:* See PV. Agents with sulfhydryl groups most likely to cause pemphigus foliaceus; main actors are captopril, penicillamine, and piroxicam.

► **Differential diagnosis:** Frequently misdiagnosed, as blisters are so uncommon. Depending on clinical variant, possibilities include drug reaction, photodermatosis, seborrheic dermatitis, lupus erythematosus.

► **Therapy:** Same approach as PV but usually more responsive to therapy. Dapsone may be helpful.

Fogo Selvagem

► **Synonyms:** Brazilian pemphigus, South American pemphigus, wildfire pemphigus (fogo selvagem is Portuguese for wildfire).

► **Definition:** Endemic form of pemphigus foliaceus.

► **Epidemiology:** Found in areas where development is pushing back the jungle in Brazil; transfer of some infectious trigger suspected; common in families; patients usually < 30 years of age; women affected more often.

► **Clinical features:** Same as pemphigus foliaceus; burning is a typical feature, perhaps because of less adequate topical care; classic lesion is denuded burning erosion with roll of pushed-back upper epidermis at periphery. Can evolve into erythroderma. No oral involvement. Without therapy, 40% die within 2 years; others develop chronic disease persisting for decades.

► **Diagnostic approach:** Same as for pemphigus foliaceus.

► **Therapy:** Usually corticosteroids and steroid-sparing agent (azathioprine) suffice; otherwise, regimens as under PV.

Pemphigus Erythematosus

► **Synonym:** Senear–Usher syndrome.

► **Definition:** Uncommon variant of pemphigus foliaceus with additional features of lupus erythematosus.

► **Pathogenesis:** More likely to be triggered by sunlight or medications than other forms of pemphigus foliaceus.

► **Clinical features:** Older patients with erythema and crusting in butterfly distribution and seborrheic areas; often eroded.

► **Histology:** Superficial acantholysis and blister formation, sometimes vacuolar change in basal layer.

► **Diagnostic approach:**

- *Direct immunofluorescence:* Intercellular IgG, sometimes with C3; deposits of IgG, IgM, and C3 at BMZ in 50–70%. IgG and IgM can be found in normal skin.

- ANA positive in 80%; usually homogenous pattern; no specific autoantibodies for lupus erythematosus.
- Check drug history.

► **Therapy:**
- Usually responds to prednisolone 1–2 mg/kg tapered to low maintenance dose; can be combined with antimalarials.
- Meticulous sun avoidance and sunscreens.
- Dapsone also sometimes effective.
- If still not responsive, whole spectrum of agents discussed under PV can be used.

IgA Pemphigus

► **Definition:** Pustular acantholytic dermatosis with intercellular IgA deposition in epidermis.

► **Pathogenesis:** Unknown, but can be associated with gammopathy. Variety of different targets on keratinocyte; most common is desmocollin 1, but also Dsg1 and Dsg3.

► **Clinical features:** Two forms are identified:
- *Subcorneal pustular dermatosis* (*Sneddon–Wilkinson disease*): Lesions are broad annular erythematous patches with peripheral flaccid pustules and central crusting. Often serpiginous or arciform borders. Favor flexures and trunk; never mouth. Pruritic.
- *Intraepidermal neutrophilic dermatosis* (*Huff syndrome*) is clinically similar; *sunflower lesions* are considered typical—multiple pustules arranged like a flower.

▶ ***Note:*** There is disagreement whether an idiopathic form of Sneddon–Wilkinson disease with IgA antibodies exists. We feel the disease is IgA pemphigus and that if the antibodies are not found, once must search again in 6–12 months or seek consultation.

► **Histology:** Usually just a pustule is seen; the subcorneal lesions are flaccid, while the deeper ones are more likely to be intact. Acantholysis is often hard to find.

► **Diagnostic approach:** Diagnosis is made on basis of direct immunofluorescence showing only IgA directed against keratinocytes, either superficially or throughout epidermis.

► **Therapy:** Most cases are responsive to dapsone; if not, corticosteroids and immunosuppressive agents can be used, as for other forms of pemphigus.

Paraneoplastic Pemphigus

► **Definition:** Uncommon blistering disease with variety of clinical patterns and target antigens associated with underlying malignancy.

► **Pathogenesis:** Most often associated with lymphoma, leukemia, Castleman tumor, or thymoma; not with squamous cell carcinomas or adenocarcinomas. Presumably there are cross-reactions between tumor antigens and desmosomal antigens such as all the plakins, desmogleins, and even bullous pemphigoid antigen. The anti-Dsg antibodies seem pathogenetically most important; cell-mediated immunity also plays a role.

► **Clinical features:**
- The most constant feature is severe, persistent painful stomatitis extending from the lips into the pharynx, larynx, and esophagus. Conjunctival involvement may lead to blindness.
- The cutaneous changes are polymorphic, ranging from erythematous macules to lichenoid papules to blisters and erosions.

Note: If a patient is sick and has lesions resembling erythema multiforme, lichen planus, and a blistering disease, be highly suspicious of paraneoplastic pemphigus.

- Some patients develop bronchiolitis obliterans, which is usually fatal.

- **Histology:** The histologic pattern is as variable as the clinical, so it rarely helps in diagnosis.
- **Diagnostic approach:** If indirect immunofluorescence is positive on rat bladder epithelium, this strongly suggests paraneoplastic pemphigus, but such a test is negative in 25% of cases. The combination of IgG antibodies against plakins and desmogleins confirms the diagnosis. In about $^1/_3$ of patients, the underlying tumor is diagnosed after the mucocutaneous disease; "tumor-free" patients deserve a thorough tumor search.
- **Differential diagnosis:** Erythema multiforme, lichen planus, PV, cicatricial pemphigoid, chemotherapy-induced stomatitis, persistent herpes simplex infections.
- **Therapy:**
  - Treating the underlying tumor comes first. The prognosis correlates with the response.
  - There is no consensus on what immunosuppressive regimen to employ, especially in those patients required chemotherapy. Recent reports of good success with anti-CD20 antibodies (rituximab).

14.3 Pemphigoid Group

Bullous Pemphigoid (BP)

- **Definition:** Subepidermal blistering disease caused by autoantibodies to components of the hemidesmosomes in the basement membrane zone (BMZ).
- **Epidemiology:** Most common autoimmune bullous disease; incidence around 1/100 000 yearly. Favors elderly, and incidence clearly much higher in older age groups; one estimate 300× more likely at 90 years of age than at 60 years of age. Men more frequently affected (male:female ratio 2:1).
- **Pathogenesis:**
  - Figure 1.**7** (p. 8) shows the components of the basement membrane zone including the hemidesmosome and extracellular proteins, which anchor the epidermis to the dermis. Structural or genetic defects in components of the hemidesmosome, which serves to anchor the epidermis to the dermis, cause epidermolysis bullosa (p. 351); autoantibodies cause BP or other related diseases.
  - Autoantibodies are directed against two hemidesmosomal proteins:
    - BP 230 or BP antigen 1 (BPAG1), a 230 kD component of the inner plaque of the hemidesmosome.
    - BP 180 or BP antigen 2 (BPAG2), a 180 kD transmembrane glycoprotein also known as type XVII collagen.
  - BP 180 is likely to be more involved in the initial immune response, since it is transmembrane.
  - The binding of autoantibodies leads to complement activation, attraction of eosinophils, release of proteases, and separation between the epidermis and dermis.
  - Less common causes include drugs (benzodiazepine, furosemide, penicillin, sulfasalazine), sunlight, and ionizing radiation.

► **Clinical features:**
- Before blisters develop, pruritus, dermatitic, and urticarial lesions may be present. The blisters tend to develop in these areas.

Note: Always keep BP in mind when confronted with an elderly patient with persistent "urticaria."

- Since the entire epidermis is the blister roof, the blisters are very stable. They are tense, often have a fluid level, and can reach 10 cm in diameter (Fig. 14.**3a,b**).
- Oral mucosal involvement in < 20%; rarely presenting sign.

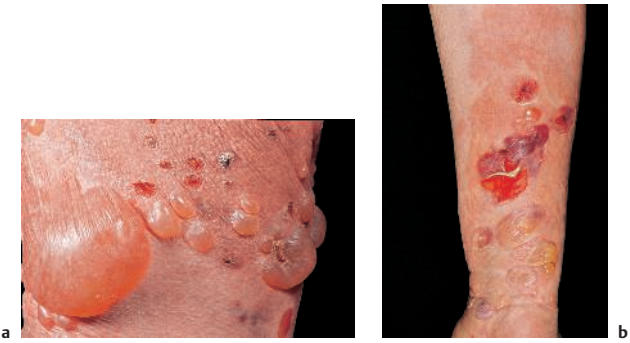


Fig. 14.**3** · **Bullous pemphigoid. a** With large blisters and hemorrhagic crusts. **b** With blisters, erosions, and crusts.

- *Several clinical variants:*
  - *Dyshidrotic BP*: Occasionally starts as acute vesicular dermatitis on palms and soles.
  - *Localized BP:* Limited to one area; typical for disease induced by ionizing radiation, but also occurs spontaneously.
  - *Erythrodermic BP:* Presents as erythroderma, with no previous blisters.
  - *Herpetiform (vesicular) BP:* Clinically mimics dermatitis herpetiformis.
  - *Prurigo nodularis–like BP:* Pruritic lesions with rapid progression into prurigo nodularis; few blisters.
  - *Pemphigoid vegetans:* Vegetating intertriginous lesions; analogous to pemphigus vegetans.
  - *Lichen planus pemphigoides:* Combination of BP and lichen planus (p. 286).

► **Histology:** In the prebullous lesions, the presence of unexpected eosinophils is a good clue. Later subepidermal blister formation. Two forms: a cell-rich form that contains many eosinophils and neutrophils and a cell-poor form with a sparse infiltrate. The lamina lucida remains on the roof of the blister; the lamina densa, on the floor.

► **Diagnostic approach:**
- *Laboratory:* Elevated sed rate, eosinophilia, increased IgE in 60%.
- *Direct immunofluorescence:* Best taken from erythematous area at periphery, not blister itself; band of IgG and C3 along BMZ.
- *Indirect immunofluorescence:* Using NaCl split skin, the autoantibodies usually attach to just the roof of the blister, but can appear on the dermal side or in both locations.

- ELISA identifies antibodies against both BP 230 and BP 180 in 60–80% of patients. Those directed specifically against the NC16 epitope of BP 180 correlate best with disease course.

► **Differential diagnosis:** Epidermolysis bullosa acquisita (see below), linear IgA disease (see below), generalized bullous fixed drug reaction, other bullous drug reactions, erythema multiforme, bullous systemic lupus erythematosus.

► **Therapy:**

- Mainstay is systemic corticosteroids:
  - Prednisolone 1 mg/kg daily.
  - As soon as control is reached, tapering to maintenance dose of 8 mg daily.
  - Try to taper to alternate-day dosage for adrenal-sparing effect.
- Most widely used steroid-sparing agent is azathioprine; mycophenolate mofetil also appears promising.
- Methotrexate 15–20 mg weekly is also effective; it can be combined with high-potency topical corticosteroids during the 4–6 weeks of induction.
- Some patients do well on high-potency topical corticosteroids; worth a try with localized disease or systemic problems (especially diabetes mellitus).
- Large open blisters and erosions may require topical antiseptics.

Cicatricial Pemphigoid

► **Synonyms:** Benign mucous membrane pemphigoid, benign mucosal pemphigoid.

► **Definition:** Chronic subepidermal blistering disease favoring mucous membranes, especially mouth and eyes.

► **Epidemiology:** Most patients > 65 years of age; women more often affected.

► **Pathogenesis:** Poorly understood; several different target antigens—BP 180, BP 230, laminin 5, α6β4 integrin.

► ***Note:*** Topical ophthalmologic medications can also cause disease; usually unilateral and resolves when medication is stopped.

► **Clinical features:**

- *Conjunctiva:* Affected in 75% of cases; when sole site—*ocular pemphigoid.* Starts unilaterally, within 2 years usually bilateral. Adhesions, ectropion, corneal damage (Fig. 14.**4**).

! ***Caution:*** The name "benign" is a misnomer—25% of patients lose their vision.

- *Oral mucosa:* Also affected in 75% of cases; vesicles, blisters, erosions, scarring. *Desquamative gingivitis* occurs. Much less painful than PV.
- Esophagus and larynx can also develop strictures, requiring surgery.
- *Genitalia:* In women, narrowing of vaginal orifice; in men, adhesions between glans and foreskin.

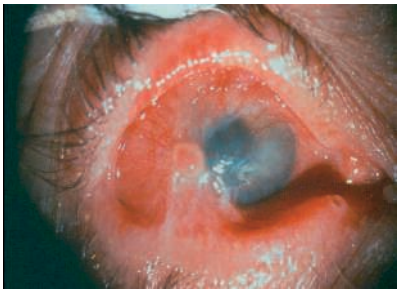


Fig. 14.**4** · Cicatricial pemphigoid with ocular involvement. (Image courtesy of Uwe Pleyer MD Berlin, Germany)

- *Skin:* Only involved in 25% of cases; usually generalized disease similar to BP. Localized form is known as *Brunsting–Perry disease* with persistent plaques on which recurrent blisters develop.

► **Histology:** Subepidermal blister, usually cell-poor.

► **Diagnostic approach:**
- *Direct immunofluorescence:* IgG (60%) and C3 (40%) along BMZ in lesional skin, also occasionally IgM and IgA; in normal skin, about 30% IgG.
- *Indirect immunofluorescence:* When NaCl split skin is used, IgG reactivity can be seen on either side of the split, or in both locations, depending on target antigen.
- *Identify target antigens:*
  - BP 180 is most common; patients have mucosal and skin disease.
  - α3 subunit of laminin 5 (formerly known as epiligrin); patients have mucosal and skin disease.
  - $\alpha 6\beta 4$-integrin; these patients have only ocular disease.

► **Differential diagnosis:** Bullous pemphigoid, epidermolysis bullosa acquisita, erosive lichen planus, paraneoplastic pemphigus, Stevens–Johnson syndrome.

► **Therapy:**
- Ocular disease: topical or systemic corticosteroids; consultation with ophthalmologist.
- Mucosal disease: try topical corticosteroids first.
- *Widespread or resistance disease:*
  - Prednisolone 1–2 mg/kg plus azathioprine 2 mg/kg or prednisolone-cyclophosphamide pulse therapy (p. 231).
  - High-dose intravenous immunoglobulins or immune absorption, maintaining immunosuppression to avoid rebound.
- Persistent localized lesions: excision and grafting (donor dominance).

Pemphigoid Gestationis

► **Synonym:** Herpes gestationis.

► **Definition:** Form of BP occurring during pregnancy.

► **Epidemiology:**
- Occurs in 1:10000–40000 pregnancies; if same father, high likelihood of recurrence in subsequent pregnancies.
- No maternal risk; no increase in birth defects, but complications of pregnancy in 15–30% with 8% fetal death rate.

► **Pathogenesis:** Mothers often HLA-B8, -DR3, or -DR4; father often HLA-DR2. Possible that mothers are sensitized against placental antigens. Target antigens are BP 180 (once again NC16 domain), less often BP 230.

► **Clinical features:**
- Sites of predilection include the protuberant abdomen and extremities; mucosal involvement $< 20\%$.
- Grouped stable blisters with pruritus develop in second or third trimester and persist until delivery. Rarely appear postpartum. Resolve within 3 months. Occasionally recur with menses or ingestion of oral contraceptives. Tends to be worse in next pregnancy.

  ▶ ***Note:*** If pemphigoid gestationis persists after delivery, a hydatidiform mole or choriocarcinoma must be excluded.
- The autoantibodies cross the placenta; the newborn can have blisters for a few weeks.

► **Histology:** Subepidermal blister, usually with cell-rich pattern.

- **Diagnostic approach:**
  - *Direct immunofluorescence:* Band of C3 along BMZ; occasionally IgG; all the others uncommon.
  - *Indirect immunofluorescence:* The IgG antibodies cannot always be demonstrated directly, but their strong complement-fixing properties allow identification (herpes gestationis factor). On NaCl split skin, the IgG attaches to the blister roof.
  - **Laboratory:** Often hypereosinophilia.
- **Differential diagnosis:** Papular eruption of pregnancy and other disorders of pregnancy (p. 570).
- **Therapy:**
  - Topical corticosteroids first; then systemic prednisolone 20–40 mg daily, which should be continued through delivery.

    Caution: The newborn is at risk of adrenal suppression and must be checked carefully.
  - In severe cases, high-dose intravenous immunoglobulins, immune absorption, or cyclosporine.
  - Persistence after delivery may be indication for luteinizing hormone-releasing hormone (administered by gynecologist).

Epidermolysis Bullosa Acquisita (EBA)

- **Definition:** Subepidermal blistering disease with predilection for areas subject to mechanical forces.
- **Epidemiology:** Uncommon disorder, seen in adults in 4th–5th decades; not to be confused with epidermolysis bullosa (p. 351).
- **Pathogenesis:** Autoantibodies directed against type VII collagen, a component of the lamina densa.
- **Clinical features:** Several different forms:
  - *Acral mechanobullous form* closely resembles porphyria cutanea tarda; fragile skin and blisters on backs of hands healing with milia and scarring; nail dystrophy. Foot involvement is clue to EBA.
  - *Inflammatory form* is very similar to BP with stable blisters; less often resembles cicatricial pemphigoid or dermatitis herpetiformis; heals with scarring; sometime scarring alopecia. About 50% of patients have mucosal involvement.
  - *Associated diseases:* Occasionally seen with inflammatory bowel disease, lupus erythematosus, or rheumatoid arthritis.
- **Diagnostic approach:**
  - *Direct immunofluorescence:* Deposition of IgG (rarely IgA) in BMZ.
  - *Indirect immunofluorescence:* IgG with ability to bind complement found in 50%. Using NaCl split skin, IgG binds to base of blister.
  - *ELISA* identifies antibodies against type VII collagen.
- **Differential diagnosis:** Before the ability to identify antibodies to type VII collagen, EBA was lost either as BP with negative immunofluorescence or as porphyria cutanea tarda with negative urine studies. Bullous lupus erythematosus also has antibodies to type VII collagen but is clinically quite different (p. 209).
- **Therapy:**
  - Corticosteroids only effective for the inflammatory form, but not as effective as in pemphigoid. With localized disease, try topical corticosteroids first.
  - Prednisolone 60–80 mg daily, combined with azathioprine 1–2 mg/kg daily, cyclosporine 3–5 mg/kg daily or cyclophosphamide 50 mg daily; steroid component tapered as soon as improvement seen.
  - Plasmapheresis can help to spare systemic medications.

- Other alternatives include dapsone 100–150 mg daily, colchicine 0.5–1.5 mg daily, high-dose intravenous immunoglobulins.

14.4 Subepidermal IgA-mediated Disorders

Linear IgA Disease of Adults (LAD)

- **Definition:** Subepidermal blistering disease caused by deposits of IgA along BMZ.
- **Epidemiology:** Uncommon disease; female: male ratio 2:1.
- **Pathogenesis:**
  - Multiple target antigens have been identified; issue still unclear. Some stain lamina lucida; others attach to type VII collagen in lamina densa.
  - Several drugs cause LAD; most common is vancomycin but also penicillin, sulfamethoxazole/trimethoprim, vigabatrin.
- **Clinical features:** LAD may be identical to dermatitis herpetiformis but without gastrointestinal involvement, or resemble BP or even cicatricial pemphigoid with ocular involvement. Over 50% have mucosal involvement; sometimes limited to these tissues. In adults, chronic disease. Histology corresponds to clinical pattern.
- **Diagnostic approach:**
  - IgA antibodies by definition present best seen with direct immunofluorescence.
  - Additional tests should include eye examination and jejunal biopsy to exclude celiac disease (see below).
- **Therapy:** Corticosteroids work best for lamina lucida type; dapsone often helpful for lamina densa type.

Linear IgA Disease of Childhood

- **Synonym:** Formerly known as chronic bullous disease of childhood.
- **Definition:** Most common subepidermal blistering disorder in childhood.
- **Epidemiology:** Usually occurs before 5 years of age and resolves spontaneously.
- **Pathogenesis:** Most common target antigen is LAD1, a proteolytic fragment of BP 180.
- **Clinical features:** Large tense blisters, almost always arranged in rosette fashion, with predilection for abdomen, groin, axillae, and face (Fig. 14.**5**). Also urticarial plaques with peripheral blisters. Mucosal disease very common; as high as 90% in some series. Gastrointestinal disease extremely rare.

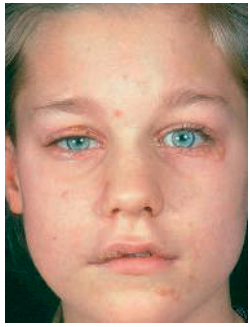


Fig. 14.**5** · Linear IgA disease of childhood with periorbital involvement.

- **Histology:** Subepidermal blister; usually with inflammatory infiltrate.
- **Diagnostic approach:** Obligatory presence of IgA deposits along BMZ identified by direct immunofluorescence in 100% and indirect immunofluorescence (when trying to avoid skin biopsy in child) in 40–70%.
- **Differential diagnosis:**
  - Bullous pemphigoid also occurs in childhood; usually even earlier. It is clinically identical except for a lower incidence of mucosal involvement and can only be identified with immunofluorescence studies. Treatment is the same.
  - Dermatitis herpetiformis only occurs in small children who are heterozygous for predisposing HLA genes.
- **Therapy:** Both dapsone (0.5–2.0 mg/kg) and sulfapyridine may be useful. If not, systemic corticosteroids.

14.5 Dermatitis Herpetiformis

- **Definition:** Pruritic vesicular disease caused by IgA autoantibodies directed against epidermal transglutaminase and presenting with granular pattern in papillary dermis.
- **Epidemiology:** Men are affected twice as often women. Disease of young adults.
- **Pathogenesis:**
  - Dermatitis herpetiformis and gluten-sensitive enteropathy are closely related. They are the result of an abnormal immune response to gluten antigens. Gluten is the main adhesive substance of many grains. The most important sensitizing protein is gliadin, which is the substrate for tissue transglutaminase. Autoantibodies against tissue transglutaminase also cross-react with the similar epidermal transglutaminase, producing dermatitis herpetiformis. The antibodies in dermatitis herpetiformis patients have more affinity for epidermal transglutaminase than do those in patients with gluten-sensitive enteropathy.
  - There is a strong HLA association, as 90% of patients are HLA-DQ2 (A1*0501 and B1*02). The other 10% are HLA-DQ8 (A1*03, B1*03). Other genetic factors are involved.
  - Rare patients with enteropathy have skin involvement; few patients with skin findings have symptomatic bowel disease, but most have an abnormal bowel biopsy.
  - Patients in both groups are at increased risk for B-cell lymphoma of the MALT type.
- **Clinical features:**
  - Sites of predilection include the knees and elbows (*Cottini type* when limited to these areas), as well as buttocks and upper trunk. Facial involvement rare.
  - Hallmark is intensely pruritic or burning tiny vesicles, which are usually scratched away by the time the patient presents (Fig. 14.**6**).
  - In undisturbed lesions, there may be a rim of peripheral vesicles arranged in herpetiform fashion. Less often there are larger blisters.
  - Occasional signs and symptoms of enteropathy with malabsorption, voluminous loose stools, and weight loss.
  - Occasional association with other autoimmune diseases such as diabetes mellitus, pernicious anemia, thyroid disease, and vitiligo.
  - Patients often are not able to tolerate iodine and flare with exposures, such as when eating seafood. Iodine challenge or iodine patch test are old diagnostic measures.
  - Spontaneous remissions may occur, but disease often lifelong.

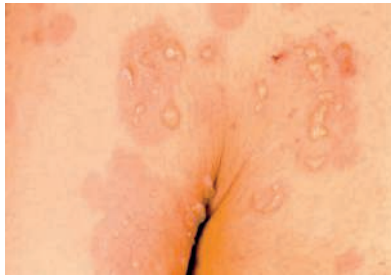


Fig. 14.**6** · Dermatitis herpetiformis.

- **Histology:** Neutrophilic microabscesses in the papillary dermis are the hallmark. Often admixed with eosinophils. Edema leads to subepidermal blister formation.
- **Diagnostic approach:**
  - Skin biopsy; often hard to obtain fresh lesion.
  - *Direct immunofluorescence:* Granular deposits of IgA in dermal papillae; sometimes granular-linear along BMZ. Present in >95% of patients, also in normal skin (buttocks); persist long after therapy is started.
  - *Indirect immunofluorescence:* IgA antibodies against smooth muscle endomysium (source of tissue transglutaminase) present in 80%.
  - *ELISA* identifies IgA antibodies against tissue transglutaminase in at least 80%; antigliadin antibodies also present, but less specific.
  - *Jejunal biopsy:* flattening of villi (85%) with intraepithelial lymphocytes in 100%.
- **Differential diagnosis:** Dermatitis herpetiformis is probably incorrectly invoked as a differential diagnostic consideration more than any other skin disease as it is suspected in anyone with pruritus where there is no obvious cause. Scabies, BP before the development of blisters, and the prurigo group are the main issues.
- **Therapy:**
  - The mainstay of therapy is a gluten-free diet (Table 14.**1**), which also protects against gastrointestinal lymphoma. The diet is hard to follow and only takes effect after months, but is essential.

Table 14.1 · **Gluten-free diet**

Forbidden	Allowed
Wheat, rye, barley, oats, spelt	Potatoes, rice, corn, millet, buckwheat, chestnut meal, quinoa, amaranth
Grain products: grits, cream of wheat, wheat germ, oatmeals, and others	Gluten-free binders, potato starch, corn starch, rice flour, soy flour
Commercial breads, cakes, cookies, crackers, pasta	Gluten-free bread and cookies, rice cakes
Malt, coffee substitutes, beer	
Careful with sausage, processed meats or fish, spices, cheeses (gluten binders), cheese substitutes, soups, sauces, puddings	Look for products with gluten-free marking Check www.gluten.net

- Dapsone is amazingly effective; hours to days after the first dose, the pruritus disappears. Usually a low dose of 25–50 mg suffices; for details on usage.

14.6 Overview of Diagnostic Approach

Table 14.2 · Diagnostic criteria for autoimmune bullous diseases

Clinical features	Histology	Direct immunofluorescence	Indirect immunofluorescence	Target antigens
Pemphigus vulgaris (PV)/pemphigus foliaceus (PF)				
Blisters, erosions on mucosa (PV) and skin (PV,PF)	Suprabasal acantholysis	Intercellular IgG and C3	Intercellular IgG (monkey esophagus)	Dsg3 (PV)[a] Dsg3 (PV,PF)[a]
Paraneoplastic pemphigus				
Hemorrhagic stomatitis, polymorphic exanthems	Suprabasal acantholysis with interface dermatitis	Intercellular IgG and C3; also IgG and C3 at BMZ	Intercellular IgG (rat bladder)	Plakins Dsg1/Dsg3[a] 170 kD antigen
IgA pemphigus				
Fragile blisters, pustules with erosions, crusts	Subcorneal or intraepidermal neutrophilic abscesses	Intercellular IgA and C3	Intercellular IgA (monkey esophagus) in 50%	Desmocollin 1 Dsg1/Dsg 3[a]
Bullous pemphigoid				
Pruritus, urticarial plaques, large stable blisters	Subepidermal blister with eosinophils	Linear IgG (IgA) and C3 at BMZ	IgG on epidermal side of split skin	BP 180[a] BP 230
Pemphigoid gestationis				
Pruritus, urticarial plaques, large stable blisters in pregnancy	Subepidermal blister with eosinophils	Linear IgG < C3 at BMZ	IgG on epidermal side of split skin	BP 180[a]

Continued Table 14.2 ▶

Table 14.2 · Continued

Clinical features	Histology	Direct immunofluorescence	Indirect immunofluorescence	Target antigens
Cicatricial pemphigoid				
Oral and ocular blisters, erosions and scars; 25% skin lesions	Subepidermal blister, later atrophy and scarring.	Linear IgG ± IgA ± C3 at BMZ	IgG ± IgA on both sides of split skin	BP180[a] Laminin 5 A6β4 integrin
Linear IgA disease				
Grouped tense blisters, mucosal involvement common	Subepidermal blister with neutrophils	Linear IgA (and C3) at BMZ	IgG on epidermal (sometimes dermal) side of split skin	LAD-1 BP 180[a] BP 230
Epidermolysis bullosa acquisita				
Inflammatory (BP-like) and atrophic (porphyria cutanea tarda-like) variants; mechanobullous; frequent mucosal disease	Subepidermal blister; often with neutrophilic infiltrate	Linear IgG and C3 at BMZ; rarely linear IgA and C3 at BMZ	IgG (or IgA) and C3 on dermal side of split skin	Type VII collagen
Dermatitis herpetiformis				
Pruritic grouped vesicles, usually excoriated	Subepidermal blister, papillary neutrophilic microabscesses	Granular IgA in papillae	IgA directed against endomysium (monkey esophagus)	Transglutaminase[a] Gliadin[a]

BMZ = basement membrane zone; Dsg = desmoglein.
[a] commercially available test systems

15 Purpura and Vasculitis

15.1 Overview

Purpura is the result of red blood cells leaking through vessel walls into the dermis. It can be caused by hematologic abnormalities, increased venous pressure, or vessel damage—*vasculitis*. The causes of vasculitis are multiple, as there are a variety of triggers and several pathological mechanisms. The classification of vasculitis is controversial but we will simply consider those forms primarily seen in the skin as "cutaneous vasculitis" and those with primary systemic findings as "systemic vasculitis."

15.2 Purpura

Classification

- **Definition:** Spontaneous small areas of bleeding into the skin. The lesions of purpura consist of *petechiae*, tiny pinpoint areas of bleeding, as well as *ecchymoses*, which are larger (Fig. 15.**1**).
- **Purpura secondary to coagulopathies:**
  - *Changes in platelet number and function:*
    - *Thrombocytopenia:* Idiopathic thrombocytopenic purpura (ITP) is caused by autoantibodies directed against platelets. Secondary causes include radiation, medications, bone marrow diseases with reduced production, splenomegaly and Kasabach–Merritt syndrome (with increased destruction).
    - *Thrombocythemia:* Too many platelets may also cause purpura; many cases are pre-leukemic.
    - *Platelet dysfunction:* Wiskott–Aldrich syndrome (p. 194) is a good dermatological example.
  - *Abnormalities in the coagulation factors:* Disseminated intravascular coagulation (DIC), including purpura fulminans (p. 81).

