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Basic Dermatology

Handbook for the foreign students

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Contents

I. History-taking

Diagnosis begins with questioning on previous diseases that is medical history taking. Typical questions for history-taking are listed below.

1/ Chief complaint

- What is the main reason for the patient's visit?
- What is the duration of the disease?
- What factors provoke the disease? (stress, infections, drugs, food, allergens or others)
- What is the course of the disease? (relapses and remissions)

2/ Present illness

- What are the patient's feelings (itch, pain, numbness or burning sensation or just a cosmetic defect)
- What is the intensity of pathological sensations?
- Are there systemic symptoms (e.g. high fever, fatigue, joint pain, muscle pain, insomnia)?
- How did the lesion progress? (What factors aggravate the disease? Does it worsen at night?)
- How does the lesion spread? (Is it spreading? Does it occur and disappear rapidly?)

3/ Family history

- Did any family members have similar symptoms? (Check the hereditary and allergic background of the patient)

4/ Past history

- Is there an associated pathology (comorbidity)?
- What was the previous treatment of the disease? (Systemic and topical therapy, their efficacy)

Primary lesions (diagnosis of many of skin diseases is based on the definition of primary morphological lesions).

Macule is a localized change of skin color: "A blind man cannot find a macule". Possible colors and their common causes:
red: hyperemia (erythema), telangiectases (small dilated vessels), leakage of blood (purpura, petechiae, ecchymosis, suggillation),
blue: cyanosis, hematoma (black eye), dermal melanin,
brown: dermal and epidermal melanin, hemosiderin
white: anemia, vasoconstriction, loss of melanin,
yellow: carotenoids, bile, solar elastosis,
grey-black: epidermal melanin, heavy metals, tar. dithranol, foreign bodies.

Petechiae are pinpoint hemorrhagic macules.

Patch a broad more than 1.0 cm, flat lesion

Papule ($\leq$ 5 mm in diameter) is a palpable lesion, caused by increased thickness in epidermis, papillary dermis, or both.

Plaque is an elevated broad lesion more than 1.0 cm in diameter.

Nodule is a dome-shaped solid indurated lesion between 1.0 cm and 2.0 cm in diameter formed by cells, deposits, or elements of connective tissue and and a thicker and deeper than a papule. Nodule is the deepest primary lesion.

Urtica (hive, wheal) is a evanescent pink papule or plaque that often has pseudopods at its periphery and blanches on diascopy whis is caused by localized dermal edema).

Pustule is an elevated, circumscribed collection of pus (neutrophils and necrotic debris of neutrophils). Most of skin pustules are infundibular rather than superficial epidermal, and most of them are idiopathic. A lot of the latter are infectious, e.g., bacterial (staphylococci), fungal (dermatophytes), viral (herpes), and spirochetal (Treponema pallidum). Pustules can be secondarily developed (from vesicles).

Vesicle is a small blister ($\leq$5 mm), filled with clear fluid. A vesicle may be intraepidermal (herpes virus), subepidermal (dermatitis herpetiformis), or both intraepidermal and subepidermal (erythema multiforme, fixed drug eruption). Clinically, it is often impossible to distinguish an intraepidermal vesicle from a subepidermal one.

Bulla ($\geq$5 mm) is filled with clear fluid. The terms vesicle and bulla are subsumed by the word "blister".

Secondary lesions (develop after primary morphological lesions)

Ulcer is a loss of the entire epidermis and at least some of the dermis, sometimes even extending into the subcutis.

Erosion, by contrast, is a superficial injury of the tissue. Results from partial or total loss of the epidermis, but none of the dermis.

Scale is a collection of cornified cells seen clinically as a dry, thin flake which may assume various sizes, shapes, and colors.

Scale-crust is a combination of scale (cornified cells, usually parakeratotic ones) and **crust** (serum that contains blood cells, either red, white, or both)

Scar is a type of fibrosis that represents the end stage of an inflammatory process that early in its course resulted in destruction of preexisting tissue, evolved through granulation tissue, and eventuated in fibroplasia.

Excoriation is a defect extending into dermis, caused by scratching.

Fissure is a linear defect that extends from the surface of the skin into the dermis. Fissures tend to occur over flexural folds, especially on palms and soles affected severely by hyperkeratotic conditions such as psoriasis, congenital keratoderma, hyperkeratotic exzema, hyperkeratotic form of tinea pedis (manum).

Crust is a serum that contains blood cells, either red, white, or both

Lichenification is a thickening of the skin secondary to rubbing forcefully for many months or years. The condition is typified clinically by accentuation of normal skin markings, hyperpigmentation, and induration of variable extent.

Specific terms and conditions on the skin

Atrophy - reduction in amount of tissue is a result of there being fewer cells and/or smaller cells and/or amount of extracellular substances.

Telangiectasia - a condition characterized by abnormal, permanent dilation of venules mainly but also, at times, of capillaries and arterioles.

Sclerosis - clinically, a condition of hardness of the skin (morphea).

Sinus - an epithelium-lined channel in the skin that opens on the surface, usually through an infundibular ostium. In contrast to **a fistula** that is open on both ends a sinus is open at one end only.

Tumor - a dome-shaped solid or cystic lesion more than 2.0 cm in diameter and formed by cells, fluid, deposits, or elements of connective tissue. Tumors in skin are usually neoplasms and, less often, cysts. Rarely they are inflammatory diseases of the skin, exceptions being some lepromas of leprosy and giant dermatofibromas.

Burrow - a tunnel, usually in the cornified layer or spinous zone of the epidermis, fashioned by a parasite.

Comedone - a dilated infundibulum stuffed by cornified cells arranged compactly or in laminated fashion, sebaceous secretion, and microorganisms, bacteria, yeasts, and mites of the normal skin flora. Comedones are nearly invariable in acne vulgaris, where they are characterized clinically by dark casts of dilated infundibula dubbed by the laity "blackheads".

A detailed description of the leions is necessary for an accurate diagnosis.

Number of eruptions: single or multiple.

Eruption shape: round, oval, polygonal, irregular, linear, circinate: arched or rounded border, annular: circular or ring-shaped, discoid, nummular: disk or coin-shaped, serpiginous:winding, twisting (snake-like), iris or cockade (target-like).

Shape of elevation: flat, domed, umbilicated, linear.

Eruption surface: smooth, rough, warty, papillary, granular, lichenoid, dry, moist, scaly, crusted, erosive, ulcerative, atrophic, shiny, necrotic, elevated.

Eruption color: colored, depigmented, hyperpigmented, pale, anemic.

Eruption texture: soft, firm, fragile, tense, elastic, movable.

Eruption distribution: localized, widespread, diffuse, centrifugal, linear (following a line), symmetrical, asymmetrical, grouped, isolated from each other, lines of Blaschko (invisible under normal conditions): following embryologic skin lines *(see fig.2)*, reticular(net-like), grouped, herpetiform (arranged in clusters, grape-like), zosteriform: following a dermatome *(see fig. 3)*, disseminated (randomly distributed).

Eruption progress: rapid or gradual, with or without recurrence.

Eruption border: sharp (well-circumscribed) or vague (blurred).

Some methods of examination of a dermatological patient the doctor can perform by hands with minimal equipment (magnifying glass, dermatological line).

Methods of examination in dermatology

Diascopy

The type of the macule could be diagnosed (inflammatory or pigmented or hemorrhagic).

In diascopy, a site with a skin lesion is pressed with transparent glass to see whether the coloration of the lesion disappears. If it so, the diagnosis is inflammatory macule (erythema). Otherwise, the diagnosis is purpura (hemorrhagic macule) or pigmentation macule (hypo or hyperpigmented). The test is also effective for distinguishing between nevus anemicus and hypopigmented macule. In the case of the latter, the whitish macule remains visible under the

pressure of diascopy. Also this method could be used for producing some specific phenomens like''apple-jelly symptom'' in lupus vulgaris) *(see fig. 1)*.

Inspection and palpation

Physical examinations might be conducted in a bright room. It is preferable to examine the entire body skin and visible mucous membranes. The doctor can find the rashes and terms used to describe the nature and feature of eruptions are listed below.

Scratching

This method is usually used for the diagnosis of the presence of scaling or/and the type of scales and for the detection of specific symptoms of skin diseases (psoriasis- Auspitz sign).

Dermographism

The term dermographism literally means writing on the skin *(see fig. 4, 5, 6)*. Firm stroking of the skin produces an initial red line (capillary dilatation), followed by an axon-reflex flare with broadening erythema (arteriolar dilatation) and the formation of a linear wheal (transudation of fluid/edema) termed the triple response of Lewis. An exaggerated response to this constitutional whealing tendency is seen in approximately 2-5% of the population and is termed urticarial dermographism. In a minority of people, it is accompanied by itching (symptomatic dermographism).

The doctor must point out some particularities of the skin of different races.

Classification of race by the skin

The classification into racial groups allows an examination of the genetic and environmental influences on human morphology and on disease. Little is known about how the races originally differentiated and why they assumed their own characteristics. Classification of races have relied on various physical characteristics such as stature, cephalic index, nasal index, prognathism, capacity of the skull, hair texture, hairiness, skin colour, hair and eye colour, and other special traits such as the epicanthic fold of the eyelid (a Mongoloid feature) or steatopygia (a heavy deposit of fat in the buttocks, seen in Bushmen and Hottentot women) and is follows:

1. Australoid: Australian aborigines, Melanesians, Papuans and Negritos.
2. Capoid: Bushmen and Hottentots.
3. Caucasoids: Europeans, peoples of the Mediterranean, Middle East and most of the Indian subcontinent, and the Ainu of Japan.
4. Mongoloids: peoples of East Asia, Indonesia and Polynesia, native Americans and Eskimos.
5. Negroids: black people and pygmies of Africa.

Some racial features of the skin

Pigmentation

The skin colour depends on the content and distribution of melanin in the epidermis. In Caucasoids it is darkest on the upper thigh and lightest on the lumbar area, whereas in black Africans the abdomen is the darkest. Males are normally darker than females in both races. The geographical distribution of racial pigmentation correlates with the areas of greatest sun exposure, although native Americans (Mongoloids) who lived on the whole continent of North America have a similar pigmentation. There are differences in size, distribution and shape of melanosomes. In Caucasoids, the melanosomes are small and aggregated in groups of three or more within a membrane in the keratinocyte and are broken up by lysosomal enzymes before reaching the stratum corneum. In black Africans and Australoids, the melanosomes are larger, distributed singly within keratinocytes, and persist up to the stratum corneum that is why the minimal erythema dose in black African skin is about 33 times as much as that for Caucasoid. Pigmented skin protects against sunlight and particularly against sunburn and skin cancer, but the disadvantages of a pigmented skin are increased heat absorption and reduced vitamin D synthesis.

Normal hyperpigmentation

Hyperpigmentation of the palms and soles

Discrete, ill-defined or mottled macular pigmentation is frequently seen on the palms and soles of African patients, especially those with a darker skin colour.

Midline hypopigmentation

This appears as a line or band of hypopigmentation, or as discrete oval macules, on the anterior chest and mid- sternal area. Lesions sometimes extend down to the abdomen or up to the neck, where lines of hypopigmentation may radiate out to the clavicles. It is commonly seen in black African males, but may occur in other races.

Mongolian spot (congenital dermal melanocytosis) refers to a slatey brown or blue-grey mac-ular pigmentation observed at birth or in the neonatal period is present in 100% of Mongoloid babies, between 70 and 96% of black Africans, and in up to 10% of Caucasoids and normally located over the sacral area, but the buttocks, flank or shoulders may be involved.

Nail pigmentation

Longitudinal bands of brown or black pigmentation may be seen frequently on the thumb and index fingernails. They are present in more than 50% of black Africans and increase with advancing age.

Oral pigmentation

Oral macular pigmentation is seen in black Africans. It most often affects the gingivae, but may also involve the hard palate, buccal mucosa and tongue.

Variations of normal pigmentation

Futcher's or Voigt's lines are demarcated bilateral lines of pigmentation that are seen at the anterolateral junction usually of the upper arms from extensor to flexor surface. The lines correspond to a dermatome. A second hyperpigmented line may occur on the postero-medial part of the lower aspect of the limbs.

Hair

The morphology and chemical composition of hair is similar in all races but there are four hair types **a straight, wavy, helical and spiral.** In Caucasoids, the hair may be straight, wavy, or helical and round or oval in cross-section but it is the thinnest in diameter of all the races. Mongoloid hair is usually straight, circular in cross-section, and with the largest diameter of all the races. The hair in black Africans and Capoids tends to be short, helical or spiral, flattened or elliptical in cross-section, and midway between the Mongoloid and Caucasoid in thickness. Black African hair tends to be drier and more brittle than the hair of other races. Mongoloids have less body hair than Caucasoids, with black Africans and Capoids occupying an intermediate position.

Specific symptoms in dermatology

Nikolsky's sign

Is a clinical dermatological sign, named after the Russian physician Pyotr Nikolsky (1858–1940). The sign is positive when slight rubbing of the skin results in exfoliation of the outermost layer. Nikolsky's sign is almost always present in: Toxic epidermal necrolysis (TEN), Pemphigus vulgaris, Epidermolysis bullosa Staphylococcal scaled-skin syndrome (SSSS). It is useful in differention between pemphigus vulgaris (where it is present or positive) and bullous pemphigoid (where it is absent).

Asboe-Hansen sign

It is also known as "indirect Nikolsky sign" or "Nikolsky II sign" refers to the extension of a blister to adjacent unblistered skin when pressure is put on the top of the bulla.

Koebner phenomenon

The "isomorphic response" means the appearing of specific skin lesions on the site of skin injury. As a rule lesions have linear distribution. The most common skin disorders with Koebner phenomenon are psoriasis, lichen nitidus, vitiligo, lichen sclerosus, kaposi sarcoma, warts. Warts and molluscum contagiosum lesions can be spread in linear patterns by self-scratching ("auto-inoculation").

