Skin Diseases (L7)

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Other topics (not treated in this lecture):

- Diseases of blood vessels of the skin
- Diseases of the lymphatic system of the skin
- Diseases of skin nerves; psychodermatology
- Diseases of the mucosa of the skin and mouth
- Diseases of the anal canal and the perianal region
- Diseases of external sex organs
Literature

G. Thews, E. Mutschler, P. Vaupel
Anatomie, Physiologie, Pathophysiologie des Menschen (6. Auflage)
Skin diseases: chapter 21, pages 863-874.

Gernot Rassner
Dermatologie: Lehrbuch und Atlas (7. Auflage)

Robbins and Cotran
Pathologic Basis of Disease (8th edition)
The Skin: chapter 25, pages 1165-1204.
The skin is a complex organ, the largest of the body, in which precisely regulated cellular and molecular interactions govern many crucial responses to the environment.

Components of the skin:

- **Epidermis**: stratified squamous epithelium composed of proliferating basal and differentiated suprabasal keratinocytes.

- **Dermis**: connective tissue rich in collagen, elastic fibres and extrafibrillar matrix. Epidermis and dermis together form the cutis.

- **Subcutis**: subcutaneous adipose tissue (insulation, energy reserve) connecting the cutis with the subjacent tissues.

- **Pigmentary system**: melanin-forming melanocytes.

- **Adnexes of the skin**: nails, hair, skin glands.

Functional and coordination systems of the skin:

- **Immune system**: macrophages (phagocytosis), mast cells (inflammation), Langerhans cells and lymphocytes (immune reaction).

- **Blood vessels** of the skin consisting of arteries, venes, blood capillaries and lymph vessels forming a plexus.

- **Nervous system** of the skin: mainly sensory and autonomous nerve fibres. Sensory afferent fibres with free nerve endings or nociceptors mediate touch temperature, pressure and pain stimuli to the CNS. Autonomous fibres(sympathicus) innervate blood vessels and skin adnexes. Motor fibres innervate the facial musculature.

- **Endocrine regulatory processes**.

Reference: Rassner, 2002
Structure of the skin

A: The skin is composed of an epidermal layer (e) from which specialized adnexa (hair follicles, h; sweat glands, g; and sebaceous glands, s) descend into the underlying dermis (d). B: This projection of the epidermal layer (e) and underlying superficial dermis demonstrates the progressive upward maturation of basal cells (b) into cornified squamous epithelial cells of the stratum corneum (sc). Melanin-containing dendritic melanocytes (m) (and rare Merkel cells containing neurosecretory granules) and mid-epidermal dendritic Langerhans cells (lc) are also present. The underlying dermis contains small vessels (v), fibroblasts (f), perivascular mast cells (mc), and dendrocytes (dc), potentially important in dermal immunity and repair.

Scheme showing the dynamic interaction between epidermis and dermis: keratinocytes at the edge of ulcerating epidermis (A) produce cytokines and other factors which influence both the formation of new keratinocytes and the processes in the subjacent dermis (B). Cells of the dermis (B) also produce cytokines which affect both endothelial cells and keratinocytes. These interactions may get out of control, the basis for the development of psoriasis (C).

Reference: Robbins & Cotran, 2010
Functions of the Epidermis

The epidermis has various functions:

• Protection against physical and chemical traumas / noxas
• Protection against penetrating microorganisms
• Barrier against loss of water, i.e. protection against dehydration

The epidermis in general has an excellent regeneration capacity (except for severe burns or wounds):

• A single adult epidermal stem cell has the (theoretical) proliferation potential to recover the entire epidermal surface.
• In mammals the epidermal stem cells are located next to the hair shaft.
• In the human epidermis, the epidermal stem cells (with high proliferation potential) are found on the basal membrane in the basal layer.
• Epidermal stem cells are pluripotent, i.e. they not only form new epidermis but also hair follicles and sebaceous glands (as demonstrated in animal experiments).

Reference: Rassner, 2002
Epidermis of Mammals

Figure 1 | The skin and its appendages. Mammalian skin consists of the epidermis and dermis, separated by a basement membrane. The epidermis is a stratified squamous epithelium that is composed of several cell layers. Resting on the basement membrane is the basal layer (BL), consisting of proliferating, transit-amplifying cells (see text). The basal layer stratifies to give rise to differentiated cell layers of the spinous layer (SL), granular layer (GL) and the stratum corneum (SC). Also shown is a cross-section of a hair follicle, which consists of an outer root sheath that is contiguous with the basal epidermal layer. At the bottom of the follicle is the hair bulb, made from proliferating matrix cells. The transit-amplifying matrix cells terminally differentiate to generate the different cell types of the follicle. Also shown is the bulge, which is part of the outer root sheath and is where epidermal stem cells reside. The dermal component of the hair follicle is the dermal papilla, which consists of specialized mesenchymal cells surrounded by the hair matrix cells.

Epidermal stem cells

Two models for stem cell-based tissue self-renewal and regeneration

A: Prevailing model of a single stem cell population located in the niche. Asymmetric division is the key mechanism to maintain balance between self-renewal and differentiation.

B: Proposed alternative and complementary model: co-existing quiescent and active stem cell populations located in adjacent zones with corresponding inhibitory and stimulatory signals. Quiescent stem cells replace damaged active stem cells (heavy arrow). Conversely, active stem cells may replace lost quiescent stem cells (light arrow). A negative feedback from either active stem cells (dashed line) or their progeny (solid line) may contribute to prevention of quiescent stem cells from activation.

Wnt: wingless-related
BMP: bone morphogenic protein
DP: dermal papilla

Zoned stem cell population and the associated microenvironmental signals in the skin: Bulge area typically provides Wnt-off and BMP-on signals thus maintaining quiescent stem cells, whereas DP provides stimulatory (Wnt-on and BMP-off) signals.

Epidermal stem cells

Structure of the hair follicle
Stem cell locations in hair follicle: Hair follicle structure with quiescent (bulge) and active (hair germ) stem/progenitor cells. Bulge area typically maintains quiescent stem cells, whereas DP provides stimulatory signals. Only during development and under injury condition, bulge stem cells give rise to stem cells in epidermis.

Hair cycle
Interaction of signals from the bulge area and the dermal papilla in the course of the hair cycle.

Adherens junctions and desmosomes

Adherens junction form a bridge between the actin cytoskeleton of neighbouring cells.

Desmosomes associate with the keratin filament cytoskeleton of cells.

Simplified models of (a) an adherens junction and (b) a desmosome, which highlight some of the main protein–protein interactions found in these structures. Adherens junctions and desmosomes mediate cell–cell contact between all cells of the epidermis and are present in all metabolically active cell layers. The adherens junctions form a bridge between the actin cytoskeleton of neighbouring cells. By contrast, desmosomes associate with the keratin filament cytoskeleton of cells. Keratin IF, keratin intermediate filaments; p120ctn, adherens junction protein p120; VASP, vasodilator-stimulated phosphoprotein.

Hemidesmosomes represent cell densifications with anchoring filaments for the attachment at the basement membrane.

This structure is based on biochemical and molecular evidence of protein-protein interactions in the hemidesmosome. \( \alpha_6\beta_4 \)-integrin heterodimers form the core of the hemidesmosome, along with BPAG2, a transmembrane protein with an extracellular domain similar to collagens. BPAG1e and plectin are two hemidesmosomal proteins that are members of the plakin family of coiled-coil proteins. These two proteins have intermediate (keratin) filament-binding domains on their non-helical carboxy-terminal (C) segments. They concentrate on the inner plate of the hemidesmosome, and seem to function by linking the keratin intermediate filament cytoskeleton to the transmembrane proteins in the hemidesmosome. BPAG1e, bullous pemphigoid antigen 1, epidermal isoform; BPAG2, bullous pemphigoid antigen 2.

A: In the absence of inflammation, skin is populated by several immune cells, some stationary and others transitory, that survey the environment and are primed for response.

B: The innate response to epithelial injury or antigen presentation activates the resident immune cells that then recruit nonspecific effector cells such as neutrophils and eosinophils.

C: The adaptive response occurs when antigen presented in the context of the major histocompatibility complex is specifically recognized by T cells and as a result, additional antigen-specific skin-homing (CLA+) T cells are recruited. TCR, T-cell receptor.