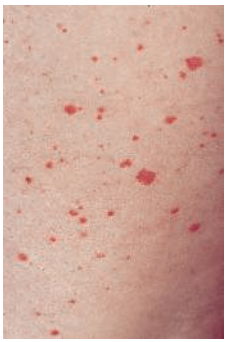


Fig. 15.**1** · Purpura with vasculitis.

- **Purpura secondary to vascular disorders:**
  - Vasculitis (palpable purpura).
  - Vasculitis with purpura and arthralgias in cryoglobulinemia and cryofibrinogenemia.
  - Vascular malformations: hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease).
  - Increased intravascular pressure: stasis purpura.
  - Toxic vessel damage (septic purpura, drug-induced purpura).
- **Purpura secondary to collagen-vascular disorders:**
  - Senile purpura (limited to severely actinically damaged skin of arms and face).
  - Steroid purpura.
  - Several genodermatoses: Pseudoxanthoma elasticum, Marfan syndrome, and Ehlers–Danlos syndrome.

Idiopathic Purpura

Note: The idiopathic purpuras are also known as the progressive pigmented purpuras or the purpuric oddities. Their etiology is unclear; some favor a localized form of increased intravascular pressure or other causes of a leaky vessel; others consider them a forme fruste of a lymphocytic vasculitis. The disorders discussed below have frequent overlaps.

- **Progressive pigmented purpuric dermatosis:**
  - *Synonym:* Schamberg disease.
  - *Epidemiology:* Men are more often affected.
  - *Clinical features:*
    - Chronic course.
    - Circumscribed several-centimeter patches, usually on shins, with tiny punctate red-brown hemorrhages at the periphery, often compared to sprinkled cayenne pepper; foci tend to become confluent centrally.
    - Lesions are entirely asymptomatic, but may rarely spread to involve entire limb or even trunk.
  - *Histology:* Lymphocytic perivascular infiltrate and hemorrhage.
- **Eczematoid purpura:**
  - *Synonyms:* Doucas–Kapetanakis syndrome.
  - *Epidemiology:* Men more often affected.
  - *Clinical features:* Starts on legs but likely to spread. Foci of purpura with dermatitic changes. Lesions pruritic.
  - *Histology:* Purpura, but also scale and spongiosis.
- **Pigmented purpuric lichenoid dermatitis:**
  - *Synonyms:* Gougerot–Blum syndrome.
  - *Epidemiology:* Men more often affected.
  - *Clinical features:* Early lesions similar to Schamberg disease, but lichenoid papules develop on the shins.
- **Purpura anularis telangiectodes:**
  - *Synonyms:* Majocchi purpura.
  - *Clinical features:* 1–3 cm patches, not limited to the legs, containing both purpuric macules and telangiectases. Chronic course.
- **Lichen aureus:**
  - *Clinical features:* Often sharply localized over or near a perforating vein, characteristic gold-brown color, more often seen in younger patients and away from the lower legs than are the other forms. Asymptomatic.
  - *Histology*: Combination of purpura and lichenoid infiltrate.

- **Differential diagnosis:** Vasculitis, drug-induced purpura, as well as the different forms of pigmented purpura. Overlaps occur; not mutually exclusive. Always exclude chronic venous insufficiency.
- **Therapy:** Topical corticosteroids can suppress the occasional itching, but there is no truly effective approach. Most patients require nothing but reassurance.

15.3 Cutaneous Vasculitis

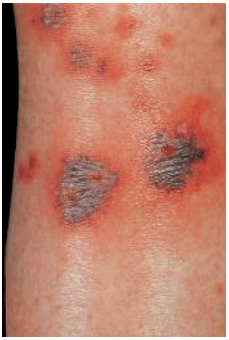
Leukocytoclastic Vasculitis

- **Synonyms:** Hypersensitivity angiitis, allergic vasculitis, "palpable purpura".
- **Definition:** Inflammation of dermal venules with immune complex deposition and fibrinoid necrosis.
- **Epidemiology:** Favors children and young adults; in older patients often drug reaction or reflection of systemic vasculitis.
- **Pathogenesis:** The many possible triggers are shown in Table 15.**1**. Usually immune complexes are formed, then deposited in the venules, where they activate complement and establish an inflammatory reaction that damages the vessel wall.

Table 15.1 · Leukocytoclastic vasculitis: associated diseases and diagnostic procedures

Associated diseases	Diagnostic procedures
Infections: streptococci, tuberculosis, hepatitis B and C	Throat culture, antistreptolysin, chest radiograph, hepatitis serology
Lupus erythematosus, Sjögren syndrome	Antinuclear antibodies, autoantibodies
Rheumatoid arthritis	Rheumatoid factor
Cryoglobulinemia	Cryoglobulins
Gammopathy	Serum protein electrophoresis
Complement defects	CH50, C3, C4
Serum sickness	History: vaccines, anti-thymocyte globulin, streptokinase, immunoglobulins
Systemic vasculitis (Wegener granulomatosis, polyarteritis nodosa)	Look for extracutaneous manifestations.
Drugs	ACE inhibitors, NSAIDs, phenytoin, sulfonamides, thiouracil and many more

- **Clinical features:**
  - The hallmark of leukocytoclastic vasculitis is purpura. More advanced lesions are often palpable. Other lesions may be urticarial, pustular, or necrotic (Fig. 15.**2a,b**).
  - Sites of predilection include the lower legs (100%), arms (15%), mucosa (15%), external ears (10%), and conjunctiva (5%).
  - The most common clinical findings are purpura (99%), papules (40%), ulcerations (30%), pustules (20%), urticaria (10%), subcutaneous nodules (10%), and livedo racemosa (< 5%).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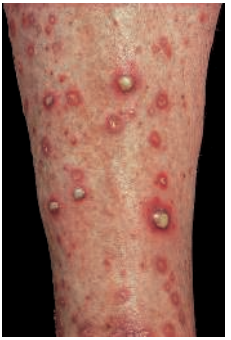
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Fig. 15.2 · **Leukocytoclastic vasculitis.**
a With necrosis.
b With pustules.

- **Specific variants:**
  - *Henoch–Schönlein purpura:* Appears primarily in children, purpura associated with gastrointestinal distress and arthralgias; IgA immune complexes in kidneys and skin.
  - *Acute hemorrhagic edema:* Target-like purpura in infant and small children.

► **Histology:** Necrotic vessel wall with fibrin, nuclear dust (leukocytoclasia), and exocytosis of erythrocytes.

► **Diagnostic approach:** A biopsy is essential for the diagnosis. Direct immunofluorescence studies are often done but rarely affect diagnosis (IgA for Henoch–Schönlein purpura).

► **Differential diagnosis:** Septic vasculitis (gonorrhea, meningococcemia, candidiasis, many others); livedo vasculitis.

! ***Caution:*** Leukocytoclastic vasculitis is common in Wegener granulomatosis and polyarteritis nodosa; a positive biopsy does not exclude systemic vasculitis.

► **Therapy:**
- If acute insult, treat the trigger.
- Often no therapy is needed; bed rest and compression stockings help.
- Corticosteroids: prednisolone 60 mg for 3–5 days.
- If recurrent, dapsone 0.5–2.0 mg/kg daily or colchicine 0.5–1.0 mg daily.

Urticarial Vasculitis

► **Definition:** Leukocytoclastic vasculitis with urticarial lesions persisting more than 24 hours, systemic signs and symptoms, and often hypocomplementemia.

► **Epidemiology:** Uncommon.

► **Pathogenesis:** Can be primary or associated with systemic lupus erythematosus, Sjögren syndrome, cryoglobulinemia, or Wegener granulomatosis.

► **Clinical features:**
- The urticarial lesions persist more than 24 hours and resolve, leaving behind hemosiderin, causing red-brown maculae.
  - ***Note:*** Even though many patients have hives persisting more than 24 hours, few have urticarial vasculitis with signs and symptoms.
- Systemic lesions include arthritis, nephritis, and abdominal distress.
- Pulmonary involvement can be fatal.

- **Histology:** Typical hive with edema but also with leukocytoclastic vasculitis. A perivascular lymphocytic infiltrate is not sufficient for the diagnosis.
- **Diagnostic approach:** Assuming biopsy is positive:
  - *Laboratory:*
    - Sed rate, C-reactive protein, serum protein electrophoresis.
    - ANA, autoantibodies (anti-SS-A/Ro; anti-SS-B/LA).
    - Assess complement levels: CH50, C3, C4.
  - Further evaluation based on signs and symptoms, but can include chest radiograph, pulmonary function testing, renal evaluation.
- **Therapy:** Difficult; try antihistamines, NSAIDs, dapsone and antimalarials; if not responsive or with systemic involvement, corticosteroids and perhaps additional immunosuppressive agents.

15.4 Variants of Cutaneous Vasculitis

There disorders show leukocytoclastic vasculitis or a variant thereof in their early lesions, although the later well-developed lesions have other clinical and histological features.

Sweet Syndrome

- **Definition:** Acute illness with fever, leukocytosis, and erythematous succulent cutaneous plaques.
- **Epidemiology:** Female:male ratio 3.5:1, more common in spring and fall.
- **Pathogenesis:** In most cases, the cause of Sweet syndrome is unclear but viral or bacterial triggers have long been suspected. Other cases are associated with an underlying malignancies or are drug reactions, particularly to granulocyte colony-stimulating factor (G-CSF). The most common associated malignances are hematologic, usually acute myelogenous leukemia, although solid tumors are also occasionally found. Finally, Sweet syndrome may appear in association with inflammatory disease such as inflammatory bowel disease, rheumatoid arthritis, or even lupus erythematosus.
- **Clinical features:**
  - Prodrome and arthralgias most common in patients with idiopathic Sweet syndrome. Not all patients have fever and leukocytosis.
  - Succulent plaques, as large as 10–15 cm, with irregular border (*rocky island pattern*); sometimes *illusion of vesiculation*—look vesicular but are solid when pressed; plaques may be dotted with pustules. Leg lesions may resemble panniculitis.
  - Oral lesions seen in 20%; more common in drug-related: aphthae, erosions.
  - Uncommon forms include chronic neutrophilic plaques and acute lesions confined to hands.
- **Histology:** Distinctive band of subepidermal edema with band-like infiltrate rich in neutrophils. Vasculitis in 30%. Early lesions dominated by lymphocytes. Later nuclear dust and ingestion of neutrophils by macrophages (*bean bag cells*). In some instances, leukemic cells identified in infiltrate.
- **Diagnostic approach:** Clinical features, histology; search for underlying tumor, infection, inflammatory disorder or drug exposure.
- **Differential diagnosis:** While the juicy plaques are distinctive, other possibilities include leukemic infiltrates, pyoderma gangrenosum, erythema elevatum et diutinum (more chronic), granuloma faciale (more chronic), leukocytoclastic vasculitis, erythema nodosum, and true abscesses.

- **Therapy:**
  - Prednisolone 60 mg daily tapered over 2–3 weeks.
  - If recurrent, consider methotrexate, clofazimine, or thalidomide.

Erythema Elevatum et Diutinum

- **Synonym:** Extracellular cholesterosis.
- **Definition:** Chronic cutaneous vasculitis with formation of fibrotic plaques.
- **Epidemiology:** Uncommon.
- **Pathogenesis:** Suspicion that streptococci are trigger for chronic immune complex reaction. Occurs in HIV/AIDS but unclear if result of immunosuppression or other factors.
- **Clinical features:** Symmetrical, slowly-developing red-brown papules and nodules favoring backs of hands, over the digital joints and knees and elbows. Rarely more widespread. Usually asymptomatic. Association with IgA monoclonal gammopathy or even multiple myeloma.
- **Histology:** Leukocytoclastic vasculitis with thickening of vessel walls; later fibrosis, granulomatous inflammation, occasional cholesterol deposits.
- **Diagnostic approach:** Skin biopsy; serum protein electrophoresis.
- **Differential diagnosis:** Sweet syndrome far more acute; granuloma faciale looks similar but has a different distribution; early lesions indistinguishable from more usual leukocytoclastic vasculitis.
- **Therapy:**
  - Limited disease; intralesional or high-potency topical corticosteroids.
  - More widespread or resistant disease: dapsone 0.5–2.0 mg/kg daily.
  - Systemic corticosteroids usually disappointing; nicotinamide and tetracycline may help.

Granuloma Faciale

- **Definition:** Chronic form of leukocytoclastic vasculitis causing red-brown facial plaques.
- **Epidemiology:** Uncommon.
- **Pathogenesis:** Unknown, perhaps similar to erythema elevatum et diutinum.
- **Clinical features:** Usually solitary or limited number of red-brown plaques limited to face, typically cheeks, chin, forehead or ears. Occasionally multiple or scattered lesions. Lesions are soft, poorly circumscribed, and asymptomatic, but a cosmetic problem.
- **Histology:** Name is misnomer, as lesion is not a granuloma. Perivascular infiltrate of neutrophils and eosinophils; initially leukocytoclastic vasculitis. Characteristic Grenz zone between normal epidermis and infiltrate. Old name of "eosinophilic granuloma" should be avoided because of confusion with Langerhans cell histiocytosis.
- **Diagnostic approach:** Skin biopsy.
- **Differential diagnosis:** Lupus tumidus, mast cell tumor, xanthogranuloma, sarcoidosis, lymphoma, leukemic infiltrate.
- **Therapy:** Intralesional corticosteroids, laser destruction, cryotherapy. Dapsone 0.5–2.0 mg/kg daily sometimes induces prompt remission.

Pyoderma Gangrenosum

- **Definition:** Neutrophilic dermatosis, noninfectious, with rapid tissue destruction.
- **Epidemiology:** Uncommon.
- **Pathogenesis:** Mechanism still unknown; abnormal neutrophil trafficking and immunologic dysfunction are the best guesses. Association with inflammatory bowel disease, rheumatoid arthritis, and monoclonal gammopathy (usually IgA) is clear; less often associated with lymphomas and leukemias.
- **Clinical features:**
  - Ulcer with prominent undermined border and boggy necrotic base (Fig, 15.**3**). Grows rapidly. May start as pustule. Can become extremely large and extend to fat, fascia, or even muscle.
  - Heals with cribriform (sieve-like) scars.
  - Displays *pathergy*: skin trauma (needle stick, insect bite, biopsy) can trigger lesions.
  - Facial pyoderma gangrenosum tends to be more superficial and less destructive.
  - Other variants include peristomal pyoderma gangrenosum and postoperative cutaneous gangrene (*Cullen syndrome*). Important to document in case of future surgeries.
- **Histology:** Massive destruction; at periphery neutrophils about vessels, but classic leukocytoclastic vasculitis is rare.
- **Diagnostic approach:** Diagnosis of exclusion—culture for bacterial, viral (herpesviruses in immunosuppressed) and deep fungal agents; suspect artifact; skin biopsy also only helps for exclusion; direct immunofluorescence identifies immune deposits but of uncertain utility.
- **Differential diagnosis:** Many infections, pemphigus vegetans, brown recluse spider bite, artifact, other forms of vasculitis, calciphylaxis, cryofibrinogenemia, coumarin, heparin necrosis.
- **Therapy:**
  - Treat associated disease.
  - Topical therapy usually inadequate; exception is intralesional corticosteroids in early lesions.
  - Systemic corticosteroids are mainstay: prednisolone 1–2 mg/kg daily tapered as healing occurs. The use of systemic corticosteroids makes it even more mandatory to exclude underlying infections.
  - Cyclosporine (and presumably also tacrolimus and pimecrolimus) is amazingly effective, suggesting that T cells play a role in the primary pathogenesis. Usual dose 5–10 mg/kg daily, reduced to half as healing starts but continued for several months.
  - Inhibitors of TNFα are also dramatically effective, even though no role for this cytokine had been expected in pyoderma gangrenosum.

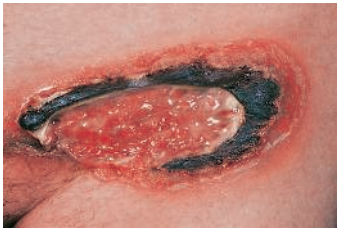


Fig. 15.**3** · Pyoderma gangrenosum.

Other Forms of Cutaneous Vasculitis

- Nodular vasculitis is a form of panniculitis, in some instances caused by *Mycobacterium tuberculosis*, when it is known as *erythema induratum.*
- All of the collagen–vascular diseases can feature vasculitis, but it is very rare for any of them to present with leukocytoclastic vasculitis. A possible exception is childhood dermatomyositis where vasculitis can be the overriding problem.

15.5 Systemic Vasculitis

The current standard Chapel Hill classification is based on the size of vessels most often involved. It fails to do justice to cutaneous vasculitis, but is very useful for understanding larger vessel disease. We have simply divided systemic or medium-sized and large vessel vasculitis into ANCA-associated and non-ANCA diseases.

ANCA-positive Vasculitis

ANCA stands for **a**nti**n**eutrophil **c**ytoplasmic **a**ntibody. ANCA are almost always of pathogenic significance; they are IgG antibodies directed against lysosomal antigens of neutrophils and macrophages. There are two major types:

- **cANCA:** directed against proteinase 3 and most common in Wegener granulomatosis.
- **pANCA:** directed against myeloperoxidase and most common microscopic polyangiitis but also seen in connective tissue vasculitis of various sorts with a wide variety of target antigens (Table 15.**2**).

Table 15.2 · **Associations with ANCA**

Type of vasculitis	cANCA	pANCA
Microscopic polyangiitis	10	60
Wegener granulomatosis	50–90	< 5
Churg-Strauss syndrome	20	20
Henoch-Schönlein purpura	–	< 5
Polyarteritis nodosa	< 5	< 5
Connective tissue diseases	–	20–50

Based on Table 16.9, p. 532 in Fritsch P, *Dermatologie, Venerologie,* 2nd ed, Springer Verlag, Berlin, 2004.

Microscopic Polyangiitis

- **Synonyms:** Pauci-immune vasculitis, microscopic panarteritis.
- **Definition:** Necrotizing vasculitis with few immune deposits, always involving smallest blood vessels but capable of affecting medium-sized vessels and with tropism for kidneys and lungs.
- **Epidemiology:** Much more common than polyarteritis nodosa; perhaps 2–5/100000 yearly.
- **Pathogenesis:** Unknown; no relation to hepatitis B.

- **Clinical features:**
  - *General findings:* Fever, weight loss.
  - *Skin:* Leukocytoclastic vasculitis (30–40%).
  - *Kidneys:* Pauci-immune necrotizing glomerulonephritis with casts (70%).
  - *Lungs:* Pulmonary vasculitis with alveolar hemorrhage and hemoptysis (10–15%).
- **Diagnostic approach:**
  - Skin biopsy doesn't help distinguish from cutaneous leukocytoclastic vasculitis.
  - Check kidneys and lungs.
  - 60% positive for pANCA.
- **Differential diagnosis:**
  - *Leukocytoclastic vasculitis:* Confined to skin, no glomerulonephritis.
  - *Wegener granulomatosis:* More severe upper airway problems, granulomatous inflammation, cANCA.
- **Therapy:** Prednisone and cyclophosphamide, as in polyarteritis nodosa (see below).

Wegener Granulomatosis

- **Definition:** Systemic vasculitis with aseptic granulomatous inflammation, primarily involving upper and lower respiratory tract, as well as kidneys.
- **Epidemiology:** Incidence 0.3/100 000 yearly; USA study: prevalence of 1/25 000.
- **Pathogenesis:** Unknown; infections have long been suspected as trigger.
- **Clinical features:**
  - *1st stage:* General signs and symptoms such as fever, malaise coupled with upper airway problems (rhinitis, sinusitis).
  - *2nd stage:* Lower airway problems: cough, dyspnea, hemoptysis, pleurisy.
  - *3rd stage:* Generalized involvement including skin.
  - *Frequency of organ involvement:* Lungs (95%), upper airway (90%), kidneys (85%), joints (70%), eyes (60%), ears (60%), skin (45%), nerves (20%), heart (10%).
  - *Skin:* Polymorphic picture including leukocytoclastic vasculitis, urticarial vasculitis, necrotizing pyodermas (mini-pyoderma gangrenosum), panniculitis.
- **Histology:** Triad of necrotizing leukocytoclastic vasculitis, necrosis, and granuloma formation. The granulomas can be in the vessel walls or adjacent; they can be palisading (thus microscopically mistaken for granuloma annulare) or rich in giant cells. The necrosis is irregular and often described as "geographic."
- **Diagnostic approach:**
  - *Tissue diagnosis:* Usually airway or renal biopsy; sometimes skin biopsy helps.
  - Investigate upper airways, lungs, and kidneys.
  - cANCA positive in 50% during early phases, >90% when generalized.
- **Differential diagnosis:**
  - *Pulmonary disease:* microscopic polyangiitis, infections.
  - *Kidneys:* other causes of glomerulonephritis.
  - Destructive upper airway disease: NK/T-cell lymphoma (nasal type), formerly known as lethal midline granuloma.
- **Therapy:**
  - Before immunosuppressive therapy, the 1 year survival for generalized Wegener granulomatosis was <20%. Now >90% response rates, although many patients are left with organ defects.
  - *Fauci regimen:* Prednisone 1 mg/kg daily and cyclophosphamide 2 mg/kg daily. If not responsive, either agent can be increased. Once response occurs, taper predinsone with goal of stopping. Cyclophosphamide is continued for at least 1 year at the standard dose before being slowly tapered.

- Many other immunosuppressive regimens under investigation, such as cyclophosphamide induction followed by methotrexate; consult literature.
- Recurrences or localized disease can often be treated with co-trimoxazole; mechanism of action is unclear but enhances speculation about infectious trigger.

Churg–Strauss Syndrome

- **Synonym:** Allergic granulomatosis and angiitis.
- **Definition:** Systemic vasculitis favoring small vessels with triad of asthma, granulomatous vasculitis of lungs and skin, and eosinophilia of tissues and blood.
- **Epidemiology:** Extremely rare; 0.3/100 000 yearly; perhaps association with atopy.
- **Pathogenesis:** Unknown; speculation about role of leukotriene antagonists in triggering this disorder.
- **Clinical features:**
  - *Asthma* is present in over 80% and often the presenting symptom, present for years before other features develop.
  - Pulmonary infiltrates and vasculitis come later. Nasal and sinus disease is not destructive.
  - Transient pulmonary eosinophilic infiltrates occur; resembles Löffler syndrome.
  - Multiple other organs involved: mononeuritis multiplex (60%), kidneys (50%), heart (40%), gastrointestinal tract (40%).
  - *Skin:* Involved in 70%: purpura, nodules, and urticarial vasculitis.
  - *Localized Churg–Strauss granulomas:* Sometimes disease process limited to skin, most often in association with rheumatoid arthritis but also infections, lymphoma, and idiopathic.
- **Histology:** Striking palisading granulomas with marked necrosis, both associated with vessels and at a distance, highlighted by marked eosinophilia, nuclear dust ,and giant cells.
- **Diagnostic approach:**
  - Tissue diagnosis: skin or lung biopsy.
  - Investigate lungs and other organs on the basis of signs and symptoms.
  - *Laboratory:* Elevated sed rate, hypereosinophilia, elevated IgE, cryoglobulins, immune complexes.
  - Both cANCA and p ANCA can be positive; estimated 20% for each.
- **Differential diagnosis:**
  - *Microscopic polyangiitis:* Pulmonary hemorrhage, no asthma or eosinophilia.
  - *Wegener granulomatosis:* Histological overlaps but different pattern of airway involvement.
  - *Allergic aspergillosis:* Identify fungus in lungs, positive skin test.
  - *Löffler syndrome:* Search for worms, other triggers.
  - *Eosinophilic pneumonia:* Impaired pulmonary function, no vasculitis.
- **Therapy:**
  - Very steroid responsive: initially use prednisolone 1 mg/kg daily.
  - Reserve immunosuppressive agents (cyclophosphamide, mycophenolate mofetil, cyclosporine) for treatment failures or life-threatening disease.
  - Both IFN-α and intravenous immunoglobulins have shown promise.

Drug-induced ANCA Vasculitis

Many drugs induce the production of ANCA but only a few produce a clinical vasculitis, often with renal disease. Examples include:

- Hematopoietic growth factors (G-CSF, GM-CSF), especially when used in patients with chronic benign neutropenia whose counts then go up as they develop vasculitis. Same factors may cause Sweet syndrome and pyoderma gangrenosum.
- Asthmatic patients receiving leukotriene inhibitors appear at risk of developing Churg–Strauss syndrome.
- Vaccination-induced vasculitis has been described with hepatitis B and influenza immunizations; it remains puzzling, but the risk is not a justification for withholding these vaccines from patients with vasculitis or collagen–vascular disorders.

Polyarteritis Nodosa

- **Synonyms:** Panarteritis nodosa, Kussmaul–Maier disease.
- **Definition:** Necrotizing segmental vasculitis involving small and medium-sized arteries with infarctions.
- **Epidemiology:** Rare; incidence 0.5/100000 yearly; most commonly affects middle-aged men.
- **Pathogenesis:** Association with hepatitis B; also with HIV/AIDS. Involvement in segmental and favors areas where branching occurs. Small aneurysms frequently develop. Thromboses lead to infracts and vessel-wall obliteration.
- **Clinical features:**
  - *General symptoms:* fever, weight loss, arthralgias.
  - *Skin:* Frequently involved; livedo racemosa, digital gangrene, subcutaneous nodules, ulcers, leukocytoclastic vasculitis.
  - *Cutaneous polyarteritis nodosa:* Disease limited to skin for long periods of time; nodules and ulcers, usually on legs.
  - *Gastrointestinal tract:* "Intestinal angina"—postprandial abdominal pain because of inadequate blood supply; drastic problems include ischemic bowel perforation and mesenteric artery thrombosis or rupture.
  - *Peripheral neuropathy:* Vasculitic neuropathy in up to 80%; involves larger peripheral nerves (mononeuritis multiplex) with sensory and in some instances motor problems.
  - *Kidney:* Almost 100% involvement, but usually subclinical except for hypertension.
  - *Heart:* Can lead to myocardial infarction or congestive heart failure.
  - *CNS:* Risk of strokes, as well as hypertensive changes.
- **Histology:** Segmental involvement makes it hard to find lesions. Initial inflammatory infiltrate is neutrophilic, later replaced by mononuclear cells with intimal proliferation, finally granulomas and fibrosis.
- **Diagnostic approach:**
  - *Histologic confirmation:* Usually skin or muscle biopsy from affected area; blind biopsies, such as testicular biopsy, have low yield.
  - *Imaging:* Angiography can reveal microaneurysms in gastrointestinal or renal arteries.
  - *Laboratory findings:*
    - Few changes considering severity of disease: elevated sed rate, anemia, thrombocytosis, microscopic hematuria.
    - Check for HBsAg positivity.
    - ANCA positive in $<5\%$.

- **Differential diagnosis:**
  - *Microscopic polyangiitis:* Glomerulonephritis, alveolar hemorrhage, pANCA).
  - *Other forms of vasculitis:* Kawasaki (children, acute picture), Wegener (head and neck, lungs, cANCA), leukocytoclastic vasculitis (little systemic involvement), lupus erythematosus (other skin findings, ANA, autoantibodies).
- **Therapy:**
  - Systemic corticosteroids: prednisolone 1 mg/kg daily; can start with pulse therapy 1.0 g daily for 3 days.
  - If unresponsive or with major organ involvement, add cyclophosphamide (2 mg/kg daily) or other immunosuppressive agents.
  - If patient is HBsAg positive, then start therapy with prednisone and plasma exchanges, followed by IFN and lamivudine—consult hepatology.

Mucocutaneous Lymph Node Syndrome

- **Synonym:** Kawasaki disease.
- **Definition:** Systemic vasculitis in children with acute onset and involvement of coronary arteries.
- **Epidemiology:** 80% of patients < 5 years of age, male:female ratio 1.7:1; incidence 100/100 000 yearly in Japan but < 10/100 000 in Germany.
- **Pathogenesis:** Infectious agent or superantigen suspected but not proven.
- **Clinical features:** Six main findings present in > 95% (except for cervical lymphadenopathy):
  - Unexplained high temperature.
  - Bilateral conjunctivitis.
  - Oral involvement with pharyngeal erythema and strawberry tongue.
  - Maculopapular or urticarial exanthem.
  - Acral edema, palmoplantar erythema and then characteristic desquamation of fingertips after 10–14 days.
  - Cervical lymphadenopathy (50%).
  - *Coronary artery disease:* The real problem is coronary artery inflammation with the formation of aneurysms, occurs in around 20% of untreated patients in week 2–3.
- **Histology:** Nonspecific changes; not diagnostically helpful.
- **Diagnostic approach:**
  - Diagnosis certain when five of six features present, or four plus coronary artery disease.

  Caution: In older children, cardinal signs and symptoms are often missing so life-threatening cardiac disease may be overlooked (*incomplete Kawasaki disease*). Be suspicious.
- **Differential diagnosis:** Scarlet fever, toxic shock syndrome, viral exanthems, Stevens–Johnson syndrome, drug reactions.
- **Therapy:** High-dose intravenous immunoglobulins (single dose 2 mg/kg over 8 hours) plus aspirin 30–40 mg/kg daily until defervescence, then 3–5 mg/kg daily for 2 months. If aneurysms are present, consult with cardiology regarding further anticoagulation and management.

Behçet Syndrome

- **Definition:** Systemic vasculitis with recurrent aphthae, genital ulcerations, and involvement of many other organs.
- **Epidemiology:** Common disease in Middle East and East Asia (*Silk Road disease*); prevalence 1/1000 in Japan; 1/500 000 in North America.