Auspitz's sign

It is used in the psoriasis diagnosis. This sign is being performed during scraping with the slide, when scales exfoliate, pointed bleeding is quickly produced.

Wickham net

There are whitish lines visible in the papules of lichen planus, typically the macroscopic appearance of the histologic phenomenon hypergranulosis, and named for Louis Frédéric Wickham.

Dennie–Morgan fold

It is also known as a Dennie–Morgan line or an infraorbital fold, it is a fold or line in the skin below the lower eyelid caused by edema in atopic dermatitis. The presence of Dennie–Morgan folds is used as a diagnostic marker for allergy.

«Apple-jelly» symptom

Diascopic examination of lupomas (tubercules) gives an apple-jelly appearance (yellow-brownish color of grains). This symptom is positive in cutaneous tuberculosis (lupus vulgaris) and in sarcoidosis of the skin (*see fig1)*.

In addition to clinical examination, laboratory testing helps the doctor in the disease diagnosis.

Lab examinations in dermatology

Fungal examinations

Potassium hydroxide (KOH) is used for observation and detection of fungi and mites *(see* fig. 7,8,9). Scales or blister contents are swabbed and applied to a glass slide onto which 20% KOH solution is dripped, and a slide cover is placed on the top. The slide is heated on a hot plate at 70° C to 80° C for 5 -10 minutes. The components of the skin such as the horny cell layers are hydrolyzed, and the fungal components become easily. By similar procedure, parasites such as mites (sarcoptes scabiei - scabies) are observed.

Cytological diagnosis (Tzanck test)

1. Herpes infection diagnosis (herpes simplex, herpes zoster)

It is conducted by apllying a slide glass to the bottom of erosion or the content of a vesicle and staining the adhered cellular components in Giemsa for observation under a light microscope. Ballooning keratinocytes produced by viral infection are observed. They look like multinucleated giant cells ("Tzanck cells") *(see fig.10).*

2. Pemphigus diagnosis

It is conducted by apllying a slide glass to the bottom of a broken blister and staining the adhered cellular components in Giemsa for observation under a light microscope. Acantholytic cells called Tzanck cells are observed in pemphigus. The term "acantolytic cell"refers to an epithelial cell that has undergone dyshesion (i.e

separation from another epithelial cell) by dissolution of intercellular bridges and has consequently become round *(see fig. 11)*.

Wood light examination

A Wood's lamp is a mercury vapor ultraviolet lamp with a filter of barium silicate glass with 9% nickel oxide. The Wood's lamp mainly emits ultraviolet light in the wavelength of 360 nanometers.

Table 1. Wood light examination in different skin disorders

Disease	**Coloration**
Fungal infection	
Tinea capitis associated with Microspora species and favus	Green coloration (*see fig. 12*)
Pityriasis versicolor	Brownish-yellow
Bacterial infection	
Erythrasma	Coral pink (*see fig. 13*)
Pigmentory disorders	
Vitiligo	Bright white

It should be noted that Tricophyton tonsurans and Tricophyton violeceum types of ringworm do not fluorescence.

Dermatoscopy (also known as dermoscopy or epiluminescence microscopy) is the examination of skin lesions with a dermatoscope. This traditionally consists of a magnifier (typically x10), a non-polarized light source, a transparent plate and a liquid medium between the instrument and the skin, and allows inspection of skin lesions unobstructed by skin surface reflections. This instrument is useful to dermatologists in distinguishing benign from malignant (cancerous) lesions, especially in the diagnosis of melanoma (*see fig. 14*).

Ultrasound examination of the skin

During the past 10 years, sonography of the skin has gained increasing importance as a noninvasive imaging method in dermatology. Ultrasound in dermatology is a non-invasive tool for the detection and verification of tumours in skin, subcutaneous tissues and in lymph node basins. Clinical applications are the preoperative determination of the extension of skin tumors, the monitoring of inflammatory lesions, and the objective judgement of patch test reactions. A main drawback of the commercially available scanners, which use transducers with center frequencies of 20–25 MHz, is their limited resolution of about 80 μm axially

and 200 μm laterally. Sonograms of normal skin (*see fig 15.*) show at their upper border a thin, very echorich line, the so-called entry echo. Below, a broad, echorich band with scattered reflexes is seen, which corresponds to the dermis. This is followed by the echolucent subcutaneous fat with its echorich connective tissue septae. The epidermis cannot be visualized, and certainly structures within the epidermis cannot be differentiated.

Indications for ultrasound examination in dermatology: melanoma,basal cell carcinoma, neavi, epidermal cysts, seborrheic keratosis, angiomas, benign tumors and pseudotumors of the nail, connective tissue diseases: scleroderma.

Pathology examination remains the ultimate gold standard for diagnosis of skin tumors. However, it is not conceivable to remove every dry skin lesion. Clinical examination (possibly assisted by dermoscopy) is often sufficient to determine whether a lesion has to be removed. However, ultrasound imaging provides additional information such as depth and lateral delimitation of the lesion, homogeneous or heterogeneous structure, and hypo- or hyperechoic appearance. These elements may of themselves be effective in terms of diagnostic accuracy and they are also valuble in the initial management or surveillance of patients.

An ultrasound examination of superficial tissues may be an adjunct tool for evaluating the progression and/or severity of rheumatic diseases in their primary or secondary manifestations.

Confocal laser scanning microscopy

The confocal laser microscope is a noninvasive tool for imaging skin lesions and subsurface skin lesions that are not visible to the naked eye or even by dermoscopy. Skin can be imaged *in vivo* or freshly biopsied (*in vitro*) skin specimens can be visualized immediately without routine histopathology. Dynamic events (real time imaging) in the epidermis, papillary dermis and superficial reticular dermis to a maximum depth of 350 mm below the stratum corneum can also be visualized. It has potential for diagnosing skin lesions with precision and could also become a tool for monitoring treatments in some cases.

The mechanism of its action is based on the principle that when a diode laser beam is passed through the skin, reflected light is used to construct detailed images of optical sections through the tissue. The laser light is reflected from a dichroic mirror.

Indications in dermatology:

1. Microscopic analysis of skin structures (including hair and nails) and components at different anatomic sites and in different conditions both physiological and pathological.
2. *In vivo* imaging of skin lesions and their margins minimizing the need for skin biopsy.
3. To detect malignant changes in actinic keratoses and other premalignant conditions and to diagnosis of melanoma *in situ*.

4. For diagnosis of dermatophyte infections, to identify fungal hyphae within the stratum corneum after potassium hydroxide application.
5. For *in vivo* noninvasive visualization of mite, *Sarcoptes scabiei.*
6. To monitor treatment for skin disorders
7. To visualize dynamic events at the cellular level in conditions like allergic contact dermatitis, folliculitis etc.
8. *In vivo* imaging of intradermal tattoos for accurate laser treatment.
9. To study the hair abnormalities in trichothiodystrophy.
10. To study Merkel cell carcinoma.
11. To quantify the number of Langerhans cells and other epidermal cell nuclei per volume unit in skin biopsies.

CLS is a rapid, noninvasive technique allowing early diagnosis and management and high resolution images as compared to computer tomographal scaning, MRI and USG for dermatological use. Disadvantages of confocal microscopy include its high cost and relatively smaller field of vision.

Optical coherence tomography

Histology represents the gold standard for morphological investigation of the skin, though biopsy may alter the original morphology, is non-repeatable on the same site and always requires an iatrogenic trauma. In the past decade, advances in optics, have enabled the development of a novel non-invasive optical biomedical imaging technique, optical coherence tomography (OCT). The latter is based on a classic optical measurement method known as low-coherence interferometry that enables non-invasive, high resolution, two- or three-dimensional, cross-sectional imaging of microstructural morphology in biological tissue in situ. Using conventional OCT with a lateral resolution of 10–15 μm, the stratum corneum of palmoplantar skin, the epidermis and the upper dermis can usually be identified, as well as skin appendages and blood vessels. For example, non-invasive monitoring of cutaneous inflammation, hyperkeratotic conditions and photoadaptive processes is possible by means of OCT. Furthermore, the development of high-output broadband light sources potentially allow the differentiation between benign and malignant tissues. Beyond a high resolution morphology in OCT images, tissue characterization by additional local physical parameters, such as the scattering coefficient and refractive index may be of great value, in particular in cosmetics and the pharmaceutical industry. Therefore, the advanced versions of OCT technique might not only lead to significant new insights in skin physiology and pathology, but also in diagnosis and therapeutic control of cutaneous disorders with respect to non-invasive diagnosis of conditions and monitoring of disease activity in addition to treatment effects over time.

Immunofluorescence testing is important for diagnosing immunobullous diseases. connective tissue diseases and vasculitis

Direct immunofluorescence (DIF) involves the overlay of fluorescein-conjugated antibodies (IgG, IgM, IgA), complement (C3), and fibrinogen onto frozen sections of tissue obtained from patients. Biopsy specimens for direct immunofluorescence in immunobullous diseases should be taken from perilesional normal-appearing skin within a few millimeters of the edge of the blister. However when a biopsy specimen is needed for diagnosis of connective tissue disease or vasculitis, a lesional biopsy is optimal (*see fig. 16, 17, 18, 19*)

Table 2. Direct immunofluorescence (DIF) in some inflammatory skin disorders

The skin disease	Deposition	The site of deposition
Pemphigus vulgaris	IgG, C3 complement	Intercellular (around keratinocytes of stratum spinosum)
Bullous pemphigoid	IgG, C3 complement	Linear in the epidermal basement membrane
Herpetiform dermatitis	IgA	Granular deposition on the papillar layer in derma
Lupus erythematosus	IgG, IgM	Linear on the basement membrane and around hair follicules
Vasculitis	IgM, IgG, C3, fibrinogen	Strong dermal blood vessels

Indirect immunofluorescence studies involve the detection of circulating autoantibodies in the patient's serum which target specific antigens in the patient's skin or mucosa. The technique for indirect immunifluorescence is helpful in immunobullous diseases. It includes incubation of patient's serum, which contains the antibodies with frozen sections of epithelial substrate. The substrate is usually a monkey esophagus, but a pig esophagus also may be. The rat bladder is used to rule out paraneoplastic pemphigus. After washing, the fluorescein-labeled animal anti-IgG-conjugate against human immunoglobulin, such as IgG is added. This fluorescein-labeled animal conjugate binds to the patient's circulating IgG, which is already bound to the target antigen on the epithelium surface.

The serology test is also used in dermatology for the detection of antibodies to syphilis and HIV.

Skin biopsy

Biopsy (from the Greek bios meaning 'life' and opsis 'sight') of skin lesions is useful to establish or confirm a clinical diagnosis. A piece of tissue is removed

surgically for histological examination and sometimes for other tests (e.g. culture for organisms).

Indications for biopsy:

- You cannot make a diagnosis;
- The disorder does not respond to treatment;
- The disorder is unusual or severe; or
- You are just not sure.

Biopsy Technique Selection

Six major methods are employed to biopsy skin: curettage, snip or scissors biopsy, shave biopsy, punch biopsy, incision biopsy, and excision *in toto*.

Curettage is frequently used to remove clinically benign epidermal lesions, a curette 3–5 mm in diameter is held like a pencil and drawn with pressure under the lesion (if epidermal) or through the lesion (e.g. presumed BCC).

Snip or scissors biopsy is an efficient technique for assessing pedunculated lesions as well as removing benign growths (e.g. acrochordons, filiform warts).

The **shave biopsy** usually provides a specimen consisting of epidermis, papillary dermis and, sometimes, reticular dermis (particularly in elevated lesions). It is a popular biopsy technique for 'planing' papular, clinically benign lesions (e.g. irritated or unwanted compound and dermal melanocytic nevi, fibrous papules of the nose) where histological confirmation is desired, also a useful procedure for diagnosing superficial carcinomas, lentigo maligna.

The **punch biopsy** supplies a cylindrical - to conically shaped specimen consisting of epidermis, dermis and, sometimes, subcutaneous fat. The volume of tissue sampled correlates with the size of the punch biopsy instrument. In general, the diameter of the metal 'barrel' varies from 2 to 6 mm, and the wider the diameter, the greater the likelihood of obtaining subcutaneous fat.

The **incisional biopsy** removes a wedge of tissue from the center or edge of a lesion and is the best option for obtaining deep subcutaneous fat or fascia for histological examination. It is also used to sample a significant portion of large-sized tumors.

Excision *in toto* removes the entire lesion and includes epidermis, dermis and subcutaneous fat. For these reasons, it is often the biopsy of choice for a presumed invasive cutaneous melanoma

Specimen Handling

Transportation of the biopsy specimen to the laboratory differs according to the processing and type of examination required. Most specimens are placed in 10% formalin, but, occasionally, special carrier media are necessary, e.g. Michel's medium for direct immunofluorescence. Fresh tissue specimens for direct immunofluorescence, immunoperoxidase, culture for bacteria, mycobacteria or fungi are sent on saline-moistened gauze and either promptly delivered to the laboratory or packed in ice; the laboratory must be in reasonable proximity and have the capability of processing the tissue immediately. For culture for viruses viral transport medium is necessary.

Site Preparation and Anesthesia

Marking the site, cleansing the skin, and draping are important procedures prior to the instillation of local anesthesia. Local anesthesia is adequate for all skin biopsies. The agent generally used is lidocaine, either at a 1% or 2% concentration. Epinephrine may be added to the lidocaine in order to reduce bleeding and prolong anesthesia, but it is avoided in patients who have a proclivity for cardiac arrhythmias. Topical agents include eutectic mixture of local anesthetics (e.g. EMLA® with lidocaine and prilocaine), tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lidocaine.

Hemostasis

All methods of biopsy require attention to hemostasis of the wound bed. For small-diameter, superficial wounds, compression alone may be used. Styptics such as aluminum chloride hexahydrate (Drysol™, Xerac AC™) and ferric subsulfate (Monsel's solution) are frequently used. Punch biopsy sites are usually closed primarily and the suturing itself creates sufficient hemostasis. Wounds created during incisional biopsy or excision *in toto* may require electrocoagulation for hemostasis before closure.

