MINISTRY OF HEALTH OF REPUBLIC OF BELARUS
GOMEL STATE MEDICAL UNIVERSITY

V. V. Kazlouskaya

SELECTED LECTURES ON DERMATOLOGY

Manual for foreign medical students

Gomel
GSMU
2008

УДК 616.5 (075.8)=20
ББК 55.8
К 59

Рецензеты:
заведующий кафедрой дерматовенерологии УО «Витебский государственный медицинский университет», доктор медицинских наук, профессор ***В. П. Адаскевич;***

заведующий кафедрой поликлинической терапии и общеврачебной практики с курсом дерматовенерологии
УО «Гомельский государственный медицинский университет»,
кандидат медицинских наук, доцент ***Э. Н. Платошкин.***

Козловская, В. В.
К 59 Курс лекций по дерматологии: учеб.-метод. пособие для студентов-медиков = Selected Lectures on Dermatology: manual for foreign medical students / В. В. Козловская. — Гомель: Учреждение образования «Гомельский государственный медицинский университет», 2008. — 160 с.

ISBN 978-985-506-210-4

Учебно-методическое пособие «Selected Lectures on Dermatology» представляет собой курс лекций по дерматологии, предназначенный для иностранных студентов 3 курса, обучающихся на английском языке. Лекции составлены в соответствии с типовой учебной программой и содержат основные разделы цикла дерматология.

Утверждено и рекомендовано к изданию Центральным учебным научно-методическим советом учреждения образования «Гомельский государственный медицинский университет» 20 ноября 2008 г., протокол № 11.

УДК 616.5 (075.8)
ББК 55.8

ISBN 978-985-506-210-4

Abbreviations Used in the Book

AA — alopecia areata
ACD — allergic contact dermatitis
AD — atopic dermatitis
AGA — allergic granulomatous angiitis
AIDS — aquired immunodeficiency syndrome
ANA — anti-nuclear antibodies
ANCA — antineutrophil cytoplasmic antibodies
AST — aspartate aminotransferase
ASO — anti streptococcal O antigen
BBL — borderline borderline leprosy
BCIE — bullous congenital ichthyosiform erythroderma
BL — lorderline lepromatous leprosy
BTL — borderline tuberculoid leprosy
CLE — cutaneous lupus erythematosus
CRP — C-reactive protein
CSF — cerebral spinal fluid
CSVV — cutaneus small vessel vasculitis
CTCL — cutaneous T-cell lymphoma
DCL — dissiminative cutaneous leishmaniasis
DDS — dapsone
DEB — dystrophic epidermolysis bullosa
DH — dermatitis herpetiformic During
DLST — drug lymphocyte stimulating test
DM — dermatopmyositis
DNA — deoxyribonuclease
DPCP — diphenylcyclopropenone
EB — epidermolysis bullosa
EED — erythema elevatum diutinum
EM — erythema mygrans
EMM — erythema multiforme
ESR — erythrocyte sedimentation rate
GABHS — group of B hemolytic streptococcus
HPV — human papiloma virus
HSV — herpes simplex virus
IL — interminate leprosy
JEB — junctional epidermolysis bullosa
KS — sarcoma Kaposi
LCL — local cutaneous leishmaniasis
LDH — lactate dehydrogenase
LE — lupus erythematosus
LGV — lymphogranulomatosis venereal
LL — lepromatous leprosy
LP – lichen planus
LR — leishmaniasis recidivans
MF — mycosis fungoides
NBCIE — nonbullous congenital ichthyosiform erythroderma
NSAIDs — non steroid anti-inflammatory drugs
OM — onichomycosis
PCAS — perifolliculitis capitis abscedens et suffodiens
PF — pemphigus foliaceus
PKADL — Post-Kala-Azar Dermal leishmaniasis
PN — polyarteritis nodosa
PUVA — psoralen plus ultraviolet A therapy
PV — pemphigus vulgaris
RA — rheumatoid arthritis
SJS — Stevens – Jonson syndrome
SLE — systemic lupus erythematosus
SS — Sezary syndrome
TA — temporal arteriitis
TAO — tromboangiitis obliterans
TEN — toxic epidermolysis
TL — tuberculoid leprosy
TSEB — total skin electron beam
VL — visceral leishmaniasis
VZV — varicella zoster virus

Content

Lecture 1. Structure and Functions of the Skin. Main Pathomorphological Processes in the Skin. Principles of the Therapy of Diseases of the Skin. **7**
Structure of the Skin **7**
Epidermis 7
Dermo-epidermal junction 8
Derma 9
The subcutaneous tissue (subdermal fatty tissue) 9
Cutaneous sensory system 9
Cutaneous vessel system 10
Sebaceous glands 12
Sweet glands 13
Nails 14
Functions of the skin 17
Dermapathological processes 17
Principles of the Therapy of Diseases of the Skin. 20
Systemic Therapy 21
Phototherapy 22
Photochemotherapy (PUVA) 22
Cryotherapy 22
Laser (Light Amplification by Stimulated Emission of Radiation) 22
Lecture 2. Observation of the Skin Patient (scheme of the case history) **23**
Lecture 3. Bacterial Infections of the Skin (Pyodermas). **32**
Staphylococcal Infections 32
Folliculitis 32
Boils (Furuncles) 33
Hydradenitis Suppurativa 33
Carbuncles 34
Paronychial Infections 34
Staphylococcal Scalded Skin Syndrome (Ritter-Lyell Syndrome) 35
Streptococcal Infections. 36
Impetigo 36
Ecthyma 37
Impetigo angularis (perleche, cheilitis angularis, stomatitis angularis, angular cheilitis) 37
Pyoderma gangrenosum 37
Pityriasis alba 38
Perifolliculitis Capitis Abscedens et Suffodiens (PCAS) 38
Lecture 4. Parasitic Diseases of the Skin **40**
Scabies 40
Pediculosis 43
Lecture 5. Mycobacterial Infections of the Skin **45**
Tuberculosis of the skin 45
Lupus vulgaris 46
TB verrucosa cutis 47
Scrofuloderma 47
Erythema induratum (Bazin disease) 48
Lichen scrofulosorum 48
Papulonecrotic tuberculid 48
TB cutis orificialis 48
Miliary TB of the skin 49
Leprosy 50
Lecture 6. Leishmaniasis **55**
Lecture 7. Fungal Infection **58**

Classification of fungi infections 58
Laboratory tests for fungal infection 58
Pseudomycoses 59
Erythrasma 560
Actynomycoses 561
Superficial fungi infection **61**
Tinea versicolor 61
Piedra 63
Dermatophytes 64
Tinea cruris 65
Tinea pedis (Athlet`s foot) 66
Onychomicosis 67
Tinea capitis. 68
Tinea capitis caused by Microsporum canis infection 70
Trichophyton infections 70
Favus (tinea favosa) 74
Deep mycoses 75
Chromoblastomycosis 75
Cryptococcosis 76
Histoplasmosis 78
Mycetoma 781
Sporotrichosis 80
Candidiasis 81
Lecture 8. Viral infections of the skin **84**
Molluscum contagiosum 84
Herpes simplex 85
Herpes zoster (shingles) 87
Warts 88
Lecture 9. Contact Dermatitis **90**
Irritant dermatitis 90
Allergic contact dermatitis (ACD) 91
Occupational Dermatoses 92
Lecture 10. Itch as a Main Symptom in Dermatology. **94**
Dermatoses Assosiated with Itch **94**
Itch as a disease and as a symptom 94
Urticaria (hives) 94
Angioedena (Quincke edema) 96
Prurigo 96
Lichen simplex (local neurodermitis) 97
Atopic dermatitis 98
Eczema 100
Dyshidrotic eczema (pompholyx eczema) 101
Nummular eczema 102
Lecture 11. Drug Eruptions **103**
Erythema multiforme 104
Stevens – Johnson (SJS) and toxic necrotic epidermolysis 106
(TEN) syndrome 106
Lecture 12. Papular Dermatoses: Psoriasis, Lichen Planus. **110**
Psoriasis 110
Lichen planus 114
Lecture 13. Bullous dermatoses. **116**
Pemphigus Group 116
Pemphigus vulgaris 116
Pemphigus foliaceus 118

Pemphigus paraneoplastic ... 119
Pemphigoid group. Bullous pemphigoid ... 119
Dermatitis herpetiformis During ... 120
Lecture 14. Diseases of the Connective Tissue ... **121**
Lupus erythematosus ... **121**
Acute CLE ... 121
Chronic LE ... 122
LE tumidis ... 122
Bullous LE ... 123
Systemic LE (SLE) ... 123
Morphea ... 124
Dermatomyositis ... 126
Lecture 15. Diseases of Skin Appendages ... **129**
Acne ... 129
Seborrhoeic Dermatitis ... 130
Alopecia Areata (AA) ... 131
Rosacea ... 132
Lecture 16. Genodermatoses. ... **134**
Ichthyosis ... 134
Ichthyosis vulgaris ... 134
X – linked ichthyosis ... 135
Bullous congenital ichthyosiform erythroderma ... 135
Non bullous congenital ichthyosiform erythroderma (NBCIE) ... 136
Lammelar ichthyosis ... 136
Epidermolysis bullosa (EB) ... 137
Keratoderma ... 139
Thost-Unna palmoplantar keratoderma ... 139
Keratoderma Mal de Meleda ... 139
Papillon-Lefevre syndrome ... 139
Lectue 17. Lymphoproliferative Skin Diseases ... **140**
Skin lymphomas ... 140
T- cell lymphomas ... 140
B-cell lymphomas ... 142
Lecture 18. Diseases of Blood Vessels ... **144**
Vasculitis ... 144
Cutaneous small-vessel vasculitis (CSVV) ... 144
Henoch-Schonlein purpura (HSP) ... 145
Erythema elevatum diutinum (EED) ... 146
Polyarteritis nodosa (PN) ... 147
Allergic granulomatous angiitis (AGA) ... 148
Wegener's granulomatosis ... 149
Temporal arteritis (TA) ... 150
Behcet's disease ... 150
Buerger's disease ... 151
Mondor disease ... 152
Malignant atrophic papulosis ... 152
Kaposi sarcoma ... 153
Lecture 19. Lyme Disease ... **155**
Lecture 20. Vitiligo ... **157**

LECTURE 1. STRUCTURE AND FUNCTIONS OF THE SKIN. MAIN PATHOMORPHOLOGICAL PROCESSES IN THE SKIN. PRINCIPLES OF THE THERAPY OF DISEASES OF THE SKIN. STRUCTURE OF THE SKIN

Skin is the largest organ of the people's body that performs many functions and also acts as the method of the communication with the outer world. Skin consists of :

1. Epidermis.
2. Derma.
3. Subcutaneous tissue.

Skin also has the appendages (nails, hair, glands).

Epidermis

The epidermis is the outer layer of skin. The thickness of the epidermis varies in different types of skin. It is thinnest on the eyelids — 0.5 mm and thickest on the palms and soles at 1.5 mm. The epidermis contains 5 layers. From bottom to top the layers are named:

1. Stratum basale (basal layer).
2. Stratum spinosum (prickle layer, spinous layer).
3. Stratum granulosum (granular layer).
4. Stratum licidum.
5. Stratum corneum (horny layer).

1. The bottom layer, the stratum basale, has cells that are shaped like columns. In this layer the cells divide and push already formed cells into higher layers. As the cells move into the higher layers, they flatten and eventually die. Interspersed amongst the basal cells are melanocytes, large dendritic cells responsible for melanin pigment production.

2. Spinous layer consists of living keratinocytes with the eosinophylic cytoplasma. The cells in this layer are connected by intercellular bridges (desmosomes) which connect adjacent cells. Scattered throughout the prickle cell layer are numbers of dendritic cells called Langerhan`s cells. Like macrophages, Langerhan`s cells originate in the bone marrow and have an antigen-presenting capacity.

3. The granular layer is composed of the living keratinocytes that have certain in the numerous darkly-staining particles known as keratohyaline granules. Also present in the cytoplasm of cells in the granular layer organelles known as lamellar granules (Odland bodies). Lamellar granules contain lipids and enzymes, and they discharge their contents into the intercellular spaces between the cells of the granular layer and stratum corneum. In the granular layer the cell membranes become thickened as a result of deposition of dense material on their inner surfaces.

4. The stratum licidum is not determined in all parts of the body (for this reason, in some text-books you may not see this layer in the classification). This layer there is only in some parts, such as palms and plants. It's the layer amorfic.

5. The top layer of the epidermis, the stratum corneum, is made of dead, flat skin cells that shed about every 2 weeks. It acts as the major physical barrier in the epidermis. The cells of the stratum corneum are held together by an overlapping mechanism and with proteins that serve as a binding «glue». The layer prevents the molecules from passing into and out of the skin, thus protecting the lower layers of skin. Disorders such as atopic dermatitis arise when this barrier function does not work properly.

There is a gradual differentiation from basal layer to the horny layer that takes about 70 days. The rate of cell production in the germinative compartment of the epidermis must be balanced by the rate of cell loss at the surface of the stratum corneum. The control mechanism of epidermopoiesis consists of a balance of stimulatory and inhibitory signals. The growth factors which stimulate the epidermal cells include: **epidermal growth factor (EGF)**, **transforming-growth-factor-alpha (TGFalpha), interleukins (IL**) and other immunological cytokines, and **basic fibroblast growth factor (bFGF)**. Growth inhibitors for keratinocytes include **chalones, transforming-growth-factor-beta (TGFbeta), alpha and gamma interferons (IFN-gamma), and tumor necrosis factor (TNF).**

There are four main types of cells in the epidermis:

1. Keratinocytes.
2. Melanocytes.
3. Langerhan`s' cell.
4. Merkel's cell.

1. Keratinocytes (85% of cells in epidermis) are present in all layers of the skin.

2. Melanocyte is the cell from neural crest, wedged between basal keratinocyte in 1 to 10 ratio. 1 melanocyte supplies pigments to 36 keratinocytes. The main functions of the melanocyte are cosmetic and protection from the sun. The color of the skin depends of the quantity of the melanocytes.

3. Merkel's cell is the cell that usually is situated in the layer basal and the function of which is the sense of touch. A Merkel cell has a lobulated nucleus and characteristic granules; it is embedded in the basal layer of epidermal cells, with which it has desmosomal connections; it contains intermediate filaments composed of low molecular weight keratin rather than neurofilament protein.

4. Langerhan`s cells (800 per sq mm) have the function of the immune response. It is the first that reacts at the effect of the antigens.

Dermo-epidermal junction

At the interface between the epidermis and dermis lies the basement membrane zone. Electron microscopy shows that it can further be divided to basal cell membrane, lamina lucida (20–40 nm), lamina densa (30–60 nm, Type

IV collagen) and sublamina densa with anchoring fibrils. The structures of the dermo-epidermal junction provide good mechanical support, adhesion and growth of the basal layer unless it is diseased.

Derma

Derma is the thickest at the palms, soles and back (3 mm) and least thick at the eyelids (0.3 mm) and penis. There are **papillary dermis** and deeper **reticular dermis**. The upper, papillary layer contains a thin arrangement of collagen fibers. The lower, reticular layer is thicker and made of thick collagen fibers that are arranged parallel to the surface of the skin. It contains many cells, fibers and amorphous ground substance. Fibroblast for synthesis of collagen, reticulin, elastin, glycosaminoglycans is the major cell in the dermis. The ground substance consists of two glycosaminoglycans: hyaluronic acid and dermatan sulphate. Other structures found in the dermis include: blood vessels, lymphatics, nerves, nerve endings and receptors, dartos muscles in scrotum, glands and their accessories e.g. arrector pili muscles.

The subcutaneous tissue (subdermal fatty tissue)

The subcutaneous tissue is the third of the three layers of skin. The subcutaneous layer contains fat and connective tissue that houses larger blood vessels and nerves. This layer is important is the regulation of temperature of the skin itself and the body. The size of this layer varies throughout the body and from person to person. It is absent in the eyelids and the male genitalia. It has abundant blood and lymphatic supplies.

Cutaneous sensory system

The skin is innervated with around one million afferent nerve fibers. Most terminate in the face and extremities; relatively few supply the back. The cutaneous nerves contain axons with cell bodies in the dorsal root ganglia. Their diameters range from 0.2–20 μm. The main nerve trunks entering the subdermal fatty tissue each divide into smaller bundles. Throughout their course, the axons are enveloped in Schwann cells and as they run peripherally, an increasing number lack myelin sheaths. Most end in the dermis; some penetrate the basement membrane, but do not travel far into the epidermis.

Sensory endings are of two main kinds: **corpuscular**, which cover non-nervous elements, and **'free'**, which do not. Corpuscular endings can, in turn, be subdivided into encapsulated receptors, of which a range occurs in the dermis, and non-encapsulated, for example Merkel's 'touch spot' in the epidermis.

The **Pacinian corpuscle** is one of the encapsulated receptors. It is an ovoid structure about 1mm in length, which is lamellated in cross-section like an onion, and is innervated by a myelinated sensory axon which loses its sheath as it traverses the core. The **Golgi-Mazzoni** corpuscle found in the subcutaneous tissue of the human finger is similarly laminate but of much simpler organization. These receptors are movement and vibration detectors.

The **Krause end bulb** is an encapsulated swelling on myelinated fibers situated in the superficial layers of the dermis. **Meissner corpuscles** are characteristics of the papillary ridges of hairless skin; they are touch receptors and have a thick lamellated capsule, 20–40 μm in diameter and up to 150 μm long. **Ruffini endings** in the human digits have several expanded endings branching from a single myelinated afferent fiber; the endings are directly related to collagen fibrils; they are stretch receptors.

'Free nerve endings', which appear to be derived from non-myelinated fibers occur in the superficial dermis and in the overlying epidermis; they are receptors for pain, touch, pressure and temperature. Hair follicles have fine nerve filaments running parallel to and encircling the follicles; each group of axons is surrounded by Schwann cells; they mediate touch sensation.

Cutaneous vessel system

Circulation through the skin serves two functions: nutrition of the skin tissue and regulation of body temperature by conducting heat from the internal structures of the body to the skin, where it is lost by exchange with the external environment (by convection, conduction and radiation).

The cutaneous circulatory apparatus is well-suited to its functions. It comprises two types of vessels: the usual nutritive vessels (arteries, capillaries and veins), and vascular structures concerned with heat regulation. The latter include an extensive subcutaneous venous plexus which can hold large quantities of blood (to heat the surface of the skin), and arteriovenous anastomoses which are large direct vascular communications between arterial and venous plexuses. Arteriovenous anastomoses are only present in some skin areas which are often exposed to maximal cooling, as the volar surfaces of hands and feet, the lips, the nose and the ear (Figure 1).

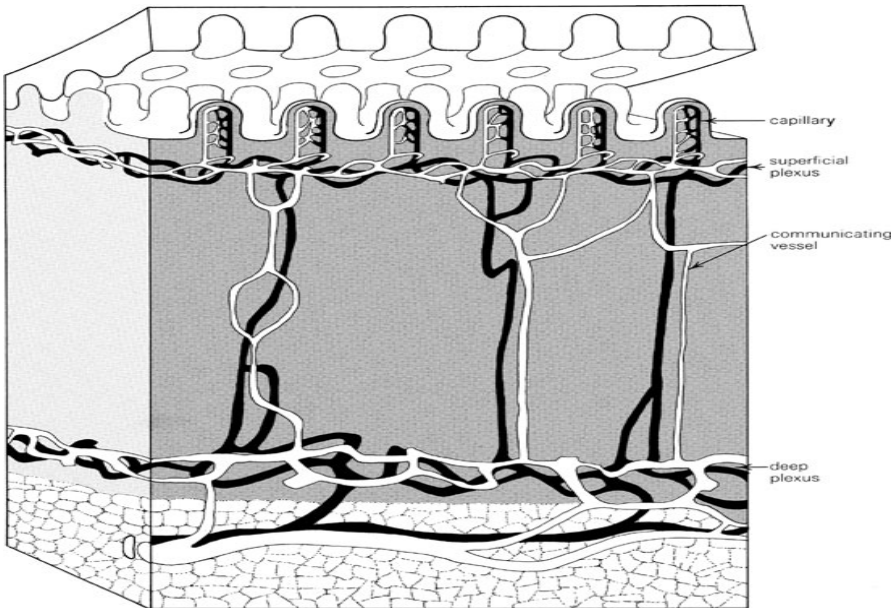

Figure 1 — Structure of skin vessels

The specialized vascular structures just mentioned, bear strong muscular coats innervated by sympathetic adrenergic vasoconstrictor nerve fibers. When constricted, blood flow into the subcutaneous venous plexus is reduced to almost nothing (minimal heat loss); while, when dilated, extremely rapid flow of warm blood into the venous plexus is allowed (maximal heat loss).

The blood flow required for the nutrition of the skin is very small (about 40 ml/min). Yet, at ordinary skin temperature, the amount of blood flowing through the skin is 10 times more than what is needed for the nutrition of the tissues.

The rate of cutaneous blood flow required to regulate body temperature varies in response to changes in the metabolic activity of the body and/or the temperature of the surroundings. Exposure to extreme cold reduces the rate of blood flow to very low values, so that the nutritive function may sometimes suffer. On the other hand, heating the skin until maximal vasodilatation occurs (as in hot climate), increases the cutaneous blood flow 7 times the normal value (2.8 L/min). This diminishes the peripheral resistance and increases the cardiac output, which may lead to the decompensation of the heart in borderline-heart-failure subjects exposed to hot weather.

Located in the anterior hypothalamus is a small center that controls body temperature. Heating this area causes vasodilatation of all the skin vessels of the body and sweating. On the contrary, cooling this center causes vasoconstriction of skin vessels and stoppage of sweat secretion. The hypothalamus exerts its controlling effect on the skin vessels through sympathetic nerves. There are also vasoconstrictor reflex centers in the spinal cord.

Sympathetic noradrenergic vasoconstrictor fibers supply the vessels of the skin throughout the body. This constrictor system is extremely powerful in the feet, hands, lips, nose and ears (areas where large numbers of arteriovenous anastomoses are found). At normal body temperature, the sympathetic vasoconstrictor nerves keep these anastomoses closed. However, when the body becomes overheated, the sympathetic discharge is greatly reduced so that the anastomoses dilate allowing large quantities of warm blood to flow into the subcutaneous venous plexus, thereby promoting heat loss from the body.

Active vasodilatation of the blood vessels of the skin of forearms and trunk may be due to the discharge of sympathetic cholinergic vasodilator fibers supplying these areas. The increased activity of sweat glands in hot weather may also contribute to the vasodilatation by releasing kallikrein, an enzyme which splits the polypeptide bradykinin from a globulin present in the interstitial spaces. Bradykinin is a powerful vasodilator.

In cold weather, when the temperature reaches 15°C, we get maximal vasoconstriction of skin blood vessels. However, in a normal subject, if the skin temperature is lowered below 15°C, the cutaneous vessels begin to dilate. This dilatation is attributed to the direct local effect of cold causing paralysis of the contractile musculosa of skin blood vessels and blocking nerve impulses to the

vessels. Maximal vasodilatation occurs at 0°C, increasing the blood flow through the skin which prevents freezing of the exposed areas of the body.

The cutaneous circulation also serves as a blood reservoir. Under conditions of circulatory stress, e. g., exercise and hemorrhage, sympathetic stimulation of subcutaneous venous plexus forces a large volume of blood (5–10% of the blood volume) into the general circulation.

Sebaceous glands

Sebaceous glands are found on all areas of the skin with the exception of the palms, soles, and dorsa of the feet. They are **holocrine glands**, i.e., their secretion is formed by complete destruction of the cells.

Most sebaceous glands have their ducts opening into hair follicles (pilosebaceous apparatus). Free sebaceous glands (not associated with hair follicles) open directly to the surface of the skin, e.g., Meibomian glands of the eyelids, Tyson's glands of the prepuce, and free glands in the female genitalia and in the areola of nipples (Figure 2).

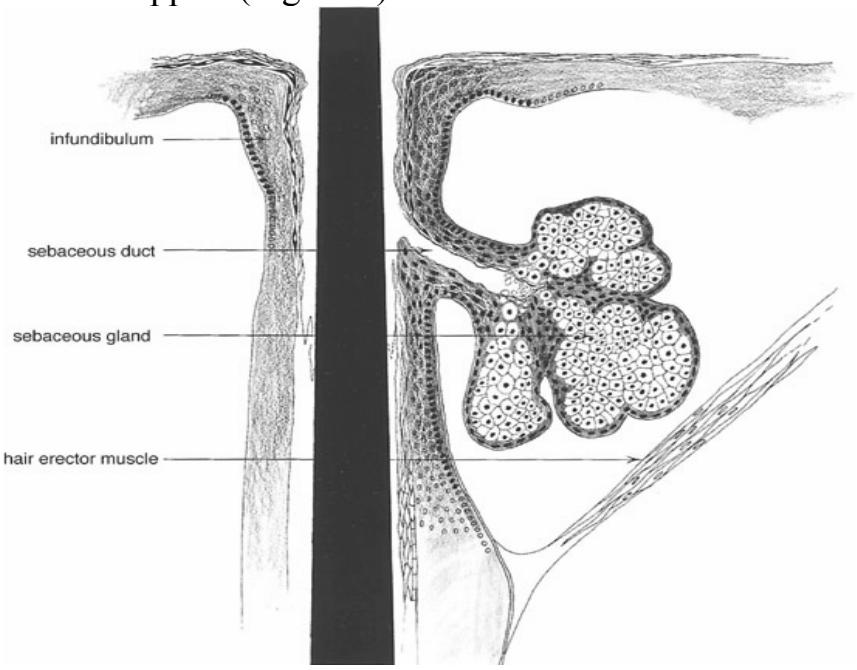

Figure 2 — Structure of the sebum gland

The production of sebum is under hormonal control and sebaceous secretion is a continuous process. Sebaceous gland development is an early event in puberty, and the prime hormonal stimulus for this glandular development is androgen. Although the sebaceous glands are very small throughout the prepubertal period, they are large at the time of birth, probably as a result of androgen stimulation in utero, and acne may be seen in the neonatal period. It should be noted that: sebum production is low in children; in adults, sebum production is higher in men than in women; in men, sebum production falls only slightly with advancing age, whereas in women it decreases

significantly after the age of 50. Orchidectomy causes a marked decrease in sebum production. Therefore, it can be assumed that testicular androgen maintains sebum production at high levels in men. The role of adrenal androgens is also important, especially in women where they play a contributory role in sebum production together with the ovaries. Estrogens have a profound effect on sebaceous gland function which is opposite of that of androgens. In both sexes, estrogen administration decreases the size of the sebaceous glands and the production of sebum.

The sebum is composed of triglycerides and free fatty acids, wax esters, squalene, and cholesterol. The sebum controls moisture loss from the epidermis. The water-holding power of cornified epithelium depends on the presence of lipids. The sebum also protects against fungal and bacterial infections of the skin due to its contents of free fatty acids. Ringworm of scalp becomes rare after puberty.

Sweet glands

Generalized sweating is the normal response to exercise or thermal stress by which human beings control their body temperature through evaporative heat loss. Failure of this mechanism can cause hyperthermia and death.

Humans have several million eccrine sweat glands distributed over nearly the entire body surface (except labia minor and glands penis). The total mass of eccrine sweat glands roughly equals that of one kidney, i.e., 100 g. A person can perspire as much as several liters per hour and 10 liters per day, which is far greater than the secretory rates of other exocrine glands such as the salivary and lachrymal glands and the pancreas. Each eccrine sweat gland consists of a secretory coil deep in the dermis, and a duct which conveys the secreted sweat to the surface. The secretory activity of the human eccrine sweat glands consists of two major functions: secretion of an ultrafiltrate of a plasma like precursor fluid by the secretory coil in response to acetylcholine released from the sympathetic nerve endings, and reabsorbtion of sodium in excess of water by the duct, thereby producing a hypotonic skin surface sweat. Under extreme conditions where the amount of perspiration reaches several liters a day, the ductal reabsorpbtive function assumes a vital role in maintaining homeostasis of the entire body.

In addition to the secretion of water and electrolytes, the sweat glands serve as excretory organ for heavy metals, organic compounds, and macromolecules. The sweat is composed of 99% water, electrolytes, lactate (provides an acidic pH to resist infection), urea, ammonia, proteolytic enzymes, and other substances.

There is a hypothalamic preoptic sweat center that plays an essential role in regulation of body temperature. Sweat secretion on palms and soles is more or less continuous (perpetual sweating) when humans are awake. In contrast, those glands on the general skin surface respond predominantly to thermal stimuli (thermal sweating). Both types of sweating can be inhibited by atropine as all

sweat glands in different areas of the body are stimulated by the same sympathetic cholinergic mechanism. Sweating induced by emotional stress (emotional sweating) can occur over the whole skin surface, but usually it is confined to palms, soles, axillae, and the forehead.

The term apocrine glands was given to sweat glands present in the axillae and anogenital area which are under the control of sex hormones, mainly androgens. But nowadays by electron microscopy, these apocrine glands (apocrine = apical part of the cell is destroyed during the process of secretion) proved to be merocrine in nature (merocrine = no destruction of the cell during the process of secretion). The «apocrine» sweat of humans has been described as milky (because it is mixed with sebum due to shared duct) and viscid, without odor when it is first secreted. Subsequent bacterial action is necessary for odor production. Unlike eccrine glands which have a duct that opens onto the skin surface independently of a hair follicle (atrichial), apocrine glands have a duct that opens into a hair follicle (epitrichial) (Figure 3).

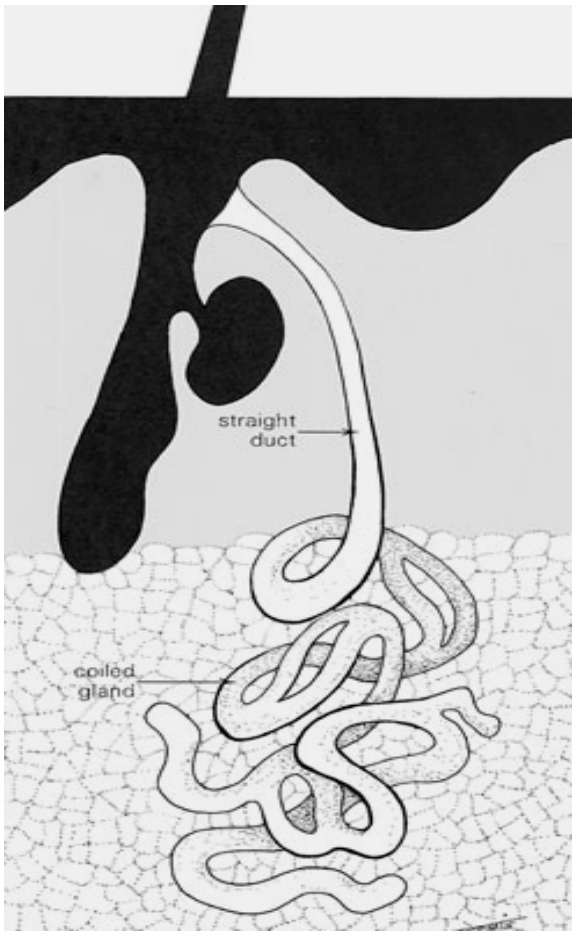

Figure 3 — Structure of hair follicule

Nails

The nail acts as a protective covering to the end of the digit and assists in grasping small objects. The nail has also a cosmetic function. The major part of this appendage is the hard nail plate, which arises from the matrix (see below). The nail plate is roughly rectangular and flat in shape but shows considerable variation in different persons. The pink color of the nail bed results from its extensive vascular network and can be seen because of the transparency of the plate. Usually in the thumbs, uncommonly in other fingers and in the large toenails, a whitish crescent-shaped lunula is seen projecting from under the proximal nail folds. The lunula is the most distal portion of the matrix and determines the shape of the free edge of the nail plate. Its color is due in part to the effect of light scattered by the nucleated cells of the matrix and in part to the thick layer of epithelial cells making up the matrix.

As the nail plate emerges from the matrix, its lateral and proximal borders are enveloped by folds of the skin termed the lateral and proximal nail folds. The skin underlying the free end of the nail is referred to as the hyponychium and is contiguous with the skin on the tip of the finger. The nail plate is formed by a process which involves flattening of the basal cells of the matrix, fragmentation of the nuclei, and condensation of cytoplasm to form horny flat cells which are strongly adherent to one another (Figure 4).

Fingernails grow faster than toenails. Nails of individual fingers of the same hand grow at different rates. There are also familial tendencies favoring similar growth rates among persons and it has been noted that nail growth is increased during summer and diminished in cold climates. Many systemic disorders may produce a decrease in the rate of nail growth or thinning and grooving of the plate. This phenomenon is best appreciated weeks after the event has occurred. Acute viral infectious diseases as mumps and measles, starvation, and some types of anemia are among the causes. Increase in the growth rate can be seen during pregnancy, nail biting, and trauma and during regrowth after avulsion.

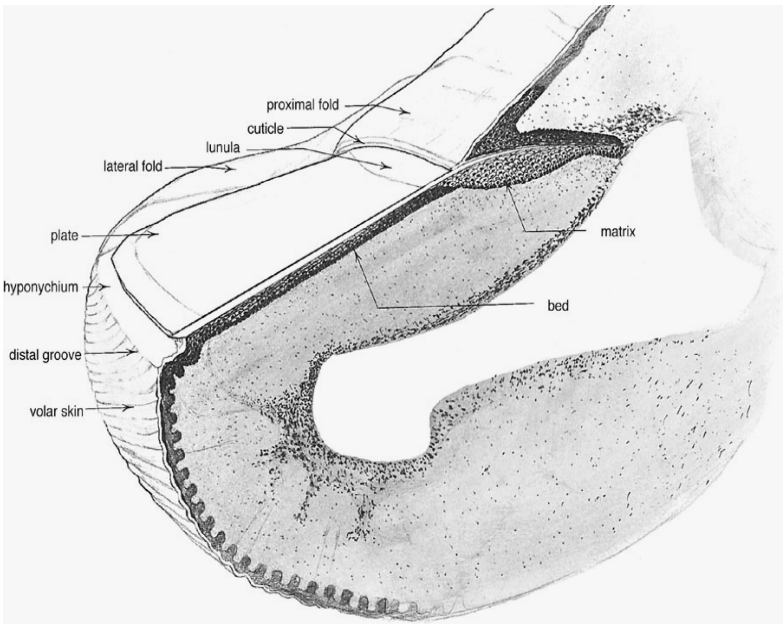

Figure 4 — Structure of the nails

Hair and hair follicules

Hair helps transmit sensory information and creates gender identity. Hair is important to the appearance of men and women. A developing fetus has all of it's hair follicles formed by week 22. At this time there are 5 million follicles on the body. One million of those are on the head, and 100,000 are on the scalp. As the size of the body increases as we grow older, the density of the hair follicles on the skin decreases.

The follicle is a stocking-like structure that contains several layers with different jobs. At the base of the follicle is a projection — papilla that contains capillaries, or tiny blood vessels, that feed the cells. The living part of the hair is bottom part of the stocking surrounding the papilla called the bulb. This bottom part is the only part fed by the capillaries. The cells in the bulb divide every 23 to 72 hours, faster than any other cells in the body (Figure 5).

The follicle is surrounded by two sheaths — an inner and outer sheath. These sheaths protect and mold the growing hair shaft. The inner sheath follows the hair shaft and ends below the opening of a sebaceous (oil) gland, and sometimes an apocrine (scent) gland. The outer sheath continues all the way up to the gland. A muscle called an erector pili muscle attaches below the gland to a fibrous layer around the outer sheath. When this muscle contracts, it causes the hair to stand up. The hair shaft is made up of dead, hard protein called keratin in three layers. The inner layer is called the medulla and may not be present. The next layer is the cortex and the outer layer is the cuticle. The cortex makes up the majority of the hair shaft. The cuticle is formed by tightly packed scales in an overlapping structure similar to roof shingles. Most hair conditioning products attempt to affect the cuticle. There are pigment cells that are distributed throughout the cortex and medulla giving the hair it's characteristic color.

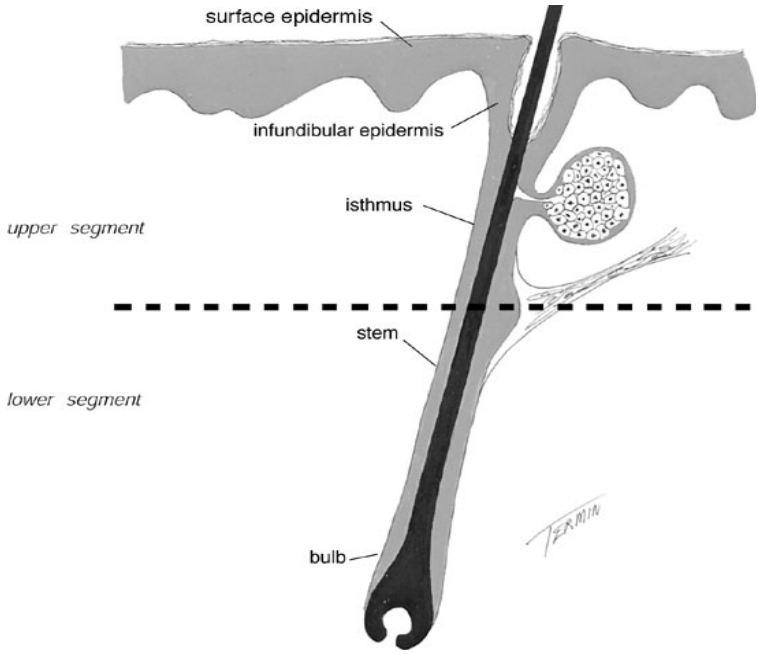

Figure 5 — Structure of the hair follicule

Functions of the skin

Function	*How it work*
Protection from harmful agents of external environment: biological germs, ultraviolet light & chemicals	This function is provided by epidermis, melanocytes, cells of Langergance
Preservation of a balanced internal environment	Thermoregulation, exchange between epidermis and environment
Absorber	This function is performed by subcutaneous fat that may absorb and contain some agents
Temperature regulation	Blood vessels
Sensation	Nerve endings
Lubrication	Glandulas
Protection & grip	Nails, hair, epidermis
Calorie reserve	Subcutaneous fat
Vitamin D synthesis	Melanocytes
Body odor and psychosocial	Nails, hair, glandulas

Dermapathological processes

1. Hyperkeratosis — increased thickness of stratum corneum, whether by normal or abnormal keratinocytes (Figure 6).

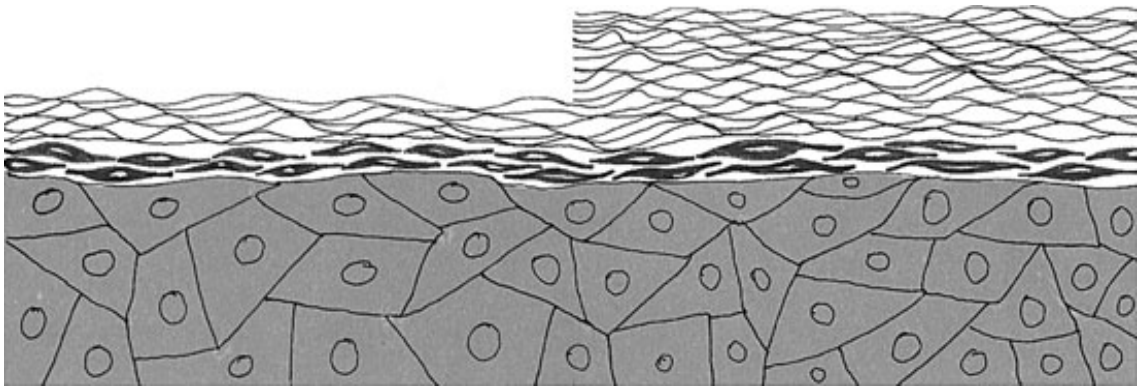

Figure 6 — Hyperkeratosis

2. Parakeratosis — process of keratinization in which the keratinocytes retain their nuclei; abnormal in skin, normal in mucous membranes (Figure 7).

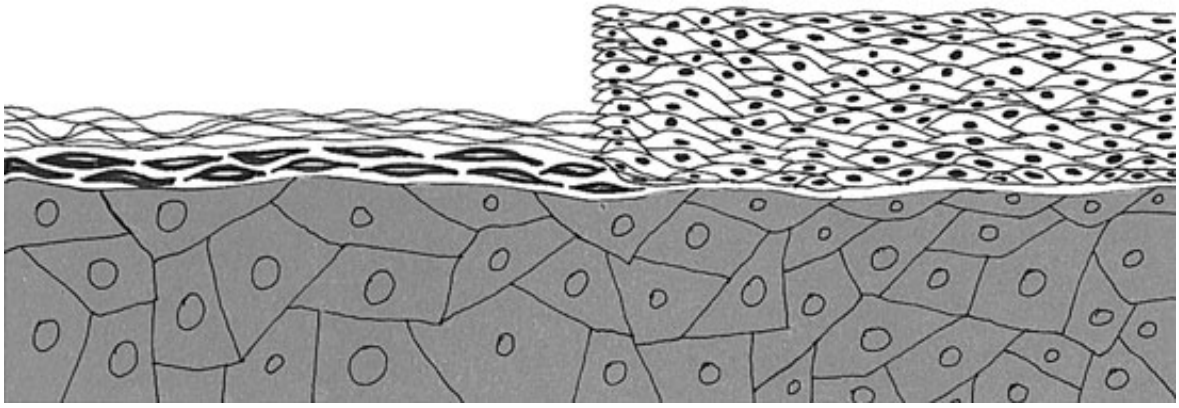

Figure 7 — Parakeratosis

3. Hypergranulosis — increase in thickness of the granular layer - is seen in lichen planus (Figure 8).

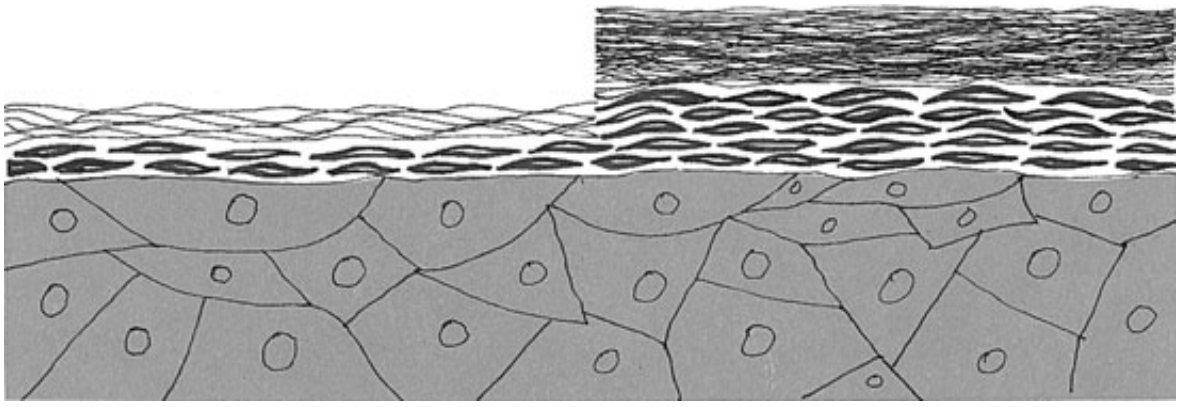

Figure 8 — Hypergranulosis

4. Acanthosis — increase in keratinocyte population of spinous layer with thickening of the epidermis; may be papillomatous or psoriasiform (Figure 9).

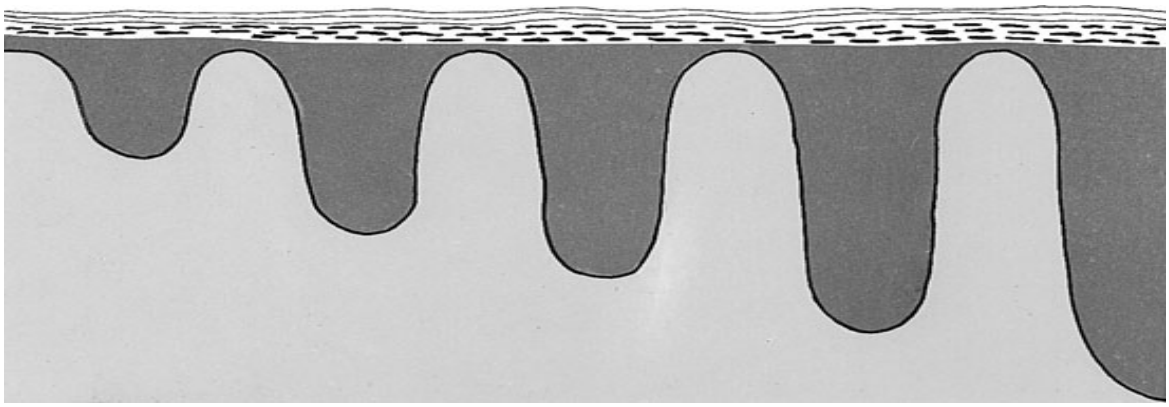

Figure 9 — Hypergranulosis

5. Papillomatosis — increase in keratinocytes with formation of projections from the surface of the skin, i.e. papillae; typical example is a wart (Figure 10).