- **Pathogenesis:** Complex; in Japan strong association with HLA-B51; heat shock proteins (especially HSP 60) may be involved in stimulating γδ + T-cell response in susceptible individuals; infectious triggers (streptococci, herpes simplex) also long suspected.
- **Clinical features:**
  - *Main features:*
    - Recurrent oral aphthae (p. 494), at least 3× in 12 months (100%).
    - Indolent genital ulcers (90%).
    - Chronic recurrent uveitis (50%).
  - *Other features:*
    - *Skin:* Erythema nodosum (80%), recurrent thrombophlebitis, pathergy (pustular response at site of trauma).
    - *Large vessel vasculitis:* Pulmonary artery aneurysms (arterial-bronchial fistula formation), aortic aneurysms.
    - *Arthritis and arthralgias:* Favor hands, wrists, ankles, knees.
    - Gastrointestinal ulcers, distal ileum and cecum.
    - *CNS:* Stroke, aseptic meningitis.
    - Kidney disease and peripheral neuropathy rare.
  - *MAGIC syndrome:* Overlap between Behçet syndrome and relapsing polychondritis.
- **Histology:** Three categories:
  - Early lesions show leukocytoclastic infiltrates similar to Sweet syndrome or sometimes leukocytoclastic vasculitis with fibrinoid change.
  - Later lesions with lymphocytic or granulomatous inflammation.
  - *Aphthae:* Intense neutrophilic infiltrate with necrosis.
- **Diagnostic approach:**
  - Diagnosis likely with two of the three main symptoms and two additional symptoms.
  - No specific laboratory tests; screen for organ involvement.
  - *Pathergy test:* Inject 0.1 mL of physiologic NaCl with fine needle on forearm; read after 24–48 hours. Pustule or papule suggests diagnosis; histology shows neutrophilic infiltrate or vasculitis.
- **Differential diagnosis:** Long list because of multisystem involvement:
  - *Other forms of vasculitis:* None typically have aphthae.
  - *Other ocular–oral–genital syndromes:* Erythema multiforme, cicatricial pemphigoid, Reiter syndrome (reactive arthritis), erosive lichen planus.
  - *Crohn disease:* Often with aphthae, and bowel changes similar.
  - Cyclic neutropenia.

  Note: Do not diagnose Behçet syndrome on the basis of severe aphthae alone.
- **Therapy:**
  - *Oral and genital lesions:* Topical or intralesional corticosteroids.
  - Cyclosporine most effective for uveitis; azathioprine also effective.
  - *Other systemic therapy:*
    - Colchicine 0.5–1.5 mg daily.
    - Dapsone 0.5–2.0 mg/kg daily.
    - Corticosteroids ± immunosuppressive agents.
  - Each of many systemic complications requires specialized therapy, often in consultation.

15.6 Livedo

- **Definition:** Net-like blue-red erythema.
- **Pathogenesis:** Livedo results from reduced arteriolar flow and accumulation of deoxygenated blood in venules. There are two forms (Fig. 15.**4**):
  - *Livedo reticularis:* Functional or physiologic, transient; result of vasoconstriction.
  - *Livedo racemosa:* Pathologic, permanent; result of vascular occlusion or malformation.
- **Clinical features:**
  - Livedo reticularis more common on legs; if arms or trunk involved, think of livedo racemosa.
  - Livedo reticularis is common:
    - *Transient:* Results from exposure to cold or other triggers; also known as *cutis marmorata*.
    - *Permanent:* Mechanisms poorly understood.
  - Livedo racemosa is persistent, progressive; associated with variety of underlying diseases; always requires investigation (Table 15.**3**).
- **Histology:**
  - *Livedo reticularis:* Normal skin.
  - *Livedo racemosa:* Fibrin in vessel wall, thrombi in small vessels, extravasation of erythrocytes.

  Note: The pathological findings are in the arterioles, which are in "normal" skin, not in the blue areas; the choice of biopsy site is extremely important.
- **Therapy:**
  - *Livedo reticularis:* None required, or warming.
  - *Livedo racemosa:* Treat associated disease.

Table 15.3 · **Diseases associated with livedo racemosa**

Inflow impaired (arterial)	Outflow impaired (venous)	Hyperviscosity
Arteriosclerosis	Leukocytoclastic vasculitis	Cryoglobulinemia
Cholesterol emboli	Thrombi	Thrombocytosis
Sneddon syndrome[a]	Emboli	Macroglobulinemia
Arteritis: polyarteritis nodosa, connective tissue disease, thromboangiitis obliterans		Cold agglutinin disease
		Anti-phospholipid syndrome

[a] Subintimal hyperplasia leads to livedo racemosa and a variety of CNS findings (seizures, stroke, hemiparesis, visual loss, speech disturbances).

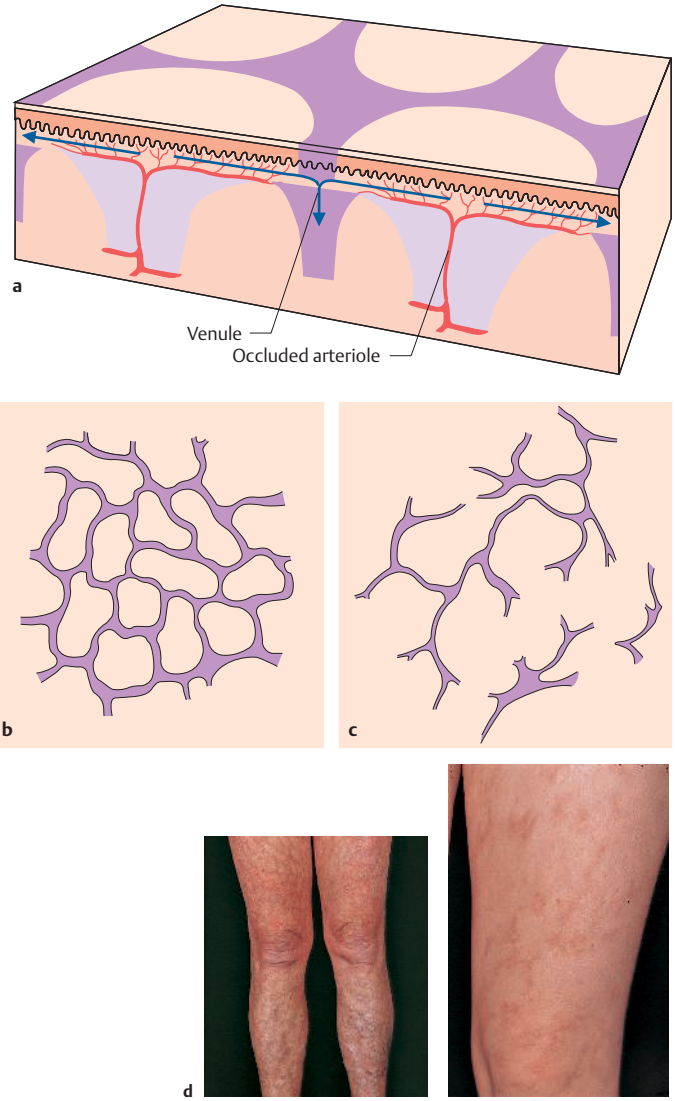


Fig. 15.4 · **Livedo. a** Anatomic basis of livedo reticularis. **b** Livedo reticularis—regular closed circles. **c** Livedo racemosa—irregular broken arcs. **d** Livedo reticularis. **e** Livedo racemosa.

15.7 Vessel Occlusion and Cutaneous Necrosis

Coumarin Necrosis

- **Definition:** Acute cutaneous necrosis occurring shortly after starting coumarin therapy.
- **Pathogenesis:** The unifying factor is reduced protein C levels; either those with heterozygous defect or secondary to disorders such as liver dysfunction, diabetes mellitus, postoperative status, disseminated intravascular coagulation, or use of oral contraceptives. Coumarin drops the protein C levels more rapidly than it interferes with the counter-regulatory factors of the prothrombin complex, so that the patient is temporarily in a hypercoagulable state.
- **Clinical features:** Onset within 1 week of starting coumarin. Vascular occlusion with extensive necrosis; usually involves fatty tissue of buttocks, breasts, thighs (Fig. 15.**5**). Far more common in women. Initially hemorrhage, then blisters, then rapid necrosis.
- **Diagnostic approach:** Determine protein C levels.
- **Differential diagnosis:** Heparin necrosis, cholesterol emboli, disseminated intravascular coagulation.
- **Therapy:** Stop coumarin and use vitamin K to counteract it; add heparin; management by hematologist.

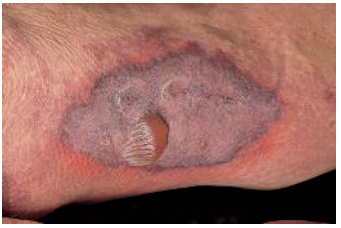


Fig. 15.**5** · Coumarin necrosis.

Heparin Necrosis

- Extremely rare; heparin causes immune-mediated platelet adherence, clotting, and necrosis. Low molecular weight heparin can thus cause necrosis at sites distant from injection.

Cholesterol Emboli

- **Pathogenesis:** Emboli from cholesterol plaques; may develop following endovascular surgery (mechanically dislodged), trauma or 3–8 weeks after starting anticoagulant therapy. Often history of coronary artery disease, aortic aneurysm, or cerebrovascular disease.
- **Clinical features:**
  - Renal involvement is life-threatening; cholesterol crystals can often be visualized in retinal vessels.
  - Skin features livedo racemosa on legs as well as "blue toe syndrome." Pedal pulses usually intact. Necrosis develops promptly. Up to 90% have skin involvement.

- **Histology:** Cholesterol crystals or clefts can be seen in vessels.
- **Diagnostic approach:** History, clinical examination, biopsy.
- **Differential diagnosis:** Exclude other forms of occlusive vascular disease, such as vasculitis, other emboli, thrombi, hyperviscosity syndrome.
- **Therapy:** No satisfactory therapy exists.

Fat Emboli

- **Pathogenesis:** Small pieces of fat get into circulation either from bone marrow (fractured femur, polytrauma) or fat (trauma, liposuction).
- **Clinical features:** Multiple petechiae, favoring axillae and conjunctivae. Variety of systemic signs and symptoms such as fever, confusion, cardiovascular problems.
- **Histology:** Cutaneous vessels occluded by particles of fat, along with hemorrhage.
- **Therapy:** Heparin, fluids, sometimes systemic corticosteroids.

Calciphylaxis

- **Pathogenesis:** Rare effect usually occurring in patients with chronic renal disease, secondary hyperparathyroidism, and elevated calcium and phosphate levels. Media of deep dermal and cutaneous vessels become calcified and then occluded.
- **Clinical features:** Livedo changes with extensive necrosis. Other organs such as coronary vessels, lungs, or fatty tissue may also show calcium deposition.
- **Histology:** Calcium salt deposits in vessel walls.
- **Therapy:** No standard therapeutic approach. Fatality rate $>50\%$, usually with sepsis. Attempt to lower calcium levels, anticoagulated with heparin; hyperbaric oxygen has shown some promise.

Nicolau Syndrome

- Cutaneous necrosis following intramuscular injection. Either medication is injected into an artery or its local irritant effects causes arteriospasm. Livedo reaction with pain, hemorrhage, bullae, and then necrosis. Onset minutes to hours after injection. No good therapy other than standard wound care. Medication can be re-administered at later date without problems.

Extravasation of Chemotherapeutic Agents

- Clinically identical to Nicolau syndrome and more common because of widespread use of locally toxic chemotherapy agents such as doxorubicin and daunorubicin. Either medication is administered outside the vein, or vessel leakage occurs. Intense pain, rapid blanching, livedo pattern, and then necrosis. In some instances antidotes are recommended, but in most cases only good wound care is available. Occasionally recall reactions occur; when same medication is administered properly at a different site, the formerly damaged site may flare up.

16 Papulosquamous Disorders

16.1 Psoriasis

Overview

- **MIM code:** 177900.
- **Definition:** A chronic recurrent dermatosis characterized by a T cell-mediated inflammatory reaction and subsequent epidermal hyperproliferation.
- **Epidemiology:**
  - 1–3% of individuals in Western Europe and USA affected.
  - Incidence varies between different ethnic groups and geographic locations.
  - Female:male ratio is 1:1.
- **Pathogenesis:**
  - *Genetics:* Polygenic inheritance with variable penetrance. Two types can be identified:
    - *Type I psoriasis:* Onset < 40 years of age, with positive family history and association with HLA-Cw6, -B13, -B57, -DR7.
    - *Type II psoriasis:* Onset > 40 years, sporadic, no HLA associations.
  - The sequence of events is unclear. The initial reaction is possibly an intrinsic defect of keratinocytes with increased cytokine production which leads to expansion of CD45RO+ T cells with resultant production of type 1 cytokines. Sequelae include epidermal proliferation, migration of neutrophils into the epidermis, proliferation of vessels in papillary dermis.
  - Known triggers include streptococcal infections, medications (angiotensin converting enzyme [ACE] antagonists, β-blockers, antimalarials, gold, interferons, lithium, some oral contraceptives), alcoholism, stress, nonspecific skin injury.
  - *Köbner phenomenon:*
    - Minor skin damage or injury can lead to the development of psoriasis in the lesion (isomorphic response).
    - Systemic factors must play a role as the Köbner phenomenon can occur anywhere on skin, but is far more likely to develop during a time when psoriasis is on the upsurge than when it is stable or resolving.

    ▶ ***Note:*** Köbner phenomenon is not restricted psoriasis; it may occur with lichen planus, vitiligo, and many other diseases..
- **Classification:**
  - *Psoriasis vulgaris:*
    - Chronic stable, plaque-type psoriasis.
    - Guttate psoriasis.
    - Inverse psoriasis.
  - *Psoriatic erythroderma.*
  - *Pustular psoriasis.*
    - Palmoplantar pustular psoriasis (Barber–Königsbeck).
    - Acrodermatitis continua suppurativa (Hallopeau).
    - Generalized pustular psoriasis (von Zumbusch).
    - Annular pustular psoriasis.
    - Impetigo herpetiformis (pustular psoriasis in pregnancy).
  - *Drug-induced psoriasis and psoriasiform drug reactions.*
  - *Psoriatic nail disease.*
  - *Psoriatic arthritis.*

Clinical Features

► **Sites of predilection:** Include scalp, retroauricular area, knees, elbows, sacrum, nails (Fig. 16.**1**).

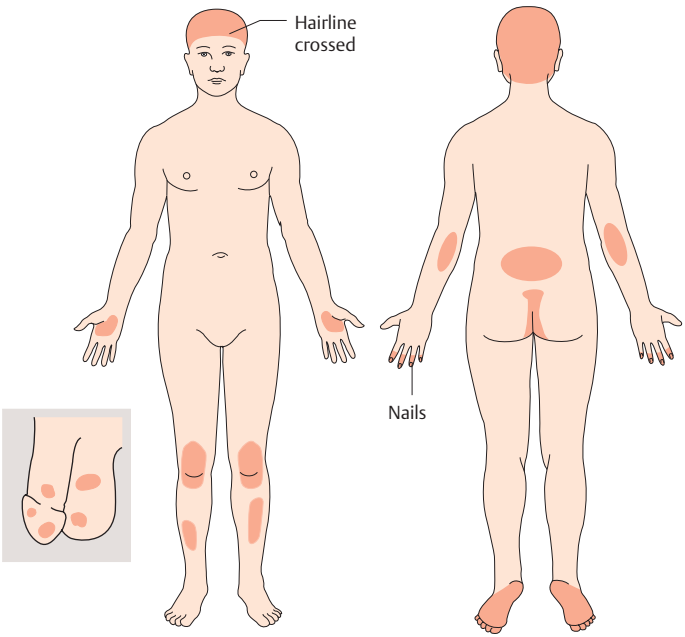
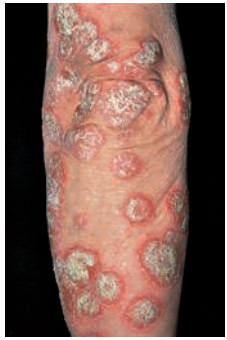


Fig. 16.**1** · Sites of predilection for plaque-type psoriasis.

► **Lesion morphology:** Sharply bordered erythematous patches and plaques with silvery scale (Fig. 16.**2**).

► **Psoriasis vulgaris:**

- *Chronic plaque-type psoriasis:*
  - Small papules evolve through confluence into large irregular, well-circumscribed plaques, 3–20 cm.
  - *Silvery scale* is extremely typical.
  - Sites of predilection include knees, elbows, sacrum, scalp, retroauricular area (Fig. 16.**3 a**).
  - Untreated, the plaques can remain stable for months or years.
  - May be less distinct in dark skin (Fig. 16.**3 b**).
- *Guttate psoriasis:*
  - Appears as exanthem over 2–3 weeks; starting with small macules and papules that evolve into 1–2 cm plaques with silvery scale (Fig. 16.**3 c**).
  - Favor the trunk, less often extremities or face.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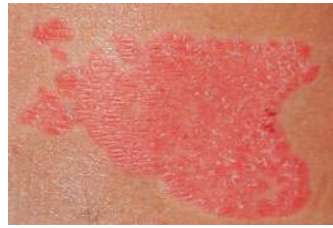
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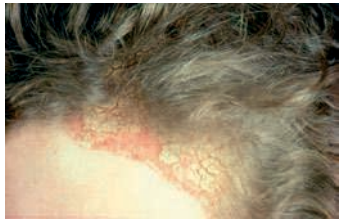
Fig. 16.2 · **Psoriasis. a** Sharply bordered erythematous plaques with silvery scale—typical of psoriasis. **b** Similar lesions after the scales have been removed with keratolytics.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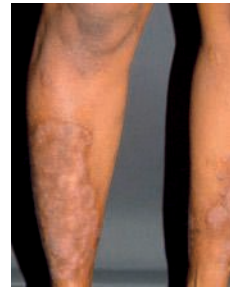
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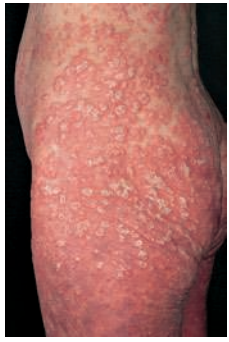
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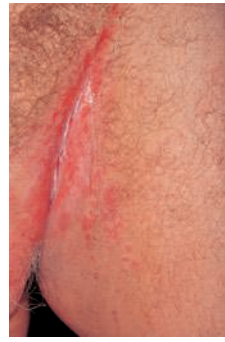
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Fig. 16.3 · **Psoriasis. a** Psoriasis of scalp; note sharp delineation between diseased and normal skin. **b** Psoriasis in dark skin. **c** Guttate psoriasis with transition to psoriatic erythroderma. **d** Inverse psoriasis without scale but with fissures.

  - Most patients are children or young adults, usually after a streptococcal pharyngitis; sometimes following treatment or tonsillectomy, the psoriasis resolves completely and never returns.
  - Differential diagnosis includes pityriasis lichenoides et varioliformis acuta, pityriasis rosea.
- *Intertriginous psoriasis* (Fig. 16.**3 d**):
  - Involves axillae and groin; often misdiagnosed.
  - Differential diagnosis includes candidiasis and other forms of intertrigo.
  - Macerated and fissured; thick plaques and silvery scale usually missing.
  - Requires less aggressive therapy.
- *Inverse psoriasis:*
  - Overlaps with intertriginous; describes form where involvement is flexural and classical sites such as knees and elbows are spared.

► **Psoriatic erythroderma:**

- Involves the entire integument: can develop suddenly out of a guttate psoriasis, or from a long-standing psoriasis following too aggressive therapy or abrupt discontinuation of medications.
- When confronted with possible psoriatic erythroderma, always think about pityriasis rubra pilaris (p. 278). In erythrodermic form, very hard to separate. Other forms of erythroderma also must be considered (p. 282).

► **Pustular psoriasis:**

- *Palmoplantar pustular psoriasis (Barber–Königsbeck):*
  - Numerous pustules on palms and soles (Fig. 16.**4 a**).
  - Always check for psoriasis elsewhere and in history.
  - Diagnosis confusing—two entities cause trouble:
  - *Palmoplantar pustulosis*: Similar clinically without evidence for psoriasis. Often blamed on foci of infection (pustular bacterid of Andrews) but little proof. Patients tend to be women who smoke; lacks HLA association to psoriasis. Female:male ratio 4:1; average age 30–50 years. We regard this entity as different from psoriasis.
  - *Dyshidrotic dermatitis* (p. 200): Initial lesions are clear vesicles; a form of hand dermatitis; may evolve into pustules.
- *Acrodermatitis continua suppurativa (Hallopeau):* Pustules limited to one or a few fingertips including nail bed. Nail loss not uncommon. Once again relationship to psoriasis controversial, but we view this as localized psoriasis.

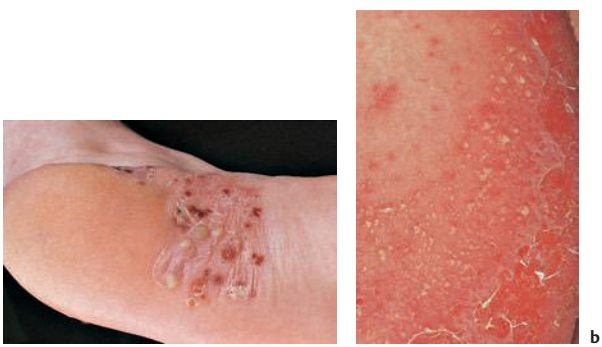


Fig. 16.**4** · **Psoriasis. a** Psoriasis with palmoplantar pustulosis. **b** Annular pustular psoriasis.

- *Generalized pustular psoriasis (von Zumbusch):* Patients with widespread psoriasis and on the verge of erythroderma develop diffuse pustules and are critically ill with fever, chills, and malaise.
- *Annular pustular psoriasis:*
  - 5–30 cm dusky erythematous lesions with peripheral rim of pustules and a collarette scale pointing toward the center (Fig. 16.**4b**).
  - Often associated with psoriasis vulgaris; in other instances, an intermediate stop on the way to erythroderma.
  - Differential diagnosis includes the figurate erythemas (p. 285).
- *Impetigo herpetiformis (pustular psoriasis in pregnancy):* Rare febrile disease of 3rd trimester with annular pustular psoriasis; abnormal calcium metabolism endangers fetus; likely to recur with subsequent pregnancies or oral contraceptives.

► **Histology:** Many distinctive features: acanthosis with parakeratosis, lack of stratum granulosum, elongation of rete ridges, dilated tortuous vessels in papillary dermis, dermal lymphocytic infiltrate, exocytosis of neutrophils into epidermis producing spongiform pustules (*Kogoj*), or subcorneal microabscesses (*Munro*).

► **Drug-induced psoriasis and psoriasiform drug reactions:**

- Medications are common triggers for psoriasis.
- The following groups can cause problems:
  - β-Blockers: mechanism well-understood; block the β_2 adrenergic receptors of keratinocytes, elevating cAMP, which increases cell proliferation. If a psoriatic patient needs a β-blocker, try to use a more cardiac-selective β_1 adrenergic blocker.
  - ACE inhibitors; use angiotensin II antagonists instead.
  - Chloroquine (although risk seems somewhat overrated, as American troops in Viet Nam all took chloroquine and there was not an epidemic of psoriasis).
  - Immunomodulators (various interferons, imiquimod).
  - Lithium salts.

► **Psoriatic nail disease:** Valuable diagnostic clues (Fig. 16.**5**):

- *Dorsal nail matrix:* Pitting of nail plate.
- *Ventral nail matrix:* Onycholysis, oil spots (greasy dark stain; preonycholysis), distal subungual debris, red spots on lunula.

Fig. 16.**5** · **Psoriasis.** Psoriatic nail changes.

Diagnosis and Differential Diagnosis

► **Diagnostic approach:**

- The diagnosis of psoriasis can usually be made clinically with ease; the problem is therapy.

Note: If you suspect the diagnosis of psoriasis, always check the gluteal cleft, scalp, and nails for typical changes.

- **Difficulties in diagnosis:**
  - Treated lesions (loss of scale or redness).
  - Early or eruptive lesions (no scale has developed, smaller lesions).
- **Skin biopsy:** Not as helpful as it sounds, because classic lesions are rarely biopsied, and clinically difficult lesions often puzzle microscopists.
- **Psoriasis Area and Severity Index** (PASI): An widely used system to assess the severity of psoriasis. It is extremely useful in following individual patients and in clinical studies.
  - The body is divided into four segments: head (H), trunk (T), upper extremities (U), and lower extremities (L), which are weighted based on percentage of body surface area: H = 0.1, T = 0.3, U = 0.2, L = 0.4.
  - The area involved (A) is then assessed for each segment: 0 = none, 1 = < 10%, 2 = 10–30%, 3 = 30–50%, 4 = 50–70%, 5 = 70–90%, 6 = 90–100%.
  - To assess severity (S), a four-point scale is used: 0 = no symptoms, 1 = sight symptoms, 2 = moderate symptoms, 3 = marked symptoms, 4 = very marked symptoms. The points erythema (E), infiltration (I), and desquamation (D) are assessed.
  - The regional scores are calculated and then summed as follows:
  - $PASI = 0.1\ (E_H + I_H + D_H)\ A_H + 0.3\ (E_T + I_T + D_T)\ A_T$.
  - $+ 0.2\ (E_U + I_U + D_U)\ A_U + 0.1\ (E_L + I_L + D_L)\ A_L$.
  - A sample PASI calculation with maximum involvement and severity in shown in Table 16.**1**. The score can range from 0 to 72, moving in 0.1 increments.

Table 16.1 · **Sample PASI calculation**

Region	Surface area	Erythema	Infiltration	Desquamation	Area of involvement	Regional score
Head	0.1	4	4	4	6	7.2
Trunk	0.3	4	4	4	6	21.6
Arms	0.2	4	4	4	6	14.4
Legs	0.4	4	4	4	6	28.8
PASI						72

- **Differential diagnosis:**
  - Considerations include tinea, contact dermatitis, nummular dermatitis. Secondary syphilis can be psoriasiform clinically; it is always so under the microscope. Acute cases resemble pityriasis lichenoides et varioliformis acuta and pityriasis rosea.
  - The distinction between psoriasis and seborrheic dermatitis can be extremely difficult. In HIV/AIDS, the two appear to overlap with Reiter syndrome.
  - Pityriasis rubra pilaris is another diagnostic challenge; if palms and soles are prominently involved, if there are areas of sparing, or if things just don't fit with psoriasis, always think of pityriasis rubra pilaris.
  - Always take a drug history; many drug reactions are psoriasiform, and in some instances lead to true psoriasis in susceptible hosts.

Basic Aspects of Therapy

► An overview of the many topical and systemic measures available for psoriasis and how we tend to employ them is shown in Table 16.**2**.

Table 16.2 · Treatment of psoriasis

Type of psoriasis	Therapy	Comments
Psoriasis vulgaris	Anthralin Vitamin D analogues Retinoids (topical, systemic) UVB 311 nm narrow band PUVA	For more severe disease: Biologicals Cyclosporine Fumaric acid Methotrexate
Psoriatic erythroderma	Biologicals Cyclosporine A Methotrexate	Low doses can be combined; treat "gently"
Pustular psoriasis	Retinoids (systemic) Cyclosporine A Methotrexate	Every case is a special case! Stop smoking!
Drug-induced psoriasis	Stop medication; find suitable alternatives	If needed, treat as above with standard measures.
Psoriatic arthritis	NSAIDs Methotrexate Cyclosporine	Biologicals (TNF-α antagonists)

► The choice of which mediation to use must always be based on the age, sex, social setting, and ability of the patient to apply topical medications or travel for light therapy, as well as on contradictions.

► ***Note:*** The social and psychological implications of psoriasis are almost impossible to overemphasize. Always be aware of how much the patients are disturbed by their disease, and seek help and support where available.

► It is important to adjust the treatment of psoriasis to fit the changing physical findings. Experience is the best teacher in this respect, but Table 16.**3** provides a few suggestions.

Table 16.3 · Psoriasis: therapeutic implications of clinico-pathologic findings

Clinical finding	Pathologic correlate	Therapy
Scales	Hyperkeratosis Parakeratosis	Keratolytics Emollients
Thickness	Acanthosis (psoriasiform hyperplasia)	Anthralin Topical corticosteroids Vitamin D analogues Phototherapy
Erythema	Dilated vessels Lymphocytic infiltrates	Topical corticosteroids Cyclosporine Fumaric acid Biologicals
Pustules	Collections of neutrophils in epidermis	Retinoids Methotrexate

Topical Therapy

- **Salicylic acid:**
  - 2–5% salicylic acid is a useful keratolytic to remove scales. It facilitates all other topical measures. Concentrations up to 20% may be used on the palms and soles.

  Caution: Salicylic acid can be irritating and then induce new lesions (Köbner phenomenon). It should not be used over wide areas in children because of the risk of systemic resorption and side effects (salicylism and nephrotoxicity).
- **Anthralin:** The keystone for most topical regimens. It requires a well-trained, compliant patient and is easier to use in in-patients than outpatients. It can easily be combined with phototherapy (Ingram regimen).
- **Vitamin D analogues:** Most widely available are calcipotriol and tacalcitol; they are most useful for small areas of moderate psoriasis. Roughly as effective as mid-potency corticosteroid, with fewer side effects. Combination products containing both vitamin D analogues and corticosteroids are available, but costs limit their use on widespread disease; also, they can potentially effect calcium metabolism.
- **Retinoids:** Tazarotene is effective in moderate psoriasis, with few irritating effects. The other more widely available retinoids are less well suited for psoriasis.
- **Corticosteroids:** Useful for small areas, on scalp and in inverse psoriasis; simple for patient to use; available in many forms (creams, ointments, lotions); can be combined with occlusion.

  Caution: Long-term widespread use of potent topical corticosteroids can lead to adrenal suppression and cushingoid effects. The most important side effect is cutaneous atrophy (p. 596). When discontinued, there is often a rebound effect. On the scalp, steroid side effects simply don't occur, so high-potency products should be used.
- **UVB 311 narrow band light (TL01):** Relatively long wavelength UVB has good penetration and has both anti-inflammatory (induces apoptosis of immune cells) and antiproliferative effects. The more carcinogenic shorter wavelength UVB is avoided. Suitable for all forms of psoriasis except pustular psoriasis.
- **Balneophototherapy:** Combination of selective ultraviolet phototherapy (SUP) (305–325 nm) with prior bath in 5–10% table salt or solution simulating ocean water. Based on climatotherapy regimens at Dead Sea and other health spas. Because the Dead Sea is 400 meters below sea level, UVB is increasingly absorbed, so the radiant light is dominated by UVA.
- **PUVA (psoralens and UVA) (p. 607):**
  - PUVA is well-established for severe forms of psoriasis.
  - In young patients, be aware of increased lifetime risk for skin cancers and increased photodamage.
  - Systemic PUVA has been to a great extent replaced in Germany by bath PUVA, which is simpler to use and just as effective. Both widespread and pustular psoriasis respond well.