Histological terms (glossary)

Abscess is a localized collection of neutrophils. An abscess may form in the epidermis, both surface and infundibular, eccrine ducts, dermis, and subcutaneous fat, or in parts of any other organ and it may come into being by virtue of infection or independent of it.

Acantholysis is a consequence of loss of connections (desmosomes) between epithelial cells, separating from one another, becoming round and eventually dying. The process ends in formation of either a cleft or a blister.

Acanthosis is an increase in thickness of the epidermis consequent to an increase in thickness of the spinous (prickle, malpighiian) zone secondary usually to an increase in number of cells.

Atrophy is a reduction in amount of tissue as a result of there being fewer cells and/or smaller cells and/or amount of extracellular substances. Atrophy can affect the epidermis, the dermis, and the subcutaneous tissue, and the skin and subcutaneous fat together.

Ballooning is an "intracellular edema" of epidermis and epithelial structures of adnexa, recognizable morphologically as swollen pale cytoplasm of affected spinous cells. Rupture of decidedly ballooned keratocytes leads to formation of a pattern of epidermis that resembles a net and, therefore, is termed reticular alteration.

Basement membrane is situated between dermis and epidermis.

Cleft is a space that does not contain fluid. A cleft may appear within the epidermis, below the epidermis, between epithelial cells and adjacent stroma.

Dermoepithelial interface is the junction between dermis and epithelial structures contiguous with it, e.g., epidermis (surface and infundibular) and adnexal (folliculosebaceous-apocrine and eccrine).

Dyskeratosis is an abnormal cornification of individual keratocytes within the epidermis and epithelial structures of adnexa. Dyskeratotic cells have pyknotic nuclei and eosinophilic cytoplasm as visualized by electron microscopy.

Fibrosis is a formation of abnormal fibrous tissue characterized usually by an increase in number of fibrocytes, an increase in amount of collagen, and an aberration in the structure of collagen as it is assessed by conventional microscopy.

Granuloma is a collection of histiocytes, usually epithelioid ones.

Hypergranulosis is an increased thickness of the granular zone of an epidermis, surface and/or infundibular, or of the upper part of an eccrine (or theoretically, an apocrine) duct as a consequence of an increased number of keratocytes whose cytoplasm contains keratohyaline granules.

Hyperkeratosis is a thickened cornified layer of an epithelium, usually an epidermis (surface and infundibular), but sometimes the upper part of an eccrine duct (and, theoretically, an apocrine duct). Hyperkeratosis may be classified as either orthokeratosis, in which no nuclei are visible in cornified cells, or parakeratosis, in which nuclei are retained overtly by cornified cells.

Infiltrate is the presence of elements in tissue in a quantity greater than normal. An infiltrate may be cellular (lymphocytes or neoplastic cells) or noncellular (mucin, colloid). Noncellular infiltrates are referred to as deposits.

Karyolysis is a disappearance of nuclei from cells during the process of cell death. Karyolysis (ghosts of nuclei), karyorrhexis (fragmentation of nuclei), and pyknosis (shrinkage and darkening of nuclei) are the three cardinal signs of necrosis.

Lamina densa is studied by electron microscopy (basal keratocyte, tonofilaments, hemidesmosome, lamina lucida).

Spongiosis is an "intercellular edema" of the epidermis and of epithelial structures of adnexa, expressed morphologically by widened spaces between spinous cells and by intercellular bridges that stretch across those extended spaces in company with inflammatory cells ones.

Vacuolar alteration is a tiny space on either side of a basement membrane situated at the dermoepidermal junction and at the junction of dermis and epithelial structures of adnexa.

Skin tests

The patch test is the most frequent test for detection of specific substance causing allergic inflammation of the skin. A patch test relies on the principle of a type **IV hypersensitivity reaction.**
The general rule for patch testing:

- Complete healing or remission need to be done before patch testing
- Avoid patch testing on markedly tanned persons
- Do not test pregnant women
- The preferred site is the upper back
- Clip hair one or two days before patch testing
- Patients should be informed as to the aim of the test: about avoidance of showers, wetting the test site, irradiation and excessive exercise, and about symptoms such as itch and discomfort.

The standard patch test technique involves application of the test allergen strips to the skin under occlusion for 48 h. Interpretation of results is performed at the third, 4-th days, and at the 7-th day after occlusion (i.e., 1, 2, and 5 days after the removal of the patch test strips).

Table 3. Scoring of patch test reactions

Score	Interpretation
—	Negative reaction
?+	Doubtful reaction; faint erythema only
+	Weak (nonvesicular) reaction; erythema, slight infiltration
++	Strong (edematous or vesicular)

	reaction; erythema, infiltration, vesicles
+++	Extreme (bullous or ulcerative)
IR	Irritant reactions of different types
NT	Not tested

Other skin tests

Stripping test is a variant of patch testing consisting of "stripping" the stratum corneum before applying the allergens in the usual way to suppress the skin barrier.

Open test. Skin allergens are dropped onto the volar forearm and allowed to spread freely. No occlusion is used.

Semi-Open test is a variant of the open test covered by a non-occlusive tape. It is thus "half-way" between open testing and conventional PT.

Repeated open application test. Allergens are applied allergens twice daily for 7 days to the outer aspect of the upper arm, antecubital fossa, or back skin (scapular area). A positive result (eczematous dermatitis) may appear on the 2–4 days but it is recom-ended to extend the applications beyond 7 days so as not to miss late-appearing reactions.

Prick test is a test method for detecting **immunoglobulin E (IgE)-mediated allergy**. Drops of allergen solutions are applied to the volar aspect of the forearm or to the upper part of the back. When drops of allergen solutions are applied to the skin, they are pierced with a special lancet for penetration of allergens into epidermis. No bleeding may occur. Conventional time reading is 15–20 min. Prick testing of allergens needs the concomitant use of controls, positive and negative. Histamine chlorhydrate solution and codeine phosphate solution (9%) is used as positive controls. Saline and/or the vehicle of the allergens is used as a negative control.

Scratch test is a common method for detecting **immediate** allergy. It is still used when only non-standardized allergens are available. A scratch of approximately 5 mm long is made with a blood lancet and bleeding is avoided. The back and arms are the preferred test sites. Scratch testing of allergens needs the concomitant use of controls, positive and negative.

Dermatological treatment

The types of the dermatological treatment are: topical treatment, systemic therapy, physical therapy, surgery and dermatological treatment may be **etiological**

(known etiology of the disease), **pathogenetic** (known pathogenic mechanism of the disease) and **symptomatic** (reduced symptoms).

Topical treatment is the first important step in the management of skin diseases.Efficiency and location of the use of topical preparations depends on the basis of the drug.

Topical vehicles

Ointments

Ointment is semi-solid grease or oil topical vehicle with little or no water. Ointments are occlusive and allow for high transcutaneous penetration of the active drug. Ointments are stable for a long period of time. Ointment is the best therapeutic option in the treatment of thick infiltrates of the skin (plaques), because they can penetrate to the deep layers of the skin. Ointments rehydrate, moisturise, but because of the greasiness they are difficult to wash off.

Powders

Promote drying and are especially useful in the intertriginous areas but in the wet areas powder can form clumps. They are used in subacute process without weeping.

Lotions

Lotion is a liquid vehicle, often aqueous or alcohol-based which may contain a salt solution. Lotions evaporate and cool the skin – useful for inflammed and exudative conditions.

Gels

Gels are transparent semi-solid non greasy emulsion, aqueos preaparations that liquefy on contact with the skin and leave a uniform film on drying. Gels are well-tolerated in hair-bearing regions.

Aerosols

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

Creams

Creams are presented as suspensions of oil in water. As the proportion of oil increases, the preparation approaches the consistency of ointment, which is the most lubricating vehicle. Creams are not greasy and easy to remove. Effects of creams are cooling, vasoconstructive, antiinflammatory. They often used in dry skin lesions. Creams act more superficial comparing with ointments.

Solutions

Cooling, anti-inflammatory, antiseptic effects. The main indication for solutions in dermatology is wet dressings in acute excudative skin surface (eczema, pyoderma).

The vehicle is prescribed according to the stage of the inflammation process. **Acute inflammation** (wepping, bright erythema, edema, erosion) - sprays, wet-drying bandages, solutions.

Acute inflammation without wepping (hyperemia, swelling) - creams, lipocreams, pastes, aerosols.
Subacute inflammation (swelling and hyperemia are soft, mild itching) - creams, lipocreams, pastes, ointments.
Chronic inflammation (lichenification, infiltration) - hot compresses (occlusion), ointment, keratolytic and keratoplastic ointment.
Hyperkeratosis (palms ahd solves) - keratolytic ointment under occlusion.

Steroids in dermatology

The steroids (local and systemic) are often used in dermatology.

Table 4. Classification of topical steroids according to potency

Potency	Steroid	Trade Name
Mild	1% Hydrocortisone acetate	Efcortelan
	0,05% Alcometasone dipropionate	Perderm
Moderate	0.05% Clobetasone butyrate	Eumovate
	0.02% Triamcinolone acetonide	Aristocort
	0.025% Fluocinolone acetonide	Synalar
	0.05% Clobetasone butyrate	Eumovate
Potent	0.025% Beclomethasone dipropionate	Propaderm
	0.05% Betamethasone dipropionate	Diprosone
	0.1% Betamethasone valerate	Betnovate
	0.1% Hydrocortisone 17-Butyrate	Locoid
	0.05% Halometasone monohydrate	Sicorten
Very Potent	0.05% Clobetasol propionate	Dermovate

The USA system utilizes 7 classes, which are classified by their ability to constrict capillaries. Class I is the strongest, or super potent. Class VII is the weakest and mildest.

Group I

Very potent: up to 600 times stronger than hydrocortisone:

- Clobetasol propionate 0.05% (Dermovate)
- Betamethasone dipropionate 0.25% (Diprolene)
- Halobetasol proprionate 0.05% (Ultravate, Halox)
- Diflorasone diacetate 0.05% (Psorcon)

Group II

- Fluocinonide 0.05% (Lidex)
- Halcinonide 0.05% (Halog)
- Amcinonide 0.05% (Cyclocort)
- Desoximetasone 0.25% (Topicort)

Group III

- Triamcinolone acetonide 0.5% (Kenalog, Aristocort cream)
- Mometasone furoate 0.1% (Elocon ointment)
- Fluticasone propionate 0.005% (Cutivate)
- Betamethasone dipropionate 0.05% (Diprosone)

Group IV

- Fluocinolone acetonide 0.01-0.2% (Synalar, Synemol, Fluonid)
- Hydrocortisone valerate 0.2% (Westcort)
- Hydrocortisone butyrate 0.1% (Locoid)
- Flurandrenolide 0.05% (Cordran)
- Triamcinolone acetonide 0.1% (Kenalog, Aristocort A ointment)
- Mometasone furoate 0.1% (Elocon cream, lotion)

Group V

- Triamcinolone acetonide 0.1% (Kenalog, Aristocort,kenacort-a vail, cream, lotion)
- Fluticasone propionate 0.05% (Cutivate cream)
- Desonide 0.05% (Tridesilon, DesOwen ointment)
- Fluocinolone acetonide 0.025% (Synalar, Synemol cream)
- Hydrocortisone valerate 0.2% (Westcort cream)

Group VI

- Alclometasone dipropionate 0.05% (Aclovate cream, ointment)
- Triamcinolone acetonide 0.025% (Aristocort A cream, Kenalog lotion)
- Fluocinolone acetonide 0.01% (Capex shampoo, Dermasmooth)
- Desonide 0.05% (DesOwen cream. lotion)

Group VII

- Hydrocortisone 2.5% (hytone cream, lotion, ointment)
- Hydrocortisone 1% (many over-the-counter brands)

The weakest class of topical steroids has poor lipid permeability, and cannot penetrate mucous membranes well.

Intralesional steroids are used for recalcitrant dermatoses, such as alopecia, keloids, scars, prurigo nodularis and lichen simplex. Triamcinalon is often used, but dermal atrophy and leukoderma may occur.

Steroid topical application may have side effects. Particular care should be taken in facial application, because of high absorptiveness of the skin there.

Skin atrophy

Repeated use of topical steroids in the same area can cause thinning of the epidermis and changes in the connective tissue of the dermis. The skin becomes lax, wrinkled, and shiny with visible telangiectasias, hypopigmentation, and prominence of underlying veins. In most cases the atrophy is reversible once topical steroid use is stopped, but it may take months for the skin to "thicken" back up.

Tachyphylaxis

Tachyphylaxis is the tolerance the skin which develops to the vasoconstrictive action of topical steroids. After repeated use of topical steroids,

the capillaries in the skin do not constrict as well, requiring higher doses or more frequent application of the steroid. The ability of the blood vessels to constrict returns 4 days after stopping therapy.

Steroid rosacea

This is a side effect commonly observed in fair-skinned people who already have rosacea. A typical example occurs when a person uses a very mild steroid on the face to counteract the facial flushing and teleangiectasia. This gives pleasing results, but tolerance develops, causing the person to use a higher strength steroid. At this point any attempt to cut down on the steroid application or stop altogether cause intense facial redness and pustules.

Striae - stretch marks

Repeated use of topical steroids in areas where skin touches skin such as the groin and armpits can result in striae, or stretch marks. Stretch marks from topical steroids are permanent and irreversible. It is recommended to progressively decrease the steroid potency until topical steroids therapy in these areas can be terminated.

Alteration of infection

Because topical steroids change the way the immune system functions, they can inhibit the skin's ability to fight off bacterial or fungal infections. A typical example of this is seen when someone applies a topical steroid to an itchy groin rash. If this is a fungal infection, the rash gets redder, itchier, and spreads more extensively than a typical fungal infection. The resulting rash is a bizarre pattern of widespread inflammation with pustules called tinea incognito.