TCR = T-Zell-Rezeptor
MHC = Major histocompatibility antigen
CLA+ = Antigen-specific skin-homing T-Zellen
Diseases of the cutis

- **Disorders of pigmentation and melanocytes**
  - Freckle (ephelis), lentigo, melanocytic nevus, dysplastic nevi, melanoma
- **Benign epithelial tumors**
  - Seborrheic keratoses, acanthosis nigricans, fibroepithelial polyp, epithelial cyst, adnexal tumors
- **Premalignant and malignant epidermal tumors**
  - Actinic keratosis, squamous cell carcinoma, basal cell carcinoma
- **Tumors of the dermis**
  - Benign fibrous histiocytoma (dermatofibroma)
- **Tumors of cellular migrants to the skin**
  - Mycosis fungoides, mastocytosis
- **Disorders of epidermal maturation**
  - Ichthyosis
- **Acute inflammatory dermatoses**
  - Acute and chronic eczematous dermatitis, exanthemas (urticaria, erythema multiforme)
- **Chronic inflammatory dermatoses**
  - Psoriasis, seborrheic dermatitis, lichen planus
- **Blistering (bullous) diseases**
  - Inflammatory blistering disorders (pemphigus, bullous pemphigoid, dermatitis herpetiformis), non-inflammatory blistering disorders (epidermolysis bullosa, porphyria)
- **Disorders of epidermal appendages**
  - Acne vulgaris, rosacea
- **Collagenoses (connective tissue disease)**
  - Cutaneous lupus erythematosus, scleroderma
- **Infections**
  - Viral infections (Herpes simplex, VZV, HPV)
  - Bacterial infections (B. anthracis, B. burgdorferi, Staphylococci)
  - Fungal infections: Candida, Tinea
- **Appendix (slides in German)**
  - Diseases of nails and nailbeds
  - Diseases of hair and hair follicles
  - Diseases of sebaceous and sweat glands
**Melanogenesis**

**The epidermal melanin unit**

The schematic figure of the epidermis shows a melanocyte located on the basement membrane which transfers melanin (packed in melanosome organelles) via its extensions (dendrites) to neighbouring keratinocytes. Following UV-exposition, the number of melanosomes in the melanocyte increases along with the melanin content in these organelles and the rate of transfer of melanin to keratinocytes is higher.

**Melanogenesis**

The enzyme tyrosinase participates in the catalysis of three steps of the melanin biosynthesis cycle: the hydroxylation of tyrosine to DOPA, the oxidation of DOPA to DOPA-chinone and the oxidation of dihydroxyindole to indol-5,6-chinone. In a form of inherited oculocutaneous albinism (OCA1), the tyrosinase gene is mutated in both alleles, with the consequence of an entire lack or a severely reduced tyrosinase activity. **Abbreviations:** Tyr, tyrosinase; TRP, tyrosine-related protein; DHICA, 5,6-dihydroxyindole-2-carboxylic acid; DHI, 5,6-dihydroxyindole.
Vitiligo

Vitiligo is a relatively frequent pigmentation disorder with partial or complete loss of functional melanocytes in the affected skin areas. There is no racial difference in the risk of acquiring vitiligo. The pathogenesis is not yet clear (autoantibodies, neurohumoral factors, self destruction of the melanocytes by toxic intermediate products of the melanogenesis).

A: Clinical manifestation of vitiligo. Functional melanocytes are lost in clearly defined areas; there is no pigment formation in these areas. B: Melanocyte with pigment granules (melanosomes) that are lost in vitiligo.

Reference: Rassner, 2002
Melanocytic nevus

Melanocytic nevus: A benign pigmented spot on the skin such as a mole (a cluster of melanocytes and supportive tissue that appears as a tan, brown, or flesh-colored spot on the skin. This is the most frequent skin lesion which in most cases are harmless. Melanocytic nevi belong to the most diversified and dynamic skin tumors. Generally they are smaller than 5-6 mm, well pigmented and either flat or raised.

Melanocytic nevus, junctional type. A: In clinical appearance, lesions are small, relatively flat, symmetric, and uniform. B: On histologic examination, junctional nevi are characterized by rounded nests of nevus cells originating at the tips of rete ridges along the dermoepidermal junction.

Melanocytic nevus, compound type. In contrast to the junctional nevus, the compound nevus (A) is more raised and dome-shaped. The symmetry and uniform pigment distribution suggest a benign process. Histologically (B), compound nevi combine the features of junctional nevi (intraepidermal nevus cell nests) with nests and cords of nevus cells in the underlying dermis.

Reference: Robbins & Cotran, 2010
Variant forms of nevocellular nevi

<table>
<thead>
<tr>
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<th>Diagnostic Architectural Features</th>
<th>Diagnostic Cytologic Features</th>
<th>Clinical Significance</th>
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<tbody>
<tr>
<td>Congenital nevus</td>
<td>Deep dermal and sometimes subcutaneous growth around adnexa, neurovascular bundles, and blood vessel walls</td>
<td>Identical to ordinary acquired nevi</td>
<td>Present at birth; large variants have increased melanoma risk</td>
</tr>
<tr>
<td>Blue nevus</td>
<td>Nonnested dermal infiltration, often with associated fibrosis</td>
<td>Highly dendritic, heavily pigmented nevus cells</td>
<td>Black-blue nodule; often confused with melanoma clinically</td>
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<tr>
<td>Spindle and epithelioid cell nevus (Spitz nevus)</td>
<td>Fascicular growth</td>
<td>Large, plump cells with pink-blue cytoplasm; fusiform cells</td>
<td>Common in children; red-pink nodule; often confused with hemangioma clinically</td>
</tr>
<tr>
<td>Halo nevus</td>
<td>Lymphocytic infiltration surrounding nevus cells</td>
<td>Identical to ordinary acquired nevi</td>
<td>Host immune response against nevus cells and surrounding normal melanocytes</td>
</tr>
<tr>
<td>Dysplastic nevus</td>
<td>Large, coalescent intraepidermal nests</td>
<td>Cytologic atypia</td>
<td>Potential precursor of malignant melanoma</td>
</tr>
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</table>

Dysplastic nevus

Frequently larger than 5-6 mm in diameter. Central part raised; similar to junction nevus (A). The tissue section shows atypical nuclei that appear dark after staining. The subjacent dermis has a lamellar, fibroid structure (B).

Reference: Robbins & Cotran, 2010
Maturation sequence of melanocytic nevi

Maturation sequence of nondysplastic melanocytic nevi. A: Normal skin shows only scattered dendritic melanocytes within the epidermal basal cell layer. B: Junctional nevus. C: Compound nevus. D: Dermal nevus. E: Dermal nevus with neurotization (extreme maturation). Nevi may exist at any stage in this sequence for variable periods of time, although many are believed to progress through this sequence.

Reference: Robbins & Cotran, 2010
Chloasma, Lentigo simplex

**Chloasma (Melasma)**
Acquired hyperpigmentation in the face, large patchy, most often chronically persistent, prevalent in women, e.g. during pregnancy or under oral contraceptives.

**Lentigo simplex**
Acquired hyperpigmentation, small patchy, distinctly confined, histologically characterized by an intra-epidermal hyperplasia of melanocytes; as Lentigo simplex harmless.
Dysplastic nevus. A: Numerous clinically atypical nevi on the back. B: One such lesion (inset A) has a compound nevus component (left side of scanning field) and an asymmetric junctional nevus component (right side of scanning field). The former correlates grossly with the more pigmented and raised central zone and the latter with the less pigmented, flat peripheral rim. C: An important feature is the presence of cytologic atypia (irregularly shaped, dark-staining nuclei). The dermis underlying the atypical cells characteristically shows linear, or lamellar, fibrosis.

Reference: Robbins & Cotran, 2010
Lentigo maligna

Lentigo maligna is an irregular, distinctly or diffusely confined lesion of different sizes and with inhomogeneous brown pigmentation and frequent bleech zones. Invasive growth.

Malignant melanoma (type lentigo-maligna melanoma)

Irregular proliferation of melanocytes and confluent nests of melanocytes in Lentigo maligna.

Reference: Rassner, 2002
Tumor progression in the dysplastic nevus

Potential steps of tumor progression in dysplastic nevi. **A:** Lentiginous melanocytic hyperplasia. **B:** Lentiginous junctional nevus. **C:** Lentiginous compound nevus with abnormal architectural and cytologic features (dysplastic nevus). **D:** Early melanoma, or melanoma in radial growth phase (large dark cells in epidermis). **E:** Advanced melanoma (vertical growth phase) with malignant spread into the dermis and vessels. The risk of malignant transformation of any single dysplastic nevus is extremely low but can occur.

Reference: Robbins & Cotran, 2010
Effect on UV on keratinocytes and melanocytes

(1) UV radiation with high or medium intensity induces DNA damage in keratinocytes and melanocytes of the epidermis (red circles in the respective cells). These damages are either repaired by the cells, or they induce apoptosis of the cell, or they lead – following additional mutations – to malignant transformation.

(2) Response of UV-damaged cells after a few days: repair (red circles disappeared), apoptosis (X) or passing on of a mutation to daughter cells (red dot).