Systemic Therapy

Note: Systemic therapy is very attractive to patients. Just try smearing your body with any cream or ointment 2–3 times a daily for a weekend and you will appreciate what psoriatic patients go through for a lifetime. It is little wonder they invariably ask about and prefer systemic therapy. Fortunately many options are available.

- **Fumaric acid:**
  - Fumaric acid esters are helpful in all forms of psoriasis and have been successfully used for moderate to severe disease. They can be tried for therapy-re-

sistant forms, such as severe scalp psoriasis, pustular psoriasis, inverse psoriasis and even psoriatic arthritis.
- The standard product in Germany is Fumaderm — a combination of fumaric acid esters, available as Fumaderm Initial and Fumaderm. The main component is dimethyl fumarate, with either 30 mg or 120 mg in the respective forms.
- The exact details for administering fumaric acid esters as Fumaderm are outlined in Chapter 42 (p. 634).
- The clinical response is slow and first comes as the dosage is slowly increased. Although almost all patients have a drop in lymphocyte count, they do not have an increased susceptibility to infections.

! Always warn the patient that a response may take as long as two months. Such a warning avoids much disappointment and explaining later on.
- Its advantages are effectiveness and a lack of cumulative toxicity. The disadvantages are flushing and gastrointestinal side effects, which can be reduced with the following therapy plan.

! If gastrointestinal problems appear when the dosage is increased, go back to the previously tolerated dosage until all problems resolve, then attempt once again to increase dosage.

► **Methotrexate** (p. 629):
- Methotrexate is the most widely used disease-modifying agent for both psoriasis and psoriatic arthritis. Dermatologists initially used methotrexate for psoriasis in dosages high enough to completely control disease (24 – 45 mg/ weekly) and encountered many side effects. Rheumatologists started with much lower dosages (7.5–15 mg / weekly with a maximum of 25 mg /weekly) and noticed that both joints and skin improved.
- The usual form of administration is the Weinstein regimen, designed to adjust timing of methotrexate dose to decreased keratinocyte cell cycle time in psoriasis and at the same time reduce toxicity. The drug is given in three divided dosages at 12-hour intervals once a week; in other words, perhaps 5 mg Saturday evening, 5 mg Sunday morning, and 5 mg Sunday evening.
- Today most experienced dermatologists in USA view methotrexate as the most effective form of systemic therapy. Nonetheless, it is clearly more toxic than fumaric acid esters. The organ of most concern is the liver, but hepatotoxicity has dropped markedly since lower dosages became standard. Methotrexate is bound to serum proteins; when other medications bind in a competitive manner, higher free concentrations of methotrexate may result with subsequent bone marrow toxicity.

► **Retinoids** (p. 622):
- The most effective retinoid for psoriasis is acitretin.
- Retinoids suppress epidermal proliferation, leading to a reduction in thickness of psoriatic lesions and therefore increasing the effectiveness of other measures, especially phototherapy. Therefore, retinoids are most often used in combination.
- Retinoids have a wide variety of side effects including elevation of serum cholesterol and triglycerides, triggering of pancreatitis, and musculoskeletal problems, as well as inevitable skin and mucosal dryness.
- They are potent teratogens and cannot be used in women capable of childbearing without undue precaution.
- Photosensitization is a common side effect, but may also explain partially the efficacy of such combination therapy. In any event, it must be closely monitored.

► **Cyclosporine** (p. 628):
- Cyclosporine is highly effective for psoriasis and capable of perhaps inducing the most rapid response of any of the systemic agents. Often improvement is seen in a manner of a few days.

- The dramatic effectiveness of cyclosporine was the first hard clue pointing to the central role of T cells in psoriasis and triggering the many investigative efforts that made possible the host of biological agents that are now available.
- The long-term side effects of cyclosporine are too great to make it a routine drug for psoriasis.

► **Biologicals:** These are therapeutic molecules that are specifically targeted in order to imitate or inhibit naturally occurring proteins. The main categories currently used are antibodies and fusion proteins, which either antagonize mediators with a central pro-inflammatory role or interfere with the interactions between T cells and endothelial cells or antigen-presenting cells (APC). Table 16.**5** summarizes the biologicals available in Europe for the treatment of psoriasis. The fascinating scientific background, targeting, efficacy, and relative paucity of side

Table 16.4 · **Biological agents for psoriasis and psoriatic arthritis**

Indications	Dose	75% PASI ↓	Joint response	Side effects
Alefacept				
Moderate to severe psoriasis	7.5 mg i. m. weekly	35% after 14 weeks	55%	↘CD4+ T cells Autoantibodies (2%)
Efalizumab				
Moderate to severe psoriasis	1 mg/kg subq. weekly	36% after 12 weeks	None	Guttate flares during initial treatment; risk of rebound when treatment stopped
Etanercept				
Psoriatic arthritis, rheumatoid arthritis	25–50 mg subq. 2× weekly	35% after 12 weeks	60–70%	Delayed hypersensitivity reaction at injection site Anti ds-DNA antibodies Infections (long-term therapy)
Infliximab				
Psoriatic arthritis, rheumatoid arthritis, Crohn disease, others	5 mg/kg i. v. at weeks 0, 2, and 6	> 80% after 10 weeks	~70%	Infusion reactions Autoantibodies (10%) Infections (tuberculosis) Anaphylaxis (< 0.1%)

effects are unfortunately balanced by a cost so high as to threaten the best of reimbursement plans.

- *Modifiers of T-cell response:*
  - *Alefacept:* A fusion protein combining LFA-3 (CD58) and the constant region (Fc) of human IgG antibody. The LFA-3 component binds to CD2 on T cells and blocks a costimulatory molecule required for interaction with APC. The antipsoriatic effect comes from the reduction in the number of CD45 RO+ memory T cells. The Fc fragment attracts natural killer (NK) cells, which cause apoptosis of these T cells. Since CD2 is highly up-regulated in activated T cells, this important component of the psoriatic pathway is to a large extent eliminated.
    The usual regimen involves a single 7.5 mg i.m. injection once weekly for 12 weeks. Effects can be seen as early as after two injections, but usually peak 6–8 weeks after therapy is concluded. About 40% of patients achieve a PASI reduction of 75%. A rebound flare is not seen. Lymphocyte counts should be monitored.
  - *Efalizumab:* A humanized monoclonal anti-CD11a antibody that blocks the interaction of CD11a (LFA-1) with a variety of molecules. It inhibits both interaction between T cells and APC, as well as the attachment of T cells to endothelium via ICAM-1.
    The usual dosage is 1 mg/kg subq. once weekly for continuous use. The PASI can be expected to drop by about 50% in most patients after 3 months. In these responders the response will continue to improve over time and side effects are remarkably low, even with long-term treatment.
    May be associated with *flares* (papular eruption in previously uninvolved sites), which may sometimes resolve with continuing treatment and in other instances get progressively worse. In the latter case, *rebound* may occur (PASI $>$ 125% as compared with status at onset), requiring cyclosporine or TNF antagonists for control.
- *TNF antagonists:* TNF α is the key pro-inflammatory cytokine in psoriasis stimulating keratinocytes and causing T-cell activation. It is produced early in psoriatic inflammation and then induces further pro-inflammatory mediators. Elevated TNF α levels are found in skin lesions, in joint fluid, and systemically in psoriatic patients. Its central role in inflammation has made TNF α an attractive target for blocking inflammation. Two biologicals that inhibit it were first proven effective in rheumatoid arthritis and then employed for both joint and skin manifestations of psoriasis. Both biologicals occasionally induce antibodies to ds-DNA and in rare instances cause a systemic lupus erythematosus-like reaction.
  - *Etanercept:* A fusion protein containing the soluble TNF α receptor protein (p75) and the Fc component of IgG. It binds to circulating TNF and blocks its function. The usual regimen is 25–50 mg subq. 2× weekly for 12 weeks or longer. The joint involvement improves in almost 75% of patients, while the PASI score can be expected to drop by 50%. Injection site reactions can occur, but otherwise well tolerated.
  - *Infliximab:* A chimeric antibody linking a murine anti-TNF monoclonal antibody to human Fc component of IgG. It too blocks TNF α and additionally induces apoptosis in cells with membrane-bound TNF. The usual regimen is 5 mg/kg i.v. in physiologic saline administered at weeks 0, 2, and 6. It can be repeated as required when the skin or joint condition worsens. Within 3 weeks, a mean 50% improvement in PASI can be seen. After 10 weeks, 80 % of patients have an improvement of 75% in PASI. Well tolerated.

Note: All patients should be checked before therapy for latent or active tuberculosis, for example with skin testing and chest radiograph. Local guidelines for the diagnosis and monitoring of tuberculosis should be followed. Activation of tuberculosis may be a problem with both etanercept and infliximab.

16.2 Psoriatic Arthritis

► **Epidemiology:**
- 3–5% of psoriatic patients have joint involvement; male:female ratio 1:1.

Note: The real problem is the 15% of adults with *arthritis sine psoriasis*—that is, they have psoriatic arthritis but no skin findings, or skin findings so subtle that a rheumatologist overlooks them.

► **Clinical features:**
- Three main types of psoriatic arthritis:
  - Mono- or oligoarthritis with muscular or tendon attachment pain (enthesitis) similar to reactive arthritis (30–50%).
  - Symmetric polyarthritis resembling rheumatoid arthritis (30–50%) (Fig. 16.**6**).
  - Axial disease resembling ankylosing spondylitis (< 10%).
- Clinical examination should search for all three types of disease, looking for swollen or painful joints. Definite identification of joint fluid is a crucial diagnostic skill. It is unusual to have psoriatic arthritis in a digit with an entirely normal nail.

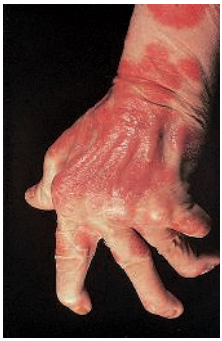


Fig. 16.**6** · Psoriatic arthritis with marked deformities.

► **Diagnostic approach:**
- Our scheme for evaluating the hands and feet in patients with psoriatic arthritis is shown in Table 16.**5**.
- Develop a standardized radiographic evaluation scheme: both hands and feet in two planes, as well as sacrum to assess sacroiliac joints; if clinical and radiographic findings do not agree, then scintigraphy or symptom-directed MRI; repeat in 2 years or with new joint disease.
- *Laboratory evaluation:* ANA, autoantibodies, rheumatoid factor, uric acid; for seronegative arthritis without skin changes, check for HLA-B13, -BW57, -B27.

Table 16.5 · Joint evaluation

Digit	Hands								Feet							
	Nails		DIP		PIP		MCP		Nails		DIP		PIP		MCP	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
I																
II																
III																
IV																
V																

► ***Note:*** Important clues to diagnose of psoriatic arthritis include:
- Skin or nail changes of psoriasis.
- Positive family history of psoriasis.
- Mono- or oligoarticular involvement at onset.
- Sausage finger(s): multiple joints on same digit involved, with marked swelling.

► **Differential diagnosis:**
- *Rheumatoid arthritis:* Female:male ratio 3:1, symmetrical involvement of small distal joints, + rheumatoid factor, ↑ sedimentation rate, distinctive radiographic appearance.
- *Gout:* Female:male ratio 1:7, usually involves single joint (great toe), ↑ serum uric acid, crystals in joint fluid.
- *Osteoarthritis:* Female:male ratio 10:1, characteristic combination of small joints of hands and feet with larger joints, such as knees, hips, sacrum, and cervical spine, no inflammation, no joint fluid, Heberden nodes, characteristic radiographic picture.

► **Therapy:**
- Mainstay is NSAIDs; COX2 inhibitors are probably best forgotten, although they initially seemed promising.
- If patients do not experience prompt control with NSAIDs, then consider should be given to disease-modifying agents such as methotrexate. Sulfasalazine has no effect on skin disease or axial skeletal disease, but is a second choice for distal joint disease.
- The next step is usually TNFα blockers, which first proved their worth in rheumatoid arthritis. Response rates in the neighborhood of 50% are expected, with improvement seen in a matter of weeks.
- Agents employed for severe psoriasis are also useful, including cyclosporine and retinoids.
- Physical therapy should be incorporated into the treatment plan at an early point, in order to maximize retention of function. Surgery may be required for severe pain or loss of function. The fear of infection when operating through or near psoriatic plaques is almost certainly overrated, but is a common point of interaction between dermatologists, rheumatologists, and orthopedic surgeons.

16.3 Reiter Syndrome

- **Definition:** A form of reactive arthritis often with psoriasiform skin changes, which may be associated with urethritis or conjunctivitis depending on the triggering agent.
- **Pathogenesis:** Genetic factors are important, as up to 75% of white patients are HLA-B27 positive; much lower in other ethnic groups; HLA-BW22 or -BW42 may also be involved. Molecular mimicry or bacterial superantigens appear to be involved, as signs and symptoms often develop 1–4 weeks after an infection. Several different clinical settings can be observed:
  - *Postdysentery Reiter syndrome*: Causative agents include *Shigella flexneri* (serotype 1b and 2a), *Salmonella typhimurium*, *Yersinia enterocolitica* (serotypes 3 and 9), *Campylobacter jejuni*. Clinical changes begin within weeks of a gastrointestinal infection, which may or may not be symptomatic. Male:female ratio is 1:1.
  - *Posturethritis Reiter syndrome* (p. 150): Causative agent *Chlamydia trachomatis* (serotypes D–K). Signs and symptoms start 1–3 weeks after sexual contact, often with a new partner. Men far more often affected.
  - *HIV-associated Reiter syndrome:* In advanced HIV infection, appearance of overlapping features of severe psoriatic arthritis and Reiter syndrome.
- **Clinical features:**
  - *Cardinal features:*
    - *Circinate balanitis*: Annular erosive lesions on glans, often polycyclic with white periphery.
    - *Keratoderma blennorrhagicum*: Pustular and hyperkeratotic lesions on palms and soles, similar to pustular psoriasis. Previously mistakenly associated with gonorrhea.
    - *Other features of psoriasis:* Nail changes, involvement of scalp, knees, elbows.
    - *Oral lesions* (much more common than in psoriasis): Erythema and even ulcerations.
    - *Arthritis:* Asymmetric, favors lower extremities; rheumatoid factor negative. Known as reactive arthritis or seronegative spondyloarthropathy. 10% have ankylosing spondylitis.
  - Patients may be ill with fever, chills, and malaise. They may have lumbar or sacral pain. Other features include urethritis or cervicitis (only when *Chlamydia trachomatis* is involved), dysentery (with other triggers), and conjunctivitis or iritis. The conjunctivitis is more common with *Chlamydia trachomatis* triggers and is bilateral. The iritis comes later and is usually unilateral. About 1–2% develop aortitis with aortic valve regurgitation and heart block; usually occurs in those with long-standing arthritis. Reactive (serum amyloid A protein, SAA) amyloidosis and an IgA nephropathy are rarely seen.
  - Course usually self-limited, with resolution within 12 months. About 15% relapse; another 15% develop chronic disease.
- **Diagnostic approach:**
  - The presence of two cardinal symptoms and one other feature should strongly suggest the diagnosis.
  - Leukocyte count, sedimentation rate, C-reactive protein all elevated.
  - Determination of HLA type may be useful.
  - EKG, eye examination, and appropriate joint imaging (including MRI) after rheumatologic evaluation.
  - If septic arthritis is suspected, then tap joint and culture fluid.
  - Search for causative organisms depending on clinical presentation (dysentery versus urethritis) and exclude HIV infection.

► **Differential diagnosis:**
- *Skin:* Primarily psoriasis, on scalp seborrheic dermatitis.
- *Joints:* Psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, septic arthritis.

► **Therapy:**
- If an infection is identified, then treat. Often doxycycline 100 mg b.i.d. is used, even empirically.
- NSAIDS are standard for arthritis; if more severe, systemic corticosteroids (prednisolone 60–100 mg daily until improvement, then taper over 2–4 weeks).
- For chronic arthritis consider methotrexate (15–25 mg weekly) or TNF antagonists (see psoriasis treatment, p. 269). Methotrexate should be used with care in HIV.
- For skin disease, standard psoriasis therapy; if severe, consider acitretin.

16.4 Seborrheic Dermatitis

► **Definition:** Erythematous scaly eruption, usually in areas rich in sebaceous glands.

► **Epidemiology:** Very common; occurs in most infants and in many elderly patients.

► **Pathogenesis:** Two main factors are presence of generous amount of epidermal lipids and colonization, at least transiently by *Malassezia* species (lipophilic, usually nonpathogenic yeasts). Immune response also plays a role; tends to be far more severe in HIV/AIDS. In our view seborrheic dermatitis overlaps with psoriasis and may well be a minimal form of this disorder.

► **Clinical features:**
- Erythematous red-yellow, poorly circumscribed patches with fine scale; only mildly pruritic (Fig. 16.**7**).
- Common sites: scalp (dandruff), eyebrows, perinasal areas, ears, retroauricular area; less often anterior chest; annular or petaloid form most common on neck.

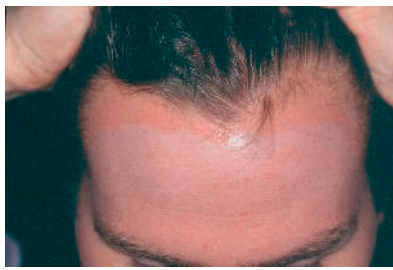


Fig. 16.**7** · Seborrheic dermatitis.

► **Diagnostic approach:** Clinical diagnosis. If severe and acute, think of HIV/AIDS.

► **Differential diagnosis:**
- *Psoriasis:* Lesions better circumscribed, thicker scale (definite overlap).
- *Allergic contact dermatitis:* more pruritic, less chronic. If in doubt, patch testing.
- *Truncal lesions:* Tinea corporis, pityriasis versicolor—do KOH examination.
- Look for atopic stigmata; scalp dermatitis in infants can be atopic, seborrheic, or a combination thereof.

- **Therapy:**
  - *Medicated shampoos:* Antimycotic forms (ketoconazole or ciclopiroxolamine), zinc pyrithione, selenium sulfide or tar; alternate with regular shampoo. Frequent shampooing helps.
  - For cutaneous lesions, either imidazole creams or lithium succinate cream. If refractory, low-potency corticosteroid cream for 2–3 days or topical immunomodulatory agent (pimecrolimus or tacrolimus).
  - Rare patients may benefit from UV light, tar, or low-potency anthralin preparations.

16.5 Pityriasis Amiantacea

- **Definition:** Not a disease, but a very uncommon reaction pattern on the scalp, seen with seborrheic dermatitis, psoriasis, contact dermatitis, or atopic dermatitis.
- **Pathogenesis:** Reasons for disordered keratinization not understood.
- **Clinical features:** Massive white adherent scales on scalp (Fig. 16.**8**); sometimes arranged like roof tiles. The scales are firmly adherent to hairs; bundles of hair frequently accompany them as they are removed.

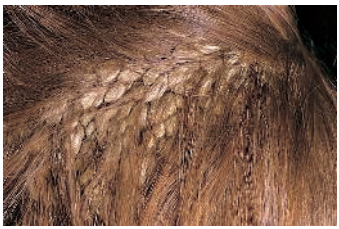


Fig. 16.**8** · Pityriasis amiantacea with thick scales and severe dermatitis.

- **Diagnostic approach:** Clinical diagnosis.
- **Differential diagnosis:** In children exclude tinea capitis—KOH examination. Look for signs of seborrheic dermatitis, psoriasis, or atopic dermatitis.
- **Therapy:**
  - The first step is to remove the scales. Apply a 5–10% salicylic acid in a washable base or mixed with a potent corticosteroid cream overnight under shower cap occlusion. In the morning, shampoo using a salicylic acid or tar shampoo. Then apply a corticosteroid lotion. Repeat the process each night until improvement is seen; then cut back on both the frequency and strength of the corticosteroids.
  - If an underlying disease can be identified, adjust the treatment to that diagnosis (i.e. tars for psoriasis, less helpful for atopic dermatitis).
  - In many instances, the patients are amazingly passive about what must be a distressing condition and do not treat their scalps aggressively. Sometimes a brief stay in the hospital or daycare clinic is useful to insure that they are actually treating themselves.

16.6 Pityriasis Rubra Pilaris

- **Definition:** Group of uncommon chronic erythematosquamous disorders with palmoplantar hyperkeratosis, follicular papules, and often erythroderma.
- **Pathogenesis:** Unknown; increased epidermal turnover but not as severe as in psoriasis. Some suspect infectious origin.
- **Classification:** The Griffiths classification is shown in Table 16.**6**.

Table 16.6 · **Classification of pityriasis rubra pilaris**

Form	E	PPK	FK	Spontaneous healing	Recurrences
Classic					
Adult	+	+	+	+	+
Juvenile	+	+	+	(+)	+
Atypical					
Adult	(+)	(+)	(+)	?	?
Juvenile	(+)	(+)	(+)	?	?
Circumscript	–	–	+	+	–

E = erythroderma; FK = follicular keratosis; PPK = palmoplantar keratoderma.

- **Clinical features:** Areas of diffuse erythema with fine scale and often weeping; follicular hyperkeratoses, often prominent on backs of fingers; salmon color; often areas of sparing (*nappes claires*, Fig. 16.**9**). Scalp, face, and palmoplantar involvement common; often site of first manifestations. Often provoked by light.
  - ***Note:*** Pityriasis rubra pilaris is often mistaken for months as psoriasis. If a case of psoriasis just doesn't look right, always think of pityriasis rubra pilaris.
- **Histology:** Difficult histologic diagnosis; may have parakeratosis at shoulders of follicles or alternating hyper- and parakeratosis. Neutrophils not prominent, in contrast to psoriasis.
- **Diagnostic approach:** Almost entirely a clinical diagnosis; skin biopsy for possible aid. Follicular areas and nappes claires are best clues.

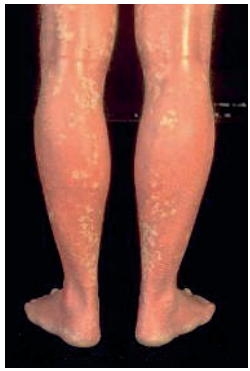


Fig. 16.**9** · Pityriasis rubra pilaris with areas of sparing (nappes claires).

- **Differential diagnosis:** Biggest problem is psoriasis; prominent facial involvement or follicular lesions speak against it. Early scalp involvement often mistaken for atopic dermatitis or seborrheic dermatitis. Early diffuse lesions confused with lichen planus, pityriasis lichenoides et varioliformis acuta.
- **Therapy:**
  - Very difficult to treat; responds poorly to many psoriasis regimens such as PUVA, methotrexate, or anthralin.
  - With acute flares, systemic corticosteroids may be useful (prednisolone 60–100 mg tapered rapidly). Introduce retinoids at same time; usually acitretin although some prefer isotretinoin; must use either dosages than in acne.
  - Recently we have seen good responses to infliximab.

16.7 Pityriasis Rosea

- **Definition:** Acute self-limited erythematosquamous exanthem with classical clinical pattern.
- **Epidemiology:** Most patients young adults; male:female ratio 1:1. More common spring and fall; tends to occur in mini-epidemics.
- **Pathogenesis:** Viral etiology long suspected, but no single virus convincingly implicated.
- **Clinical features:**
  - Initial lesion is often large 2–6 cm annular patch with collarette scale (*herald patch*, Fig. 16.**10a**); usually on trunk.
  - After 1–2 weeks, typical exanthem with 1–3 cm patches with fine scale (Fig. 16.**10b**), often arranged along skin folds creating *Christmas tree pattern* on back. Typically not found on face or distal extremities. Easily irritated, producing dermatitic appearance.

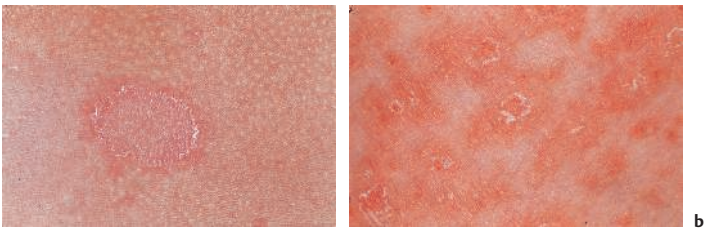


Fig. 16.**10** · **Pityriasis rosea. a** Typical herald patch. **b** Multiple inflamed patches.

  - Pruritus rare, unless treated with drying agents.
  - Typically resolves spontaneously over 6–12 weeks.
  - In blacks, facial and acral involvement common; known as *inverse pityriasis rosea*. More chronic, often pruritic, heals with hypopigmentation.
- **Histology:** Microscopic picture not diagnostic; helpful only for differential diagnostic considerations.
- **Diagnostic approach:** Almost exclusively a clinical diagnosis; KOH examination and syphilis serology.

- **Differential diagnosis:** Herald patch often mistaken for tinea corporis.
  - ***Note:*** If patient gives history of tinea corporis spreading rapidly under therapy, suspect pityriasis rosea.
  - Diffuse exanthem suggests secondary syphilis, subacute cutaneous lupus erythematosus, guttate psoriasis, pityriasis lichenoides et varioliformis acuta.
- **Therapy:**
  - The most important step is to lubricate the skin and avoid drying therapies (frequent washing, antibacterial soaps, lotions, alcohol-based products).
  - On occasion, topical corticosteroids may be used briefly; low to midpotency in emollient base b.i.d.
  - Topical antipruritic agents and systemic antihistamines are rarely needed for the pruritus.

16.8 Small-Patch Parapsoriasis

- **Synonyms:** Chronic digitate dermatitis, parapsoriasis *en petites plaques*.
- **Definition:** Chronic superficial scaly dermatosis with distinctive clinical pattern and controversial relationship to large-patch parapsoriasis and mycosis fungoides.
- **Epidemiology:** Most common in adults >50 but seen in all ages; male:female ratio 5:1.
- **Pathogenesis:** Unknown; some consider it related to T-cell lymphoma.
- **Clinical features:**
  - Sites of predilection include trunk, upper arms, thighs.
  - Oval poorly circumscribed macules with fine (pityriasiform) scale, often following skin lines. Wrinkled appearance but not truly atrophic. Usually yellow-brown, not red.
  - Lesions are chronic; may be present for decades.
- **Histology:** Banal dermatitis with slight spongiosis and mild parakeratosis. Marked interface change suggests large-patch parapsoriasis.
- **Diagnostic approach:**
  - Clinical picture, chronicity, and lack of evidence of mycosis fungoides on biopsy.
  - Molecular biology not answer; over 50% have circulating monoclonal T-cell population, but such a clone is rarely found in the skin. Significance unclear.
- **Differential diagnosis:**
  - Main question is mycosis fungoides; we believe useful to separate, as so few patients with small-patch parapsoriasis advance to mycosis fungoides.
  - Other possibilities include pityriasis lichenoides chronica, psoriasis, lichenified dermatitis of all type, tinea corporis.
- **Therapy:**
  - Usually asymptomatic and no treatment required.
  - Phototherapy is most useful; bath PUVA or narrow-band 311 nm irradiation work best.
  - Topical midpotency corticosteroids can be used for pruritic or inflamed lesions; also emollients containing urea.

16.9 Erythema Multiforme

- **Definition:** Acute self-limited inflammatory reaction with typical target or iris lesions.
- **Epidemiology:** Affects young adults (20–40 years of age) with male dominance.
- **Pathogenesis:** The vast bulk of recurrent cases are triggered by herpes simplex virus (HSV) infections. Immune complexes containing HSV DNA can be found in the lesions. Other triggers include mycoplasma and only rarely drugs.
- **Clinical features (Fig. 16.11a):**
  - The classic lesion is a target lesion (Fig. 16.**11b**) found on the distal extremities. The rings come from:
    - Central dark hemorrhagic zone, which becomes blue-violet.
    - Intermediate white area.
    - Peripheral erythematous ring.

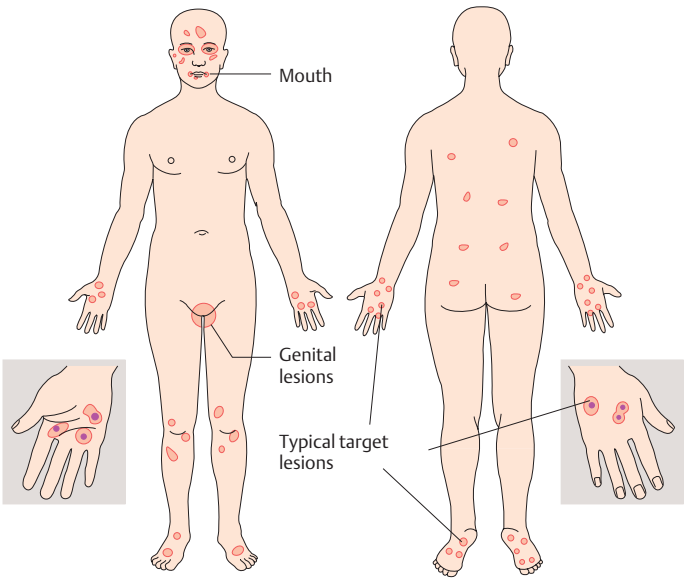


Fig. 16.**11** · **Erythema multiforme.** **a** Pattern of distribution. **b** Target lesions on hands.

- Typically 1–3 cm in diameter; rarely clinically bullous or urticarial. Heals spontaneously over weeks, sometimes with residual hyperpigmentation.
- The presence of a prodrome is often emphasized, but the prodrome is caused by the HSV, mycoplasma, or underlying disease requiring drug therapy. While erythema multiforme can involve the mucosa, in most cases lip involvement is HSV, not erythema multiforme.
- The assessment of erythema multiforme is usually straightforward when HSV is the trigger. In the case of other causes, the picture is complicated by a series of other more severe skin findings:
  - *Erythema multiforme-like drug eruption:* Lesions are usually on the trunk, not forming excellent target lesions (Fig. 16.**12**) and far more likely to progress to Stevens–Johnson syndrome and toxic epidermal necrolysis (p. 184).