Topical steroid allergy

Some people may be allergic to a component of the topical steroid base, or vehicle. Patch-testing of a group of patients with dermatitis revealed 4-5% were allergic to topical steroids. People who have chronic skin conditions and use multiple prescription or over-the-counter topical steroids are at higher risk of developing allergies to topical steroids.

Glaucoma

Glaucoma is a disease in which the pressure inside the eye increases to the point of damaging the optic nerve.

As long as the doses of steroids are appropriate, systemic side effects are rare. However, when strong steroids are applied on a large area for a long period or when they are used in occlusive therapy, side effects similar to those caused by steroid systemic administration may be produced (table 4). Moreover special care should be taken in administration of steroids to infants, since side effects tend to be systemic.

Table 5. Side effects of systemic steroids

Severe	Relativly mild
Secondary adrenal dysfunction	Moon face, central obesity
Sideration and exacerbation of diabetes	Hyperphagia

Sideration and exacerbation of hypertension	Leukocytosis
Hyperlipidemia	Skin streaks
Psychiatric effects	Subcutaneous hemorrhage, purpura
Muscular atrophy	Steroid acne
Cataract, glaucoma	Hypertrichosis
Gastric ulcer	Alopecia
Osteoporosis	Edema
Aseptic necrosis of bone	Insomnia
Susceptibility to various infectious conditions	

Antihistamines

There are several types of antihistamine agents that bind to histamine receptors to inhibit their functions. H_1 receptor inhibiting drugs, widely used in dermatological treatment, are extremely effective in the treatment of allergic inflammatory skin disorders. Antihistamines suppress the histamine-induced wheal response (swelling) and flare response (vasodilatation) by blocking the binding of histamine to its receptors on nerves, vascular smooth muscle, glandular cells, endothelium, and mast cells. They exert a competitive antagonism to histamines. Itching and sneezing are suppressed by antihistamine blocking of H1-receptors on nasal sensory nerves.

In common use, the term antihistamine refers only to H_1 antagonists, also known as H_1 antihistamines. Antihistamines are divided into three generations. Sedation is a common side-effect of first generation antihistamines, such as diphenhydramine and doxylamine, which are also used to treat insomnia. However, second-generation antihistamines, such as Loratadine, Cetirizine, Fexofenadine do not cross the blood-brain barrier, and as such do not cause drowsiness and also they have a long serum half-life.

H_3-antagonists have a stimulant and nootropic effect, and are being investigated for the treatment of conditions such as ADHD, Alzheimer's disease, and schizophrenia, whereas H_4-antagonists appear to have an immunomodulatory role and are being investigated as anti-inflammatory and analgesic drugs.

The main indications for H_1 antihistamines in skin are suppression of pruritus in urticaria and atopic eczema, both of which are associated with increased mast cell numbers and tissue histamine levels. However the evidence basis for their use in atopic eczema is ambiguous and controversial, even though these drugs are widely used in practice. Currently, significant side-effects are mainly confined to the first-generation compounds and are especially troublesome in the elderly. Psychomotor impairment may persist throughout the day following administration. Anti-cholinergic and anti-α-adrenergic blockade and cardiotoxicity may also occur with first-generation antihistamines. Two early low-sedation second-generation antihistamines cause arrhythmias in a small number of patients but these

compounds have now been withdrawn (Hismanal (astemiozole). Generally, the second-generation H_1 antihistamines are well tolerated.

Table 6. Systemic antihistamines

First generation (sedative)	
Brompheniramine	Dimotane
Chlorpheniramine	Piriton
Clemastine	Tavegil
Cycloheptadine hydrochloride	Periactin
Diphenhydramine	
Hydroxyzine hydrochloride	Atarax, Ucerax
Promethazine hydrochloride	Phenergan
Promethazine teoclate	Avomine
Trimeprazine	
Second generation (nonsedative)	
Cetirizine hydrochloride	Zirtek (UK) Zyrtec (US) Reactine (Canada)
Fexofenadine hydrochloride	Telfast (UK), Allegra (US and Canada)
Loratadine	Claritin and Claritin Redi Tabs (US), Clarityn (UK)
Desloratidine	Neoclarityn (UK), Clarinex (US)
Levocabastine	Levostin (UK)
Mizolastine	Mistamine (UK), Mizollen (UK)
Acrivastine	Semprex (UK)
Levocetirizine dihydrochloride	Xyzal (UK)

Side effects of antihistamines

The frequency and severity of adverse effects will vary between drugs. Not all adverse reactions will apply to every member of this class.

Table 7. Side effects of antihistamines

Central nervous system reactions	**Gastrointestinal problems**	**Hematologic reactions** (rare, but may be severe)	**Some of the other adverse effects**
headache insomnia	increased appetite	anemia	chest tightness
drowsiness weakness	decreased appetite	leukopenia	wheezing
sedation	nausea	bone marrow failure	nasal stuffiness
dizziness	vomiting		dry mouth, nose and throat
excitation	diarrhea,		sore throat
tremor	constipation		respiratory depression
seizures			
disturbed			

coordination			
restlessness			

When taking antihistamines during pregnancy: chlorpheniramine (Chlor-Trimeton), dexchlorpheniramine (Polaramine), diphenhydramine (Benadryl), brompheniramine (Dimetapp), cetirizine (Zyrtec), cyproheptadine (Periactin), clemastine (Tavist), azatadine (Optimine), loratadine (Claritin) are all listed as category B. Azelastine (Astelin), hydroxyzine (Atarax), promethazine (Phenergan) are category C.

Regardless of chemical class of the drug, it is recommended that mothers not breast feed while taking antihistamines.

Contraindications

The following are absolute or relative contraindications to use of antihistamines. The significance of the contraindication will vary with the drug and dose: glaucoma, hyperthyroidism (overactive thyroid), high blood pressure, enlarged prostate, heart disease, ulcers or other stomach problems, stomach or intestinal blockage,liver disease, kidney disease, bladder obstruction, diabetes.

Topical antihistamines

Topical antihistamines are produced in creams, nasal sprays and other agents that can be applied locally. **Fenistil gel** is often used in the treatment of allergic skin diseases.

Retinoids

The **retinoids** are a class of chemical compounds that are related chemically to vitamin A. Retinoids include naturally occurring molecules and synthetic compounds that have specific biologic activities that resemble those of vitamin A or bind to the nuclear receptors for retinoids.

There are three generations of retinoids:

- **First generation retinoids:** which include retinol, retinal, tretinoin (retinoic acid, Retin-A), isotretinoin (Roaccutan, Accutan), and alitretinoin.
- **Second generation retinoids**: which include etretinate and its metabolite acitretin (Neotigason).
- **Third generation retinoids:** which include bexarotene, tazarotene, and adapalene.

The biological functions and actions of retinoids:

1. Reproduction, embryonic growth, and morphogenesis.
2. Modulation of proliferation and differentiation of epithelium.
3. Decrease in sebaceous gland size (isotretinoin).
4. Immunological and anti-inflammatory effects.
5. Tumor prevention and treatment.
6. Effect on extracellular matrix components.

Systemic treatment with acitretin is effective in several disorders of keratinization. Darier's disease, ichtyosis vulgaris, congenital ichtyosis (particularly dry lamellar type), various types of palmaplantar keratoderma, and also erythrokeratodermia figurate variabilis today represent standard indications for oral acitretin treatment. Treatment of topical retinoids is an effective alternative in mild forms of these diseases and especially in Darier's disease.

Oral acitretin belongs nowdays to the mainstream systemic antipsoriatic treatment, particularly in severe pustular and erythrodermic types of the disease. It acts on a pathological epidermis to reduce proliferation and stimulate differentiation. Acitretin is usually prescribed in combination with other modalities (mild corticosteroids, dithranol, tar, vitamin D derivates) and/or with phototherapy (Re-PUVA). Palmoplantar pustulosis, psoriasis of nails, HIV-associated psoriasis significantly improve under systemic acitretin. In pityriasis rubra pilaris, a beneficial effect can be expected, especially in juvenile type of the disease.

Oral isotretinoin is only one drug currently available that affects all four pathogenic factors of acne, directly suppressing abnormal desquamation of sebaceous follicle epithelium and sebum production. The basic patterns of use of retinoids are described in table 7.

Table 8. Retinoids in Dermatology

Retinoids	Skin disorder	Clinical forms	Recommended dose
Isotretinoin	**Acne**	Nodulocystic Severe scaring Severe acne-associated psychological distress	0.5 – 1.0 mg/kg/day p o.
Isotretinoin	**Rosacea**	Nodulocystic Papulo-pustular	10-20 mg/day
Acitretin **Etretinate**	**Psoriasis**	Palmo-plantar pustular Pustular generalizied Erythrodermic Psoriasis of nails	25-30 mg/day. Maintenance dose: 25-50mg/day may be given after initial response to treatment (12-16 weeks).
Acitretin	**Lichen planus**	Oral and skin forms	10-30 mg/day
Etretinate	**Cutaneous T-cell lymphoma**	Sezary syndrome with no organ involvement	0.2-0.5 mg/kg\day
Bexaroten		Early IA, IB, IIA stages	300 mg/m2 day p.o.
Alitretinoin	**Sarcoma Kaposi**		45 mg/m2 per day
	Epithelium tumor		
Acitretin	**Ichtyiosis**	Lamellar ichtyiosis X-linked ichtyiosis Epidermolytic ichtyiosis Ichtyosis vulgaris	10-20 mg/day

Acitretin **Isotretinoin**	**Darier Disease**		0,5-1.0 mg/kg/day
Etretinate	**Pityriasis rubra pilaris**		10-30 mg/day
Acitretin **Etretinate**	**Lichen sclerosus and atrophicus**	Genitalia region localization	20-30 mg/day
Alitretinoin	**Chronic hand eczema** **Seborrhea**		10-30 mg/day

Topical retinoids alone or in combination today are the first line treatment of moderate and mild forms of acne. Tretinoin, adapalen, isotretinoin, tazaroten are effective comedolytic agents.

Topical tretinoin is effective in actinic keratosis, plane warts.

Isotretinoin and tazaroten were found to improve photoaging skin changes. Epidermal melasma, actinic lentigines, superficial postinflammatory hyperpigmentation also respond to topical tretinoin, either alone or in combination with hydroquinone and hydrocortisone.

Table 9. Topical retinoids

Substance	Concentration, basis	Indications
Adapalen (Differin)	0.1 % gel, solution. cream	Mild/moderate acne
Alitretinoin (Panretin)	0.1 % gel	AIDS-related Kaposi`s sarcoma
Bexaroten (Targetin)	0.1 % gel	Cutaneous T-cell lymphoma
Isotretinoin (Isotrex)	0.05% gel, 0,05, 0,1 % cream	Mild/moderate acne Photoaging
Tazaroten (Zorac, Tazorac)	0.005, 0,1 % gel	Psoriasis, mild/moderate acne
Tretinoin (Airol, Retin A)	0.025, 0.01,0.05. 0.1, 0.4% cream 0.025 % gel, 0.05%, 0.1, 0.2 solution 0,1% ointment	Mild/moderate acne Photoaging Cosmetic indications
Tretinoin	0.025% cream	Inflammatory rosacea

Side effects of retinoids

- Teratogenicity
- Cheilitis, xerosis, skin peeling, pruritus, conjunctivitis are common.
- Reversible abnormal results on laboratory tests: hyperlipidemia increased liver enzyme levels, and hypothyroidism (bexaroten).
- Blood and lymphatic system: anemia, increased red blood cell sedimentation rate, thrombocytosis, neutropenia.

- Depression, anxiety (rare)
- Sun sensitivity
- Musculoskeletal and nervous system side effects are rare.
- Headache (rare)
- Gram positive infections (mucocutaneous), bacterial infection (very rare).

Contrainidications: pregnancy, breast-feeding.

Pregnancy is recommended to be excluded in female patients two weeks prior to commencement of Isotretinoin, and patients should use two simultaneous forms of effective contraception at least one month prior to commencement, during, and for at least one month following isotretinoin therapy. Women of childbearing age should either abstain from sexual intercourse or use 2 effective methods of birth control for at least 1 month before, while taking, and for 3 years after taking Acitretin.

Immunosuppresive drugs

Methotrexate (MTX) is an antimetabolite and antifolate drug. MTX competitively inhibits dihydrofolate reductase (DHFR), which converts dihydrofolate to tetrahydrofolate, which is a necessary cofactor in the synthesis of thymidylate and purine nucleotides, which are required for DNA/RNA synthesis; increases local tissue concentrations of the potent anti-inflammatory mediator adenosine (by inhibiting aminoimidocarboxyamido-ribonucleotide transformylase); reduces production of the proinflammatory mediator S-adenyl methionine (by inhibiting methionine synthase). MTX also exerts partially reversible inhibition of thymidylate synthetase, inhibiting cell division in the S phase.

Indications

MTX is use for severe, debilitating or recalcitrant **psoriasis,** pityriasis rubra pilaris (PRP), pityriasis lichenoides et varioliformis acuta (PLEVA), lymphomatoid papulosis, Reiter's disease, dermatomyositis and sarcoidosis, certain types of vasculitic, neutrophilic and immunobullous dermatoses, in particular **bullous pemphigoid**.

Dosages

MTX is administered as a once-weekly dose of up to 30 mg (individually for each disease) in three doses over 24 hours (8 a.m. and 8 p.m. day 1, and 8 a.m. day 2). Once disease control has been attained for at least 1-2 months, the MTX can be tapered by 2.5 mg every 1-2 weeks to the lowest dose that still maintains disease control. Intramuscular, subcutaneous administration is available.

Contraindications

Absolute contraindications to MTX use are pregnancy and lactation. Relative contraindications include significant liver disease or elevated liver

enzymes and excessive alcohol intake. The presence of active infection or immunodeficiency, and the desire for imminent pregnancy are relative contraindications to MTX therapy. In the elderly, serum creatinine levels may be deceptively low and may not reflect true renal function.