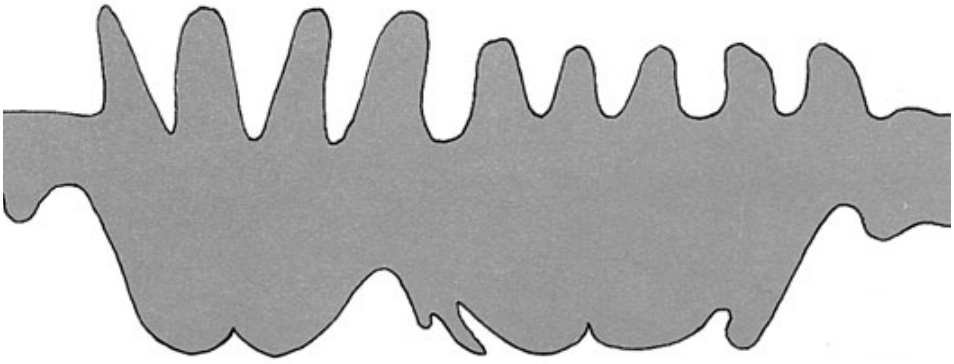

Figure 10 — Papillomatosis

6. Spongiosis — widening of the interspaces between keratinocytes due to edema fluid without detachment of cells from each other (Figure 11).

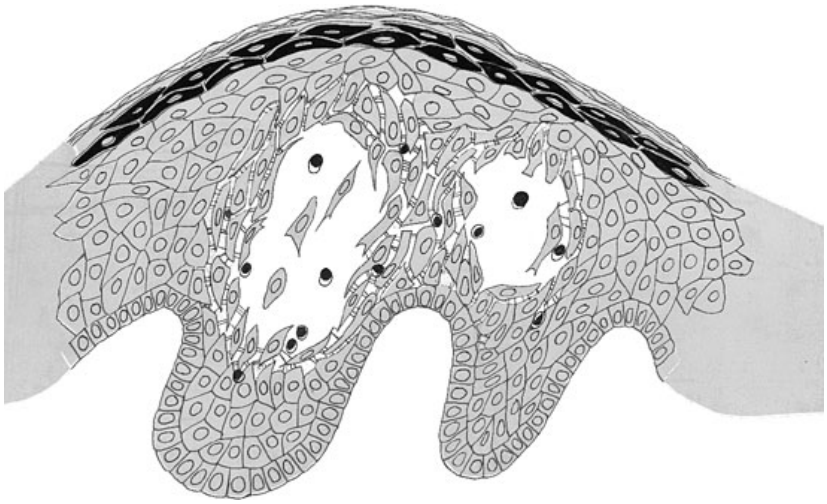

Figure 11 — Spongiosis

7. Acantholysis — detachment of keratinocytes from each other due to loss of intercellular contacts. This often is associated with the cell assuming a spherical shape, i.e., a round profile in sections (Figure 12).

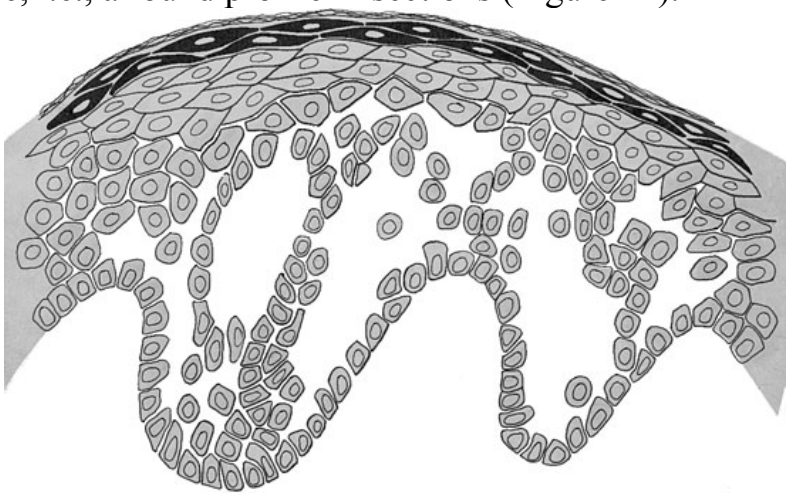

Figure 12 — Acantholysis

8. Ballooning degeneration — intracellular edema with cellular swelling. This is often secondary to viral injury or nutritional deficiency (Figure 13).

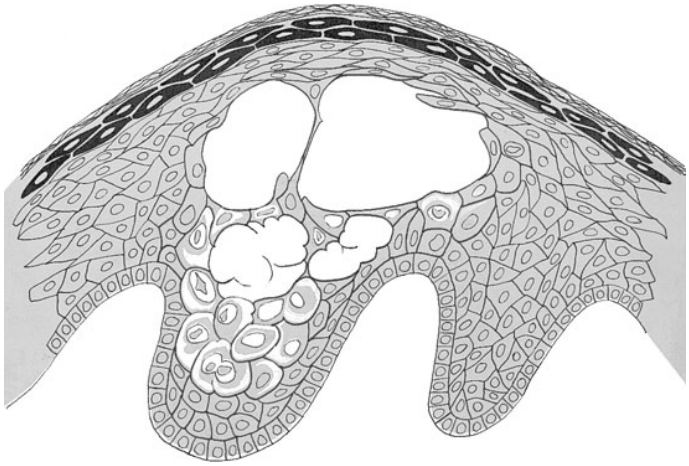

Figure 13 — Acantholysis

Principles of the Therapy of Diseases of the Skin

Medical therapy in Dermatology consists of: topical, systemic, phototherapy and surgical procedures.

Topical therapy

The advantage of direct delivery and reduced systemic toxicity make topical treatment quite attractive. Topical treatments are usually consist of a vehicle an an active ingredient. Some examples of topical vehicles include:

• **Cream** — a semi-solid emulsion of oil-in-water; contains a preservative to prevent overgrowth of micro-organisms. Stabilized by an emulsifier. Mostly water so mostly evaporates; non-greasy so easy in application and removal.

• **Gel** — a semi-solid transparent non-greasy emulsion.

• **Lotion** — liquid vehicle, aqueous or alcohol based, which may contain a salt in solution. Lotions evaporate to cool the inflamed or exudative skin.

• **Ointment** — a semi-solid grease/oil, sometimes also contains powder, but little or no water. The active ingredient is suspended. Usually, no preservative needed. Ointments are best suited for dry skin disorders — rehydrate and occlude. Because they are greasy, they are difficult to remove.

•**Paste** — an ointment with a high proportion of powder which gives a stiff consistency. Pastes can be applied to well-demarcated lesions. Due to its ointment base, they are difficult to remove.

• **Foam** — a mass of tiny bubbles formed on the surface of liquids.

• **Suspension** — biphasic, powder in aqueous solutions.

• **Emollients** — are useful in dry-skin disorders due to their ability to re-establish the surface lipid layer and enhancing rehydration of the epidermis. There are several emollient ointments, creams and oils added to baths.

Overview of Topical Medications		
Drug	**Pharmacology**	**Indications**
Antibiotics	Inhibit the groeth of bacteria	Acne, folliculitis, impetigo, infected eczema, rosacea
Antifungals	Inhibit the growth of fung	Fungal infection of the skin, Candidiasis
Antiseptics	Prevents the growth of bacterial flora	Skin sepsis, leg ulcers
Antivirals	Prevents the replication of viruses	Herpes simplex and zoster
Coal tar	Presumed anti-inflammatory and anti-proliferative effects	Eczema, psoriasis
Corticosteroids	Anti-inflammatory, anti-proliferative, vasoconstrictive; different strengths available	Eczema, discoid lupus erythematosus, lichen planus, lichen sclerosus, mycosis fungoides, psoriasis
Dithranol	Anti-proliferative	Psoriasis
Vitamin D analogues	Inhibit keratinocyte proliferation and promote differentiation	Psoriasis
Keratolytics	Lysis of dry keratinocytes	Acne, scaly eczemas.
Parasiticidals	Kill skin parasites	Lice, scabies.
Retinoids	Antiproliferative	Acne, psoriasis

Calcineurin inhibitors	Immunomodulatory, anti-inflammatory	Atopic dermatitis

Systemic Therapy

Systemic therapy is reserved for more serious condition and infections.

Group	Indications
Antiandrogens	Acne (only in females)
Antibiotics	Acne, rosacea, skin sepsis
Antifungals	Fungal Infection
Antihistamines	Eczema, urticaria, atopic dermatitis
Antileprotic	Dermatitis herpetiformis, leprosy, vasculitis
Antimalarials	Lupus erythematosus, prophyria cutanea tarda
Antivirals	Herpes simplex/zoster Herpes zoster, genital herpes simplex
Corticosteroids	Bullous disorders, connective tissue disease, vasculitis
Cytotoxics	Psoriasis, sarcoidosis, bullous disorders
Immunosuppressant	Psoriasis, atopic dermatitis, eczema, bullous disorders, lupus erythematosus
Retinoids	Keratinization disorders, acne

Phototherapy

Sunlight helps certain skin conditions, both UVB and UVA are employed. UVB (290–320 nm) is given 3 times a week. The initial dose is determined from the patients skin type or *minimal erythema dose* (MED). With each visit, the scheduled dosage is increased. Commonly, 10–30 treatments are the normal course. UVB can be used in children and pregnant women. It may be used in psoriasis, mycosis fungoides, atopic eczema. Side effects include acute sunburn and increase risk of skin cancer.

Photochemotherapy (PUVA)

UVA alone has minimal effect, thus it is used in combination with photosensitizing psoralens given topically or systemically. PUVA means «**P**soralens plus **U**ltra**V**iolet **A**». Commonly, oral 8-methoxypsoralens is taken 2 hours before UVA (320–400 nm). The psoralens are photoactivated, which results in DNA cross-linking, inhibition of cell division, and suppression of cell-mediated immunity. Like UVB, the initial dose of UVA is determined by MED or skin type; and dosage is increased a scheduled visits. PUVA is usually given 2–3 times per week for 15–25 treatments. PUVA can be combined with acitretin (RePUVA) but not methotrexate. There are some variants of PUVA — for example bath PUVA or local PUVA with topical psoralen that may be effective in psoriasis and dermatitis involving the hands or feet. PUVA may be given for psoriasis, mycosis fungoides, atopic eczema, polymorphic light eruption or vitiligo. Acute side effects include pruritus, nausea, erythema; long-term side-effects of premature skin ageing and

skin cancer depend on the number an total dose of UVA. Cataracts are possible and UVA-opaque sunglasses must be worn for 24 hours after taking psoralen.

Cryotherapy

Liquid nitrogen (-196°C) is delivered by cotton wool bud or spray gun and injures cells by ice formation. After immersion into liquid nitrogen, the cotton wool bud is applied to the lesion for 10–15 seconds until a thin frozen halo appears at the base. The spray gun is used at a distance of 10 mm for a similar amount of time. Longer freezing times are given for malignant tumors. Blisters may develop within 24 hours. These are punctured and a dry dressing applied. Side effect may include hypopigmentation of pigmented skin, ulceration (especially on the lower legs of the elderly). Treatment may be repeated in 4 weeks if needed. Cryotherapy may be used for viral warts, seborrheic keratosis, molluscum contagiosum, intraepidermalcarcinoma.

Laser (Light Amplification by Stimulated Emission of Radiation)

High intensity light energy is applied to the tissue. Laser surgery is a rapidly changing field in which new types of lasers, as well as the conditions amenable to treatment, are continually being introduced. Lasers vary from a continuous-wave carbon dioxide laser to a short-pulsed pigment Q-switched ruby laser. Uses for lasers are equally varied and include: port wine stain nevi, telangiectasia, viral warts, some tumors, and tattoos.

LECTURE 2. OBSERVATION OF THE SKIN PATIENT (SCHEME OF THE CASE HISTORY)

The examination of the skin patient has some peculiarities. For the examination it is necessary some circumstances: good lighting (some lesions may change the color in a different light), adequate privacy (skin patients often have psychological problems), light torch, spatula, magnifying glass and transparent glass slide for diascopy.

General impression on the patient is very important. General health, pallor, intellectual assessment, queer personality etc. should be picked up by an observant doctor.

Be certain that the patient is completely undressed. Examination of the face and exposed extremities does not constitute full assessment. Patients may be unaware of lesions or problems in areas that are inaccessible to them (back, feet). Carefully examine skinfolds (axillary, under breasts). Be certain to remove shoes and socks to inspect bottom of the feet and between toes.

Case history consists of several parts:

1. **Passport data** includes short information about the name of the patient, age of the patient, address, profession, how long the patient has been hospitalized, what was the first diagnosis.

2. **Complains of the patient.** The first thing that physitian has to find out is if the patient has raptures of the skin, were they are situated, if the patient has

pruritus or pain. It`s necessary also to find out the character of the itch, when the itch is more severe. The student has to identify what complains are the most important and compare them with the raptures in the skin.

3. **Anamnesis morbi.** During this part the main questions should be asked: when did the disease begin? Does the patients has pruritus, pain? In what part of the body did the lesions begin? How did they change? During what period? Does the patient can determine what factors provoke the disease? Did the patient had the treatment before? What treatment? Does anybody of the family had had skin diseases before?

4.**Anamnesis vitae** includes data about race, geographical factors (especially for immigrants), occupation, sports, hobbies, social background, ethnic tradition (dietary habits), past medical history: allergy to medication, hay fever, asthma, past major illness or operation. Social & occupational history: travel abroad, hobbies and details of the type of work, substances in contact.

5. **Status present** is described according to the principles of general therapy. All main systems are described: respiratory, blood circulating, urinary, intestinal.

Also the general look of the skin is described: the color, elacticy, lubrication, dryness, turgor.

Descriptive terms used to describe skin color may include:

— **Carotenaemia** — excessive circulating beta-carotene (vitamin a precursor derived from yellow/orange coloured vegetables and fruit) results in yellow/orange skin colouration. Tends to be pronounced on palms and soles. Does not affect cornea.

— **Hyperpigmentation** — hypermelanosis or haemosiderin deposits result in skin colour that is darker than normal.

— **Hypopigmentation** — loss of melanin results in skin colour that is paler than normal but not completely white.

— **Leukoderma** — white skin. Also known as **achromia**.

— **Infarcts** — black areas of necrotic tissue due to interrupted blood supply.

— **Jaundice** — excessive circulating bilirubin results in yellow/green skin colour, prominent in cornea.

— **Erythema** — red skin due to increased blood supply and blanch with pressure (diascopy).

— **Erythroderma** — the skin condition affects the whole body or nearly the whole body, which is red all over.

— **Telangiectasia** — prominent cutaneous blood vessel.

6. **Status localis.** Skin lesions may be isolated (solitary or single) or multiple. The localization of multiple lesions in certain regions helps diagnosis, as skin diseases tend to have characteristic distributions. What is the extent of the eruption and its pattern?

Some termins that characterized determination:

— **Acral** — affects distal portions of limbs (hand, foot) and head (ears, nose).

— **Dermatomal** — corresponding with nerve root distribution.

— **Extensor** — involving extensor surfaces of limbs. Contrast with **flexor** surfaces.

— **Flexural** Involving skin flexures (body folds); also known as **intertriginous**.

— **Follicular** — individual lesions connected with follicles. These may be grouped into confluent plaques.

— **Generalised** — universal distribution: may be mild or severe, **scattered** or **diffuse**.

— **Herpetiform** — grouped umbilicated vesicles, as arise in *Herpes simplex* and *Herpes zoster* infections.

— **Koebnerised** — rising in a wound or scar. The Koebner phenomenon refers to the tendency of several skin conditions to affect areas subjected to injury.

— **Photosensitive** — favouring sun exposed areas. Does not affect skin that is always covered by clothing.

— **Pressure areas** — affecting areas regularly prone to injury from pressure at rest: tops of the ears when sleeping, buttocks when sitting, heels when lying.

— **Seborrhoeic** — the areas generally affected by seborrhoeic dermatitis, with a tendency to oily skin (seborrhoea). Scalp, behind ears, eyebrows, nasolabial folds, sternum and interscapular.

— **Symmetrical** — in the same regions, the left side is affected in a similar way to the right side.

— **Truncal** — rarely affects limbs.

— **Unilateral** — wholly or predominantly on one side of the affected region.

Primary elements:

Lesions may be solitary or multiple. If there are widespread eruption of lesions it is called **rash**. The rash may consist of one type of elements **(monomorphic)** or have different elements **(polymorphic)**.

— **Macule:** flat area of altered colour or texture (less than 0.5 cm). **Patch** is a large macule (more than 2 cm). Macules may be hemorrhagic, pigment, inflammatory (Figure 1).

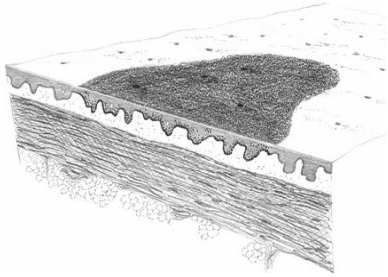

Figure 1 — Macule

— **Papule:** elevated solid lesion (less than 0.5 cm). They are raised above the skin surface. They may be acuminate (pointed), dome-shaped (rounded), filiform

(thread-like), flat-topped**,** oval or round**,** pedunculated (with a stalk), sessile (without a stalk), umbilicated (with a central depression), verrucous (warty) (Figure 2).

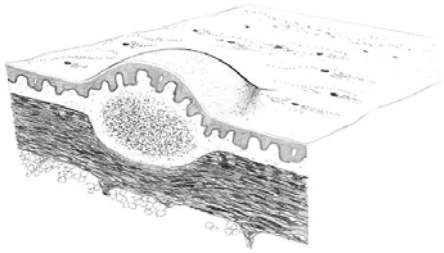

Figure 2 — Papule

— **Nodule:** elevated solid lesion (more than 0.5 cm) (Figure 3).

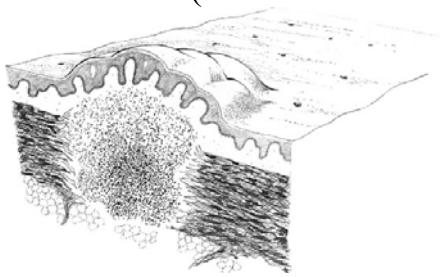

Figure 3 — Nodule

— **Plaque:** elevated area of skin of more than 2 cm in diameter, a disc shaped lesion, formed by extension or coalescence of papules or nodules. They may be annular (ring shaped), arcuate (half-moon), polygonal (varied non-geometric shape), polymorphic (varied shape), serpiginous (in the shape of a snake), poikilodermatous (variegated appearance, usually mixed pallor, telangiectasia & pigmentation).

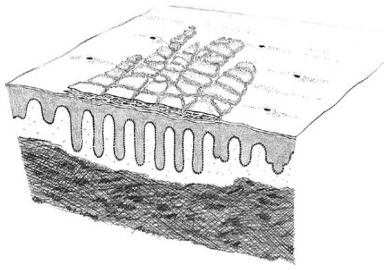

Figure 4 — Plaque

— **Vesicle:** fluid filled blister (less than 0.5 cm).
— **Bulla:** larger blister (more than 0.20 in).

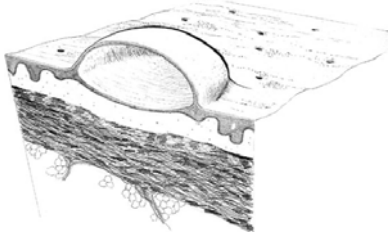

Figure 5 — Blister (intraepidermal)

— **Pustule:** elevated, circumscribed, palpable encapsulated structure filled with purulent liquid.

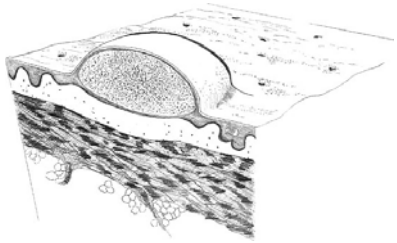

Figure 6 — Pustule

— **Tumor:** elevated, solid structure, may or may not be clearly marked, greater than 2 cm.

— **Wheal (blister, urticaria):** oedematous papule or plaque caused by swelling in the dermis. Wealing often indicates urticaria (Figure 7).

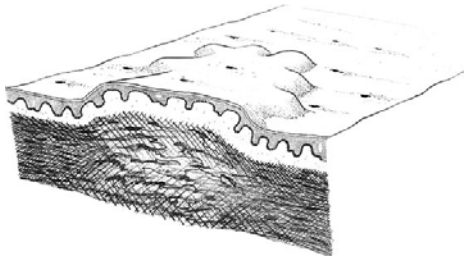

Figure 7 — Wheal

Secondary elements:

— **Lichenification** is caused by chronic rubbing, which results in palpably thickened skin with increased skin markings and lichenoid scale. It occurs in chronic atopic eczema and lichen simplex (Figure 8).

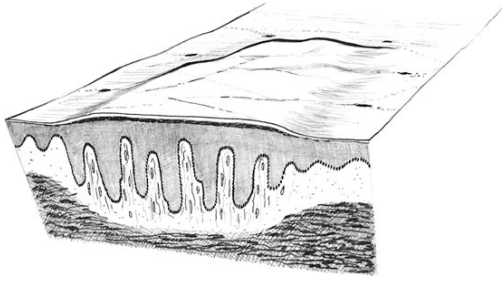

Figure 8 — Lichenification

— **Crusting** occurs when plasma exudes through an eroded epidermis. It is rough on the surface and is yellow or brown in colour. Bloody crust appears red, purple or black (Figure 9).

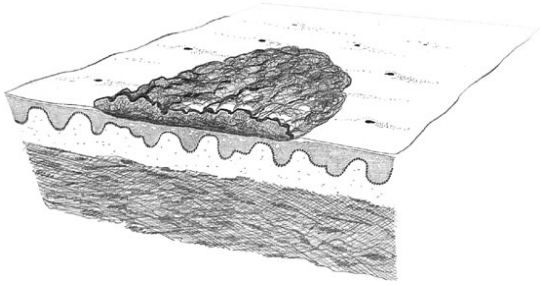

Figure 9 — Crust

— An **excoriation** is a scratch mark. It may be linear or a picked scratch (**prurigo**). Excoriations may occur in the absence of a primary dermatosis.

— **Erosion** is caused by loss of the surface of a skin lesion; it is a shallow moist or crusted lesion (Figure 10).

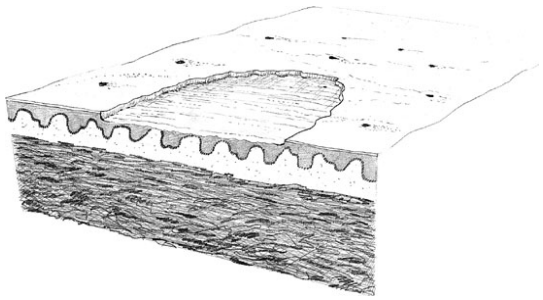

Figure 10 — Erosion

— **Fissure** is a thin crack within epidermis or epithelium, and is due to excessive dryness (Figure 11).

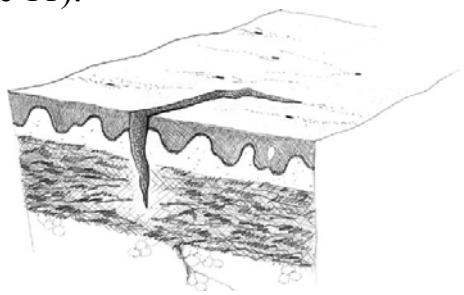

Figure 11 — Fissure

— **Ulcer** full thickness loss of epidermis or epithelium (Figure 12)**.**

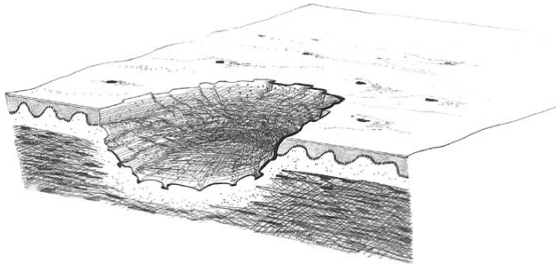

Figure 12 — Ulcer

— **Hypertrophy** is a component of the skin such as a scar **(cicatrix)** is enlarged or has grown excessively. The opposite is **atrophy** or thinned skin (Figure 13 and 14).

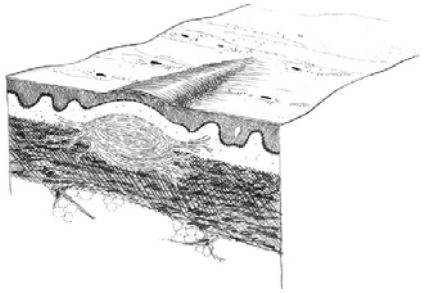

Figure 13 — Scar

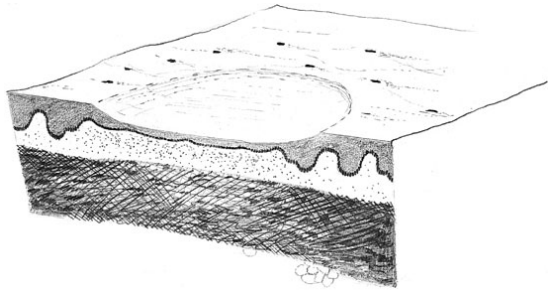

Figure 14 — Atrophy

— **Scaling** is an increase in the dead cells on the surface of the skin (stratum corneum) (Figure 15).

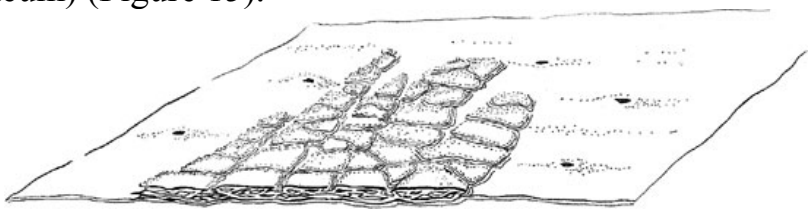

Figure 15 — Scaling

— **Vegetation** is an increased growth of prickle layer of epidermis that results as formation of papillary structures.

Configuration of the elements:

Skin lesions are often grouped together. The pattern or shape may help in diagnosis as many skin conditions have characteristic configuration.

— **Nummular** — round (coin-shaped) lesions. Also known as **discoid**.

— **Linear** — linear shape to a lesion often occurs for some external reason such as scratching. Also **striate**.

— **Target** — concentric rings like a dartboard. Also known as **iris** lesion.

— **Gyrate** — a rash that appears to be whirling in a circle.

— **Annular** — lesions grouped in a circle.

Morfology of the skin elements:

- Skin lesions may be **flat**, **elevated** above the plane of the skin or **depressed** below the plane of the skin.
- They may be **skin coloured** or **red, pink, violaceous, brown, black, grey, blue, orange, yellow**.
- Consistency may be **soft**, **firm**, **hard**, **fluctuant** or **sclerosed** (scarred or board-like).
- The lesions may be **hotter** or **cooler** than surrounding skin.
- They may be **mobile** or **immobile**.

The skin surface of a skin lesion may be normal or smooth because the pathological process is below the surface, either dermal or subcutaneous. Surface changes indicate epidermal changes are present.

7. Laboratory findings and special methods

General methods:

Magnification with hand (palpation) is important to note the fine details of skin lesions: if they are profound, their surface, elevation.

Diascopy consists of pressing a transparent slide or plastic spatula over a skin lesion. Examiner will find this of special value to distinguish erythema or purpura. It is useful to detect the glassy yellow-brown appearance of papules in sarcoidosis, tuberculosis and other granuloma. Nikolsky's sign is positive when a new blister is generated with ease by applying shearing force to skin.

Scratching may reveal some phenomenons as Auspitz's sign when slight scratching or curetting of a scaly lesion reveals punctate bleeding points within the lesion which suggests of psoriasis.

Specific methods:

Skin Biopsy

May be punch, scalpel or shaved. The specimen is prepared in the Department of Pathology and seen with the microscope. The result may be helpful for to make the proper diagnosis.

Wood's Lamp Examination

Ultraviolet light of 365 nm wavelength is obtained by passing the beam through a Wood's filter composed of nickel oxide containing glass. The examination has to be done in a dark room. Infected hair in tinea capitis caused by Microsporum canis will fluoresce bright green, skin lesion of active pityriasis versicolor will fluoresce yellow, fresh urine in porphyria cutanea tarda fluoresces a reddish colour, erythrasma will fluoresce coral red, vitiligo lesion appears more white and ashleaf macule in Tuberous sclerosis is more apparent, coral red fluorescence of teeth in congenital erythropoietic porphyria. Make sure

that there are no artificial cream or cosmetic are left in the area of skin examined by Wood's light because many creams or dyes will fluoresce under Wood's light.

Patch Test

This tests the type IV hypersensitivity reaction and it is a confirmatory test for allergic contact dermatitis. Standard patch test is used to screen and confirm allergic contact dermatitis. Further breakdown of the test may require patch test with different series e.g. fragrance series. The test materials are applied to the back under aluminium discs with occlusion. The sites are inspected at 48 hours and test materials removed. The sites are re-inspected at 96 hours for delayed reaction.

Mycology Examination

Superficial fungi can be identified by examination of the skin scraping, nail or hair. The scales, nail or hair should be collected onto a slide and a drop of 10 to 20 percent KOH to dissolve the keratin. It can be hastened by gently warming the preparation but never over warm to cause bubbles with artefacts affecting microscopic examination. It takes 10 to 15 minutes to prepare for scales, but it takes longer for nail clipping from 30 to 45 minutes for best preparation. Then it can be examined under low power objective and then the high power objective for detail. The tissue can also be sent for mycology culture. The result may not be available for 3 weeks.

Blood & Urine Tests

Just like that in general internal medicine, appropriate tests e.g. muscle enzymes to exclude dermatomyositis, urine sugar test to exclude diabetes mellitus.

Radiology Examination

The commonest tests done are X-ray chest to exclude pulmonary tuberculosis and X-ray joints for psoriatic arthropathy. CT scan is important for exclusion of internal enlarged lymph nodes in cutaneous lymphoma and to exclude brain lesions in a case of neurofibromatosis.

8. **Statement of the Diagnosis.** It is made on the basis of the previous parts: anamnesis vitae, morbi, laboratory tests, and complains. Diagnosis must be explained correctely.

9. **Differential Diagnosis** is performed with the similar diseases, all the factors are analyzed. It may be done in the form of a table.

10. **Individual Treatment and prophylaxis** includes paln of regimen, diet, general therapy, topical therapy, physiotherapy.

LECTURE 3. BACTERIAL INFECTIONS OF THE SKIN (PYODERMAS)

Pyodermas form the group of the diseases of the skin that are provoked by bacterial infection, usually by staphylococcus and streptococcus. These diseases are the most common diseases of the skin and are seen in 30–40 % of skin patients.

In the skin of a health person there are many microorganisms. Streptococcus is normally seen mostly in the folds of the skin, and staphylococcus in the follicules of the skin. The skin has regulating mechanisms for to protect itself from the pathogenic bacteria. The mechanism includes the protective function of stratum corneum, pH of the skin, permanent renewal of the skin cells and work of the immune system. Many factors may lead to beginning of the disease. All the factors may be divided in exogenic and endogenic.

In the most cases disease begins from the transformation of the coccus in the pathogenic forms. This transformation is the result of microtraumas of the skin,

influence of temperature (excessive high or low temperature may cause the changes in the regulatory mechanism of the skin). Chronic diseases of the internal organs (diabetes mellitus, tuberculosis) and immunodeficitis take part in the formation of chronic pyoderma. One of the reasons of the formation of chronic pyoderma is the prolonged use of corticosteroids for the treatment of others diseases.

All the pyodermas may be classified as according to their connection to follicules:

(Have the connection with follicules) — Staphilococcal	(Doesn't have connection with the follicules) — Streptococcal
Folliculitis, osteofolliculitis	Impetigo
Sycosis	Ectima
Boil (furunculitis)	Impetigo angularis
Carbuncle	Paronychial infections
Hydradenitis	

Staphylococcal Infections

Folliculitis

It`s a superficial (**osteofolliculitis**) or deep bacterial infection and inflammation of the hair follicles, usually caused by S. aureus but occasionally caused by other organisms. A superficial pustule or papule surrounds the hair follicle. The condition may follow or accompany other pyodermas. Infected hairs are easily removed, but new papules tend to develop. Folliculitis may become chronic in the places where the hair follicles are numerous or deep in the skin, as in the bearded area **(sycosis barbae).** Chronic low-grade irritation or inflammation without significant infection may occur when stiff hairs in the bearded area emerge from the follicle, curve, and reenter the skin.

Systemic therapy is only necessary in chronic and generalized forms. Topical antibiotics and antiseptics (eg, chlorhexidine) may be useful adjuncts to systemic therapy. Prompt treatment with systemic antibiotics may prevent chronic infection.

Boils (Furuncles)

It is an acute, tender, perifollicular inflammatory nodules resulting from infection by staphylococci. The condition often occurs in healthy young persons. Clustered cases may occur among teenagers living in crowded quarters with relatively poor hygiene or among contacts of patients infected with virulent strains.

Furuncles occur most frequently on the neck, breasts, face, and buttocks but are most painful when on skin closely attached to underlying structures (eg, on the nose, ear, or fingers). The initial nodule becomes a 5 to 30 mm elevated pustule in the erythematous skin that discharges a **core of necrotic tissue** and sanguineous pus. Furuncles may recur. Material for culture should be obtained

NB! A patient with a furuncle in the nose or central facial area and patients with multiple

from patients with single furuncles on the nose or central face, from patients with multiple furuncles, and from immunosuppressed.

A single furuncle is treated with intermittent hot compresses to allow the lesion to point and drain spontaneously.

Incision and drainage sometimes is necessary when it is well formed and incapsulated. Patients with recurrent furunculitis should be evaluated for predisposing factors, including obesity, diabetes, occupational or industrial exposure to inciting factors, and nasal carriage of S. aureus.

Hydradenitis Suppurativa

It is a painful local inflammation of the apocrine glands resulting in obstruction and rupture of the ducts. Usually S. aureus is initially involved.

The lesions may be confused with furuncles but tend to be more persistent and are diagnosed primarily by their location and clinical course. Clinically, the lesions are typically tender, reddish purple nodules resembling furuncles but occurring in apocrine sweat gland-bearing areas, including (in decreasing frequency) the axillae, the groin, around the nipples, and around the anus. Pain, fluctuation, discharge, and sinus tract formation are characteristic among patients who have had the disorder for years. In other chronic cases, coalescence of inflamed nodules may cause palpable cordlike fibrotic bands in the axillae. The condition may become extensive and disabling; if the pubic and genital areas are involved, walking may be difficult, and odors may be unpleasant. Although incision biopsy can be diagnostic, the diagnosis is invariably made on clinical grounds. Bacterial cultures may be helpful.

Susceptible patients should avoid irritants such as antiperspirants. Early simple cases are treated with incision and drainage, moist heat, and prolonged systemic antibiotic therapy. Intralesional corticosteroids may be effective in isolated lesions. Surgical excision and repair or grafting of the affected areas may be necessary if the disease persists. Botulinum toxin (Botox) can be injected in axillae region in severe sweeting.

Carbuncles

It is a cluster of furuncles with subcutaneous spread of staphylococcal infection, resulting in deep suppuration, often extensive local sloughing, slow healing, and a large scar. Carbuncles occur most frequently in males and most commonly on the nape of the neck. Although carbuncles occur in healthy persons, diabetes mellitus, debilitating diseases, and old age are predisposing

factors. Carbuncles develop more slowly than single furuncles and may be accompanied by fever and prostration. Treatment is the same as of furuncles.

Paronychial Infections

It is an acute or chronic infection of the periungual tissues. In acute paronychia, the causative organisms are usually S. aureus. They enter through a break in the epidermis resulting from a hangnail, trauma to a nail fold, or chronic irritation (eg, from water and detergents). Chronic paronychia usually occurs in occupations involving prolonged water contact (eg, waiters, bartenders, dishwashers) or is secondary to finger sucking. It is caused by infections of mixed bacteria and fungi, usually C. albicans.

The infection may follow the nail margin (lateral and proximal nail folds) or may extend beneath the nail and suppurate. Rarely, the infection penetrates deep into the finger; necrosis of the tendons and extension of the infection along the tendon sheaths may result. Eventually, the chronically infected nail becomes distorted. Acute paronychia may begin as a hangnail or ingrown nail and develop into an abscess in the paronychial fold adjacent to the nail plate. It causes rapid onset of pain, swelling, and erythema around a fingernail or toenail. Chronic paronychia is relatively insidious in onset. In chronic recurrent inflammation, subungual debris should be cultured for bacteria and for C. albicans.

Acute infection is treated with a systemic antibiotic. The accumulated debris is painful, and a purulent pocket (abscess) should be drained. Infection extending along the tendon sheaths requires prompt surgical incision, drainage, and referral to a hand surgeon. In chronic recurrent infections, the nail should be cut back to its point of detachment from the underlying skin. If C. albicans is not present on several cultures, applying tincture of iodine helps keep the subungual and paronychial areas dry and free of infection. If C. albicans is present, an antifungal lotion (eg, ciclopirox, miconazole) or cream (eg, ketoconazole) should be applied to the paronychial and subungual areas.

Staphylococcal Scalded Skin Syndrome (Ritter-Lyell Syndrome)

Staphylococcal scalded skin syndrome (SSSS) almost always occurs in infants, children < 6 yr old, and immunosuppressed adults or adults with renal failure. Epidemics may occur in nurseries, presumably transmitted by the hands of personnel in contact with an infected infant. However, nursery personnel may be nasal carriers of *S. aureus*. Sporadic cases also occur.

Pathogenesis:

SSSS cause group II coagulase-positive staphylococci that are often resistant to penicillin. Bacteria elaborate **exfoliatin** (also called **epidermolysin**), an epidermolytic toxin that splits off the upper part of the epidermis just beneath the granular cell layer. The inciting infection may be on the skin but usually is in the

eye or nasopharynx. The toxin enters the circulation and affects the skin systemically.

Clinics:

In infants, illness often begins during the first few days of life with a localized crusted infection (often impetigo-like), most often at the umbilical stump or in the diaper area. Sporadic cases often start with a superficial crusted lesion, frequently around the nose or ear. Within 24 h, tender scarlet areas appear around the crusted area and may become painful and generalized. Tissue **paper - like wrinkling** of the skin is followed by the appearance of large blisters that arise on the erythematous skin and quickly break and produce erosions. The epidermis peels off easily, often in large sheets, when the red areas are rubbed **(Nikolsky's sign).** Widespread desquamation of the skin occurs within 36 to 72 h, and patients may become very ill with systemic manifestations (eg, malaise, chills, fever). Loss of the protective skin barrier can lead to sepsis and to fluid and electrolyte imbalance.

Differential diagnosis:

Symptoms and signs are indistinguishable clinically from toxic epidermal necrolysis (TEN); yet SSSS must be distinguished rapidly from TEN because therapy is different. Cultures should be obtained from the skin and nasopharynx. Differential diagnosis includes drug hypersensitivity (most notably, TEN), viral exanthemas, and scarlet fever. Bullae, erosions, and an easily loosened epidermis occur in thermal burns, genetic bullous diseases (eg, some types of epidermolysis bullosa), and acquired bullous diseases (eg, pemphigus vulgaris, bullous pemphigoid).

Treatment:

With prompt diagnosis and therapy, death rarely occurs. Systemic penicillin's-resistant antistaphylococcal antibiotics (eg, cloxacillin, dicloxacillin, **cephalexin**) must be started as soon as the clinical diagnosis is made, **without waiting for culture results**. Maintaining fluid and electrolyte intake is necessary. **Corticosteroids are contraindicated** and topical therapy and patient handling must be minimized. If the disease is widespread and the lesions are weeping, the skin should be treated as if it were burned. The number of dressing changes should be minimized. Because the split is high in the epidermis, the stratum corneum is quickly replaced and healing is usually within 5 to 7 days after the start of treatment.

Streptococcal Infections

Impetigo

Impetigo is a highly contagious gram-positive bacterial infection of the superficial layers of the epidermis. It is often called «chool sores»because it affects children and is quite contagious. The 2 forms of the disease, **bullous and nonbullous** (crusted) impetigo, are caused by *Staphylococcus aureus* and group

A of beta-hemolytic streptococci (GABHS). Both organisms can be present at the same time. Impetigo presents as either a primary pyoderma of intact skin or a secondary infection of preexisting skin disease or traumatized skin. Impetigo rarely progresses to systemic infection, although poststreptococcal glomerulonephritis is a rare complication.

Bullous impetigo

The characteristic lesion of bullous impetigo is a vesicle that develops into a superficial flaccid bulla less than 1 cm in diameter on intact skin, with minimal or no surrounding redness. Initially, the vesicle contains clear fluid that becomes turbid. The roof of the bulla ruptures, often leaving a peripheral collarette of scale or a tubelike rim at the periphery. A varnishlike crust develops centrally, which if removed, reveals a moist red base. Intact bullae usually are not present. When present, intact bullae do not demonstrate a positive Nikolsky sign. Lesions of a primary skin disease, such as atopic dermatitis or varicella, may be present. Lesions may be localized or scattered widely. Lesions often are found on the face but may appear anywhere on the body. No regional lymphadenopathy is present. Rarely, infants may present with signs of pneumonia, septic arthritis, or osteomyelitis.

Nonbullous impetigo

The characteristic lesion of nonbullous impetigo is a fragile vesicle or pustule that readily ruptures and becomes a honey-yellow, adherent, crusted papule or plaque of less than 2 cm and with minimal or no surrounding redness. Lesions develop on either normal or traumatized skin or are superimposed on a preexisting skin condition (eg, scabies, varicella, atopic dermatitis). Lesions are located around the nose, mouth, and exposed parts of the body (eg, arms, legs), sparing the palms and soles. Localized lymphadenopathy usually is present, and nodes may be tender. If left untreated, lesions spread by autoinoculation then spontaneously resolve after a few weeks. Individual lesions resolve within 10-15 days. Rarely, pedal edema and hypertension may be noted in an individual with nonbullous impetigo. Both are signs of renal dysfunction most likely resulting from glomerulonephritis. No signs of pharyngitis are present.

Treatment depends on the extent and severity of the infection. Usually combination of topical and systemic antibiotics is used.

Ecthyma

Ecthyma begins as a vesicle or pustule overlying an inflamed area of skin that deepens into a dermal ulceration with overlying crust. The crust is gray — yellow and is thicker and harder than the crust of impertigo. A shallow, punched — out ulceration is apparent when adherent crust is removed. The deep dermal ilcer has a raised and indurate surrounding margin. Ecthyma;esions can remain fixed in size (sometimes resolving without treatment) or can progressively enlarge to 0,5–3 cm in diameter. Ecthyma heals slowly and commonly produces a scar. Regional lymphadenopathy is common, even with solitary lesions. Ecthyma can

be seen in areas of previously sustained tissue injury (excoriations, insect bites, dermatitis) and in patients who are immunocompromised (diabetes, neutropenis).

Impetigo angularis (perleche, cheilitis angularis, stomatitis angularis, angular cheilitis)

It is an acute or chronic inflammation of the skin and contiguous labial mucous membrane at the corners of the mouth. It is characterized by erythema, erosions and fissuring radiating from the labial commissures. A variety of factors are implicated, alone or in combination, including infective agents (Candida species, staphylococci, streptococci), mechanical factors, disease of the skin (atopic dermatitis, seborrhoeic dermatitis), and nutritional deficiencies.

Atypical bacterial infections

Pyoderma gangrenosum

Pyoderma gangrenosum is an uncommon cause of skin ulceration. It may affect any part of the skin, but the lower legs are the most common site. It is thought to be an autoimmune disorder. Pyoderma gangrenosum often affects a person with an underlying internal disease such as: inflammatory bowel diseases (ulcerative colitis and Crohn's disease), rheumatoid arthritis, myeloid blood dyscrasias, chronic active hepatitis.

Pyoderma gangrenosum usually starts quite suddenly, often at the site of a minor injury. It may start as a small pustule, red bump or blood-blister. The skin then breaks down resulting in an ulcer. The ulcer can deepen and widen rapidly. Characteristically, the edge of the ulcer is purple and undermined as it enlarges. It is usually very painful. Several ulcers may develop at the same time. Untreated, the ulcers may continue to enlarge, persist unchanged or may slowly heal. Treatment is usually successful in arresting the process, but complete healing may take months. Pyoderma gangrenosum is diagnosed by its characteristic appearance. There is no specific test. The wound should be swabbed and cultured for micro-organisms, but these are not the cause of pyoderma gangrenosum. Biopsy may be necessary to rule out other causes of ulceration.

Treatment is non-surgical. The necrotic tissue should be gently removed. Wide surgical debridement should be avoided because it may result in enlargement of the ulcer. Often conventional antibiotics are prescribed prior to making the correct diagnosis. These may be continued if bacteria are cultured in the wound (secondary infection) or there is surrounding cellulitis (red hot painful skin), but they are not helpful for uncomplicated pyoderma gangrenosum. Small ulcers are best treated with: topical steroid creams, intralesional steroid injections, oral anti-inflammatory antibiotics. More severe disease requires immunosuppressive therapy: oral steroids or ciclosporin.

Pityriasis alba

Pityriasis alba is a common hypopigmented dermatitis that occurs primarily in school-aged children. The diagnosis is made clinically, and the treatment of this self-limited disorder is often unrewarding. Some authors suggest that it is an abortive form of the impetigo.

Pityriasis alba is generally an asymptomatic dermatitis. Half of patients have lesions limited to the face. A more severe variant of the disease is extensive pityriasis alba, which presents with lesions on the trunk and extremities. The extensive variant may be of longer duration and occurs in older patients more often than pityriasis alba does.

Clinically a flaky, hypopigmented, patchy dermatitis with fine scales involving the face and, at times, the neck and shoulders typically is found. There can be numerous (up to 20 or more) hypopigmented macules, which are ill defined and range in size from 1–4 cm.

A subgroup pf patients has associated atopy, in which stigmata of that disorder may be found. For the state of the diagnosis is necessary to perform mycological examination to exclude fungi infection. Treatment includes topical antibiotic creams.