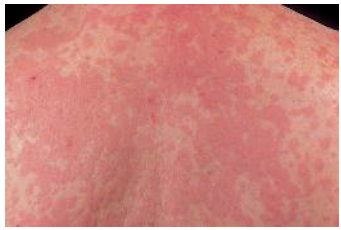


Fig. 16.**12** · Erythema multiforme-like drug eruption which is truncal and lacks target lesions.

- **Histology:** Necrotic keratinocytes, vacuolar degeneration in basal layer, papillary dermal edema with lymphocytic perivascular infiltrates.
- **Diagnostic approach:**
  - Clinical pattern, history of HSV (often missing) or drug exposure, related signs and symptoms.
  - Skin biopsy.
- **Differential diagnosis:** Erythema multiforme-like drug eruption, erythema multiforme-like lupus erythematosus (Rowell syndrome).
- **Therapy:**
  - Short course of systemic corticosteroids (prednisolone 60–80 mg for 3–5 days) dramatically shortens course. Topical corticosteroids less helpful.
  - If recurrent, suppressive therapy with antiherpetic medications (p. 615) is most useful.

16.10 Erythroderma

- **Definition:** Abnormal redness (erythema) of the skin covering wide areas or the entire skin surface.
- **Epidemiology:** Reliable information on incidence is not available. Men are more frequently affected, and mean age of onset is around 50 years of age. Three main causes (Fig. 16.**13**):
  - Exacerbation of underlying dermatitis (atopic dermatitis, psoriasis, pemphigus foliaceus).
  - *Drug reactions:* Most common drugs include barbiturates, captopril, carbamazepine, cimetidine, NSAIDs, furosemide, sulfonamides, thiazides.
  - Malignancies, including lymphomas and paraneoplastic reactions.

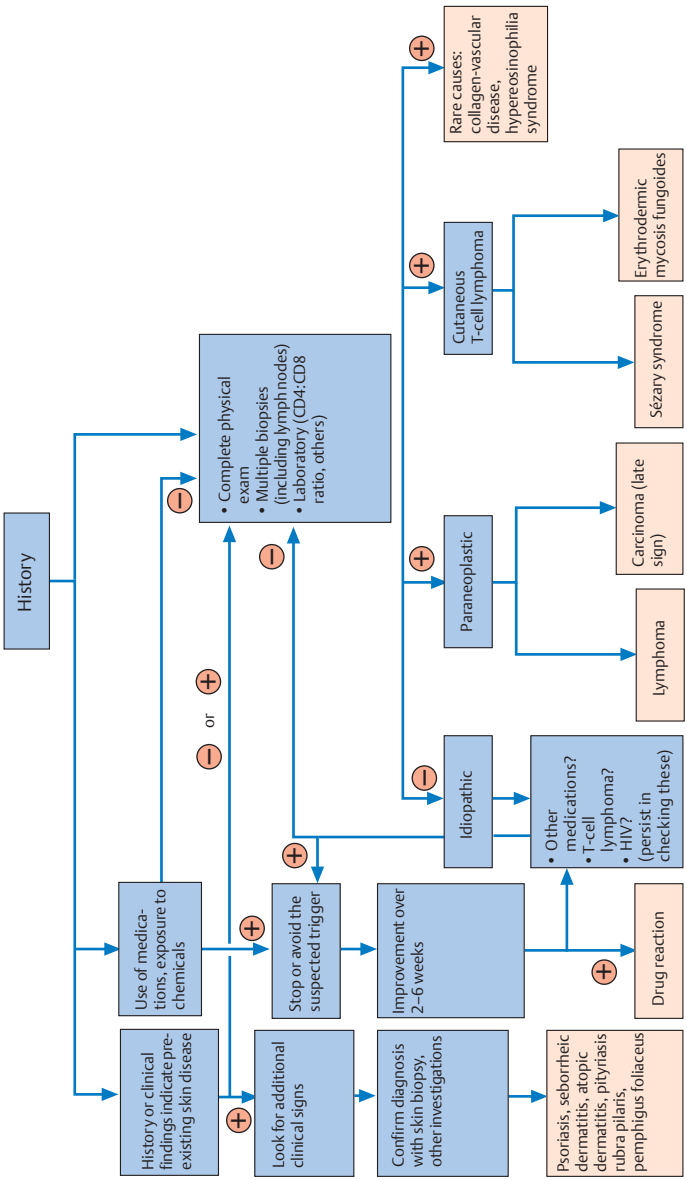


Fig. 16.**13** · Practical approach to patients with erythroderma

- In one large series, the most common causes were dermatitis (24%), psoriasis (20%), drug reactions (19%), cutaneous T-cell lymphoma (8%). Table 16.**7** shows possible causes of erythroderma in adults.

Table 16.7 · **Possible causes of erythroderma**

Disease	Comments
Common	
Psoriasis	Usually pre-existing disease, especially pustular; flares likely with discontinuation of corticosteroids or methotrexate
Atopic dermatitis	Intensely pruritic, usually multiple atopic stigmata
Drug reactions	Usually start as morbilliform reaction; can be purpuric; resolves when drug is stopped
Idiopathic	More common in elderly people. Detailed clinical and histological studies reveal no cause; re-examine periodically to exclude cutaneous T-cell lymphoma (also called red man syndrome)
Less common	
Cutaneous T-cell lymphoma	Both Sézary syndrome and erythrodermic mycosis fungoides possible; massive lymphadenopathy; circulating atypical lymphocytes
Pityriasis rubra pilaris	Often starts on hands, scalp; islands of sparing and follicular involvement
Contact dermatitis	Distant spread; history usually clear
Chronic actinic dermatitis	Usually starts on face and neck, intensely pruritic
Paraneoplastic	Usually occurs late in course of solid-organ malignancies; not really a clue to diagnosis
Bullous diseases	Pemphigus foliaceus especially likely to evolve into erythroderma; occurs less often in bullous pemphigoid and paraneoplastic pemphigus
Rare	
Hypereosinophilia syndrome Ofuji syndrome Crusted scabies Severe collagen-vascular disorders Lichen planus Dermatophyte infections	
Erythroderma in children	
Ichthyoses Immunodeficiency syndromes Atopic dermatitis Staphylococcal scalded skin syndrome	

Note: Even after extensive evaluation, the cause of erythroderma remains unclear in about $^1/_3$ of patients.

- **Pathogenesis:**
  - Erythroderma demonstrates the "systemic signs of cutaneous disease".
  - Erythroderma is major medical problem; patients suffer from impaired temperature control (too much skin blood flow) with chills, as well as protein loss (scales) and water loss.
  - Problems include edema (ankle, facial), tachycardia, both hyperthermia (increased blood flow) and hypothermia (evaporative cooling). They may develop a enteropathy because of the protein loss. 20% have hepatomegaly.
  - Lymphadenopathy is the most common extracutaneous finding and does not always indicate cutaneous T-cell lymphoma. *Dermatopathic lymphadenopathy* as a response to severe cutaneous disease is a well-established clinicopathologic entity.
- **Histology:** Microscopic examination is essential, but not always capable of providing the answer. Severe psoriasis may appear similar to severe atopic dermatitis or a drug reaction. Sézary syndrome and mycosis fungoides can, however, usually be identified.
- **Diagnostic approach:** The most information is obtained form a detailed history, examination of old records or biopsies, and search for subtle clues to underlying disease.
- **Therapy:**
  - Initially, good supportive care, fluid management, and attention to secondary infections are essential.
  - Systemic corticosteroids are sometimes used empirically with an initial dose of 1–3 mg/kg daily of prednisolone tapered rapidly to 0.5 mg/kg daily.
  - Cyclosporine 4–5 mg/kg daily for 3 months as a last resort.
  - Topical treatment should be bland.
  - Once the erythroderma is resolving, primary treatment for the underlying disease can be started.

16.11 Figurate Erythemas

- **Definition:** The figurate erythemas are a group of totally unrelated disorders, having in common only the tendency to form annular or polycyclic lesions (p. 711).
  Note: The most common figurate diseases are urticaria, tinea, and erythema migrans. Always think of them first.
- **Classification:** The figurate erythemas are typically divided into superficial and deep, based clinically on tendency to have scale or not. Some authors regard perivascular cuffing as suggestive of figurate erythema and then histologically divide based on involvement of superficial vascular plexus alone or both the superficial and deep plexuses. These distinctions are not clinically helpful.
  - *Erythema annular centrifugum* is the classic figurate erythema. It presents as slowly expanding erythematous rings often with collarette scale. Roughly the same factors that trigger urticaria are implicated in erythema annulare centrifugum. It is usually asymptomatic, but cosmetically disturbing. Most important is search for underlying cause.
  - *Erythema gyratum repens* moves more rapidly than erythema annulare centrifugum, has a *woodgrain* pattern and is almost always a sign of underlying malignancy (p. 486).
  - *Erythema marginatum* is associated with rheumatic fever (p. 224).

- *Necrolytic migratory erythema*: Marker for glucagonoma; acral and orificial erosions plus figurate erythema (p. 486).
- *Granuloma annulare:* Ring-shaped but rarely polycyclic and extremely slowly expanding (p. 292).
- *Subacute cutaneous lupus erythematosus* is often annular and can evolve into complex patterns (p. 207); *lupus tumidus* is the classic example of a deep figurate erythema.
- *Sjögren syndrome* in Japanese patients often has associated annular erythema.
- Carrier females of x-linked recessive chronic granulomatous disease have an *arcuate erythema*—subtle and very rare.
- Some cases of hereditary angioedema are annular.
- *Acral erythema:* Recurrent eruption in summertime in patients lacking the M component of lactate dehydrogenase.

16.12 Lichenoid Dermatitis

The term lichenoid is confusing; clinically it suggests a disease resembling lichen planus (flat-topped papules, violaceous color) but histologically it refers to a band-like infiltrate of lymphocytes at the dermoepidermal junction.

Lichen Planus

► **Definition:** Common inflammatory disease featuring pruritus, distinctive violaceous flat-topped papules and often oral erosions.

► **Epidemiology:** Appears at all ages, but most common between 30–60 years of age.

► **Pathogenesis:**
- Infiltrate of Th1 cells and cytotoxic cells → IFN-γ and TNF → expression of HLA-DR8+ adhesion molecules on keratinocytes → basal cell layer damage → reactive hyperkeratosis (model of T-cell-mediated epidermal damage).
- In some countries, especially Italy, association between lichen planus and hepatitis viruses (usually hepatitis C). IFN therapy for hepatitis can trigger lichen planus.
- Eruptions resembling lichen planus are frequently induced by medications (a long list, including pain medications, antibiotics, antiepileptics, chloroquine, quinidine, ACE inhibitors, antituberculosis agents, and hypoglycemic agents and chemicals) and chemicals (most often color film processing materials).

► **Clinical features:**
- *Classic skin finings:*
  - Classic lesions are glistening *violaceous flat-topped papules* (Fig. 16.**14 a**), usually 2–10 mm in diameter. Fine lacy white markings on top of papules known as *Wickham striae.* Scratching and trauma induce new lesions: Köbner phenomenon. In exanthematous form, sudden development of widespread disease.
  - Pruritus usually present and sometimes intense.
  - Sites of predilection include inner aspects of wrists, ankles, anterior shins, buttocks.
- *Many cutaneous variants:*
  - *Hypertrophic lichen planus*: Verrucous persistent plaques, especially shins and ankles; painful when on soles.

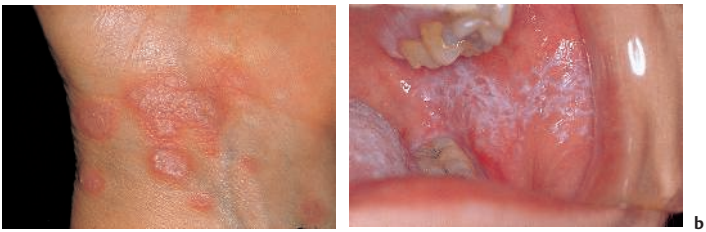


Fig. 16.**14** · **Lichen planus. a** Violaceous flat-topped papules. **b** Lacy network on oral mucosa.

  - *Lichen planopilaris:* Hyperkeratotic follicular papules, usually on scalp (*Graham–Little syndrome*); infiltrate confined to follicular epithelium; can lead to scarring alopecia (p. 506) and one of precursors of pseudopelade.
  - *Linear lichen planus:* Linear grouping of lichen planus papules that cannot be explained by Köbner phenomenon; usually on legs of children.
  - *Erosive lichen planus:* Most common on oral mucosa, less often genital mucosa or soles; painful, often chronic erythematous erosions.
  - ***Note:*** The chronic irritation can lead to development of squamous cell carcinoma, so erosive lichen planus must be monitored closely.
  - *Bullous lichen planus:* Sometimes ordinary lesions become bullous because of intensity of dermoepidermal junction damage.
  - *Lichen planus pemphigoides:* Combination of lichen planus and bullous pemphigoid (p. 236); separation from bullous lichen planus has been controversial, but now better established. Also triggered by drugs such as captopril, PUVA, and cinnarizine.
  - *Atrophic lichen planus:* Atrophic, often hyperpigmented areas, sometimes with violaceous rim.
- *Mucosal findings:*
  - Large lacy white network on buccal mucosa, less often on tongue, lips or labial mucosa (Fig. 16.**14 b**). Painful erosions also present, often on hard palate.
  - Similar reticulate pattern with erosions can be seen on genital mucosa.
- 80–90% clear within 2 years; isolated mucosal disease more likely to be chronic.

► **Histology:** Acanthotic epidermis with prominent stratum granulosum and saw tooth pattern of rete ridges; band-like dermal lymphocytic infiltrate that damages basal layer. In drug-induced lichen planus, histologic changes often less pronounced.

► **Diagnostic approach:** Clinical features, histology, drug history; depending on local pattern, hepatitis screening.

► **Differential diagnosis:**
- *Classic lesions:* Lichenoid drug eruptions, lichen nitidus, secondary syphilis, pityriasis lichenoides et varioliformis acuta, early pityriasis rubra pilaris.
- *Hyperkeratotic lesions:* Lichen simplex chronicus, prurigo nodularis, warts.
- *Linear lesions:* Lichen striatus, linear epidermal nevus, linear psoriasis.
- *Lichen planopilaris:* Early lesions → keratosis pilaris, other follicular keratoses, Darier disease, early pityriasis rubra pilaris. Advanced lesions → lupus erythematosus; other forms of scarring alopecia.
- *Erosive lichen planus:* Oral lesions → lupus erythematosus, autoimmune bullous diseases. Soles → secondary syphilis.

- **Therapy:**
  - In most instances, high-potency topical corticosteroids, perhaps under occlusion are most effective. For erosive lichen planus, either corticosteroid solutions or intralesional injections; hypertrophic lesions may also do better with intralesional corticosteroids.
  - Systemic corticosteroids is needed for widespread or rapidly spreading disease. Usually 60 mg daily, tapered over 6–8 weeks.

    Caution: Risk of rebound flare is considerable; it is wise to taper slowly, if medically tolerable.
  - Other choices include acitretin, antimalarials, and even cyclosporine as a last resort.
  - Bath and cream PUVA are promising alternatives; effective and with much less risk of triggering flare than ordinary PUVA.

Lichen Nitidus

- **Definition:** Uncommon dermatosis featuring tiny white papules; considered by some as lichen planus variant.
- **Epidemiology:** Either more common or more easily noticed in blacks.
- **Clinical features:**
  - Multiple pinhead-sized glistening white papules, favoring forearms, abdomen, penis, buttocks. May be accompanied by typical lesions of lichen planus.
  - Mucosal lesions less common; tiny yellow papules, less often lacy network as in lichen planus.
  - Pruritus uncommon.
- **Histology:** Small granulomatous infiltrate just beneath the epidermis, involving only 2–3 rete ridges; very early lesions may have minuscule band-like infiltrate.
- **Diagnostic approach:** Clinical examination, biopsy.
- **Differential diagnosis:** Lichen planus, sarcoidosis, disseminated granuloma annulare, eruptive xanthomas, plane warts.
- **Therapy:** Nothing standard, spontaneous healing occurs; if symptomatic, try topical corticosteroids.

Pityriasis Lichenoides et Varioliformis Acuta

- **Synonyms:** PLEVA, pityriasis lichenoides acuta, Mucha–Habermann disease.
- **Definition:** Acute dermitis with hemorrhagic crusted papules.
- **Epidemiology:** Most patients are children or young adults.
- **Pathogenesis:** Cause unknown, but viral triggers long suspected.
- **Clinical features:** Sudden appearance of red-brown 0.5–3.0 cm papules that rapidly develop hemorrhagic crusts. Sometimes necrotic, ulcerated, and heal with scars. Rarely associated with systemic signs and symptoms.
- **Histology:** Prototype of lymphocytic vasculitis with dense wedge-shaped lichenoid infiltrate and vascular damage in upper dermis.
- **Diagnostic approach:** Clinical examination, biopsy.
- **Differential diagnosis:** Severe varicella, leukocytoclastic vasculitis, secondary syphilis, drug reaction. Some patients with lymphomatoid papulosis (p. 478) clinically have this disorder, but reveal highly atypical CD30 + lymphocytes on biopsy.
- **Therapy:** Often resolves spontaneously. Systemic antibiotics (erythromycin or tetracycline) frequently tried. If symptomatic, consider systemic corticosteroids or PUVA. Exquisitely sensitive to methotrexate but rarely indicated in young patients.

Pityriasis Lichenoides Chronica

- **Synonyms:** Parapsoriasis guttata, Juliusberg disease.
- **Definition:** Chronic lichenoid dermatitis with persistent scale.
- **Pathogenesis:** In some instances, evolves out of PLEVA, but also occurs spontaneously.
- **Clinical features:** Flat brown papules, usually on trunk, covered with a sheet of large adherent scale that can be peeled off in one piece; fancifully compared to communion wafers in some countries (Fig. 16.**15**). Lesions symmetrical, often following skin lines. Asymptomatic, but lasts for years or decades.
- **Histology:** Hyperkeratotic scale with parakeratosis, modest lichenoid infiltrate.
- **Diagnostic approach:** Clinical examination, biopsy.
- **Differential diagnosis:** Lichen planus, small-patch parapsoriasis, PLEVA, secondary syphilis, nummular dermatitis.
- **Therapy:** Extremely difficult; light is best—either PUVA or SUP. Oral antibiotics can also be tried, but less helpful than with PLEVA. Methotrexate not as effective as in PLEVA and not warranted because of chronic course.

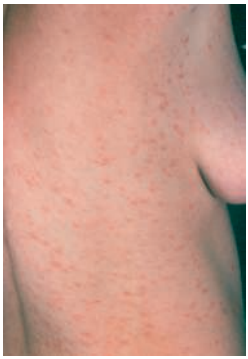


Fig. 16.**15** · Pityriasis lichenoides chronica.

Other Lichenoid Disorders

- **Lichen sclerosus** (p. 217): Often has a band-like infiltrate but rarely papules. Closely related to morphea and not to other lichenoid disorders.
- **Lichen aureus**: Is a form of pigmented purpura (p. 246) but may have a lichenoid infiltrate.
- **Lichen Striatus**.
  - **Definition:** Grouped usually linear lichenoid papules most common in children.
  - **Pathogenesis:** Unknown, most likely inflammatory response in area limited by mosaicism (p. 350).
  - **Clinical Features:** Initially non-distinct erythematous papules whose linear arrangement soon becomes apparent. Typically as linear band down leg. Usually self-limited with spontaneous regression.
  - **Histology:** Subacute dermatitis with scattered dyskeratotic cells in epidermis and dermal lymphocytic infiltrate without lichenoid pattern.
  - **Differential Diagnosis:** Linear lichen planus, perhaps early cases of ILVEN.
  - **Therapy:** No good therapy; if pruritic, try topical corticosteroids or calcineurin inhibitors.

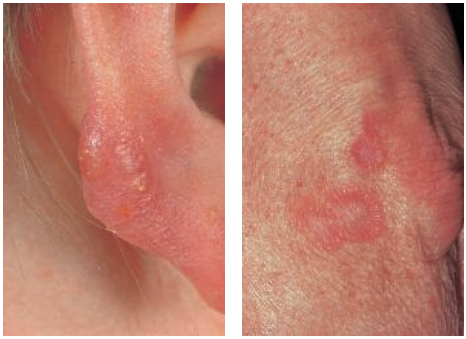
17 Granulomatous and Necrobiotic Disorders

17.1 Granulomatous Disorders

A granuloma is a small nodular aggregate of macrophages, often admixed with inflammatory cells and giant cells. This chronic inflammatory response in the skin is most often elicited by infections and foreign bodies. In this section, we consider two idiopathic granulomatous disorders.

Sarcoidosis

- **Synonym:** Boeck disease.
- **Definition:** Multisystem granulomatous disease that favors the lungs, lymph nodes, and skin.
- **Epidemiology:** Prevalence in Western Europe 20–30/100000, but tremendous regional and racial variation. For example, in southeastern USA more common among blacks. Male:female ratio 1:1; onset typically < 40 years of age.
- **Pathogenesis:**
  - Etiology unclear. An infectious cause has long been suspected, but no agent has been unequivocally identified.
  - The T-cell response is diminished while at the same time B-cell and antibody response is stimulated. Such a constellation is common in infections.
- **Clinical features:**
  - *Systemic findings:* Any organ can be involved, but most commonly affected are the hilar lymph nodes, lungs, joints, and skin. Refer to internal medicine textbook for details.
  - *Cutaneous findings*:
    - *Erythema nodosum:* Usually associated with fever, arthralgias; appears in 10% of patients and is good prognostic sign (p. 540). *Löfgren syndrome:* erythema nodosum, hilar lymphadenopathy, arthritis.
    - *Lupus pernio*: Red-violet chronic infiltrate on tip of nose; looks as if it should be cold-related (true pernio) but is not; often associated with chronic pulmonary involvement and digital bone cysts (*Jüngling syndrome*).
    - *Nodular sarcoidosis:* Red-brown plaques and nodules, often symmetrical, favor the thighs; associated with hilar lymphadenopathy and splenomegaly (Fig. 17.**1a**).
    - *Maculopapular sarcoidosis:* Transient red-brown papules, appear early in disease and may reappear, heralding disease flares. Favor trunk, but may appear on face and extremities. Can be annular (Fig. 17.**1b**), especially in blacks.
    - *Scar sarcoidosis:* Nodular changes in scars may be early sign of sarcoidosis. Sometimes subtle trauma, such as venipunctures is sufficient trigger.
- **Histology:** Small well-circumscribed dermal granulomas with few accompanying lymphocytes (naked granulomas) and variety of giant cells.
  Caution: The presence of a foreign body in a cutaneous granuloma does not exclude sarcoidosis, as patients with sarcoidosis are more likely to react to such materials.
- **Diagnostic approach:**
  - Clinical examination, biopsy; skin is often easiest place to document sarcoidal granuloma histologically.



a b

Fig. 17.1 · **Sarcoidosis.**
a Nodular infiltrate.
b Annular lesion.

- Chest and hand radiographs.
- Serum calcium level (granulomas produce 1,25-dihydroxycholecalciferol) and serum angiotensin-converting enzyme (ACE) level may both be elevated, as are urine hydroxyproline and calcium levels.
- Document increased antibodies and reduced cellular immune response.
- Ophthalmologic consultation.

► **Differential diagnosis:**
- *Lupous pernio:* Pernio, granulomatous rosacea, lupus vulgaris.
- *Nodular sarcoidosis:* Lymphoma, leukemic infiltrates, lupus tumidus, lymphadenosis cutis benigna.
- *Maculopapular sarcoidosis:* Disseminated granuloma annulare, lichen planus, lichen nitidus, secondary syphilis.

► **Therapy:**
- Treatment based on general condition of patient.
- Topical corticosteroids usually helpful for cutaneous lesions; if not, consider PUVA for maculopapular disease.
- Allopurinol has been successful in some cases of skin involvement; can also be combined with pentoxifylline.
- Both systemic corticosteroids and methotrexate may be employed, but usually for systemic problems, not skin changes alone.

Melkersson–Rosenthal Syndrome

► **Definition:** Rare combination of granulomatous cheilitis, facial nerve paralysis (*Bell palsy*), and fissured tongue.

► **Pathogenesis:** Unknown.

► **Clinical features:**
- *Granulomatous cheilitis:* Initially spontaneous swelling of lips (usually upper) with resolution but frequent recurrences; over time, permanent swelling and distortion (*tapir lip*). Other sites rarely involved.

  ► ***Note:*** Granulomatous cheilitis may also appear as isolated disease, or in association with sarcoidosis or Crohn disease.
- *Facial nerve paralysis:* Either isolated attack or persistent disease.
- *Fissured tongue:* Present long before other findings, but connection totally mysterious.

- *Other findings:* Patients may have lymphadenopathy (mistaken for sarcoidosis), migraine headaches, visual disturbances, hearing problems.

► **Histology:** Initially edema and perivascular infiltrate, later small granulomas; often difficult to find.
► **Diagnostic approach:** Clinical examination, biopsy.
► **Differential diagnosis:** Angioedema, recurrent herpes simplex, recurrent erysipelas, *Ascher syndrome* (double lip, blepharochalasis, and thyroid problems), hemangioma, lymphedema, amyloidosis.
► **Therapy:**
- Intralesional corticosteroids (triamcinolone 10 mg/mL dilated 1:3 with lidocaine) are best approach; painful but effective.
- Excision and plastic repair, if disease is stable.
- Clofazimine 100 mg daily or q.o.d. for 6–12 months or dapsone 50–100 mg daily for same time period.

17.2 Necrobiotic Disorders

Necrobiosis is a very bad term—poorly defined and linguistically impossible. It literally means "condition of living and dying," but describes a peculiar histological change in the dermis with basophilia, mucin deposition, swelling, and distortion of collagen fibers.

Granuloma Annulare

► **Definition:** Dermatosis usually with small grouped papules or subcutaneous nodules that show necrobiosis on biopsy.
► **Epidemiology:** Typically affects children and young adults; more common in those with atopy.
► **Pathogenesis:** Unknown.
► **Clinical features:**
- Classic lesion is ring on dorsum of hand or foot consisting of many small papules 1–3 mm in diameter (Fig. 17.**2**). Often with a distinction pale blue-red color. Entire lesion up to 5 cm. Also appear on distal extremities. Asymptomatic and usually resolves spontaneously without scarring (75% disappear over 2 years).
- *Variants:*
  – *Giant granuloma annulare:* Lesions up to 20 cm.

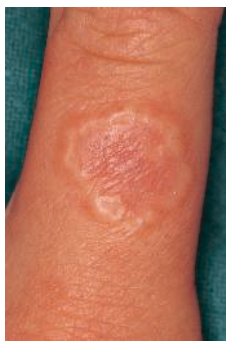
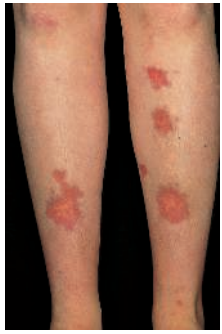


Fig. 17.**2** · Granuloma annulare.

  - *Disseminated granuloma annulare:* Young adults, favors wrists and ankles, but also trunk; many tiny papules without annular pattern, often hyperpigmented and generally persistent. In older adults, associated with diabetes mellitus.
  - *Subcutaneous granuloma annulare:* Deep nodules, usually on palms and soles, or near joints; *pseudo-rheumatoid nodules*.
  - *Light-induced granuloma annulare*.
  - *Perforating granuloma annulare:* Discharge of damaged collagen through epidermis with crust and scars.
- **Histology:** Foci of basophilic collagen surrounding by macrophages (*palisading macrophages*); sometimes with mucin.
- **Diagnostic approach:** Clinical examination usually suffices; biopsy if questions exist. Rule out diabetes mellitus in older patients.
- **Differential diagnosis:**
  - Abundant opportunities for mistakes:
    - The classic lesions in small children usually misdiagnosed as tinea corporis because they are annular, even though no scale or inflammation is seen.
    - The subcutaneous nodules are designated rheumatoid nodules and the patient worked up for rheumatoid arthritis; if no other signs and symptoms, subcutaneous granuloma annulare is the answer.
  - *Disseminated disease:* Planar warts, eruptive xanthomas, steatocystoma multiplex, eruptive vellus hair cysts, sarcoidosis, lichen planus (should itch), drug reactions.
- **Therapy:**
  - Since spontaneous resolution is the rule, usually no therapy is required.
  - Lesions often disappear following biopsy or other minor trauma.
  - Topical corticosteroids under occlusion or intralesional.
  - For disseminated disease, bath PUVA or short burst of systemic corticosteroids. Isolated reports of good responses to fumaric acid for 6 weeks.

Necrobiosis Lipoidica

- **Definition:** Chronic atrophic dermatosis usually on shins with distinctive yellow telangiectatic appearance, often associated with diabetes mellitus.
- **Epidemiology:** Female:male ratio 2:1; usually middle-aged women. 60–70% of patients have diabetes mellitus but only 0.3% of patients with diabetes mellitus have necrobiosis lipoidica.
- **Pathogenesis:** Primary event appears to be vasculopathy, followed by damage to collagen and granulomatous response.
- **Clinical features:**
  - Asymptomatic oval dark red patches and plaques, almost always on shins. Slowly spread, coalesce, and develop diagnostic yellow color with numerous telangiectases (Fig. 17.3). Borders remain irregular, sharply defined, and dark red.
  - Biggest problem is ulceration, which develops in 25% and is very difficult to heal.
  - Other sites of involvement include thigh, distal extremities, trunk, and even scalp (with scarring alopecia).
  - Disseminated necrobiosis lipoidica, also known as granulomatosis disciformis chronica and progressiva may rarely occur.
- **Diagnostic approach:** Clinical examination; biopsy sites often heal poorly. Exclude diabetes mellitus.
- **Differential diagnosis:** Typical lesion on shins unique and diagnostic; perhaps confused with statis dermatitis and dermatosclerosis, but latter is far more diffuse. Disseminated disease overlaps with granuloma annulare and actinic granuloma.