Side effects

The most important side effects of MTX include pancytopenia (typically develops early) and hepatotoxicity (the higher the cumulative dose of MTX, the greater the risk of significant liver damage). Compounding risk factors for hepatic impairment include: previous or current excessive alcohol intake, persistent abnormal liver chemistries, a history of liver disease (including hepatitis B and C viral infections), family history of inheritable liver disease, diabetes mellitus. obesity, and a history of significant exposure to hepatotoxic drugs or chemicals. Photosensitivity and gastrointestinal intolerance may occur. MTX may cause reversible oligospermia in very high doses.

Azathioprine (Imuran, Azasan) is a parent's of drug 6-mercaptopurine (6-MP) and is moderately potent anti-inflammatory and immunosuppressive effects. It should be reserved for more serious, life-threatening or recalcitrant dermatoses after other therapies have failed.

Mechanism of Action

The active metabolite of azathioprine (6-Thioguanine) is a purine analogue similar in structure to both adenine and guanine. Incorporation of 6-thioguanine into DNA and RNA inhibits purine metabolism and cell division. 6-Thioguanine has other activities which are not well understood, such as **suppression of T-cell function and B-cell antibody production**. It also decreases the number of Langerhans cells in the skin and inhibits their ability to present antigens.

Indications

Azathioprine is most often used as a corticosteroid-sparing agent in the treatment of immunobullous diseases such as **pemphigus vulgaris, bullous pemphigoid** and cicatricial pemphigoid, **cutaneous vasculitis**, severe, recalcitrant **atopic dermatitis** and chronic actinic dermatitis in adults, connective tissue diseases such as **SLE** and **dermatomyositis**, it may improve the cutaneous manifestations as well. There may be a delay of 4-6 weeks in the onset of full clinical benefits.

Dosages

Available in 25, 50, 75 and 100 mg tablets, empiric dosing is generally started at 50 mg/day and increased to a maximum of 2.5 mg/kg/day according to clinical efficacy and careful monitoring.

Contraindications

Absolute contraindications to azathioprine therapy include the history of a hypersensitivity reaction. Active serious infection and pregnancy are relative contraindications.

Side Effects

Major side effects are related to the immunosuppressive effects of azathioprine: Pancytopenia, increased risk for malignancies, especially lymphoproliferative disorders and squamous cell carcinomas of the skin and female genitourinary tract, life-threatening hypersensitivity reaction, which most commonly develops during the first month of therapy and when the drug is used in combination with cyclosporine or methotrexate.

Cyclosporine is a cyclic peptide of 11 amino acids, and has clinical immunosuppressive effects. Two forms are available, the original preparation (Sandimmune) and a predigested microemulsion (Neoral) that is more completely and consistently absorbed.

Mechanism of Action

Cyclosporine binds to cyclophilin, a member of the family of intracytoplasmic proteins called immunophilins. This complex blocks the dephosphorylation of $NFAT_c$ and the subsequent upregulation of IL-2 and IL-2 receptors, resulting in a decrease in the number of $CD4^+$ and $CD8^+$ (cytotoxic) T cells in the epidermis.

Dosages

Cyclosporine is best used on a short-term basis (<6-12 months) to control flares of psoriasis and to provide an alternative to the patient's current regimen. It is reasonable to use cyclosporine as sequential therapy with acitretin, methotrexate or other systemic therapies. After psoriasis clearance has been initiated by cyclosporine, the alternative medicine may be started and advanced to the therapeutic dose. At the same time, cyclosporine may be weaned by 1 mg/kg/day each month until the patient is receiving acitretin or methotrexate alone. Historically, the maximum dermatologic dose for cyclosporine is 5 mg/kg/day.

Indications

Cyclosporine can be beneficial for patients with psoriasis who have failed or cannot tolerate other therapies and for those with widespread, atopic dermatitis, severe pyoderma gangrenosum,

Contraindications

Absolute contraindications: significant renal impairment, uncontrolled hypertension, and hypersensitivity to cyclosporine. Relative contraindications: age

<18 years or >64 years, controlled hypertension, and medication usage that may interfere with cyclosporine metabolism or worsen renal function.

Side Effects

Cyclosporine is associated with a wide variety of adverse effects, including hypertension, hepatotoxicity, myositis, hyperlipidemia, hypertrichosis, gingival hyperplasia and renal failure. Patients with skin diseases on cyclosporine for less than 2 years and on lower 'dermatologic' doses have not been observed to have a similar risk.

Biologicals

Biologicals are novel compounds composed of antibodies or other peptides that act through one of three mechanisms: inhibiting inflammatory cytokine signaling (typically tumor necrosis factor or TNF), inhibiting interleukins, T-cell activation, or depleting B-cells. They are being used more frequently to treat a multitude of systemic inflammatory conditions. In the past ten years, biologic drugs have emerged as an important advance in the treatment of inflammatory disease such as rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease and ulcerative colitis.

Classification

Biologics are divided into three groups:

1. **Recombinant human cytokines and growth factors** (Interferon α (IFNα), Interferon γ (IFNγ), Interleukin 1 Receptor antagonist (IL1Ra), Interleukin 2 (IL-2), Interleukin 4 (rhIL-4), Interleukin 10 (rhIL-10), Interleukin 11 (rhIL-11), Granulocyte macrophage colony stimulating factor (GM-CSF), Platelet derived growth factor (PDGF).

2. **Monoclonal antibodies**
   - Anti-TNFα: Infliximab, Adalimumab, Certolizumab, Golimumab
   - Anti-LFA1: Efalizumab
   - Anti-CD20: Rituximab
   - Anti-IL-12 and anti-IL-23 monoclonal antibody: Ustekinumab
   - Anti-CD2 antibody: Siplizumab
   - Anti-CD4 antibody: Orthoclone (OKTcdr4a)
   - Anti-CD25 antibodies: Basiliximab, Daclizumab
   - Anti-CD80r: Galiximab (IDEC 114)
   - Anti-IgE: Omalizumab

3. **Fusion antibody proteins** (Fusion proteins, also known as chimeric proteins)

- Etanercept
- Alefacept
- Abatacept

Infliximab (a chimeric monoclonal anti-TNF antibody) **(Remicade®), adalimumab** (a fully human anti-TNF monoclonal antibody) **(Humira®),** and **etanercept** (a recombinant soluble decoy TNF-receptor) **(Enbrel®)** exert therapeutic effects via the suppression of TNF-α, a cytokine released by macrophages that is central to cell-mediated immunity.

Ustekinumab (Stelara®), is a fully human monoclonal antibody that binds with high specificity and affinity to the cytokines interleukin (IL)-12 and IL-23, thereby suppressing IL-12- and IL-23-mediated inflammation associated with psoriasis.

Indications for the biological treatment: autoimmune disorders.

Psoriasis: Unresponsive cases to **standard therapy** or significant, coexistant, unrelated comorbidity which precludes the use of systemic agents such as cyclosporine or methotrexate.

- in **psoriatic arthritis**
- severe, unstable, life-threatening clinical form of psoriasis: **erythrodermic or pustular psoriasis**

Standard therapy for psoriasis treatment could be, for example proposed by the British Association of Dermatology guidelines the following:

- Acitretin 25 to 50 mg daily or;
- Cyclosporine 2.5 to 5 mg per kg daily or;
- Methotrexate single weekly dose (oral, subcutaneous, intramuscular) 15 mg, max 25 to 30 mg or;
- Narrow band UVB or psoralen photochemotherapy (non-response, rapid relapse, or exceeding recommended maximum doses) 150 to 200 treatments for PUVA, 350 treatments for narrowband UVB.

Other Autoimmune skin disorders: pemphigus vulgaris, lichen planus.

Side effects:

1. **Risk of malignancy:** TNF-alpha inhibitors are associated with some degree of risk for lymphoma, breast cancer, colorectal cancer, melanoma, leukemia, and head and neck cancers in smokers. Alefacept is associated with solid organ malignancies, lymphomas, and melanomas. Ustekinumab is associated with breast, colon, head and neck, kidney, prostate, and thyroid cancers.

2. **The infectious complications** associated with immune modulation are even more important. Of particular concern is the risk for developing atypical and opportunistic infections including tuberculosis, herpes zoster, Legionella pneumophila, and Listeria monocytogenes.

Miscellaneous

Dapsone is a sulfone drug, and sulfones are related to the sulfonamide family. Dapsone is effective against tuberculosis and leprosy. Since 1953, dapsone (the parent compound of sulfoxone) has been the mainstay of treatment for dermatitis herpetiformis. Dapsone has also proven useful in the treatment of several forms of autoimmune bullous diseases and vasculitis syndromes.

Mechanism of Action

Dapsone inhibits neutrophil myeloperoxidase, thus reducing damage from the neutrophil respiratory burst mediated by this enzyme. Furthermore, dapsone has been shown to inhibit neutrophil chemotaxis to *N*-formyl-methionyl-leucyl-phenylalanine and to interfere with the CD11b/CD18-mediated neutrophil binding that induces chemoattractant signal transduction. IgA adherence is also inhibited. It is of clinical interest that dapsone also inhibits eosinophil myeloperoxidase activity.

Indications

Dapsone is very useful in diseases such as **HD (herpetiform dermitatis),** linear IgA bullous dermatosis, bullous eruption of SLE and erythema elevatum diutinum, other autoimmune bullous diseases **(e.g. pemphigus foliaceus, bullous pemphigoid) and selected vasculitic syndromes.**

Dosages

Dapsone is available in 25, 50 and 100 mg tablets. The initial dose is often 50 mg/day in a single dose. Most conditions require 50-200 mg/day for adequate control of symptoms; rarely are dosages up to 300 mg/day required.

Contraindications

The absolute contraindication to dapsone therapy is prior hypersensitivity to dapsone. Relative contraindications include a low glucose-6-phosphate dehydrogenase (G6PD) level, significant cardiopulmonary disease, and an allergy to sulfonamide antibiotics (because of the possibility of cross-reactivity).

Side Effects

Serious systemic side effects of dapsone are ethemoglobinemia and hemolytic anemia, agranulocytosis, peripheral neuropathy and dapsone hypersensitivity.

Antimalarials

The most common antimalarials are **hydroxychloroquine (Plaquenil®), chloroquine (Aralen®)**

Mechanism of Action

The mechanism of action of the antimalarials is not well known (can inhibit interleukin-2 (IL-2) release from T-helper ($CD4^+$) cells and may inhibit macrophage expression of major histocompatibility complex (MHC) antigens) and so exert various anti-inflammatory effects and they decrease platelet aggregation.

Indication

The antimalarials is a second-line therapy for cutaneous LE, after topical or intralesional corticosteroids. Antimalarials are especially useful in patients with widespread discoid lesions and in those with the annular or papulosquamous lesions of subacute cutaneous LE (SCLE). Other diseases are: polymorphous light eruption, sarcoidosis, lichen planus

Dosages

Most conditions will respond to dosages between 200 and 400 mg per day of hydroxychloroquine or 250 mg per day of chloroquine.

Contraindications

The only true contraindication is hypersensitivity to the drug. Caution should be used in patients with severe blood dyscrasias or hepatic disorders, because hepatitis and bone marrow suppression can occasionally occur.

Side Effects of antimalarials are reversible (early) pancytopenia, hemolysis, irreversible retinopathy, vision changes.

Antifungal agents

Topical antifungal agents

There is a wide variety of topical antifungal agents but there is no truly effective topical agent for onychomycosis, although nail varnishes are now available. The spectrum of action of topical antifungal agents reflex in the table 9.

Table 10. Topical antifungal agents and their spectrum of action

Agent	Spectrum		
	Dermatophytes	Yeasts	Molds
Polyenes			
- Amphotericin B		+	
- Nystatin		+	

- Natamycin	+	+	+
Imidazoles (more than 20)	+	+	+
Allylamines			
- Naftifine	+		
- Terbinafine	+		
Hydroxypyridones			
- Ciclopirox	+	+	+
Morpholines			
- Amorolfin	+		
Benzylamine			
- Butenafine	+		
Others			
- Tolnaftate	+		
- Clioquinol	+		
- Undecylenic acid	+		
- Iodoquinol			

Ciclopirox 8% and **Amorolfin (LOCERYL®)** nail lacquer are used for treatment of onychomycosis.

Other topical agents with antifungal action are selenium sulfide, sodium thiosulfate, salicylic acid and sulfur, zinc pyrithione, haloprogin, mafenide, propylene glycol and benzoyl peroxide.

Systemic antifungal agents

The prescribtion of systemic antifungals depends on their spectrum of action (table 10)

Table 11. Systemic antifungals and their spectrum of action

Agent	Spectrum		
	Dermatophytes	Yeasts	Molds
Griseofulvin	+++	—	—
Terbinafine	+++	++	—
Intraconasol	+++	+++	+++
Ketaconasol	++	+	—
Fluconasol	++	+++	—

Griseofulvin is produced by culture of some strains of the mold Penicillium griseofulvum.

Mechanism of action: The drug binds to tubulin, interfering with microtubule function, thus inhibiting mitosis. The **micronized** forms are better absorbed and distributed.

Indications: Dermatophyte infections; griseofulvinis is not effective against yeasts and molds. Organism should be cultured before starting therapy.

Dosage:Griseofulvinis is still the only agent approved for **tinea capitis** in children; it
has been replaced in most of its other uses by the more effective imidazoles. Children10 mg/kg daily; adults 500- 100 mg p. o. daily.

Contraindications: Liver disease, porphyria, LE, pregnancy.

Side effects: Hepatic toxicity, gastrointestinal bleeding, leukopenia, granulocytopenia, exanthems, urticaria, photosensitivity. May trigger acute intermittent porphyria or systemic lupus erythematosus.

Itraconazole is a triazole antifungal drug.

Mechanism of action: Inhibits cytochrome P450-dependent synthesis of ergosterol, a key component of fungal cell walls. Because of its ability to inhibit cytochrome P450, caution should be used when considering interactions with other medications

Indications: Effective against dermatophytes, molds, and many yeasts. Excellent against Candida albicans and Candida krusei; moderately effective against other Candida species, cutaneous mycoses, including onychomycoses, mycoses in HIV/AIDS, mucocutaneous and systemic candidiasis, recurrent vaginal candidiasis, aspergillosis, soft tissue mycoticinfections.