Perifolliculitis Capitis Abscedens et Suffodiens (PCAS)

The condition can be associated with acne conglobata, hidradenitis suppurativa, and pilonidal cysts, with follicular blockage as the proposed common mechanism. As retention of material dilates follicles and causes them to rupture, keratin and organisms from the damaged hair follicles can initiate a neutrophilic and granulomatous response. Bacterial infection appears to be a secondary event, not an etiologic factor in the pathogenesis.

Clinical presentation. Vertex and occipital regions of the scalp are sites most often affected by PCAS. The main physical signs, depending on the disease stage, are perifollicular pustules, tender nodules (some discharging pus or a jellylike substance), intercommunicating sinuses between nodules, and patchy alopecia with scarring. Shedding hair from the surface of nodules and sparing in between the inflamed areas can be observed. Regional

lymphadenopathy is rarely noted. Spondyloarthropathy has been reported in patients with PCAS.

Treatment. Several methods and medicines have been tried in the treatment of PCAS, with most of them yielding disappointing results. Oral isotretinoin may be considered the treatment of choice. Intralesional corticosteroids (eg, triamcinolone acetonide at 5 mg/mL) can be injected into boggy nodules and sinus tracts. This results in a prompt decrease in inflammation and may reduce the severity of long-term scarring and hair loss. However, the benefit is short-lived, and intralesional corticosteroids should be considered a temporizing measure.

LECTURE 4. PARASITIC DISEASES OF THE SKIN

Scabies

Scabies — is an intensely pruritic, highly contagious infestation of the skin by the arachnid mite *Sarcoptes scabiei,* variety *hominis*.

Scabies has played an important role in world history, with epidemics partially coinciding with military activities and major social events. Scabies has been recognized as a disease for approximately 2500 years. Historically, it was treated with topical sulfur, a treatment still in use today. Like syphilis, scabies has come to be known as the great imitator. Its spectrum of clinical manifestations may lead the practitioner to the wrong diagnosis.

Pathophysiology. The mite, *S scabiei,* spreads disease through direct and prolonged contact with the host. The mite remains viable for 2–5 days on inanimate objects; therefore, transmission through fomites, such as infected bedding or clothing, is possible, but less likely. Once bound to their host, 10–15 mites mate on the surface of the skin. After mating, the male mite dies. The female mite burrows into the epidermis of the host using her jaws and front legs, where she lays up to 3 eggs per day for the duration of her 30 to 60 day lifetime. An affected host harbors approximately 11 adult female mites during a typical infestation. The eggs hatch in 3–4 days. The larvae leave the burrow to mature on the skin. A delayed type IV hypersensitivity reaction to the mites, their eggs, or scybala (packets of feces) occurs approximately 30 days after infestation. This reaction is responsible for the intense pruritus, which is the hallmark of the disease. Individuals who are already sensitized from a prior infestation can develop symptoms within hours.

Scabies is usually transmitted by direct contact with an affected individual. Although disputed, some believe one can become infested by indirect contact with the personal items or clothing of an affected person because the mite can survive away from the skin for 2–5 days. This is much more likely to occur in the environment of someone with crusted or **hyperkeratotic scabies.**

Clinics:

The diagnosis of scabies can be suspected in any patient presenting with a recent onset of intense itching, especially at night. An increase in the intensity of the pruritus often forces the patient to seek medical attention. Importantly, attempt to elicit a history of pruritus in family members, sexual partners, close contacts, and pets.

Itch is usually present in the palms, interdigital areas, axillaes, gluteae region, stomach, but can be generalized. In grown-ups the rash usually doesn`t

affect face and neck However, in infants and young children, the lesions are localized to the face, neck, trunk, palms, and soles. Patients with crusted scabies may itch only 50% of the time (Figure 1).

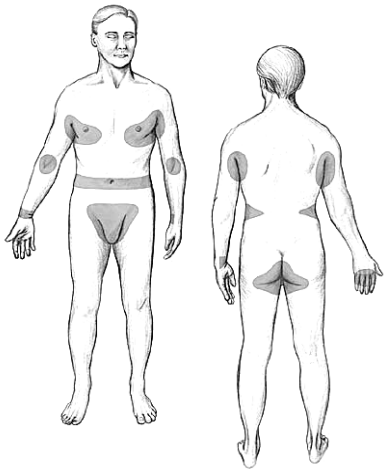

Figure 1 — Typical location of scabies

The burrow appears as a **straight, curved, or S-shaped line**. It is usually 2–5 millimeters long, slightly elevated, and pinkish-white. A **black dot** may be seen at one end of the burrow, indicating the presence of a mite. Common locations include the webbed spaces of the fingers, flexor surfaces of the wrists, elbows, axillae, belt line, feet, and scrotum in men and areolae in women. In infants, burrows are commonly located on the palms and soles (Figure 2).

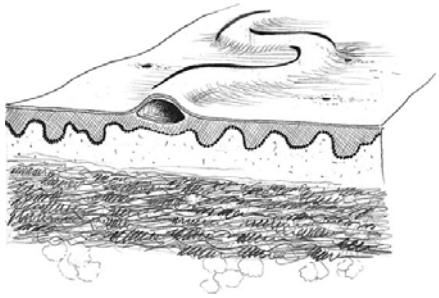

Figure 2 — Burrow

Vesicles and papule**s** usually pared can be seen near burrows or alone. Vesicles appear as discrete lesions filled with serous rather than purulent fluid.

Secondary elements are usually the result of excessive scratching. Characteristic findings include excoriations, postinflammatory hyperpigmentation, generalized eczematous dermatitis, erythroderma, prurigolike lesions, and pyoderma.

Specific additional symptoms of scabies:

- **Gorchakov`s symptom** — hemorrhagic crusts in the area of the elbows.
- **Ardi symptom** — impetigo-like elements around elbow area.

• **Triangular symptom** — crusts, excoriations, papular-pustular elements in the glutea and sacral areas.

Atypical forms of scabies:

1. In 1848, Norwegians Danielssen and Boeck described a highly contagious variant of scabies that occurs in immunocompromised patients. **Crusted or hyperkeratotic scabies**, as it has come to be known, is an overwhelming scabies infestation. This rare form of scabies occurs in elderly or mentally incompetent patients. Because of an impaired antibody response, these individuals can be infested with thousands to a couple million mites.

2. Nodular scabies occurs in 7–10% of patients with scabies. Pink, tan, brown, or red nodules can be seen. They range from 2–20 millimeters in diameter

NB! Papules rarely contain mites and most likely are due to a **hypersensitivity reaction.** Papules are common on the shaft of the penis in men

3. Scabies without a burrow can develop in patients that wash hands often. In such cases the clinics can be not so prominent.

4. Scabies developed during use of corticosteroids. Corticosteroids that are used for the treatment of other diseases may prevent the development of the inflammation and make the diagnosis more difficult.

5. Scabies of the animal`s mites. Animals can transmit nonhuman scabies to people. Human infestation with animal scabies is known to be self-limiting, and, clinically, burrows are often absent. Cases have been documented of transmission from horses, cattle, goats, camels, llamas, sheep, foxes, and, most commonly, dogs. In fact, canine scabies is known as mange.

Laboratory examination. The most common and useful technique used to diagnose scabies is examination of skin scrapings under light microscopy. A definitive diagnosis is made if the scraping contains a mite, larvae, eggs, or fecal pellets.

Treatment:

1. In adults and children over five years of age, 5 % **permethrin cream** is a standard therapy for scabies. This agent is highly effective, minimally absorbed, and minimally toxic. Adverse effects include itching and stinging on application. After the patient bathes or showers, 5 % permethrin cream is applied to the entire body from the neck down. The cream is washed off after eight to 14 hours. Unless new lesions develop within 10 days, retreatment is unnecessary. The 5 percent permethrin cream may be used in infants **more than two months of age**. In children less than five years of age, the cream must be applied to the head and neck, as well as the body. Permethrin is a pregnancy category B drug and has been used without apparent ill effects in pregnant women. Its safety in

breastfeeding is unknown. When a nursing mother has to be treated with permethrin, it would be appropriate for her to bottle-feed her infant and discard pumped breast milk until residual cream has been washed off thoroughly.

2. Previously, 1 % **lindane** lotion was the standard treatment for classic scabies. Although lindane is generally effective, treatment resistance has occurred. The chief advantage of lindane is its low cost. The primary disadvantage is the potential for neurotoxicity, if misused, which may be increased in patients with major breaks in their skin (e.g., those with crusted scabies) or in infants and small children. Lindane lotion is applied like permethrin cream, but it is washed off after six hours and reapplied one week later.

3. 5 or 10% precipitated **sulfur** in petrolatum is effective. This agent is inexpensive and can be made by a compounding pharmacy. It should be applied to the entire body (including the head and neck in newborns) for 24 hours and then reapplied every 24 hours for the next 5–7 days. A bath should be taken before each application and 24 hours after the last application. All clothing and bed linens should be changed when treatment is completed. Environmental control is essential for successful treatment.

4. **Benzylbenzoate** — 10 % in the form of lotion or cream is used in the 1st and 4th days of the treatment.

Pediculosis

Infestation with lice is referred to as pediculosis. Lice are ectoparasites that live on the body. The 3 types of lice that parasitize humans are ***Pediculus humanus capitis*** **(head louse),** ***Pediculus humanus corporis*** **(body louse)**, and ***Pthirus pubis*** **(pubic louse)**. The disease is spread from person to person by close physical contact or through fomites (eg, combs, clothes, hats, linens). Overcrowding encourages the spread of lice. The body louse is the vector of typhus, trench fever, and relapsing fever.

Pathogenesis. Lice have claws on their legs that are adapted for feeding and clinging to hair or clothing. Head and body lice are similarly shaped, but the head louse is smaller. The pubic or crab louse is quite distinct in appearance; it has pincerlike claws resembling those of sea crabs. Lice are blood-sucking insects. They move freely and quickly, which explains their ease of transmission. The eggs **(nits)** are attached to the hair shaft, close to the skin surface, where the temperature is optimal for incubation. The eggs hatch in about 8 days. Nits are cemented to the hair shaft with chitin and are very difficult to remove. Pubic lice may be found on the short hairs of the body, areolar hair, axillary hair, beard, scalp margins, eyebrows, and eyelashes, in addition to pubic hair. Body lice and their eggs are predominantly found on clothing and should be looked for in the seams of clothes.

Clinical picture. Itching occurs, most commonly at night, scratching may cause inflammation and a secondary bacterial infection. Head lice are found most often on the back of the head and neck and behind the ears. Eyelashes may be involved. Adult body lice and nits are found in clothing seams. Uninfected bites present as erythematous papules, 2–4 mm in diameter, with an erythematous base. Pubic hair is the most common site of the pubic lice. Pubic lice may spread to hair around the anus, abdomen, axillae, and chest. Risk factors include overcrowding, poor hygiene, debilitated and malnourished individuals, sexual promiscuity.

Treatment: includes 1 % permethrin, 1 % lindane shampoo.

Topical agents are more likely to be effective when they are applied to dry hair. Screening of household contacts and treatment of those infested or sharing the same bed may reduce reinfestation. Treatment should be repeated after seven to 10 days if live lice are present. Use of a 50 % vinegar and water rinse after shampooing may help slightly with nit removal.

Pubic lice are readily transmitted sexually. Perhaps they occasionally may be transmitted through contaminated clothing or towels, although this is controversial. The presence of pubic lice should prompt an evaluation for other common sexually transmitted diseases, such as chlamydial infection and gonorrhea. Treatment is the same as for head lice. Sexual contacts also should be treated if infested.

Patients with body lice infestations should wash their entire body thoroughly and then put on clean clothing. If the infestation is severe, topically administered permethrin, pyrethrin, or malathion also may help. Clothing and bedding should be decontaminated by hot-water washing (60°C) and heated drying, or by dry cleaning. Body lice may transmit typhus and trench fever. Outbreaks of trench fever have occurred in homeless persons in the United States.

LECTURE 5. MYCOBACTERIAL INFECTIONS OF THE SKIN TUBERCULOSIS OF THE SKIN

Mycobacterium tuberculosis is the causative agent of tuberculosis (TB). In 1882, Robert Koch discovered and isolated the tubercle bacillus (*M tuberculosis*). TB is an ancient disease. Signs of skeletal TB (Pott disease) were evident in Europe from Neolithic times (8000 BCE), in ancient Egypt (1000 BCE), and in the pre-Columbian New World. TB was recognized as a contagious disease by the time of Hippocrates (400 BCE), when it was termed «phthisis» (Greek from *phthinein*, to waste away).

World incidence of TB increased with population density and urban development so that by the Industrial Revolution in Europe (1750), it was responsible for more than 25 % of adult deaths. Indeed, in the early 20th century, TB was the leading cause of death in the US. Neil Finsen won the Nobel Prize in Medicine in 1903 for introducing UV light into the treatment of skin TB. Just as systemic tuberculosis can be protean and diverse in its clinical manifestations, so tuberculosis of the skin is also highly variable in its clinical appearance, significance, and prognosis. Five factors that are important for the clinical presentation of cutaneous tuberculosis are:

1. The pathogenicity of the organism.
2. Its antibiotic resistance profile.
3. The portal of infection.
4. The immune status of the host, particularly the presence or absence of acquired immunodeficiency syndrome (AIDS) secondary to infection with human immunodeficiency virus (HIV), and
5. Various local factors in the skin (eg, relative vascularity, trauma, lymphatic drainage, and proximity to lymph nodes).

The incidence of tuberculosis has been increasing since 1984 owing to the following factors:

- Immigration of previously infected people from developing countries.
- Increasing homelessness and malnutrition.
- Worsening urban economic and social environments.
- Increased drug resistance.

• The relaxation, reduction, or elimination of tuberculosis-control programs over the past two decades.

• Physicians who have not treated their patients in accordance with recommended treatment guidelines.

• The increasing prevalence of AIDS.

The worldwide incidence of tuberculosis in 1990 was estimated by the World Health Organization (WHO) to be 7.5 million cases, with the greatest number occurring in Southeast Asia and the western Pacific regions with 4.9 million cases, followed by India with 2.1 million, then China with 1.3 million, and Indonesia with 0.4 million.

Microbiology. The bacterium *M. tuberculosis* measures 2.5 to 3.5 m in length by 0.3 to 0.6 nm in width. This slightly curved, sporeless, motile, obligate aerobic, Grampositive bacterium is acid, alkali, and alcohol-fast. It has a high lipid content and a slow growth rate. Its peptidoglycan skeleton contains approximately 30 different antigenic substances, of which the most important is the tuberculoprotein, the active component of tuberculin, which is the agent used for intradermal testing for delayed hypersensitivity. There are two types of *M. tuberculosis* — human and bovine —but apparently no clinical difference between infections caused by either type.

TB is an airborne communicable disease that occurs after inhalation of infectious droplets expelled from patients with laryngeal or pulmonary TB during coughing, sneezing, or speaking. Each cough can generate more than 3000 infectious droplets. Droplets are so small (1–5 μm) that they remain airborne for hours. The probability that disease transmission will occur depends upon the infectiousness of the tuberculous patient, the environment in which exposure takes place, and the duration of exposure. Approximately 20% of people in household contact develop infection (tuberculin skin test positive). Microepidemics have occurred in closed environments such as transcontinental flights and submarines. Tuberculin sensitivity develops 2–10 weeks after infection and usually is lifelong. Without treatment, an approximate 10% lifetime chance exists of developing active disease after TB infection (5% within the first 2 years, 5% thereafter). Increased risk of acquiring active disease occurs with HIV infection, drug abuse, diabetes mellitus, silicosis, immunosuppressive therapy, cancer of the head and neck, hematologic malignancies, end-stage renal disease, intestinal bypass surgery or gastrectomy, chronic malabsorption syndromes, low body weight, and in infants younger than 2 years. Because TB induces a strong immune response, individuals with positive tuberculin reactions are at a significantly lower risk of acquiring new TB infection. In HIV-infected individuals, active TB more likely occurs from reactivation of existing disease than from superinfection with a new mycobacterial strain.

Classification of the different forms of the tuberculosis of the skin

Local forms	Dissiminated forms
Lupus vulgaris	Lichen scrofulosorum
TB verrucosa cutis	Papulonecrotic tuberculid
Scrofuloderma	Miliary TB of the skin
TB cutis orificialis	Erythema induratum (Bazin disease)

Lupus vulgaris

Lupus vulgaris is a chronic and progressive form of cutaneous TB that occurs in tuberculin-sensitive patients. In most series, it is the most common form of cutaneous TB and has the most variable presentation. Lesions appear in normal skin as a result of direct extension of underlying tuberculous foci, of lymphatic or hematogenous spread, after primary inoculation, BCG vaccination, or in scars of old scrofuloderma. Historically, lupus vulgaris was most prevalent in northern Europe (cause of lower prevalence in Asian countries is not known), with affected females outnumbering males by 2–3:1.

Lesions usually are solitary, and more than 90 % involve the head and neck. Small, sharply marginated, red-brown papules **(tubercules)** of gelatinous consistency **(apple-jelly nodules)** slowly evolve by peripheral extension and central atrophy into large plaques. However, many clinicians in Asian countries who see large numbers of this entity have questioned the descriptive term «apple jelly nodules», since this is not seen in many pigmented patients. If we`ll press the tubercule we`ll see the depressing of the element that is called the **symptom of Pospelov.**

Reappearance of new nodules within previously atrophic or scarred lesions is characteristic. Cartilage (nose, ears) within the affected area is progressively destroyed (lupus vorax); bone usually is spared. Buccal, nasal, and conjunctival mucosas may be involved primarily or by extension.

TB verrucosa cutis

TB verrucosa cutis is an indolent warty plaque that occurs after **direct inoculation of TB** into the skin of individuals previously infected with *M tuberculosis* or *M bovis*. Reinfection of TB can result from accidental exposure to tuberculous tissue in high-risk groups, such as physicians, pathologists, and laboratory workers (anatomists' wart, prosectors' wart, verruca necrogenica). Farmers, butchers, and veterinarians contract this form of reinfection TB from tuberculous cattle. Individuals, especially children from lower socioeconomic groups, also can contract this lesion after contact with tuberculous sputum.

Lesions most commonly occur on the hands and, in children, the lower extremities. Infection starts as an asymptomatic warty papule often mistaken for verruca vulgaris. Slow growth and irregular peripheral extension occur. The lesion may show central involution with an atrophic scar or form massive papillary excrescence with fissures. Pus and keratinous material may extrude

from these fissures. Lesions usually are solitary, and regional nodes are not affected unless secondary bacterial infection occurs. Lesions may evolve and persist for years. Spontaneous resolution with scarring can occur.

Scrofuloderma

Scrofuloderma results from breakdown of skin overlying a tuberculous focus, usually at a lymph node but also at the skin over infected bones or joints. Historically, a high prevalence of scrofuloderma was seen in children infected with *M. bovis* from contaminated milk. The oral or tonsillar primary lesion progresses to cervical adenitis, formation of cold abscesses, and secondary breakdown of overlying skin.

Lesions present as firm, painless, subcutaneous nodules that gradually enlarge and suppurate, then form ulcers and sinus tracts in overlying skin. Typical ulcers have undermined edges and a floor of granulation tissue. Typical tubercles with acid-fast bacilli are found in the lower dermis and walls of the ulcer or abscess. Tubercle bacilli usually can be isolated from the purulent discharge. Tuberculin sensitivity usually is marked. Spontaneous healing can occur but often takes years and is accompanied by the formation of hypertrophic scars. Lupus vulgaris may develop in the vicinity of healing scrofuloderma.

Metastatic tuberculous abscess (tuberculous gumma) is a variant of scrofuloderma that occurs following hematogenous spread of mycobacteria to skin in tuberculin-sensitive individuals. Painless, fluctuant, subcutaneous abscesses form singly or at multiple sites, then break down into fistulas and ulcers resembling scrofuloderma. Typically, these lesions occur in malnourished children or in severely immunosuppressed patients.

Erythema induratum (Bazin disease)

Erythema induratum is a persistent or recurring condition associated with past or active TB. Inflammatory cutaneous and subcutaneous nodules that may ulcerate and scar occur in the posterior calves of women's legs (<10% of affected patients are men).

Lesions arise in small numbers as tender indurated plaques and nodules that may progress to ulceration and scarring. In early stages, inflammation occurs in venous walls with adventitial thickening and endothelial proliferation. A perivascular inflammatory infiltrate also may be present. Septal panniculitis is present, which may extend into fat lobules. Tubercle bacilli are not seen, and mycobacterial cultures usually are negative. Erythema induratum often recurs for years.

Lichen scrofulosorum

Lichen scrofulosorum is an eruption of asymptomatic, grouped, closely set, 1–2 mm, perifollicular, lichenoid papules affecting children and young adults with underlying TB. The eruption becomes more extensive for weeks, then slowly regresses for months without scarring. Recurrences are possible.

Papulonecrotic tuberculid

Papulonecrotic tuberculid occurs as a chronic and recurrent symmetric eruption of necrotizing skin papules appearing in clusters and healing with varioliform scars. Tubercle bacilli are difficult to demonstrate, but patients usually have an internal focus of TB and are tuberculin sensitive, and skin lesions resolve after anti-TB therapy.

TB cutis orificialis

Orificial TB results from autoinoculation of mycobacteria into the periorificial skin and mucous membranes in patients with advanced TB. Underlying disease can be pulmonary, intestinal, or genitourinary TB. Infectious mycobacteria shed from these foci are inoculated into surrounding mucous membranes and skin. Patients typically are older men. Tuberculin sensitivity is strong. The site of the periorificial lesion often is determined by trauma.

In orificial TB, the tip and lateral margins of the tongue are affected most frequently; however, hard and soft palate lesions also are common. Autoinoculation of tooth sockets can occur after extraction. Perianal skin, the vulva, the urinary meatus, and the glans penis also are described sites. Lesions start as red papules that evolve into painful, soft, punched-out, shallow ulcers. Tubercles with acid-fast bacilli can be found in the deep dermis and ulcer walls. Usually, patients that develop orificial TB have severe internal organ disease and the appearance of these lesions portends a poor prognosis.

Miliary TB of the skin

Miliary TB of the skin is a rare manifestation of fulminant miliary TB resulting from hematogenous spread of mycobacteria to multiple organs, including skin. The initial site of infection usually is pulmonary or meningeal. This disease occurs predominantly in children and may be coincident with other infections such as measles. Tuberculin sensitivity is absent and bacillary load is high, which is consistent with an overwhelming infection. Currently, numerous instances of miliary TB of the skin are reported in immunosuppressed individuals infected with HIV.

Disseminated lesions occur on all parts of the body, especially the trunk. Lesions erupt as small (millet-sized) red macules or papules. Purpura, vesicles, and central necrosis are common. Affected patients are gravely ill, and the prognosis is poor.

Diagnostics includes absolute criteria: culture, guinea pig inoculation, positive PCR and relative criteria: history and skin examination, active, visceral TB, positive tuberculin reaction, histopathology, response to the specific therapy.

Treatment. Isolate patients with possible TB infection in a private room with negative pressure (air exhausted to outside or through a high-efficiency particulate air filter). Medical staff must wear high-efficiency disposable masks

sufficient to filter the tubercle bacillus. Continue isolation until sputum smears are negative for 3 consecutive determinations (usually after approximately 2–4 wk of treatment). Unfortunately, these measures are neither possible nor practical in countries where TB is a public health problem.

Treatment regimens adequate for pulmonary TB also are effective for extrapulmonary disease. Treat infants and children with miliary TB, bone or joint TB, or TB meningitis for a minimum of 12 weeks.

Because of increased drug resistance among TB isolates, TB treatment regimens must contain multiple drugs to which the isolated bacillus is susceptible. These regimens must be taken regularly and for a sufficient period.

In most patients, initiate anti-TB treatment with a 4-drug regimen and include **ethambutol** or **streptomycin** in the initial regimen until results of drug susceptibility is known or the chance of drug resistance is minimized. Short-course therapy (for drug-susceptible strains in HIV-seronegative patients) lasts for 6 months. The initial phase of 4-drug treatment is for 2 months. The drugs are used as follows:

- Isoniazid: 5 mg/kg/d in adults; 10–20 mg/kg/d in children, not to exceed 300 mg.
- Rifampin: 10 mg/kg/d in adults; 10–20 mg/kg/d in children, not to exceed 600 mg.
- Pyrazinamide: 15–30 mg/kg/d in adults and children, not to exceed 2000 mg.
- Ethambutol: 15-25 mg/kg/d in adults and children or streptomycin: 15 mg/kg/d in adults; 20–40 mg/kg/d in children, not to exceed 1000 mg

If TB isolates are susceptible to isoniazid and rifampin, the second phase of treatment consists of isoniazid and rifampin for 4 months. Additional anti-TB drugs and longer treatment intervals often are needed.

Leprosy

Leprosy is a chronic granulomatous disease, caused by *Mycobacterium leprae,* which affects principally the skin and peripheral nervous system.

The earliest description of leprosy comes from India around 600 BC. It was then described in the Far East around 400 BC. In the fourth century, the disease was imported into Europe, where its incidence peaked in incidence in the 13 th century. The disease has now nearly disappeared from Europe. Affected immigrants spread leprosy to North America. Armauer Hansen discovered *M leprae* in Norway in 1873. It was the first bacillus to be associated with human disease. Despite this discovery, leprosy was not initially thought to be an infectious disease. Animal reservoirs of leprosy have been found in 3 species: 9-banded armadillos, chimpanzees, and mangabey monkeys.

Pathophysiology. The areas most commonly affected by leprosy are the superficial peripheral nerves, skin, mucous membranes of the upper respiratory tract, anterior chamber of the eyes, and testes. These areas tend to be cooler parts of the body. Tissue damage depends on cell-mediated immunity, the extent of bacillary spread and multiplication, immunologic complications (ie, lepra

reactions), and the development of nerve damage and its sequelae. *M leprae* is an obligate intracellular acid-fast bacillus with a unique ability to enter nerves.

Clinical picture. The disease is usually diagnosed on the basis of the following characteristic findings: anesthesia of a skin lesion or in the distribution of a peripheral nerve, thickened nerves, and typical skin lesions. Prodromal symptoms are generally so slight that the disease is not recognized until a cutaneous eruption is present. Actually, 90 % of patient present with numbness first, sometimes years before the skin lesions appear.

Temperature is the first sensation that is lost. Patients cannot sense extremes of hot or cold. The next sensation lost is light touch, then pain, and finally deep pressure. These losses are especially apparent in the hands and feet.

A hypopigmented macule is often the first cutaneous lesion. From this stage, most lesions evolve into the lepromatous, tuberculoid or borderline types.

According to the classification of Ridly-Dzopling (1966) there are some kinds of leprosy:

1. Interminate leprosy (IL).
2. Tuberculoid leprosy (TL).
3. Borderline tuberculoid leprosy (BT).
4. Borderline borderline leprosy (BB).
5. Borderline lepromatous leprosy (BL).
6. Lepromatous leprosy (LL).

WHO (1967) recommends identify only 3 forms — IL, LL and TL.

Indeterminate leprosy (IL)

This early form causes one to a few hypopigmented, or sometimes erythematous, macules. Sensory loss is unusual. Most cases evolve from this state into one of the other forms, depending on the patient's immunity to the disease. Those with strong immunity may become cured of disease. In some, the disease may persist in this indeterminate form. In those with weaker immunity, the disease progresses to one of the other forms.

Tuberculoid leprosy (TT)

Skin lesions are few in number. Usually, one erythematous large plaque is present, with well-defined borders that are elevated and slope down into an atrophic center. The lesions can become arciform or annular, and they can be found on the face, limbs or elsewhere, but spare intertriginous areas and the scalp. Another presentation involves a large asymmetric hypopigmented macule. Both types of lesions are anesthetic and involve alopecia. Spontaneous resolution can occur in a few years, leaving pigmentary disturbances or scars. Progression can also occur, leading to borderline-type leprosy. In rare instances in which a patient is untreated for many years, the lepromatous type can develop.

Neural involvement is common in TT leads to tender, thickened nerves with subsequent loss of function. The great auricular nerve and superficial peroneal nerves are often prominent.

Lepromatous leprosy (LL)

Early cutaneous lesions consist mainly of pale macules. Later, infiltrations are present, with numerous bacilli. Macular lesions are small, diffuse, and symmetric. The skin texture does not change, and little or no loss of sensation occurs. The nerves are not thickened, and sweating is normal.

The lateral eyebrows are affected by alopecia (ie, **madarosis**), which spreads to the eyelashes and then the trunk. Scalp hair remains intact. Lepromatous infiltrations can be diffuse, nodules (called **lepromas**), or plaques. The diffuse type results in the appearance of a **leonine facies**. Neuritic lesions are symmetric and slow to develop.

Eye involvement occurs, causing pain, photophobia, decreased visual acuity, glaucoma, and blindness. Testicular atrophy results in sterility and gynecomastia. Lymphadenopathy and hepatomegaly can result from organ infiltration. Stridor and hoarseness are a result of laryngeal involvement. Nasal infiltration can cause a saddle-nose deformity. Aseptic necrosis and osteomyelitis can occur with repeated trauma after joint invasion. Brawny edema of the lower extremities is a late finding. Unlike the other types of leprosy, LL cannot convert back to the less severe borderline or tuberculoid types of disease.

Diagnostics.

- Tissue smear testing. An incision is made in the skin, and the scalpel blade is used to obtain fluid from a lesion. The fluid is placed on a glass slide and stained by using the Ziehl-Neelson acid-fast method to look for organisms. The bacterial index (BI) is then determined.
- Histamine testing. This test is used to diagnose postganglionic nerve injury. Histamine diphosphate is dropped on normal skin and affected skin, and a pinprick is made through each site. The site forms wheal on normal skin but not where nerve damage exists.
- Skin biopsy. The skin biopsy sample should be examined for morphologic features and the presence of acid-fast bacilli. Biopsy is useful for determining the morphologic index (MI), which is used in the evaluation and treatment of patients. It is the number of viable bacilli per 100 bacilli in the leprous tissue.
- Sensory testing.
- Lepromin testing.

To perform this test, bacillary suspension is injected into the forearm. When the reaction is assessed

NB! This test indicates host resistance to *M leprae.* It results **do**

at 48 hours, it is called the **Fernandez** reaction and indicates delayed hypersensitivity to antigens of *M leprae* or mycobacterium that cross react. When the reaction is read at 3–4 weeks, it is called the **Mitsuda** reaction and indicates that the immune system is capable of mounting an efficient cell-mediated response

not confirm the diagnosis, but they are useful in determining the type of leprosy. **A positive finding indicates cell-mediated immunity, which is observed in TT. A negative finding suggests a lack of resistance to disease and is observed in LL. A negative result indicates a poorer prognosis**

• Polymerase chain reaction (PCR) analysis

PCR can be used to detect and identify *M leprae*. The technique is used most often when acid-fast bacilli are detected but clinical or histopathologic features are atypical. It is not useful when acid-fast bacilli are not detectable by means of light microscopy.

Treatment. The goals of pharmacotherapy are to reduce morbidity, prevent complications, and eradicate the disease.

Antimicrobials are used to eliminate organisms. The first-line drugs are **dapsone, rifampin, and clofazimine**. Other antibiotics include **minocycline, ofloxacin, and clarithromycin.**

For drug treatment purposes, infections are classified as **paucibacillary or multibacillary**. Paucibacillary disease can be treated with a combination of 2 drugs, whereas multibacillary disease requires triple-drug therapy. The length of treatment depends on the type of disease and the access to medicine.

Eyes, nerves, and the nose should be examined at follow-up to ensure the timely recognition of reactive disease. The real challenge in managing leprosy is the treatment of reactional states. Systemic steroids are effective in reducing inflammation and edema in reversal reactions; thus, they are the most helpful medications in preventing nerve damage. Emergency surgery may be necessary if a patient with profound nerve inflammation presents with a nerve abscess or loss of nerve function secondary to compression.

Consultations with an ophthalmologist, plastic surgeon, orthopedic surgeon, otolaryngologist, neurosurgeon, and/or neurologist may be necessary.

Further care. Patients with leprosy patients may need hospitalization for acute complications. Sanatoria, which were widely used in the past, are no longer necessary. Most patients can be treated on an outpatient basis.

WHO recommends 2 years of follow-up for paucibacillary disease and 5 years of follow-up for multibacillary disease. Patients should be monitored for possible lepra reactions. In some regions of the world, self-administration of medications is difficult. Medical posts or mobile units can be set up for the administration of medications and management of health-related issues. Supervision may be required

to achieve the maximum benefit from therapy. In patients taking dapsone, the complete blood count should be checked at frequent intervals early during the therapy and at less frequent intervals later during therapy. Sensation and muscle strength in the hands, feet, and eyes should be checked on a regular basis.

Deterrence/Prevention. Household contacts of patients with lepromatous disease should be annually monitored for 5 years after diagnosis. Children especially should be observed for the development of disease. **Dapsone prophylaxis is no longer advocated.** Attempts have been made to develop a vaccine against leprosy. The bacille Calmette-Guerin (BCG) vaccine has variable results in protection.

Prognosis. The prognosis depends on the stage of disease. In borderline cases, the disease has the potential to be down-graded to LL; these patients may have nerve damage. Even with corticosteroid treatment, neuritis may not be curable. The prognosis also depends on the patient's access to therapy, the patient's compliance, and the early initiation of treatment.

Patient Education. Patients first need an explanation of the diagnosis and prognosis. Their fears should be addressed because of the cultural stigma associated with leprosy. They may need psychological counseling because they may have difficulty in coming to terms with the disease or in feeling rejected by society. Patients need education on how to deal with anesthesia of a hand or foot. They must learn to carefully inspect their extremities for trauma and should be told to wear proper footwear. Inspecting limbs and eyes for onset of anesthesia or weakness is also important. Physical therapy and occupational therapy are important tools in rehabilitation. Patients need to learn how to recognize the onset of lepra reactions, and they should be told to seek immediate medical attention if these develop. Potential deformities can be prevented by educating patients about how to deal with existing nerve damage and by treating any sequelae of this damage.

LECTURE 6. LEISHMANIASIS

Leishmaniasis is a protozoan disease whose clinical manifectations depend both on the infecting sprices of Leishmania and the immune response of the host. Tramnsmission of the disease occurs by the bite of a sandfly infected with Leishmania parasites. Leishmaniasis is often classified as Old World Leishmaniasis (disease that appeared in Asia or Europe) and New World Leishmaniasis (usually America species).

Infection may involve only the skin — local (LCL), dissiminative (DCL), recidivans (LR) or Post-Kala-Azar Dermal leishmaniasis or the mucous membranes and internal organs — visceral leishmaniasis (VL). It has been recognized as an opportunistic disease in immunocompromised patients, particularly those infcted with HIV.

Clinical forms:

The form	Presence of the organisms	Infiltrate	Montenegro test
LCL	++++early lesions ±late lesions	Diffuse	Positive in 92 %
DCL	+++	Diffuse	Negative, may become positive with the treatment and that is the better prognosis
LR	±	Well organised granulomas	Strongly positive in 98 %
PKDL	±	Well organised granulomas	Most patients positive

MCL	±	Diffuse	Positive in 97 %
VL	Organisms are present in the skin, lymph node, spleen, bone marrow, blood (rarely)	Diffuse	Most patients positive 12 months after treatment

LCL (Localized Cuteneous Leishmaniasis)

Usually it affects unclothed parts of the body – face, neck, arms. It commonly presents with the solitary primary lesion. After the incubation period of 1 week-to 3 months a red papule apperes that enlarges into the plaque or nodule. The lesion develops into an ulcer, which is well circumscribed with a violaceous border. The ulcer base is granulomatous and crusted, and the margins are hypertrophic. Painless, rubbery subcutaneous nodules or cords rarely develop around the ulcer as a result of local lymphangitic spread of the organism. Draining of lymph nodules may reveal parasites. Itching and pain if present are mild. After approximately 1–36 months the ulcer spontaneously regresses leaving a scar with hypo- or hyperpigmentaion.

DCL (diffuse cutaneous leishmaniasis)

Lesions are disseminated, resemble lepromatous leprosy. Usually they begin as initially primary lesion and than dissiminates to the other areas of the skin. The lesions are presented as nonulcerative nodules full of parasites. Unlike leprosy, there is no nerve involvement. The disease does not affects internal organs, but only partially responds to treatment and can be chronic.

LR (Leishmaniasis recidivans)

LR appear near the periphery or the scar of the healed acure lesion of leishmaniasis. Clinically commonly presents as scaly, erythematous papules within scars or healed lesions, although ulcers, psoriasiform lesions and verrucous form can occur.

PKDL (Post-Kala-Azar Dermal leishmaniasis)

It is primary caused by Leishmania Donovani and is endemic in East Africa and India. Indian PKDL occurs in 20 % of patients approximately 1 to 2 years after recovery fron the visceral leishmaniasis. Hypopigmentd maculas are usually the first manifestation of PKDL in India, beginning from the small maculas that enlarge to the large irregular patches. Lesions are usually bilateral, symmetrical, apper primary on the chest and back, arms and neck. The pigmentary loss is never complete, and there is no change in the hair overlying the lesions. Erythematous maculas develop next, often on the face but can also develop in the hypopigmented areas. Finally, soft, painless, nonulcerative, yellowish-pink nodules replace the hypopigmented maculas and develop de novo. Nodules effect face, earlobes, trunk and genitalia, less frequently occur on

the hands and feet. Cases of PKDL are resistant to the therapy require longer duration of the therapy. Hypopigmented areas almost never completely repigment.

MCL (Mucocutaneous leishmniasis)

Is caused by L. braziliensis and L. panamensis. It is most common in the New World. 50 % of patients develope MCL within 2 years of the initial cutaneous lesions, 90 % within 10 years. One-third of the patients have no prior history of skin lesions. Mucous membrane involvement probably develops as a result of hematogenous or lymphatic dissemination, or occasionally from direct extension of nearby skin lesions. Factors associated with the development of MCL include male sex, large or multiple primary lesions, persistant lesions lasting longer than 1 year, inadecuate treatment of primary lesions. The disease often begins from the nasal septum, wich becomes inflamed and infiltrated and may perforate. MCL has a predilection for the distal cartilaginous part of the nose, resulting deformation has been named as a «tapir`s nose». On rare occasions dissemination to the mucous membranes of the eye and genitals is seen.

Diagnostics. In endemic areas diagnosis is made on the clinical ground including:

1. Small number of the lesions.
2. Lesions on the exposed area.
3. Lesions are resistant to the therapy.
4. There is no pain or itching.

Historically microscopy and the culture – is the golden standart for the treatment. Blood samples can be observed for to reveal anti-Leismania antibodies but it is more likely for the VL.
PCR reaction is useful for to reveal the specimen of the organism

NB! The introdermal leishmanian **test (Montenegro)** is useful in non-endemic areas. The test consists of intradermal injection of 0,10 to 0,20 ml of a suspension of antigen. The reaction is read at 48–72 houres and positive if there is induration and erythema over 10 mm in diameter. A positive test indicates that the patient has or has had leishmaniasis.

Treatment. In humans, treatment of leishmania infections is by pentavalent antimony compounds, applied locally, or given intravenously. The drug of choice is sodium antimony gluconate. Alternative drugs for some forms of infection are amphotericin B and pentamidine. In endemic areas, sandflies should be controlled by spraying dwellings with insecticides. Rodents, which can be an important reservoir should be controlled. Insect repellents and

protective clothing should be used to reduce the risk of sandfly bites. Dogs should be kept indoors after sunset and infected dogs removed. Vaccination against L. donovani infection has not proven effective. However vaccination against L. tropica has been useful in protecting children from the disease.

LECTURE 7. FUNGAL INFECTION

Fungal infections of the skin are also known as «mycoses». They are common and generally mild. However, in very sick or otherwise immune suppressed people, fungi can sometimes cause serious disease.

Growing fungi have branched filaments called **hyphae**, which make up the **mycelium** (like branches are part of a tree). Some fungi are compartmented by cross-walls (called **septae**). **Arthrospores** are made up of fragments of the hyphae, breaking off at the septae. Asexual **spores (conidia)** form on conidiophores. The sexual reproductive phase of many fungi is unknown; these are «fungi imperfecta» and include those which infect humans.

Yeasts form a subtype of fungus characterised by clusters of round or oval cells. In some circumstances they form a chain of cells called a **pseudomycelium**. All the fungi can be subdivided as:

- Anthropophylic — effect humans.

Zoophylic — effect animals.

Anthropozoophylic — effect animals and humans.

Geophylic — live in the sole may be not pathogenic.

Classification of fungi infections

- Superficial infections: affect stratum corneum.

- Dermatophytes (tinea): affect epidermis and upper layer of the derma.
- Subcutaneous infections: involve the deeper layers of the skin (the dermis, subcutaneous tissue and even bone).
- Systemic infection may result from breathing in the spores of fungi, which normally live in the soil or rotting vegetation or as opportunistic disease in immune compromised individuals.

Laboratory tests for fungal infection

To establish or confirm the diagnosis of a fungal infection, skin, hair and nail tissue are collected for microscopy and culture (mycology). Specimens for fungal microscopy and culture may include: scrapings of scale, skin stripped off with adhesive tape, hair which has been pulled out from the roots, brushings from an area of scaly scalp, nail clippings, skin biopsy.

The material is examined by **microscopy** by Potassium hydroxide (KOH) preparation or stained with blue or black ink. Microscopy can identify a dermatophyte by the presence of: fungal hyphae (branched filaments) making up a mycelium, arthrospores (broken-off spores), arthroconidia (specialised external spores), spores inside a hair (endothrix) or outside a hair (ectothrix).

Fungal elements are sometimes difficult to find, especially if the tissue is very inflamed, so a negative result does not rule out fungal infection. A yeast infection can be identified by the presence of: yeast cells, which may be dividing by budding and pseudohyphae (branched filaments similar to those of a dermatophyte) forming a pseudomycelium.

Culture identifies which organism is responsible for the infection. Growing the fungus in culture may take several weeks, incubated at 25–30ºC. The specimen is inoculated into a medium such as Sabouraud's dextrose agar containing at 37°C.

Pseudomycoses

Erythrasma

Erythrasma is a chronic superficial infection of the intertriginous areas of the skin. The incriminated organism is *Corynebacterium minutissimum,* which is usually present as a normal human skin inhabitant.

Pathogenesis. Corynebacteria invade the upper one-third of the stratum corneum; under favorable conditions such as heat and humidity, these organisms proliferate. The stratum corneum is thickened. The organisms are seen in the intercellular spaces as well as within cells, dissolving keratin fibrils. **The coral red fluorescence of scales** seen under Wood light is secondary to the production of porphyrin by these diphtheroids.

Clinical picture. Dark discoloration usually is limited to body folds. Infection commonly is asymptomatic, but it can be pruritic. Duration ranges from months to years. Widespread involvement of trunk and limbs is possible. The typical appearance is well-demarcated, brown-red macular patches. The

skin has a wrinkled appearance with fine scales. Infection commonly is located over inner thighs, crural region, scrotum, and toe webs. Axillae, submammary area, periumbilical region, and intergluteal fold are less commonly involved. Toe web lesions appear as maceration.

Lab Studies. Wood light examination reveals coral red fluorescence of lesions. Results may be negative if patient bathed prior to presentation. Gram stain reveals gram-positive rods.

Treatment. Erythromycin ointment is usually administered. Infection may be treated with topical and/or oral antibiotic.

Actynomycoses

Actinomycosis is caused by gram-positive filamentous bacteria that do not form spores and are not acid-fast. They belong to the order of Actinomycetales, family Actinomycetaceae, genus *Actinomyces.* Members of the genera *Propionibacterium, Actinobaculum,* and *Bifidobacterium* may cause similar clinical syndromes. These bacteria grow slowly in anaerobic-to-microaerophilic conditions, forming colonies with a characteristic molar tooth appearance. The most common isolated species are *Actinomyces israeli* and *Actinomyces gerencseriae, Actinomyces turicensis, Actinomyces radingae, Actinomyces europaeus*.

Actinomycosis is characterized by contiguous spread, suppurative and granulomatous inflammation, and formation of multiple abscesses and sinus tracts that may discharge sulfur granules. The most common clinical forms of actinomycosis are cervicofacial (lumpy jaw), thoracic, and abdominal. In women, pelvic actinomycosis is possible.

Pathogenesis. Actinomycetes are prominent among the normal flora. As these microorganisms are not virulent, they require a break in the integrity of the mucous membranes and the presence of devitalized tissue to invade deeper body structures and cause human illness. Furthermore, actinomycosis generally is a polymicrobial infection, with isolates numbering as many as 5–10 bacterial species. Establishment of human infection may require the presence of such companion bacteria, which participate in the production of infection by elaborating a toxin or enzyme or by inhibiting host defenses. These companion bacteria appear to act as copathogens that enhance the relatively low invasiveness of actinomycetes. Specifically, they may be responsible for the early manifestations of the infection and for treatment failures.

Clinical picture. Cervicofacial actinomycosis is the most common manifestation, comprising 50–70% of reported cases. Infection typically occurs following oral surgery or in patients with poor dental hygiene. This form of actinomycosis is characterized in the initial stages by soft-tissue swelling of the perimandibular area. Direct spread into the adjacent tissues occurs over time,

along with development of fistulas (sinus tracts) that discharge purulent material containing yellow (sulfur) granules. Invasion of the cranium or the bloodstream may occur if the disease is left untreated.