(3) Further steps of the repair process: (a) melanogenesis, (b) additional repair, (c) replacement of lost cells by apoptosis by new cells.

(4) Repetitive exposure to UV radiation leads to either reiteration of steps (1–3) or to further mutations in cells that have already undergone mutations. The consequences are malignant transformation and proliferation of transformed cells.

(5) Increased proliferation of cells with multiple mutations.
Melanoma

A: Typically, lesions are irregular in contour and pigmentation. Macular areas correlate with the radial growth phase, while raised areas usually correspond to nodular aggregates of malignant cells in the vertical phase of growth.

B: Radial growth phase, showing irregular nested and single-cell growth of melanoma cells within the epidermis and an underlying inflammatory response within the dermis.

C: Vertical growth phase, demonstrating nodular aggregates of infiltrating cells.

D: High-power view of melanoma cells. The inset shows a sentinel lymph node with a tiny cluster of melanoma cells (arrow) staining for the melanocytic marker HMB-45. Even small numbers of malignant cells in a draining lymph node may confer a worse prognosis.

Reference: Robbins & Cotran, 2010
Signalling pathways in melanoma

Pathways important in melanoma. The PI-3K/PTEN/AKT and BRAF/ERK pathways regulate cell survival and proliferation. Proteins altered in melanoma are indicated by asterisks. Inhibitors of these pathways are being studied as therapeutic agents; some specific examples are listed in red.
Melanoma

Incidence rate, 1995 survey (Europe):
1 in 200 persons in a life-time

Incidence rate, 2002 survey (USA):
1 in 75 persons in a life-time

Incidence rate, 1997 survey (Australia):
*Men:* 1 in 23 persons in a life-time
*Women:* 1 in 33 persons in a life-time

Reference: Rassner, 2002
Melanoma

Malignant melanoma (acrolentigous melanoma). 8 x 4 cm area with nodules of different sizes on the left foot.

Missed chance of early detection of malignant melanoma.

Nodular melanoma derived from a quiet lesion existing on the left calf since birth. The transformation occurred within a few weeks.

Formation of satellite and transit metastases on the right leg a year after removal of a malignant melanoma from the ankle of the same leg (level IV, >5 mm thick = high-risk melanoma).

Reference: Rassner, 2002
Diseases of the cutis

- **Disorders of pigmentation and melanocytes**
  Freckle (ephelis), lentigo, melanocytic nevus, dysplastic nevi, melanoma

- **Benign epithelial tumors**
  Seborrheic keratoses, acanthosis nigricans, fibroepithelial polyp, epithelial cyst, adnexal tumors

- **Premalignant and malignant epidermal tumors**
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  Fungal infections: Candida, Tinea

- **Appendix (slides in German)**
  Diseases of nails and nailbeds
  Diseases of hair and hair follicles
  Diseases of sebaceous and sweat glands
Seborrheic keratoses, acanthosis nigricans

Seborrheic keratoses are common epidermal tumors that occur most frequently in middle-aged or older individuals. They arise spontaneously and are particularly numerous on the trunk, although the extremities, head and neck may also be involved. In people of color, multiple small lesions on the face are termed dermatosis papulosa nigra.

Acanthosis nigricans is a condition marked by thickened, hyperpigmented skin with a "velvet-like" texture; 80% of the cases are benign. The malignant type refers to lesions arising in association with underlying cancers.

Right: Multiple seborrheic keratoses (this patient has a history of metastasizing carcinoma of the rectum).

Left, upper figure: Verucca seborrheica. Part of the epidermis is thickened in a confined area, typical for acanthosis. The keratinocytes are small and monomorph and they resemble basal cells. There are many pseudo horn cysts, typical for verucca seborrheica.

Left, lower figure: Solitary pigmented seborrheic keratosis (acanthosis nigricans); slow growth along with increasing pigmentation.

Pathogenesis: A familial form of both conditions is associated with a germline activating mutation of the fibroblast growth factor receptor type 3 (FGFR3).

Reference: Rassner, 2002 and Robbins & Cotran, 2010
Adnexal tumors of the skin

There are hundreds of benign adnexal tumors which in most cases remain localized and do not spread. Nevertheless, they may be mistakenly taken for skin carcinomas. Adnexal tumors generally appear as solitary papules or as groups of papules.

A: Multiple cylindromas of the forehead. B: The cylindromas consist of islets of basal cells that are arranged in a puzzle-like fashion. C: Multiple trichoepithelioma. D: Basaloid cells are growing in bud-like manner, similar to primitive hair follicles; in addition, microcysts are observed which are filled with keratin.

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<th>Mature Counterpart</th>
<th>Histologic Features</th>
<th>Clinical Significance</th>
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<tr>
<td>Trichoepithelioma</td>
<td>Hair follicle</td>
<td>Hair matrix, outer root sheath differentiation</td>
<td>Multiple trichoepitheliomas, dominant inheritance</td>
</tr>
<tr>
<td>Trichofolliculoma</td>
<td></td>
<td></td>
<td>Association with internal malignancy</td>
</tr>
<tr>
<td>Sebaceous adenoma</td>
<td>Sebaceous gland</td>
<td>Cytoplasmic lipid vacuoles</td>
<td></td>
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<tr>
<td>Sebaceous epithelioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syringocystadenoma</td>
<td>Apocrine gland</td>
<td>Apocrine type (“decapitation”) secretion</td>
<td>May develop in mixed epidermal-adnexal hamartomas of face and scalp termed nevus sebaceous</td>
</tr>
<tr>
<td>papilliferum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syringoma</td>
<td>Eccrine gland</td>
<td>Eccrine ducts lined by membranous eosiophilic cuticles; tadpole-like epithelial structures</td>
<td>May be confused with basal cell carcinoma clinically</td>
</tr>
</tbody>
</table>

Reference: Robbins & Cotran, 2010
Actinic keratosis

The development of epidermal malignancy is typically preceded by a period of progressively worsening dysplastic changes. Actinic keratoses usually occur in sun-damaged skin, exhibit hyperkeratosis and are found with particularly high incidence in lightly pigmented individuals. Actinic keratoses are usually less than 1 cm in diameter; are tan-brown or skin colored and have a rough, sandpaper-like consistency. Some lesions may produce so much keratin that a “cutaneous horn” develops.

A: Excessive scale formation in this lesion has produced a "cutaneous horn." B: Basal cell layer atypia (dysplasia) is associated with marked hyperkeratosis and parakeratosis. C: Progression to full-thickness nuclear atypia, with or without the presence of superficial epidermal maturation, heralds the development of squamous cell carcinoma in situ.

Reference: Robbins & Cotran, 2010
Actinic keratosis

Additional examples of UV-induced precanceroses:


Right, top: Solar keratosis. In the lower part of the epidermis gemmiform proliferates of keratinocytes are observed.

Right, bottom: Solar keratosis. A reddish spot developed two years ago: Risk of development of a squamous cell carcinoma.

**Therapy:** Cryotherapy (for initial lesions) or, respectively, superficial-tangential surgical ablation (for advanced lesions). Local cytostatics (5-FU). Excision if carcinoma is suspected. Protection from UV light is indispensable.

Reference: Rassner, 2002
Squamous cell carcinoma

Squamous cell carcinoma is the second most common tumor arising on sun-exposed sites in older people, exceeded only by basal cell carcinoma. These tumors have a higher incidence in men than in women. Less than 5% of these tumors metastasize to regional nodes. The most important pathogenic causes for squamous cell carcinoma is UV-induced DNA damage. Tumor incidence is proportional to the degree of life-time sun exposure. An increased risk for tumor development exists in patients with immunosuppression whereby viral infects (e.g. HPV) play a crucial role.

Multiple tumors caused by light. This patient had continuous UV exposition for many years (professionally and privately). Ulceration accompanied by inflammation around the tumors.

A: Lesions are often nodular and ulcerated as seen in this scalp tumor. B: Tongues of atypical squamous epithelium have transgressed the basement membrane, invading deeply into the dermis. C: A magnified image reveals invasive tumor cells showing enlarged nuclei with angulated contours and prominent nucleoli.

Reference: Rassner, 2002 and Robbins & Cotran, 2010
Keratoacanthoma

Keratoacanthomas are rapidly growing neoplasms that clinically and histologically resemble squamous cell carcinomas. In contrast to the latter, spontaneous disappearance of the tumor may happen. Keratoacanthomas appear on sun-exposed facial skin of persons >50 years and are more frequently observed in men than women.

A: This keratoacanthoma consists of a nodule with crater-like appearance and a prominent central keratin cone.

B: The crater-like structure is well visible in the tissue section.

C: Higher magnification shows pearly squamous epithelial cells and central islets with eosinophil keratin.