Dosage. The is available as 100 mg capsules and a 10 mg/ml cherry-caramel-flavored solution. Pediatric dosing is 3 to 5 mg/kg daily. Adult oral dosages for various indications are: for onychomycosis of toenails - 200 mg po qd for 12 weeks or 200 mg po bid for 1 week, then 3 weeks without treatment, repeated twice more for a total of three **pulses** of therapy, tinea pedis - 100 mg po qd for 2 weeks or 200 mg po qd for 1 week, tinea corporis, tinea cruris - 100 mg po qd for 2 weeks or 200 mg po qd for 1 week

Contraindications: Pregnancy; contraception until 4 weeks after the end of therapy.

Side effects: nausea, abdominal pain, anorexia, vomiting, constipation, increase in liver transaminases, hepatitis, headache, dizziness, peripheral neuropathy, fatigue,

drowsiness, hypertension, chronic heart failure,dysmenorrhea, albuminuria, itching, urticaria.

Fluconazole is a triazole antifungal drug

Mechanism of action: Inhibits cytochrome P450-dependent synthesis of ergosterol, a key component of fungal cell walls.

Indications: Effective against dermatophytes and yeasts; not molds. Effectiveness reduced against Trichophyton mentagrophytes, Candida glabrata, and Candida guil liermondii. Useful for candidiasis in almost all settings from acute vaginal to HIV/AIDS to chronic mucocutaneous candidiasis, dermatophyte infections, including onychomycoses.

Dosage: Vaginal candidiasis: Single dose of 150 mg

Contraindications: Severe liver disease, pregnancy and nursing; contraception until 7days after completing therapy.

Side effects: Seizures, leukopenia, thrombocytopenia. Hepatic injury: monitor liver enzymes. Toxic epidermal necrolysis: be very cautious about continuing in patients developing an exanthema.

Ketoconazoles is structurally similar to imidazole, and interferes with the fungal synthesis of ergosterol, a constituent of fungal cell membranes

Indications: Ketoconazole inhibits growth of dermatophytes and yeast species such as Candida albicans.

Dosage: Adults with skin infections are prescribed an oral dose of 200 mg / day once.

Contraindications: hypersensitivity to ketoconazole, liver diseases, pregnancy and lactation.

Side effects: nausea, headache, dizziness, photophobia, paresthesia, thrombocytopenia, rash, itching, rarely - alopecia, urticaria, rash and other symptoms of allergic reactions, in rare cases, gynecomastia and reversible oligospermia, decrease in testosterone levels in the blood plasma, very rarely hepatitis develops.

Terbinafine is a synthetic **allylamine** antifungal .

Mechanism of action: Inhibits sterol biosynthesis by blocking squalene perox-

idase causing accumulation of squalene and cell death.

Indications: Primarily dermatophytes.

Dosage: Cutaneous disease 250mg daily p.o. for 2–4 weeks; onychomycosis 250 mg daily p.o. for 6–12 weeks or interval therapy. In tinea capitis in children: children over 2 years old and under 20 kg – 62, 5 mg q.d, children over 2 years old and 20 40 kg – 125 mg q.d, children over 2 years old and under 40 kg – 250 mg q.d

Contraindications: Renal or hepatic disease.

Side effects: No common serious side effects; elevated liver enzymes, disturbed taste; rarely toxic epidermal necrolysis.

The new antifumgal agents are echinocandins (caspofungin, micafungin, and anidulafungin) and azoles II generation such as voriconazole and fluconazole (ravukonazol is a fluconazole derivated), and posaconazole and albakonazol – are itraconazole derived used for treatment of systemic candidasis.

Table 12. Antifungals for systemic use

Drug	Mechanism of action	Indications:	Dosage:	Side effects
Terbinafine	Inhibits sterol biosynthesis by blocking squalene peroxidase causing accumulation of squalene and cell death	Primarily dermatophytes (Tinea corporis, Tinea capitis, Tinea pedis, Tinea unqum)	**Cutaneous disease** 250mg daily p.o. for 2–4 weeks; **onychomycosis** 250 mg daily p o. for 6–12 weeks or interval therapy. **In tinea capitis** in children: **children over 2 years old and under 20 kg** – 62, 5 mg q.d, **children over 2 years old and 20 40 kg** – 125 mg q.d, **children over 2 years old and under 40 kg** – 250 mg q.d	No common serious side effects; elevated liver enzymes, disturbed taste, rarely toxic epidermal necrolysis
Griseofulvin	The drug binds to tubulin, interfering with microtubule func-tion, thus inhibi-ting	Dermatophyte infections (TINEA CAPITIS). Griseofulvin is	**Children:** 10 mg/kg daily; **Adults:** 500–100 mg p. o. daily.	Hepatic toxicity, gastrointestinal bleeding, leukopenia, granulocytopenia, exanthems, urticaria,

	mitosis. The **micronized** forms are better absorbed and distrib-uted	not effective against yeasts and molds.		photosensitivity. May trigger acute intermittent porphyria or systemic lupus erythematosus
Itraconazole	Inhibits cytochrome P450-dependent synthesis of ergosterol, a key component of fungal cell walls. Because of its ability to inhibit cytochrome P450, caution should be used when considering interactions with other medications	All tinea disorders	**Pediatric dosing** is 3 to 5 mg/kg daily **Adult oral dosages:** **for onychomycosis of toenails** - 200 mg po qd for 12 weeks or 200 mg po bid for 1 week, then 3 weeks without treatment, repeated twice more for a total of three **pulses** of therapy; **tinea pedis** - 100 mg po qd for 2 weeks or 200 mg po qd for 1 week; **tinea corporis, tinea cruris:** 100 mg po qd for 2 weeks or 200 mg po qd for 1 week	nausea, abdominal pain, anorexia, vomiting, constipation, increase in liver transaminases, hepatitis, headache, dizziness, peripheral neuropathy, fatigue, drowsiness, hypertension, chronic heart failure, dysmenorrhea, albuminuria, itching, urticaria.
Fluconazole	Inhibits cytochrome P450-dependent synthesis of ergosterol, a key compo-nent of fungal cell walls.	Candidiasis dermatophyte infections, including onychomycoses.	Vaginal candidiasis: Single dose of **150 mg**	Seizures, leukopenia, thrombocytopenia. Hepatic injury: monitor liver enzymes. Toxic epidermal necrolysis: be very cautious about continuing in patients developing an exanthema
Ketoconazole	Structurally similar to imidazole, and interferes with the fungal synthesis of ergosterol, a constituent of fungal cell membranes	Dermotophyte (tinea cruris, tinea corporis, tinea pedis) and Candida albicans infection	Adults with skin infections are prescribed an oral dose of **200 mg/day** once.	nausea, headache, dizziness, photophobia, paresthesia, thrombocytopenia, rash. itching, rarely - alopecia, urticaria, rash and other symptoms of allergic reactions, in rare cases, gynecomastia

				and reversible oligo-spermia, decrease in testosterone levels in the blood plasma, very rarely hepatitis develops

Table 13. Indications for systemic antifungals drugs

Chronic recurrent tinea disorder	Tinea pedis: dishydrotic and hyperkeratotic forms
Spreading lesions	Tinea capitis (hair is affected)
Acute tinea infllammation (vesicles, papules, pustules)	Tines ungum (total-dystrophic, proximal forms)

Antiviral Agents

Acyclovir is a synthetic purine nucleoside analogue, blocks viral DNA synthesis by competitively inhibiting and inactivating viral DNA polymerase.

Valacyclovir is the prodrug of acyclovir, has an oral bioavailability approximately three times greater than that of acyclovir (55% versus 15-30%, respectively) and is also more conveniently dosed than acyclovir.

Penciclovir is an acyclic guanosine analogue with a mechanism of action similar to acyclovir. It is less potent because it does not cause chain termination of viral DNA, and it has a poor oral bioavailability. This medication is only available in topical form.

Famciclovir is the prodrug of penciclovir. Like valacyclovir, it is converted to its active form in the gastrointestinal tract and liver.

Foscarnet is an intravenous antiviral used for CMV retinitis or CMV skin infection in HIV-infected patients and for acyclovir-resistant herpes simplex infections. Foscarnet is an inorganic pyrophosphate analogue that selectively inhibits viral DNA polymerase.

Docosanol, also known as behenyl alcohol, is a saturated 22-carbon aliphatic alcohol that exhibits antiviral activity against several lipid-enveloped viruses including HSV. After the virus has attached to the host cell, n-docosanol prevents the fusion of the HSV envelope with the plasma membrane of uninfected cells.

Topical antiviral agents are indicated for the herpes genitalis, mucocutaneous herpes simplex infections.

Table 14. Topical antiviral agents

Generic name	Some trade name(s)®	Formulations
Acyclovir	Aciclor, Aciclosina, Acivir, Herpex, Vacrovir, Vicorax, Zovir, Zovirax, Zyclir	5% ointment, cream
Penciclovir	Denavir, Vectavir	1% cream
Docosanol	Abreva	10% cream

Systemic antiviral drugs

The systemic antiviral drugs are: Valacyclovir, Cidofovir, Famciclovir, Foscarnet sodium injection, Ganciclovir.

Table 15. Comparative susceptibility of herpesviruses to antiviral drugs

Antiviral drug	Viral susceptibility			Formulations
	HSV-1	HSV-2	VZV	
Acyclovir	+++	+++	++	200 mg capsules; 400 mg and 800 mg tablets
Valacyclovir	+++	+++	++	500 mg and 1000 mg tablets
Cidofovir	+	+	++	500 mg tablets, iv solution 1 ml 75 mg
Famciclovir	+++	+++	++	125 mg, 250 mg and 500 mg tablets
Foscarnet sodium injection	++	++	+	24 mg/mL, foscarnet sodium hexahydrate in Water for Injectio
Ganciclovir	+	+	+	250 мг capsuls, 500 mg liofizat for solution

Acyclovir, vaiacyclovir and famciclovir are all effective against herpes labialis when used intermittently or suppressively, and they are all effective in treating herpes zoster.

Intravenous acyclovir is used in immunocompromised patients with disseminated HSV or VZV and in patients with severe herpes zoster.

Famciclovir is indicated for herpes zoster, primary or recurrent genital herpes, herpes suppression in immunocompetent patients and recurrent herpes simplex in HIV-infected patients.

Foscarnet is an intravenous antiviral used for CMV retinitis or CMV skin infection in HIV-infected patients and for acyclovir-resistant herpes simplex infections.

Contraindications

Antiviral agents are contraindicated in patients with hypersensitivity to the drug, prodrug or any components of the formulation. Systemic antivirals need to be dose-adjusted for patients with impaired renal function, and in patients taking nephrotoxic medications, renal function needs to be monitored.

Side effects

The maior side effects of systemic antiviral agents are: morbilliform eruption, Stevens-Johnson syndrome, urticaria, angioedema, nausea, vomiting, diarrhea, abdominal pain, aplastic anemia, leukopenia, thrombocytopenia, headaches.

Physiotherapy

The classification of skin types known as the Fitzpatrick skin type (or phototype) depends on the amount of melanin pigment in the skin and helps the doctor to prescribe phototherapy. The detection of the type of skin is very important in the appointment of phototherapy

Table 16. Skin types

Skin type	Typical Features	Tanning ability
I	Pale white skin, blue/hazel eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

Phototherapy

Phototherapy is nowadays one of the main methods used in dermatology. It can be used alone or in combination with oral and/or topical treatment. The action of ultraviolet radiation *(see fig.20)* is exploited for the treatment of many diseases. The first report of the use of phototherapy in the treatment of skin disorders dates from 1400 BC from India when patients with vitiligo were given certain plant extracts (whose active ingredients included psoralens) and then exposed to the sun. The real interest in the use of ultraviolet (UV) irradiation in the treatment of various skin diseases started in the 19th century when Niels Finsen received the Nobel Prize (1903) for his therapeutic results with UV irradiation in lupus vulgaris, the only dermatologist ever to be awarded one.

Ultraviolet light is divided to three wavelength ranges. From longest to shortest, they are UVA (320 nm till 400 nm), UVB (290 nm till 320 nm), and UVC (200 nm to 290 nm). The shorter wavelength, the lower is the penetration and the greater is the energy of light. UVA and UVB directly or indirectly damage DNA by exciting UVB absorbing molecules or they produce free radicals that injury cells.

Types of Phototherapy

UVB-therapy (290 nm till 320 nm) – the type of immunosuppressive therapy that inhibits the function of Langerhance cells. **Narrowband UVB – therapy (311 nm)** – it is thought to be more effective than broadband UVB in the treatment of skin diseases.

Indications for UVB-therapy:

1. Vitiligo
2. Psoriasis
3. Pitiriasis lichenoid chronica
4. Atopic dermatitis
5. Lichen planus
6. Alopecia areata
7. Pruritus
8. Mycosis fungoides

Photochemotherapy (PUVA)

(Psoralen- ultraviolet therapy) - administration of oral psoralens – phototoxic substances (8-MOP – 8 methoxipsoralen or TMP – 4,5,8-trimethylpsoralen), followed by irradiation with long wave ultraviolet (320 to 400nm) (UVA), is an established, effective, widely used form of treatment (Psoralens + UVA = PUVA). The combination is used to treat psoriasis on the whole body or isolated sites such as the hands and feet. PUVA clears psoriasis for more than 85% of patients who use it, and it induces long remission times even

without maintenance therapy. PUVA- therapy is deeply penetrative but it has little energy.

Topical PUVA: using of topical fotosensebilisative solutions with further radiation (usefull for example for palmar-plantar psoriasis).