Thoracic actinomycosis accounts for 15–20% of cases. Aspiration of oropharyngeal secretions containing actinomycetes is the usual mechanism of infection. Thoracic actinomycosis commonly presents as a pulmonary infiltrate or mass, which, if left untreated, can spread to involve the pleura, pericardium, and chest wall, ultimately leading to the formation of sinuses that discharge sulfur granules.

Actinomycosis of the abdomen and pelvis accounts for 10–20% of reported cases. Typically, patients have a history of recent or remote bowel surgery (perforated acute appendicitis, perforated colonic diverticulitis following trauma to the abdomen) or ingestion of foreign bodies (eg, chicken or fish bones), during which actinomycetes is introduced into the deep tissues. The ileocecal region is involved most frequently, and the disease presents classically as a slowly growing tumor. Diagnosis is usually established postoperatively, following exploratory laparotomy for a suspected malignancy. Involvement of any abdominal organ, including the abdominal wall, can occur by direct spread, with eventual formation of draining sinuses. Actinomycosis of the pelvis most commonly occurs by the ascending route from the uterus in association with intrauterine contraceptive devices (IUCDs). In such cases, an IUCD has been in place for an average of 8 years.

Lab. studies. Anemia and mild leukocytosis are common. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are often elevated. Chemistry results usually are normal, with the exception of a frequently elevated alkaline phosphatase level in hepatic actinomycosis. Because actinomycosis is difficult to diagnose on the basis of the typical clinical features, direct identification and/or isolation of the infecting organism from a clinical specimen or from sulfur granules is necessary for definitive diagnosis in most cases. Acceptable specimen material is obtained from draining sinuses, deep needle aspirate, or biopsy specimens; swabs, sputum, and urine specimens are unacceptable or inappropriate. Prompt transport of the specimens to the microbiology laboratory is necessary for optimal isolation of actinomycete organisms, preferably in an anaerobic transport device. A Gram-stained smear of the specimen may demonstrate the presence of beaded, branched, gram-positive filamentous rods, suggesting the diagnosis. Cultures should be placed immediately under anaerobic conditions and incubated for 48 hours or longer; the isolation and definitive identification of actinomycetes may require 2–3 weeks. The preliminary diagnosis of actinomycosis also can be made by examining sulfur granules. Granules should be crushed between 2 slides, stained with 1% methylene-blue solution, and examined microscopically for features characteristic of actinomycetes.

Treatment. High-dose penicillin, administered over a prolonged period, is the cornerstone of therapy for actinomycosis. The risk of actinomycetes developing penicillin resistance appears to be minimal. Lack of a clinical response to penicillin usually indicates the presence of resistant companion bacteria, which may require modification of the antibiotic regimen (addition of an agent that is active against these copathogens). Antibiotics that possess no activity against *Actinomyces* species include metronidazole, aminoglycosides, aztreonam, co-trimoxazole (TMP-SMX), and penicillinase-resistant penicillins (methicillin, nafcillin, oxacillin, cloxacillin) and cephalexin. The data concerning the fluoroquinolones (ciprofloxacin, gatifloxacin and moxifloxacin) are insufficient.

Prognosis. When actinomycosis is diagnosed early and treated with appropriate antibiotic therapy, the prognosis is excellent. The more advanced and complicated actinomycotic forms require aggressive antibiotic and surgical therapy for optimal outcome; however, deaths can occur despite such therapy.

Superficial fungi infection

Tinea versicolor

Tinea versicolor is a common, benign, superficial cutaneous fungal infection usually characterized by hypopigmented or hyperpigmented macules and patches on the chest and the back. In patients with a predisposition, the condition may chronically recur. The fungal infection is localized to the stratum corneum.

Tinea versicolor is caused by the dimorphic, lipophilic organism, Malassezia furfur, which is the yeast-like microorganism.

Tinea versicolor occurs more frequently in areas with higher temperatures and higher relative humidities. Tinea versicolor occurs worldwide, with prevalences reported to be as high as 50 % in the humid. The disease is most common in persons aged 15–24 years. Its occurrence before puberty or after age 65 years is uncommon.

NB! M. furfur is a member of normal human cutaneous flora, and it is found in 18 % of infants and 90–100 % of adults. The organism can be found on normal skin and on skin regions demonstrating cutaneous disease. In patients with clinical disease, the organism is found in both the yeast (**spore**) stage and the filamentous (**hyphal) form**. Factors that lead to the conversion of the saprophytic yeast to the parasitic, mycelial morphologic form include a genetic predisposition; warm, humid environments; immunosuppression; malnutrition; and Cushing disease. Even though M furfur is a component of the normal flora, it can also be an opportunistic pathogen

Clinical picture. Tinea versicolor is a benign skin disease that causes scaly macules or papules on the skin. As the name implies (versi means several), the condition can lead to discoloration of the skin, with colors ranging from white to

red to brown. The condition is not considered to be contagious because the causative fungal pathogen is a normal inhabitant of the skin.

The involved skin regions are usually the trunk, the back, the abdomen, and the proximal extremities. The face, the scalp, and the genitalia are less commonly involved. The most common appearance of the disease is as numerous, well-marginated, finely scaly, oval-to-round macules scattered over the trunk and/or the chest, with occasional extension to the lower part of the abdomen, the neck, and the proximal extremities. The macules tend to coalesce, forming irregularly shaped patches of pigmentary alteration. As the name versicolor implies, the disease characteristically reveals a variance in skin hue. The involved areas can be either darker or lighter than the surrounding skin. A fine, dustlike scale covers the lesions. Patients often complain that the involved skin lesions fail to tan in the summer. Occasionally, a patient also complains of mild pruritus.

Lab Studies. The clinical presentation of tinea versicolor is distinctive, and the diagnosis is often made without any laboratory documentation. **Baltzer probe** can be performed with the solution of the iodium in the macula. Usually hyperpigmentation is seen because of accumulation of the iodium in the stratum corneum. The ultraviolet black (Wood) light can be used to demonstrate the coppery-orange fluorescence of tinea versicolor. However, in some cases, the lesions appear darker than the unaffected skin under the Wood light, but they do not fluoresce.

The diagnosis is usually confirmed by potassium hydroxide (KOH) examination, which demonstrates the characteristic short, cigar-butt hyphae that are present in the diseased state. The KOH finding of spores with short mycelium has been referred to as the **«spaghetti and meatballs or the bacon and eggs»** sign of tinea versicolor. For better visualization, ink blue stain and methylene blue stain can be added to the KOH preparation.

Special media are required for culture. Because the diagnosis is usually clinically suspected and can be confirmed with a KOH preparation, cultures are rarely obtained.

Patients should be informed that tinea versicolor is caused by a fungus that is normally present on the skin surface and is therefore not considered contagious. The condition does not leave any permanent scar or pigmentary changes, and any skin color alterations resolve within 1–2 months after treatment has been initiated. Recurrence is common, and prophylactic therapy may help reduce the high rate of recurrence.

Treatment. Tinea versicolor can be successfully treated with various agents during two weeks. Effective topical agents include selenium sulfide and azole, ciclopiroxolamine, and allylamine antifungals.

Oral therapy is also effective for tinea versicolor and is often preferred by patients because of convenience. Ketoconazole has been used both as a 14 day 200 mg daily. Itraconazole is used in regimen 200 mg daily during 14 days.

Piedra

Piedra, which means «stone» in Spanish, is an asymptomatic superficial fungal infection of the hair shaft. In 1911, Horta classified piedra into 2 types. The first is black piedra, which is caused by *Piedraia hortae.* The second is white piedra. The etiological agents of white piedra are now called *Trichosporon asahii* and 5 other species: *Trichosporon ovoides, Trichosporon inki, Trichosporon mucoides, Trichosporon asteroides,* and *Trichosporon cutaneum.* These 6 organisms are all causative agents of white piedra.

The 2 types of piedra occur in different climatic conditions. Black piedra is most common in the tropical regions of the world that have high temperatures and humidity. For example, black piedra may occur in many central South American countries, including Brazil, as well as in Southeast Asia. White piedra is more common in temperate and semitropical climates, such as those in South America, Asia, Europe, Japan, and parts of the southern United States. In addition, the 2 types of piedra affect the hair in different body locations. Black piedra usually affects scalp hair, whereas white piedra more commonly affects pubic hair, axillary hair, beards, mustaches, and eyebrows and/or eyelashes. However, in Brazil, white piedra is reported to affect scalp hair most commonly. White piedra affects horses and monkeys, in addition to humans. Black piedra occurs in monkeys and humans.

Pathogenesis. The environment and typical skin flora are the 2 main sources of infectious agents that cause piedra. The source of infection in black piedra, *P hortae,* appears to be in the soil; however, infection also has been traced to organisms in stagnant water and crops. The source of infection for white piedra, typically *T asahii,* can be present in the soil, air, water, vegetable matter, or sputum or on body surfaces. However, the mode of infection in man is not clear.

Clinical picture. White piedra shows irregular, white, cream-colored, or brown soft nodules or gelatinous sheaths along the hair shaft. They can be easily detached from the hair shaft. White piedra is found in the hair of the beard, moustache, genitals, and axilla. Eyebrow and eyelash involvement can also be present, while on the scalp, white piedra appears to be less common. Piedra may be asymptomatic in many patients. Patients may not be able to see the minute nodules that haphazardly develop on the hair shaft; however, they may feel the gritty nodules. Patients may hear a metallic sound when they brush their hair.

Black piedra consists of darkly pigmented, firmly attached nodules that vary in size to as large as a few millimeters in diameter. The nodules feel hard. The most commonly affected area of the body is the scalp hair. Black piedra less frequently affects beards, mustaches, and the pubic hair. The fungus grows into

the hair shaft; ultimately, it may cause hair breakage because of structural instability. In both varieties of piedra, the surrounding skin is healthy.

Lab. diagnosis. Place hair shaft nodules into a 10–15% potassium hydroxide preparation on a glass slide. If the nodule is from black piedra, tightly packed and pigmented hyphae, asci, and ascospores are seen attached to the hair shaft. If the nodule is from white piedra, darkly stained and loosely arranged hyphae, blastoconidia, and arthroconidia are seen attached to the hair shaft.

P hortae, the cause of black piedra, grows slowly on Sabouraud dextrose agar and is not inhibited by cycloheximide. Microscopic examination reveals septate hyphae, chlamydospores, and irregularly shaped hyphal elements. These cultures are of the asexual phase of the fungus. Organisms in the sexual phase are difficult to grow in culture. *T asahii,* the typical cause of white piedra, rarely grows on Sabouraud dextrose agar because of inhibition by cycloheximide.

Treatment. Shaving or cutting the hair is the treatment of choice. Black piedra is treated by using oral terbinafine. White piedra can be treated by using topical antifungals, including imidazoles, ciclopirox olamine, 2% selenium sulfide, 6% precipitated sulfur in petroleum, chlorhexidine solution, Castellani paint, zinc pyrithione, and amphotericin B lotion.

Dermatophytes

Dermatophytes have the ability to invade keratinized tissue (eg, hair, nails, any area of the skin) but are restricted to the dead cornified layer of the epidermis. Humid or moist skin provides a very favorable environment for the establishment of fungal infection. Clinically, tinea infections are classified according to the body region involved.

- Tinea capitis is infection of scalp hair.
- Tinea corporis is infection of the trunk and extremities.
- Tinea manuum and tinea pedis is infection of palms, soles, and interdigital webs.
- Tinea cruris is infection of the groin.
- Tinea barbae is infection of the beard area and neck.
- Tinea faciale is infection of the face.
- Tinea unguium (onychomycosis) is infection of the nail.

Tinea cruris

Tinea cruris, a pruritic superficial fungal infection of the groin and adjacent skin, is a common clinical presentation for dermatophytosis.

The most common etiologic agents for tinea cruris is **Epidermophyton floccosum**. Tinea cruris is a contagious infection transmitted by fomites, such as contaminated towels or hotel bedroom sheets, or by autoinoculation from a reservoir on the hands or feet (tinea manuum, tinea pedis, tinea unguium). The etiologic agents produce keratinases, which allow invasion of the cornified cell layer of the epidermis. The host immune response may prevent deeper invasion.

Risk factors for initial infection or reinfection include wearing tight-fitting or wet clothing or undergarments.

Patients complain of pruritus and rash in the groin. Additional historical information may include recently visiting a tropical climate, wearing tight-fitting clothes (including bathing suits) for extended periods, sharing clothing with others, participating in sports, or coexisting diabetes mellitus or obesity. Prison inmates, members of the armed forces, members of athletic teams, and people who wear tight clothing may be subject to independent or additional risk for dermatophytosis.

Clinical picture. Tinea cruris manifests as a symmetric erythematous rash in the groin. Large patches of erythema with central clearing are centered on the inguinal creases and extend distally down the medial aspects of the thighs and proximally to the lower abdomen and pubic area. Scale is demarcated sharply at the periphery. In acute infections, the rash may be moist and exudative. Chronic infections typically are dry with a papular annular or arciform border and barely perceptible scale at the margin. Central areas typically are hyperpigmented and contain a scattering of erythematous papules and a little scale. The penis and scrotum typically are spared; however, the infection may extend to the perineum and buttocks. Secondary changes of excoriation, lichenification, and impetiginization may be present as a result of pruritus. Chronic infections modified by the application of topical corticosteroids are more erythematous, less scaly, and may have follicular pustules. Approximately one half of patients with tinea cruris have coexisting tinea pedis.

Lab. tests. Microscopic examination of a potassium hydroxide (KOH) wet mount of scales is diagnostic. Growth on Mycosel or Sabouraud agar plates usually is sufficient within 3–6 weeks to allow specific fungal identification. Wood lamp examination may be helpful to exclude erythrasma, which reveals coral red florescence of the affected area.

Treatment. Clinical cure of an uncomplicated infection usually can be achieved using atopical antifungal agents of the imidazole or allylamone family. Prevention of reinfection is an essential component of disease management. patients with tinea cruris pften have concurrent dermatophyte infection of the feet and hands. It is necessary to treat all active areas of infection simultaneously to prevent reinfection of the groin from other body sites.

Tinea pedis (Athlet`s foot)

T. rubrum, T. interdigitale (mentagrophytes) and **Epidermophyton floccosum** most commonly cause tinea pedis, with **T. rubrum** being the most common cause worldwide:

Tr. rubrum	**Tr. interdigitale**
Affects soles and palms	Doesn't affect palmes
May affect all interdigital areas	Usually affects 3d and 4d interdigital area

Affects all nails in the palms and soles	Affects only 1st and 5th nails of the soles

Clinical picture. Commonly, patients describe pruritic, scaly soles and, often, painful fissures between the toes. Less often, patients describe vesicular or ulcerative lesions. Some patients, especially the elderly, may simply attribute their scaling feet to dry skin.

Patients with tinea pedis have 4 possible clinical presentations.

1. **Interdigital.** The interdigital presentation is the most characteristic type of tinea pedis, with maceration, fissuring, and scaling, most often between the fourth and fifth toes. The dorsal surface of the foot is usually clear, but some extension onto the plantar surface of the foot may occur.

2. **Chronic hyperkeratotic.** The hyperkeratotic type of tinea pedis is characterized by thick epidermis of the soles or palms resembling keratoderma.

3. **Inflammatory/vesicular.** Painful, pruritic vesicles or bullae, most often on the instep or anterior plantar surface, characterize the inflammatory/vesicular type. The lesions can contain either clear or purulent fluid; after they rupture, scaling with erythema persists. Cellulitis, lymphangitis, and adenopathy can complicate this type of tinea pedis.

4. **Scaly.** This clinical form is characterized by slight scaling and moderate erythema.

Lab Studies. Direct potassium hydroxide (KOH) staining is used for fungal elements. Usually, the fungal elements are easily identified from scaly lesions. A fungal culture may be performed to confirm the diagnosis and to identify the pathogenic species.

Prevention. Infection can occur through the contact with infected scales on bath or pool floors, so wearing protective footwear in communal areas may help decrease the likelihood of infection. Infected scales can be present on clothing, so frequent laundering is a good idea. Occlusive footwear promotes infection by creating warm, humid, macerating environments where dermatophytes live; therefore, patients should try to minimize foot moisture by limiting the use of occlusive footwear.

Treatment. Tinea pedis can be treated with topical or oral antifungals or a combination of both. Topical agents are used for 1–6 weeks. For interdigital tinea pedis, even though symptoms may not be present, a patient should apply the topical agent not only to the interdigital areas but also to the soles because of the likelihood of plantar-surface infection.

Recurrence of the infection is often due to a patient's discontinuance of medication after symptoms abate. Patients with extensive chronic hyperkeratotic tinea pedis or inflammatory/vesicular tinea pedis usually require oral therapy, as do patients with onychomycosis, diabetes, peripheral vascular disease, or immunocompromising conditions.

Tinea corporis

Usually it is caused by Tr. rubrum. Affects usually elderly and immunosuppressive persons. The rash can be generalized and resemble psoriasis, eczema. The primary elements — large patches of the different form with scaling. Combination of oral and local antifungals is used for the treatment.

Onychomicosis

Onychomycosis (OM) refers to a fungal infection that affects the toenails or the fingernails. It may involve any component of the nail unit, including the nail matrix, the nail bed, or the nail plate. OM is not life threatening, but it can cause inconvenience, pain, discomfort, and often serious physical and occupational limitations. Psychosocial and emotional effects resulting from OM are widespread and have a significant impact on the quality of life.

OM is caused by 3 main classes of fungi: dermatophytes, yeasts, and nondermatophyte molds. The clinical appearance of OM is indistinguishable based on the species of fungus causing the infection. Dermatophytes (including the genera Epidermophyton, Microsporum, and Trychophyton) are by far the most common cause of OM worldwide. Yeasts and nondermatophyte molds account for 8 % and 2 % of OM, respectively. T.rubrum is the most common pathogen.

Risk factors for OM include family history, increasing age, poor health, prior trauma, warm climate, participation in fitness activities, immunosuppression, communal bathing, and occlusive footwear.

The main subtypes of OM are:

1. Distal lateral subungual.
2. White superficial OM.
3. Proximal subungual OM.
4. Total dystrophic OM.

Clinical picture.

1. Distal lateral form presents as a thickened and opacified nail plate, nail bed hyperkeratosis, and onycholysis. Discoloration ranges from white to brown. The edge of the involved area is often dystrophic.

2. White superficial onychomycosis is usually confined to the toenails, and it presents as small, white speckled or powdery patches on the surface of the nail plate. The nail becomes roughened and crumbles easily.

3. Proximal subungual presents as an area of leukonychia in the proximal nail fold, and it may extend to deeper layers of the nail. The nail plate becomes white proximally and remains normal distally.

4. Total dystrophic OM presents as a thickened, opaque, and yellow-brown nail and involves the entire nail plate and matrix.

Treatment includes topical and systemic antifungals. The use of topical agents are limited to the patients that have 2–3 nails affected. Topical treatments alone are generally unable to cure OM because of insufficient nail plate peneration. They may be useful as adjunctive therapy in combination with oral therapy.

The newer generation of oral antifungal agents (**itraconazole and terbinafine**) has replaced older therapies in the treatment of OM. They offer shorter treatment regimens, higher cure rates, and fewer adverse effects. **Fluconazole** offers an alternative to itraconazole and terbinafine. The efficacy of the newer antifungal agents lies in their ability to penetrate the nail plate within days of starting therapy.

To decrease the adverse effects and duration of oral therapy, topical and surgical treatments may be combined with oral antifungal management.

Scheme of administration of therapy in different forms of onychomycosis

Drug	Scheme of administration
Itraconazole	Pulse therapy — one course per month of 200 mg 2 times per day during 7 days, during 3–4 months
Terbinafine	250 mg per day 6 months

Surgical Care. Surgical approaches to OM treatment include surgical nail avulsion and matrixectomy by chemical or mechanical means. Chemical removal by using urea compound should be reserved for patients with very thick nails or for those who may not tolerate mechanical avulsion. Removal of the nail plate should be considered an adjunctive treatment in patients undergoing oral therapy. A combination of oral, topical, and surgical therapy can increase efficacy and reduce cost.

Tinea capitis

Tinea capitis is a common disease affecting mostly children and characterized by hair loss, erythema, and scaling. In spite of preventive measures the rate of tinea capitis worldwide is still high and in some countries it is a significant problem affecting young people.

Epidemiology and distribution. The distribution of tinea capitis causative agents varies in different countries. *Trichophyton tonsurans* is registered more often in the USA and the UK and is registered in about 90 % of all cases of tinea capitis. The rate of *Microsporum canis* infection is higher in Mediterranean countries, Eastern Europe, Israel. Modern trends of distribution of tinea capitis include more frequent incidence of antropophilic dermatophytes. *Trichophyton tonsurans* and *Trichophyton violaceum* are more often registered in the UK and *Trichophyton soudanense* and *Microsporum audouinii* in France.

In Belarus the rate of tinea capitis decreases every year but is still very high. It is explained by low income of the population in the former USSR countries, great number of homeless animals and lack of sanitary measures.

Antropophilic *Microsporum audouinii* was not registered at the territory of Belarus since World War II and zoophilic *Microsporum canis* is the most frequent agent that causes tinea capitis. Although transmission from person to person can not be excluded totally, it is considered that if several children are infected in the family or a child group it is due to the contact with the same sick animal.

The infection begins after a direct contact with an animal or after a contact with hair or scales of a sick animal (indirect way). Infected animals are rarely cured but more often thrown out that leads to the further dissemination of the infection. Sometimes clinically healthy cats can be the reservoir of the infection. In such cases lamp Wood examination and cultural examination of the animal hair are necessary. The infection can be transmitted through the soil but fungi do not live in the soil for a long time (usually about 3 months). The main group of patients is children of a different age. Adults are infected rarely. If Microsporum infection is not treated in childhood after the puberty it can be self cured. It happens because of the presence of fungistatic substances in the hair of grown ups.

Morbidity with Microsporum canis infection has seasonal character that depends on an increase of cats and more frequent contacts with animals in summer. The disease begins at the end of summer, the peak is in October-November, the decrease is in March-April.

The rate of Trichophyton infection is low and doesn't exceed 2 per 100 000. Trichophyton infections are usually caused by *Trichophyton verrucosum* and *Trichophyton gypseum*. Usually this type of infection is seen in patients from rural regions who had a contact with sick cattle.

Pathogenesis. The fact of inoculation in the skin does not lead to the development of the disease. Important factors that lead to the development of tinea capitis include microtrauma, loss of skin defense, high blood glucose level, disturbances of microcirculation, low phagocyte and complement system activity, sebum production, immunodeficiency. Vitamin misbalance, hormonal dysfunction (hypo- and hyperthyroidism), disbacetriosis caused by prolonged antibiotic usage are also very important factors in the development of the disease.

The distribution of tinea capitis depends on individual susceptibility and social factors. Children are more susceptible to tinea capitis due to physiological peculiarities.

Classification of Microsporum species

There are about 20 species of Microsporum. Pathogenic fungi can be classified as:

• Antropophilic — *M. ferrugineum, M. audouinii, M. distorum, M. rivalieri, M. langeronii.*

• Zoophilic — *M. canis, M. nanum, M. persicolor.*

• Geophilic — *M. gypseum, M. cookeii, Keratynomyces ajelloii*.

Tinea capitis caused by Microsporum canis infection

The incubation period in zoophfilic Microsporum infection is 5–7 days. The classical form of *Microsporum canis* affection of hair is presented by **gray patch tinea capitis.**

There are usually several round lesions 5 cm in diameter with well defined borders. The first days fungi are located in the hair follicle. It is possible to see white scale around the hair shaft resembling cuffs. In 6–7th day the hair is involved. It becomes fragile and is broken at the level of 4–6 mm. Hair looks as if cut and with these displays it is explained the general name for «cutting deprive». At stroking the broken off hair it doesn't come back in its initial position. The rests of hair have a grey cover that is composed by the spores of fungi. The lesion may be covered by little gray scales and inflammatory skin is seen after their removal. In Wood lamp examination green fluorescence is noticed. It is considered that it happens because of interaction of fungi products and hair components.

Clinical presentation of tinea corporis caused by Microsporum canis infection. Closed parts as well as open parts of the body can be affected by *Microsporum canis*. Usually there is neither itch nor burning sensations. The number of lesions can be different reaching sometimes several hundreds. In the place of inoculation of the fungi red macule appears with well defined borders that progressively enlarges and gets infiltrated. At the peripherial part the infiltration is more prominent presented by tiny papules, crusts, vesicles. In the center there is less inflammation, and the lesion begins to resemble a ring — «ringworm».

The affection of palms, soles, and nails is rarely seen. In the soles dyshydrotic or squamous lesions are seen. In onychomycosis caused by Microsporum usually proximal part of the nails is affected. The nail becomes atrophyc and can be totally destroyed. While Wood lamp examination green fluorescence of the nail is seen. If not treated onychomycosis can be a reason for the re-infection.

Trichophyton infections

Trichophyton infection of the scalp and skin can be caused by antropophilic and zoophilic trichophytons.

Atropophylic species include *Trichophyton tonsurans (crateriforme)* and *Trichophyton violaceum*. In Belarus antropophilic Trichophytons are rare and the most frequent form is antropozoophilic tinea capitis caused by *Trichophyton mentagrophytes var. granulosum (syn. Trichophyton gypseum)* and *Trichophyton verrucosum (syn. Trichophyton faviforme)*. *Trichophyton verrucosum* has large spores and is transmitted by cattle. *Trichophyton gypseum* has little spores and mice are usually its source.

Clinical presentations of Trichophyton infections. Tinea capitis caused by zoophilic Trichophytons is usually divided into superficial and profound forms. The majority of patients are people working with animals or who have animals at home or work with meat.

Superficial form of tinea capitis caused by Trichophyton is characterized by erythematous squamous lesions with peripherial infiltration formed by tiny papules and vesicles. If the inflammation persists it can lead to kerion when the skin is painful, hyperaemina is prominent. While pressing the plaque pus is discharged from the hair follicules resembling honey. Usually infiltrated form heals forming a scar on the scalp or the skin.

Differential diagnosis. Differential diagnosis of tinea capitis is performed with other diseases affecting scalp: alopecia areata, psoriasis, seborrhoeic dermatitis, lupus erythematosus, syphilis, bacterial infections, etc. In alopecia areata skin is usually not involved, there are no inflammation and scaling. In seborrhoeic dermatitis ringworms are not observed. Inflammation and scaling are seen all over the scalp and doesn`t have well defined borders. Bacterial infections show more inflammatory signs with pain, malaise, and the enlargement of lymph nodes. Lupus erythematosus is rarely seen in children and skin biopsy can help in confirming the diagnosis. Syphilis is diagnosed by means of blood tests. In spite of all these clinical differencies laboratory examination must be performed in any case of involvement of the scalp in a child older than 3 months.

Diagnosis of tinea capitis. The diagnosis of tinea capitis is performed on the base of clinical presentation, anamnesis, epidemiological data, laboratory examination. Laboratory examination usually includes microscopy, culture, Wood lamp examination. Despite the fact that making the diagnosis of tinea capitis seems to be simple there are cases when it is misdiagnosed. It happens usually in Trichophyton infections when Wood lamp examination is negative and in unusual clinical presentations.

Microscopy

Hair, scales and nails can be studied in the microscope. The material is taken by scrapings, swabs or with adhesive tape method. If the lesion is not well defined Wood lamp is used to localize it. The material is taken from the fresh lesions in the peripherial part. Microscopy can be performed by classical KOH method. In case of Microsporum infection spores are situated outside the hair shaft causing exotrix infection, Trichophyon species show different pattern.

Culture

Cultural examination helps to reveal the species of fungi. Usually liquid or solid Sabouraud`s agar is used for the cultural examination. Material is taking by scratching or cytobrush method. Dermatophytes grow beginning from 4^{th} day of

the incubation. Optimal growth is seen on 7–10th day but it is necessary to observe the culture during 30 days.

Wood lamp examination

Wood lamp examination is a perfect method for the observation of large groups, contacts, control of treatment and for the check-up of animals. In case of Microsporum infection light green fluorescence is seen.

Treatment of tinea capitis and corporis caused by Microsporum and Trichophyton species. In spite of relative simplicity of diagnostics tinea capitis treatment is rather difficult. The course of treatment is quite long and as far as the main group of patients is children they need a special tactics. Griseofulvin, Itraconazole, Fluconazole, and Terbinafine are used all over the world for tinea capitis. Systemic treatment is administered if there is scalp involvement and in case of spread involvement of the skin (usually more than 3 lesions).

Griseofulvin

Griseofulvin can bind the ergosterin in the membrane of fungi cell and increases its permeability for ions. As a result the cell loses ions and pH inside the cell decreases up to 5,2 and cytoplasm coagulates that causes the damage of hyphae. *Microsporum canis* is more resistant to Griseofulvin than Trichophyton infections.

Griseofulvin is the first systemic drug that is used for tinea capitis. Despite the fact that now there is a wide spectrum of systemic antifungal therapies used all over the world it is the only drug approved by FDA and the only drug that is officially licensed in the USA and the UK. It is produced in tablets and suspension that optimize its usage by children. For *Microsporum canis* infection the recommended dosage in Belarus is 22 mg/kg. If there is Trichophyton infection the dosage can be lower — 20mg/kg/day. Griseofulvin is taken with the spoon of oil that helps to increase the solution of the drug and prolongs makes longer its activity (alfa — tocoferol that is present in the oil blocks metabolism of Griseofulvin in the liver). For younger children suspension of Griseofulvin can be given (8 ml of the suspension is equal to 125 mg of a tablet). The middle duration of treatment of tinea capitis with Griseofulvin is 1,5–2 months.

Terbinafine

Allilamines inhibit scvalenepocsidase that converts scvalen in 2,3-oxydoscvalen. The suseptibility of scvalenepocsidase of fungi cell is much higher than of human cell that explains the selectivity and specific action of terbinafine.

Terbinafine as well as Griseofilvin is less effective against *Microsporum canis*. The dosages recommended in Belarus are: 62,5 mg/day if the weight is 10–20 kg, 125 mg/day if the child is up to 40 kg, 250 mg/day if the weight is more than 40 kg.

But in case of treatment Microsporum canis infections about one third of children do not respond on Terbinafine treatment.

Itraconazole

The mechanism of the action of azoles is the inhibition of cytochrom 450-dependent monooxygenase reactions that convert lanosterin in dymethil — ergostattrienol. Synthesis of lanosteril is the same for humans and for fungi, that is why azols may have side effects connected with cholesterin synthesis.

Itraconazole is a triazole that is active against Trichophyton, Microsporum, Epidermophyton, Cryptococcus, Pityrosporum, Candida, and fungi that cause deep infections (Aspergillus, Histoplasma, Paracoccidioides, Sporothrix, Cladosporium, Blastomyces). There are not enough data concerning its usage in tinea capitis. But it is considered that the drug is active against Microsporum species as well as against Trichophyton. There are different methods of administration of Itraconazole in children. In pulse therapy Itraconazole is administered for children with the weight up to 30 kg in the dosage 100 mg/day, up to 40 kg — once in 2 days 100 mg and 200 mg (300 mg/2 days), up to 50 kg — 200 mg/day. The other effective regimen is the usage of Itraconazole in the dosage 100 mg/day for children up to 25 kg and 200 mg/day if a child is more than 25 kg. The advantage of Itraconazole is that it can be used in the form of solution; 1 ml of Itraconazole solution contains 10 mg of Itraconazole.

Local treatment

Local treatment as the only method of therapy can be used only if there are less than tree elements on the skin. Different antifungal creams can be used: bifonazole, izoconazole, clotrimazole, naftifin, terbinafine, cuclopiroxe, amorolfine, nitrofungine, etc. In clinical forms with inflammation terbinafine spray can be used.

In infiltrative forms when prominent inflammation is seen usually corticosteroids and antibiotics are added to the therapy. For the prophylaxis Ketokonazole shampoo 2 % is used once per two days first two weeks and after — two times a week. Shampoo can be administered twice a week to the family of the sick child. For the mechanical removal of the hair shaving is used once per 4 or 10 days.

Prophylaxis of tinea capitis. In Belarus children with tinea capitis are treated in hospital. Long isolation of a child causes negative reaction of his family and psychological problems in a child. A child can attend school only after negative microscopy examination after appropriate systemic and local therapy.

Homeless animals cause the infection in many cases but 56 % of parents can not reveal the source of the infection and this doesn`t allow to perform epidemiologic measures.

Prophylaxis of tinea capitis includes several types of measures. The most important is revealing and treating patients and sources of the infection. Annual

mass check-ups of children before and after the vacation help to reveal the disease. Veterinary service finds, observes and treats homeless animals.

In Belarus medical service works together with sanitary service. A special document is sent to the sanitary service and it performs disinfection in the place of living of a patient with tinea capitis. As far as tinea is a widespread disease citizens should receive more information from mass media and doctors.

Favus (tinea favosa)

Favus, also termed tinea favosa, is a chronic inflammatory dermatophytic infection usually caused by *Trichophyton schoenleinii*. Rarely, favus is caused by *Trichophyton violaceum*, *Trichophyton mentagrophytes* var *quinckeanum*, or *Microsporum gypseum*. Favus typically affects scalp hair but also may infect glabrous skin and nails. Foci of favus have been seen worldwide, including Poland, Southern and Northern Africa, Pakistan, the United Kingdom, Australia, South America (Brazil), and the Middle East. Favus appears in both children and adults.

Pathogenesis. Typically, hair is not as heavily infected as in trichophytosis caused by *Trichophyton tonsurans*. Hair is able to grow, and frequently, long hairs are observed in the disease state. The most characteristic feature is the formation of air spaces between hyphae within the infected hair. These air spaces (air tunnels) form as a result of autolysis of the hyphae. Arthroconidia rarely are seen within the hair. Such infected hair commonly is termed favus-type hair. In the sera of patients, antibodies to causative fungi are found by charcoal agglutination and immunodiffusion assay; however, the exact role of antibodies is not clear.

Clinical presentation. Favus usually is acquired during childhood or adolescence and typically persists into adulthood. It usually begins on the scalp, often in childhood, and persists for many years as unsightly crusted plaques. According to the severity of the disease, 3 main stages are described.

- First stage: only erythema of the scalp is seen, primarily around follicles. Hairs are not loose or broken.
- Second stage: formation of scutula is seen with the beginning of hair loss.
- Third stage: the most severe stage involves large areas of the scalp (at least one third); extensive hair loss, atrophy, and scarring result. Formation of new scutula at the periphery of plaques is common.

The scutulum, a yellow cup-shaped crust that surrounds a hair and pierces its center, is characteristic. Scutula form a dense plaque, each composed of mycelia and epidermal debris. Often, a secondary bacterial infection occurs in the plaque. Plaque removal leaves an erythematous moist base. The dense masses of yellow crusts may be solitary or numerous, and in patients who are severely affected, involve the entire scalp. A mousy odor typically is present. Glabrous skin may show similar yellow crusting.

On glabrous skin, favus is a papulovesicular and papulosquamous eruption in which typical scutula may be evident. As an onychomycosis, tinea favosa resembles other forms of tinea unguium.

In addition to typical scutular favus on the scalp, several atypical manifestations of favus have been described.

Laboratory examination. Base the diagnosis on mycologic examination via direct microscopy and culture. Wood lamp examination may demonstrate a dull green or yellow fluorescence. With favus, hair must be examined immediately after adding KOH solution to observe the bubbling of KOH through the air spaces between hyphae elements. Examination of scutulum fragments shows segmental filaments and spores. The causative organism is identified on culture, which usually is performed on Sabouraud agar.

Treatment. Although favus is not highly contagious, several family members may be affected, and all should be treated simultaneously. Treatment outcome depends on the stage at which the disease is arrested. Severe long-lasting disease can cause irreversible scarring alopecia.

In most patients, favus involves hair; therefore, the disease requires systemic treatment. Additional topical agents, such as shampoo (2 % ketoconazole, 2.5 % selenium sulfide), lotion, and cream may be helpful. General hygiene of the scalp must be improved, and debris and crusts must be removed.

Favus usually is controlled by griseofulvin, the standard treatment of tinea capitis; however, a longer treatment course than usual for tinea capitis may be advisable. Currently, favus is uncommon; therefore, no clinical trials with newer antifungals are available. In vitro studies indicate that *T schoenleinii* is sensitive to newer antifungal drugs, similar to other dermatophytes. Terbinafine, itraconazole, and fluconazole in a similar dosage schedule to tinea capitis may eradicate the fungus and cure the disease.

Deep mycoses

Chromoblastomycosis

Chromoblastomycosis is a chronic fungal infection of the skin and the subcutaneous tissue caused by traumatic inoculation of a specific group of dematiaceous fungi (usually *Fonsecaea pedrosoi, Phialophora verrucosa, Cladosporium carrionii,* or *Fonsecaea compacta*) through the skin. Several cases of infection by *Exophiala* species have appeared in the literature. Chromoblastomycosis is classified among the subcutaneous mycoses and is ubiquitous; however, the prevalence is higher in rural populations in countries with a tropical or subtropical climate, such as Madagascar in Africa and Brazil in South America.

Pathogenesis. The infection usually results from a traumatic cutaneous injury that is often not remembered or realized by the patient. The agents often gain entry into the human body by contact with wood splinters or thorns. Several authors have demonstrated that a number of different dematiaceous fungi can be isolated from nature.

Clinical picture. The lesions develop slowly at the site of implantation, producing a warty nodule, which tends to be limited to the skin and the subcutaneous tissue. Over the years, the nodule grows centripetally. In many instances, the central parts of the lesion heal, leaving ivory-colored scars. The disease tends to spread to neighboring healthy skin, forming plaques, which, at times, can involve a whole limb. When nodular lesions predominate over the plaques, the disease assumes a typical cauliflower aspect. Both lymphatic dissemination and cutaneous dissemination have been described.

Laboratory tests. Among the possible laboratory tests to be obtained, direct examination of 10 % potassium hydroxide cleared lesion scrapings is by far the most useful. Typical, thick-walled, cigar-colored, sclerotic cells, also known as **Medlar bodies,** are readily seen. Although these cells are pathognomonic of chromoblastomycosis, they do not give specific information on the agent. Eventually, dematiaceous hyphae can also be observed. Identifying the agent is easier when the specimens collected include the black dots present in the lesions. In culture, each causative agent produces a similar pattern, that of a slow-growing, dark, velvety colony with a black obverse. Identification of individual species is handled in the usual manner by observing various characteristics, including conidia production.

Treatment. One of the most characteristic features of chromoblastomycosis is its refractoriness to treatment. Treatment options include oral itraconazole, locally applied heat therapy, and cryosurgery. Heat therapy is another treatment. Especially in Japan, the use of pocket warmers has proven successful in the treatment of a limited number of cases. Apparently, an increase in skin temperature somehow impairs fungal development.

Cryptococcosis

Cryptococcus neoformans is an encapsulated yeast. Since the initial reports, researchers have identified the diverse spectrum of host responses to cryptococcal infection. The responses range from a harmless colonization of the airways and asymptomatic infection in laboratory workers (resulting in a positive skin test result) to meningitis or disseminated disease. Although virulence in animals and, possibly, humans varies among strains of cryptococci, virulence probably plays a relatively small role in the outcome of an infection. The crucial factor is the immune status of the host. The most serious infections usually develop in patients with defective cell-mediated immunity. For example, patients with AIDS, patients undergoing organ transplantation, patients with

reticuloendothelial malignancy, patients undergoing corticosteroid treatment (but not those with neutropenia or immunoglobulin deficiency), and patients with sarcoidosis develop the most serious infections.

With the global emergence of AIDS, the incidence of cryptococcosis is increasing and now represents a major life-threatening fungal infection in these patients. *C neoformans* is distributed worldwide. Naturally occurring cryptococcosis occurs in both animals and humans, but neither animal-to-human transmission nor person-to-person transmission via the pulmonary route has not been documented. Transmission via organ transplantation has been reported when infected donor organs were used.

Pathogenesis. Of the 19 species that comprise the genus *Cryptococcus,* human disease is associated with only *C neoformans*. Animal models provide much of the understanding of the pathogenesis and the host defense mechanisms involved in *C neoformans* infections. The organism is primarily transmitted via the respiratory route and not directly from human to human. Following inhalation, the yeast are deposited into the pulmonary alveoli, where they must survive the neutral-to-alkaline pH and physiologic concentrations of carbon dioxide before they are phagocytized by alveolar macrophages.

Clinical picture. *C neoformans* can cause an asymptomatic pulmonary infection followed later by the development of meningitis, which is often the first indication of disease. If limited to the lungs, *C neoformans* infection may cause pneumonia, poorly defined mass lesions, pulmonary nodules, and, rarely, pleural effusion.

Approximately 10–15% of patients infected with *C neoformans* develop skin involvement. In immunocompetent hosts, the skin may be the only site of infection; however, immunosuppressed patients, especially those with AIDS, have skin involvement that must be considered evidence of disseminated disease. Cutaneous lesions include nodules, ulcers, papules, and vasculitic lesions.

Lab. diagnosis. The physician establishes the diagnosis based on skin biopsy findings evaluated after fungal staining and culture. Even with widespread disease, the routine laboratory tests (eg, leukocyte count, hematocrit, sedimentation rate) may yield normal results.

Conduct a CSF examination, which is essential in diagnosing CNS disease. Elevated opening pressure is associated with a poor prognosis. CSF glucose levels are depressed, the protein concentration is usually elevated, and the leukocyte counts are 20/µL or higher, with lymphocytes generally outnumbering neutrophils. CSF can be normal at times, as in cases involving patients with AIDS who are unable to mount an adequate inflammatory response or in persons

with early asymptomatic infection. Microscopy and cultural methods can be used takening smears from CSF and blood.

Latex agglutination test to detect cryptococcal polysaccharide in serum or CSF is an extremely important adjunct to the diagnosis. In patients with meningitis, detection of cryptococcal antigen has a sensitivity of 94.1 % in CSF and a sensitivity of 93.6 % in serum. Some clinicians use bronchoalveolar lavage fluid, pleural fluid, and urine specimens to obtain a cryptococcal antigen; however, these tests are not standardized. Anticryptococcal antibodies do not have diagnostic significance, and low concentrations develop in a significant percentage of healthy people.

Therapy. In patients who are co-infected with HIV and *C neoformans,* the therapeutic goal may differ from that in patients with cryptococcal infection uncomplicated by HIV infection. For cryptococcal infections in patients with concomitant HIV infection without a CD4 count of greater than 100 cells/μL, the therapeutic goal is to control the acute infection, followed by life-long suppression of *C neoformans*. For patients infected with HIV with a CD4 count of greater than 100–200 CD4 cells/μL, suppressive therapy may be safe to discontinue as long as their CD4 counts do not fall below 100 CD4 cells/μL. For patients with cryptococcal disease not complicated by HIV infection, the therapeutic goal is to achieve a permanent cure of the fungal infection. Administering amphotericin B alone or in combination with flucytosine may provide the appropriate therapy. Amphotericin B can be administered alone for 6–10 weeks or in conjunction with flucytosine for 2 weeks, followed by fluconazole for a minimum of 10 weeks.

Histoplasmosis

Histoplasma capsulatum is a dimorphic fungus that remains in a mycelial form at ambient temperatures and grows as yeast at body temperature in mammals. Although the fungus can be found in temperate climates throughout the world, it is endemic to the Ohio, Missouri, and Mississippi River valleys in the United States. The soil in endemic areas provides an acidic damp environment with high organic content that is good for mycelial growth. Highly infectious soil is found near areas inhabited by bats and birds. Birds cannot be infected by the fungus and do not transmit the disease; however, bird excretions contaminate the soil, thereby enriching the growth medium for the mycelium. In contrast, bats can become infected, and they transmit the fungus through droppings. Contaminated soil can be potentially infectious for years.

Most individuals who are infected are asymptomatic. Those who develop clinical manifestations are usually immunocompromised or are exposed to a high quantity of inoculum. *Histoplasma* species may remain latent in healed granulomas and recur, resulting in cell-mediated immunity impairment.

Clinical picture. The initial pulmonary infection may disseminate systemically, with hematogenous spread, and produce extrapulmonary

manifestations. Hematogenous spread to regional lymph nodes may occur through the lymphatics or the liver and spleen. Progressive disseminated histoplasmosis is rare in adult hosts who are immunocompetent. Systemic spread usually occurs in patients with impaired cellular immunity and typically involves the CNS, liver, spleen, and rheumatologic, ocular, and hematologic systems.

Lab. studies. Mild anemia may be present in chronic pulmonary histoplasmosis. In acute progressive disseminated histoplasmosis, pancytopenia occurs in 70-90% of patients, with a platelet count less than 70,000. Pancytopenia may occur at a lower rate in chronic progressive disseminated histoplasmosis. Levels of alkaline phosphatase are elevated in acute progressive disseminated histoplasmosis and chronic pulmonary histoplasmosis.

Culture of sputum results are positive in 60% of specimens from patients with chronic pulmonary histoplasmosis. Blood cultures are positive in 50–90% of patients with acute progressive disseminated histoplasmosis.

Treatment. Most infections in individuals who are immunocompetent are self-limiting and do not require therapy. In cases of prolonged infection, cases of systemic infection, or those involving individuals who are immunocompromised, medical treatment is recommended with different antifungals (ketokonazole, itraconazole, amphotericin B).

Mycetoma

Mycetoma is a chronic subcutaneous infection caused by actinomycetes or fungi. This infection results in a granulomatous inflammatory response in the deep dermis and subcutaneous tissue, which can extend to the underlying bone. Mycetoma is characterized by the formation of grains containing aggregates of the causative organisms that may be discharged onto the skin surface through multiple sinuses.