Reference: Rassner, 2002
Basal cell carcinoma

Basal cell carcinoma is the most common invasive cancer in humans, with nearly 1 million estimated cases per year in the USA. These are slowly growing tumors that rarely metastasize. They mainly occur in sun-exposed sites of lightly pigmented persons and they have a higher incidence in immunosuppressed patients. Pathogenetically, the PTCH gene seems to play a crucial role in a genetic syndrome associated with basalioma development.

Top and bottom: Early stage of two cases of nodular basalioma, slowly growing (since 3 years), without pain.

Pearly, telangiectatic nodules (A) are composed of nests of uniformly atypical basaloid cells within the dermis (B) that are often separated from the adjacent stroma by thin clefts (C), an artifact of sectioning.

Reference: Robbins & Cotran, 2010
Normal and oncogenic hedgehog signaling. **Left**, Normally, PTCH and SMO form a receptor complex that binds sonic hedgehog (SHH). In the absence of SHH, PTCH blocks SMO activity. When SHH binds PTCH, SMO is released to trigger a signal transduction cascade that leads to activation of GLI1 and other transcription factors. **Right**, Mutations in *PTCH*, and less often in *SMO*, allow SMO to signal without ligand binding and underlie the nevoid basal cell carcinoma (Gorlin) syndrome.
Langerhans cell histiocytosis

The Langerhans cell histiocytosis is a clonal proliferation of Langerhans cells of the epidermis. There are different forms of histiocytoses affecting various organs or tissues. The acute disseminated Langerhans cell histiocytosis (Letterer-Siwe disease) appears mainly at the age of <2 years; rarely adult people are affected. In the skin, a large number of lesions are visible, resembling the manifestation of a seborrheic dermatitis. The pathogenesis is largely unknown.

A: The lesions can appear in different forms and they display an erythema-like scale structure. B: Strong infiltration of the dermis with mononuclear cells. C: Immunohistochemical staining of CD1a antigen confirms the origin from Langerhans cells.

Reference: Rassner, 2002
Keloids and fibromas

**Keloids**

A keloid is a type of scar which is composed mainly of type III (early stage) or type I (late stage) collagen. It is a result of an overgrowth of granulation tissue at the site of a healed skin injury which is then slowly replaced by collagen type I. Keloids are firm, rubbery lesions or shiny fibrous nodules, and can vary from pink to flesh-coloured or red to dark brown in colour. A keloid scar is benign, non-contagious and sometimes accompanied by severe itchiness and pain.

**Fibroma**

Fibromas are benign tumors that are composed of fibrous or connective tissue. They can grow in all organs, arising from mesenchyme tissue. The term “fibroblastic” or “fibromatous” is used to describe tumors of the fibrous connective tissue. When the term fibroma is used without modifier, it is usually considered benign, with the term fibrosarcoma reserved for malignant tumors.

Formation of a keloid in a young girl a few months after a splash-like scalding: distinctly but irregularly confined squamous-type thickened skin areas. Pain upon touch or compression.

Hard fibroma (dermatofibroma). No pain upon touch or compression.

Reference: Rassner, 2002
### Tumors of the dermis

**Benign fibrous histiocytoma (dermatofibroma).** This firm, tan papule on the leg (A) shows a localized proliferation of benign-appearing spindle cells within the dermis (B). C: Note the characteristic overlying epidermal hyperplasia and the tendency of fibroblasts to surround individual collagen bundles.

**Dermatofibrosarcoma protuberans.** A: The tumor usually presents as a flesh-colored to erythematous nodule, and has a fibrotic appearance on sectioning. B + C: Characteristic storiform cellularity is noted histologically, and the lesion often infiltrates the subcutis in a manner that resembles "Swiss cheese" to some afficianados.
Tumors of the dermis

Cutaneous T-cell lymphoma. **A**: Several ill-defined, erythematous, often scaling, and occasionally ulcerated plaques. **B**: Microscopically, there is an infiltrate of atypical lymphocytes that show a tendency to accumulate beneath the epidermal layer and to invade the epidermis.

Mastocytosis. **A**: Solitary mastocytoma in a 1-year-old child. **B**: By routine histology, numerous ovoid cells with uniform, centrally located nuclei are observed in the dermis. **C**: Giemsa staining reveals purple, "metachromatic" granules within the cytoplasm of the cells.

Reference: Robbins & Cotran, 2010
Diseases of the cutis

- **Disorders of pigmentation and melanocytes**
  - Freckle (ephelis), lentigo, melanocytic nevus, dysplastic nevi, melanoma

- **Benign epithelial tumors**
  - Seborrheic keratoses, acanthosis nigricans, fibroepithelial polyp, epithelial cyst, adnexal tumors

- **Premalignant and malignant epidermal tumors**
  - Actinic keratosis, squamous cell carcinoma, basal cell carcinoma

- **Tumors of the dermis**
  - Benign fibrous histiocytoma (dermatofibroma)

- **Tumors of cellular migrants to the skin**
  - Mycosis fungoides, mastocytosis

- **Disorders of epidermal maturation**
  - Ichthyosis

- **Acute inflammatory dermatoses**
  - Acute and chronic eczematous dermatitis, exanthemas (urticaria, erythema multiforme)

- **Chronic inflammatory dermatoses**
  - Psoriasis, seborrheic dermatitis, lichen planus

- **Blistering (bullous) diseases**
  - Inflammatory blistering disorders (pemphigus, bullous pemphigoid, dermatitis herpetiformis), non-inflammatory blistering disorders (epidermolysis bullosa, porphyria)

- **Disorders of epidermal appendages**
  - Acne vulgaris, rosacea

- **Collagenoses (connective tissue disease)**
  - Cutaneous lupus erythematosus, scleroderma

- **Infections**
  - Viral infections (Herpes simplex, VZV, HPV)
  - Bacterial infections (B. anthracis, B. burgdorferi, Staphylococci)
  - Fungal infections: Candida, Tinea

- **Appendix (slides in German)**
  - Diseases of nails and nailbeds
  - Diseases of hair and hair follicles
  - Diseases of sebaceous and sweat glands
Non-allergic and allergic hypersensitivity reactions

Non-allergic reactions

Non-allergic contact dermatitis: irritant contact dermatitis by chemical irritants (e.g. various chemical solvents, powdered chemicals, latex, surfactants, alkalis, cleaners, or plants) or by physical irritants.

Pseudoallergy: Although pseudoallergies have symptoms very similar to “true” allergies, they are not involved with the immune system. The allergy-like symptoms are not reactions with antibodies, rather, certain foods cause the reactions directly. The severity of the reaction depends on the dose. Pseudoallergens include various food additives, histamine, biogenic amines, salicylic acid.

Allergic reactions

Type I reactions: immediate hypersensitivity reactions (e.g. urticaria, anaphylactic shock. Liberation of mast cell substances.

Type II reactions: cytolytic antibody reactions (e.g. immune cytopenic purpura. Antigen-antibody reactions (IgG, IgM).

Type III reactions: immune complex mediated reactions (e.g. vasculitis allergica). Continuous formation of immune complexes during chronic infections, autoimmune reactions.

Type IV reactions: cell-mediated (delayed) reactions e.g. allergic contact eczema. Antigen T cell reactions with different consecutive reactions and tissue damage.
Non-allergic and allergic contact dermatitis

Non-allergic contact dermatitis (irritant contact dermatitis) of a cleaner lady.

This disease is usually reversible; if the exposition is persisting, the disease is recurrent or chronic-progressive with tendency to develop to chronic non-allergic contact eczema.

*Therapy:* Exposure to irritants must be avoided, e.g. by wearing gloves or applying protection creams.

Eczematous dermatitis. **A:** Acute allergic contact dermatitis, with numerous vesicles on erythematous skin due to antigen exposure (in this case, laundry detergent in clothing). **B:** Histologically, intercellular edema within the epidermis creates small, fluid-filled intra-epidermal vesicles.

Reference: Rassner, 2002 and Robbins & Cotran, 2010
Eczemas

“Eczema” is a medical term that has been used for more than 2000 years. Its origin is found in Greek medicine (ekzein = to well, to boil up). Eczemas are amongst the most frequent and important skin diseases. Within the group of inflammatory skin diseases eczemas comprise non-infectious inflammatory dermatoses with the following characteristics:

1. confined to the skin, obligate injury of the epidermis
2. no scars after healing
3. inherited or acquired disposition for eczema
4. progression frequently chronic or chronic-recurrent
5. different types of eczemas:
   - irritant contact eczema (irritant contact dermatitis)
   - allergic contact eczema (allergic contact dermatitis)
   - atopic contact eczema
Stages of eczema development

A: Initial dermal edema and perivascular infiltration by inflammatory cells is followed within 24 to 48 hours by epidermal spongiosis and microvesicle formation (B). C, Abnormal scale, including parakeratosis, follows, along with progressive acanthosis (D) and hyperkeratosis (E) as the lesion becomes chronic.