PUVA-bathes:

Indications:

1. Psoriasis
2. Atopic dermatitis
3. Mycosis fungoides
4. Palmoplantar pustulosis
5. Vitiligo
6. Alopecia areata
7. Prurigo nodularis

Side effects:

1. Sun burn that increase the risk of skin cancer.
2. Cataracta.
3. Toxic effect to liver and kidney functions in the case of psoralens oral taking.

UVA1 long-wave (340 nm-400nm)

Unlike UVB radiation that can penetrate at the most into the papillary dermis, longer wavelengths in the UVA region have the capacity to reach the subcutis as well. Accordingly, as well as due to its lesser antiproliferative activity, UVB irradiation has not been established in the treatment of sclerotic disorders except for occasional cases of graft-versus-host disease (GvHD).

Mechanism of action: UVA1 irradiation has been shown to initiate apoptotic cell death in dermal T lymphocytes and dermal immunoregulation. At least UVA1 irradiation induces the formation of several cytokines and soluble factors e.g. interleukin-1 and/or interleukin-6 stimulating the synthesis of collagenase.

Indications:

1. Lupus erythematosus
2. Scleroderma
3. Exacerbated atopic dermatitis
4. Cutaneous T cell lymphoma,
5. Parapsoriasis or mucinosis follicularis
6. Polymorphic light eruption, actinic prurigo, the cutaneous porphyrias.

Long Term Use and Adverse Effects

As with other forms of UV exposure, in addition to the expected immediate sunburn effects, chronic NB-UVB exposure is likely to increase photoaging and the risk of carcinogenesis. Presently there is insufficient human data available to provide recommendations regarding the safe maximum NB-UVB dose. However, according to a dose response model it has been calculated that the long-term risk for carcinogenesis with its use may be less than that of PUVA therapy. After the

first course of one year, they recommend a resting period of three months to minimize the annual cumulative dose of UVB. In children, the maximum duration allowed is 12 months. Subsequently, if required, only limited areas should be exposed. If no response is observed after six months, further therapy should be discouraged. Further, the risk of cutaneous malignancies in vitiligo can be reduced by skin saving principles, i.e. covering the parts that have repigmented satisfactorily and shielding the genitals.

Photodinamic therapy

Photodynamic therapy (PDT) is used clinically to treat a wide range of medical conditions, including age-related macular degeneration and malignant cancers. and is recognised as a treatment strategy which is both minimally invasive and minimally toxic. Photodynamic therapy (PDT) uses exogenously administered or endogenously formed photosensitizers activated by light to induce cell death via formation of singlet oxygen and other free radicals.

Photodynamic therapy is a 2-step procedure. In the first step, the photosensitizer is administered to the patient by one of several routes (eg, topical, oral, intravenous), and it is allowed to be taken up by the target cells. The second step involves the activation of the photosensitizer in the presence of oxygen with a specific wavelength of light directed toward the target tissue. Because the photosensitizer is preferentially absorbed by hyperproliferative tissue and the light source is directly targeted on the lesional tissue, photodynamic therapy achieves dual selectivity, minimizing damage to adjacent healthy structures. For dermatological purposes, incoherent lamps or light-emitting diode arrays can be used for light activation.

Mechanism of action. The basis of PDT is the interaction of light with photosensitive agents to produce an energy transfer and a local chemical effect. Beyond direct phototoxic effects on target tissue, photodynamic therapy with various photosensitizers has been shown to modify cytokine expression and induce immune-specific responses. Immunologic effects include the production of interleukin 1-beta, interleukin 2, tumor necrosis factor-alpha, and granulocyte colony-stimulating factor. Photodynamic therapy generally has a low potential for causing DNA damage, mutations, and carcinogenesis.

Photosensitizers: *5-aminolevulinic acid (ALA or Levulan®), Methyl ester of ALA (Metvixia® cream).*

Indications for PDT in dermatology:

Basal Cell Carcinoma
Bowen Disease
Squamous cell carcinoma.
Actinic keratosis
Malignant Melanoma
Mycosis Fungoides
Kaposi Sarcoma

Nontumoral Applications of Topical ALA-PDT:
Psoriasis
Acne vulgaris
Viral warts.
Alopecia areata
Photoaging

Topical ALA-PDT is speculated to be comparable with anthralin in psoriasis therapy and may be based on the inhibition of inflammatory cytokines. Advantages of this approach would be higher lesion selectivity of the PS compared with psoralen, deeper tissue penetration of red light compared with UV-A, and avoidance of generalized cutaneous photosensitization.

For the treatment of acne. preferential targeting of sebaceous glands and *Propionibacterium acnes* reduction are believed to be the main mechanisms involved. Because *P acnes* has been shown to naturally accumulate porphyrins, blue or red light alone can also have a direct therapeutic photodynamic effect on the bacteria. The exact mechanisms involved in ALA photodynamic therapy for the treatment of photoaging are not well known, but increased collagen synthesis has been demonstrated following ALA photodynamic therapy.

Side effects:

1. Phototoxic reactions: burning sensation or, less commonly, pruritus, is observed during light exposure after ALA or MAL application for photodynamic therapy (PDT). These sensations usually decrease rapidly once the light source is paused or exposure is terminated.
2. Pigmentary abnormalities and hypersensitivity reactions: hyperpigmentation is sometimes seen after photodynamic therapy. It tends to fade over a few months. Hypopigmentation at treated sites has also been reported. Cases of allergic contact dermatitis and urticaria to MAL have been reported.
3. Systemic absorption potential: extensive topical application of ALA could theoretically lead to systemic absorption. In clinical trials, ALA has been given orally at doses of up to 120 mg/kg. Cases of increased liver enzyme levels have been reported in patients treated with oral doses of ALA of 30 mg/kg or more.

Laser therapy

Laser—Light Amplification by Stimulated Emission of Radiation – produces high energy radiation.

Lasers used in dermatology emit specific wavelengths within the UV (10-400 nm), visible (400-720 nm) and IR (720–1 000 000 nm) portions of the electromagnetic spectrum. Intense pulsed light (IPL) devices emit broadband visible and near-IR light (400-1200 nm), whereas radiofrequency devices emit broadband radiofrequency energy.

In dermatology a laser of the two types are used: low-intensity - for a laser therapy, and - high-intensity for laser surgery.

Low-intensity laser radiation has the following effects: anti-inflammatory, antioxidant, anesthetic, mmunomodulatory, and is used to treat atopic dermatitis, psoriasis, alopecia areata.

The penetration of the laser radiation depends on wavelength, decreasing from the long to the short-wave radiation.

Laser application in medicine:

- destructive effect of biological structures and processes
- biostimulation (in physical therapy);
- diagnostics - the study of biological structures and processes (Doppler spectroscopy, cytometry, laser microscopy, etc.).

By the active medium type laser are divided into:

- solid (ruby, neodymium)
- gas - HE-NE (He-Ne), CO^2;
- semiconductor (or diode);
- liquid (for inorganic and organic dyes);
- metal-vapor lasers (the most common: a copper vapor or gold).

High-intensity is obtained using CO^2, Er: YAG-laser and argon laser. CO2 laser is mainly used in dermatology and cosmetology for laser removal (destruction) of nevi, warts, tumors scars and for dermabrasion.

Relative contraindications to the use of laser therapy are: cancer, diabetes mellitus, hypertension, hyperthyroidism, arrhythmias,

Surgical treatment

Skin lesions are easily accessible for removal or biopsy. The procedure used needs to be appropriate to the site and type of lesion involved. It is important also to keep scarring to a minimum.

Destruction of skin lesions is carried out with:

- Electrocautery
- Cryotherapy
- Laser treatment

This is suitable for lesions where the diagnosis is certain, as no specimen is available or histology.

Cryotherapy – is the destruction of tissues by extreme cold.

Current methods used are:

Carbon dioxide

Solid carbon dioxide (temperature - 64^0C) is produced by allowing rapid expansion of the compressed gas from a cylinder. This can be mixed with acetone to form a slush that can be applied with a cotton wool bud. A solid carbon dioxide stick, for direct application to lesions, is produced by an apparatus using "sparklet" bulbs. The lesion must be frozen solid with a 1–2 mm margin of surrounding tissue. After thawing the freezing cycle should be repeated.

Liquid nitrogen (- 196^0C)

This can be simply applied using a cotton wool bud dipped in the vacuum flask of liquid nitrogen. Freezing takes a little longer than using spray apparatus. Various types of such apparatus are available with dif ferent sizes of nozzle. The larger ones are used for seborrheoic keratoses on the back, for example, and the smaller sizes for small lesions on the face. Freezing takes a few seconds and after thawing a further application can be made if necessary.

Nitrous oxide

A cylinder of compressed gas is used to cool a probe to approximately -80^{0}C. It is usually used for the treatment of warts and requires a 30 second freezing cycle.

Precautions

Cryotherapy produces pain and inflammation. Blistering and haematoma may occur. This can be diminished by the practical procedures and application of a strong steroid cream immediately after freezing, except when treating viral warts as it tends to encourage proliferation of the warts.

Damage to deeper structures is rare but may occur when freezing the deeper tissues—for example, treating basal cell carcinoma.

Skin lesions suitable for freezing: Viral warts (these may require several treatments at two to three week intervals), seborrhoeic keratoses, papillomata and skin tags, dysplastic lesions (early lesions, which are potentially neoplastic or of low grade malignancy) Bowen's disease (if confirmed by incisional biopsy), basal cell carcinoma (the superficial spreading typ).

Electrocautery

There are two forms of treatment:

(1) Heat from an electrically heated element, which is used for removal of skin tags and for treatment of the surface after curettage of warts, also seborrhoeic keratoses.

(2) High energy, low current "electrodesiccation" equipment which produces a high energy spark that can coagulate blood vessels or destroy some more papillomata. A fine needle point should be used for small telangiectatic naevi or milia. A larger needle is used for larger surfaces, for example after curettage.

Laser surgery

Lasers can be used as a cutting tool and studies have shown them to be a very effective means of producing incisions in the skin.

Curettage

This is a simple way of removing epidermal lesions. A curette has a metal spoon shaped end with a sharp cutting edge. There are a variety of shapes and sizes suitable for different lesions, from large seborrhoeic keratoses or papillomata to smaller ones for minute keratin cysts. A specimen is provided for histology but completeness of removal cannot be accurately assessed. Local anaesthetic is used.

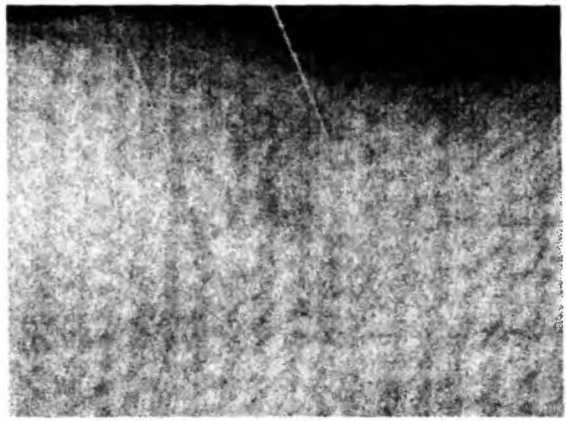

Fig.1 Apple-jelly symptom.

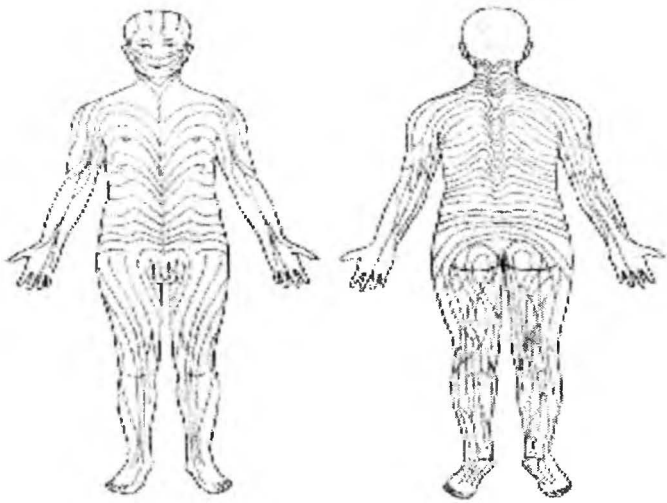

Fig. 2 Blashko lines.

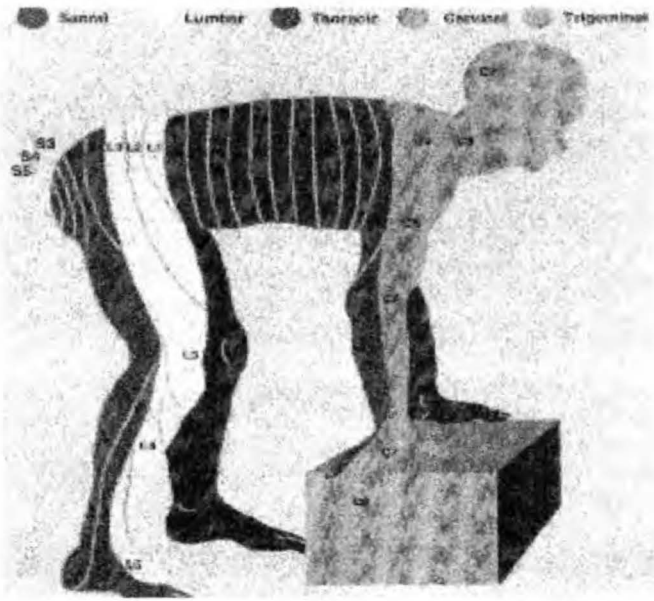

Fig. 3. Skin dermatomas.