The body parts affected most commonly in persons with mycetoma include the foot or lower leg, with infection of the dorsal aspect of the forefoot being typical. The hand is the next most common location; however, mycetoma lesions can occur anywhere on the body. Lesions on the chest and back are frequently caused by *Nocardia* species, whereas lesions on the head and neck are usually caused by *Streptomyces somaliensis.*

The causative organism enters through sites of local trauma (eg, cut on the hand, foot splinter, local trauma related to carrying soil-contaminated material). A neutrophilic response initially occurs, which may be followed by a granulomatous reaction. Spread occurs through skin facial planes and can involve the bone. Hematogenous or lymphatic spread is uncommon.

Clinical picture. The earliest sign of mycetoma is a painless subcutaneous swelling. Some patients have a history of a penetrating injury at that site. Several years later, a painless subcutaneous nodule is observed. After some years, massive swelling of the area occurs, with induration, skin rupture, and sinus tract formation.

As the infection spreads to contiguous body parts, old sinuses close and new ones open. Nearly 20 % of patients with mycetoma experience associated pain, usually due to secondary bacterial infection or, less commonly, bone invasion.

Lab. examination. Hematoxylin-eosin staining of a biopsy sample allows for detection of mycetoma grains. Actinomycetoma or eumycetoma can be seen. Actinomycetoma is homogenously eosinophilic with hematoxylin-eosin stain; and eumycetoma has brownish color with hematoxylin-eosin stain.

Culture the grains obtained from a deep wedge biopsy or a sample obtained via puncture and fine-needle aspiration. Serologic diagnosis is available in a few centers and can be helpful in some cases for diagnosis or follow-up care during medical treatment.

Treatment. Actinomycetoma is a bacterial infection that can respond to antibiotics if treatment is administered early in the course of the disease. A combination of 2 drugs in 5-week cycles is used. If needed, the cycles can be repeated once or twice. The following agents have been used in combination: trimethoprim-sulfamethoxazole, dapsone (diaminodiphenylsulfone), and streptomycin sulfate. An effective and convenient regimen combining a short course of intravenous gentamicin with a 6-month oral course of cotrimoxazole and doxycycline has recently been described.

Eumycetoma may respond partially to antifungal agents, although surgical therapy is preferred for localized disease. *Madurella mycetomatis* mycetoma may respond to ketoconazole (200 mg bid). *P boydii (S apiospermum)* mycetoma should be treated primarily with voriconazole, although it may also respond to itraconazole. Other agents that cause eumycetoma may respond intermittently to itraconazole (200 mg bid) or amphotericin B. The minimum treatment duration is 10 months.

Sporotrichosis

Sporotrichosis is a subacute or chronic infection caused by the soil fungus *Sporothrix schenckii*. The characteristic infection involves suppurating subcutaneous nodules that progress proximally along lymphatic channels (lymphocutaneous sporotrichosis). Rarely, a primary pulmonary infection (pulmonary sporotrichosis) occurs, or direct inoculation into tendons, bursae, or joints occurs. Osteoarticular sporotrichosis occurs from direct inoculation or hematogenous seeding. Rarely, a disseminated infection occurs with disseminated cutaneous lesions and involvement of multiple visceral organs; this occurs most commonly in patients with acquired immunodeficiency syndrome (AIDS).

Infection with the dimorphic soil fungus *S schenckii* usually is acquired through cutaneous inoculation. The initial reddish, necrotic, nodular papule of cutaneous sporotrichosis generally appears 1–10 weeks after a penetrating skin injury. The lesion is a suppurating granuloma that consists of histiocytes and giant

cells, with neutrophils that accumulate in the center and that are surrounded by lymphocytes and plasma cells. The fungus spreads from the initial lesion along lymphatic channels, forming the chain of indolent nodular and ulcerating lesions that typifies the lymphocutaneous form of the disease. Other tissues are involved by direct extension and, less often, by hematogenous dissemination. The most common extracutaneous sites are in the bones, joints, tendon sheaths, and bursae. Hematogenous dissemination-particularly in immunocompromised hosts-results in widely disseminated cutaneous and visceral infection, including meningitis.

A rare form appears to result from inhalation of the organism. A chronic, cavitary pneumonia, which is clinically and radiographically indistinguishable from tuberculosis and histoplasmosis, occurs in patients who usually have severe underlying chronic obstructive pulmonary disease. Sporotrichal infection of the larynx and paranasal sinuses has also been described.

Clinical picture. In cutaneous or lymphocutaneous sporotrichosis an initial papule or nodule forms at the site of cutaneous inoculation, usually 1–10 weeks after inoculation. The initial small nodule enlarges, reddens, becomes pustular, and ulcerates. In the lymphocutaneous form, an ascending chain of nodules develops along skin lymphatic channels. Older, distal lesions ulcerate and drain, while more proximal lesions appear as nodules and undergo the same evolution.

Lab. diagnosis. Definitive diagnosis at any site requires the isolation of *S schenckii* in specimen culture from a normally sterile body site. The organism can be recovered by fungal culture from sputum, pus, subcutaneous tissue biopsy, synovial fluid, synovial biopsy, bone drainage or biopsy, and cerebrospinal fluid (CSF). The concentration of organisms in synovial fluid and, particularly, CSF often is low. Therefore, repeated large-volume cultures may be necessary for diagnosis.

Occasionally, the organism (cigar-shaped yeast) can be visualized in biopsied tissue specimens that are stained with periodic acid-Schiff, Gomori methenamine-silver, or immunohistochemical stains.

Antibody measurement techniques are available. Such tests demonstrate significant interlaboratory variability in sensitivity and specificity; therefore, they rarely should serve as the sole basis for diagnosis. They can be useful to raise diagnostic suspicion and inspire more aggressive attempts to acquire appropriate specimens for culture. The ratio of CSF to serum antibody titer may suggest the presence of sporotrichotic meningitis (CSF antibody titer higher than serum antibody titer). Polymerase chain reaction-based techniques for diagnosis of sporotrichosis have been described but are not available for routine use.

Treatment. The orally available azole antifungals are the drugs of choice for cutaneous or lymphocutaneous sporotrichosis in the developed world. Ketoconazole has been used but, by historical comparison is less effective than itraconazole or fluconazole and, thus, is no longer indicated. Terbinafine has been demonstrated to be effective in treatment of lymphocutaneous sporotrichosis, but

no comparative data with itraconazole therapy exist. Itraconazole is the DOC for cutaneous or lymphocutaneous sporotrichosis, pulmonary sporotrichosis, and osteoarticular sporotrichosis. Treat sporotrichotic meningitis with amphotericin B.

Candidiasis

Candida species are ubiquitous fungi and the most common fungal pathogens affecting humans. The growing problem of mucosal and systemic candidiasis reflects the enormous increase in the pool of patients at risk and the increased opportunity that exists for *Candida* species to invade tissues normally resistant to invasion.

Candida species produce a wide spectrum of diseases, ranging from superficial mucocutaneous disease to invasive illnesses, such as hepatosplenic candidiasis, *Candida* peritonitis, and systemic candidiasis. Management of serious and life-threatening invasive candidiasis remains severely hampered by delay in diagnosis and the lack of reliable diagnostic methods that allow detection of both fungemia and tissue invasion by *Candida* species.

Pathogenesis. *Candida* species are yeastlike fungi that can form true hyphae and pseudohyphae. For the most part, *Candida* species are confined to the human and animal reservoirs; however, they frequently are recovered from the hospital environment, including on foods, counter tops, air-conditioning vents, floors, respirators, and medical personnel. They also are **normal commensals** of diseased skin and mucosal membranes of the gastrointestinal, genitourinary, and respiratory tracts.

Candida species also contain their own set of well-recognized virulence factors. Although not well characterized, several virulence factors may contribute to their ability to cause infection. The main virulence factors are surface molecules that permit adherence of the organism to other structures (human cells, extracellular matrix, prosthetic devices), acid proteases, and the ability to convert to a hyphal form.

As with most fungal infections, host defects also play a significant role in the development of candidal infections. Numerous host defects are associated with candidal infections. Risk factors associated with Candidiasis include the following: granulocytopenia, bone-marrow transplantation, solid-organ transplantation (liver, kidney), parenteral hyperalimentation, hematologic malignancies, foley catheters, solid neoplasms, recent chemotherapy or radiation therapy, corticosteroids, broad-spectrum antibiotics, burns, prolonged hospitalization, severe trauma, recent bacterial infection, recent surgery, gastrointestinal tract surgery, central intravascular access devices, premature birth, hemodialysis.

Cutaneous candidiasis syndromes:

1. **Generalized cutaneous candidiasis**. This is an unusual form of cutaneous candidiasis that manifests as a diffuse eruption over the trunk, thorax, and extremities. The patient has a history of generalized pruritus, with increased severity in the genitocrural folds, anal region, axillae, hands, and feet. Physical examination reveals a widespread rash that begins as individual vesicles that spread into large confluent areas.

2. **Intertrigo.** The patient has a history of intertrigo affecting any site where the skin surfaces are in close proximity, providing a warm and moist environment. Pruritic red rash occurs. Physical examination reveals a rash that begins with vesiculopustules, which enlarge and rupture, causing maceration and fissuring. The area involved has a scalloped border, with a white rim consisting of necrotic epidermis that surrounds the erythematous macerated base. Satellite lesions frequently are found that may coalesce and extend into larger lesions.

3. **Metastatic skin lesions**. Characteristic skin lesions occur in about 10 % of patients with disseminated candidiasis and candidemia. The lesions may be numerous or few. Lesions are generally described as erythematous, firm, nontender macronodular lesions with discrete borders. Biopsied specimens of these lesions demonstrate yeast cells, hyphae, or pseudohyphae, and cultures are positive for *Candida* species approximately 50 % of the time.

4. **Paronychia and onychomycosis.** Frequently, paronychia and onychomycosis are associated with immersion of the hands in water and with diabetes mellitus. The patient has a history of a painful and erythematous area around and underneath the nail and nail bed. Physical examination reveals an area of inflammation that becomes warm, glistening, tense, and erythematous and may extend extensively under the nail. It is associated with secondary nail thickening, ridging, discoloration, and occasional nail loss.

5. **Mucous membranes candidiasis.** Usually it is characterized by white flakes and erosions on the mucous membranes. Vulva and oral cavity are affected.

Treatment. Treatment of *Candida* infections varies substantially and is based on the anatomic location of the infection, the patients' underlying disease and immune status, the patients' risk factors for infection, the specific species of *Candida* responsible for infection, and, in some cases, the susceptibility of the strain to antifungal drugs.

Cutaneous candidiasis: may be treated with any number of topical antifungal agents (eg, clotrimazole, econazole, ciclopirox, miconazole, ketoconazole, nystatin). If the infection is a paronychia, the most important aspect of the therapy is drainage of the abscess, followed by oral antifungal therapy with either fluconazole or itraconazole.

In cases of extensive cutaneous infections, infections in patients who are immunocompromised, folliculitis, or onychomycosis, systemic antifungal therapy is recommended. Drugs of choice are Fluconazole and Itraconazole.

For *Candida* two treatment regimens are available — with fluconazole and itraconazole. Fluconazole is used in the dosage 150 mg per week and itraconazole is taken in pulsed-dose regimen 7 days, followed by 3 weeks off therapy. The cycle is repeated every month for 3–4 months. Treatment takes up several months.

LECTURE 8. VIRAL INFECTIONS OF THE SKIN

Molluscum contagiosum

Molluscum contagiosum virus is a member of the poxvirus group. It is a large DNA virus which replicates in the cytoplasm of infected cells. With experimental transmission to humans, it has been shown that molluscum contagiosum virus has an incubation period of **two to seven weeks**.

The MC virus causes 2 distinct disease patterns in 2 different patient populations. Children acquire the MC virus through either direct skin-to-skin contact or indirect skin contact via fomites such as gymnasium equipment and public baths. Lesions typically occur on the chest, arms, trunk, legs, and face. In adults, MC is considered a sexually transmitted disease (STD). In almost all cases involving healthy adults, patients exhibit few lesions, which are limited to the perineum, genitalia, lower abdomen, or buttocks. Generally, in populations that are immunocompetent, MC is a self-limited disease.

Clinical picture. Firm, smooth, umbilicated papules, usually 2–6 mm in diameter (range 1–15 mm) may be present in groups or widely disseminated on the skin and mucosal surfaces. The lesions can be flesh-colored, white, translucent, or even yellow in color. The number of lesions varies from 1-20 up to hundreds in some reports. Lesions generally are self-limited but can persist

for several years. Beneath the umbilication lies a white currant-like core which may be easily expressed.

In children, lesions are situated mainly on the trunk and extremities. In adults, lesions often are located on the lower abdominal wall, inner thighs, pubic area, and genitalia. Although rarely found in the mouth or on the palms and soles, cases of molluscum contagiosum involving the oral mucosa, including the lips, buccal mucosa, hard palate, retromolar pad, and tongue, have been reported. The average duration of an untreated lesion is 6–9 months but may be as long as 5 years.

Diagnosis. Usually the diagnosis is not difficult and based on the clinical picture. The cellular material contained within the central umbilication may be extracted manually, flattered between 2 microscope slides, and stained. microscopic examination of this preparation reveals the intracytoplasmic molluscum inclusion bodies (Henderson-Paterson bodies).

Surgical Care. Frequently, multiple treatment sessions are necessary due to recurrence of treated lesions and/or the appearance of new lesions by autoinoculation. Each technique may result in scarring or postinflammatory pigment changes.

- Curettage. Individual lesions may be removed with a hand-held curette, with little discomfort. Follow curettage with application of a topical irritant.
- Cryosurgery. Apply liquid nitrogen for 10–15 seconds per lesion. Liquid nitrogen therapy may be quite painful and can result in blistering. Temporary or permanent depigmentation may occur in individuals who are more darkly pigmented.
- Electrodesiccation may be used for lesions that are refractory to curettage or cryosurgery. This technique can cause significant discomfort; consider using local anesthesia.

Herpes simplex

The herpes simplex viruses comprise 2 distinct types, **HSV-1 and HSV-2**. HSV-1 causes mostly oral lesions and HSV-2 — genital lesions. Herpes simplex viruses contain a core of double-stranded DNA surrounded by a protein coat with symmetrically arranged sub-units, in an outer envelope which encloses the inner structures (nucleocapsid).

HSV, belonging to the family Herpesviridae and to the subfamily Alphaherpesvirinae, is a double-stranded DNA virus characterized by the following unique biological properties:

- **Neurovirulence** — the capacity to invade and replicate in the nervous system.
- **Latency** — the establishment and maintenance of latent infection in nerve cell ganglia.
- **Reactivation**: The reactivation and replication of latent HSV can be induced by a variety of stimuli (eg, fever, trauma, emotional stress, sunlight, menstruation),

resulting in overt or covert recurrent infection and peripheral shedding of HSV. Reactivation is more frequent and severe in immunocompromised patients.

Distribution of HSV is worldwide. Humans are the only natural reservoirs, and no vectors are involved in transmission. The mode of transmission is by close personal contact, and infection occurs via inoculation of virus into susceptible mucosal surfaces (eg, oropharynx, cervix, conjunctiva) or through small cracks in the skin. The virus is readily inactivated at room temperature and by drying.

After the patient begins to produce antibodies, the infection becomes latent in the sensory ganglia. HSV-1 infection remains latent in the trigeminal ganglia, and HSV-2 in the sacral ganglia. The viruses become reactivated secondary to certain stimuli, including fever, physical or emotional stress, ultraviolet light exposure, and axonal injury.

Recurrent infections tend to be less severe because of existing cellular and humoral immunity from prior exposures. Infection by HSV requires a break in the skin's barrier; intact skin is resistant to the virus.

Pathogenesis. HSV-1 infections are spread via **respiratory droplets** or direct exposure to infected saliva. HSV-2 usually is transmitted via **genital contact**. Herpes viruses cause cytolytic infections; therefore, pathologic changes are due to cell necrosis as well as inflammatory changes. Fluid accumulates between the dermis and the epidermal skin layers and causes **vesicle formation**. The fluid then is absorbed, crusts are formed, and healing is completed without evidence of scarring. Shallow ulcers form after the vesicles rupture on mucous membranes.

The clinical diagnosis can usually be made on the characteristic presentation of the disease. Primary oral herpes infection may involve the entire oral cavity (gingivostomatitis), whereas recurrent infection usually occurs on the lip and perioral skin (labialis). The etiologic agent is usually HSV-1, although HSV-2 infection can occur. Among patients who get recurrences, 60 % to 85 % experience prodromal symptoms, such as tingling, pain, burning, or itching at the site of subsequent eruption. These symptoms occur usually for less than six hours prior to erythema or vesicle. However, they can last for as long as two days prior to a lesions. Lesions begin with erythema and progress rapidly to vesiculation usually within 12 hours. Herpes infection of the eye is the leading infectious disease cause of corneal blindness. While the primary infection is usually limited to conjunctivitis, recurrences of herpetic keratitis are common. The dendritic lesions, which are characteristic of the disease, can interfere with the vision and are quite painful.

Lab Studies. Scrapings from suspected lesions (Tzanck smear), viral culture, monoclonal antibody testing and cerebrospinal fluid (CSF) analysis can be used.

The quickest and least expensive diagnostic technique for cutaneous herpes simplex infection is the **Tzanck smear**. An intact vesicle or fresh erosion is selected for study, epithelial debris is scraped from the base of the lesion, and the material is smeared thinly onto a glass slide. The slide is allowed to air-dry and is stained. The cytopathogenic effects of HSV infection are manifested as giant, multinucleated epithelial cells that are two to five times the diameter of normal leukocytes. Hematoxylin-eosin stain is easiest to read because the cytoplasm of the multinucleated giant cell stains pink around the large blue-staining nuclei. It is important to note that the Tzanck smear will not be positive after the third or fourth day of recurrent lesion. Herpes zoster and varicella also yield positive Tzanck smear, but they are usually clinically distinguishable from herpes simplex infection. Herpes simplex virus can also be grown on live tissue culture.

Serum antibodies to herpes simplex virus are of little diagnostic value because the presence of serum antibodies indicates nothing more than previous exposure of the patient to the virus. A positive antibody test result does not prove that an extant or recurrent clinical lesion was due to HSV. Nor does the titer of serum antibodies to HSV vary to the activity of recurrent disease. Therefore, acute and convalescent serum sample analyses are not diagnostically helpful.

Treatment. Overall, medical treatment of HSV revolves around specific antiviral treatment. In situations in which constitutional effects such as fever occur, symptomatic treatment can be used. Appropriate wound care is needed, and treatment for secondary bacterial skin infections may be required.

Acyclovir is a synthetic acyclic purine nucleoside analogue with in vitro and in vivo inhibitory activity against herpes simplex virus. Patients given acyclovir have significantly shortened virus excretion, significantly decrease in pain or cessation of pain, shorter time to crusting, and shorter total healing time. Currently the only oral drug approved for use in herpes virus infections, acyclovir is prescribed for acute infection as 200 mg, five times per day for the period of infection.

NB! Currently it was proven that local antiviral therapy doesn`t affect the course of the disease and systemic acyclovir should be administered in any case of herpes infection.

Complications include bacterial and fungal superinfection, ocular infections, skin infections: eczema herpeticum. Central nervous system complications (aseptic meningitis, ganglionitis and myelitis, Herpes simplex encephalitis) are rare.

Herpes zoster (shingles)

Varicella zoster virus (VZV) is the causative agent of both varicella (chickenpox) and herpes zoster (shingles). Chickenpox is the primary infection, whereas herpes zoster represents reactivation of previous infection.

Chickenpox is a common and generally benign illness of childhood that is characterized by an exanthematous vesicular rash. Following this primary infection, VZV becomes latent in dorsal root ganglia. Generally, a decrease in cellular immunity is believed to trigger the reactivation of the virus. Reactivation typically occurs in elderly and immunocompromised patients when cellular immunity is decreased. VZV reappears in neurons and satellite cells and spreads to the skin through peripheral nerves.

The clinical manifestations of herpes zoster can be divided into the pre-eruptive phase (preherpetic neuralgia), acute eruptive phase, and chronic phase (postherpetic neuralgia).

Preeruptive phase. This phase is characterized by unusual skin sensations. As many as 80 % of patients experience burning, itching, or paraesthesia that is typically localized to a **dermatomal distribution**. These symptoms usually last for several days but occasionally can last for longer than a week before the cutaneous eruption appears. The burning pain prior to the characteristic eruptions may present a diagnostic dilemma because it can simulate any number of painful conditions, including migraine headache, cholecystitis, hepatitis, renal colic, appendicitis, pleurisy, pulmonary embolism, or myocardial ischemia. During this time, patients also may experience malaise, myalgia, headache, and fever. These symptoms may precede the eruptive phase by several days to a week or more and gradually resolve as cutaneous eruptions appear.

Eruptive phase. This phase is marked by the emergence of **vesicular eruptions** and possible constitutional symptoms. Almost all adult patients experience pain **(acute neuritis)** during the eruptive phase. Crust formation and drying occur over 7–10 days and are followed by resolution at 14–21 days. **Patients are infectious until lesions are dried**. Anyone who has not previously had varicella is at risk of acquiring this readily transmitted virus. Pregnant women and immunosuppressed patients have the highest risk of serious sequelae.

The initial rash presents as a swath of patchy, erythematous, swollen elements from which **clusters of small vesicles arise**. This eruption is virtually diagnostic of shingles. The extent of **dermatomal involvement** varies among patients and may involve all or part of a dermatome. It usually affects a single dermatome and rarely crosses the body midline. Eruptions in a bilateral distribution are very rare. The vesicles arise in clusters and many become purulent by day 4^{th}. Variation in size is common. Only a few vesicles may be present initially, but successive eruptions for 5–7 days may occur. Vesicles either umbilicate or erupt prior to drying and crusting. Crusts will fall off within 3 weeks.

In elderly and immunocompromised patients, the eruptive phase is longer and more extensive. It occasionally results in hemorrhagic blisters, skin necrosis, and secondary bacterial infections. Typically affected dermatomes include thoracic (56 %), cervical (17 %), trigeminal nerve (12 %), lumbar (10 %), and sacral (5 %).

Chronic phase (postherpetic neuralgia). Postherpetic neuralgia is persistent or reoccurring pain lasting 30 or more days after the acute infection or after all lesions have crusted. Pain resolves gradually in most patients but can persist for years. Most people report a deep, burning or aching pain, paraesthesia, dysesthesia, hyperesthesia, or electric shock-like pains. The pain can be extremely severe and incapacitating, leading to depression and even suicide. Postherpetic neuralgia and intractability of pain increase with age, from 27 % of untreated adults aged 55 years to 47 % of untreated adults aged 60 years to 73 % of untreated adults aged 70 years. Pain lasting for more than 1 year occurs in 48 % of patients older than 70 years.

Lab Studies. The condition is usually diagnosed clinically. Tzanck smear, viral culture remains, Electron microscopy, PCR can be taken.

Therapy. Topical therapy can include cool tap compresses several times a day, especially with extensive eruptions. **Lidocaine injections** may eliminate pain during the eruptive stage. Sympathetic nerve blocks are useful for treating pain. Antiviral therapy (acyclovir orally or intravenously) must be used.

Warts

Warts are benign proliferations of skin and mucosa caused by **human papilloma viruses** (HPV). Currently, more than 150 types of HPV have been identified.

Warts can affect any area on the skin and mucous membranes. Infection is confined to the epithelium and does not result in systemic dissemination of the virus. Replication occurs in differentiated epithelial cells in the upper level of the epidermis; however, viral particles can be found in the basal layer.

Warts can occur at any age. They are unusual in infancy and early childhood, increase in incidence among school-aged children, and peak at 12–16 years. HPV is spread by direct or indirect contact. It can resist desiccation, freezing, and prolonged storage outside of host cells. Autoinoculation also may occur, causing local spread of lesions. The incubation period for HPV ranges from 1–6 months; however, latency periods of up to 3 years or more are suspected.

Clinical picture:

1**. Common warts** are also termed verruca vulgaris. They appear as hard papules with a rough irregular scaly surface. They range from smaller than 1 mm to larger than 1 cm papule. They can occur on any part of the body but are seen most commonly on the hands and knees.

• **Filiform warts** are long slender growths, usually seen on the face around the lips, eyelids, or nares.

• **Deep palmoplantar warts** also are termed myrmecia. They begin as small shiny papules and progress to deep endophytic, sharply defined, round lesions with a rough keratotic surface, surrounded by a smooth collar of thickened horn. Because they grow deep, they tend to be more painful than common warts. Myrmecia warts that occur on the plantar surface usually are found on weight-bearing areas, such as the metatarsal head and heel. When they occur on the hand, they tend to be subungual or periungual.

• **Flat warts** are also termed plane warts or verruca plana. They are characterized as flat or slightly elevated flesh-colored papules that may be smooth or slightly hyperkeratotic. They range from 1–5 mm or more, and numbers range from a few to hundreds of lesions that may become grouped or confluent. These warts may occur anywhere; however, the face, hands, and shins tend to be the most common areas. They may appear in a linear distribution as a result of scratching or trauma **(Koebner phenomenon).** Regression of these lesions may occur, which usually is heralded by inflammation.

• **Subunguales warts** are seen at the proximal side of the nail and usually are mixed with onychomycosis.

Treatment. Cryosurgery, lasers, electrodesiccation and curettage and surgical excision are the most simple ways to remove warts. Some chemical agents (podophyllotoxin, 5-Fluorouracil, Imiquimiod) can be used. Salicylic acid is a first-line therapy used to treat warts. Many preparations are available over the counter. Therapeutic effects are enhanced by removing surface keratin or by occlusion with adhesive plasters. Cure rates from 70–80 % are reported. Salicylic acid is available without a prescription and can be applied by the patient at home.

LECTURE 9. CONTACT DERMATITIS

Contact dermatitis is a skin reaction on external stimuli. Stimuli that can cause dermatitis can be classified as:

- Chemical (acids, alkali, phenols, etc.)
- Physical (heat, cold, radiation, etc.)
- Biological (plants, secretions of some animals, etc.)
- Mechanical (pressure)

Factors may be obligatory — that cause dermatitis in every person — for example strong acids or non obligatory that can cause dermatitis only in predisposed persons or under certain circumstances.

There are two main forms of contact dermatitis — irritant and allergic contact dermatitis. Accordinf to the severity of and period of exposion to the factor dermatitis can be acute, subacute and chronic.

Among workers' compensation claims for dermatologic conditions, 90 % are for contact dermatitis. The most common antigens are nickel, potassium

dichromate, and paraphenylenediamine. Contact dermatitis is the reason for 4–7 % of dermatology consults. Hand dermatitis affects 2% of the population at a given time, and 20 % of females are affected at least once in their lifetime.

Irritant dermatitis

Irritant dermatitis results from direct injury to the skin. It affects individuals exposed to specific irritants and generally produces discomfort immediately following exposure. Irritative contact dermatitis affects very young and very old patients more severely and it is common in children. The most common cause in children is diaper dermatitis. Usually open parts of the body are affected. Hands is the most frequent location.

An irritant produces direct local cytotoxic effect on the cells of the epidermis, with a subsequent inflammatory response in the dermis. Atopic individuals have an inborn constitutional skin weakness

NB! Severity of the reaction in irritant dermatitis is related to the amount and duration of exposure to the

Clinical picture. Most cases of contact dermatitis have a similar appearance regardless of the mechanism or cause of inflammation. Acute contact dermatitis presents as clear fluid-filled vesicles or bullae that appear on bright red edematous skin. As the lesions break, skin becomes exudative and weeps clear fluid. Subacute contact dermatitis is characterized by less edema and formation of papules. Chronic contact dermatitis presents with minimal edema. Scaling, skin fissuring, and lichenification may be noted. Contact urticaria has a wheal and flare response at the site of exposure.

Allergic contact dermatitis (ACD)

It is a cell-mediated type IV delayed hypersensitivity reaction results from specific antigens penetrating the epidermal skin layer. The antigen combines with a protein mediator and travels to the dermis, where T lymphocytes become sensitized. On the next presentation of the antigen, the allergic reaction takes place.

Causes. Approximately 25 chemicals appear to be responsible for as many as one half of all cases of ACD. Nickel is the leading cause of ACD in the world. ACD to nickel typically is manifested by dermatitis at the sites where earrings or necklaces containing nickel are worn or where metal objects containing nickel are in contact with the skin. Allergy to chemicals in rubber gloves is suggested in any individual with chronic hand dermatitis who is wearing them. ACD to chemicals in rubber gloves typically occurs maximally on the dorsal aspects of the hand. Usually, a cutoff of dermatitis occurs on the forearms where skin is no longer in contact with the gloves.

Preservative chemicals added to cosmetics, moisturizers, and topical medications are major causes of ACD. Formaldehyde is a major cause of ACD. Certain preservative chemicals widely used in shampoos, lotions, other moisturizers, and cosmetics are termed formaldehyde releasers. Individuals may develop allergy to fragrances. Fragrances are found not only in perfumes, colognes, aftershaves, deodorants, and soaps, but also in numerous other products, often as a mask to camouflage an unpleasant odor. Deodorants may be the most common cause of ACD to fragrances because they are applied to occlude skin. Occasionally, individuals develop photo ACD. ACD may be accentuated by ultraviolet (UV) light, or patients may develop an allergic reaction only when a chemical is present on the skin and when the skin is exposed sufficiently to ultraviolet light A (UV-A; 320–400 nm).

Clinical presentation. In acute ACD, lesions appear within 24–96 hours of exposure to the allergen. Certain allergens (eg, neomycin) penetrate intact skin poorly, and the onset of dermatitis may be delayed up to a week following exposure. In contrary with irritant dermatitis the amount of allergen does not affect the severity of skin reaction. The main symptom, in addition to the lesion, is pruritus. Most heavily contaminated areas break out first, followed by areas of lesser exposure.

The possibility of an external cause of dermatitis always must be considered if the dermatitis is linear or sharply defined. The immediate onset of dermatitis following initial exposure to material suggests either a cross-sensitization reaction, prior forgotten exposure to the substance, or nonspecific irritant contact dermatitis provoked by the agent in question.

Acute ACD is characterized by pruritic papules and vesicles on an erythematous base. Lichenified pruritic plaques may manifest chronic ACD. Occasionally, ACD may affect the entire integument (ie, erythroderma, exfoliative dermatitis). The initial site of dermatitis often provides the best clue regarding the potential cause of ACD.

Diagnosis. Diagnosis of irritant contact dermatitis is performed on the base of typical clinical picture and thorough anamnesis. Patch testing is required in case od ACD to identify the external chemicals to which the person is allergic. Small amounts of appropriate labeled dilutions of chemicals are applied to the skin and occluded for 2 days. The patch test must be read not only at 48 hours, when the patch tests customarily are removed, but again between 72 hours and 1 week following initial application.

Treatment. The first measure is the removal of offending agent. A detailed history, both before and after patch testing, is crucial in evaluating individuals with ACD. Potential causes of ACD and the materials to which individuals are exposed should be patch tested. Patients with ACD require a much more

detailed history compared to those with most other dermatologic disorders. Usually topical corticosteroids and emollients are used.

Occupational Dermatoses

Work-related skin disease — is a disease to which occupational exposure is a major causal or contributory factor.

The problem of the work-related skin diseases is not only the question of the treatment, it`s also the problem of the large expenses, that are caused by disability, medical care, loss of productivity and quality, rehabilitation. That is the problem that should solve not only dermatologists but the Health organizations as well as government.

In many occupations the skin is exposed to the damaged factors like chemicals, biological materials, physical forces. Work-related diseases are developed if the balance between the resistance of the skin and the force of the damage factor is disturbed. Work-related diseases usually affect face and hands and have the clinical look of the contact, allergic contact dermatitis and eczema. Sick-leave as the result of the work-related skin diseases is mainly determined by:

- Limitation of the manual skills.
- Acceptance of the disease by collegues.
- Risk of the spread of the infection (food sector).
- Negative image.

Some predisposal factors may of the skin of the person may aggravate the situation and make the resistancy of the skin barrier lower, they are: atopic dermatitis, dry skin and sensible skin, psoriasis, age, sex, eczema. There are also risk occupations that may develop skin work related skin disease – agricultural, animal health care, automobile, bakeries, chemical industry, cleaners, construction, food industry, metal industry, paint industry, pharmacological industry, plastic industry, rubber industry, etc.

Work-related skin diseases are distinguished from the other skin diseases by characteristics revealed by the physical examination as well as analysis of the work place, occupation conditions. The clinical feature and localization provide important arguments against or for a work relation of the professional skin diseases. Pre-existing skin diseases are important modifying factors for the development of work-related skin disease. Sometimes the eczema and dermatitis are improved in the conditions what the person doesn`t work.

Prevention of occupational dermatoses. Prevention of work related diseases is based on primary prevention — inhibition of the onset of the disease and secondary prevention — inhibition of the relapses. There are main principles of prevention of occupational dermatoses:

1. Identification of allergens and irritants.
2. Labeling of chemicals.

3. Elimination or replacement of harmful substances.
4. Technical measures.
5. Organisation.
6. Special training of workers.
7. Personal protection.
8. Pre-employment screening.
9. Training of medical personnel working at the factories and industry.
10. Information for patients, consumers, workers.
11. Research on prevention.

LECTURE 10. ITCH AS A MAIN SYMPTOM IN DERMATOLOGY. DERMATOSES ASSOSIATED WITH ITCH

Itch as a disease and as a symptom

Itch may be the sign of many dermatological and systemic diseases. Pathology of the itch sensation is not studied yet. It is proposed that itch and pain are transmitted through the same nerve pathway but different fibers. Some tissue mediators may cause itching. For example, histamine causes the itch after the injection under the skin. Itch can be localized and generalized. Location of the itch in different parts of the body is typical for the different skin diseases:

Head — seborrhoeic dermatitis, seborrhoeic eczema, psoriasis.

Eyelids — allergic reaction on some allergens from the environment.

Palms — scabies, dyshidrotic eczema.

Feet — fungi infections, eczema.

Genital region — intertrigo, fungi infection, diabetis mellitus.

The itch is usually characterized by excoriations. The chronic itch may lead to the lichenification of the skin. Nails may have the typical «polish look» due to permanent scratching. The elements of the main skin disease may be seen in the skin.

There are many reasons for the generalized itch. Usually patients with dry skin suffer from the itch. Dry skin can be because of age, some skin diseases — eczema, atopic dermatitis, and ichthyosis. For some skin diseases itch is a main clinical sign:

1. Scabies.
2. Pediculosis.
3. Atopic dermatitis.
4. Lichen planus.
5. Herpetiformic dermatosis Duhring.
6. Toxiderma.
7. Urticaria.
8. Prurigo.

For some diseases itch is not the main complain but is quite common: psoriasis (40%), pityriasis rose, fungi infections. Generalized itch can be a symptom not only for the skin diseases but may be a clinical sign of the other pathology.

For to remember all the cases of the itch you can use the word **BLINKED:** B — blood disease; L — liver disease; I — infection, immunological or autoimmune disease, N — neoplastic disease, neurological disease, K — kidney disease, E — endocrinologic disease; D — drug.

Urticaria (hives)

Urticaria, or hives, is a common skin condition that affects 15–25 % of the population at some point in their lives. Most cases of urticaria are self-limited and of short duration, but when urticaria becomes chronic, it can be a very problematic and frustrating condition, both for the patient and for the clinician.

Urticaria is classified as either **acute or chronic.** Acute urticaria is defined as urticaria that has been present for less than 6 weeks. Chronic urticaria is defined as urticaria that has been continuously or intermittently present for at least 6 weeks. The 6-week period is a guide and not an absolute demarcation. When no underlying cause is found, chronic urticaria is referred to as **chronic idiopathic urticaria (CIU).**

Pathogenesis. Skin lesions and pruritus occur, caused by an allergic or nonallergic mechanism. Histamine is thought to be the most important biochemical mediator in urticaria. It is known to cause the classic wheal-and-flare response that is observed in urticaria and with positive results on allergy skin tests. Studies have shown that histamine is present in fluid taken from

urticaria wheals. Mast cells are the major histamine-releasing cells of the skin. Some studies report increased numbers of mast cells in urticaria lesions. The mast cell possesses high-affinity receptors for immunoglobulin E (IgE). Histamine and the other mediators can be released by other nonallergic mechanisms as well. For example, neuropeptides are known to cause mast cell degranulation by a nonallergic mechanism. Neuropeptides may well be involved in dermographism and in emotional exacerbation of urticaria. In addition to histamine, other mast cell mediators are also thought to play a role in urticaria.

The cause of urticaria can be: food allergies, drug allergies, contact urticaria (allergic reaction to a substance that comes into contact with the skin), physical causes (physical urticaria) — cold, pressure, vibration, sunlight, water, exercise.

Clinical presentation. Typical lesions are described as edematous pink or red wheals of variable size and shape, with surrounding erythema. The lesions are often described as welts or hives. The lesions are generally pruritic. Dermographism is often observed in conjunction with urticaria. The skin can be scratched with the end of a tongue blade or similar blunt object and observed over the next 5–15 minutes for the development of whealing with erythema.

Individual lesions usually fade within 24 hours, but new lesions may be developing continuously. With delayed pressure urticaria, lesions may last as long as 48 hours.

Treatment. H-1 antagonists (antihistamines) — primary agents used for urticaria. The older, 1st generation H-1 antagonists are effective in reducing the lesions and pruritus but can produce a number of adverse effects, such as drowsiness and antocholinergic effects. Commonly used first — generation agents include diphenhydramine, hydroxyzine, chlorpheniramine, and cyproheptadine. They can be used as primary treatment of acute episodes, but the adverse affects may limit their isefullness for chronic urticaria. The 1st generation agents can sometimes be useful if administered at bedtime because the sedative effects can help with sleep, but the sedation and cognitive effects may continue until the next day.

The newer second-generation antihistamines are nonsedating in most patients, with very few side effects reported. The second-generation agents that are currently available cetirizine, desloratadine, loratadine, and fexofenadine. All 4 are active in chronic urticaria. Therefore, many specialists prefer the use of second-generation agents for chronic urticaria, with first-generation agents reserved for acute or refractory cases.

Angioedena (Quincke edema)

Angioedema and urticaria should be viewed as varying manifestations of the same pathologic process. Postcapillary venule inflammation results in fluid leakage and edema in both conditions. However, angioedema involves vessels in the layers of the skin below the dermis, while urticaria is localized superficial to

the dermis. Complications range from dysphonia or dysphagia to respiratory distress, complete airway obstruction, and death.

Common sources of antigens causing urticaria and angioedema include the following:

1. Food allergies such as fresh berries, shellfish, fish, nuts, tomatoes, eggs, milk, chocolate, food additives, and preservatives
2. Local trauma (eg, dental procedure, tonsillectomy)
3. Exposure to water, sunlight, cold, or heat
4. Animal dander (from scales of shed skin)
5. Emotional stress
6. Post infection or illness, including autoimmune disorders such as thyroid autoimmunity and leukemia
7. Drugs associated with urticaria and angioedema include: radiocontrast agents, opiates, dextran, angiotensin-converting enzyme (ACE) inhibitors, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs)
8. Chronic urticaria (increasingly associated with *Helicobacter pylori* bacteria).

Clinical picture. Patients usually present with the acute onset of well-demarcated cutaneous edema of distensible tissues (eg, lips, eyes, earlobes, tongue, uvula). The face, extremities, and genitalia are most commonly affected. Severe attacks can herald the onset of systemic anaphylaxis, characterized initially by dyspnea.

Therapy. The initial goal of theapy os airway management. Most patients with mild acute angioedema may be treated the same way as those with an allergic reaction. Severe symptoms require steroids, H-1 and H-2 blockers, and subcutaneous epinephrine in addition to antihistamines.

Prurigo

The term «prurigo» designates an intensely pruritic skin lesions that have no apparent cause. The disease is usually considered as one of the most prurigenic skin diseases and therefore, the lesion is accompanied by skin thickening and pigmentation.

Prurigo is characterized by the **prurigo nodule (seropapule) that is dome-shaped and topped with a small vesicle,** which usually appears as an excoriated lesion due to severe scratching. The crusted nodules are usually seen rather than the primary papule with its topped vesicle.

The most common types of prurigo are:

1. Prurigo in adults
2. Prurigo in children

Chronic prurigo of adults is a poorly defined entity that mimics the widespread papular urticaria of insect bites. The cause is unknown although emotional stress seems to be a contributory factor in some cases. Insect bites especially after repeated exposure in susceptible persons may play an important role. The disorder is more common in adults, with an onset in the spring and

summer months. The characteristic lesions are found on the trunk and neck, and present as itchy red papules which occasionally coalesce to a reticular pattern, and reticular hyperpigmentation. Prurigo occasionally occurs with malignant disease, especially Hodgkin‘s lymphoma and in polycythaemia.

The individual lesion is a hard globular nodule, 1–3 cm in diameter, with a raised warty surface. The early lesion is red and may show a variable urticarial component, but all the lesions tend to be pigmented. Crusting and scaling may cover recently excoriated lesions. There is an irregular ring of hyperpigmentation immediately around the nodules. The lesions are usually grouped. New nodules develop from time to time, but existing nodules may remain pruritic indefinitely although some may regress spontaneously to leave scars.

The treatment is usually symptomatic. Courses of corticosteroids, antihistamines may be necessary.

Lichen simplex (local neurodermitis)

Lichen simplex, also called neurodermatitis, is a common skin problem. It generally affects adults, and may result in one, or many itchy patches. Lichen simplex is a type of dermatitis, and is usually the result of repeated rubbing or scratching. The stimulus to scratch may be unrecognized, perhaps a mosquito bite, stress, or simply a nervous habit.

The areas most commonly affected by lichen simplex chronicus include outer lower portion of lower leg, wrists and ankles, back and side of neck (lichen simplex nuchae), forearm portion of elbow, scrotum, vulva, anal area, pubis, upper eyelids, opening of the ear, fold behind the ear.

Clinical picture. The affected skin is thickened, often appearing as a group of small firm papules. The skin markings are more visible, and the hairs are often broken-off. The colour may be darker or sometimes paler than the surrounding skin. Lichen simplex tends to be very persistent, and readily recurs despite often initially effective treatment.

Treatment. Treatment of the itching is necessary to stop the scratching and resulting skin damage. Heat and fuzzy clothing worsen itching; cold and smooth clothing pacify it. If the itching is persistent, dressings may be applied to the affected areas. Among the topical medications that relieve itching are a number of commercial preparations containing menthol, camphor, eucalyptus oil, and aloe. Topical corticosteroids are also used. In the places with the more thick skin we can apply potent corticosteroids. For broken skin, topical antibiotics help prevent infection. These should be used early to forestall further damage to the skin. Reducing the buildup of thick skin may require medicines that dissolve or melt keratin, the major chemical in skin's outer layer. These keratolytics include urea, lactic acid, and salicylic acid. Sedatives or tranquilizers may be prescribed to combat the nervous tension and anxiety that often accompanies the condition.

All these methods may be combined with the physiotherapy for better penetration — ultrasound, electrophoresis can be used for the damaged areas.

Atopic dermatitis

Atopic dermatitis (AD) — is a chronic inflammation of the skin that occurs in persons of all ages but is more common in children. The condition is characterized by intense pruritus and a course marked by exacerbations and remissions.

Precise etiology is unknown, but current theories center on a disordered immune response, especially an imbalance of cytokines. The disease also appears to have a hereditary component; family history is positive for atopy (ie, asthma, allergic rhinitis, atopic dermatitis) in two thirds of patients. AD typically manifests in infants aged 1–6 months. Approximately 60 % of patients experience their first outbreak by age 1 year and 90 % by age 5 years. Onset of AD in adolescence or later is uncommon and should prompt consideration of another diagnosis. Disease manifestations vary with age. AD has been reported to affect 10–15 % of children. Although the symptoms of AD resolve by adolescence in 50 % of affected children, the condition can persist into adulthood.

Predisposal factors: genetic background (atopy), immune dysfunction, impaired barrier function (dry skin), inflammation, microbial colonization, dysfunction of the peripheral nervous system, psychosomatic disorders, non-immune factors.

Diagnosis. Unfortunately, no specific laboratory findings or histologic features define AD. Although elevated IgE levels are found in 80 % of affected patients, IgE levels are also elevated in patients with other atopic diseases.

The diagnosis requires the presence of at least **three major features and at least three minor**

NB! Major features of AD include:

1. Pruritus.
2. Chronic or relapsing dermatitis.
3. Personal or family history of atopic disease.
4. Typical distribution and morphology of atopic dermatitis rash (fascial and extensor surfaces in infants and young children and flexure lichenification in older children and adults)

Minor features include affection of infraorbital folds, facial pallor, cheilitis, palmar hyperlinearlity, xerosis, pityriasis alba, white dermographism, ichtyosis, keratosis pilaris, nonspecific dermatitis of the hands and feet, nipple eczema, positive type I hypersensitivity skin tests, propensity for cutaneous infections, elevated serum IgE level, food intolerance.

Clinical presentation. Clinical forms of AD include vesicular crusty, erythematous scaly, erythematous scaly with lichenification, lichenoid and prurigo-like.

Clinical picture depends on the age of the patient. In infants up to 1 year old predominant area of AD lesions is cheeks. At this age there is also dermatitis on the scalp. Excoriations are characteristic clinical feature in this age group. In addition to the head, there may be dermatitis on the **extensor** aspects of the extremities. Crawling of infants may cause hand eczema with large plaques of thickened skin on the wrists. Dermatitis around the mouth may be caused by saliva and various food. Infants with AD easily develop miliaria rubra. It is very pruritic rash with small papules due to the inflammation around the sweat glands.

By the 2–7 years the clinical picture of AD changes. In this age AD is typically seen in the elbow and knee **flexures**. Fissures in the dermatitis are colonised with S.aureus and it can lead to impetigo. Virus infection may cause multiple mollucum contagiosum or cause eczema herpeticum.