Reference: Robbins & Cotran, 2010
Pathogenesis of allergic eczema

Antigen is taken up by Langerhans cells and transported to regional lymph nodes where the antigens is presented to CD4+ T cells, thus activating these cells. After renewed antigen exposure, the memory T cells migrate to the affected tissue where they release cytokines and chemokines. This provokes the invasion of inflammatory cells leading to (local) inflammation.

Reference: Robbins & Cotran, 2010
Allergic contact eczema

Acquired allergic contact eczema, sporadically induced by exogenic allergens (eczematogens) and subsequent allergic type IV reaction resulting in eczematous dermatitis.

Acute allergic contact eczema
(acute phase)

Chronic allergic contact eczema
(exsudative phase)

Edematous state of the epidermis caused by intercellular edema (spongiosis). The skin is covered by a serum scab; infiltration by lymphocytes.

The epidermis is irregularly broadened (acanthosis). The spongiosis is markedly reduced (compared to the acute phase). The stratum papillare is fibrotically condensed.

Reference: Rassner, 2002
Atopic eczema

Atopic eczema (neurodermitis atopica): complex eczematous disease, not precisely definable, provoked by environmental allergens and impaired immune responses as well as non-immunological causes (psycho- and neurovegetative disorders). Frequently observed in combination with other forms of atopia.

Atopia: (atopos (gr.) = crazy) includes various clinical manifestations of hypersensitivity reactions of type I. The reaction is triggered by degranulation of mast cells after binding of allergen-specific IgE molecules to their Fc receptor. Clinical manifestations include atopic eczema, rhinitis allergica, allergic asthma, allergic conjunctivitis, allergic enteritis.

Atopic eczema of wrist, popliteal fossa or cubital joint. Reddish-brownish areas and papules.

Atopic eczema on fingertips (pulpitis sicca)

Young patient (18 years old) previously suffered from allergic rhinoconjunctivitis (induced by grass and rye pollen); for the first time his fingertips and toestips were affected.

Infantile or neonatal seborrheic dermatitis (cradle cap or milk crust) is a yellowish/reddish, patchy, greasy and scaly skin rash (atopic eczema) with erosions and purulent crusts.

Reference: Rassner, 2002
Exanthems

Exanthems (*gr. exanthemas*) are inflammatory disorders of the skin which – in contrast to eczemas – may also involve mucosas and extracutaneous organs and mainly affect connective tissue of blood vessels (hyperemia, edemas, infiltrates). Exanthems manifest themselves as erythemas, urticarias or papulous Infiltrates. Healing without residual defects.

1. **Urticarias**: may have an allergic or non-allergic origin, with the possible complication of an anaphylactic reaction. Urticarias are usually confined to the skin with a patchy appearance.

2. **Angioedema**: is the subcutaneous equivalent of an urticaria reaction which may occur alone or in combination with urticaria.

   Allergische Angiödem ausgelöst durch einen Bienenstich in der Nähe der Oberlippe.

   Allergic urticaria induced by penicillin in combination with jeans worn too tightly.

3. **Anaphylactic reactions and shock**: maximal form of allergic immediate reactions with acute symptomatology.

Reference: Rassner, 2002
Erythema multiforme, drug exanthem

Erythema multiforme is an uncommon, self-limited disorder that seems to be a hypersensitivity reaction to certain infections and drugs. Erythema multiforme or drug exanthems are usually confined to the skin. The clinical morphological appearance is quite diverse (maculate, maculate-papulous, rarely psoriatic, bullous).

**Drug exanthem** caused by cephalosporin therapy.

**Bullous drug exanthem** on the left arm, caused by sulfonamide (8 days after application).

**Fixed drug exanthem**: This patient has a recurrent skin lesion at exactly the same location after ingesting a phenacetin-containing painkiller.

**Erythema multiforme.**

A: The target-like clinical lesions consist of a central blister or zone of epidermal necrosis surrounded by macular erythema.

B: Early lesions show lymphocytes collecting along the dermoepidermal junction where basal keratinocytes have begun to become vacuolated. With time, necrotic/apoptotic keratinocytes accumulate in the overlying epithelium.

Reference: Rassner, 2002 and Robbins & Cotran, 2010
Psoriasis

Psoriasis (vulgaris) is a common inflammatory dermatosis affecting as many as 1–2 % of all ages of the population. It most frequently affects the skin of the elbows, knees, scalp, lumbosacral areas, intergluteal cleft, and glans penis. Psoriasis may be associated with arthritis, myopathy, enteropathy, spondylitic joint disease and acquired immunodeficiency. The typical lesion is a well-demarcated, pink to salmon-colored plaque covered by loosely adherent silver-white scales.

Clinical evolution of psoriasis. A: Early and eruptive lesions may be dominated by signs of inflammation, including small pustules and erythema (left). Established, chronic lesions demonstrate erythema surmounted by characteristic silver-white scale (right). B: Histologically, established lesions demonstrate marked epidermal hyperplasia, parakeratotic scale, and neutrophils within the superficial epidermal layers.

Pathogenesis

The pathogenesis of psoriasis is multifactorial, with an important genetic and environmental contribution. There is a strong association between psoriasis and the HLA-Cw*0602 allele in about 10% of the patients. Thus other factors interact with this MHC molecule in causing disease susceptibility. Sensitized populations of CD4+ TH1 and TH17 cells and activated CD8+ effector T cells enter the skin and accumulate and interact in the epidermis. Cytokines stimulate keratinocyte growth.
Lichen planus

Lichen planus is usually a self-limited disease and most commonly resolves spontaneously 1–2 years after onset, often leaving zones of proinflammatory hyperpigmentation. Mucosal lesions may persist for years. Squamous cell carcinoma has been noted to occur in chronic mucosal and paramucosal lesions of lichen planus. The characteristics include the “six p’s”: pruritic, purple, polygonal, planar papules and plaques.

Histologically, lichen planus is characterized by a dense, continuous infiltrate of lymphocytes along the dermo-epithelial junction, a prototypic example of interface dermatitis. Details of the pathogenesis are not known.

A: This flat-topped pink-purple, polygonal papule has a white lacelike pattern that is referred to as Wickham stria.

B: Biopsy specimen demonstrating a bandlike infiltrate of lymphocytes at the dermoepidermal junction, hyperkeratosis, hypergranulosis and pointed rete ridges (sawtoothing) as a result of chronic basal cell layer injury.

Reference: Robbins & Cotran, 2010
Pemphigus

Pemphigus is a blistering disorder caused by autoantibodies that result in the dissolution of intercellular attachments within the epidermis and mucosal epithelium. There are different forms of pemphigus, the most abundant being pemphigus vulgaris (80%). Generally, pemphigus is a rare disease appearing in the 4th to 6th decade of life. Men and women are equally affected.

Histologically, the common denominator of all forms of pemphigus is acantholysis, the dissolution or lysis of intercellular adhesions that connect squamous epithelial cells. Acantholytic cells dissociated from one another, lose the polyhedral shape and become rounded. The suprabasal acantholytic blister that forms is characteristic for pemphigus vulgaris.

Pemphigus vulgaris. A: Eroded plaques are formed on rupture of confluent, thin-roofed bullae, here affecting axillary skin. B: Suprabasal acantholysis results in an intraepidermal blister in which rounded (acantholytic) epidermal cells are identified (inset). C: Ulcerated blisters in the oral mucosa are also common as seen here on the mucosal portion of the lip.

Reference: Robbins & Cotran, 2010
Desmogleins 1 and 3 (Dsg1, Dsg3) are functionally interchangeable components of desmosomes, but have different distributions within the epidermis (left panel). In pemphigus vulgaris, autoantibodies against Dsg1 and Dsg3 cause blisters in the deep suprabasal epidermis, whereas in pemphigus foliaceus, the autoantibodies are against Dsg1 alone, leading to superficial, subcorneal blisters. In bullous pemphigoid, autoantibodies bind BPAG2, a component of the hemidesmosomes, leading to blister formation at the level of the lamina lucida of the basement membrane. Dermatitis herpetiformis is caused by IgA autoantibodies to the fibrils that anchor hemidesmosomes to the dermis. The various forms of epidermolysis bullosa are caused by genetic defects in genes encoding proteins that either form or stabilize desmosomes or hemidesmosomes. α6/β4, α6/β4 integrin.