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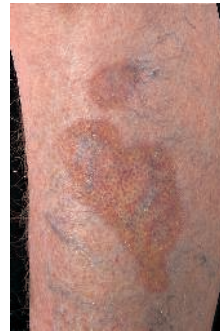


b

Fig. 17.**3** · **Necrobiosis lipoidica. a** General appearance. **b** A close-up view shows the distinctive yellow color.

► **Therapy:**

- Despite atrophy, best approach is topical corticosteroids under occlusion or intralesional corticosteroids.
- If lesions are identified early, anti-inflammatory therapy with dapsone or colchicine may help.
- Cream PUVA also effective in early phase.
- Compression stockings and pentoxifylline may be useful.
- If ulcerated, consider excision and coverage with mesh graft.

► ***Note:*** Control of diabetes mellitus is essential, but does not influence necrobiosis lipoidica.

Other Conditions with Necrobiosis

- Rheumatoid nodules (p. 224), usually in patients with obvious rheumatoid arthritis; thus not a diagnostic clue.
- *Actinic granuloma:* Also known as elastolytic granuloma or O'Brien granuloma. May be granuloma annulare in sun-damaged skin. Large bizarre atrophic patches with prominent red-brown border. Typically sites include arms, face, and nape. Biopsy shows necrobiosis, solar elastosis, and ingestion of elastin by giant cells. Treatment same as granuloma annulare.
- *Necrobiotic xanthogranuloma:* Rare condition with yellow patches and plaques; almost always periorbital findings (initially mistaken for xanthelasma) but also involves face or trunk (Fig. 17.**4**). Biopsy shows necrobiosis, foam-laden macrophages, and lymphoid clusters. Associated with monoclonal gammopathy. No effective treatment.

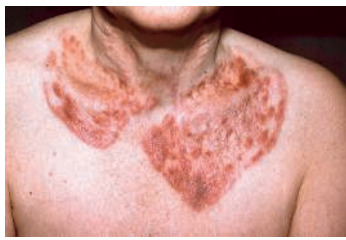


Fig. 17.**4** · Necrobiotic xanthogranuloma (Image courtesy of Prof. N. Hass MD, Berlin, Germany)

18 Dermatoses Caused by Physical and Chemical Agents

18.1 Photodermatoses

Overview

- **Definition:** Skin diseases caused or exacerbated by exposure to light.
- Almost all cutaneous light reactions are caused by UV radiation of wavelength 280–400 nm. Shorter wavelengths are filtered out by the atmosphere; longer wavelengths only rarely play a role. The electromagnetic spectrum is shown in Table 18.**1**.

Table 18.1 · **Electromagnetic spectrum**

Region	Wave length (nm)
Gamma	0.0001–0.14
X-ray	0.0005–20
Ultraviolet	
	UVC
40–280	
	UVB
280–320	
	UVA
320–400	
	UVA2
320–340	
	UVA1
340–400	
Visible light	400–800
Infrared	800–10^5
Radio waves	10^5 – 10^{15}

- **Minimal erythema dose**: The amount of light required to produce a barely visible erythema (p. 49); it depends on the wavelength, skin type, and amount of previous light exposure. UVB is about 1000× as rich in energy as UVA; in other words, about 1000× as much UVA exposure is required to produce the same erythema.
- **Depth of penetration:** Depends on wavelength; the longer wavelengths penetrate deeper. Thus UVA reaches deeper into the dermis than UVB, while lasers designed to selectively reach and interact with dermal vessels or pigment are all in the visible light spectrum or longer.
- **Physiological light protection:** The skin has many intrinsic mechanisms to protect against light damage:
  - Epidermal acanthosis and hyperkeratosis. Reaches maximum after 2–3 weeks.

  Note: For a long time the major role of the stratum corneum in light protection was overlooked or underestimated.

- Increased melanin synthesis and transfer of melanosomes to keratinocytes.
- Natural free radical or activated oxygen scavengers (glutathione, catalase, vitamin C, vitamin E, melatonin, others).
- DNA repair mechanisms, most important is nucleoside excision repair to remove thymine dimers and photo adducts.

► **Other important physiologic processes** in the skin include:

- Synthesis of vitamin D and *cis–trans* isomerization of urocanic acid.
- *Immunosuppressive effects:* Inhibition of Langerhans cells and release of suppressive cytokines that can have systemic effects.

Sunburn

► **Definition:** Acute sun damage to skin, caused primarily by UVB.

► **Clinical features:** Known to everyone; painful, sharply demarcated erythema limited to areas of sun exposure (Fig. 18.**1**); if severe, blister formation; later, peeling.

! ***Caution:*** A widespread blistering sunburn is comparable to a second-degree burn and requires similar treatment.

► **Histology:** Apoptotic keratinocytes (sunburn cells), widened vessels, marked edema, lymphocytic infiltrate.

► **Differential diagnosis:** Always consider a phototoxic drug reaction as a possible contributing factor to bad sunburn.

► **Therapy:**

- Immediate use of NSAIDs may help.

  ! ***Caution:*** Paradoxically, NSAIDs can also cause phototoxic reactions.
- If sunburn is severe, then fluid replacement may become important. Otherwise, simply lubricate the skin and await natural healing.

  ▶ ***Note:*** Both topical and systemic corticosteroids are overrated in sunburn. The popular topical anesthetics and antihistamines sold over the counter in the USA and Europe are likely causes of allergic contact dermatitis.

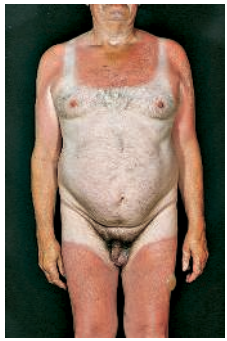


Fig. 18.**1** · Sunburn.

Phototoxic and Photoallergic Reactions

- **Definition:** The combination of light and certain topical or systemic agents can lead to an enhanced reaction.
- **Epidemiology:** Phototoxic reactions are far more common than photoallergic reactions. Some substances, such as psoralens, cause a phototoxic reaction in almost everyone exposed to them and the appropriate wavelength of light.
- **Pathogenesis:** In contrast to the discussion of allergic versus toxic contact dermatitis, the situation with photodermatoses is less clear. It can be difficult to decide if a reaction is toxic or allergic, and some medications cause both.
  - A *phototoxic reaction* is an exaggerated sunburn; the photosensitizers make the skin make sensitive to light, often by causing the production of free oxygen radicals. A phototoxic reaction can occur the first time the patient uses the medication or product. The likelihood of reaction is dose-related (Figs. 18.**2**, 18.**3**).
  - Causes of phototoxic reactions include:
    - *Tars* and their derivatives such as acridine or anthracene.
    - *Dyes:* Bengal red, eosin, fluorescin, methylene blue, riboflavin, acridine, thiopyronine.
    - *Medications:* Amiodarone, furosemide, NSAIDs (especially piroxicam, carprofen, diclofenac), psoralens, phenothiazines, tetracyclines (especially doxycycline).
    - *Furocoumarins* in a wide variety of plants and grasses; also source of psoralens; plants include giant hogweed (most notorious in Europe), celery, parsley, turnip, citrus fruits (including bergamot), St. John's wort.
    - Exposure to plant sap or juice plus sun exposure leads to streaking bullous dermatosis, known as *phytophotodermatitis* (*dermatitis pratensis* or meadow grass dermatitis). Individuals exposed to giant hogweed may have large blisters mistaken for burns.
    - *Berloque dermatitis* is caused by using perfumes or after shave lotions containing bergamot oil; typical picture is streaked hyperpigmented rash on side of neck where perfume is often applied. Acute reaction often overlooked; only pigmentary changes noted.
  - In contrast, a *photoallergic reaction* requires previous exposure, the development of sensitization and then a repeated exposure with the right combination of sensitizer and light exposure. Sometimes a different wavelength of light is required for the sensitization and then the re-elicitation of the dermatitis, which can have a variable morphology ranging from exanthem to urticaria.
  - Typical causes of photoallergic reactions include:
    - *Medications:* Benzodiazepines, nalidixic acid, NSAIDs, phenothiazines, sulfonamides, sulfonylureas, thiazides, triacetyldiphenylisatin (laxative).
    - *Antimicrobial agents*, such as halogenated salicylanilides formerly added to deodorant soaps.
    - *Bleaches and blankophores* in laundry soaps.
    - *Sunscreens* (*para*-amino benzoic acid, benzophenone).
    - *Cyclamates* (artifical sweeteners).
- **Clinical features:** Clinical features and localization are distinctive.
- **Diagnostic approach:** Clinical examination and history usually suffices for phototoxic dermatitis. For photoallergic dermatitis, photopatch testing useful (p. 45).
- **Differential diagnosis:**
  - *Phototoxic dermatitis:* Sunburn, other toxic (non-photo) reactions.
  - *Photoallergic dermatitis:* Allergic contact dermatitis via aeroallergens.
- **Therapy:** Same as for allergic and toxic contact dermatitis (p. 199).

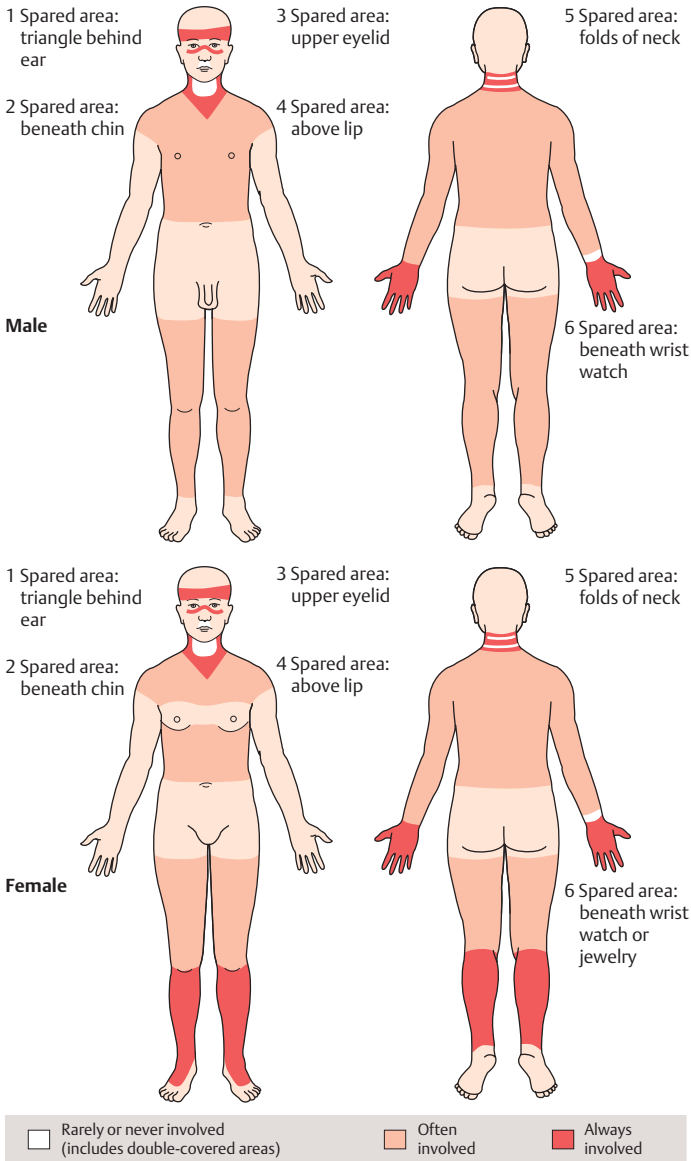
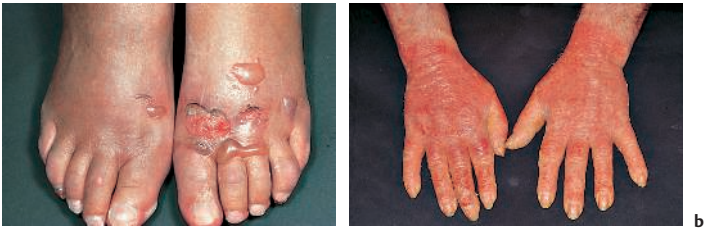


Fig. 18.2 · Typical localization of photoallergic and phototoxic reactions.



a b

Fig. 18.3 · **a** Phototoxic dermatitis. **b** Photoallergic dermatitis.

Chronic Actinic Dermatitis

- **Synonyms:** Persistent light reaction, actinic reticuloid (when histology shows atypical lymphocytes).
- **Definition:** Persistent photoallergic dermatitis following sensitization but without further antigen exposure.
- **Pathogenesis:** Poorly understood; presumably photohaptens induce autoimmune response including persistent lymphocytic infiltrates.
- **Clinical features:** Pruritic chronic dermatitis in light-exposed areas, most common on nape. Lichenified skin with multiple excoriations and erosions.
- **Histology:** Acanthosis, dermal fibrosis, lymphocytic infiltrates which in some instances may show marked atypia (actinic reticuloid). Progression to lymphoma most uncommon.
- **Diagnostic approach:** Clinical examination, biopsy. Photo provocation (UVA, UVB, and visible light) as well as photopatch testing.
- **Differential diagnosis:** Atopic dermatitis, mycosis fungoides, Sézary syndrome.
- **Therapy:** Azathioprine 50 mg daily or 3× weekly can be almost miraculous; PUVA hardening also helpful. In severe cases, cyclosporine.

Polymorphous Light Eruption

- **Definition:** Idiopathic eruption caused by UV exposure; appears in hours to days with morphology varying considerably between patients.
- **Epidemiology:** Far and away the most common photodermatosis, with an estimated prevalence of 10–20%. Usually starts in adolescents or young adults.
- **Pathogenesis:** Unknown; perhaps autoimmune response to damaged keratinocytes.
- **Clinical features:** Wide spectrum of clinical patterns ranging from papulovesicular exanthem (most common) to plaques, erythema multiforme–like lesions, hemorrhagic or purpuric changes (Fig. 18.4). The eruption is usually most prominent following the first UVA exposure in the spring—thus often a feature of a winter trip to sunny climes. Appears hours to days after exposure, lasts for several days and resolves spontaneously without scarring. Some degree of hardening over the summer and recurrences each year are to be expected.
- ***Note:*** The lesions in any one patient are relatively uniform and remain so over the life of the disease. The term polymorphous refers to the *different patterns in different patients*.
- **Histology:** Dermal edema, lymphocytic perivascular infiltrates and minimal epidermal damage; no mucin (in contrast to lupus erythematosus).

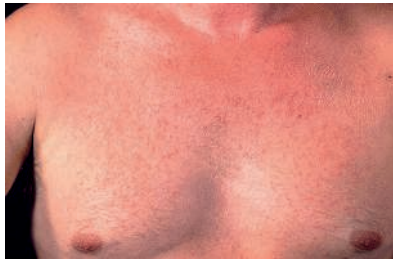


Fig. 18.**4** · Polymorphous light eruption.

- **Diagnostic approach:** Clinical examination; provocation testing is useful; 60–100 J/cm^2 UVA to individual site of predilection can reproduce lesions.
- **Therapy:**
  - Avoidance of sunlight via sunscreens and protective clothing; gradual increases in light exposure rather than intensive exposure on first day.
  - Use of antioxidant for 1 week before exposure; then on vacation combination of antioxidant and sunscreen (for example Eucerin Phase 1 and Phase 2 gel-cream containing α-glucosyl rutin as antioxidant).
  - Hardening with UVB or PUVA before exposure.
  - If lesions develop, topical corticosteroids and oral antihistamines.
  - Severe, persistent disease: consider azathioprine 50–100 mg daily to 3× weekly for 3 months.

Mallorca Acne

- **Synonym:** Acne aestivalis.
- **Definition:** Acneiform eruption developing following excessive sun exposure.
- **Epidemiology:** First described in European tourists going to Mallorca in mid-winter; more common in women 20–40 years of age.
- **Pathogenesis:** Unclear, but likely variant of polymorphous light eruption. Most patients without history of acne vulgaris, but develop follicular lesions with sun exposure. Roles of sweating and topical agents such as emollients or sunscreens long disputed.
- **Clinical features:** Monomorphic small skin-colored follicular papules with tiny red rim; usually on shoulders, mid–upper back, or upper arms. Generally pruritic. Face spared; no comedones or pustules. Changes persist for days to weeks; little hardening, so unlucky patients are affected from spring to fall.
- **Histology:** Follicular plugging with inflammatory reaction.
- **Diagnostic approach:** Clinical examination; search for acne elsewhere; exclude photoallergic reaction; later try to reproduce lesions with photo provocation.
- **Differential diagnosis:** Acne vulgaris is common and Mallorca acne uncommon. Sun-aggravated acne vulgaris with comedones and pustules is not Mallorca acne.
- **Therapy:** Sun avoidance; clothing better than sunscreens; gels preferred over creams because of confusion over role of topical occlusion. Topical corticosteroids for pruritus. Same hardening approaches as tried for polymorphous light eruption may help here.

Actinic Prurigo

- **Definition:** Common form of photosensitivity among natives of North and South America, with distinctive clinical pattern.
- **Epidemiology:** Rare and sporadic in Europe; usually associated with atopic dermatitis. Among Native Americans, prevalence rates can be as high as 20–30%, varying with tribe.
- **Pathogenesis:** Unknown, but distinct HLA-DR4 associations.
- **Clinical features:** Starts in childhood or adolescence as overlap between atopic dermatitis and photosensitivity. More common in women. Pruritic dermatitic lesions that evolve into prurigo papules and lichenified plaques. Some patients have vesicular hydroa vacciniforme–like lesions on nose and ears. Lesions begin in spring or summer months and recurrences are the rule. Among Native Americans, associated with cheilitis and conjunctivitis with pterygium formation.
- **Histology:** Varies with stage of lesion and is not diagnostic: lymphocytic infiltrates and spongiosis dominate.
- **Diagnostic approach:** Clinical examination, detailed history; look for associated atopy; perhaps photo provocation.
- **Differential diagnosis:** Polymorphous light eruption, light-sensitive atopic dermatitis, and in adults chronic actinic dermatitis.
- **Therapy:** Avoidance and sun protection; easier to achieve among European patients than Native Americans. Topical corticosteroids; pulses of systemic corticosteroids for severe flares.

Hydroa Vacciniforme

- **Definition:** Rare photodermatosis in children with blisters and scars formerly felt to resemble the morphology of smallpox.
- **Pathogenesis:** Unknown, but Epstein–Barr virus (EBV) may play a role.
- **Clinical features:** Blue-red erythema that develops into blisters with serous or hemorrhagic contents (Fig. 18.**5**). Almost always involves face, occasionally hands. Heals with hypopigmented scars.
- **Histology:** Similar to polymorphous light eruption.
- **Diagnostic approach:** Clinical examination, biopsy. exclude porphyrias via blood, urine and stool examinations; search for herpes simplex virus and EBV.
- **Differential diagnosis:** Erythropoietic porphyria and erythropoietic protoporphyria can be similar; initially severe herpes simplex virus infection often sus-

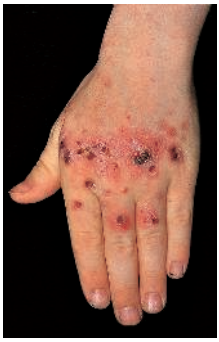


Fig. 18.**5** · Hydroa vacciniforme.

pected. A form of panniculitic T-cell lymphoma has been described in Japan and Mexico that clinically resembles hydroa vacciniforme.

- **Therapy:** Mainstay is light avoidance and maximum sunscreen protection. UVB or PUVA hardening is difficult but worth trying. Neither β-carotene nor antimalarials proven effective. For flares, zinc oxide shake lotions or topical corticosteroids.

Pellagra

- **Definition:** Deficiency in nicotinic acid, part of the vitamin B complex.
- **Epidemiology:** Common worldwide dietary defect, often association with other deficiencies such as kwashiorkor. In the early 1900s, very common in rural southeastern USA; Goldberger won Nobel Prize for identifying vitamin deficiency.
- **Pathogenesis:** In addition to inadequate dietary vitamins and malabsorption, nicotinic acid deficiency can result from interference by various medications such as isoniazid and phenytoin.
- **Clinical features:** The classic features are the 4 Ds: diarrhea, dementia, dermatitis, and death. Patients have photosensitivity and develop hyperpigmented scaly patches; the lesions on the V of the neck as known as *Casal necklace*; other typical sites include cheeks, backs of hands and backs of feet in those working outdoors barefoot.
- **Therapy:** Adequate diet and nicotinic acid replacement.

Light-sensitive Dermatoses

There are many dermatoses that can worsen with light exposure, including the following:

- Lupus erythematosus.
- Dermatomyositis.
- Rosacea.
- Recurrent herpes simplex virus infections.
- Erythema multiforme (via connection with herpes simplex).
- Lichen planus.
- Darier disease.
- Disseminated superficial actinic porokeratosis.
- Pityriasis rubra pilaris.
- Allergic contact dermatitis; for example, allergy to chromium salts in cement workers.
- Atopic dermatitis.

Note: Some of these diseases are routinely treated with light, such as atopic dermatitis. Most patients will improve with UVA1 or selective UVB phototherapy (SUP), but some will worsen. Therefore, always ask about previous improvement or worsening with sunlight exposure before starting phototherapy.

18.2 Light-induced Aging and Photocarcinogenesis

Skin and Light

Modest sun exposure has healthy effects, including stimulation of vitamin D synthesis and a positive influence on the psyche. All that is needed for healthy living is 10–15 minutes a day. In the past 50 years there have been dramatic changes in lifestyle, such as vacations in sunny climates in the winter, population shifts toward sunnier climates (in the USA), more outdoor living, and greater emphasis on tanning especially with artifical light sources (tanning studios). All these factors have contributed to overwhelm the skin's intrinsic defense and regeneration mechanisms, leading to an increase in photoaging and carcinogenesis. The loss of atmospheric ozone has also contributed by allowing more UVB light to reach the Earth's surface, but this contribution is far less than that of lifestyle changes.

Molecular Biology

UV irradiation is a potent and complete carcinogen. Absorption of UVB by DNA leads to formation of thymine dimers. Incorrect or inadequate repair leads to carcinogenesis by producing stable mutations in critical growth control genes. UVA leads more to breaks in DNA and DNA–protein complexes. In addition, the irradiation reduces Langerhans cells and causes cutaneous immunosuppression.

Chronic Effects of Light on the Skin

- **Aging:** One must distinguish between intrinsic aging and extrinsic or photoaging. Intrinsic aging is best seen on the buttocks; there is epidermal atrophy, a loss in dermal connective tissue, and other relatively minor changes. A dramatic comparison is that the buttock skin of a 60-year-old is about as "aged" as the facial skin of a 20-year-old.
- **Photoaging:** There are many stigmata of chronic light exposure. The degree of photoaging is proportional to the total UV exposure; the skin never forgets a ray of sunlight. Many different names have been applied to photoaged skin:
  - *Sailor's skin* or *farmer's skin:* Two names applied to the overall appearance.
  - *Solar elastosis:* The most common change skin microscopically is basophilic staining of the dermis, reflecting an increase in abnormal elastic fibers. Occasionally focal intense elastosis presents as a yellow nodule or plaque. The following terms all refer to various manifestations of elastosis:
    - *Cutis rhomboidalis nuchae*: Multiple deep furrows as seen on the nape.
    - *Favre–Racouchot disease*: Cysts and comedones especially in periorbital location.
    - *Lemon skin*: Pale yellow color and thickened skin.
  - Focal areas of hypopigmentation: *idiopathic guttate hypomelanosis*, most common on arms and less often legs.
  - *Solar lentigines (actinic lentigenes)*: Irregular hyperpigmented macules with increased basal layer melanin; most common on face and backs of hands. Flat seborrheic keratoses. Unlike freckles (ephilides), not reversible as exposure is decreased.
  - *Poikiloderma:* Combination of hyper- and hypopigmentation, telangiectases, and atrophy.
- **Carcinogenesis:** Skin cancers are the most common human malignancies. For the three main types, there are varying degrees of evidence for solar carcinogenesis.

Many other co-factors are involved, such as exposure to other forms of ionizing radiation, heat, trauma and chemical carcinogens, certain scars (such as those associated with tuberculosis and osteomyelitis), immunosuppression, and selected pre-existing dermatoses such as mucosal lichen planus or lichen sclerosus. The main tumor types are all covered later in more detail.

- **Squamous cell carcinoma (p. 417):** The most common cutaneous tumor is actinic keratosis, which is microscopically a squamous cell carcinoma in situ. There are atypical keratinocytes with individual cell keratinization and mitoses. Almost every white individual with even modest sun exposure develops some actinic keratoses. Long-term regular exposure seems to be the risky behavior. The rate of conversion to squamous cell carcinoma is low and not exactly defined; one rule of thumb is that 1% convert each year, but this seems high to us.
- **Basal cell carcinoma (p. 433):** In most instances this is a malignant tumor of hair follicle origin. Most tumors occur in sun-exposed skin, but are rare on the back of the hands (high sun exposure) and also occur on nonexposed skin. Patients with nevoid basal cell carcinoma syndrome have a mutation in the *PTCH* gene and numerous basal cell carcinomas; the same mutation is seen in sporadic basal cell carcinoma.
- **Malignant melanoma (p. 396):** Has been increasing dramatically in incidence; the rate in Australia is now 40–50/100 000 year and in Western Europe 10–15/100 000. Sun exposure appears to be a major factor; studies in the USA have shown that incidence increases with decreasing latitude (living further south) and, for the same latitude, increases with increasing altitude. Exposure during childhood, and occasional excessive exposure (weekends or vacations), appears more dangerous than long-term chronic exposure; the latest studies in Western Europe and USA show that the most excessive overexposure occurs in teenage and young adult life.

18.3 Photosensitive Genodermatoses

All these disorders present with varying degrees of photosensitivity in infancy or childhood. In each instance the differential diagnostic considerations include most of the other disorders, depending on the associated findings such as premature aging or mental retardation. In photosensitivity in infants, erythropoietic porphyria and other forms should be excluded; at birth, neonatal lupus erythematosus must also be considered.

Xeroderma Pigmentosum

- **MIM code:** 278700; gene locus 9q22.3–31 and at least three other loci.
- **Definition:** Defect in DNA excision repair mechanism with autosomal recessive inheritance, leading to marked photosensitivity and multiple cutaneous malignancies.
- **Epidemiology:** Prevalence of 1–3/million.
- **Pathogenesis:** Divided into 10 different complementation groups, each representing a different defect in part of the complex DNA excision repair mechanism. When fibroblasts from patients in two different complementation groups are fused, they have normal repair capabilities.
- **Clinical features:**
  - Clinical variations depending on the complementation group.
  - Predominant feature is extreme photosensitivity with sunburn as infant with minimal exposure.

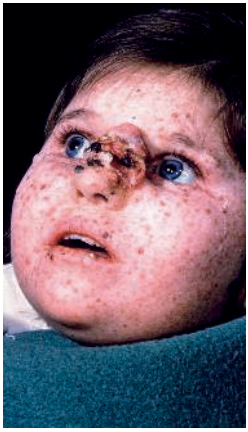


Fig. 18.**6** · Xeroderma pigmentosum: child with destructive basal cell carcinoma and marked actinic damage.

- Soon multiple actinic lentigines of varying size and color develop, along with areas of hypopigmentation, telangiectases, and atrophy, leading to poikiloderma at an early age (Fig. 18.**6**).
- *Multiple skin tumors:* Most common are basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Incidence of basal cell carcinoma estimated at 1000× normal. Almost every patient has a malignant melanoma by 20 years of age.
- Internal malignancies are also increased by 10–20-fold, including oral squamous cell carcinomas, CNS tumors, and almost every other organ.
- *Associated disorders:*
  - *DeSanctis–Cacchione syndrome:* Several complementation groups have associated neurological disorders including mental retardation and motor defects.
  - Overlaps with Cockayne syndrome (see below) and trichothiodystrophy (p. 512).
  - *Pigmented xerodermoid:* Also known as xeroderma pigmentosum variant, adults with later onset of photosensitivity, similar clinical picture, but no established repair defect.

► **Histology:** Nothing in tumors offers clue to xeroderma pigmentosum except early age of patients.

► **Diagnostic approach:** Clinical examination; repair defect can be identified in fibroblasts and complementation group typing performed; both highly specialized.

► **Therapy:**

- Absolute light avoidance; development of nocturnal habits; careful use of sunscreens is not enough.
- High-dose retinoids reduce incidence of tumors but have considerable side effects.
- Topical bacterial endonuclease (T4) shows promise to improve cutaneous repair mechanisms.
- Regular monitoring and prompt removal of tumors at less advanced stage.

Cockayne Syndrome

- **MIM code:** 216400.
- **Definition:** Rare disorder with photosensitivity and growth defects, inherited in autosomal recessive manner.
- **Pathogenesis:** Two responsible genes (*CKN1* and *CKN2*). Also overlaps with several xeroderma pigmentosum groups (B, D, G).
- **Clinical features:** Patients present with photosensitivity, growth retardation, premature aging, optic atrophy, and deafness. Profound retardation. Develop characteristic bird-like facies. Those with xeroderma pigmentosum–Cockayne syndrome overlap have more photosensitivity and freckling but do not develop tumors as do ordinary xeroderma pigmentosum patients.
- **Diagnostic approach:** Genetic diagnostic methods are only way to sort out complex picture.
- **Therapy:** Nothing effective; death at early age.

Trichothiodystrophy

Some patients with trichothiodystrophy (p. 512) have photosensitivity. In one form the genetic defect is linked with xeroderma pigmentosum complementation groups B and D and the patients are photosensitive, but do not develop cutaneous malignancies at an early age.

Bloom Syndrome

- **MIM code:** 210900: gene locus 15q26.1.
- **Definition:** Rare genodermatosis with triad of photosensitivity, facial telangiectases, and dwarfism.
- **Pathogenesis:** Defect in *BLM* gene, encoding a DNA helicase known as RecQL3 3.
- **Clinical features:** Patients present with low birth weight as well as both telangiectases and photosensitivity in infancy. Also have café-au-lait macules. No increase in cutaneous malignancies, but high lifetime risk of systemic malignancies, especially leukemias and lymphomas.
- **Diagnostic approach:** Clinical suspicion, genetic studies; exclude porphyria.
- **Therapy:** Sun protection; monitoring for internal malignancies.