During 7–16 years flexural dermatitis continues to be the main characteristic manifestation of AD. Other characteristic features include mechanical irritation. On the soles of the feet dermatitis plantaris sicca (atopic winter feet in children) may be seen. A similar type of dermatitis develops on fingertips. Frequent, long showers, enjoyed by most teenagers, dry out the skin and damage the skin barrier, resulting in dehydration, pruritus and dermatitis. Ichthyosis is common especially in the shins of older children with AD. Keratosis pillaris with follicular keratotic papules may also be seen. Pithyriasis alba is post-inflammatory hypopigmentation following nummular or annular AD lesions.

After 16 years involvement of face and upper trunk is seen alone with classical flexure involvement. Mechanical irritation can lead to treatment resistant dermatitis on the nipples from rubbing against clothing. Some adults with severe AD may develop generalized erythroderma with red, infiltrated, scaly skin.

Treatment. Prevention is the mainstay of treatment for atopic dermatitis. The emergency physitian must properly diagnose, educate, and treat acute exacerbations or complications. If secondary infection is present, initiate therapy with antibiotics is helpful.

Educate patients and their parents about common triggers and the necessity of avoiding them. Explain that no cure exists, but exacerbations can be

minimized with proper skin care. Instruct patients to take short baths or showers in lukewarm water and limit the use of soap on axilla, groin, and feet. Recommend bathing on alternate days during the winter. Liberal use of a good skin moisturizer cannot be overemphasized, especially in winter and immediately after bathing or swimming. Emphasize minimizing contact with cosmetics, deodorants, detergents, solvents, or other known triggers.

Use lubricants to keep as much moisture in the skin as possible. The best lubricant is also the greasiest. Patients can choose which moisturizer works best for them. Using a moisturizing soap is recommend.

Treat acute attacks with a low-to-moderate potency topical corticosteroid. Inform the patient about adverse effects of topical steroids (eg, atrophy, hypopigmentation, striae, telangiectasia, thinning of the skin). Medium-to-high potency topical steroids should not be used on the face or neck area because of these potential adverse effects.

Patients with severe flare-ups or weeping lesions may benefit from a 7-day course of oral prednisone (40–60 mg/d for adults, 1 mg/kg/d for children). As the lesions begin to dry, apply a topical steroid.

To control itching, many dermatologists place patients on an **antihistamine**, an adjunct to education, lubrication, and corticosteroids. The sedative effects may be more beneficial than its antipruritic properties. In AD, because the pruritus is not histamine mediated, it does not respond well to histamine blockade. However, patients have a tendency to scratch in their sleep, and sedating them with an antihistamine at bedtime reduces scratching. Because scratching plays a major role in perpetuating rash, reducing it can improve the rash.

The new class of the drugs that can be used in AD are local immunosuppressors (cream, ointment) — **Pimecrolimus, Tacrolimus**. They have no side effects as corticosteroids and may be used continuously.

Eczema

Eczema is a chronic recurrent allergico-inflammatory disorder caused by different agents. Eczema may be caused by endogenic (chronic infections) and exogenic factors (chemicals, bacteria, physical agents, some food agents). It is characterized by **multi sensibilisation** of the immune system. Relapses may be provoked by the contact with chemicals, intake of food, drugs.

Clinical forms of eczema include:

1.Dyshidrotic eczema (pompholyx eczema)
2.Nummular (discoid or microbic) eczema
3.Professional (contact eczema)
4.Seborrhoeic eczema (severe form of seborrhoic dermatitis)
5.Infantil eczema (atopic dermatitis)

In this chapter we will discuss only dyshidrotic eczema and numullar eczema. Infantile eczema is considered to be a form of atopic dermatitis and should be treated as one of its symptoms. Seborrhoeic dermatitis is a worsening of seborrhoeic dermatitis. Professional eczema is connected with occupational irritants but has no distinguishable signs from other forms of eczema.

All eczematous conditions have some features in common. Whatever the agent is responsible for the eczema the epidermis becomes edematous. Initially individual keratynocites swell and later fluid collects between the cells giving rise to the characteristic feature of **spongiosis**. If the process is rapid the fluid collects into small vesicles – a characteristic and valuable sign of eczema. As the acute phase pass scaling and cracking appear at the skin surface.

All these phases may be seen altogether in one patient (Figure 1).

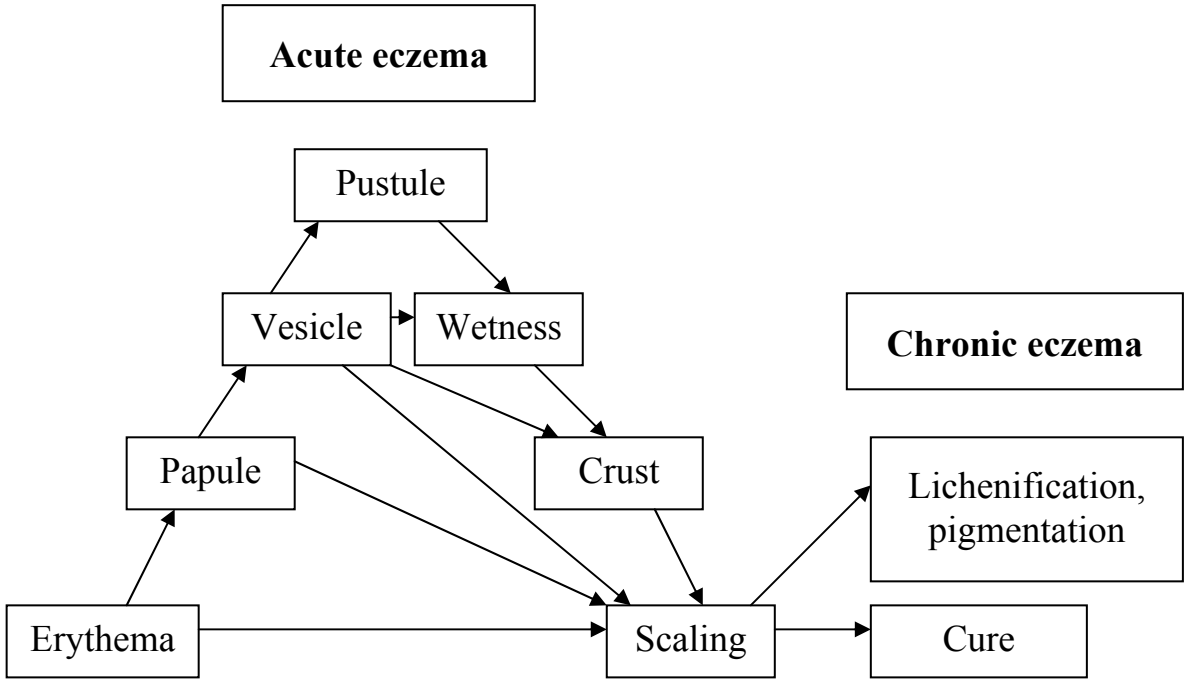

Figure 1 — Scheme of pathological process in eczema

Dyshidrotic eczema (pompholyx eczema)

Dyshidrotic eczema is a recurrent or chronic relapsing form of vesicular palmoplantar dermatitis of unknown etiology. Dyshidrotic eczema also is termed pompholyx, which derives from *cheiropompholyx*, which means «hand and bubble» in Greek. The etiology of dyshidrotic eczema is unresolved and believed to be multifactorial. It is considered a reaction pattern caused by various endogenous conditions and exogenous factors.

Several hypotheses exist for the pathophysiology of dyshidrotic eczema. Exogenous factors (eg, contact dermatitis to nickel, balsam, cobalt; sensitivity to ingested metals; dermatophyte infection; bacterial infection) may trigger

episodes. Emotional stress and environmental factors (eg, seasonal changes, hot or cold temperatures, humidity) reportedly exacerbate dyshidrosis.

Patients complain on pruritus of hands and feet with sudden onset of vesicles. Burning pain or pruritus occasionally may be experienced before blisters appear. Episodes vary in frequency from once per month to once per year. Patients may report a variety of factors that possibly are related to eruptions.

Symmetric crops of clear vesicles and/or bullae on the palms and lateral aspects of fingers characterize dyshidrotic eczema and the lateral aspects of toes also may be affected. The rash can be generalized due to scratching. In mildly affected patients, vesicles are present only on the lateral aspects of fingers and, occasionally, involve feet and toes. Vesicles are deep seated with a tapiocalike appearance, without surrounding erythema. Typically resolve without rupturing, followed by desquamation. Hands are involved solely in 80 % of patients, feet solely in 10 %, and both hands and feet are involved in 10 % of patients. Interdigital maceration and desquamation of the interdigital spaces often are present, despite the possible absence of a dermatophyte infection. Vesicles and/or bullae may become infected secondarily, and pustular lesions may be present. Cellulitis and lymphangitis may develop. It is usually complicates tinea pedis.

Nummular eczema

Nummular (meaning coinlike) eczema is an idiopathic disease that manifests as discrete round plaques. These plaques can be dry or exudative. It is a chronic condition with relapse and recurrence often at the same sites. Lesions wax and wane with changes in environmental conditions; it worsens in the winter, in low relative humidity, and in the presence of heaters. It is considered to be one of the forms of microbal eczema.

Treatment of eczema is complex. Hypoallergenic diet should be recommended (avoiding allergic components — oranges, chocolate, etc.). antihistamine drugs (diazoline, dimedrol, loratadine) are used for to remove itch as the main complain of the patients. Systematic corticosteroids may be administrated in severe cases for the short time.

Local treatment depends on the stage of the disease. When there is an acute stage and vesicles are present it is important to use compresses with solutions (10 % aluminum acetate, acidi borici, furacilinum, tannini) until the surface is dry. In subacute stage creams (corticosteroids) and pastas (zinc pasta) are applicated. In chronic eczema with lichenification corticosteroid ointments are used. Pimecrolimus and tacrolimus are used in subacute stage for maintain the results of the therapy.

LECTURE 11. DRUG ERUPTIONS

Skin and mucocutaneous lesions induced by a drug or by its metabolites are called drug eruptions.

Some cutaneous drug reactions present a specific morphological pattern. However, most drug eruptions can present the appearance of any cutaneous lesion. Maculopapular or morbilliform eruptions may be the most common of all cutaneous drug reactions. Drug eruptions may be accompanied by general symptoms including fatigue, fever, lymph node enlargement, disfunction of the internal organs such as liver, kidneys or bone marrow, hypotension and shock. It is necessary for dermatologists to take a detailed patient's history of medication use as well as a medical history.

Some of the best studied causes and clinical presentations of drug eruptions are presented in the table:

Clinical presentation	Drug
Macularpapular rash	Ampicillin, amoxicillin, carbamazepine
Photosensitive	Ampiroxicam, giseofulvin, ketoprofene, doxicyclin
Fixed drug eruption	Allylisopropylacetyl urea, mefenamic acid, ethenzamide, barbital, minocycline, sulfamethoxazole, piroxicam, fluorouracil
Erythema multiforme	Iohexol, carbamazepine, amoxicillin, tiopronin, phenytoin, diltiazem, mexiletine
Lichenoid	Tiopronin, captopril, interferon ***a***, cyanamide, oxatomide
Urticarial	Cefaclor, minocycline, iohexol, aspirin, cetraxate, mefenamic acid
Toxic epidermal necrolysis	Cefzonam, penicillin, phenobarbital, chlormezanone, carbamazepine, methazolamide, acetaminophen, allopurinol, diclofenac
Stevens-Johnson syndrome	Penicillin, chlorpromazine, sulfamethoxazole, sodium aurothiomalate, phenytoin
Erythrodermic	Carbamazepine, sodium aurothiomalate, cyanamide, allopurinol, ampicillin

Vesiculo-bullous	D-penicillamine, tiopronin, captopril, bucillamine, alacepril
Eczematous	Penicillin, chlorpromazine, chlorthiazide, promethazine
Purpuric	Sodium aurothiomalate, sulfamethoxazole, penicillin, aspirin

There are several mechanisms of the development of drug reactions:

1. Immunologic

- Type I hypersensitivity (via IgE antibodies; acute onset within 2 hours after drug intake).
- Type II hypersensitivity (eruption caused by thrombocytopenia and hemolysis resulting from complement activation).
- Type III hypersensitivity (immunocomplex deposition in skin components).
- Type IV hypersensitivity (reactions caused by activated T cells).

2. Non immunologic

- Pharmacological effects (drug-induced skin reactions may be produced by essential pharmacological action of the drug. Hair loss caused by anticancer agents and exfoliation in palms and soles caused by retinoids are examples).
- Accumulation (a drug accumulates in the skin or mucous membranes from prolonged use — arsenic melanoderma and argyria are examples of accumulation disorders).
- Drug interaction (one drug may inhibit another drug's metabolism or excretion, or it may influence protein binding, leading to the same symptoms as those in drug overdose).
- Patient-specific conditions (inherited enzyme deficiency may cause drug reactions).

Diagnosis. History is taken on drug-induced skin reactions and on exacerbation or remission of eruptions influenced by use or discontinuation of a drug. If the eruption is suspected to be drug-induced reactions, tests listed below are conducted for identification:

- Skin test (scratch test, prick test, intradermal test).
- Patch test.
- Drug lymphocyte stimulation test (DLST).

Treatment. Firstly it is important to eliminate a drug that has caused the reaction. Desintocsication therapy (intravenous infusions) can help to eliminate immune complexes in drug reactions. Corticosteroids and antihistaminals can be used in severe conditions.

Erythema multiforme

In 1860, Ferdinand von Hebra initially described erythema multiforme as an acute, self-limited condition with characteristic red papular skin lesions. The

papules evolve into pathognomonic target lesions or iris lesions that appear within a 72-hour period and begin on the extremities. Lesions remain in a fixed location for at least 7 days and then begin to heal.

It is estimated that EMM is a cell-mediated immune reaction leading to the destruction of keratinocytes expressing various antigens. However, the underlying pathomechanism is not known. In the early stages of epidermal EM, there is lymphocytic infiltration into the dermo-epidermal junction and vacuolar degeneration of basal cells. As the disease progresses, lymphocytes (CD8+T cells) infiltrate into the epidermis, and necrosis of epidermal cells and subepidermal blistering are found.

EMM is usually associated with infection or some drug reaction. Infection by the herpes simplex virus or mycoplasma pneumoniae is the dominant causative factor of EMM, but drug-sensitivities are also an important cause:

Conditions associated with EMM

Infections	Virus (e.g., human herpes simplex virus), bacteria (*Streptococcus, Mycoplasma, Mycobacterium*), tinea, *Chlamydia*, *Rickettsia*
Drug reactions	Antibiotics, NSAIDs, anticonvulsants, antineoplastic agents, etc.
Collagen and allergic diseases	Insect bite, systemic lupus erythematosus (SLE)), sarcoidosis, Crohn's disease
Other	Physical stimulation (e.g., cold), hematopoietic malignant disorders, pregnancy, etc.

Clinical presentation**.** EM may occur in patients of all ages, but it occurs predominantly in adolescents and young adults. Eruptions occur symmetrically on the extensor aspects of the joints (e.g., the dorsal hands, elbows, knees) as erythematous papules or edematous erythema, and they spread centrifugally in about 48 hours to form sharply circumscribed, round or irregularly shaped erythema. The center of the erythema is concave, presenting either as a target lesion or iris formation, also called exudative erythema. The affected area simultaneously shows new and old lesions that may fuse into map-like patterns. EMM may be accompanied by blistering (bullous EMM) and erosions of the oral mucosa. EMM frequently occurs in the young and middle-aged, and it tends to appear during the spring and summer. Infectious symptoms including high fever and pharyngodynia may precede the onset. In cases caused by herpes simplex infection, EMM tends to occur 1 to 3 weeks after the onset of the herpes simplex symptoms (post-herpetic EMM).

Laboratory examination and diagnostics. Because of inflammation, CRP may be positive and the erythrocyte sedimentation rate is elevated. The herpes simplex virus antibody titer, *Mycoplasma* antibody titer and antistreptolysin O (ASO) titer may be elevated in some cases. In cases involving bacterial

infection, there is an increase in neutrophils. EMM is relatively easy to diagnose by its characteristic clinical features and by the distribution of the eruptions. History of previous diseases, such as infectious diseases, supports the diagnosis. Identifying the pathogenesis is important not only for treatment but also for prevention of recurrence.

Treatment. The underlying infectious disease should be treated. Topical steroids, oral antihistamines, NSAIDs and potassium iodides may also be used. Severe cases need the application of systemic corticosteroids. EMM regresses spontaneously within 2 to 4 weeks. When caused by herpes simplex infection, acyclovir administration may be effective; however, EMM tends to recur.

Stevens-Johnson (SJS) and toxic necrotic epidermolysis (TEN) syndrome

SJS is a mucocutaneous disorder. It was first described by Stevens and Johnson in 1922 as febrile erosive stomatitis, severe conjunctivitis, and disseminated cutaneous eruption. Lesions typically begin on the face and trunk. They are flat, atypical lesions, described as irregular purpuric macules with occasional blistering. Most patients also have extensive mucosal involvement. More than 50 % of all cases are attributed to medications. It is a serious illness and is potentially life threatening.

Lyell first described TEN in 1956. His original description made no reference to the work of Stevens and Johnson. The distinction between SJS and TEN is not clear. ISJS and TEN have similar precipitating factors, identical histopathologic lesions, and similar

NB! Previously SJS was considered to be a variant of erythema multiforme. But today SJS and TEN are classified as the same condition but of different stages of severity

Pathogenesis.The pathophysiology has not been fully elucidated; however, various theories have received wide acceptance. These conditions are believed to be immune-related cytotoxic reactions aimed for destroying keratinocytes that express a foreign antigen. The condition mimics a hypersensitivity reaction, with its characteristic delayed reaction to an initial exposure and more rapid reaction with repeated exposure. Explanations for the generalized nature of TEN include the belief that overexpression of tumor necrosis factor-alpha (TNF-alpha) in the epidermis occurs. Therefore, TNF-alpha is likely to play an important role in epidermal destruction directly through apoptosis, indirectly through stimulating cytotoxic T cells, or both.

The 4 etiologic categories are:

1.I nfectious — viral diseases that have been reported include herpes simplex virus (HSV), AIDS, Coxsackie viral infections, influenza, hepatitis, mumps, mycoplasmal infection, lymphogranuloma venereum (LGV), rickettsial

infections and variola. Bacterial etiologies include group A beta Strep., diphtheria, Brucellosis, mycobacteriae, Mycoplasma pneumonia, tularemia and typhoid. Coccidioidomycosis, dermatophytosis and histoplasmosis are the fungal possibilities. Malaria and trichomoniasis have been reported as protozoal causes. In children, Epstein-Barr virus and enteroviruses have been identified.

2. Drug-induced — drug etiologies include penicillins, sulfas, phenytoin (and related anticonvulsants), carbamazepine, and barbiturates.

3. Malignancy-related — various carcinomas and lymphomas have been associated.

4. Idiopathic — 25–50% of cases.

The mortality rate of SJS is approximately 5 % and is directly proportional to the total body surface area of sloughed epithelium. Sepsis secondary to loss of the cutaneous barrier is the principle cause of death. Advanced age, visceral involvement, increased serum urea nitrogen level, and prior bone marrow transplant are poor prognostic factors.

All age groups are susceptible. The median age is approximately 48 years. Elderly individuals have an increased incidence and severity of disease. Patient history may include the presence of an influenza-like prodrome consisting of fever, cough, and malaise.

Clinical picture of SJS. Discrete, irregular, flat, dark red, purpuric macules first appear in the skin. Macules begin as symmetrically distributed lesions over the face and trunk. Over the course of a few hours or days, the lesions rapidly progress to involve the abdomen, back, and proximal extremities. By definition, lesions cover less than 10 % of total body surface area. The center of each lesion may reveal a blister or a denuded, red, oozing dermis. Mucous membrane involvement is noted in 90 % of patients. The most common sites in order of frequency are the oropharynx, conjunctivae, genitalia, anus, tracheobronchial tree, esophagus, and bowel. Hyperventilation and mild hypoxia may result from anxiety or tracheobronchial involvement. Mild temperature elevation is usually noted. Dehydration may range from mild to massive as a result of the following factors: evaporation through open skin lesions, poor oral intake secondary to oropharyngeal mucous membrane involvement, profuse diarrhea from involvement of bowel mucosa, increased insensible losses secondary to elevated core body temperature. Mortality rate is about 5 %.

Clinical picture of TEN. Mortality is estimated to be 25–70 %, depending on the quality of care and the rapidity with which treatment is initiated. TEN may occur in all age groups. Elderly persons may be at greater risk because of their tendency to be using multiple medications. Patients may describe a history that includes a prodrome characterized by 2–3 days of malaise, rash, fever, cough, sore throat, myalgia, rhinitis, and anorexia. TEN is associated with an acute phase (8–12 d) consisting of persistent fevers, generalized epidermal sloughing, and mucous membrane involvement. Complications include stomatitis and mucositis,

which are painful and hinder oral intake; therefore, patients are at risk for dehydration and malnutrition. The conjunctivas commonly are affected 1–3 days prior to the appearance of skin lesions. Buccal, nasal, pharyngeal, vaginal, urethral, esophageal and perineal and tracheobronchial denudation and erosion may be present. The chief complaint is often generalized pain associated with a rash. Vital signs may include hyperthermia, hypotension secondary to hypovolemia, and tachycardia. Skin lesions begin as warm, erythematous, morbilliform macules that are initially discrete and then confluent. The epidermis sloughs in sheets, leaving a characteristic moist, denuded dermis. **A positive Nikolsky sign is evident when pressure is applied laterally to the epidermal surface, and the epidermis easily separates from its underlying surface.** Hemorrhagic crusting of the lips is a common finding. Conjunctivitis commonly is observed before full sloughing of the epidermis (with associated pain). Pneumonia is a major complication, resulting in acute respiratory failure and the need for intubation.

Lab Studies. No laboratory tests are specific to SJS and TEN. Lymphopenia is present in 90 % of patients and is thought to result from the depletion of CD4 lymphocytes. Neutropenia is present in 30 % of patients and indicates a poor

NB! SJS is diagnosed when there are less than 10 % of body surface involved. TEN is diagnosed when there are more than 30% involved. 10–30% is thought to be intermediate condition and can result is SJS or

Thrombocytopenia is present in 15 % of patients with SJS. Elevated erythrocyte sedimentation rate, elevated serum aminotransferase are seen.

Treatment. The most important components of the treatment of SJS and TEN are rapid recognition and aggressive treatment. Death is frequently a consequence of inappropriate, incorrect, or delayed therapy. Maintain a high index of clinical awareness for this rare but potentially life-threatening disorder. No specific treatment exists for this disease, and survival and recovery ultimately depend on aggressive supportive care and removal of the offending agent. Symptomatic supportive care is administered to keep the patient alive through the initial phase of the disease and the subsequent healing process. Transfer the patient to an intensive care burn unit under isolation precautions to decrease the risk of nosocomial infection. The altered immunologic function of patients with SJS and TEN makes the likelihood of developing sepsis much greater. Sepsis is the leading cause of death in these conditions. Immediately withdraw all potentially causative drugs (this includes all medications begun during the preceding 2 months, discontinue all unnecessary medications). The

healing process usually takes about 2 weeks, during which time proper skin care is essential. Practice aseptic handling and avoid adhesive materials.

Corticosteroids commonly are employed to cease progression, but this is highly controversial. In some studies, corticosteroids have increased the incidence of mortality.

Fluid and electrolytes may be lost through the disrupted skin barrier, from profuse diarrhea, or from increased core body temperature. The patient's ability to increase fluid intake may be compromised secondary to oral eruptions. Fluid and electrolyte resuscitation are approximately 66–75% of that required for a similarly sized burn wound. Administer warmed fluids through a peripheral intravenous angiocatheter at a site removed from the skin eruptions. Maintain thermoregulation by keeping the environmental temperature at 30–32°C, administering only warmed fluids, and using heating lamps or warming blankets. Patients with tracheobronchial involvement may present with hyperventilation and mild hypoxemia. Careful monitoring and aggressive pulmonary support may lead to early detection and treatment of diffuse interstitial pneumonitis.

Start systemic antibiotics for documented infection or signs of sepsis. Empiric antimicrobial therapy should include broad-spectrum antimicrobials that cover gram-negative, gram-positive, and anaerobic organisms. If staphylococcal infection is involved, administer an appropriate antistaphylococcal agent (ie, nafcillin/oxacillin for methicillin-sensitive organisms or vancomycin for methicillin-resistant organisms).

Consider use of plasmapheresis, if available, daily for 3 days. Plasmapheresis may enhance elimination of the drug or offending agent and should be considered.

LECTURE 12. PAPULAR DERMATOSES: PSORIASIS, LICHEN PLANUS.

Psoriasis

Psoriasis is a noncontagious skin disorder that most commonly appears as inflamed skin lesions covered with a silvery white scale.

Pathogenesis of psoriasis is unknown, but many of the factors may be due to the onset of psoriasis. Psoriasis fundamentally is an inflammatory skin condition with reactive abnormal epidermal differentiation and hyperproliferation. Current research suggests that the inflammatory mechanisms are immune based and most likely initiated and maintained primarily by T cells in the dermis.

Pathogenesis. Both genetic and environmental factors have been implicated in the pathophysiology of psoriasis. Genetic factors include HLA-B13, -B17, and -Cw6 that are all associated with plaque psoriasis. Multifactorial inheritance mechanisms and etiologies without any genetic component have not yet been ruled out, although many families appear to exhibit autosomal dominant patterns of inheritance with decreased penetrance. Environmental factors include infection and a number of physical agents (eg, HIV infection, alcoholism, smoking, UV light) all can affect the course, duration, and clinical appearance of plaque psoriasis. Perceived stress can cause exacerbation of psoriasis. Some authors suggest that psoriasis is a stress-related disease and offer findings of increased concentrations of neurotransmitters in psoriatic plaques. Significant evidence is accumulating that psoriasis is an autoimmune disease. Lesions of psoriasis are associated with increased activity of T cells in underlying skin. Guttate psoriasis has been recognized to appear following certain immunologically active events, such as streptococcal pharyngitis, cessation of steroid therapy, and use of antimalaria drugs.

Clinical picture of psoriasis. There are numerous clinical forms of psoriasis:

Plaque psoriasis is characterized by raised inflamed lesions covered with a silvery white scales. This is most common on the extensor surfaces of the knees, elbows, scalp, and trunk. Patients commonly recognize that new lesions appear at sites of injury or trauma to the skin. This reaction is called **isomorphic phenomenon (Koebner reaction)** and the lesions typically occur 7–14 days after the skin has been injured. Psoriatic plaques are well defined and have sharply demarcated boundaries. Psoriatic plaques occasionally appear to be immediately encircled by a paler peripheral zone referred to as the **halo or ring of Woronoff.** The color of psoriatic lesions is very distinctive with a rich full red color that has most often been described as salmon-colored. Lesions sometimes carry a blue or violaceous tint when present on the legs. Psoriatic plaques classically have a dry, thin, silvery-white or micaceous scale; however, the amount and thickness of this scale is quite variable. Removing the scale reveals a smooth, red, glossy membrane with tiny punctate bleeding points. These points represent bleeding from enlarged dermal capillaries after removal of the overlying suprapapillary epithelium. This phenomenon is known as the **Auspitz sign.** Psoriatic plaques tend to be symmetrically distributed over the body. Lesions typically have a high degree of uniformity with few morphologic differences between the two sides. Pruritus is present in 40 % of cases.

Guttate psoriasis presents as small red dots of psoriasis that usually appear on the trunk, arms, and legs; the lesions may have some scale. It frequently appears suddenly after an upper respiratory infection (URI).

Intertriginal psoriasis occurs on the flexural surfaces, armpit, groin, under the breast, and in the skin folds and is characterized by smooth, inflamed lesions without scaling.

Seborrhoeic psoriasis affects approximately 50 % of patients, presenting as erythematous plaques with greesy scales on the scalp and seborrhoeic regions (chest, upper back).

Nail psoriasis. Nail changes are commonly observed in patients with plaque psoriasis. Nails may exhibit pitting, onycholysis, subungual hyperkeratosis, or **the oil-drop sign**. A proper assessment of any patient suspected of having psoriasis should include careful examination of the nails.

Complicated forms:

Psoriatic arthritis affects approximately 10 % of those with skin symptoms. The arthritis is usually in the hands, feet, and, at times, in larger joints. It produces stiffness, pain, and progressive joint damage.

Erythrodermic psoriasis presents as generalized erythema, pain, itching, and fine scaling. The 70–90 % of the body is effected.

Pustular psoriasis presents as sterile pustules appearing on the hands and feet or, at times, diffusely, and may cycle through erythema, pustules, and scaling.

The psoriasis can be **progressive (**when the new lesions are appeared) and **non-progressive** (when there are no new lesions).

Usually the sun helps to heal the psoriasis lesions but in some patients it can be aggravated by UV. That is why define tree types of psoriasis: **summer** (when the patients have remission during winter), **winter** (when the patients have remission in summer) and **mixed.**

Treatment. Psoriasis is a chronic skin condition. Any approach to the treatment of this disease must be considered for the long term. Treatment regimens must be individualized according to age, sex, occupation, personal motivation, other health conditions, and available resources. Disease severity is not only defined by the number and extent of plaques present, but also by the patient's perception and acceptance of the disease. Treatment therefore must be designed with the patient's specific expectations in mind rather than focusing on the extent of body surface area involved. Many treatments exist for psoriasis; however, the construction of an effective therapeutic regimen is not necessarily complicated.

Three basic treatment modalities exist that uphold the overall management of psoriasis, ie, **topical agents, phototherapy, and systemic agents.** All of these treatments may be used alone or in combination with one and other.

Topical therapy.

Outpatient topical therapy is the first-line approach in the treatment of the psoriasis. A number of topical treatments are available. No single ideal topical agent exists for plaque psoriasis. With the different adverse effect profiles that exist for the various agents, using a rotational therapeutic approach in which different topical agents are used sequentially over time in the same patient is common.

- Topical corticosteroids. These agents are used to reduce plaque formation. These agents have anti-inflammatory effects and may cause profound and varied metabolic activities. In addition, these agents modify the body's immune response to diverse stimuli. The local side effects of the corticosteroids include atrophy of the skin, formation of acne, striae distensae.
- Coal tar. An inexpensive treatment that is available over the counter in shampoos or lotions for use in widespread areas of involvement. It is particularly useful in hair-bearing areas.
- Keratolytic agents. Used to remove scale, smooth the skin, and to treat hyperkeratosis. Usually are used preparations with urea or salycilic acid.
- Vitamin D-3 analogs (Calcipotriene). Used in patients with lesions resistant to older therapy or with lesions on the face or exposed areas where

thinning of the skin would pose cosmetic problems. May be used only if the patient has less than 20 % of the skin involved.

• Topical retinoids — made in the base of vitamin A. There is no threat of worsening if the therapy is withdrawn, as with steroids. These drugs should not be used in women if pregnancy is a possibility.

Phototherapy:

Is administrated in the non progressive stage of psoriasis. Proper facilities are required for the 2 main forms of phototherapy:

• Ultraviolet B (UVB): UVB irradiation utilizes light with wavelengths 290–320 nm (visible light range is 400–700 nm). UVB therapy is usually combined with one or more topical treatments. UVB more commonly is now combined with topical corticosteroids, calcipotriene, tazarotene, or simply bland emollients. UVB phototherapy is extremely effective for treating moderate-to-severe plaque psoriasis. The major drawback of this therapy is the time commitment required for treatments and the accessibility of the UVB equipment.

• PUVA photochemotherapy: This therapy (also known as PUVA) uses the photosensitizing drug methoxsalen (8-methoxypsoralens) in combination with ultraviolet A (UVA) irradiation to treat patients with more extensive disease. UVA irradiation utilizes light with wavelengths 320–400 nm. PUVA interferes with DNA synthesis, decreases cellular proliferation, and also induces apoptosis of cutaneous lymphocytes leading to a localized immunosuppression. More than 85 % of patients report relief of disease symptoms with 20–30 treatments. Therapy is usually administered 2–3 times per week on an outpatient basis, with maintenance treatments every 2–4 weeks until remission. Adverse effects of PUVA therapy include nausea, pruritus, and burning. Long-term complications include increased risks of photo damage to the skin and (more importantly) skin cancer. PUVA has been combined with oral retinoid derivatives to decrease the cumulative dose of UVA radiation to the skin.

Systemic treatment.

• Retinoids. These agents have a variety of actions. They cause differential expression of proteins by altering genomic functions. They stimulate cell differentiation and inhibit malignant transformation in the skin. Retinoid derivatives alter the delayed hypersensitivity response and increase the number of Langerhans cells in the psoriatic lesions. For plaque psoriasis, retinoids can be used in combination with UV phototherapy to minimize the dose of each. Otherwise, the use of oral retinoid monotherapy has shown limited efficacy for chronic stable plaque psoriasis.

• Immunosuppressive. Psoriasis is now considered to be an immunologic skin disorder, and systemic immunosuppressive agents (eg, methotrexate, cyclosporine) can be used for patients with extensive, widespread, or resistant disease.

• Inhibitors of the TNF (tumor necrosis factor) — are used for the treatment of psoriatic arthritis.

Different forms of psoriasis may need different treatment.

In the cases of erythrodermic psoriasis is used aggressive therapy: PUVA, retinoids, immunosuppressive therapy, solutions of the electrolytes, plasmopheresis. It is recommended to avoid systemic corticosteroids because they may aggravate the condition after their use is stopped. Local forms usually are treated with topical agents, physiotherapy (UV, baths). In the cases of arthritic psoriasis is necessary to administrate the inhibitors of the TNF or immunosupressors. In the cases of the pustular psoriasis and in the cases of guttae psoriasis associated with infections antibiotic therapy sometimes is used.

The course of psoriasis is unpredictable. Predicting the duration of active disease, the time or the frequency of relapses, or the duration of a remission is impossible. The disease rarely is life threatening but often is intractable to treatment with relapses occurring in the majority of patients. Both early onset and family history of disease are considered poor prognostic indicators. Some suggest that stress is also associated with an unfavorable prognosis. Patient education is one of the foundations for managing this chronic and typically relapsing disorder. Not only is psoriasis associated with morbidity, its treatment can also cause significant adverse effects. Patients should be familiar with these details in order to make proper informed decisions about therapy. Alcoholism can also be considered a complication of psoriasis. Male patients with severe disease are particularly at risk for this type of substance abuse.

Lichen planus

Lichen planus (LP) is a **pruritic, papular** eruption characterized by its **violaceous color; polygonal shape;** and, sometimes, fine scale. It is most commonly found on the flexor surfaces of the upper extremities, on the genitalia, and on the mucous membranes. LP is most likely an immunologically mediated reaction.

The exact cause of LP is not known. The pathogenesis of LP is immunologically mediated. Whether the foreign antigen is a virus or a drug is not known. Langerhans cells process antigens, which are then presented to T lymphocytes. This stimulated lymphocytic infiltrate is epidermotropic and attacks keratinocytes. During this lymphocytotoxic process, the keratinocytes release cytokines that attract more lymphocytes. This process has been referred to as the lichenoid tissue reaction. Also, recent studies reveal a disruption in the epithelial anchoring system. Some patients with LP have a positive family history. LP may be found with other diseases of altered immunity; these conditions include ulcerative colitis, alopecia areata, vitiligo, dermatomyositis, morphea, lichen sclerosis, and myasthenia gravis. An association is noted

between LP and hepatitis C virus infection, chronic active hepatitis, and primary biliary cirrhosis.

Clinical picture. The initial lesion is usually located on the flexor surface of the limbs, such as the wrists. After a week or more, a generalized eruption develops with maximal spreading within 2–16 weeks.

Pruritus is common but varies in severity depending on the type of lesion and the extent of involvement. Hypertrophic lesions are extremely pruritic. In mre than 50 % of patients with cutaneous disease, the lesions resolve within 6 months, and 85 % of cases subside within 18 months. On the other hand, oral LP had been reported to have a mean duration of 5 years. Large, annular, hypertrophyc lesions and mucous membrane involvement are more likely to become chronic.

In addition to the oral mucosa, LP can involve the mucous membranes, the genitalia, the nails, and the scalp. The clinical presentation of LP has several forms: **actinic, annular, atrophic, erosive, follicular, guttate, hypertrophic, linear, and vesicular.** The papules are violaceous, shiny, and polygonal; varying in size from 1 mm to greater than 1 cm in diameter. They can be discrete or arranged in groups of lines or circles. Characteristic fine, white lines, called **Wickham stria (Wickham symptom)**, are often found on the papules, especially if cover the papule with oil or cream.

Treatment. No specific treatment exists, all drugs are symptomatic. The first-line treatments of cutaneous LP are **topical steroids**, particularly class I or II ointments. A second choice would be **systemic steroids** for symptom control and possibly more rapid resolution. For LP of the oral mucosa, topical steroids are usually tried first. **Cyclosporin** has been tried with some success. Other options include **oral or topical retinoids**. Even with these effective treatments, relapses are common**. Psoralen with ultraviolet light A (PUVA) therapy** for 8 weeks has been reported to be effective. Risks and benefits of this treatment should be considered. PUVA is carcinogenic. Long-term risks include dose-related actinic degeneration, squamous cell carcinoma, and cataracts. A phototoxic reaction with erythema, pruritus, phytophotodermatitis, and friction blisters could occur. **Antihistaminals** help in cases of severe itch. The patient should be examined for the case of chronic internal diseases, malignancy. The prognosis for LP is good, as most cases regress within 18 months. Some cases recur.

LECTURE 13. BULLOUS DERMATOSES

Bullous dermatoses are defined in a separate group of diseases because the primary element is bulla, unless their pathogenesis may be different.

Classification of Bullous Dermatoses:

- Pemphigus group.
- Pemphigoid group.
- Dermatitis herpetiformis.
- Mixed bullous dermatoses.

Pemphigus Group

The term «pemphigus» refers to a group of **autoimmune blistering diseases of the skin and mucous membranes** characterized histologically by intradermal blister and immunopathologically by the finding of in vivo bound and circulating immunoglobulin G (IgG) antibody directed against the cell surface of keratinocytes.

The 3 primary subsets of pemphigus include:

- pemphigus vulgaris (PV);

• pemphigus foliaceus;
• paraneoplastic pemphigus.

Each type of pemphigus has distinct clinical and immunopathologic features. PV accounts for approximately 70 % of pemphigus cases.

Pemphigus vulgaris

PV is an **autoimmune, intraepithelial, blistering disease** affecting the skin and mucous membranes and is mediated by circulating autoantibodies directed against keratinocyte cell surfaces. In 1964, autoantibodies against keratinocyte surfaces were described in patients with pemphigus. Clinical and experimental observations indicate that the circulating autoantibodies are pathogenic. An immunogenetic predisposition is well established.

Blisters in PV are associated with the binding of IgG autoantibodies to keratinocyte cell surface molecules. These intercellular or PV antibodies bind to keratinocyte desmosomes and to desmosome-free areas of the keratinocyte cell membrane (Figure 1). The binding of autoantibodies results in a loss of cell-cell adhesion, a process termed acantholysis.

Incidence rate is 0.5–3.2 cases per 100 000, affects all races. PV predominates in Jewish population. Male-to-female ratio is approximately equal. Mean age of onset is 50–60 years.

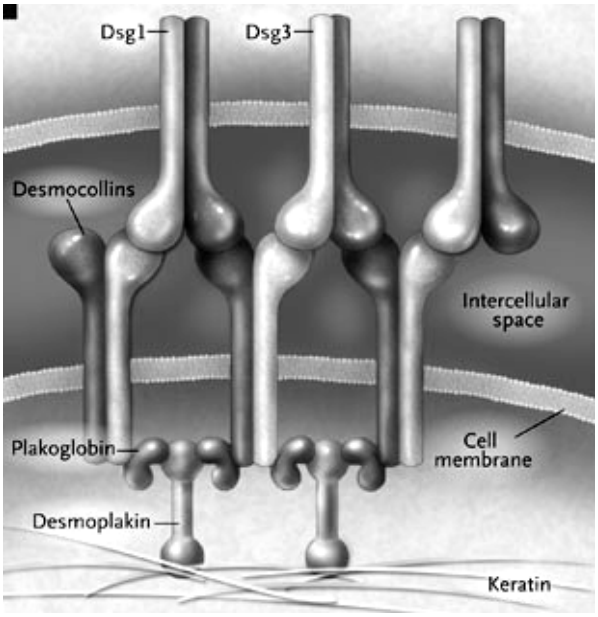

Figure 1 — Structure of desmosomes

Clinical presentation. PV tends to appear in the oral cavity. Intact bullae are rare in the mouth. More commonly, patients have ill-defined, irregularly shaped, gingival, buccal or palatine erosions, which are painful and slow to heal. The erosions extend peripherally with shedding of the epithelium. The mucous

membranes most often affected are those of the oral cavity, which is involved in almost all patients with PV and sometimes is the only area involved. Erosions may be seen on any part of the oral cavity. Erosions can be scattered and often extensive. Erosions may spread to involve the larynx with subsequent hoarseness. The patient often is unable to eat or drink adequately because the erosions are so uncomfortable. Other mucosal surfaces may be involved, including the conjunctiva, esophagus, labia, vagina, cervix, penis, urethra, and anus.

The primary skin lesion of PV is a **flaccid blister filled with clear fluid that arises on normal skin or on an erythematous base**. The blisters are fragile; therefore, intact blisters may be sparse. The contents soon become turbid, or the blisters rupture producing painful erosions, which is the most common skin presentation. Erosions often are large because of their tendency to extend peripherally with the shedding of the epithelium. **Nikolsky sign** develops in patients with active blistering, when firm sliding pressure with a finger separates normal-appearing epidermis, producing an erosion. This sign is not specific for PV and is found in other active blistering diseases. **Asboe-Hansen sign is** when lateral pressure on the edge of a blister may spread the blister into clinically unaffected skin.

Vegetating PV is one of the variants of PV, when ordinary PV erosions may develop vegetation. Lesions in skin folds readily form vegetating granulations. In some patients, erosions tend to develop excessive granulation tissue and crusting, and these patients display more vegetating lesions. This type of lesion tends to occur more frequently in intertriginous areas and on the scalp or face. The vegetating type of response can be more resistant to therapy and can remain in one place for long periods of time.

Diagnostics of PV. Typical clinical features — positive Nikolsky and Asboe-Hansen signs — can help in diagnosis. Tzank-Test — a smear taken from the base of a blister or an oral erosion that contains acantholytic cells. It is the most simple but non specific method for to diagnose PV.

Histology reveals intradermal blisters and suprabasal acantholysis. Direct immunofluorescence (DIF) on normal-appearing perilesional skin finds IgG to desmoglein 1 and 3 deposits on the surface of the keratinocytes in and around lesions. Indirect immunofluorescence (IDIF) using the patient's serum if DIF is positive can reveal circulating IgG antibodies to epidermal antigens.

Treatment. Treatment includes obligatory use of corticosteroid hormones — prednisolone, prednisone, methylprednisolone, triamycinolone, kenacort, polcortolon (daily dose 120 mg). Corticosteroids are used continuously during all the life of a patient. Patient should be consulted by therapeutist periodically to exclude hypertension, osteoporosis, and other problems related with side effects of corticosteroids.

Cytostatics (azatioprine 2.5 mg/KG body weight daily, methotrxate 35–50 mg weekly) can help to lessen the dosage of corticosteroids and lessen their side effects. Immunosuppressants (cyclosporine A, mikophenolat mofetil) are also widely used. Plasmapheresis is used in severe cases of PV. Treatment of bacterial and fungous infections should be immediately performed.

Complications include secondary infection, bronchopneumonia, sepsis, cachexia.

Prognosis. Treatment with systemic steroids has reduced the mortality rate to 5–15 %. Most deaths occur during the first few years of disease, and if the patient survives 5 years, the prognosis is good. Early disease probably is easier to control than widespread disease, and mortality may be higher if therapy is delayed. Morbidity and mortality are related to the extent of disease, the maximum dose of prednisolone required to induce remission, and the presence of other diseases. The outlook is worse in older patients and in patients with extensive disease.

Pemphigus foliaceus

The primary lesions are small, superficial blisters; however, these flaccid bullae are difficult to find because they are transient and transform into erosions. Typical PF has scaly, crusted erosions on an erythematosus base confined mainly to so-called seborrhoic areas (eg, face, scalp, upper part of the trunk). The erosions can become numerous, showing a tendency to generalize. Occasionally, erythrodermia develops. Atrophic changes of the nails and the hair are sometimes evident. The erosions may be accompanied by a burning sensation and local pain. In contrast to PV, in PF, little or no involvement of the mucous membranes occurs. In contract with PV only IgG to desmoglein — 1 are found in bioptats. Acantolysis in biopsy specimen is not so prominent as in PV and hyperplasia of epidermis is noticed.

Endemic PF, or fogo selvagem, is the erythrodermic form of PF that is frequent in rural areas of Latin America and seems to be induced by a viral infection transmitted by insects.

Therapy for PF is usually less aggressive than that of PV because of lower morbidity and mortality rates. Topical glucocorticosteroids may be sufficient in cases of limited involvement. In more extensive cases (similar to PV), adjuvant immunosuppressants, including systemic corticosteroids, cyclophosphamide, and cyclosporin A, may be necessary. Photoprotection is appropriate for some patients because UV-B may trigger acantholysis and cause a flare-up of the disease.