Reference: Robbins & Cotran, 2010
Pemphigus

Pathogenesis:
(see also previous slide)

Form of disease:

Schematic representation of histologic levels of blister formation. A: In a subcorneal blister the stratum corneum forms the roof of the bulla (as in pemphigus foliaceus). B: In a suprabasal blister a portion of the epidermis, including the stratum corneum, forms the roof (as in pemphigus vulgaris). C: In a subepidermal blister the entire epidermis separates from the dermis (as in bullous pemphigoid).

Reference: Robbins & Cotran, 2010
Epidermolysis bullosa constitutes a group of disorders caused by inherited defects in structural proteins that lend mechanical stability to the skin. The common feature is a proclivity to form blisters at sites of pressure, rubbing or trauma, at or soon after birth. In the simplex type, defects of the basal layer of the epidermis result from mutations in the genes encoding keratins 14 or 5. These two keratins normally pair with one another. In the junctional type, blisters occur in otherwise histologically normal skin at precisely the level of the lamina lucida (see tissue section below, right). In the scarring dystrophic type, blisters develop beneath the lamina densa, in association with rudimentary or defective anchoring fibrils; the gene involved is COL7A1, encoding type VII collagen. Squamous cell carcinoma can sometimes arise in these chronic blisters.

Epidermolysis bullosa. A: Junctional epidermolysis bullosa showing typical erosions in flexural creases. B: A noninflammatory subepidermal blister has formed at the level of the lamina lucida.
Diseases of the cutis

- **Disorders of pigmentation and melanocytes**
  Freckle (ephelis), lentigo, melanocytic nevus, dysplastic nevi, melanoma

- **Benign epithelial tumors**
  Seborrheic keratoses, acanthosis nigricans, fibroepithelial polyp, epithelial cyst, adnexal tumors

- **Premalignant and malignant epidermal tumors**
  Actinic keratosis, squamous cell carcinoma, basal cell carcinoma

- **Tumors of the dermis**
  Benign fibrous histiocytoma (dermatofibroma)

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  Mycosis fungoides, mastocytosis

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  Ichthyosis

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  Acute and chronic eczematous dermatitis, exanthemas (urticaria, erythema multiforme)

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  Cutaneous lupus erythematosus, scleroderma

- **Infections**
  Viral infections (Herpes simplex, VZV, HPV)
  Bacterial infections (B. anthracis, B. burgdorferi, Staphylococci)
  Fungal infections: Candida, Tinea

- **Appendix (slides in German)**
  Diseases of nails and nailbeds
  Diseases of hair and hair follicles
  Diseases of sebaceous and sweat glands
Acne vulgaris is virtually universal in adolescents and affects both males and females, whereby males tend to have a more severe disease. It is believed to occur as a result of physiologic hormonal variations and alterations in hair follicles, particularly the sebaceous gland.

Acne is divided into noninflammatory and inflammatory types. Noninflammatory acne consists of open and closed comedones (see below and next slide). Inflammatory acne is characterized by erythematous papules, nodules and pustules. Severe variants (e.g. acne conglobata) result in sinus tract formation and physical scarring.

**Acne vulgaris**

Noninflammatory type

B: A hair shaft pierces the follicular epithelium, eliciting inflammation and fibrosis. C: Open comedone.

Inflammatory type

Reference: Robbins & Cotran, 2010
Acne vulgaris

Forms and role of comedones

Comedones are the skin-coloured, small bumps (papules) frequently found on the forehead and chin of persons with acne.

- Open comedones are blackheads; black because of surface pigment (melanin) rather than dirt.
- Closed comedones are whiteheads (microcysts); the follicle is completely blocked. Propionibacteria may infect the comedones and accentuate the inflammation.
- Macrocomedones are facial closed comedones that are larger than 2-3 mm in diameter.
- Solar comedones are found on the cheeks and chin of older people, and are thought to be due to sun damage.
- Larger and deeper uninflamed bumps are called nodules. They are more common on the trunk than on the face.
Morbus Pringle or tuberous sclerosis is a hereditary blastoma-forming disorder of connective tissue and glia. Formation of nodules in the skin, brain and other organs.

**Acne vulgaris**
Noninflammatory type

**Acne vulgaris**
Inflammatory type

**Morbus Pringle**
Frequently very severe disease with markedly reduced physical appearance. Other constraints include neurologic symptoms and a reduced life expectancy.

Reference: Rassner, 2002 and Robbins & Cotran, 2010
Collagenoses (connective tissue diseases)

Connective tissue diseases (collagenoses) are acquired, chronic, mostly severe and frequently life-threatening diseases. They are caused by autoimmunity, i.e. immune responses against the body’s own cells and tissues. Autoantibodies (e.g. non-organ-specific antinuclear antibodies) and autoreactive immune cells attacking components of the normal tissue. Examples: systemic lupus erythematoses, scleroderma, rheumatoid arthritis, Sjögren’s syndrome, Graves’ disease.

Chronic cutaneous lupus erythematoses

This patient has suffered from a slowly increasing number of scarring skin lesions over the last 8 years.

Atrophic epidermis with follicular hyperkeratosis.
Collagenoses (connective tissue diseases)

Scleroderma

Initial symptoms of scleroderma typically include thickening and hardening of the skin of fingers, toes and/or the face. There are two forms of scleroderma: (1) limited systemic scleroderma (chronic cutaneous scleroderma) and (2) diffuse systemic scleroderma. The latter is characterized by systemic sclerosis of the connective tissue of the skin and inner organs. Vascular symptomatology at the beginning of the disease: The small blood vessels narrow in fingers, toes and face, accompanied by painful convulsive attacks (Raynaud’s phenomenon). The consequence is asphyxia which may cause, reflexively, an overfilling of the arteries with blood (hyperemia). Scleroderma is more often seen in women than in men (5:1) and it has a chronic progressive course with many different forms of disease dynamics; progressively increasing functional impairment of the skin and inner organs, frequently lethal outcome.

**Systemic scleroderma** (early phase)
Progressive swelling/thickening of the fingers.

**Systemic scleroderma** (late phase)
Slowly progressive disease over ten years (note bended fingers).

Reference: Rassner, 2002
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  Viral infections (Herpes simplex, VZV, HPV)
  Bacterial infections (B. anthracis, B. burgdorferi, Staphylococci)
  Fungal infections: Candida, Tinea

- Appendix (slides in German)
  Diseases of nails and nailbeds
  Diseases of hair and hair follicles
  Diseases of sebaceous and sweat glands
Viral infections of the skin

Viral infections
Several common childhood viral infections cause widespread exanthems (rashes), e.g.
• Rubella (German measles)
• Morbilli (measles)
• Varicella (chickenpox)
Other viruses may lead to warts (e.g. human papilloma virus, HPV) or blistery-erosive infections (e.g. Herpes simplex).

Herpes simplex
Superficial, blistery-erosive infection of the skin. Various forms, depending on the viral subtype and the resistance/defence of the host.

Varicella zoster virus (VZV)
Varicella-zoster virus (VZV) is an extremely common virus responsible for a wide variety of dermatologic and neurologic manifestations. More than 90% of adults have serologic evidence of VZV infection. The skin manifestations of VZV are generally more severe than those observed with H. simplex. VZV not only affects skin and mucosa, but also other organs (e.g. peripheral nerves).
Verrucae (warts)

Verrucae are common lesions of children and adolescents although they may occur at any age. They are caused by human papillomaviruses (HPV). Transmission usually involves direct contact between individuals or auto-inoculation. Verrucae are generally self-limiting, regressing spontaneously within 6 months to 2 years.

Verruca vulgaris. A: Multiple papules with rough pebble-like surfaces (A1: magnification). B (low power) and C (high power): histology of the lesions showing papillomatous epidermal hyperplasia and cytopathic alterations that include nuclear pallor and prominent keratohyaline granules. D: In situ hybridization demonstrating viral DNA within epidermal cells.

Reference: Rassner, 2002 and Robbins & Cotran, 2010
Anthrax (cutaneous form)

Anthrax is an acute bacterial disease caused by the *Bacillus anthracis*. Whereas the cutaneous form is usually reversible, anthrax of the lungs or intestines is frequently lethal.

Anthrax of the skin develops after an incubation period of 1–3 days at the site of infection with the formation of small pustules (*pustula maligna*) that develop into anthrax carbuncles (skin lesions) surrounded by inflammatory edema and ulceration. Fever and swelling of regional lymph nodes; spontaneous healing.

**A**: Characteristic black incrustation and erosions as well as massive edema on back of the hand. The lesions do not cause pain.

**B-D**: Progression of a lesion on the face of a person during 7 days. On day 0 (**B**) small black incrustations. On day 1 (**C**) formation of extended edema and ulceration. On day 7 (**D**) begin of the healing process.