Rothmund–Thomsen Syndrome

- **MIM code:** 268400; gene locus 8q24.3.
- **Definition:** Combination of early onset of poikiloderma associated with cataracts, photosensitivity, dwarfism, and hypogonadism.
- **Pathogenesis:** Most patients have defect in DNA helicase RecQL4. Unclear if different genetic defects lead to different clinical patterns.
- **Clinical features:** Rothmund first described patients with poikiloderma and cataracts, while Thomsen's patients had no cataracts. This controversy still continues. Patients present with photosensitivity and poikiloderma; about half have juvenile cataracts. Later develop hyperkeratotic lesions over flexors. Adults have increased risk of squamous cell carcinoma. Facies features a saddle nose with prominent forehead and chin. Growth retardation, hypogonadism, and multiple epithelial defects (hair, nails, teeth). High risk of osteosarcoma.
- **Diagnostic approach:** Clinical suspicion, genetic studies.
- **Therapy:** Sunscreens, cataract surgery, baseline bone surveys and then monitoring for osteosarcoma.

Hartnup Syndrome

- **MIM code:** 234500; gene locus 11q13.
- **Definition:** Disturbance in intestinal absorption and renal reabsorption of neutral amino acids; autosomal recessive inheritance.
- **Pathogenesis:** The most striking problem is low levels of tryptophan, leading to reduced levels of nicotinic acid.
- **Clinical features:**
  - Photosensitivity, usually appearing in childhood. May sometimes mimic hydroa vacciniforme. Red-brown hyperpigmentation with scaling develops.
  - Neurological findings include ataxia and other cerebellar problems.
- **Diagnostic approach:** Prenatal screening performed in some countries; for example Massachusetts where incidence is 1/15000 births (the Hartnups were a Massachusetts family). Otherwise, measure urine amino acid levels or indol bodies.
- **Therapy:** Nicotinic acid replacement dramatically improves the skin and usually helps the neurological signs and symptoms. Usual dose 50–100 mg daily. Sunscreens.

18.4 Diseases Caused by Cryoproteins

Cryoproteins are proteins with special physicochemical properties, whose structures or binding capacities change with temperature. In the human system, the relevant cryoproteins are those that are not aggregated at body temperature but aggregate when modest degrees of cooling take place, usually in acral sites. They can be found in a variety of disorders and lead to a number of dermatologic signs and symptoms.

Cryoglobulinemia

- **Definition:** Presence of circulating immunoglobulin complexes that precipitate when incubated at $< 4\,^{\circ}C$.
- **Pathogenesis:**
  - There are three types of cryoglobulins, as shown in Table 18.**2**.
  - Types II and III are known as mixed cryoglobulinemias; when no underlying disease is present, the term essential mixed cryoglobulinemia may be employed. Over 80% are associated with hepatitis C infection; the main difference between types II and III is a higher incidence of renal disease in the former.

Table 18.2 · **Cryoglobulins**

Type	Composition	Associated disease	Clinical features
I	Monoclonal IgG or IgM	Myeloma, Waldenström macroglobulinemia, lymphoma	Thrombosis, livedo, Raynaud syndrome, ulcers
II	Monoclonal IgM (rheumatid factor) plus polyclonal IgG	Same B-cell disorders as for type I, Sjögren syndrome, rheumatoid arthritis, hepatitis C	Chronic immune complex vasculitis, skin and kidneys
III	Polyclonal Ig	Connective tissue disease, primary biliary cirrhosis, hepatitis C	Chronic immune complex vasculitis, skin and kidneys

- **Clinical features:** The unifying clinical feature is acral skin changes in response to cold exposure, sometimes as subtle as entering an air-conditioned building.
  - In type I disease, thrombosis, hyperviscosity, Raynaud phenomenon, necrotic lesions and CNS lesions dominate.
  - In types II and III disease, the classic finding is leukocytoclastic vasculitis with superficial ulcerations, favoring the region about the ankles. Raynaud phenomenon, cold urticaria, purpura, arthralgias, polyneuritis, and glomerulonephritis (up to 50%) are seen.
- **Diagnostic approach:** The blood must be transported to the laboratory at 37°; there it is cooled to < 4°C; then cryocrit is determined and then the proteins selectively analyzed. Reactive hypocomplementemia. Other laboratory testing is designed to exclude various underlying diseases.
- **Differential diagnosis:** Other forms of vasculitis; other cryoprotein disorders.
- **Therapy:**
  - Avoid cold, especially sudden shifts in temperature.
  - When hepatitis C is involved, then treatment with interferon (pegylated IFN-α2b) and ribavirin is most important.
  - If underlying disease is indicated, then appropriate follow-up and therapy.
  - For progressive disease, methotrexate or cyclophosphamide plus systemic corticosteroids, perhaps combined with plasma exchange.

Cryofibrinogenemia

Patients have fibrinogen that aggregates at lower temperatures, creating a complex of fibrin, fibronectin and fibrinogen. They develop a combination signs and symptoms based on thrombi and coagulation defects. Skin findings include Raynaud phenomenon, acrocyanosis, urticaria, and purpura. Diagnosis is based on identifying the abnormal cryofibrinogen. Treatment includes streptokinase or urokinase for acute thrombosis, as well as plasma exchange to reduce risk.

Cold Agglutinin Disease

- **Definition:** Disease caused by erythrocyte aggregation following exposure to cold.
- **Pathogenesis:** Cold agglutinins are antibodies that agglutinate erythrocytes more efficiently at temperatures below body temperature. They are usually IgM antibodies directed against erythrocyte polysaccharides. Caused by proliferation of B cells; sometimes they appear transiently following mycoplasma, EBV, or *Treponema pallidum* infection. When chronic, often associated with low-grade B-cell lymphoma. Following cold exposure, there is intravascular coagulation (vessel occlusion) and hemolysis (hemolytic anemia). Key factor is how active antibodies are at 30°C.
- **Clinical features:** Typical cutaneous features include acrocyanosis following cold exposure, accompanied by paresthesias and rarely necrosis. May also present as cold urticaria or livedo racemosa. Also episodes of hemolytic anemia following cold exposure; if severe and persistent, hepatosplenomegaly.
- **Diagnostic approach:**
  - Blood clots at room temperature; must be kept at body temperature until serum is separated.
  - Sedimentation rate increased at room temperature, normal at body temperature.
  - Measure cold agglutinins and determine target antigen (anti-I suggests infection; anti-i suggests EBV or lymphoma).

- **Differential diagnosis:** Other cryoprotein disorders. Raynaud phenomenon has three phases; cold agglutinin response faster and much more dramatic. Also exclude anticardiolipin, lupus erythematosus, systemic sclerosis.
- **Therapy:** Nothing very good for chronic form; avoid cold. In severe chronic forms, immunosuppressive therapy with chlorambucil or cyclophosphamide, perhaps combined with plasmapheresis. Corticosteroids ineffective. Watch for hemochromatosis.

18.5 Disease Caused by Cold

Pernio

- **Synonym:** Chilblain.
- **Definition:** Localized erythema caused by exposure to damp cold.
- **Pathogenesis:** Trigger is modest cold (freezing temperatures not required) coupled with moisture; usually toes involved, but also perniones of thighs in riders.
- **Clinical features:** Blue-purple papules and nodules, slowly developing; usually on toes, can also involve shins, thighs, fingers; more common in women who are overweight and not physically active.
- **Histology:** Papillary dermal edema and lymphocytic perivascular infiltrates.
- **Diagnostic approach:** Exclude hyperviscosity syndrome, other myeloproliferative disorders.
- **Differential diagnosis:** Lupus erythematosus (chilblain lupus), sarcoidosis (lupus pernio). In both instances, permanent and not cold-related.
- **Therapy:** Protection from cold; if severe and chronic, topical calcium channel blockers (usually nifedipine) may help.

19 Metabolic Diseases

19.1 Porphyrias

- **Definition:** Porphyrias are the result of enzymatic defects in heme synthesis (heme or its ferric chelate is the active site in hemoglobin).
- **Classification** (summarized in Table 19.**1**):
  - *Based on most severely affected organ:*
    - Erythropoietic porphyrias.
    - Hepatic porphyrias.
  - *Based on clinical features:*
    - Acute porphyrias that can present with life-threatening crises and neurological signs and symptoms (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria).
    - Chronic, non-life-threatening porphyrias (all the erythropoietic porphyrias and porphyria cutanea tarda).

Table 19.1 · **Important features of the porphyrias**

Enzyme	Disease	Main site of involvement	Excess production of:	Skin findings	Inheritance
PBG deaminase	Acute intermittent porphyria	Liver	PBG, ALA	–	AD
Uroporphyrinogen-III-co-synthetase	Congenital erythropoietic porphyria	RBC	Uroporphyrin I, coproporphyrin II	+++	AR
Uroporphyrinogen decarboxylase	Acquired type I PCT	Liver	Uroporphyrin	+ →	Acquired
	Hereditary type II PCT	(also RBC)	(Protoporphyrin in RBC in hepatoerythropoietic porphyria)	+++	AD
	Hepatoerythropoietic porphyria				AR
Coproporphyrinogen oxidase	Hereditary coproporphyria	Liver	Coproporphyrin III	–	AD
	Homozygous coproporphyria		PBG, ALA	+	Homozygous AD
Protoporphyrinogen oxidase	Porphyria variegata	Liver	Protoporphyrin, coproporphyrin, PBG, ALA	+	AD
Ferrochelatase	Erythropoietic protoporphyria	RBC	Protoporphyrin	++	AD

AD = autosomal dominant; ALA = aminolevulinic acid; AR = autosomal recessive; PBG = porphobilinogen; PCT = porphyria cutanea tarda

Congenital Erythropoietic Porphyria

- **Synonyms:** Günther disease, erythropoietic uroporphyria.
- **MIM code:** 263700.
- **Definition:** Rare defect in heme synthesis caused by point mutations in uroporphyrinogen-III co-synthetase gene; autosomal recessive inheritance.
- **Clinical features:** Extreme photosensitivity; marked mutilation of sun-exposed skin; massive porphyrinuria (dark-red urine); fluorescent teeth; onset of problems in infancy.
- **Diagnostic approach:** Markedly elevated uroporphyrin I, coproporphyrin I in urine, feces, RBC, and plasma; stable fluorescence of RBC.
- **Differential diagnosis:** Other childhood photosensitivity disorders.
- **Therapy:** Light avoidance or extreme photoprotection (clothing better than sunscreens); bone marrow transplantation successful in some cases.

Erythropoietic Protoporphyria

- **MIM code:** 177000.
- **Definition:** Defect in ferrochelatase; autosomal dominant inheritance.
- **Pathogenesis:** Ferrochelatase mutation on one paternal allele (*cis*) and low expression of ferrochelatase polymorphism on the allele (*trans*).
- **Clinical features:**
  - Onset of photosensitivity in first year of life; either sunburn or urticarial lesions can appear, sometimes followed by purpura.
  - Evolves into persistent acral or nasal lichenoid papules, pitted scars and thickening (Fig. 19.**1**).
  - In 5–10% of cases, rapid hepatic fibrosis with liver failure and need for transplantation.
- **Diagnostic approach:** Elevated protoporphyrin levels in RBC, which show transient fluorescence.
- **Differential diagnosis:** Other childhood photosensitivity disorders, hyalinosis cutis et mucosae, p. 354.
- **Therapy:**
  - Light avoidance or extreme photoprotection (clothing better than sunscreens).
  - Systemic β-carotene is effective; dosage of 75–100 mg daily (adjusted for season and weight of patient); takes several weeks to be effective (skin must get a bit orange); start in February, discontinue in November.

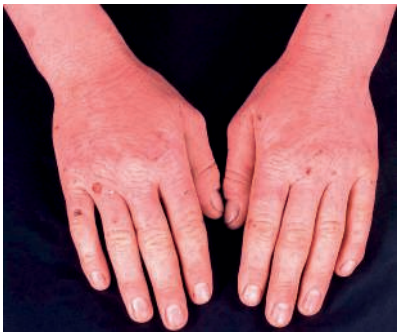


Fig. 19.**1** · Erythropoietic protoporphyria.

Porphyria Cutanea Tarda (PCT)

- **MIM codes:** 176100; 176090.
- **Definition:** Defect in uroporphyrinogen decarboxylase that can be either acquired or inherited, causing hepatic and cutaneous findings.
- **Classification:**
  - *Acquired PCT (type I) (MIM code 176090):* Caused by liver damage (estrogens, alcohol, viral hepatitis, hexachlorobenzene [insecticide], drug-induced hepatic dysfunction, hemochromatosis).
  - *Autosomal dominant PCT (type II) (MIM code 176100):* Provoked by same factors.
  - *Hepatoerythropoietic porphyria:* Autosomal recessive defect in uroporphyrinogen decarboxylase gene.
- **Clinical features:**
  - Skin changes in sun-exposed areas, especially backs of hands and face. Patients are photosensitive, but rarely enough to be a complaint.
  - Increased skin fragility; minor trauma leads to erosions, blisters, and crusts (Fig. 19.**2**); usually first finding noticed by patient. Later hyperpigmentation, blisters, and milia. Hypertrichosis on cheeks and temples. Marked solar elastosis.
  - Rarely, patients develop sclerotic plaques (pseudoscleroderma, p. 222).
  - In homozygotes, clinical picture is that of congenital erythropoietic porphyria.

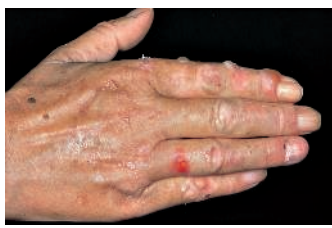


Fig. 19.**2** · Porphyria cutanea tarda with blisters and crusts in light-exposed areas.

- **Diagnostic approach:**
  - Total porphyrins and uroporphyrins raised in urine; coproporphyrins raised in stool; porphobilinogen (PBG) and δ-aminolevulinic acid (ALA) normal.
  - Acquired and inherited forms distinguished by enzyme essay or mutation analysis.
  - Exclude other causes of hepatic dysfunction (liver function, hepatitis serology, CBC, Hgb, Hct, ferritin (iron overload common).
  - Careful history of medications and occupational or hobby exposure to potential hepatotoxins.
- **Differential diagnosis:** Limited differential diagnostic considerations when classic picture present; some forms of epidermolysis bullosa acquisita look similar, as does drug-induced pseudoporphyria (usually furosemide) in renal dialysis patients.
- **Therapy:**
  - Avoid hepatotoxic agents.
  - If hepatitis C is documented, treat it with interferon and ribavirin.
  - Chloroquine 125 mg 2 × weekly. Chloroquine makes the uroporphyrin crystals in the liver more soluble so they can be excreted. One must start treatment slowly, ideally on an inpatient basis, and increase dosage slightly as urine values stabilize. Fever and arthralgias sometimes develop during induction.

Caution: Chloroquine is also one of the drugs that can trigger PCT. The dosage for PCT is only 250 mg weekly, in contrast to 250–500 mg daily for anti-inflammatory action (as in collagen–vascular diseases).

- *Bloodletting:* Remove 500 mL every 2 weeks, monitoring Hgb, iron, and ferritin. Decrease frequency of bleeding when clinical improvement has occurred and Hgb is at low normal level.

Acute Intermittent Porphyria

- **MIM code:** 176000.
- **Definition:** Defect caused by reduced activity of porphobilinogen deaminase; autosomal dominant inheritance.
- **Clinical features:**
  - No cutaneous findings.
  - Patients experience acute life-threatening attacks, usually triggered by medications (barbiturates, estrogens, psychotherapeutic agents).
  - *Findings include:*
    - *Gastrointestinal:* bowel cramps, constipation, diarrhea, ileus, vomiting.
    - *Cardiovascular:* tachycardia, hypertension (rarely hypotension).
    - *Neurological:* paresis, psychosis, sensory disturbances, seizures.
    - Others: anemia, dark urine, decreased urine output.

  Note: When any of these findings are present and not clearly explained, think of acute intermittent porphyria. Remember that porphyria variegata and hereditary coproporphyria can present in the same way.
- **Diagnostic approach:** Reduced porphobilinogen deaminase activity; during acute attack, increased amounts of porphobilinogen, aminolevulinic acid, uroporphyrin, and coproporphyrin in urine.
- **Differential diagnosis:** The trick is thinking of acute intermittent porphyria when confronted with a critically ill patient. Lead poisoning can produce a similar laboratory picture, but is easily excluded by lead levels.
- **Therapy:**
  - Treatment should be multidisciplinary.
  - Stop all possible triggering medications.
  - Pain control with opiates (preferably pethidine).
  - Antiemetics (promazine, chlorpromazine).
  - Infusion of heme arginate 3 mg/kg in 100 mL saline over 20 minutes; daily for 4 days (Heme arginate is not available in the USA, but other heme products can be used.).
  - Watch fluids carefully.
- **Prophylaxis:**
  - Instruct patient and family doctor on medications that can trigger attacks.
  - *Safe list:*
    - *Analgesics:* Aspirin, indomethacin.
    - *Sleep:* Chloral hydrate, phenothiazine, lorazepam.
    - *Coughing:* Codeine, dihydrocodeine.
    - *Local anesthetics:* Amethocaine, bupivacaine, procaine.
    - *General anesthetics:* Nitrous oxide, atropine, cyclopropane, suxamethonium, tubocurarine.

Porphyria Variegata

- **MIM code:** 176200.
- **Definition:** Defect in protoporphyrinogen oxidase, autosomal dominant inheritance; variegata means "variable" or "changing".

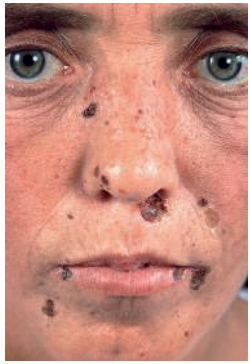


Fig. 19.**3** · Porphyria variegata caused by estrogens.

- **Epidemiology:** Very common in Scandinavia and in whites in South Africa (massive founder effect from single immigrant with disease).
- **Clinical features:** Combination of skin changes of porphyria cutanea tarda and acute disturbances of acute intermittent porphyria; either can dominate (Fig. 19.**3**).
- **Diagnostic approach:** Increased uroporphyrin and coproporphyrin in urine; in contrast to PCT the precursor substances are also increased. Protoporphyrin and coproporphyrin in stool.
- **Therapy:** Photoprotection usually suffices for skin; antimalarials or bleeding rarely needed. Acute attacks and prophylaxis as for acute intermittent porphyria.

Hereditary Coproporphyria

- **MIM code:** 121300.
- **Definition:** Defect in hepatic coproporphyrinogen oxidase, autosomal dominant inheritance.
- **Clinical features:** Same as porphyria variegata.
- **Diagnostic approach:** Increased levels of coproporphyrin in urine and stool; normal RBC porphyrin level.
- **Therapy:** Same as porphyria variegata.

19.2 Disorders of Lipid Metabolism

- **Definition:** Complex group of disorders of cholesterol and triglyceride metabolism, with abnormal or increased plasma lipoproteins.
- **Clinical features:** The cutaneous consequence of elevated plasma lipoprotein levels is the uptake of lipids by macrophages following leakage through vessels, leading to the formation of xanthomas and xanthelasma. The difference types of xanthoma include:
  - *Plane xanthoma:* Irregular yellow-tan macules and flat-topped papules.
  - *Tuberous xanthoma:* Larger red-brown or yellow nodules on pressure points—elbows, knees, hands, feet.
  - *Tendon xanthoma:* Large subcutaneous nodules over Achilles' or digital tendons.
  - *Eruptive xanthoma:* Numerous small yellow papules, often with red border, that appear suddenly.

- *Palmar xanthoma:* Yellow streaks (*striate*) or papules in the palmar creases.
- *Xanthelasma:* Most common xanthoma; yellow flat-topped papules and plaques on lids, especially upper lid; no clear association with lipid abnormalities.

► **Diagnostic approach:** The role of the dermatologist is to identify a lesion as a xanthoma. Then the patient must evaluated first for abnormalities of cholesterol and triglyceride metabolism and treated according the latest guidelines.

► ***Note:*** There is no point in trying to guess the underlying defect based on the skin findings.

Normolipemic Xanthomas

In some instances, xanthomas are identified clinically but the serum cholesterol ands triglyceride levels are normal. Possibilities include xanthomas composed of plant sterols (sitosterolemia, cerebrotendinous xanthomatosis), apolipoprotein defects, xanthomatous forms of Langerhans cell histiocytosis or xanthogranulomas, storage disorders, foreign bodies (some tissue fillers look xanthomatous under the microscope), and even trauma.

There are several rare but distinctive forms of normolipemic xanthomas:

► **Diffuse normolipemic plane xanthoma:** Large yellow-tan patches and plaques favoring trunk, flexures, neck, eyelids; associated with gammopathy.

► **Necrobiotic xanthogranuloma:** Yellow nodules and plaques, favor periorbital region; associated with gammopathy (p. 294).

► **Xanthoma disseminatum:** Diffuse yellow-orange papules involving axilla, groin, neck, and eyelids; mucosal surfaces also affected; pituitary involvement with diabetes insipidus occurs, but disease is entirely distinct from Hand–Schüller–Christian disease.

► **Verruciform xanthoma:** Verruciform papule with foam cells in tips of elongated dermal papilla. Most common on lips and genitalia following trauma, but also occurs in resolving severe dermatoses and in the lesions of CHILD syndrome (p. 414).

► **Diagnostic approach:** Clinical examination, biopsy, normal cholesterol and triglyceride levels.

► **Therapy:** Normolipemic xanthomas do not respond to diet and medical management as do true xanthomas. Localized lesions can be ablated or excised; there is no satisfactory treatment for widespread disease.

19.3 Disorders of Amino Acid Metabolism

Some disorders of amino acid metabolism with skin findings are listed in Table 19.**2**.

Table 19.2 · **Skin findings in disorders of amino acid metabolism**

Disease	MIM code	Pathogenesis	Skin findings
Phenylketonuria (p. 373)	261600	Phenylalanine hydroxylase deficiency	Pale skin and hair, photosensitivity, rarely sclerosis.
Hartnup syndrome (p. 307)	234500	Resorption disturbance for neutral amino acids	Pellagra-like signs and symptoms.
Alkaptonuria (p. 381)	203500	Homogentisic acid dioxygenase deficiency	Darkening of nasal, auricular cartilage

Continued Table 19.2 ▶

Table 19.2 · Continued

Disease	MIM code	Pathogenesis	Skin findings
Homocystinuria	236200	Cystathionine synthetase deficiency	Livedo reticularis, atrophic scars, facial erythema, Marfanoid facies, thin hair
Richner–Hanhart syndrome (p. 347)	276600	Tyrosine aminotransferase deficiency	Palmoplantar keratoses

19.4 Disorders of Mineral Metabolism

Hemochromatosis

- **Definition:** Disorder due to deposition of hemosiderin causing tissue damage.
- **Epidemiology:** The most common genetic disease, as about 10% of individuals have one abnormal *HFE* gene and in Europe about 1:300 are homozygous for the defect.
- **Pathogenesis:** Patients with two abnormal *HFE* genes are at risk of developing iron overload. HFE controls the intestinal absorption of iron. The most common mutation is C282Y; other mutations are less damaging. Only about 25% of homozygotes develop clinical findings. Men develop problems far more often (M:F 10:1) and earlier than women, because of the protective efforts of menstruation. Secondary hemochromatosis occurs following repeated transfusions for a variety of hematological diseases. Juvenile hemochromatosis is caused by mutations in a different gene and is very rare but much more aggressive.
- **Clinical features:**
  - The major problems result from iron deposition in the liver (cirrhosis, liver cancer, more problems with PCT), pancreas (diabetes mellitus, *bronze diabetes*), heart (conduction disturbances, congestive heart failure), joints (arthritis), and gonads (loss of libido, secondary sexual characteristics).
  - The skin becomes bronzed but the increased pigment is melanin, not iron; patients with vitiligo and hemochromatosis have no bronzing in their white spots.
- **Diagnostic approach:** Serum transferrin saturation and then serum ferritin levels, followed by genetic testing and perhaps liver biopsy.
- **Therapy:** Therapeutic withdrawal of blood.

Acrodermatitis Enteropathica

- **MIM code:** 201100.
- **Definition:** Defect in intestinal zinc transport gene *SLC39A4* with distinctive cutaneous findings; autosomal recessive inheritance. Acquired zinc deficiency produces the same clinical picture.
- **Pathogenesis:** SLC39A4 is primarily expressed in the duodenum and jejunum, and functions as a zinc-specific intestinal transport protein. Both homozygous and heterozygous mutations lead to abnormal zinc metabolism. The body normally stores 4 g of zinc; the average daily requirement is 10–15 mg. Table 19.**3** provides more details.

Table 19.3 · Zinc deficiency and related parameters

Zinc status	Plasma zinc level	Hair growth rate	Hair zinc levels
Normal	Normal	Normal	Normal
Mild deficiency	Normal	Normal	↓
Severe deficiency	↓	↓	Normal/ ↑

- **Clinical features:**
  - Acral, well-circumscribed, erythematous weeping plaques; most prominent around mouth, nares, anogenital region. When not moist, such as on the hands, can be psoriasiform. Also telogen effluvium loss of eyebrows and eyelashes.
  - Frequent secondary infections, usually with *Candida albicans*.
  - Diarrhea, photophobia, loss of smell.
  - Most common causes of acquired zinc deficiency are inflammatory bowel diseases; today, all parenteral nutrition includes adequate zinc.
- **Diagnostic approach:** Serum for determination of zinc level must be obtained using zinc-free needles and collecting system; marked diurnal variation, so always draw in a.m. Values vary from laboratory to laboratory, so always use same service; in our hospital 10–20 μmol/l is normal.
- **Differential diagnosis:** Most patients initially misdiagnosed as severe candidiasis.
- **Therapy:** Oral zinc replacement therapy produces miraculous results: improvement within days and soon total clearing.

Menkes Syndrome

- **Synonym:** Kinky hair syndrome.
- **MIM code:** 309400.
- Rare defect in copper transport protein inherited in x-linked recessive manner. Patients have sparse, brittle, twisted scalp hair (pili torti and trichorrhexis nodosa), profound mental retardation, and elastic fiber defects, primarily in arteries. Death occurs in infancy.

19.5 Endocrine Disorders

Pituitary Gland

- **Prolactinoma** is caused by a pituitary adenoma composed of lactotrophs secreting excessive amounts of prolactin. The main side effects are delayed puberty in either sex, galactorrhea–amenorrhea in women, and decreased libido in men. Some drugs (including haloperidol, trifluoperazine, metoclopramide) also cause elevated prolactin levels, as does hypothyroidism and other tumors in or near the pituitary gland. Treatment consists of bromocriptine or cabergoline as well as neurosurgery.
- **Acromegaly** (MIM code 102200) results from oversecretion of growth hormone by pituitary tumors, in adolescents or adults resulting in excessive bone growth of the face, hands and face with coarsening of facial features, and a host of medical problems. Dermatologic findings include thickening of the skin, seborrhea, hyperhidrosis, hypertrichosis, and acanthosis nigricans (p. 485).

► **Cushing disease** is the result of hyperadrenocorticism caused by excessive pituitary secretion of ACTH, usually because of a pituitary adenoma.

Thyroid Gland

► **Hyperthyroidism:**
- Warm moist skin, telogen effluvium with increased number of dystrophic hairs, onycholysis, increased incidence of alopecia areata and vitiligo.
- In the case of immunogenic hyperthyroidism (Graves disease) associated proliferation of fibroblasts, T cells and then mucin:
  - *Pretibial myxedema:* Red-yellow plaques over shins, often with orange peel texture.
  - *Acropathy:* Swollen fingers.
  - *Orbital deposits* cause exophthalmos.

► **Hypothyroidism:**.
- *Generalized myxedema:* Widespread puffy, doughy skin; usually cool and dry; hair loss (primarily occipital and frontal).
- More prominent edema infraorbital and on backs of hands (Fig. 19.**4**).
- Yellow skin tones because reduced conversion from carotene to retinal.

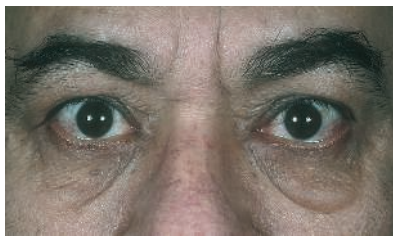


Fig. 19.**4** · Hypothyroidism: yellow skin tones and lid edema.

Parathyroid Gland

► **Hyperparathyroidism:** Skin findings most common with renal disease and secondary hyperparathyroidism including pruritus, calcinosis, and sometimes *calciphylaxis* (intravascular calcification causes lightening strike—like livid erythema with subsequent necrosis). Treatment consists of excision of all parathyroid glands, with one placed in an accessible subcutaneous location.

► **Hypoparathyroidism:** Associated with T-cell defects because of close origins of parathyroid glands and thymus; seen in mucocutaneous candidiasis, Di George syndrome; most common following thyroid surgery with accidental removal of parathyroids. Clinical findings: tetany, dry skin, and hair.

Adrenal Glands and Gonads

► **Cushing syndrome:** Endogenous or exogenous excess amount of corticosteroids leads to steroid acne, hirsutism, hyperpigmentation, striae, telangiectases, hypertrichosis and purpura (weakened vessels).

▶ ***Note:*** Cushing **disease** is a neurosurgical problem, as the hyperadrenocorticism results from a pituitary tumor in most cases; Cushing **syndrome** is the result of hyperadrenocorticism from any other cause.

- **Addison disease:** Diffuse bronze hyperpigmentation, even darker with light exposure, darkened scars, reduced sebum flow.
- **Androgens:** Secreted by adrenal glands and gonads; terminal hair follicles and sebaceous glands are major target organs for testosterone and its conversion product 5-hydrotestosterone. Clinical findings include androgenetic alopecia, hirsutism, acne. In women with atypical acne, consider Stein–Leventhal syndrome.
- **Adrenogenital syndrome:** Includes a variety of syndromes in which defective production of cortisol leads to elevated ACTH levels, which trigger the overproduction of intermediary hormones by the adrenal with potential virilization and sometimes precocious puberty. The most common defect is 21-hydroxylase deficiency, inherited in an autosomal recessive manner. Some patients may have late-onset disease, presenting with therapy-resistant acne.
- **Pheochromocytoma:** Rare adrenal tumor (85% of cases); may also arise in parasympathetic ganglia (paraganglioma). Most are benign and often bilateral; about 15–20% are malignant. Associated with neurofibromatosis 1, von Hippel–Lindau syndrome, and MEN2 syndrome. Oversecretion of catecholamines, usually epinephrine and norepinephrine. Main symptom is hypertension, but occasionally cause pale skin. Often mistakenly included in approach to flushing (p. 707), but usually erroneously. Diagnosis based on increased urine or serum catecholamines.