Pemphigus paraneoplastic

It is a severe form of pemphigus, characterized by typical clinical picture of PV and association with malignancies. Clinically there are no distinguishable features but PP is characterized by rapid onset, severe course, and onset in

elderly persons. Antibodies are found to desmoglein — 3, BP — 230, envoplakin and periplakin.

Pemphigoid group. Bullous pemphigoid

Bullous pemphigoid is a chronic auto-immune blistering skin disease which course is relatively benign. The patients' age is usually more than 60 years. The onset of BP may be either subacute or acute, with widespread, tense blisters. Significant pruritus is frequently present. BP has been reported to be precipitated by ultraviolet irradiation, x-ray therapy, and exposure to some drugs. Drugs associated with BP include furosemide, ibuprofen and other nonsteroidal anti-inflammatory agents, captopril, penicillamine, and antibiotics. BP has been reported to develop shortly after vaccination, particularly in children. It can also be a sign of paraneoplastic prosses.

Clinical picture. Tense bullae arise on any part of the skin surface, with a predilection on the flexural areas of the skin. Oral and ocular mucosa involvement rarely occurs and, when seen, is of minor clinical significance. The bullae can occur on normal-appearing, as well as erythematous, skin surfaces. The bullae usually heal without scarring or milia formation.

Diagnosis is based on typical clinical features. Hystology founds subdermal blisters, in DIF IgG and C3-complement deposits on the basal membrane are found. IDIF reveals antibodies to basal membrane.

Treatment includes anti-inflammatory agents (corticosteroids, tetracyclines, dapsone, immunosupprassants — azathioprine, methotrexate, mycophenolate mofetil).

Dermatitis herpetiformis During

The initial description of dermatitis herpetiformis was made in 1884 by Louis Duhring, the American dermatologist. Dermatitis herpetiformis (DH) is an **immune-mediated blistering skin disease with an associated, most often asymptomatic, gluten-sensitive enteropathy (GSE).**

Clinical picture. Characteristic skin lesions found in patients with DH are **extremely itchy grouped vesicles most frequently located on extensor surfaces.** Flesh-colored-to-erythematous vesicles appear in a herpetiform pattern, symmetrically distributed over extensor surfaces including elbows, knees, buttocks, shoulders, and the posterior (nuchal) scalp. Patients often present with erosions and crusts in the absence of vesicles. Typical symptoms include burning, stinging, and intense pruritus. Patients often note stinging or burning of the skin before the appearance of new lesions. Oral mucosa lesions occur infrequently in patients with DH. DH is a lifelong disease, although periods of exacerbation and remission frequently are seen.

Diagnostics. Granular IgA deposits in dermal papillae of perilesional skin observed by direct immunofluorescence is the criterion standard of diagnosis. Application of iodine to the skin or orally can lead to exacerbation of HD that can be a diagnostic criteria.

Treatment. Skin lesions of DH can be treated with dapsone, with relief of symptoms within 24–48 hours of the start of therapy. Alternatively, many patients can control the skin disease with a gluten-free diet, often without medication. Dapsone (diaminodiphenyl sulfone) and sulfapyridine are the primary medications used to treat DH. Dapsone often is used initially; sulfapyridine is substituted in patients unable to tolerate dapsone. The mechanism for therapeutic effect of dapsone in DH is unclear. Improvement may be dramatic; symptomatic improvement of skin lesions often begins within hours. No new lesions form for up to 2 days after a dose of dapsone; however, dapsone does not improve gastrointestinal mucosal pathology.

Other, less effective treatments for DH include colchicines, cyclosporine, and prednisone. Cyclosporine should be used with caution in patients with DH because of a potential increase in intestinal lymphoma. Iodides may elicit or exacerbate DH. Most patients (as many as 80%) respond to gluten free diet with control of their skin disease. Some patients are able to discontinue the use of dapsone totally. Compliance with gluten free diet requires a motivated patient, and the best treatment response occurs with absolute gluten restriction in the diet. Strict dietary vigilance may be required for 5-12 months before the dapsone dose can be reduced. Gluten free diet is the only sustainable method of eliminating the disease, not only from the skin but also from the gastro intestinal mucosa. Elemental diets may improve the disease within weeks. These diets consist of free amino acids, small amounts of tryglycerides, and short chain polysaccarides.

LECTURE 14. DISEASES OF THE CONNECTIVE TISSUE

Lupus erythematosus

Lupus Erythematosus (LE) is an autoimmune disease that includes a broad spectrum of clinical forms, ranging from skin lesions to systemic LE (SLE). Cutaneous LE most often affects young adult women (aged 20 to 50). Clinical studies have demonstrated women predominance. Cutaneous LE can be provoked by sunlight but it is actually more common in dark skinned than in fair skinned people.

Expression of skin involvement in patients with LE is very common and showgs great variation. That is why it is difficut to create a unifying concept.

Classification of cutaneous lupus erythematosus (CLE):

1. Acute CLE.
2. Subacute CLE.
3. Chronic CLE:

- Discoid CLE (hypertrophic or verrucous variant and teleangiectoid variant).
- LE profundus.
- Chilblain LE.

4. Intermittent CLE (LE tumidis)

5. Bullous lesions in LE (LE — specific lesions, LE — nonspecific skin lesions, primarily bullous skin disorders associated with LE)

Acute CLE

Acute CLE is characterised by localized erythema known as «malar rash» or «butterfly rash» in the central pertion of the face that is frequent misdiagnosied with the sunburn. Generalised rash is known as «photosensitive lupus rash» is less common. In most cases systemic manifestations are strongly associated with acute CLE and may develop soon. The localized form of acute LE usually begins as small, discret erythematous macules or papuls, associated with fine scales involving the malar areas and the bridge of the nose while sparing the nasolabial folds. «Malar rash» can disappear without scarring and pigmemtation or gradually become hyperkeratotic. Similar lesions may occur in V-neck and forehead. Patients may have diffuse thinning of the hair in hairline and teleangiectasias or erythema at the nail plate. Superficial ulcerations of the oral cavity may occur. Sometimes generalized rash appear first.

Subacute LE

Subacute LE is present as erythematous macules and papules that evolve into scaly plaques. Approximately 50 % patients have psoriasiform lesions and other 50 % — annular lesions. Lesions can heal without scarring and leave long lasting areas of vitiligo — like depigmentation that is a «clue» for the diagnosis.

Chronic LE

Discoid LE is the most frequent form of chronic LE. It can be localized or generalized, with or without systemic manifestations. The localized form affects sculp and face whereas generalized involves regions above the neck. It usually occurs in the 4^{th} decade of the life. It begins as sharply demarcated erythematous macules or papules with a scaly surface. Early lesions evolve in coin – shaped «discoid» plaques of varying size. When the adherent scale is peeled back from more advanced lesions, follicule — sized keratotic spikes similar to carpet tacks are seen in the undersurface of the scale («the carpet tack sign» — Besnier Meschersky sign). Pigmentary changes are common. Skin lesions are progressive and leave scarring. Scarring alopecia occurs. Mucous membrane involvement is seen in 25 % of patients. The nails can be afftected as a very uncommon site of occurrence, but periungual teleandiectasias and erythema of the proximal nail fold are significant cutaneous features that can occur in patients with discoid LE.

Hypertrophic lesions in association with CLE are rare and are present as dull, red, indurated lesions that can appear as unique or multiple papularnodular elements covered by keratotic scale. Extensor sites of the arms and limbs are the most frequent sites. Patients with hypertrophic form develop systemic LE rarely, but the elements are heald slowly.

Teleangiectoid variant of LE is extremely rare, consisting of purplish plaques or blotchy teleangiectasia that may develop on the face, neck, ears, dorsal aspects of the hands, breast, front of the knees. This form can appear after healing of inflammatory plaques of discoid LE.

Chiliblain LE is a rare manifectation of LE. This form is probably provoked by cold, damp weather, or a drop in temperature. It is characterized by symmetrical distributed, circumscribed, sometimes infiltrated, pruriginous or painful areas of livid purple plaques that exacerbate during cold. The lesions of chiliblain LE may involve lateral parts of the hands, feet, ears, nose, elbows, knees, calves.

LE profundus (synonime: «Kaposi-Irgang disease») is also known as lupus panniculitis. Single or multiple sharply defined, persistent, asymptomatic or painful nodules of different sizes are typical for LE profundus. The overlying skin becomes attached to the firm nodules produsing a deep depression. dystrophic calcifications or ulcerations within older lesions leaving atrophic scars occur.

LE tumidis

It is a rare form of LE. Scarring, the hallmark of LE does not occur in LE tumidis, even in patients that have been ill during many years. Follicular plugging and adherent hyperkeratotic scaling does not occur also. The prognosis is more favorable. Lesions look like as annular urticaria — like plaques. Rash is common in face, upper trunk, V-area of the neck, extensors of extreminies and never has been reported situated below the waist.

Bullous LE

Bullous lesions are seen in 5 % of cases of LE. Bullas may develop in the lesions of acute LE as a extension of the vacuolar degeneration of the epidermal basal layer. On unusual occasions, bullous eruptions or vesiculobullous lesions, unassosiated with LE skin lesions occur. Such lesions are situated on the extremities and respond dramatically to dapsone.

Systemic LE (SLE)

As far as discoid and acute LE may result in a systemic disease it is necessary to state the criteria for SLE. For the moment American College of Rheumatology criteria are used (Table 1).

Table 1 — American College of Rheumatology criteria for SLE

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences,

	tending to spare the nasolabial foldes
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging, atrophic scarring
Photosensibility	Skin rash as a resut of unusual reaction to sunlight, by patient history or observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
Arthritis	Nonserosive arthritis involving 2 peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis — convincing history of pleuritic pain or rubbing heard by physitian or evidence of pleural diffusion
Renal disorder	Persistant proteinuria — > 0,5 g/d or more than 3 if quantification is not performed
Neurologic disorder	Seizeures — in the absence of offending drug or known metabolic derangements. Psychosis — in the absence of offending drug or known metabolic derangements (uremia, ketoacidosis, electrolyte imbalance)
Hematologic disorder	Hemolytic anemia — with reticulocytes Leucopenia — less than 4000/mm total on 2 ocasions Lymphopenia — less than 1500/mm on 2 ocasions Thrombocytopenia — less than 100000/mm in the absence of offending drugs
Immunologic disorder	Anti-DNA — antibody to native DNA in abnormal titer Anti-Sm —— presence of antibody to SM nuclear antigen Antiphospholipid antibodies (positive reaction at 2 time points with at least 6 weeks separation) — increased IgG or highly icreased IgM anti-cardiolipin antibodies or positive lupus anticoagulants usung a standart method or positive serologic test results for syphilis
Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in the time and in the absence of drugs known to be associated with «drug – induced» lupus syndrome

Laboratory diagnostics. Skin biopsy and immunohistochemistry is necessary for stating the diagnosis of skin lupus erythematosus. Laboratory examinations to exclude SLE (see table 1) should be performed.

Treatment includes antimalarials (chloroquine, hydroxychloroquine, quinacrine), antileprosy drugs (dapsone, thalidomide), methotrexate, cyclosporine, azatioprin, glucocorticoids. Topically corticosteroids are used. In CLE it is necessray to perform 2–3 dapsone treatment courses per year. Prophylaxis by wearing sun glasses, sun protective hats and using sun protective creams is essential.

Prognosis depends on the severity of visceral involvement. Usually 10-year survival in discoid LE is more than 80 %. Several risk factors may influence the severity of LE: genetic predisposition, race and sex, clinical presentation, age at disease onset, triggering factors (esposion to UV), light and oral medications.

Morphea

Morphea (localized scleroderma) is a disorder characterized by thickening and induration of the skin and subcutaneous tissue due to excessive collagen deposition.

Pathogenesis. Overproduction of collagen by lesional fibroblasts is common to all forms of morphea, but the exact mechanism is unknown. Proposed factors involved in the pathogenesis include endothelial cell injury, immunologic and inflammatory activation, and dysregulation of collagen production. An autoimmune etiology is supported by the frequent presence of autoantibodies in patients with morphea.

Classification of morphea:

1. Plaque-type morphea is the most common and benign morphea subtype and includes guttate morphea and keloidal (nodular) morphea variants. These lesions are relatively superficial, involving only the dermis and occasionally are present with the superficial panniculus.

2. Generalized morphea is more severe form of the disease, with widespread morphea plaques.

3. Linear morphea is the most common morphea subtype in children and adolescents and includes the en coup de sabre and progressive hemifacial atrophy variants. Linear morphea often qualifies as deep morphea in a linear pattern, involving the deep dermis, the subcutaneous tissue, the muscle, and the underlying bone.

4. Deep morphea, also referred to as subcutaneous morphea or morphea profunda, may involve the deep dermis, the subcutaneous tissue, the fascia, the muscle, and even the bone. Variants of deep morphea include eosinophilic fasciitis and disabling pansclerotic morphea of children.

Clinical picture. Linear morphea tends to affect children and adolescents, with 67 % of cases occurring before age 18 years. Other morphea subtypes most often develop later in life, with a mean age of onset in persons aged 33–38 years and with 75 % of cases occurring in persons aged 20–50 years.

Morphea is usually asymptomatic, and, most often, the onset of lesions is insidious, although they can occasionally develop rapidly. Physical findings in morphea are primarily in the skin and underlying tissues, with different clinical manifestations and levels of tissue involvement in the various subtypes.

Morphea lesions are characterized as circumscribed indurated plaques that are 1–30 cm in diameter. They often begin as poorly defined areas of nonpitting edema, with sclerosis developing as the disease progresses. The surface becomes smooth and shiny over time, with the loss of hair follicles and the inability to sweat. Eventually, over a period of months to years, the skin softens and becomes atrophic. Plaque-type morphea often begins as an area of erythema. In early active phases of the disease, a violaceous border (lilac ring) often

surrounds the indurated area. With disease progression, the center of the lesion gradually develops a waxy, ivory color. As lesions eventually involute, an area of hypopigmentation and/or hyperpigmentation often remains. Plaque-type morphea lesions are typically oval or (less often) round in shape. Plaque-type morphea lesions are most often single or few in number, although they may be multiple. When bilateral, lesions are generally asymmetrical.

Linear morphea lesions are most often single and unilateral in 95 % of cases. If both the upper extremities and the lower extremities are involved, lesions are usually homolateral. The distribution pattern of linear morphea is controversial. Although linear morphea following the lines of Blaschko has been described in several recent reports, some authors have stated that it probably does not follow the lines of Blaschko; other authors have noted that linear morphea may appear to be dermatomal in distribution. Usually, linear morphea lesions occur along the length of a limb, but sometimes a band surrounds a limb or a finger, resembling ainhum.

Scalp involvement results in scarring alopecia, as seen in the variant known as en coup de sabre. Loss of eyebrows or eyelashes may also occur in this variant. Nail dystrophy may occur in linear lesions located on an extremity or in pansclerotic morphea.

Lab Studies. No diagnostic laboratory tests are available for morphea. Eosinophilia has been found to correlate with disease activity in patients with linear and generalized morphea (although this is not a consistent finding) as well as in patients with eosinophilic fasciitis and other variants of deep morphea. Rheumatoid factor is positive in 25–41 % of patients, especially children with linear morphea; titers are correlated with disease severity. Antinuclear antibody (ANA) test results are positive in 50 % of patients with plaque-type or generalized morphea and in 67 % of those with linear morphea, usually with a homogeneous staining pattern. A biopsy is often useful to confirm the diagnosis and to differentiate among the subtypes.

Therapy. No proven effective treatments for morphea exist. Most patients with plaque-type morphea experience very gradual (eg, over 35 y) spontaneous remission. Therapy with topical or intralesional corticosteroids offers little or limited benefit. Treatment with topical calcipotriene may be attempted. Patients with generalized, linear, and deep morphea may require more aggressive therapy. Physical therapy to preserve range of motion is of utmost importance. Numerous therapeutic agents have been used, including systemic corticosteroids, antimalarial agents, D-penicillamine, and other anti-inflammatory and immunosuppressive agents. However, no large randomized studies of these agents in patients with morphea exist. The use of low-dose UV-A phototherapy has produced marked clinical improvement of treated morphea lesions. PUVA bath photochemotherapy has also been reported to be helpful in

patients with plaque-type or linear morphea, and PUVA is considered to be one of the best treatment options available.

Dermatomyositis

Dermatomyositis (DM) is an idiopathic inflammatory myopathy with characteristic cutaneous findings. DM is a systemic disorder that frequently affects the esophagus and the lungs and, less commonly, the heart.

Pathogenesis. The cause of DM is unknown. A genetic predisposition may exist. Rarely, DM manifests in multiple family members. Immunologic abnormalities are common in patients with DM. Patients frequently have circulating autoantibodies. Abnormal T-cell activity may be involved in the pathogenesis of both the skin disease and the muscle disease. In addition, family members may manifest other diseases associated with autoimmunity.

Infectious agents, including viruses and human immunodeficiency virus [HIV]), *Toxoplasma* species, and *Borrelia* species, have been suggested as possible triggers of the disease.

Clinical picture. DM can occur at any age. The most common age at onset is in the fifth and sixth decades of life. Patients often present with skin disease as one of the initial manifestations. In as many as 40 % of patients, the skin disease may be the sole manifestation at the onset. Muscle disease may occur concurrently, it may precede the skin disease, or it may follow the skin disease by weeks to years.

Patients often notice an eruption on exposed surfaces. The disease is often pruritic, and, sometimes, intense pruritus may disturb sleep patterns. Patients may also complain of a scaly scalp or diffuse hair loss. Muscle involvement manifests as proximal muscle weakness. Patients often begin to note fatigue of their muscles or weakness when climbing stairs, walking, rising from a sitting position, combing their hair, or reaching for items in cabinets that are above their shoulders. Muscle tenderness may occur, but it is not a regular feature of the disease. Systemic manifestations may occur; therefore, a review of systems should assess for the presence of arthralgias, arthritis, dyspnea, dysphagia, arrhythmias, and dysphonia. Malignancy is possible in any patient with DM, but it is much more common in adults older than 60 years. The history should include a thorough review of systems, as well as an assessment for previous malignancy. Children with DM may have an insidious onset that hides the true diagnosis until the dermatologic disease is clearly observed and diagnosed. Calcinosis is a complication of juvenile DM, but it is rarely observed at the onset of disease. However, during the initial examination, the patient should be questioned about hard nodules on the skin.

The characteristic and possibly pathognomonic cutaneous features of DM are the **heliotrope rash and Gottron papules**. The heliotrope rash consists of a violaceous to dusky erythematous rash with or without edema in a symmetrical

distribution involving the periorbital skin. Sometimes, this sign is subtle and may consist of only a mild discoloration along the eyelid margin. A heliotrope rash is rarely observed in other disorders; therefore, its presence is highly suggestive of DM. Gottron papules are found over bony prominences, particularly the metacarpophalangeal joints, the proximal interphalangeal joints, and/or the distal interphalangeal joints. They may also be found overlying the elbows, the knees, and/or the feet. The lesions consist of slightly elevated, violaceous papules and plaques. A slight scale may be present, and, occasionally, a thick psoriasiform scale is observed. These lesions may resemble lesions of lupus erythematosus, psoriasis, or lichen planus (LP).

Nail fold changes consist of periungual telangiectases and/or a characteristic cuticular change with hypertrophy of the cuticle and small, hemorrhagic infarcts in this hypertrophic area. Poikiloderma may occur on exposed skin, such as the extensor surfaces of the arm, the V of the neck, or the upper part of the back **(Shawl sign).** With the exception of the heliotrope rash, the eruption of DM is photodistributed and photoexacerbated. Patients rarely complain of photosensitivity, despite the prominent photodistribution of the rash. Facial erythema may also occur in DM.

Lab Studies. Muscle enzyme levels are often abnormal at some time in patients with DM. The most common enzyme level to obtain is the creatine kinase level. However, an aldolase level test and other tests, such as aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) tests, may also yield abnormal results. At times, the elevation of the enzyme levels precedes clinical evidence of myositis. Therefore, if a patient who is presumably stable develops an elevation in an enzyme level that was previously normal, the clinician should assess the possibility of a flare of the muscle disease.

Treatment. The therapy for DM involves general measures, measures to control the muscle disease, and measures to control the skin disease. Also, in some patients, treating other systemic manifestations or complications may be necessary. Therapy of the muscle component involves the use of corticosteroids with or without an immunosuppressive agent. The skin disease is treated by avoiding sun exposure and by using sunscreens, topical corticosteroids, antimalarial agents, and/or methotrexate. The mainstay of therapy for the muscle disease is systemically administered corticosteroids. Traditionally, prednisone (0.5–1 mg/kg/d) is given as initial therapy. The drug should be slowly tapered to avoid relapse of the disease. Because most patients develop steroid-related toxic effects, many authorities administer an immunosuppressive or cytotoxic agent early in the course. Use of drugs, such as methotrexate, azathioprine, cyclophosphamide, cyclosporin, mycophenolate mofetil, and chlorambucil, has been reported to be steroid sparing in some patients or in small open-label studies. For conditions that do not improve, the use of monthly high-dose intravenous immune globulin has proved to be beneficial.

Therapy for the cutaneous disease is often difficult. The first-line of therapy is recognizing that the patient is photosensitive and advising the patient to avoid sun exposure and to use sun protective measures, including broad-spectrum sunscreens. Hydroxychloroquine and chloroquine have been beneficial in small open-label case studies. Methotrexate is also useful. Recently, mycophenolate mofetil has been reported to be useful. Intravenous immune globulin not only benefited the muscle but also cleared the skin lesions in the patients in whom it was used.

Prognosis. The prognosis depends on the severity of the myopathy, the presence of a malignancy, and/or the presence of cardiopulmonary involvement. Patients with DM who have malignancy, cardiac involvement, or pulmonary involvement and those with DM who are elderly (> 60 y) have a poorer prognosis. The disease may spontaneously remit in as many as 20 % of patients. About 5 % of patients have a fulminant progressive course, with eventual death. Therefore, many patients require long-term therapy.

LECTURE 15. DISEASES OF SKIN APPENDAGES

Acne

Acne vulgaris is a self limited disease involving the sebaceous follicules observed primarily in teenagers and adolescents. Occasionally, it is present at birth, and mild cases may be observed in the neonatal period. During puberty, acne typically becomes a common problem.

Acne usually affects the face and, to a lesser degree, the back, chest, and shoulders. On the trunk, lesions tend to be near the midline. The 4 major pathophysiologic features of acne are the following:

- Hyperkeratinization;
- Sebum production;

- Bacterial proliferation;
- Inflammation.

Lesions can be described in 3 categories:

Noninflammatory: Comedones are either open (black heads) or closed (whiteheads). The open comedo appears as a flat or slightly raised lesion with a central dark-colored follicular impaction of keratin and lipid. The closed comedo is a pale, slightly elevated, small papule without a visible orifice and is a potential precursor for the larger inflammatory lesions.

Inflammatory: Inflammatory lesions vary from small papules with an inflammatory areola to pustules (papulopustular) to large, tender, fluctuant nodules (nodular).

Scars: These appear as punched out pits of varying size and may have multiple openings.

Exacerbations of acne vulgaris may follow the ingestion of several drugs, such as iodides, bromides, glucocorticoids, and lithium, as well as the application of oil-containing compounds.

Classification of acne is based on the predominant primary elements seen in the skin of an acne patient:

1. Comedonic acne
2. Papular pustular acne
3. Nodular acne
4. Acne conglobata

Acne conglobata (AC) is an uncommon and unusually severe form of acne characterized by burrowing and interconnecting abscesses and irregular scars (both keloidal and atrophic), often producing pronounced disfigurement. The comedones often occur in a group of 2 or 3, and cysts contain foul-smelling seropurulent material that returns after drainage. The nodules are usually found on the chest, the shoulders, the back, the buttocks, the upper arms, the thighs, and the face. AC may develop as a result of a sudden deterioration of existing active papular or pustular acne, or it may occur as the recrudescence of acne that has been quiescent for many years.

Laboratory studies. Although many laboratory studies have been performed, the findings have not been significant in general. Androgen levels may be appropriate in select cases.

Treatment. Topical and oral agents act at various stages in the evolution of an acne lesion and may be used alone or in combination to enhance efficacy. Most cases are controlled with benzoyl peroxide, drying and peeling agents, and antibiotics. Topical agents should be applied to the entire affected area to treat existing lesions and to prevent the development of new ones.

The therapy of choice for acne conglobata is isotretinoin 0.5–1 mg/kg for 4–6 months. Simultaneous use of systemic steroids, such as prednisone 1 mg/kg/d for 2–4 weeks, may also prove beneficial, particularly if systemic symptoms

NB! Avoid use of retinoids in women of reproductive age. If necessary, administrate them with contraceptic pills that have to be used several months before and after the treatment.

Alternatives include oral tetracycline 2 g/d or erythromycin 2 g/d, either alone or with isotretinoin or prednisone. Along with vigorous medical therapy, emotional support is essential. Large hemorrhagic nodules may be aspirated. Intralesional triamcinolone or cryotherapy may also be valuable. Occasionally, surgical excision of interconnecting large nodules may be beneficial.

Seborrhoeic Dermatitis

Seborrheic dermatitis is a papulosquamous disorder patterned on the sebum-rich areas of the scalp, face, and trunk. In addition to sebum, this dermatitis is linked to *Malassezia,* immunologic abnormalities, and activation of complement. It is commonly aggravated by changes in humidity, changes in seasons, trauma (eg, scratching), or emotional stress. The severity varies from mild dandruff to exfoliative erythroderma. Seborrheic dermatitis may worsen in Parkinson disease and in AIDS.

Pathogenesis. Seborrheic dermatitis is associated with normal levels of *Malassezia* but an abnormal immune response. Helper T cells, phytohemagglutinin and concanavalin stimulation, and antibody titers are depressed compared with those of control subjects. The contribution of *Malassezia* may come from its lipase activity — releasing inflammatory free fatty acids — and from its ability to activate the alternative complement pathway.

Scalp appearance varies from mild, patchy scaling to widespread, thick, adherent crusts. Plaques are rare. From the scalp, seborrheic dermatitis can spread onto the forehead, the posterior part of the neck, and the postauricular skin, as in psoriasis. Skin lesions manifest as branny or greasy scaling over red, inflamed skin. Hypopigmentation is seen in blacks. Infectious eczematoid dermatitis, with oozing and crusting, suggests secondary infection. A seborrheic blepharitis may occur independently. Distribution follows the oily and hair-bearing areas of the head and the neck, such as the scalp, the forehead, the eyebrows, the lash line, the nasolabial folds, the beard, and the postauricular skin. Presternal or interscapular involvement is more common. Intertrigo of the umbilicus, axillae, inframammary and inguinal folds, perineum, or anogenital crease rarely may be present.

Treatment. Early treatment of flares is encouraged. Behavior modification techniques in reducing excoriations are especially helpful with scalp involvement. Topical corticosteroids may hasten recurrences, may foster dependence because of a rebound effect, and are discouraged except for short-term use. Skin involvement responds to ketoconazole, naftifine, or ciclopirox creams and gels. Alternatives include calcineurin inhibitors (ie, pimecrolimus, tacrolimus), sulfur or sulfonamide combinations, or propylene glycol. Class IV or lower corticosteroid creams, lotions, or solutions can be used for acute flares. Systemic ketoconazole or fluconazole may help if seborrheic dermatitis is severe or unresponsive.

Dandruff responds to more frequent shampooing or a longer period of lathering. Use of hair spray or hair pomades should be stopped. Shampoos containing salicylic acid, tar, selenium, sulfur, or zinc are effective and may be used in an alternating schedule. Overnight occlusion of tar may help to soften thick scalp plaques. Selenium sulfide (2.5 %), ketoconazole, and ciclopirox shampoos may help by reducing *Malassezia* yeast scalp reservoirs. Shampoos may be used on truncal lesions or in beards but may cause inflammation in the intertriginous or facial areas.

Seborrheic blepharitis may respond to gentle cleaning of eyelashes with baby shampoo and cotton applicators. The use of ketoconazole cream in this anatomical region is controversial.

Alopecia Areata (AA)

AA is an autoimmune disease characterized by patchy hair loss.

Pathogenesis is unknown but high frequency of family history, especially in patients with early onset is seen. Major associations include vitiligo and thyroid disease, with increased prevalence of antithyroid antibodies and thyroid microsomal antibodies in AA. Other autoimmune diseases shown to be associated: pernicious anemia, diabetes, LE, myasthenia gravis, RA, polymyalgia rheumatica, ulcerative colitis. Emotional stress may be precipitating factor in some cases. AA may be a result of in-take of some drugs.

Clinical Features. Prevalence of AA is 0.1–0.2 %, it affects men and women equally. Pull test may be positive at margins, indicating early disease. Usually AA is asymptomatic, but some patients perceive pruritus, tenderness, burning, or pain preceding hair loss. Classification of AA is based on the percentage of hair loss:

- Areata — partial loss of scalp hair.
- Totalis — total loss of scalp hair.
- Universalis — 100% loss on scalp, eyebrows, eyelashes, and rest of body.
- Nail dystrophy may be seen in one, some, or all nails, preceding, coinciding, or occurring after hair disease. Pitting with irregular pattern or in organized rows; trachyonychia: longitudinal striations resulting in sandpaper

appearance; Beau's lines; onychorrhexis; thinning or thickening; koilonychia; red-spotted lunula; punctate or transverse leukonychia are seen.

Prognosis. AA has unpredictable course and pattern. Most patients see complete regrowth within one year without treatment, 10 % develop severe chronic form. Predictors for poor prognosis are: atopic dermatitis, childhood onset, widespread involvement, ophiasis (loss of hair on the border of hair growth), duration for longer than five years, onychodystrophy.

Treatment. Spontaneous recovery is extremely common, with most showing regrowth within 1 year. First line treatment includes local steroids and Minoxidil 5 % that stimulates follicular DNA synthesis and regulates hair physiology.

Other treatment include anthralin 0.25–1.0 % and squaric acid dibutyl or DPCP (diphenylcyclopropenone) — whose aim is to maintain low-grade tolerable erythema, scaling, and pruritus, relapse after discontinuation occurs commonly. Cyclosporine works, but systemic use associated with adverse effects and high recurrence rate.

Rosacea

Rosacea is an inflammatory disease that is present with papules and papulopustules in central region of face against a vivid background with telangiectases. Later, diffuse hyperplasia of connective tissue with enlarged sebaceous glands happens.

Rosacea predominates in fair — skinned individuals especially of North Europe heritage. The onset of the disease is usually 20–50 years. Females are affected more often than males.

Rosacea is localized to nose, cheeks, chin, forehead, glabella; less commonly affected areas include the retroauricular, V-shaped chest area, neck, back, scalp.

Pathogenesis of rosacea is not known. There are a lot of triggers that can provoke the onset of rosacea. Demodex folliculorum mites, frequently found in facial follicules, were previously thought to be the cause of rosacea. These mites may not play a significant role in the aetiology, however, a high density of demodex mites may aggravate the flare – up of rosacea.

Classification of rosacea includes:

1. Erythematotelangiectatic.
2. Papulopustular.
3. Phymatous.
4. Ocular.
5. Granulomatous.

Clinical picture. The erliest manifestations of rosacea include flushing and blushing, or episodic erythema. Such patients are advised to avoid physiological and environmental stimuli that cause rosacea. The most frequent triggers are UV,

heat, cold, chemical irritation, strong emotions, alcoholic beverages, hot drinks, and spices. After progressing erythema becomes stable and teleangiectasias appear.

Papuls and pustules appear after of the erythematous base. Pustules are usually sterile. Ocular rosacea is a common associate of the disease but is often misdiagnosed. The symptoms of rosacea are non specific and include a foreign body, gritty, or dry sensations, burning, tearing, or redness. Phymatous stage of rosacea presents as hyperplasia of sebaceous glands. Phymas usually develop at the nose (rhinophyma), but can be at chin — gnathophyma, forehead — metophyma, earlobes — otophyma, eylids — blepharophyma.

Unusual forms of rosacea include:

- Persistent edema of rosacea (rosacea lymphedema or Morbihan's disease) — hard, nonpitting edema, often misdiagnosed as cellulitis
- Steroid rosacea — a patient resulting from from steroid use. Steroid atrophy with resultant telangiectases are seen. The face is flaming red with severe scaling and multiple papules. Severe pain and discomfort are seen. Withdrawal of steroid accompanied by exacerbation of disease. Slow tapering of steroid over months is required.
- Rosacea fulminans (pyoderma faciale) — occurs almost exclusively in post-adolescent women. Large coalescent nodules and confluent draining sinus occupy most of the face. Prognosis is excellent, and recurrences rare.

Treatment. There is no perfect treatment for rosacea. Topical antibiotics can be often effective. Topical clindamycin, erythromycin, and metronidazole are active against papules and pustules, but not telangiectasia and flushing. Topical sulfur-based preparations, azelaic acid can be used. Sunscreens must be applied to prevent sun damage. Green-tinted makeup concealer can neutralize redness.

Systemic antibiotics are generally used. Rosacea responds well to tetracyclines and erythromycin. Anti-helicobacter pylori therapy may help.

Isotretinoin is indicated in phymas; but rosacea often rapidly recurs after discontinuation of isotretinoin.

NB! Topical steroids unless help to reduce redness are contraindicated in rosacea patients and cause steroid induced rosacea. The only situation when they can be used — is fulminant rosacea

Treatment for rosacea fulminans includes oral glucocorticoids, 1.0 mg/kg per day for 7–10 days. After isotretinoin can be added with slow tapering of steroid, for 3–4 months until all inflammatory lesions disappeared. Topical potent steroids are used for the first two weeks.

Laser treatment is sometimes helpful in teleangiectasias.

LECTURE 16. GENODERMATOSES

Ichthyosis

Ichthyosis is a group of diseases characterized by generalized dryness of the skin resulting in scaling. It is caused by abnormality in keratinization and exfoliation of the horny cell layer. The skin is covered with what appear to be fish-like scales. Patients with ichthyosis have a congenital abnormality in keratinization and scaling, and most cases are classified as hereditary keratoses. However, some may appear later in life as acquired conditions; these cases often accompany malignant tumors. Ichthyosis is classified by clinical features, inheritance pattern, and affected sites into more than ten subtypes.

More frequent inheritant forms of ichthyosis include:

- Ichthyosis vulgaris.
- X-linked ichthyosis.
- Bullous congenital ichthyosiform erythroderma (BCIE).
- Nonbullous congenital ichthyosiform erythroderma (NBCIE).
- Lamellar ichthyosis.
- Harlequin ichthyosis.

Ichthyosis vulgaris

Pathogenesis. Filaggrin mutation is a major predisposing factor for atopic dermatitis, and atopic disorders are strongly associated with ichthyosis vulgaris. The causative gene has recently been identified as the filaggrin gene. As a result of a decrease in the production of filaggrin, which moisturizes the epidermis, there is abnormal exfoliation of horny cells and dryness and scaling of the skin. Ichthyosis vulgaris is semidominantly inherited (homozygous patients have more severe symptoms than heterozygous patients) and often runs in families. There is thickening of the horny cell layer and reduction or loss of keratohyaline granules and granular cell layer because of loss or reduction of filaggrins.

Clinical picture. The onset is early childhood. It is progressive until the patients reach about the age of 10, the symptoms subsiding in adolescence in most cases. The skin dries, appearing pityroid and lamellar. The extensor surfaces of the legs and the back region are the most commonly affected; the flexure of joints in the extremities, axillary fossae genitals and thoraco-abdominal region are unaffected. Subjective symptoms and itching are rarely observed. The symptoms subside during the summer and aggravate during the winter, when the skin tends to dry.

Diagnosis. Ichthyosis vulgaris is diagnosed by the clinical and pathological features, family history and filaggrin gene mutation. In other hereditary ichthyoses, the onset is the time of birth, and the flexures of the joints in the extremities are often involved. Acquired ichthyosis can be differentiated from ichthyosis vulgaris by the age of onset, the clinical course, and the presence of malignant tumor in the case of the former.

Treatments are symptomatic. Moisturizer, urea ointments, salicylic acid petrolatum, and vitamin D3 ointments are applied. The symptoms subside after adolescence.

X-linked ichthyosis

Pathogenesis. It is caused by mutation in the steroid sulfatase gene on X-chromosome. Steroid sulfatase is the enzyme that breaks down cholesterol sulfate, a substance which promotes intercellular adhesion in the horny cell layer. The lack of steroid sulfatase causes accumulation of cholesterol sulfate, leading to delayed exfoliation of horny cells. X-linked ichthyosis is recessively inherited and occurs in males.

Clinical picture. X-linked ichthyosis manifests shortly after birth and does not improve with age. The cutaneous symptoms are severe; the scales are large and dark brown. The whole body of newborns may be encased in a translucent covering (collodion baby). Not only the extensor surfaces but also the flexures of extremities are affected. The abdomen is most severely affected. Corneal opacification may occur as a complication. As with ichthyosis vulgaris, X-linked ichthyosis aggravates during the winter and subsides during the summer.

Diagnosis. Thickening of the horny cell layer, and normal or mildly thickened granular and suprabasal cell layers are present. Follicular keratinization is rarely found. Absence or marked reduction of steroid sulfatase is observed in the horny cell layer, peripheral leukocytes, and fibroblasts. Estriol in the urine decreases in the mothers (carriers) of children with X-linked ichthyosis. Ichthyosis vulgaris is differentiated from X-linked ichthyosis by the decrease of steroid sulfatase in the case of the latter.

The treatments are symptomatic and the same as those for ichthyosis. Retinoids can be used in severe cases.

Bullous congenital ichthyosiform erythroderma

Pathogenesis. The cytoskeleton (intermediate filament) of suprabasal cells is composed of keratin 1 and keratin 10. Because of mutation in the keratin 1 or keratin 10 gene, abnormal keratin fiber formation, cytoskeleton distortion, and epidermal blistering occur, leading to secondary thickening of the horny cell layer. BCIE is autosomal dominantly inherited. The horny and suprabasal cell layers thicken, keratin fibers aggregate, and there are vacuolated cells containing large keratohyaline granules in the granular and suprabasal cell layers (granular degeneration).

Clinical picture. Patients with bullous congenital ichthyosiform erythroderma (BCIE) are sometimes born as collodion babies. Diffuse flushing and blistering recur for several weeks after birth. Scales gradually thicken, leading to severe keratinization in later childhood. The thickly keratinized

plaques are accompanied by flush and a characteristic odor. The whole body including the flexures of joints and extremities appear erythrodermatic and dark rose in color. The prognosis is good.

Blistering is marked, particularly in newborns. It is necessary to differentiate BCIE from epidermolysis bullosa, incontinentia pigmenti and impetigo contagiosa by the pathological findings. The treatments are oral retinoid and application of moisturizer.

Non bullous congenital ichthyosiform erythroderma (NBCIE)

The pathogeneses. It is autosomal recessively inherited. The pathogeneses are various. Six or more genes are thought to be associated with occurrence of NBCIE. A certain mutation in the ABCA12 gene, the causative gene for harlequin ichthyosis, also causes NBCIE. The transglutaminase 1 gene, the causative gene for lamellar ichthyosis, can also cause NBCIE. Complete absence of transglutaminase 1 activity causes typical lamellar ichthyosis; severe reduction in such activity leads to NBCIE. The mechanism of NBCIE is known to be a marked decrease in physical and functional strength of keratin.

Clinical picture. Most of the patients are born as collodion babies. Two to three days after birth, the collodion covering exfoliates, leaving the whole body surface with diffuse flushing and scaling. The affected sites include the flexures of joints. Ectropion of eyelids may also occur. There are minor changes in the symptoms with season. NBCIE progresses until the age of 10, at which point it stops and subsides. The clinical manifestations range from mild to severe.

Treatment. Oral retinoid (a vitamin A derivative) is effective. The skin should be kept clean to prevent secondary infection.

Lammelar ichthyosis

In approximately half of all cases of lamellar ichthyosis, the cause is an absence of transglutaminase 1; however, its activity is normal in some cases. Transglutaminase 1 is a calcium-dependent enzyme that is necessary for the formation of cornified cell envelopes in keratinocytes. The pathogeneses of lamellar ichthyosis are various. The scales in lamellar ichthyosis are clinically rough and large in most cases, dark brown, and plate-like or lamellar; these characteristics distinguish the scales from those in nonbullous congenital ichthyosiform erythroderma (NBCIE).

Summury features of the most common types of ichthyosis are presented in the table:

	Ichthyosis vulgaris	**X-linked ichthyosis**	**BCIE**	**NBCIE and lammelar ichthyosis**
Frequency	Common	Uncommon	Rare	Rare

Inheritance	SD	XR	AD	AR
Site	Extremities, trunk, back, extensor surface	Abdomen is most prominent	Whole body	Whole body
Scales	Fine	Large, dark, brown	Severe hyperkeratosis	Lamellar scales
Causative agent	Fillagrin	Steroid sulfatase	Keratin 1 or 10	Transglutaminase 1
AD: autosomal dominantly inherited, AR: autosomal recessively inherited, XR: x-linked recessively inherited, SD: semidominantly inherited				

Epidermolysis bullosa (EB)

EB is a group of rare heritable skin disorders characterized by increased skin fragility after relatively minor trauma.

The classification of EB includes 3 major types:
1. EB simplex.
2. Junctional EB.
3. Dystrophyc EB.

NB! Types of EB present different level damage. In simplex EB the separation is within keratynocytes. In JEB the level of separation is lamina lucida of the basement membrane. In DEB the defect is below lamina densa.

Clinical picture includes formation of blisters and erosions after trauma. In severe cases atrophy or deformations are seen. Condition can be complicated with secondary infection.

For to perform the diagnosis biopsy is essential. It is performed on an unblistered site which is gently rubbed for 1 min before removing a superficial piece of tissue. The biopsy is studied for indirect immunofuorescence to identify the presence of protein components, especially collagen VII.

EB simplex is autosomal dominant and it is mostly superficial disease (although severe forms are seen) and erosions are healed without scar formation. JES is autosomal recessive and its lesions generally heal with no or mils atrophic scar. Lesions of DEB heal with scarring that is one of the hallmarks of this disease. DEB can be autosomal dominant and autosomal recessive.

Diagnosis. Clinical picture and biopsy are used to confirm the diagnosis. Each of the variants of the EB can result in a spectrum of severity from mild to severe and even lethal in the neonatal period. For this reason, families in which a child has been born with a severe form of EB often request prenatal testing. In 1979 1st prenatal testing was performed, using fetoscopy to obtain a fetal skin sample which was studied by electron microscopy to identify whether the structural defect was present in fetal skin. Immunohistochemistry of fetal skin also allows for rapid diagnosis. The disadvantage of fetal skin biopsy is that it is

performed on the late stages of pregnancy (about 16–18 weeks) when the fetal skin has developed sufficiently so that the diagnostic structures are visible.

Treatment. Wound healing is a major aim of management of EB. Extensive areas of denuded skin represent loss of the stratum corneum barrier to microbial penetration. Antibiotics should be administered in early signs of the infection. Prevention of infection is the preferred strategy. With extensive areas of crusting and denudation, a strict wound care regimen should be followed. Such a regimen entails regular whirlpool therapy followed by application of topical antibiotics. The wound should be covered with semiocclusive nonadherent dressings. Tumors often arise in chronic cutaneous lesions in patients with EB.

The most disabling complication of EB are esophageal lesions. These lesions are managed in several ways. One medical approach is to use phenytoin and oral steroid elixirs to reduce the symptoms of dysphagia. In addition, if oral candidiasis is present, an anticandidal medication is helpful. In other cases surgery is necessary.

Patients with EB can experience recurrent blepharitis in 1 or both eyes along with bullous lesions of the conjunctivae, corneal ulcerations, corneal scarring, obliteration of tear ducts, and eyelid lesions. Corneal erosions are treated supportively with application of antibiotic ointment.

Good dental hygiene is essential for patients with EB, and regular visits to the dentist are recommended. If possible, a dentist familiar with EB should be consulted. Despite their best efforts, many patients with JEB and DEB develop dental caries because of enamel defects. In addition, significant oral mucosal involvement can accompany severe forms of JEB and DEB. Avoid harsh mouthwashes containing alcohol. Normal saline rinses can help gently clean the mucosal surfaces.

Potential future therapies include protein and gene therapies. Model systems using these approaches show promise for significant advances in future therapies.

In protein therapy, the missing or defective protein is produced in vitro by recombinant methods and applied directly to blistered skin. Protein therapy may be most useful in EB subtypes involving a defect or deficiency in laminin 5 because this protein does not require complex processing or transmembrane cellular anchorage.

In gene therapy, the goal is to deliver genes targeted to restore normal protein production.

Prognosis. EB is a lifelong disease. Some subtypes, especially the milder EB forms, improve with age.

Keratoderma

Keratoderma means thickening of stratum corneum. Usually it is most prominent in palms and soles. Palmoplantar keratoderma is a generic term for

diseases that hereditarily cause hyperkeratosis in the palms and soles. It is subclassified by clinical features and patterns of inheritance.

There is no effective treatment for any types. Oral retinoid (a vitamin A derivative) and topical application of petrolatum salicylate or moisturizer are the main treatments.

Thost-Unna palmoplantar keratoderma

Thost-Unna palmoplantar keratoderma is autosomal dominantly inherited. Localized diffuse lesions with a red halo form on the palms and soles of infants. Thickening of the horny cell layer and epidermis is seen. In recent years, cases with mutation in the keratin 1 gene have been reported. The palms and soles of patients with Thost-Unna palmoplantar are usually hyperhidrotic.

Keratoderma Mal de Meleda

Synonym: Meleda disease.

