جامعة تكريت – كلية الطب البيطري

الدراسات العليا \ فرع الادوية والفسلجة والكيمياء الحياتية

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Advanced Pharmacology

DRUGS ACTING ON THE SKIN

Skin and drugs

- “It is easy to do more harm than good with potent drugs, and this is particularly true in skin diseases. Many skin lesions are caused by systemic or topical use of drugs, often taking the form of immediate or delayed hypersensitivity”
- “If its wet, dry it; if its dry, wet it. The traditional advice contains enough truth to be worth repeating. One or two applications a day are all that is usually necessary unless common sense dictates otherwise”

Objectives

- To have a clear understanding on:
- The basic and clinical pharmacology of drugs acting on the skin .
- Different formulations available.
- Pharmacotherapeutics of skin disorders.

Introduction

- **The integument or skin is the largest organ of the body, making up 16% of body weight, with a surface area of 1.8m^2.**
- **It has several functions, the most important being to form a physical barrier to the environment, allowing and limiting the inward and outward passage of water, electrolytes and various substances while providing protection against micro-organisms, ultraviolet radiation, toxic agents and mechanical insults.**

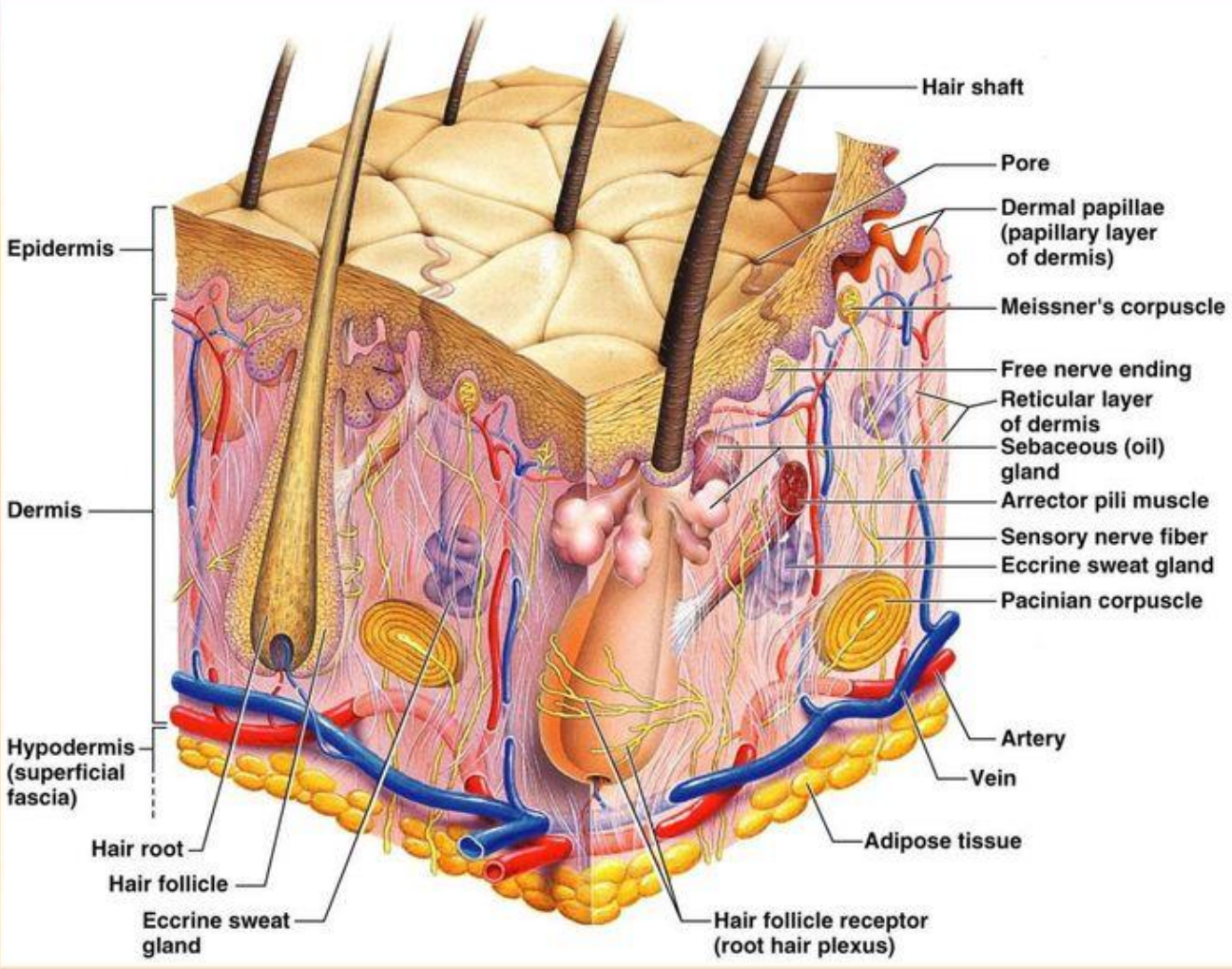
The Architecture of the Skin

2 Principal portions

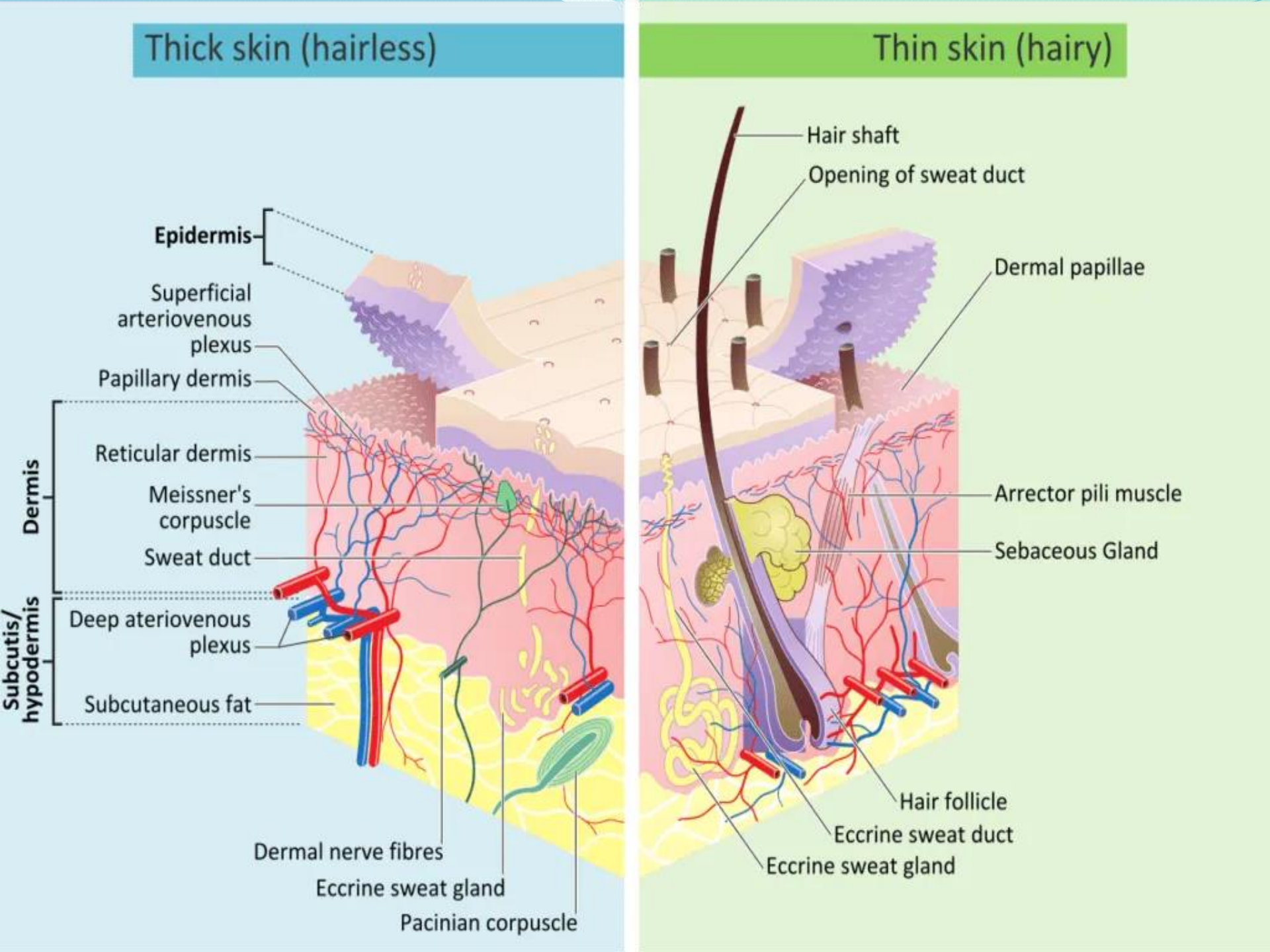
1. Epidermis - epithelium
2. Dermis – areolar and dense irregular fibrous connective tissue