Pancreas: Diabetes Mellitus

30–70% of patients with diabetes mellitus have cutaneous changes, which can be divided into four groups:

- **Skin infections:** *Candida albicans* is the most common pathogen, causing perlèche, vulvitis, balanitis, paronychia, common bacterial infections include staphylococcal and streptococcal pyodermas, and erythrasma. Less common but more serious are mucormycosis, clostridial gangrene, and malignant otitis externa (*Pseudomonas aeruginosa*).
- **Markers of diabetes mellitus:**
  - *Necrobiosis lipoidica* (p. 293): Over 50% of patients with necrobiosis lipoidica have or develop diabetes mellitus, but less than 0.1% of diabetics have this skin change (female:male 3:1).
  - *Disseminated granuloma annulare* (p. 292) is likely to be marker, but not highly predictive.
  - Acanthosis nigricans (p. 485), lipodystrophy (p. 538) signs of insulin resistance.
  - Glucagonoma syndrome (*necrolytic migratory erythema*), hyperlipidemia, PCT reflect underlying metabolic problems.
  - *Bullous disease of diabetes:* Controversial disease; most have either bullous pemphigoid or epidermolysis bullosa acquisita; some suggest associated with retinal disease.
  - *Prurigo:* Diabetes mellitus may lead to renal failure and then a vicious cycle of pruritus leading to nodular skin lesions (prurigo) and perhaps other perforating dermatoses (p. 330).
  - Scleredema (see below).
  - Hemochromatosis or *bronze diabetes* (see above).
- **Complications of diabetes:**
  - *Macroangiopathy:* Cutaneous atrophy, especially on soles, dry skin, hypothermia, nail dystrophy, hair loss.
  - *Microangiopathy:* Perhaps *Binkley spots*: tiny brown macules on shins.
  - *Diabetic stiff skin syndrome.*
  - *Neuropathy:* Hyperhidrosis, malum perforans.

- **Complications of diabetic therapy:**
  - Oral hypoglycemic agents: allergic reactions, photosensitivity.
  - *Insulin:* Allergic reactions (5–10%), lipoatrophy, lipohypertrophy.

Neuroendocrine Tumors

- The scope of neuroendocrine tumors is beyond this book. Patients have tumors of the pancreas, intestine, thyroid gland, and many other sites secreting hormones such as insulin, glucagon, gastrin, histamine, serotonin, and calcitonin (medullary or C-cell of thyroid). Several points are of dermatologic interest.
- Patients with multiple endocrine neoplasia (MEN) have a variety of cutaneous findings, including multiple mucosal neuromas, angiofibromas, connective tissue nevi, and lichen amyloidosus (p. 324).
- Pancreatic glucagonomas are often associated with necrolytic migratory erythema (p. 486).
- Carcinoid tumors may cause flushing when they release serotonin or bradykinin. About 70% of patients have flushing, often associated with warmth or sweating and sometimes evolving into cyanosis. Diagnosed on elevated serum serotonin levels or elevated urine 5-hydroxy indolacetic acid (5-HIAA) levels.

19.6 Mucinoses

- **Definition:** Deposition of mucopolysaccharides (ground substance) in dermis. Unifying factor is histological identification of mucin, either with H&E stain as thready basophilic material or with alcian blue or Hale stain for more specific confirmation.
- There are a number of disorders with mucin deposits, including:
  - **Thyroid-associated mucinoses:** Pretibial myxedema and generalized myxedema (p. 318).
  - **Lichen myxedematosus and scleromyxedema:**
    - Lichen myxedematous presents with multiple small papules or urticarial lesions. When the papules are disseminated, likely to progress to sclerotic changes (scleromyxedema); latter sometimes presenting problem.
    - Unifying feature is thickening of the skin with mucinous infiltrate. Lichen myxedematosus: pruritic firm 5 mm white papules, closely grouped; usually on extremities. Scleromyxedema often has mask-like facies, tightened digits, and diffuse sclerosis.
  - Almost always associated with monoclonal gammopathy (IgG with γ light chains); also in HIV/AIDS.
  - Therapy very unsatisfactory. Plasmapheresis, extracorporeal photophoresis, bath PUVA, and systemic retinoids worth trying.
- **Nephrogenic fibrosing dermopathy** (p. 222): Resembles scleromyxedema but associated with renal dialysis.
- **Scleredema adultorum:**
  - Patients develop thickened, tightened skin on nape and upper back (Fig. 19.**5**); when arms are pushed backward, skin of back forms into folds. Typically follows infections, such as streptococci, measles, influenza, HIV; usually regresses.
  - Also associated with diabetes mellitus; little likelihood of regression.
  - Prompt treatment of initial infection. Penicillin G 1 million IU daily for 14 days sometimes tried empirically. Both systemic corticosteroids and penicillamine controversial. Physical therapy to retain motility.

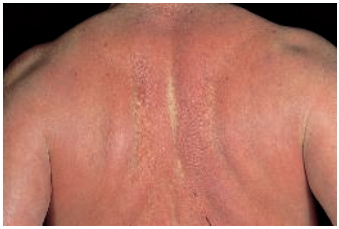


Fig. 19.**5** · Scleredema adultorum.

- **Reticulated erythematous mucinosis:** REM syndrome, sometimes considered form of cutaneous lupus erythematosus with reticulated erythematous plaques on midback and chest. Responds to antimalarials.
  - ***Note:*** The most common cause of mucin identified histologically is lupus erythematosus. Always exclude this diagnosis.
- **Focal cutaneous mucinosis:** Isolated papules or nodules containing mucin, with no obvious cause. Excision if disturbing.

19.7 Cutaneous Signs of Monoclonal Gammopathy

- **Cutaneous plasmacytoma:** Terminology confusing, as in some European countries multiple myeloma is known as plasmacytoma; in others, plasmacytoma is a type of B-cell lymphoma unrelated to multiple myeloma. Cutaneous involvement by multiple myeloma is very rare. Plasma cell infiltrates more likely to be reactive; always do light-chain clonality studies. One typical clinical setting is in the pseudo-recurrence following a curetted or otherwise ablated basal cell carcinoma or squamous cell carcinoma, in which a red-brown nodule develops and causes clinical alarm but is found to be a reactive polyclonal plasma cell infiltrate.
- **Increased tumor and infection rate:** Presumably because of immunosuppression; a variety of infections as well as squamous cell carcinoma, basal cell carcinoma, malignant melanoma, and Kaposi sarcoma are more common.
- **Cutaneous deposits:** Amyloidosis, scleromyxedema, scleredema, POEMS syndrome, diffuse normolipemic plane xanthoma, necrobiotic xanthogranuloma, xanthoma disseminatum, IgM papules.
- **Neutrophilic dermatoses:** Pyoderma gangrenosum, Sweet syndrome especially when atypical, IgA pemphigus (Sneddon–Wilkinson variant), erythema elevatum et diutinum, leukocytoclastic vasculitis.
- **Urticarial dermatoses:** Angioedema with C-1 esterase deficiency; Schnitzler syndrome (urticaria plus IgM gammopathy).
- **Autoimmune disorders:** Epidermolysis bullosa acquisita, paraneoplastic pemphigus, IgA pemphigus, atypical scleroderma, Sjögren syndrome.
- **Side effects of immunoglobulins:** Hyperviscosity syndrome, cryoglobulinemia (type I), Waldenström macroglobulinemia, Waldenström purpura, Raynaud phenomenon, follicular hyperkeratoses and spikes (crystalloid immunoglobulins).
- **Acquired cutis laxa:** Rare disease but can accompany gammopathy.

POEMS Syndrome

- POEMS is an acronym for **p**olyneuropathy, **o**rganomegaly, **e**ndocrine disorders, **m**onoclonal gammopathy, **s**kin disease.
- Diffuse sclerosis with hyperpigmentation.
- Glomeruloid hemangiomas, perhaps caused by elevated VEGF levels.

19.8 Gout

- **Definition:** Hyperuricemia associated with crystal-induced arthritis, tophi and in some instances renal stones.
- **Pathogenesis:** Over 99% of cases associated with decreased renal excretion of uric acid. Rarely, overproduction of uric acid (*Lesch–Nyhan syndrome* with self-mutilation). Secondary elevation in leukemia, polycythemia, hemolytic anemia, tumor chemotherapy; also caused by diuretics, chronic renal disease, and ketoacidosis (diabetes mellitus, fasting).
- **Clinical features:** Acute arthritis with exquisite pain, swelling; most often involves great toe (*podagra*) (60%), less often other digits (10%), feet (10%), or other joints. Renal stones a risk. Cutaneous findings include uric acid deposits (*tophi*) most often on ears or periarticular; in later case, differential diagnostic considerations include rheumatoid nodule.
- **Therapy:** Acute flares treated with NSAID or colchicine; prophylaxis with diet, probenecid or allopurinol.

19.9 Amyloidosis

Introduction

- **Definition:** A condition where amyloid, a β-pleated stable protein, is deposited in tissues.
- **Diagnostic approach:**
  - Amyloid can only be diagnosed with certainty with a biopsy. The following stains can be used:
    - *Congo red:* When examined in polarized light, amyloid is doubly refractive and apple green.
    - *Thioflavine S:* Yellow fluorescence.
    - *Acridine orange:* Red fluorescence.
  - Immunohistochemical studies with antibodies can also be used to further identify the type of amyloid.
  - *Biopsy sites:* Most useful sites for primary amyloidosis include:
    - Rectal mucosa (85%).
    - Transverse carpal ligament (almost 100%).

  Note: If patient presents with bilateral carpel tunnel syndrome, always think amyloid.
    - Subcutaneous fat tissue (biopsy or aspirate; $<50\%$).
    - Bone marrow (circa 40%, but only for primary amyloidosis).
    - Other sites may include skin, oral mucosa, muscle, sural nerve, liver, gastrointestinal wall, heart (depending on type of involvement).

Overview

The unifying theme of amyloid is β-pleated protein sheets combined with glycoprotein components. Most typical is amyloid A protein, which is related to the serum amyloid A (SAA) protein and in turn to C-reactive protein. Table 19.**4** lists some of the different types of amyloid and Table 19.**5** summarizes the different types of amyloidosis, some of which are discussed below.

Table 19.4 · Types of amyloid

Type	Abbreviation	Clinical designation	Precursor protein
Immune amyloid	AL	Primary amyloidosis	Light chain immunoglobulins (λ > κ)
Classic amyloid	AA	Secondary amyloid (leprosy, rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever, many more)	Apolipoprotein with properties of acute phase protein (SAA)
Endocrine amyloid	AE	APUD tumors (thyroid C cells, islet cells, others)	Prohormone
Familial amyloid	AF	Usually associated with polyneuropathy	Prealbumin variant
	AF	Nonneuropathic form (renal disease)	SAA
Senile amyloid	AS	Cerebral or cardiac forms	Variety of precursor proteins; related to prion disease and Down syndrome
Hemodialysis amyloid	AH	Side effects of long-term hemodialysis; carpel tunnel syndrome and cystic bone lesions	B2 microglobulin
Cutaneous amyloid	AK	Localized skin involvement	Keratins

Table 19.5 · Cutaneous amyloidosis

Type	Characteristics
Primary cutaneous amyloidosis	
Lichen amyloidosus	Papules on shins
Macular amyloidosis	Intra-scapular hyperpigmentation and papules
Nodular amyloidosis	Yellow nodules with central atrophy; can be primary or secondary to AL amyloid

Continued Table 19.5 ▶

Table 19.5 · Continued

Type	Characteristics
Secondary cutaneous amyloidosis	
With epithelial tumors	Basal cell carcinoma, seborrheic keratosis, actinic keratosis
With actinic elastosis	
With excessive light exposure or PUVA therapy	
Cutaneous signs of systemic amyloidosis	
AL type	Hemorrhage and deposits about vessels; rarely nodular deposits
AA type	Hemorrhage and deposits around vessels
Amyloid elastosis	Rare, progressive fatal variant

Lichen Amyloidosus

- **Epidemiology:** Most common form of cutaneous amyloidosis; more common in Asians.
- **Pathogenesis:** Patients have severe pruritus, whatever the cause. Excessive scratching and rubbing damages keratinocytes; keratin drops into dermis and is somehow processed into amyloid.
- **Clinical features:** Pruritic, closely grouped firm glistening papules; often with fine scale; pink to red-brown; almost always on shin (Fig. 19.**6**).
  - ***Note:*** Amyloid deposits in AL and AA amyloid never itch.
- **Histology:** Dermal papillae dilated and filled with subtle deposits of amyloid K. Incontinence of pigment, acanthosis confirm previous manipulation.
- **Diagnostic approach:** Clinical examination, biopsy. No extensive immunologic workup needed.
- **Differential diagnosis:** Lichen planus, lichen simplex chronicus.
- **Therapy:** No good solution; antipruritic measures (such as topical corticosteroids, perhaps under occlusion), PUVA, or even systemic retinoids.

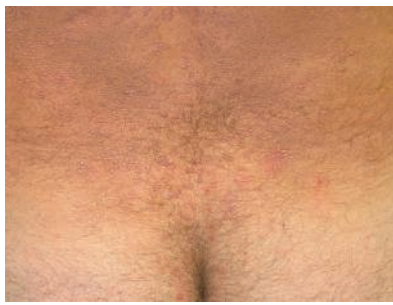


Fig. 19.**6** · Lichen amyloidosus.

Macular Amyloidosis

- **Synonyms:** Interscapular amyloidosis, bath brush amyloidosis.
- **Epidemiology:** Uncommon; seen more often in Asians and darker-skinned individuals; usually affects adults.
- **Pathogenesis:** Once again self-induced in patients with marked pruritus; often associated with notalgia paresthetica. Some patients use a back scratcher or bath brush to alleviate itching on their back.
- **Clinical features:** Modest pruritus, disseminated often confluent small tan macules; poorly circumscribed. Typically interscapular but can occur at other sites. Overlaps with lichen amyloidosis.
- **Histology:** Very subtle deposits of amyloid A in dermal papillae; easily missed.
  - ***Note:*** In pure cutaneous amyloidosis with amyloid K, there are no perivascular deposits.
- **Diagnostic approach:** Clinical examination, biopsy.
- **Differential diagnosis:** Postinflammatory hyperpigmentation, atopic dermatitis, other forms of dermatitis, lichen simplex chronicus, fixed drug reaction.
- **Therapy:** As for lichen amyloidosus; capsaicin solution once daily for long period of time has helped some.

Nodular Amyloidosis

- **Synonyms:** Amyloidosis cutis nodularis atrophicans, plaque-like amyloidosis.
- **Pathogenesis:** Association with AL; some patients have isolated cutaneous disease, other share evidence of systemic involvement.
- **Clinical features:** Red-brown nodules and plaques, often with central thinning so that underlying fat is seen with yellow shimmer; often on scalp.
- **Histology:** Massive deposits of amyloid L, diffusely filling dermis, also involves vessels and sweat glands.
- **Diagnostic approach:** Clinical examination, biopsy. Exclude systemic involvement with gammopathy.
- **Differential diagnosis:** Nevus lipomatosus, lipoma, cysts, lymphoma; histologically, all forms of amorphous deposits, such as gout and nodular elastosis.
- **Therapy:** Excision.

Secondary Cutaneous Amyloidosis

Secondary deposits of amyloid K in the skin are almost always an incidental finding in histology reports. The presence of secondary amyloid has no clinical significance. The most common setting is in tumors such as basal cell carcinoma, seborrheic keratosis, and actinic keratosis. Any lichenified dermatitis may also show deposits, as can skin damaged by light or PUVA.

Primary Systemic Amyloidosis

- **Synonym:** Immunocyte-derived amyloidosis.
- **Definition:** Amyloidosis caused by a monoclonal gammopathy with deposition of AL in many organs.
- **Pathogenesis:** Uncommon disorder; associated with variety of monoclonal B-cell proliferations including multiple myeloma, Waldenström macroglobulinemia, plasma cell dyscrasia with Bence Jones proteins, heavy chain disease, and B-cell lymphomas. In some instances, no underlying disease is found and the cause provisionally designated as "idiopathic" but the disease eventually evolves into a gammopathy.

- **Clinical features:**
  - A wide variety of organs can be involved, so the signs and symptoms are highly variable. Most commonly involved organs include kidneys, heart, peripheral nervous system, tongue, gastrointestinal tract.
  - Skin findings include:
    - Spontaneous purpura, often facial with many colorful names such as "pinch purpura" or "postproctoscopic purpura." The message is that minor trauma damages vessel walls infiltrated by amyloid and leads to unexpected purpura.
    - Tiny amyloid deposits, often periorbital or intertriginous, and often with subtle purpura.
    - Nodular amyloidosis (see above).
    - Macroglossia.
    - Peripheral neuropathy can indirectly lead to malum perforans; involvement of carpel ligament to carpel tunnel syndrome.
- **Histology:** Deposits of amyloid found in small blood vessels in dermis or subcutaneous fat. If skin lesions are present, yield is high. Best site for blind biopsy is rectal mucosa or subcutaneous fat.
- **Diagnostic approach:** Clinical examination, biopsy; once amyloid has been confirmed, then extensive search for underlying disease.
- **Differential diagnosis:**
  - All the different causes of purpura.
  - *Papules:* Xanthoma, xanthelasma, lipoid proteinosis, lichen myxedematosus.
  - *Nodules:* Cysts, lipomas, nevus lipomatosus, lymphoma, and others.
- **Therapy:** Skin disease requires no therapy; B-cell proliferations treated by hematology-oncology, with secondary signs and symptoms managed in multidisciplinary fashion.

Secondary Systemic Amyloidosis

- **Synonyms:** Reactive amyloidosis, wear-and-tear amyloidosis.
- **Pathogenesis:** Deposition of AA amyloid secondary either to chronic inflammatory diseases (tuberculosis, leprosy, inflammatory bowel disease, rheumatoid arthritis) or to variety of malignant tumors. Familial Mediterranean fever features an abnormality in SAA and invariably progresses to AA deposits.
- **Clinical features:**
  - Depend heavily on underlying disease; most likely organs are kidney, liver, spleen adrenal glands, and gastrointestinal tract. Main problem is progressive renal failure.
  - Cutaneous findings uncommon: purpura or rarely deposits.
- **Histology:** Same as with AL amyloid; blind skin biopsies once again unlikely to be useful.
- **Therapy:** Treat underlying disease; possibility of regression if control is achieved.

19.10 Smoking and the Skin

Overview

The detrimental effects of smoking are well known. In Germany about 25% of the population smokes, with an disturbing increase in young smokers, especially young women. About 25% of deaths are blamed on smoking, although some estimates are

much higher. The main problems are carcinoma of the lung and cardiovascular disease. There is no other risk factor with such clearly proven adverse effects on human health.

Cutaneous Manifestations

- **Premature aging:** Smokers' skin is often excessively wrinkled, has a yellow-orange tint. Although excessive sun exposure is a greater risk factor, the two effects are cumulative. Favre–Racouchot disease is especially common in smokers.
- **Yellow fingers:** Direct discoloration of the finger tips and nails from smoke.
- **Impaired wound healing:** Combination of impaired collagen synthesis, reduced oxygen supply because of excessive carbon monoxide and decreased circulation (nicotine-induced vasoconstriction, hyperviscosity).

Diseases Associated with Smoking

- **Well established:**
  - Palmoplantar pustulosis.
  - Psoriasis, especially pustular psoriasis.
  - Acne inversa.
  - Squamous cell carcinoma of the lips and oral mucosa.
  - Condylomata acuminata (and carcinoma of cervix).
- **Possible associations:**
  - Atopic dermatitis; also passive exposure from smoking parents.
  - Malignant melanoma (smokers have worse prognosis).
  - Lupus erythematosus (also worse response to antimalarials).
- **Other dangers:** Smokers should not be prescribed inflammable topical agents, such as those in alcohol base.
- **Possible positive effects:** There are rare diseases that seem to improve with smoking—Behçet syndrome and Crohn disease. We mention them only for completeness, and do not encourage patients with either of these disorders to start smoking.

20 Pruritus and Prurigo

20.1 Pruritus

Overview

- **Definition:** *Pruritus or itching* is an unpleasant cutaneous sensation that makes the individual scratch.
- **Pathogenesis:** Pruritus is a physiologic protective mechanism, stimulating the host to scratch away stinging insects or scabies mites. It is thus similar to other protective mechanisms against heat, cold, or pain. Numerous mediators, including histamine, cytokines, opiates and others, can induce pruritus. Itch impulses are transmitted by slow-firing unmyelinated C fibers. The receptors have not been completely identified, but probably consist of a group of structures that cross-modulate each other. Minimal stimulation of single fibers can cause itching, tickling, or tingling; more aggressive stimulation of bundles of fibers by rubbing or scratching temporarily inhibits the unpleasant stimuli.
- **Clinical features:** Pruritus may be localized or generalized. It tends to be worse at night when the patient is less distracted. Patients with pruritus may have either normal skin or excoriations, as well as signs of an underlying skin disease.

Diagnostic Approach

- ***Note:*** The challenge is to determine whether the patient has a pruritic skin disease that has not been identified or whether an underlying systemic disease is causing their symptoms (Table 20.**1**).
- **History:** Severity of pruritus, interferes with sleep.

Table 20.1 · **Causes of pruritus**

Category	Examples
Metabolic and endocrine diseases	Diabetes mellitus, hyperthyroidism, hypothyroidism, chronic renal disease, uremia, carcinoid syndrome
Malignancy	Hodgkin disease (most common), other lymphomas and solid tumors
Hematologic diseases	Polycythemia vera, monoclonal gammopathy, mastocytosis, hypereosinophilia syndrome
Hepatic disease	Primary biliary cirrhosis, hepatitis, cholestasis (pregnancy, drug-induced), biliary obstruction
Infections and infestations	Scabies, pediculosis, onchocerciasis, arthropod assault reactions, any systemic worm infestation
Psychogenic factors	Acute—reaction to stress, anxiety, depression Chronic—delusions of parasitosis
Skin diseases	Allergic contact dermatitis, atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, dermatophyte infections, fiberglass dermatitis, pediculosis, polymorphous light eruption, scabies, urticaria, xerosis

- **Physical examination:** Excoriations, xerosis, scabies, pediculosis, dermographism, lymphadenopathy.
- ***Note:*** Scabies can present with virtually no cutaneous findings, especially in meticulous patients (*scabies of the cleanly*).
- **Laboratory:** Sedimentation rate, CBC, liver function tests, glucose, serum IgE, hepatitis serology, stool for ova and parasites.
- **Imaging:** Chest radiograph.
- **Additional studies:** Based on the history, additional studies might include thyroid function tests, α-fetoprotein, carcinoembryonic antigen (CEA), ferritin, creatinine, creatinine clearance, blood urea nitrogen (BUN), serum protein electrophoresis, serotonin levels, urine electrophoresis.

Therapy

- Treat the underlying disease, if one has been identified.
- Antihistamines, tranquilizers, opiate antagonists.
- Topical capsaicin.
- Optimal skin care (lubricants).
- **UVB irradiation:**
  - **Uremic pruritus:** UVB irradiation, charcoal tablets, lidocaine i.v., cholestyramine, ondansetron, naloxone i.v, plasmapheresis, subtotal parathyroidectomy.
  - *Cholestatic pruritus:* UVB irradiation, cholestyramine, plasmapheresis.

20.2 Prurigo

Overview

The combination of pruritus and associated skin lesions, produced by scratching, is known as prurigo. The cause of prurigo is unknown. It is unclear why in some clinical settings pruritus leads to excoriations, and in others to the development of dome-shaped papules. Many different unrelated diseases are lumped together under the rubric of prurigo; we will discuss only a few common examples. All can be treated in the same way with systemic antihistamines, topical anesthetics (polidocanol), or distractors (menthol), and in some instances with topical corticosteroids.

Prurigo Simplex Acuta

Acute reaction usually in children, induced by arthropod bites or stings, also known as *strophulus.* Typical prurigo seropapule (tiny papule with marked edema producing a vesicle at top) develops; intensely pruritic. Self-limited; treat with antihistamines.

Prurigo Simplex Subacuta

The least well-defined member of a fuzzy group. We view this as synonymous with *"pruritogenic excoriation."* Patients present with papules, excoriations, and the history that the pruritus is greatly relived when the papules are excoriated and damaged. When only the face is involved, the term *acne urticata* is applied. Probably many different causes of pruritus, which meet in a common pathway in susceptible individuals. Chronic problem; extremely difficult to treat. Try antihistamines, anesthetics, topical corticosteroids; some patients respond to phototherapy or minor tranquilizers.

Prurigo Nodularis

- **Clinical features:** Patients develop red-brown hyperkeratotic nodules several centimeters across, typically on the extremities. Formerly felt to be almost pathognomic of uremia, but also seen in atopic dermatitis and without obvious cause. More common in women. Complain of pruritus.
- **Histology:** Prototype of pseudoepitheliomatous hyperplasia, with marked acanthosis and hyperkeratosis. In some instances, hypertrophied cutaneous nerves, but unclear if causative or reactive.
- **Diagnostic approach:** Look for other signs of atopic dermatitis; exclude renal disease and other systemic causes of pruritus if clinically plausible.
- **Differential diagnosis:** Difficult to separate from verrucous lichen planus; look for signs of disease elsewhere.
- **Therapy:** Most effective are high-potency corticosteroids under occlusion or intralesional corticosteroids, coupled with systemic antihistamines.

Lichen Simplex Chronicus

- **Clinical features:** One or several lichenified patches, almost always on nape or dorsal aspect of hands or feet. Facial involvement uncommon. Patient manipulates just this localized area, in contrast to prurigo nodularis where broad areas are attacked. Rarely complain of pruritus. When examined closely, often consists of central plaque surround by multiple small papules and rim of postinflammatory hyperpigmentation. Also more common in atopic dermatitis.
  - ***Note:*** Often the patient will manipulate the area during the short course of an office visit.
- **Histology:** Epidermal reaction as in prurigo nodularis but less severe.
- **Diagnostic approach:** Look for other signs of atopic dermatitis.
- **Differential diagnosis:** Usually diagnosis is obvious, but patient is unwilling to accept. Occasionally confused with tinea or lichen amyloidosus; overlaps with prurigo nodularis.
- **Therapy:** Same as prurigo nodularis; see above.

Perforating Disease of Renal Dialysis

- **Synonyms:** Perforating folliculitis, hyperkeratosis follicularis et parafollicularis in cutem penetrans (Kyrle disease).
- **Definition:** Pruritic papules usually in patients with diabetes mellitus, renal failure, and dialysis, although all three components are not always present.
- **Pathogenesis:** Although this disorder is common in dialysis patients, it is nonetheless surrounded by both linguistic and scientific confusion. Kyrle disease is illogical; he described epidermal keratoses penetrating into the dermis. Perforating folliculitis is an oxymoron, as all folliculitis shows some degree of follicle wall damage by definition. These patients have pruritus induced by their renal disease (or occasionally by other factors), and react with a follicular type of prurigo nodularis.
- **Clinical features:** Intense pruritus; numerous 3–6 mm hyperkeratotic nodules, usually clearly in a follicle, are seen on the shins, forearms, and sometimes elsewhere on the body. Areas with no follicles, such as palms, soles, and mucosa are spared.
- **Histology:** Highly confusing; varying combinations of follicular plugging, follicle wall damage, reactive epidermal changes, excoriations, chronic inflammation.
- **Diagnostic approach:** Clinical examination and history.

- **Differential diagnosis:** The perforating dermatoses are considered under elastosis perforans serpiginosa (p. 359). The true differential diagnostic considerations are lichen simplex chronicus and prurigo nodularis; we view the three entities as part of a spectrum.
- **Therapy:**
  - Maximize management of renal disease; investigate dialysis system with nephrologists, as some feel types of filters and dialysates plays a role; UV light effective for renal pruritus; also try topical antipruritic agents.
  - In more severe cases, charcoal tablets (12–16 daily), lidocaine i.v., cholestyramine, ondansetron, naloxone i.v, plasmapheresis, subtotal parathyroidectomy.

Prurigo Pigmentosa

- **Definition:** Uncommon pruritic disorder that heals with distinctive hyperpigmentation.
- **Epidemiology:** Originally described in Japanese, but seen occasionally in all races; more common in women.
- **Clinical features:** Intensely pruritic inflammatory papules usually favoring breasts and anterior chest; often arranged in reticular pattern. Heal with striking postinflammatory hyperpigmentation.
- **Histology:** Dense subepidermal lymphohistiocytic infiltrate with pronounced epidermotropism and numerous necrotic keratinocytes.
- **Therapy:** Symptomatic care, topical corticosteroids or anesthetics (polidocanol).

Other Types of Prurigo

Many other diseases are designated as prurigo. All are pruritic are some point in their course, but not otherwise related. Table 20.**2** summarizes this mixed group.

Table 20.2 · **Other types of prurigo**

Disease	Comments
Actinic prurigo	Uncommon form of photosensitivity combining dermatitis, cheilitis and prurigo; most common in Native Americans
Prurigo aestivalis (Hutchinson prurigo)	Polymorphous light eruption in childhood
Besnier prurigo	Atopic dermatitis with prurigo nodularis
Prurigo diabetic	Diabetes mellitus with prurigo nodularis
Prurigo dermatographica (Marcussen prurigo)	Prurigo following pressure urticaria
Prurigo gestationis	Old term for pruritic disease in pregnancy; probably represents flare of atopic dermatitis in pregnancy, but unclear
Prurigo hepatica	Prurigo secondary to liver disease
Prurigo melanotica (Pierini–Borda)	Prurigo plus postinflammatory hyperpigmentation, usually in dark-skinned individuals
Prurigo uremica	Prurigo in renal failure; formerly very common diagnosis