This autosomal recessively inherited disease is often seen in offspring of consanguineous marriages. It hardly ever occurs in Asians. Hyperkeratosis accompanied by flush appears immediately after birth. Keratinization progresses and extends as the patient ages. In many cases, not only are the palms and soles affected, but so are the dorsal hands and feet, arms and legs. It is progressive until the patients become elderly. Mental retardation may occur. Psoriasiform lesions may be seen on the knees and elbows.

Papillon-Lefevre syndrome

Flush and hyperkeratosis occur on the palms, soles, the dorsal surfaces of hands and feet, and the extremities. The syndrome is characterized by periodontal disease. It is autosomal recessively inherited.

LECTUE 17. LYMPHOPROLIFERATIVE SKIN DISEASES

Skin lymphomas

Lymphomas — lymphoproliferative disorders characterized by localization of neoplastic T or B lymphocytes in the skin.

T-cell lymphomas

Cutaneous T-cell lymphoma (CTCL) is a term coined in 1979 to describe a group of lymphoproliferative disorders characterized by localization of neoplastic T-lymphocytes to the skin at presentation. Of all primary cutaneous lymphomas, 65 % are of the T-cell type. The most common immunophenotype is CD4-positive. T-cell lymphomas can be primary cutaneous and other T and NK cell lymphomas with cutaneous involvement.

There are lots of classifications of CTCL but in 2005 unified Worls Health Organisation and European Organisation for Research of T-Cell Lymphomas (WHO-EORTIC) classification was accepted. Primary cutaneous T-cell lymphomas are classified as:

a. Mycosis fungoides (MF) — «classical», erythrodermic (Sezary syndrome), follicular MF, pagetoid reticulosis, granulomatous slak skin.

b. Primary cutaneous anaplastic large cell lymphoma.

c. Lymphomatoid papulosis.

d. Subcutaneous panniculiticlike T-cell lymphoma.

e. Primary cutaneous CD 4+ small/medium pleomorphic TCL.

«Classical» MF is developing during tree stages that can be seen altogether in one patient.

Patch phase MF is characterized by flat, usually erythematous, macules that may have a fine scale, may be single or multiple, and may be pruritic. In dark-skinned individuals, the patches may appear as hypopigmented or hyperpigmented areas. As patches become more infiltrative, they evolve into palpable plaques. Plaques tend to be raised, demonstrating fine-scale, well-demarcated, erythematous shapes with irregular borders. Annular or serpiginous patterns with central clearing and pruritus are common. Patches and plaques may affect any area of the skin, but they often are distributed asymmetrically in the areas that a bathing suit would cover (ie, hips, buttocks, groin, lower trunk, axillae, breasts). Patients with evidence or a history of patchy or plaquelike skin lesions also can have tumors. Tumors are red-violet nodules that may be dome-shaped, exophytic, or ulcerated.

Skin erythroderma (Sezary syndrome — SS) often is intensely symptomatic, with pruritus and scaling that can be profound. The patients experience thickening of the skin folds in the face (leonine facies), hyperkeratosis and fissuring of the palms and soles, onychodystrophy, ectropion of the eyelids, and edema. Sun exposure may be painful as well as pruritic.

Extracutaneous involvement is more clinically evident as the stage and extent of MF increases. Peripheral lymphadenopathy is the most frequent site of extracutaneous involvement in MF.

Classification system (TNMB) is developed for to rate T-cell lymphomas:

T	T0	Nondiagnostic (parapsoriasis)
	T1	Limited patch/plaque (less than 10% total skin surface)
	T2	Generalized patch/plaque (more than 10% total skin surface)
	T3	Tumors
	T4	Erythroderma
N	N0	Lymph nodes clinically uninvolved
	N1	Lymph nodes enlarged, histologically uninvolved
	N2	Lymph nodes clinically uninvolved, histologically involved
	N3	Lymph nodes enlarged and histologically involved
M	M0	No visceral involvement
	M1	Visceral involvement
B	B0	Circulating atypical / Sezary cells (less than 5% of lymphocytes)
	B1	Circulating atypical / Sezary cells (more than 5% of lymphocytes)

TNMB classification is used for staging of T-cell lymphomas:

Stage	T	N	M	Study definition
Ia	1	0	0	Limited patch/plaque
Ib	2	0	0	Generalized patch/plaque
IIa	1–2	1	0	Not studied
IIb	3	0–1	0	Tumor stage
III	1–4	0–1	0	Erythroderma/Sezary syndrome
IVa	1–4	2–3	0	Not studied
IVb	1–4	0–3	1	Not studied

Laboratory examination. Skin biopsy is the first diagnostic tool. Atypic lymphocytes should be found. It is not possible to reveal them in early stages of lymphomas when lymphocyte infiltration is not so prominent. Such patients are observed under the diagnosis «parapsoriasis». That is why stating the diagnosis may take several years. Biopsy should be performed regularly. Immunophenotyping and T-cell receptor gene rearrangement are the best techniques, the only disadvantage is their cost. Bone marrow examination is performed if the patient has proven blood or nodal involvement. Lymph node biopsy is necessary if the nodes are palpable. Sezary cells (cerebriform lymphocytes) are found in Sezary syndrome.

Treatment. Multiple therapeutic modalities for T-cell lymphoma exist, ranging from topical therapy, phototherapy, photopheresis (extracorporeal photochemotherapy), radiation therapy, immunotherapy, chemotherapy, or newer agents such as anti-tumor vaccines and antibody fusion toxins. Commonly used topical agents include high-potency topical corticosteroids, carmustine, and mechlorethamine (nitrogen mustard). Phototherapy may consist of psoralen with ultraviolet A photochemotherapy (PUVA), ultraviolet-B (UVB) broadband (280–320 nm), and more recently narrowband UVB, and others. Electron beam radiation has been used locally and for total body irradiation. Systemic agents include interferons (mostly α-interferon), retinoids, methotrexate, and other agents. Photopheresis has been employed against erythrodermic MF or Sézary syndrome. The above treatments can be used as monotherapy and some treatments have been used together in combination or in sequence. Unfortunately, randomized studies of the efficacy of different types of therapies are not available. Offered treatments according to stages of T-cell lymphoma are shown at the table:

Stage Ia	Most effective	PUVA
	Least effective	Topical corticosteroids
Stage Ib	Most effective	PUVA
	Least effective	Topical corticosteroids
Stage IIb	Most effective	TSEB
	Least effective	Methotrexate
Stage III	Most effective	Photophoresis
	Least effective	TSEB
PUVA=psoralen + UVA photochemotherapy TSEB=total skin electron beam		

Prognosis. Patients with limited patches and plaques of MF appear to have a near-normal life expectancy compared to age-matched controls. In contrast, SS is an aggressive lymphoma regarded by many as an erythrodermic leukemic variant of MF, with a reported 5-year survival of 33 %. The chance of developing extracutaneous disease for MF and SS generally correlates with the extent of cutaneous involvement; rates of 30–42 % are seen for tumor or erythroderma patients, compared to 8 % for generalized plaques.

B-cell lymphomas

B-cell lymphomas are characterized by skin infiltration with malignant B-lymphocytes. Usually B-cell lymphomas are situated in deeper layers of the skin and have worse prognosis than T-cell lymphomas. They are more often localized and are present as solitary tumor.

WHO-EORTIC classification of B-cell lymphomas:

Non-aggressive B-cell lymphomas:

- Marginal zone B-cell lymphoma.
- Follicular – center B-cell lymphoma.

Aggressive B-cell lymphomas

- Diffuse large B-cell lymphoma, leg type.
- Diffuse large B-cell lymphoma, other type.
- Intravascular large BCL.

Lab. examination includes biopsy and immunophenotyping.

Treatment. The two drugs that are usually given to treat diffuse large B-cell lymphoma are doxorubicin and cyclophosphamide. They are usually given together with other anti-cancer drugs.

Radiotherapy may be used when the lymphoma is confined to one or two areas of lymph nodes in the same part of the body (stage 1 or 2). It may also be given in addition to chemotherapy. Radiotherapy is also sometimes given to improve symptoms, such as pain.

Steroids are drugs which are often given with chemotherapy to help treat lymphomas. They also help you feel better and can reduce feelings of sickness. Monoclonal antibodies are drugs that recognise, target, and stick to specific proteins on the surface of cancer cells, and can stimulate the body's immune system to destroy these cells. Rituximab is a monoclonal antibody that is commonly used to treat diffuse large B-cell lymphoma. It is usually given with chemotherapy, as part of the R-CHOP regimen, this includes the chemotherapy with vincristine, the steroid prednisolone, and rituximab, which is a monoclonal antibody. The chemotherapy can usually be given to you as an outpatient at hospital, and continues for 4–6 months.

LECTURE 18. DISEASES OF BLOOD VESSELS

Vasculitis

Vasculitis means inflammation of blood vessels and is divided into several types according to the diameter of the artery or vein at the principal site of inflammation (Figure 1).

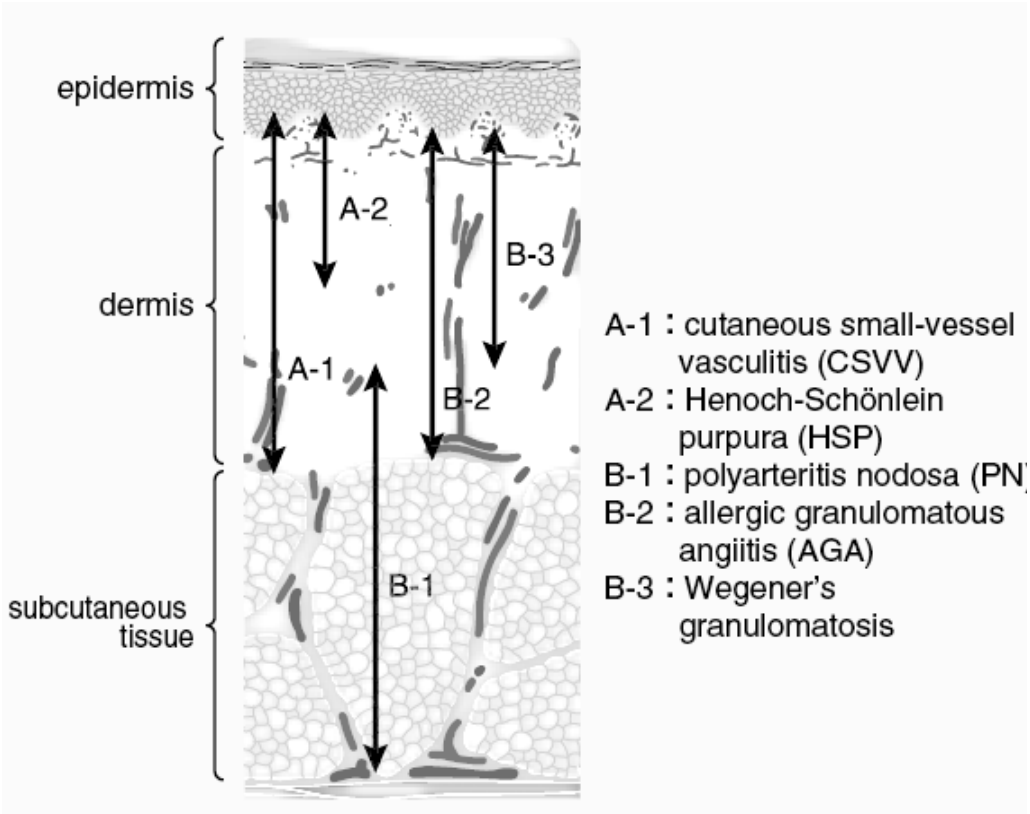

Figure 1 — Location of vasculitis in the skin

Purpura is a general term for reddish-purple skin lesions produced by bleeding in the dermis or subcutaneous tissues. It is classified by the size of bleeding into petechia (diameter up to 2 mm) or ecchymosis (diameter larger than 2 mm). The major causative factors are vascular abnormality (from vasculitis or mechanical injury), blood flow abnormality (e.g., hypergammaglobulinemia, which often accompanies a systemic disease), decrease or functional abnormality of platelets, and coagulopathy. However, the etiology is unknown in many cases.

Cutaneous small-vessel vasculitis (CSVV)

Synonyms: leukocytoclastic vasculitis, necrotizing vasculitis, allergic vasculitis, cutaneous allergic vasculitis.

Cutaneous small-vessel vasculitis (CSVV) is a general term for diseases that present pathological features of leukocytoclastic vasculitis, i.e., diseases with pathological perivascular neutrophilic infiltration and fibrinoid degeneration of the vascular walls. Henoch-Schonlein purpura and urticarial vasculitis are included under a broad definition of CSVV; however, they are usually treated as distinct diseases. CSVV is considered to be a disease caused by small-vessel vasculitis in the dermis (in and between the middle and deep layers of the dermis).

An immune complex of an antigen (e.g., bacterium, virus, drug) and the antibody against that antigen deposit on the arteriolovenular walls. These activate the immune system and cause vasculitis (type III allergic reaction). Penicillin, sulfa drugs and other drugs, chemical substances, hemolytic streptococcus bacteria, or viruses may be the foreign antigen. Collagen diseases and antibodies against malignant tumors can also be causes.

Tests for immune complex are sometimes positive. When CSVV immunocomplex is accompanied by systemic symptoms, renal lesion tends to occur, and proteinuria and hematuria are found. CSVV is diagnosed by skin biopsy. Since there are many diseases that cause CSVV, special care should be taken in diagnosis. When the cause is a drug or infection, those should be removed. For a lesion in the lower extremities, the legs should be raised and kept warm and the patient should get bed rest. Oral application of NSAIDs and DDS (dapsone) is effective in relieving symptoms. Systemic corticosteroid therapy and immunosuppressants are useful for severe cases with systemic symptoms.

Henoch-Schonlein purpura (HSP)

Synonym: anaphylactoid purpura.

It is a specific type of cutaneous small-vessel vasculitis. The cause is IgA immune complex deposition on the vascular walls. HSP is a type III allergy.

Pathogenesis. HSP is seen mostly in children. In children, the onset is mostly after upper respiratory infection; association with hemolytic streptococcus has been pointed out. Drugs (penicillin, aspirin) and certain kinds of foods (milk, eggs) are known to be antigens. These antigens combine with antibodies (mainly IgA) in the body, and the immunocomplex deposits on the vascular walls. Immunoreaction is induced to cause vasculitis and purpura.

Clinical picture. Multiple palpable purpura occur mostly in the lower legs, and they are accompanied by arthralgia, digestive disorder and kidney disorder. Henoch-Schonlein purpura (HSP) is in the pathological category of cutaneous small-vessel vasculitis (CSVV); however, it is localized in the dermal upper layer, and there is IgA deposition on the vascular walls. The most severely affected organs and locations are the skin, joints, digestive organs, and kidneys. Although children are most commonly affected, HSP may also occur in adults. It may be preceded by a headache, pharyngeal pain, and symptoms of the common

cold. Disseminated palpable purpura of several millimeters to 10 mm in diameter occur, mainly in the lower extremities and dorsum of the foot, but sometimes on the thighs, upper extremities, and abdomen. Blisters, ulcers, and old and new eruptions may be present together. In some cases there is transient edema with slight pressure pain. Arthritic symptoms in the legs, knees, hands and elbows, sharp pain in the abdomen, and gastrointestinal symptoms such as nausea, vomiting, hematemesis, and melena are found. HSP may be accompanied by renal symptoms including acute nephritis that progresses to nephrosis. Renal symptoms are closely related to the prognosis.

Diagnosis. Leukocytoclastic vasculitis accompanied by fibrinoid degeneration is seen on the vascular walls in the upper dermal layer. IgA deposition is observed by direct immunofluorescence. The histology of the kidney in HSP patients often shows crescentic glomerulonephritis. When HSP is caused by hemolytic streptococcal infection, antistreptolysin O and antistreptokinase values increase. In half of the patients, serum coagulation factor XIII decreases. In cases with renal lesion, hematuria and proteinuria occur. When the purpura described above occurs in youth, HSP is suspected. History-taking should inquire into not only HSP but also other diseases before examinations and histopathological tests are conducted. It is necessary to differentiate HSP from other purpura, polyarteritis nodosa, Goodpasture syndrome, nephritis after infection caused by hemolytic streptococcus, and systemic lupus erythematosus (SLE). In adults, differential diagnosis from polyarteritis nodosa is important.

Treatment. Bed rest is the first-line treatment, followed by the administration of a vessel-strengthening drug and hemostatics, and systemic administration of steroids. When the disease is caused by hemolytic streptococcus, antibiotics are used. Administration of factor XIII may be effective. HSP generally has a good prognosis and resolves within several weeks in most cases; however, it may recur. Serious complications may occur in other organs, such as nephritis with IgA deposition in the mesangium area, enterorrhagia, intussusception, intestinal perforation, or cerebral hemorrhage.

Erythema elevatum diutinum (EED)

Erythema elevatum diutinum (EED) frequently occurs in men and women of middle age and older. It is a skin lesion that is accompanied by symmetrical infiltration on the extensor surface of elbows and knees. Although the pathogenesis is unknown, an immune reaction caused by deposition of immune complex in the blood vessels is thought to be involved. Appearing as soft, slightly elevated, purplish-red erythema at first, the eruptions gradually become fibrotic and keloidal. There is an atypical type with blistering. Leukocytoclastic vasculitis occurs in the dermis. It is nearly asymptomatic, however, it recurs

repeatedly and persistently. Oral ulcer, arthritis, lung fibrosis, IgA myeloma, and viral infection may accompany EED.

Granuloma faciale

Granuloma faciale, a soft, infiltrative, reddish-brown plaque with a sharp margin, occurs on the face. It is known to be a chronic leukocytoclastic vasculitis. Deposition of immunoglobulins on the vascular walls has been reported, from which the possibility of an immunoreactiont. Granuloma faciale is intractable. Liquid nitrogen cryotherapy, local injection of steroids, and dye laser treatment have been used in recent years.

Polyarteritis nodosa (PN)

Pathogenesis. The etiology is unknown. The hepatitis B virus, bacterial infectious diseases (e.g., streptococcus), and drug hypersensitivity are known to precede or induce PN.

Clinical presentation. Polyarteritis nodosa (PN) most frequently occurs in men and women in their 30s to 60s. There are 2 forms of PN – systemic and cutaneous. There is no significant differences in cutaneous manifestations between systemic PN and cutaneous PN, and cutaneous symptoms are seen in 10 % to 60 % of systemic PN cases. Palpable subcutaneous nodules of 1 cm to 2 cm in diameter, purpura, livedo and ulceration occur mainly parallel to the superficial arteries. Tenderness may be present. PN becomes chronic with repeated recurrences and regressions. Urticaria and transient erythema may also occur. Livedo reticularis (livedo racemosa) is commonly found. Systemic PN may be accompanied by fever, fatigue, weight loss, arthralgia, and visceral symptoms such as renal failure, cardiac infarction, cardiac failure, pericarditis, high blood pressure, abdominal pain, neuritis and myalgia. The kidneys are the most commonly affected organs, and death from renal failure is possible.

Diagnosis. Biopsy is the most informative diagnostic tool. Patients with microscopic PN may develop acute progressive nephritis, interstitial pneumonia, and pulmonary hemorrhage. PN is leukocytoclastic vasculitis that is accompanied by swelling in the tunica media of small and medium-sized arterial walls, fibrinoid degeneration, and neutrophilic cellular infiltration. As PN progresses, thromboembolism, aneurysm and bleeding occur, leading to the formation of epithelioid cell granuloma. In cutaneous PN, these symptoms occur in the arteries in the deep dermal layer and subcutaneous fat tissue. Lesions occur in almost all the nutrient arteries in systemic PN; nevertheless, the lungs are rarely affected. The thickness of the blood vessels and the depth from the skin surface for PN and other vasculitises are compared in.

Immune complex deposition may be found in the area with eruptions. Aneurysm is frequently observed by angiography. PN is diagnosed by the clinical features, laboratory findings and skin biopsy. It is necessary to

differentiate it from systemic lupus erythematosus (SLE), cutaneous small-vessel vasculitis, erythema nodosum, erythema induratum and cryoglobulinemia.

Treatment. Cutaneous PN with mild clinical severity is treated by bed rest with the lower extremities raised, and administration of vasodilators, NSAIDs and DDS. Steroids are temporarily administered orally during acute aggravation. For systemic PN, steroids and immunosuppressive drugs are necessary in high doses. Cutaneous PN has a good prognosis. The eruptions heal in several weeks; however, they are persistent and recur for years. In contrast, the prognosis of systemic PN is poor, because of various internal-organ disorders (e.g., renal failure, intracranial hemorrhage, cardiac infarction).

Allergic granulomatous angiitis (AGA)

Synonym: Churg-Strauss syndrome.

AGA is a vasculitis syndrome. Allergic symptoms such as asthma, fever, and increase of eosinophils and IgE precede AGA. Necrotizing vasculitis in small and medium-sized arteries and the formation of granuloma are the primary diseases. Interstitial pneumonia and lung granuloma occur.

Clinical picture. In most cases intractable bronchitis and other allergic diseases occur for several months to several years before the onset of allergic granulomatous angiitis (AGA). Infiltrated subcutaneous nodules, purpura and erythema frequently appear. Peripheral nerve disorder (usually mononeuropathy multiplex) and gastrointestinal lesions are also found. Lung involvement is common; migrating polymorphic interstitial pneumonia resembling Loffler syndrome is observed by chest X-ray. In comparison with PN, prodromes are common and renal dysfunction is rare in AGA. The typical symptoms of AGA are summarized in table:

Bronchial asthma	Expiratory wheezing or high-pitched rales
Eosinophilia	Eosinophils accounting for 10 % or more of the fraction of peripheral leukocytes
Neuropathy, mono or poly	Numbness accompanied by pain, with glove-stocking distribution
Pulmonary infiltrates, non-fixed	Migrating or transient pulmonary infiltration (X-ray)
Paranasal sinus abnormality	Sharp pain or tenderness in paranasal sinus, or abnormal findings in X-ray
Extravascular eosinophils	Extravascular eosinophils in the skin and lung, observed pathologically

Diagnosis. In AGA, as in PN, there is leukocytoclastic vasculitis in small and medium-sized arteries and small veins. Granuloma occurs in the vascular or perivascular walls, and there is marked eosinophilic infiltrate in the tissue. Notable increase of leukocytes, eosinophils and serum IgE are seen. The patient often tests positive for a kind of anti-neutrophil cytoplasmic antibody (ANCA).

Treatment. With systemic high-dose application of steroids in the early stages, AGA subsides in a relatively short time. Their use in combination with immunosuppressants is recommended in intractable cases.

Wegener's granulomatosis

This rare vasculitis syndrome is preceded by upper respiratory symptoms such as paranasal sinusitis. It is accompanied by fever and systemic fatigue.

Diagnosis. The etiology of Wegener's granulomatosis is unknown; however, an autoimmune mechanism is suspected. Autoantibodies which are anti-neutrophil cytoplasmic autoantibodies, are thought to activate neutrophils and monocytes, causing Wegener's granulomatosis.

Clinical picture. Wegener's granulomatosis most commonly occurs in men and women between the ages of about 25 and 55 years. Necrotizing granuloma lesions in the upper and lower respiratory tracts cause foul-smelling rhinorrhea, mucosal erosion in the upper respiratory tract, nasal hemorrhage, paranasal sinusitis, ocular proptosis, hemosputum and breathing disruption. As the lesions progress, saddle nose may be caused. The lesion gradually spreads to the kidneys, leading to rapidly progressive renal failure. Cutaneous symptoms are found in approximately half of all cases. Various eruptions, such as gangrenous papules, blisters, erythema, purpura, pustules, nodules and ulcers, are produced symmetrically in the extremities and buttocks. In the early stages, a skin lesion resembling pyoderma gangrenosum may be found; it may be useful for early diagnosis.

Leukocytoclastic vasculitis in the upper dermal layer and granuloma formation in the periphery are found. Elevated erythrocyte sedimentation rate, increases in leukocytes and platelets, and elevated levels of human immunoglobulins are found. Skull fracture may be observed by head X-ray. In a chest X-ray, there is shading that closely resembles that of pulmonary tuberculosis and pulmonary metastatic tumor, and cavitary circular shading with a thin wall is seen in 30 to 50% of cases. C-ANCA is useful for diagnosis as a specific antibody and is associated with disease severity. The antibody titer decreases during the course of successful treatment. It is necessary to differentiate Wegener's granulomatosis from sarcoidosis, lymphoma, Goodpasture syndrome, malignant tumor, PN, AGA and cutaneous small-vessel vasculitis. Diagnosis follows the diagnostic criteria of the American College of Rheumatology:

Nasal or oral inflammation	Development of painful or painless oral ulcers or purulent or bloody nasal discharge
Abnormal chest radiograph	Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
Urinary sediment	Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
Granulomatous inflammation on biopsy	Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)

Treatment: Systemic steroids and immunosuppressants (cyclophosphamide in particular) are used. Wegener's granulomatosis was once regarded as having a poor prognosis and usually leading to death from renal failure or other disorder within a year after onset. Currently, it may subside as long as it is treated in the early stages.

Temporal arteritis (TA)

Synonym: Giant-cell arteritis.

TA is a vasculitis syndrome. The superficial temporal arteries and ophthalmic arteries are affected.

The pathogenesis of TA is unknown; however, the involvement of viral or bacterial infection, or drug allergy is suspected. Since HLA-DR4 is associated with TA, genetic factors may be involved in the occurrence of TA.

Temporal arteritis (TA) most frequently occurs in persons over age 50, with a ratio of 1 male to 3 females. Temporal arteries are mainly affected. Cord-like thickening of the temporal arteries, reddening, pain and swelling are present. Throbbing headache, difficulty of opening the mouth, blistering, ulceration, necrosis in the scalp, and hair loss occur. When the lingual artery is affected, the tongue becomes red, swollen and erosive. When the ophthalmic artery is affected, visual impairment results, with blindness following in 10 % of cases. A temporary visual disorder (amaurosis fugax) may also occur. When an artery in the brain is affected, bulbar palsy and dementia occur as well.

Diagnosis. Elevated erythrocyte sedimentat sedmentation rate and increased CRP are observed. Autoantibodies are absent. The serum complement titer and myogenic enzyme are normal. By biopsy, TA appears as granulomatous inflammation accompanied by cellular infiltrate mainly caused by mononuclear cells and production of giant cells.

Treatment. To prevent visual impairment, steroids are used systemically in the early stages of TA. If the symptoms subside, the medication may be discontinued.

Behcet's disease

Behcet's disease is an inflammatory disease with an unknown cause. It occurs mostly in middle-aged men. Recurrent oral aphtha, eye symptoms (uveitis), ulceration in the genitalia, and cutaneous symptoms (erythema-nodosum-like eruptions) typically occur.

Behcet's disease first manifests in men and women in their 20s and progresses over a long period of time. The typical cutaneous symptoms are erythema-nodosum-like eruptions, thrombophlebitis, and folliculitis and acne-like eruptions. The erythema-nodosum-like eruptions most commonly occur in the lower extremities and forearms and are accompanied by pressure pain. They subside in about 1 week; however, they tend to recur. Thrombophlebitis appears as palpable painful subcutaneous linear cord in the extremities, and it often migrates. Folliculitis and acne-like eruptions produce multiple follicular sterile pustules; they are presumably caused by increased irritability, and they produce a pustule where a needle has been inserted, 24 to 48 hours after insertion **(needle reaction test).** The disease is also characterized by ulceration in the genitalia. Deep ulcers with sharp margins form in the scrotum in men and in the labia majora and minora in women. These are painful, and they leave scarring when they heal. Aphthae in the oral mucosa form sharply margined ulcers that are persistently painful. They heal in about 10 days and then recur. More than 60 % of patients with Behcet's disease experience oral aphtha as an early symptom; this has diagnostic significance. In addition, uveitis accompanied by hypopyon often occurs; there is a high risk of blindness. Fever, fatigue, arthritic symptoms, gastrointestinal symptoms (in the ileocecal region, in particular), epididymitis, vasculitis symptoms, and central nervous.

Diagnosis. The primary disease is thought to involve increased neutrophil activity; however, vasculitis plays a central role. Behcet's disease is strongly correlated with the HLA-B51 allele, and abnormality in immunity is known to be associated with the occurrence of the disease. The involvement of bacterial allergy (especially hemolytic streptococcus) is suggested as an initiating factor. Antiphospholipid antibodies and autoimmunity are thought to be involved in the formation of thrombi. In erythema-nodosum-like eruptions, neutrophilic or lymphocytic cellular infiltration is found in the peripheral blood vessels in the deep dermal layer and subcutaneous fat tissues (septal panniculitis). Unlike in erythema nodosum, vasculitis may be found. In thrombophlebitis, thrombus tends to occur in the small veins of the subcutaneous fat tissues. Needle reaction test is positive in 70 % of cases, from enhanced irritability of the skin. Positive HLA-B51 is also an important finding in diagnosing Behcet's disease. Increased erythrocyte sedimentation rate, positive CRP, increased immunoglobulins, and leukocytosis (particularly neutrophilic) are seen from inflammation. When the disease progresses, complement activity increases.

Treatment. When colchicines, which inhibit neutrophils and NSAIDs, are ineffective, immunosuppressants (cyclosporine A, tacrolimus) are useful. Anticoagulation therapy is performed on thrombosis.

Buerger's disease

Synonym: Thromboangiitis obliterans (TAO).

Buerger's disease most commonly occurs in male smokers in their 20s or older. It is caused by arterial obstruction and contraction of small arteries, and contractive ischemia. At onset, Raynaud's phenomenon appears; that is, the skin color changes from white to purplish blue or red and sharp pain occurs in distal fingers and toes, cool sensation in fingers occur, and cyanosis is observed. Over time, a minor injury may trigger ulceration in the fingers, toes and peripheral nails. When a relatively large artery in the extremities is affected, weakened arterial pulse, intermittent claudication, and pain during rest may occur. It is accompanied by migrating thrombophlebitis in 20 to 30 % of cases. Most patients with Buerger's disease are male smokers; the disease is strongly associated with cigarette smoking. Multiple segmental blockages are found in the main peripheral arteries of the lower extremities (popliteal arteries) by arteriography. Thickening and inflammation are seen in the tunica intima of arterial walls in the medium-sized and large arteries. Accordingly, stenosis and blockage are caused by thrombosis. Necrotizing of the vascular walls does not occur.

Treatment. Smoking should be discontinued immediately. It is important to keep the body warm, to maintain blood circulation in the affected sites, and to avoid external injury. Vasodilators, anticoagulants, and prostaglandins are administered. Revascularization or sympathetic nerve block is performed as a surgical treatment.

Mondor disease

Subcutaneous linear cord with a diameter of 3 mm to 10 mm appears on the chest, upper abdomen and upper extremities. Mondor disease is usually characterized by obliterative phelebitis, and it most frequently occurs in women between the ages of 30 and 60. However, it may also occur in men at the root of the penis and in the coronal sulcus. The primary disease is thrombophlebitis or lymphangitis in the subcutaneous fat tissues. It is induced by external injury or operation in the upper chest, or by infection. It may be accompanied by spontaneous pain. There may be some tenderness or discomfort, but there are often no symptoms until the patient discovers a red linear cord running from the lateral margin of the breast. The lumens of the vascular channels in the lesion are narrow and blocked by new connective tissue. Both the inner and outer membranes become thickened and fibrotic. Cellular infiltration is not seen. The

disease usually resolves naturally in several weeks. Clinical follow-up is fundamental.

Malignant atrophic papulosis

Synonym: Degos' disease.

Multiple rose-pink papules occur in the upper extremities. Several days after onset, they form peculiar eruptions with atrophy or telangiectasia at the center. Pathologically, lymphocytic infiltration is seen in the periphery of the blood vessels. Malignant atrophic papulosis has a poor prognosis, and it is known to cause cerebral infarction or perforative peritonitis several years after onset. Since eruptions that are pathologically similar to malignant atrophic papulosis are seen in SLE, systemic sclerosis, rheumatoid arthritis, dermatomyositis and Crohn's disease, it is necessary to examine the eruptions thoroughly to determine whether there is an underlying disease. There is controversy over whether malignant atrophic papulosis is an independent disease.

Kaposi sarcoma

Pathogenesis. The exact pathogenesis of sarcoma Kaposi (KS) is unknown. It can be associated with human herpesvirus 8 (HHV-8), and HIV. There are also endemic regions where KS is seen frequently. Development of sarcoma can be provoked by immunosupression, this fact is supported by documented cases of KS after immunosuppressive therapy.

There are 4 forms of KS:

1. Classic KS — KS has an overwhelming male predominance, with a male-to-female ratio of approximately 10–15:1. elderly persons are usually affected.
2. Endemic — is seen in Central Africa, and some Mediterranian countries,
3. Epidemic (AIDS — associated),
4. Yatrogenic (caused by immunosuppressive therapy). This form usually has a better prognosis and can result as a remission after finishing of the therapy.

Clinical picture. KS is a neoplasm that often manifests with multiple vascular nodules in the skin and other organs. Although true metastases appear to occur, a multifocal origin is most common. The pattern of KS is variable, with a course ranging from indolent (only skin manifestations) to fulminant (extensive visceral involvement). KS also may arise primarily in the oral mucosa, lymph nodes, and/or viscera without skin involvement.

KS is described in 3 forms including localized nodular, locally aggressive, and generalized KS. KS typically occurs in 6 stages including patch, plaque, nodular, exophytic, infiltrative, and lymphadenopathic.

Cutaneous KS usually begins as discrete red or purple patches that are bilaterally symmetric and initially tend to involve the lower extremities. Patches

become elevated, evolving into nodules and plaques. Nodules may be spongy to the touch. KS also occurs as a large infiltrating mass or as multiple cone-shaped friable tumors. Cutaneous KS rarely may be infiltrative or exophytic.

Lab Studies. In KS-AIDS, cytopenia of 1 or more cell lines is frequent. Anemia, if present, may result from gastrointestinal bleeding or may be associated with an autoimmune hemolytic anemia or a hematologic malignancy.

In AIDS-related KS, early lymphatic and hepatosplenic involvement may be evident. Evaluation for KS should include a complete physical examination and a biopsy of suspected lesions including lymph nodes.

Treatment. Since the natural history of KS is variable, assessment of therapy may be difficult. Treatment usually is based on the extent of disease and the patient's immune status. The optimal therapy of KS-AIDS is yet to be determined.

Management modalities for KS include surgical removal of skin nodules or severely affected areas, laser surgery, conventional and megavoltage radiotherapy, chemotherapy, immunotherapy, antiviral drugs, and cessation of immunosuppressive therapy in iatrogenically immunosuppressed patients.

Localized nodular disease may respond well to surgical excision, radiotherapy, and intralesional and outpatient low-dose vinblastine chemotherapy. The latter combination of local and systemic regimens may be preferable. The authors usually inform patients that this is a multicentric disease that has silent gut lesions that also may regress with the systemic approach.

Radiotherapy often produces good therapeutic results with classic nodular KS but tends to be only palliative in patients with KS and AIDS. Electron-beam radiotherapy, which has limited penetration beyond the dermis, may be a good modality for superficial lesions.

Multiagent intravenous chemotherapy, rather than single agent usage, is preferred by some for disseminated aggressive KS. No particular combination regimen has been established yet. The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine may be effective.

Prognosis. Prognosis appears to correlate with the CD4 count. Localized nodular KS has the best prognosis, with few deaths directly attributable to KS. Generalized KS, the form seen most commonly in patients with KS-AIDS, has a 3-year survival rate closer to 0 % without therapy.

LECTURE 19. LYME DISEASE

Lyme disease is a systemic infection caused by the spirochete *Borrelia burgdorferi.* The bacterium is inoculated into the skin by a tick bite. The tick is almost always of the genus *Ixodes.*

Pathogenesis. The pathophysiology of Lyme disease is incompletely understood. While active infection by the spirochete causes many manifestations, others may be caused by immunopathogenic mechanisms. Although any body part can be involved, the organism shows a distinct tropism for the skin, CNS, heart, joints, and eyes.

The bacterium is introduced into the skin with a bite from an infected *Ixodes* tick. Once in the skin, the spirochete can be overwhelmed and eliminated by host defense mechanisms; remain viable and localized in the skin where it produces the pathognomonic skin lesion, or erythema migrans (EM); or disseminate through the lymphatics or blood. Hematogenous dissemination can occur within days to weeks of initial infection; the organism can travel to the skin, heart, joints, CNS, and other parts of the body. The organism can also persist in skin (and possibly in the CNS) for years without causing symptoms. Clinically, organisms have been cultured from skin many years after primary infection. This mechanism may allow the spirochete to elude the normal host defense mechanisms directed against it.

As with syphilis, the disease classically is divided into stages: early localized, early disseminated, and late. However, distinct cutoff points between the stages are frequently unclear.

Early localized Lyme disease refers to isolated EM and patients with an undifferentiated febrile illness. Early disseminated disease refers to the extracutaneous manifestations and secondary skin lesions that occur during the first weeks to months after infection. Late Lyme disease refers to later manifestations (usually in the nervous system and joints) that occur months to years later. Many patients initially have EM; however, in others, neurologic or rheumatologic complaints may be the initial symptoms, either because EM is not present or because it was unrecognized or misdiagnosed.

Clinical picture. Classic EM is an erythematous papule or macule that occurs at the site of the tick bite (1–33 d later; average, 7–10 d). Often, a central punctum is found at the site. The size varies enormously (as large as 70 cm; average, 16 cm) and depends on disease duration. Although lesions are defined, for surveillance purposes, as being greater than 5 cm in size, smaller lesions that are culture positive for *B burgdorferi* have been reported. EM usually is flat, round, or oval and monocyclic. Generally, neither itching nor pain is present. The rash enlarges a few centimeters per day and fades, even if untreated, after a few weeks.

EM rarely is found on the hands and feet (unlike spider and other arthropod bites). Approximately 20 % of patients with EM have secondary lesions. These lesions generally are smaller than the primary one, lack the central punctum, and are not necrotic or vesicular. Borrelial lymphocytoma most frequently is observed in European patients. This finding can be early or late and can follow or occur concurrently with EM. It is a reddish purple nodule on the ear lobe or the nipple (other locations are possible).

Acrodermatitis chronicum atrophicans is nearly exclusively observed in European patients. The two phases are an inflammatory phase with edema and erythema in the distal extremities and a scarring phase with atrophy and skin as thin as cigarette paper. *B burgdorferi* has been cultured from lesions in which the primary infection occurred over 10 years prior.

Neurologic, cardiovascular, musculoskeletal, and ocular signs can be seen. Other signs include splenomegaly, hepatomegaly, regional lymphadenopathy.

Laboratory testing depends entirely on the presenting problem of the patients. The patient with solitary, typical EM requires no laboratory testing whatsoever. Expected results for the CBC and erythrocyte sedimentation rate are likely normal. At this stage of illness, serologic testing is unnecessary because the pretest probability of Lyme disease is high, and the sensitivity of the serologic test is low (during the first several weeks).

Because of the organism's fastidious growth requirements, culture has not been a useful test in the past; however, this situation is improving. Its usefulness depends on the specimen being cultured. Nevertheless, in routine practice, borrelial cultures are often unavailable. In other body fluids (eg, blood, synovial fluid, CSF), the yield is lower.

Serologic testing for Lyme disease is complex. Rational ordering and interpretation of these test results requires some understanding of the basic underlying principles and performance characteristics of the test. Most importantly, the most commonly performed test measures antibodies to various proteins of the spirochete, some of which are very specific for the organism and others of which are nonspecific. The test results do not rule in or rule out Lyme disease; however, the results make a clinical diagnosis of Lyme disease more (or less) likely.

Treatment. Oral antibiotics (eg, amoxicillin, doxycycline, cefuroxime axetil, erythromycin, azithromycin, amoxicillin-clavulanate) should be administered for 10–30 days.

LECTURE 20. VITILIGO

Vitiligo is an acquired pigmentary disorder of the skin and mucous membranes, and it is characterized by circumscribed depigmented macules and patches. It is a progressive disorder in which some or all of the melanocytes in the affected skin are selectively destroyed. Vitiligo affects 0.5–2 % of the world population, and the average age of onset is 20 years.

Pathogenesis. Vitiligo is a multifactorial polygenic disorder with a complex pathogenesis. It is related to both genetic and nongenetic factors. Although several theories have been proposed about the pathogenesis of vitiligo, the precise cause remains unknown. Generally agreed upon principles are an absence of functional melanocytes in vitiligo skin and a loss of histochemically recognized melanocytes, owing to their destruction. However, the destruction is most likely a slow process resulting in a progressive decrease of melanocytes. Theories regarding destruction of melanocytes include autoimmune mechanisms, cytotoxic mechanisms, an intrinsic defect of melanocytes, oxidant-antioxidant mechanisms, and neural mechanisms.

Vitiligo may appear at any time from birth to senescence, although the onset is most commonly observed in persons aged 10–30 years. It rarely is seen in infancy or old age. Nearly all cases of vitiligo are acquired relatively early in

life. The average age of onset is approximately 20 years. The age of onset is unlikely to vary between the sexes.

Clinical pictures. Vitiligo manifests as acquired white or hypopigmented macules or patches. The lesions are usually well demarcated, and they are round, oval, or linear in shape. Lesions enlarge centrifugally over time at an unpredictable rate. Lesions range from millimeters to centimeters in size. Initial lesions occur most frequently on the hands, forearms, feet, and face, favoring a perioral and periocular distribution.

Vitiligo lesions may be localized or generalized, with the latter being more common than the former. Localized vitiligo is restricted to one general area with a segmental or quasidermatomal distribution. Generalized vitiligo implies more than one general area of involvement. In this situation, the macules are usually found on both sides of the trunk, either symmetrically or asymmetrically arrayed. The most common sites of involvement are the face, neck, and scalp.

Involvement of the mucous membranes is frequently observed in the setting of generalized vitiligo. Vitiligo often occurs around body orifices such as the lips, genitals, gingiva, areolas, and nipples. Body hair (leukotrichia) in vitiliginous macules may be depigmented. Vitiligo of the scalp usually appears as a localized patch of white or gray hair, but total depigmentation of all scalp hair may occur. Scalp involvement is the most frequent, followed by involvement of the eyebrows, pubic hair, and axillary hair, respectively. Leukotrichia may indicate a poor prognosis in regard to repigmentation. Spontaneous repigmentation of depigmented hair in vitiligo does not occur.

Trichrome vitiligo has an intermediate zone of hypochromia located between the achromic center and the peripheral unaffected skin. The natural evolution of the hypopigmented areas is progression to full depigmentation. This results in 3 shades of color — brown, tan, and white — in the same patient. Marginal inflammatory vitiligo results in a red, raised border, which is present from the onset of vitiligo (in rare cases) or which may appear several months or years after the initial onset. A mild pruritus may be present. Quadrichrome vitiligo is another variant of vitiligo, which reflects the presence of a fourth color (ie, dark brown) at sites of perifollicular repigmentation. A case of pentachrome vitiligo with 5 shades of color has also been described. Blue vitiligo results in blue coloration of vitiligo macules. This type has been observed in a patient with postinflammatory hyperpigmentation who then developed vitiligo. Koebner phenomenon is defined as the development of vitiligo in sites of specific trauma, such as a cut, burn, or abrasion. Minimum injury is required for Koebner phenomenon to occur.

Clinical classifications of vitiligo

The classification system is important because of the special significance assigned by some authorities to each type of vitiligo. The most widely used

classification of vitiligo is localized, generalized, and universal types and is based on the distribution, as follows:

Localized

- Focal: This type is characterized by one or more macules in one area, most commonly in the distribution of the trigeminal nerve.
- Segmental: This type manifests as one or more macules in a dermatomal or quasidermatomal pattern. It occurs most commonly in children. More than half the patients with segmental vitiligo have patches of white hair or poliosis. This type of vitiligo is not associated with thyroid or other autoimmune disorders.
- Mucosal: Mucous membranes alone are affected.

Generalized

- Acrofacial: Depigmentation occurs on the distal fingers and periorificial areas.
- Vulgaris: This is characterized by scattered patches that are widely distributed.
- Mixed: Acrofacial and vulgaris vitiligo occur in combination, or segmental and acrofacial vitiligo and/or vulgaris involvement are noted in combination.
- Universal: This is complete or nearly complete depigmentation. It is often associated with multiple endocrinopathy syndrome.

Lab. diagnosis. Although the diagnosis of vitiligo generally is made on the basis of clinical findings, biopsy is occasionally helpful for differentiating vitiligo from other hypopigmentary disorders. Vitiligo may be associated with other autoimmune diseases, especially thyroid disease and diabetes mellitus. Other associated autoimmune diseases include pernicious anemia, Addison disease, and alopecia areata. Patients should be made aware of signs and symptoms that suggest the onset of hypothyroidism, diabetes, or other autoimmune disease. If signs or symptoms occur, appropriate tests should be performed.

Treating. Corticosteroids have anti-inflammatory properties and cause profound and varied metabolic effects. In addition, these agents modify the body's immune response to diverse stimuli. These drugs are used to stop spread of vitiligo and accomplish repigmentation. Data supporting the efficacy of such treatment is largely anecdotal. More study is needed to establish the safety and efficacy of systemic agents.

Учебное издание

Козловская Виктория Владимировна

Курс лекций по дерматологии
(на англ. языке)

Учебно-методическое пособие для студентов-медиков

Подписано в печать 19. 12. 2008
Формат 60×84 1/16. Бумага офсетная 65 г/м2. Гарнитура «Таймс»
Усл. печ. л. 9,3. Уч.-изд. л. 10,2. Тираж 100 экз. Заказ № 409

Издатель и полиграфическое исполнение
Учреждение образования
«Гомельский государственный медицинский университет»
246000, г. Гомель, ул. Ланге, 5
ЛИ № 02330/0133072 от 30. 04. 2004