Hypodermis

- "beneath the dermis"
- the subcutaneous layer next to:
  - adipose layer or
  - muscle or
  - bone



- There are three structural layers to the skin: the epidermis ; the epidermis and subcutis
- The skin is an area of the body that gives a disproportionate number of therapeutic problems, particularly in small animals.
- The underlying cause of persistent eczemas is often obscure, leaving the veterinary surgeon little choice but to attempt symptomatic treatment with what agents he/she has at his/her disposal.


Thick skin (hairless)
Thin skin (hairy)
Epidermis
Dermis
Subcutis/ hypodermis
Superficial arteriovenous plexus
Papillary dermis
Reticular dermis
Meissner's corpuscle
Sweat duct
Deep ateriovenous plexus
Subcutaneous fat
Dermal nerve fibres
Eccrine sweat gland
Pacinian corpuscle
Hair shaft
Opening of sweat duct
Dermal papillae
Arrector pili muscle
Sebaceous Gland
Hair follicle
Eccrine sweat duct
Eccrine sweat gland

- **Drugs acting on the skin and mucous membranes can be broadly classified in to the following categories:**

1\ Dermatological vehicles

2\Preparations for allergic, inflammatory and other immune mediated skin conditions. These include:

- **a). Corticosteroids**
- **b).Immunosuppressant's**
- **c). Antihistamines**
- **d).Essential fatty acid preparations**
- **e). Prostaglandin E_1 analoques**