Reference: Rassner, 2002 and Robbins & Cotran, 2010
Anthrax

Pathophysiology of Anthrax

Pathogenic *Bacillus anthracis* endospores reach a primary site in the subcutaneous layer, gastrointestinal mucosa, or alveolar spaces. For cutaneous and gastrointestinal anthrax, low-level germination occurs at the primary site, leading to local edema and necrosis. Endospores are phagocytosed by macrophages and germinate. Macrophages containing bacilli detach and migrate to the regional lymph node. Vegetative anthrax bacilli grow in the lymph node, creating regional hemorrhagic lymphadenitis. Bacteria spread through the blood and lymph and increase to high numbers, causing severe septicemia. High levels of exotoxins are produced that are responsible for overt symptoms and death. In a small number of cases, systemic anthrax can lead to meningeal involvement by means of lymphatic or hematogenous spread. In cases of pulmonary anthrax, peribronchial hemorrhagic lymphadenitis blocks pulmonary lymphatic drainage, leading to pulmonary edema. Death results from septicemia, toxemia, or pulmonary complications and can occur one to seven days after exposure.

The inset shows the effects of anthrax exotoxins on macrophages. Vegetative anthrax bacilli secrete two exotoxins that are active in host cells. Edema toxin is a calmodulin-dependent adenylate cyclase that increases intracellular levels of cyclic AMP (cAMP) on entry into most types of cell. This is believed to alter water homeostasis, resulting in massive edema. Lethal toxin is a zinc metalloprotease that causes a hyperinflammatory condition in macrophages, activating the oxidative burst pathway and the release of reactive oxygen intermediates, as well as the production of proinflammatory cytokines, such as tumor necrosis factor (TNF-α) and interleukin-1β, that are responsible for shock and death. MAPKK denotes mitogen-activated protein kinase kinase.

Reference: Rassner, 2002 and Robbins & Cotran, 2010
**Lyme borreliosis**

**Lyme borreliosis** (erythema migrans disease) is caused by the gram-negative spirochete *Borrelia burgdorferi* (originally isolated by Burgdorfer et al., 1982). The name *Lyme borreliosis* is associated with Old Lyme, Connecticut, where a dozen children suffered from an *erythema migrans* and later from lyme arthritis in 1975.

**Pathogenesis:** Following infection, *B. burgdorferi* is recognized by polynuclear cells of the innate immune system (via Toll-like receptors that bind bacterial lipoproteins): inflammatory reaction (erythema migrans). The mechanism leading to the chronic form of Lyme disease are not yet understood. In about 90% of the cases of Lyme arthritis, antibiotics lead to a complete recovery; in about 10% of the patients, the disease persists.

**Ixodes** ticks which transmit the *B. burgdorferi*. **North America:** *Ixodes scapularis* (photo) und *I. pacificus*. **Europe:** *Ixodes ricinus*. Ticks in the adult and nymph state (*upper part:* comparison with a sesame seed (right) and mm scale). **Lower part:** Unfed and fed (48 h) ticks in the nymph state.

**Acrodermitis** is observed after about 12 months after the initial infection and is manifested as unilateral extensive, atrophic lesion of the skin (cigarette paper-type, purple, wrinkly, hairless and transparent skin). Frequently pain in the subjacent joints, along with formation of scars.

**Erythema migrans:** The inflammation begins several days to 8 weeks after the tick bite at the site of the bite (A) and slowly expands.
Impetigo contagiosa

Impetigo contagiosa is a superficial bacterial infection of the skin; it is highly contagious and usually involves exposed skin such as the face and the hands, most frequently found in children. The most abundant pathogen is *staphylococcus aureus* but *streptococcus pyogenes* may also be involved. The infection may either cause small or large blisters (vesicles). The incubation time of the pathogen is 2–10 days. Hygiene is most important for the healing process which may be assisted by fusidic acid.

Reference: Rassner, 2002
Mycoses

Candidiasis
Residing normally in the skin, mouth, gastrointestinal tract, and vagina, Candida species usually live as benign commensals and seldom produce disease in healthy people. However, C. albicans is the most frequent cause of fungal infections. These infections may be confined to the skin or mucosa or may disseminate widely in the body. C. albicans may also be sexually transmitted, leading to infections of the glans penis or vulva and vagina (vulvovaginitis). Babies may suffer from diaper mycosis caused by candida originating via intestinal infection. Mycoses are manifested as erythematous, vesicular or pustular infections.

Superficial fungal infections
*Tinea* capitis, *tinea corporis*, *tinea pedis* and other variants cause superficial infections confined to the stratum corneum, as opposed to deep fungal infections which involve the dermis and subdermis. *Tinea pedis* affects 30–40% of the population at some time in their lives.

Reference: Rassner, 2002 and Robbins & Cotran, 2010
Zooparasite-induced skin disorders

Zooparasite-induced disorders that also affect the skin are caused by different living parasites such as worms, insects or protozoa. In addition to the two examples of nematodes infection shown here, skin disorders may also be induced by trypanosoma, leishmania, entamoeba, trematodes, cestodes, and arthropodes.

Filaria (wucheria) bancrofti

Lymphatic filariosis is caused by two related nematodes: *Filaria (wucheria) bancrofti* and *brugia malayi*. These worms are widespread parasites and the causative agents of *elephantiasis*. Propagation of infectious larvae by mosquitoes. Adult worms live in lymph glands and ducts. In severe cases, lymph passage can be blocked, causing enormous tissue growth (*elephantiasis,* see photo).

Larvala migrans cutanea

Larvae of different nematodes may penetrate and invade the skin of animals or humans. The humans are dead-end hosts, and the nematodes, after aimless digging, will die within weeks or months.

Reference: Rassner, 2002
Zooparasite-induced skin disorders

Louse infestation

Human lice are hematophagous permanent ectoparasites with marked host specificity: Headlouse (pediculus capitis), clothes louse (pediculus vestimentorum), crab louse (Pediculus pubis). Size 2–4 mm. Egg tray into head hair, pubic hair, underwear. Generation time: 2–3 weeks.

Cimicosis: blood-feeding bedbugs

The bedbug (cimex lectularius) is a hematophagous temporary ectoparasite (5 mm long) which is bloodsucking at night: the result are itchy lesions (urticarias) with central hemorrhage at the injection site that later transform into papules. Bedbugs are stinking (secretion).

Reference: Rassner, 2002
Diseases of the cutis

- Disorders of pigmentation and melanocytes
  Freckle (ephelis), lentigo, melanocytic nevus, dysplastic nevi, melanoma

- Benign epithelial tumors
  Seborrheic keratoses, acanthosis nigricans, fibroepithelial polyp, epithelial cyst, adnexal tumors

- Premalignant and malignant epidermal tumors
  Actinic keratosis, squamous cell carcinoma, basal cell carcinoma

- Tumors of the dermis
  Benign fibrous histiocytoma (dermatofibroma)

- Tumors of cellular migrants to the skin
  Mycosis fungoides, mastocytosis

- Disorders of epidermal maturation
  Ichthyosis

- Acute inflammatory dermatoses
  Acute and chronic eczematous dermatitis, exanthemas (urticaria, erythema multiforme)

- Chronic inflammatory dermatoses
  Psoriasis, seborrheic dermatitis, lichen planus

- Blistering (bullous) diseases
  Inflammatory blistering disorders (pemphigus, bullous pemphigoid, dermatitis herpetiformis), non-inflammatory blistering disorders (epidermolysis bullosa, porphyria)

- Disorders of epidermal appendages
  Acne vulgaris, rosacea

- Collagenoses (connective tissue disease)
  Cutaneous lupus erythematosus, scleroderma

- Infections
  Viral infections (Herpes simplex, VZV, HPV)
  Bacterial infections (B. anthracis, B. burgdorferi, Staphylococci)
  Fungal infections: Candida, Tinea

- Appendix (slides in German)
  Diseases of nails and nailbeds
  Diseases of hair and hair follicles
  Diseases of sebaceous and sweat glands
Appendix: Diseases of skin adnexes

**Erkrankungen von Nagel und Nagelbett**
- Erbliche Nageldystrophien
- Nagelveränderungen bei Genodermatosen
- Warzen
- Paronychie
- Nagelmykosen
- Nagelbildungsstörungen durch verschiedene Faktoren

**Haare und Haarfollikel**
- Erbliche Bildungsstörungen
- Follikulitis und Furunkel
- Trichomykosen
- Alopecie
- Hirsutismus
- Haarerkrank. durch verschiedene Faktoren; Neubildungen

**Erkrankungen der Schweissdrüsen**
- Erbkrankheiten, Fehlbildungen
- (Genuine) Hyperhidrose
- Miliaria
- Dyshidrosissyndrom
- Hidrandenitis
- Störungen durch versch. Faktoren; Neubildungen

**Reference: Rassner, 2002**
Diseases of nail and nail bed

Nägel (Unguis, Onyx = Nagel) sind Hautadnexe in Form taschenartiger Kutiseinstülungen an Finger- und Zehenendgliedern mit Umdifferenzierung der Hornschicht zur Nagelplatte (hartes Nagelkeratin).