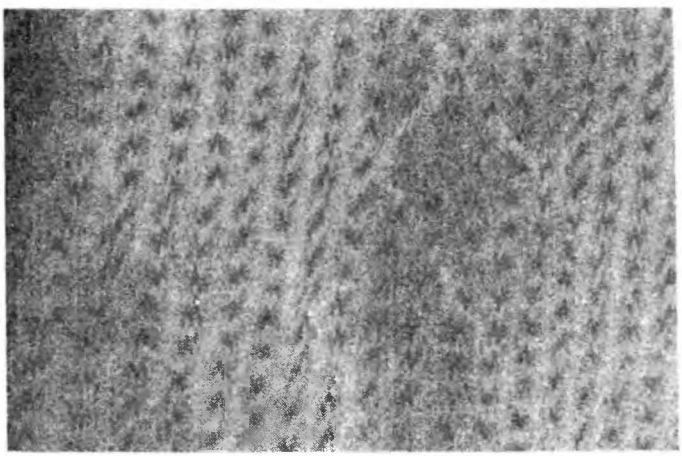

Fig.4. White dermographism.

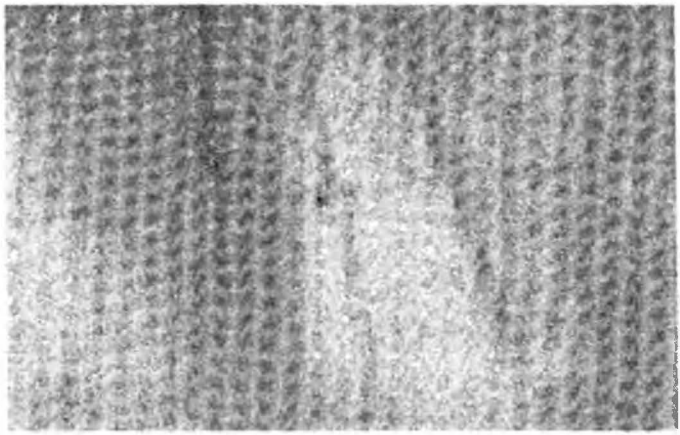

Fig.5. Red dermographism.

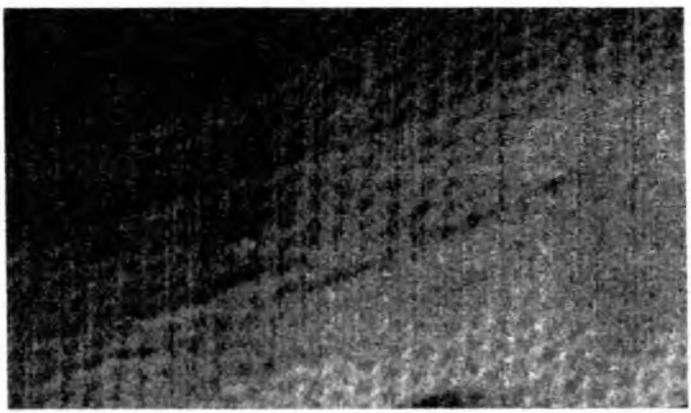

Fig. 6. Urticarial dermographism.

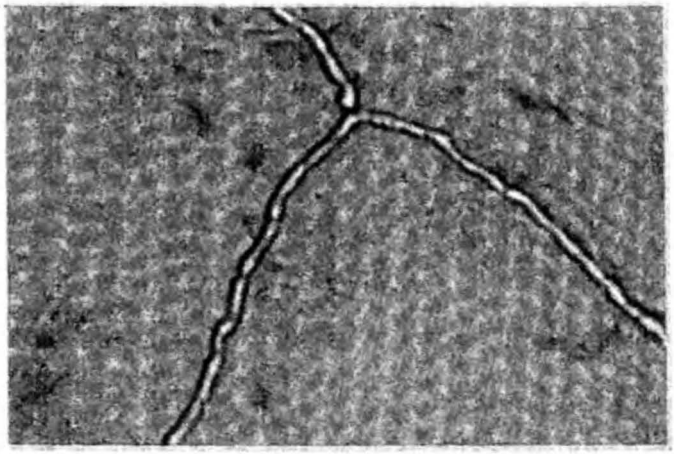

Fig. 7. Dermatophytes.

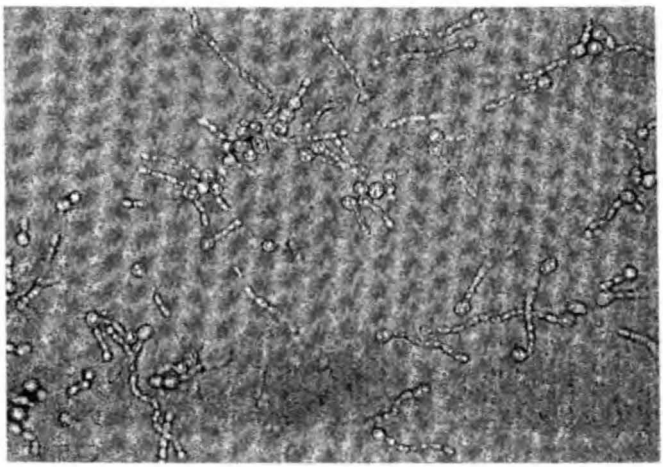

Fig. 8. Fungal hyphae.

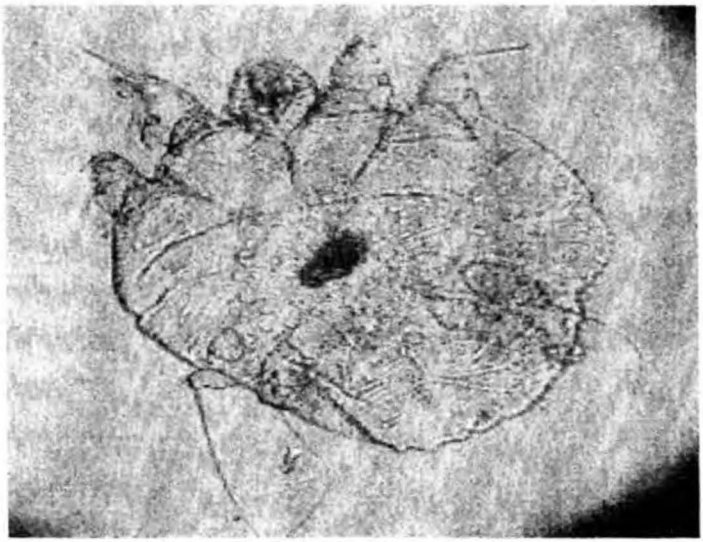

Fig. 9.Sarcoptes scabiei.

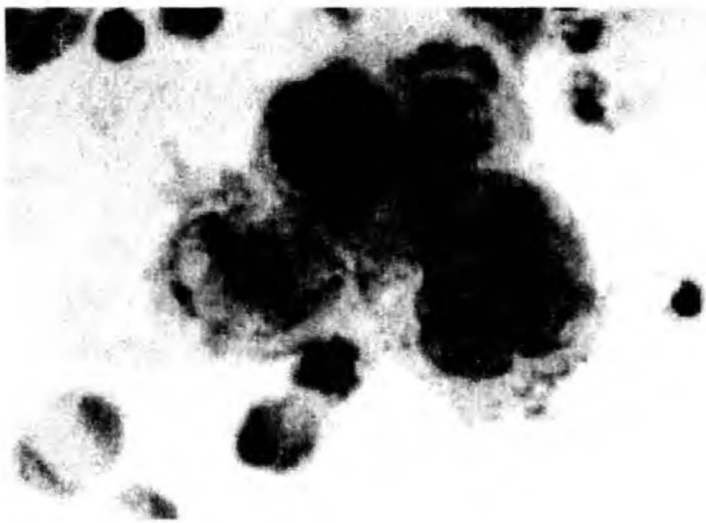

Fig. 10.Tzanck cells in herpes infection.

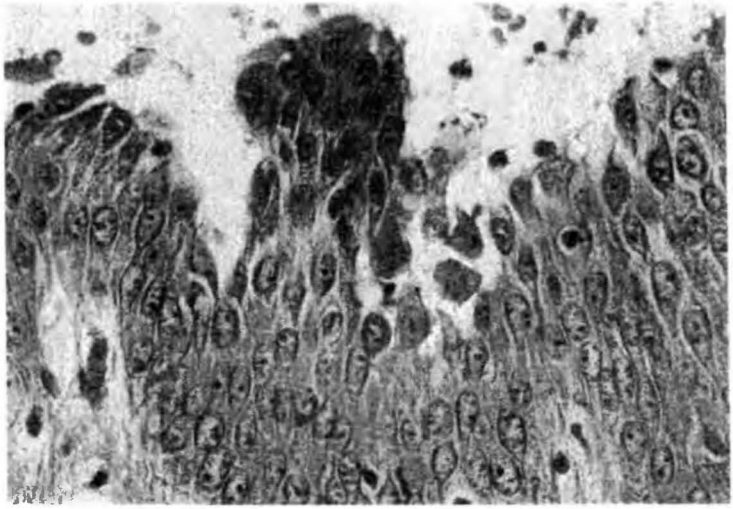

Fig. 11. Acantolytic cells.

Fig. 12. Green collor in M. canis infection.

Fig. 13.Corall red coloration in erythrasma.

Fig.14. Dermatoskope.

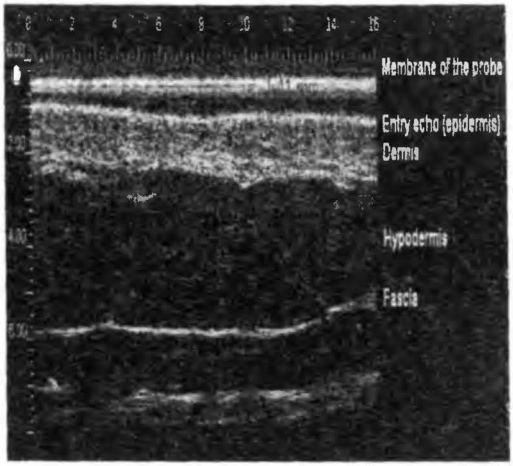

Fig.15 Ultrasound examination of normal skin.

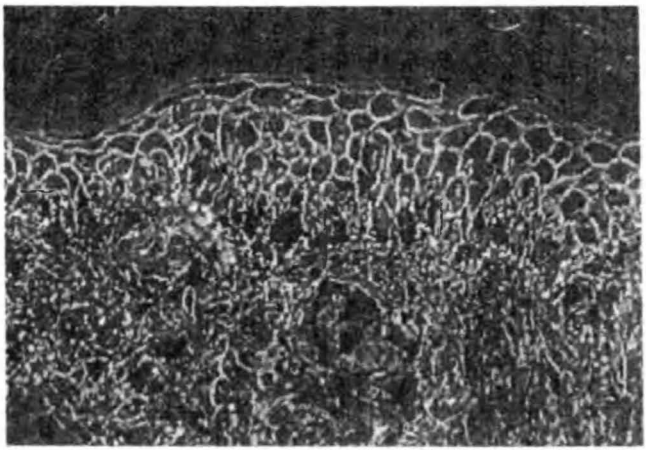

Fig.16 DIF of the skin of a patient with pemphigus vulgaris. Intercellular deposition of IgG and C3.

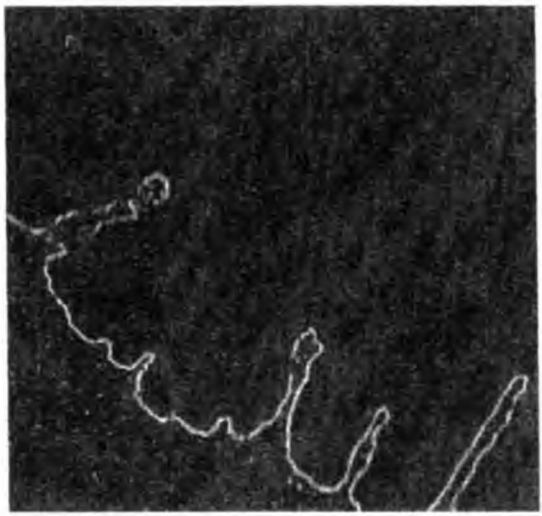

Fig. 17. DIF of the skin of a patient with bullous pemphigoid.Linear deposition of IgG in the epidermal basement membrane.

Fig.18. DIF of a patient with dermititisherpetiformis. Granular deposition of IgA on dermal papillae.

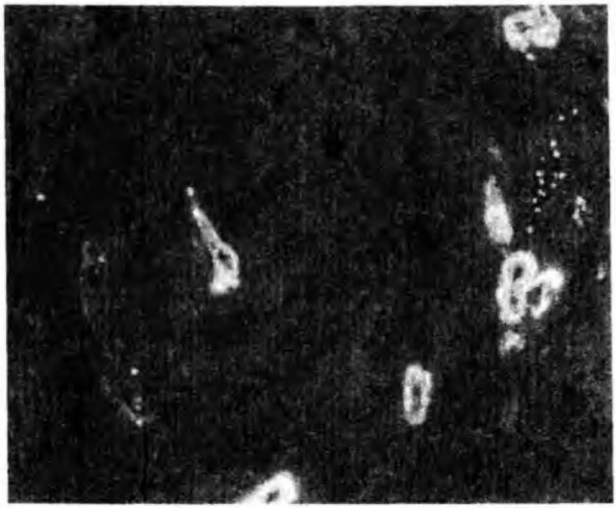

Fig.19. DIF in patient with vasculitis. Strong vessels with IgM deposition.

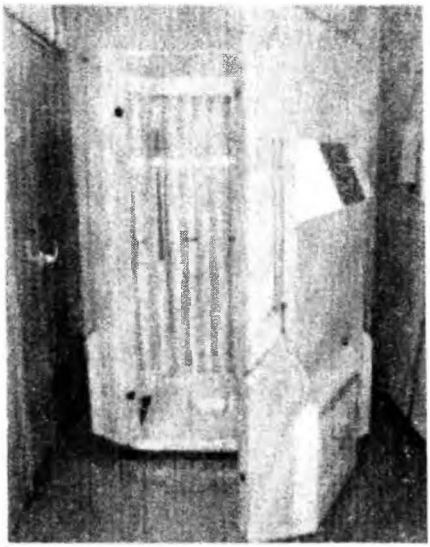

Fig.20. Ultraviolet radiation device.

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