3\ Sunscreens

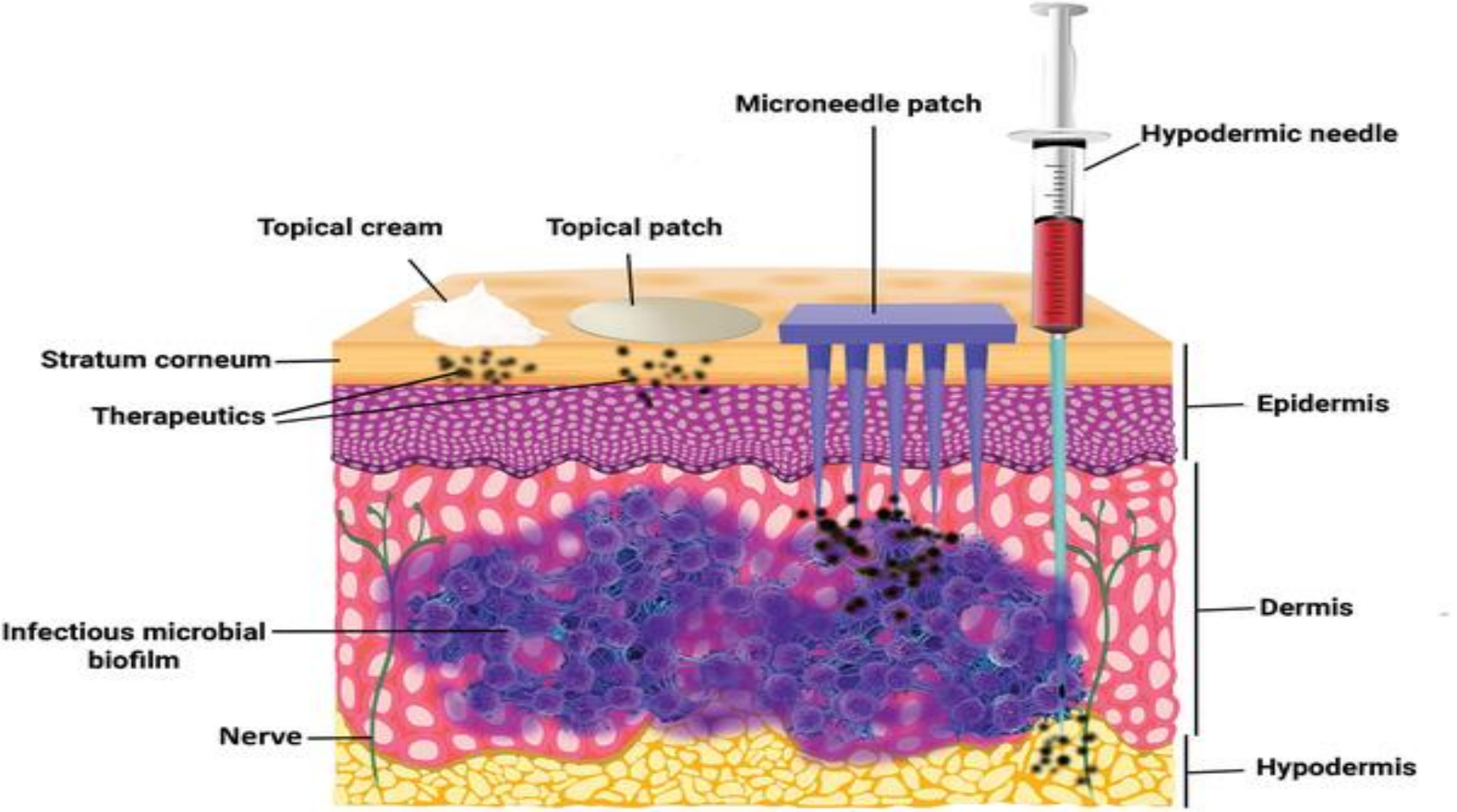
4\ Anti-infective skin preparations

5\ Keratolytics and Keratoplastic agents

6\ Shampoos

7\ Preparations for the ear

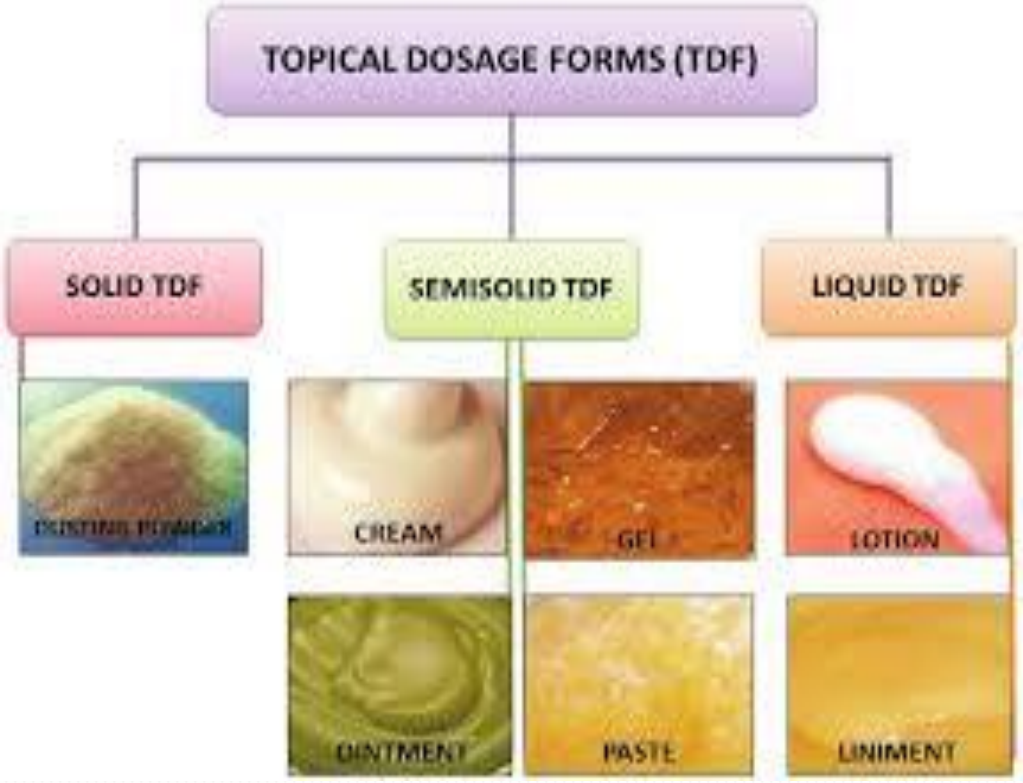
Comparison of the skin penetration depths of different drug delivery.



Systemic disorders may also be responsible for clinical signs affecting the skin- e.g. hormonal disturbances including hypothyroidism or hyper-adreno-corticism, nutritional deficiency of for example zinc (Leading to parakeratosis- defined as : hyperkeratinization of the epithelial cells of skin and esophagus

A). DERMATOLOGICAL AGENTS

- For skin disorders, formulations are available as **powders, sprays, shampoos, lotions, gels, creams and ointments**. The choice of vehicle depends on the type of lesion and convenience of application.