Erbliche Nageldystrophien

Pachyonychia congenita
Genetisch heterogene Gruppe von angeborener, hypertropher Dystrophie (Keratin synthetestörungen) mit verdickten, tütenförmig eingerollten Nagelplatten und subungualen Keratosen.

Epidermolysis bullosa dystrophica
Durch lokale Vernarbung allmählicher Verlust der Finger bzw. der Fussnägel.

Nagelorgan

1 Nagelfalz, proximal, lateral (Perionychium)
2 Nagelhäutchen
3 Nagelplatte
4 Matrix
5 Nagelbett
6 Hyponychium
7 Lunula

Nagelveränderungen bei Genodermatosen

Morbus Pringle
Koenen-Tumoren bei Morbus Pringle: subunguale bzw. paraunguale Fibrome.

Psoriasis
Die psoriatische Verhornungsstörung kann in der Nagelmatrix lokalisiert sein, im Nagelbett, Hyponychium oder von Nagelmatrix und Nagelbett ausgehen.

Reference: Rassner, 2002
Erworbene Nageldystrophien

Subunguale Warzen
In diesem Beispiel langsame Entwicklung über zwei Jahre. - **Generell**: die häufigste virale Infektion des Nagels sind Viruswarzen. Therapie: rechtzeitige Kryotherapie in Lokalanästhesie, lokale Warzenmittel (z.B. Fluorouracil).

Nail dystrophies

Paronychie durch Staphylokokken

Onychomykose (dystrophische Form)

Onychomykose (distal-subunguale Form mit eingewachsenem Nagel)

Reference: Rassner, 2002
Nail dystrophies

Exogene Nagelbildungsstörungen
Physikalische und chemische Noxen sowie Medikamente können zu verschiedenartigen Nagelbildungsstörungen führen, z.B. A: Nagelbett-Hämatom durch traumatisch bedingte Blutung; B: Meessche Streifen durch regelmässiges Schneiden und Abschieben der Nagelhäutchen; C: Onychodystrophe nach Einklemmen des Fingers in Autotüre.

Lokal bedingte und endogene Nagelbildungsstörungen
D: Onychodystrophie bei endogenem Ekzem; E: Löffelnagel bei Eisen- und Vitaminmangel.

Nagelmelanose und Nagelmelanom
Auch im Nagelorgan kommen melanozytische Zellen vor, von denen gutartige und bösartige Neubildungen ausgehen können.

Melanonychia striata

Nagelbettmelanom
Immer wieder vorkommende Lokalisation (ca. 3% aller Hautmelanome). Melanomtyp: meist akro-lentiginöses Melanom.
Nagelbettmelanome treten meist in zwei Formen auf:
1. Lentiginös-fleckige Form
2. Entzündlich-proliferative Form
Therapie: Bei Melanomverdacht Klinikeinweisung.

Reference: Rassner, 2002
Hair and hair follicle

**Haare** (pilus, crini, tricho = Haar) sind Hautadnexe in Form von handschuhfingerartiger Kutiseinstülpungen (Haarwurzel), aus welcher das äußerlich sichtbare Haar (Haarschaft) herauswächst (vergleichbar mit der Bildung der Nagelplatte aus der Tiefe der Nageltasche). Wichtige Aspekte zusammengefasst:

1. **Gesamtzahl** der Haare/Haarfollikel: ca. 5 Mio. (Kopfhaut: ca. 100’000), 40-800/cm².
2. **Keine Haarneogenese**, d.h. die Zahl der pränatal angelegten Haarfollikel nimmt nicht mehr zu.
3. Die einzelnen **Haarfollikel** können im Verlauf des Lebens **verschiedene Haartypen** bilden.
4. Haare **wachsen nicht kontinuierlich** wie Nägel, sondern unterliegen einem Wachstumszyklus.

**Haarzyklus mit Anagen-Phase, Katagen-Phase und Telogenphase**

A **Anagen-Phase**: Wachstum maximale Follikellänge; Jahre
B **Katagen-Phase**: Übergang Follikelverkürzung; Wochen
C **Telogen-Phase**: Ruhe weitere Rückbildung; 3-4 Monate
D **neue Anagen-Phase**

- 1 Bindegewebe Papille
- 2 Haarmatrix
- 3 Haarbalgmuskel
- 4 Talgdrüse
- 5 Haarmatrix-Verhornung
- 6 Kolbenhaar

Reference: Rassner, 2002
Diseases of hair and hair follicles

Erbliche und erworbene Krankheiten der Haare und Haarfolikel
Haarschaftsdystrophien und Folikelstörungen gehören zu den erblichen Erkrankungen, während Follikulitis, Furunkel und Trichomykosen zu den erworbenen Krankheiten der Haare und Haarfolikel gezählt werden.

Multiple Trichoepitheliome

Trichomykosen
Therapie: systemisch-orale antimykotische Therapie.

Follikulitis
Meist infektionsbedingte entzündliche follikuläre Papel oder Pustel, meist von Haar durchbort. 
Therapie: lokal-antimikrobiell.

Furunkel
Abszedierende Entzündung (Einschmelzung des Follikels). Entzündlicher Knoten mit zentralem Pfropf; regionale Lymphknotenschwellung.
Therapie: nie ausdrücken! Systematische Chemotherapie.

Reference: Rassner, 2002
Diseases of hair and hair follicles

Alopecia areata


Therapie: Lokalkortikoide; in schweren Fällen topische Immunkortikoide, UV-Bestrahlung, PUVA-Therapie u.a.

Chronische androgenetische Alopezie


(1) Genetische Disposition, (2) Androgenwirkung (kein Auftreten bei Eunuchen), (3) Altersdisposition.

Die androgenetische Alopezie entwickelt sich durch zunehmende Verkürzung der Anagenphase und allmähliche Umschaltung auf Verlusthaarbildung.

Therapie: (1) Männer: Keine befriedigend wirksame Behandlungs methode bekannt. (2) Frauen: Lokalbehandlung mit östrogen haltigen Lokaltherapeutika; in schweren Fällen Versuch einer systemischen Hormontherapie (z.B. Antiandrogene); Behandlung einer bestehenden Endokrinopathie; Haarersatz.

Einteilung der Stadien einer androgenetischen Alopezie.
Sweat glands

Schweissdrüsen der Haut (Glandulae sudoriferae) sind exokrine, tubuläre Drüsen, die in ekkrine (freie, nicht-folikelgebundene) und apokrine (folikelgebundene) Schweissdrüsen unterteilt werden und ekkrinen bzw. apokrinen Schweiss (sudor (lat.), hidros (gr.)) bilden.

Ekkrine Schweissdrüsen
Vorkommen: gesamtes Integument, 300/cm², total ca. 3x10⁶; Dichte erhöht auf Fusssohlen, Handinnenflächen und Stirn.
Ekkriner Schweiss: farblos, dünnflüssig, 99% Wasser, CO₂, NaCl, Harnstoff, Milchsäure, Aminosäuren u.a.m. Normale Tagesmenge ca. 0.8 l, Maximalmenge bis zu 10 l (Tropen, Schwerstarbeit).
Formen des Schwitzens:
- Perspiratio insensibilis (kontinuierliche, unsichtbare Schweissabgabe)
- Thermoregulatorisches Schwitzen (hypothalamisch gesteuerte Wärmeabgabe)
- Emotionelles Schwitzen (vegetative Adaptation)

Apokrine Schweissdrüsen
Vorkommen: im gesamten Integument angelegt, bilden sich jedoch zurück, bis auf Achsel-, Inguinal- und Anogenitalregion.
Apokriner Schweiss: trübe und lipidreich (u.a. Cholesterin); er riecht nach bakterieller Zersetzung intensiv.

Pathologie
Hereditäre sowie exogene, lokale und endogene Ursachen. Pathogenese:
1. Sekretionsstörungen
2. Veränderungen der Schweisszusammensetzung
3. Schweisstransportstörungen
4. Entzündungen (schweissdrüsenbezogen (ekkr.) bzw. folikelbezogen (apokr.))
**Diseases of the sweat gland**

**Genuine ekkrine Hyperhidrose**


**Idiopathische Dyshidrose**


*Therapie:* Lokale Behandlung mit austrocknend-adstringierenden Externa wie Zinkschüttelmixtur, Lotionen mit synthetischem Gerbstoff (Tannolact®, Tannosynt®).


*Therapie:* Keine, da selbstlimitiert nach Beseitigung der Ursachen.

Reference: Rassner, 2002