B).Prep. for allergic, Infl. &other immune-mediated skin conditions

- **A wide variety of causative factors may be involved in these skin conditions. The selection of the type and duration of treatment depends on the inflammatory disease present. In every case, the underlying cause(s) should be identified and eliminated, if possible. If this can be done, long-term anti-inflammatory therapy is unnecessary.**
- **The following drug classes are used:**

Cont.

- 1. Corticosteroids
- 2. Immunosuppressants
- 3. Antihistamines
- 4. Topical anti-inflammatory skin preparations
- 5. Essential fatty acid preparations
- 6. Prostaglandin E_1 analogues

1.Corticosteroids

- Systemic corticosteroids are of great value in the treatment of inflammatory and immune-mediated skin conditions.
- **Oral preparations with a short duration of action are preferred because therapy can be discontinued swiftly if adverse effects are seen. This is not possible with longer acting, injectable agents.**
- In addition, fewer side-effects are associated with the use of short acting oral drugs than with other formulations of corticosteroids.
- **However in severe acute diseases, short acting injectable corticosteroid formulations may be favored.**
- In chronic diseases where corticosteroids are indicated, alternate day therapy should be used to minimize the risk of adrenal suppression.
- **Depot corticosteroids such as methylprednisolone acetate should be reserved for cases in which the use of short acting preparations is impaired, for example in dogs or cats that will not tolerate oral dosing and the patient cannot be medicated by mouth.**
- The dose and the type of corticosteroid used depend on the form and severity of the disease present.

2.Immunosuppressants

Ciclosporin (Cyclosporin):

- Ciclosporin blocks the transcription of the genes encoding several cytokines.
- **Its main effect is achieved by blocking transcription of IL-2 and subsequently its synthesis.**
- Secondary effects include inhibition of IFN gamma (Interferon gamma); IL-3, IL-4, IL-5, IL-8 and granulocyte macrophage colony stimulating factor (GM-CSF).
- **As a result, ciclosporin affects the function of mast cells, eosinophils, and antigen presenting cells.**
- These effects include inhibition of eosinophil survival, release of toxic granules, cytokine secretions and recruitment of eosinophils to the site of inflammation, inhibition of mast cell survival, activation, degranulation and reduction in the number of epidermal langerhans cells and cytokine secretion from keratinocytes.
- **Ciclosporin is a potent immunomodulator used for organ transplantation and immune-mediated dermatological conditions in humans.**

Ciclosporin

- **Drug interactions**
- Interactions with drugs that inhibit cytochrome P-450 microsomal enzyme activity increase serum ciclosporin concentration, which can potentiate toxicity.
- **Most of the evidence is documented in humans and mice; however, interaction with ketoconazole has been reported in dogs.**
- Monitoring levels of ciclosporin in the blood is recommended when combined with ketoconazole or other drugs known to interfere with ciclosporin metabolism.
- **Indications**
- Atopic dermatitis; ocular disease; immune-mediated diseases as an immunosuppressant; peri-anal fistula; furunculosis; sebaceous adenitis.

3.Antihistamines

- Antihistamines are antagonists of the histamine H_1 receptor and include: chlorphenamine; clemastine; diphenhydramine; hydroxyzine; promethazine; mepyramine; tripelennamine and alimemazine. H_2 receptor antagonists are ineffective.
- **Antihistamines diminish or abolish the main actions of histamine in the body by competitive reversible blockade of histamine receptor sites.**
- Histamine is only one of many autacoids involved in hypersensitivity reactions and so antihistamines have limited use in the treatment of allergic dis-orders in animals.
- **The effects of antihistamines may not be observed for 1 to 2 weeks and they are most effective for preventing rather than for rapidly reducing pruritus.**

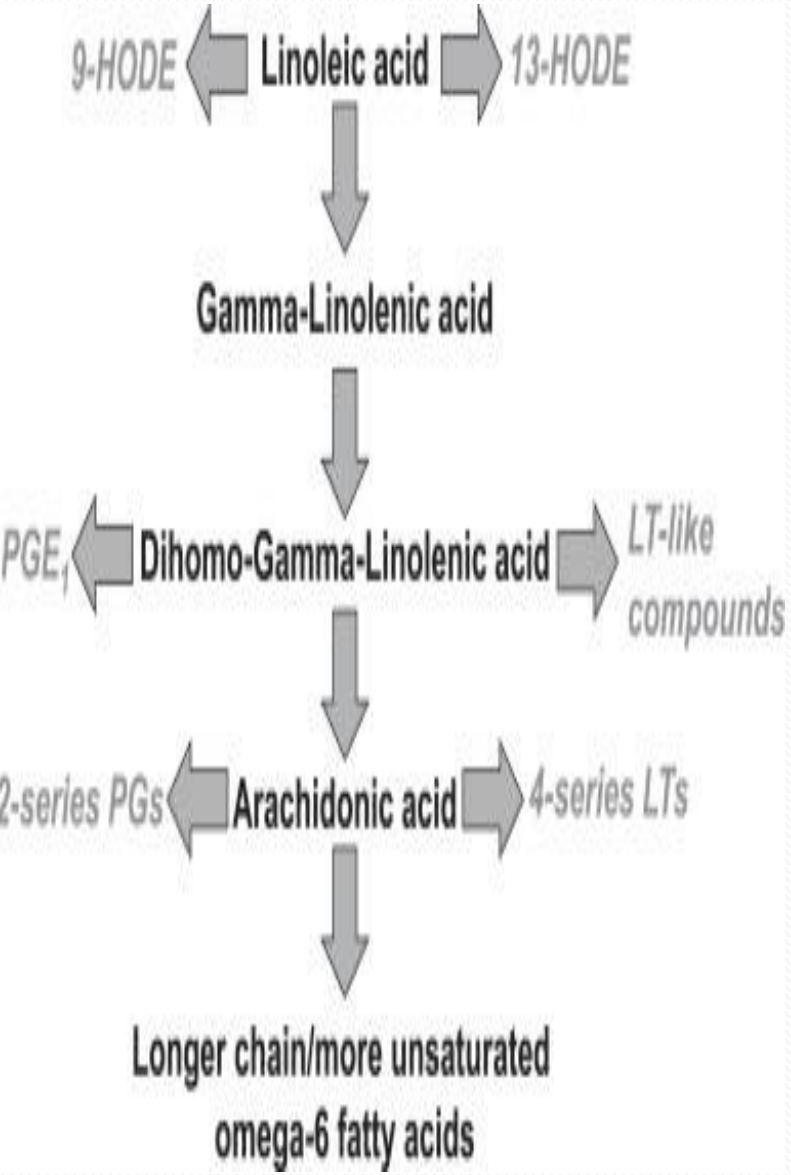
Antihistamines

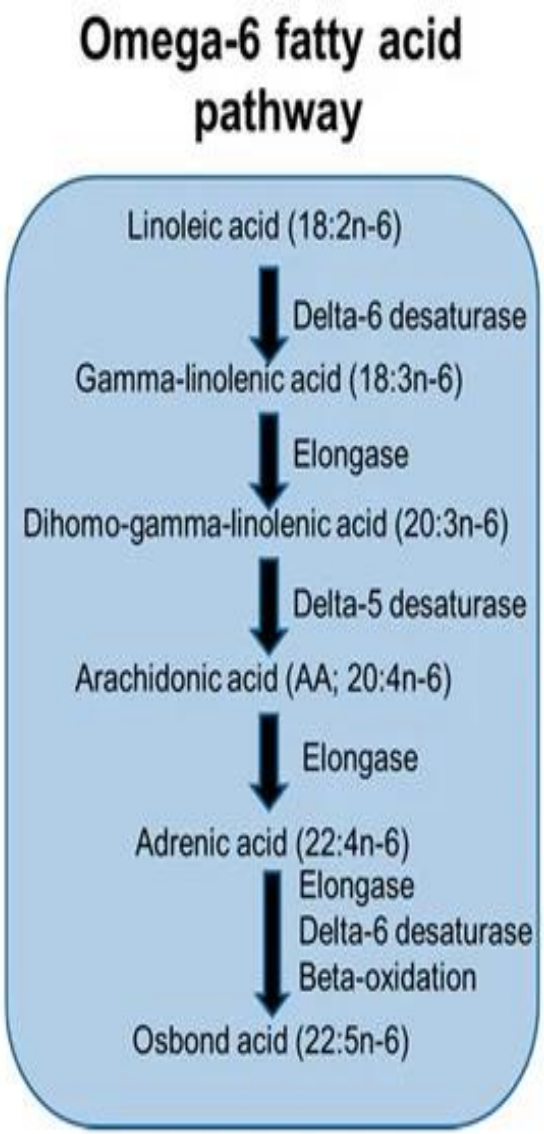
- Systemic antihistamines may be used to control pruritus in allergic reactions such as urticaria and allergic skin problems including food allergies.
- **It is generally accepted that 10% to 15% of patients are likely to respond to treatment with H_1 receptor antagonists but there is considerable individual variation and it is not possible to predict which antihistamines will be effective in any particular patient.**
- Orally administered antihistamines reported to be effective include: chlorphenamine; clemastine; diphenhydramine; hydroxyzine and alimemazine.
- **Antihistamines are frequently sedative. Combination preparations of antihistamines and corticosteroids are available in some countries.**

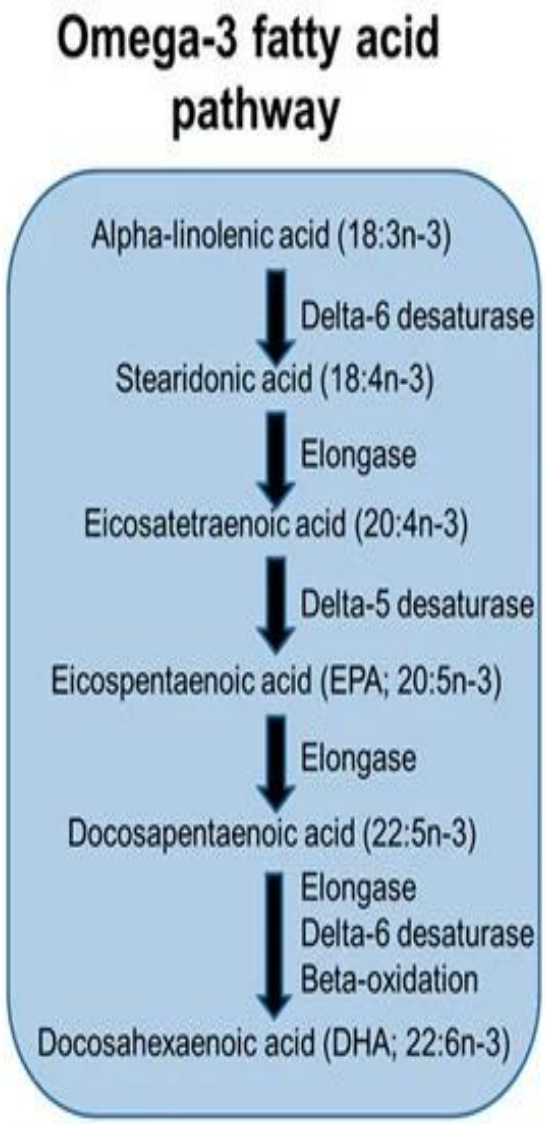
4. Essential fatty acids (EFAs).

- **Zinc, niacin, retinol (Vitamin A) and vitamin C are co-factors favoring the conversion of dihomogamma-linolenic acid to the anti-inflammatory 1 series.**
- **EFA deficiency leads to the development of a dry, scurfy coat, hair loss, epidermal peeling and exudation, skin lichenification and increased susceptibility to infection.**
- **Frank EFA deficiency is uncommon in animals and humans fed normal diets but may occur as a result of intestinal mal-absorption, and hepatic or pancreatic impairment.**
- **There is evidence that EFA supplementation can ameliorate allergic skin diseases, particularly atopy.**

Pathway of long-chain polyunsaturated fatty acid (LCPUFA) biosynthesis from essential fatty acid precursors.







5. Prostaglandin E_1 analogues

Misoprostrol

- Misoprostrol, a synthetic analogue of prostaglandin E_1, selectively inhibits the late phase reaction by blocking the secretion of cytokines by TH1 cells-T lymphocytes expressing CD4 cells are also known as helper T cells, divided into Th1 and Th2.
- **(Th1) cells produce interferon-gamma, interleukin (IL)-2, and tumour necrosis factor (TNF)-beta, which activate macrophages and are responsible for cell-mediated immunity and phagocyte-dependent protective responses.**
- **By contrast, type 2 Th (Th2) cells produce IL-4, IL-5, IL-10, and IL-13, which are responsible for strong antibody production, eosinophil activation, and inhibition of several macrophage functions, thus providing phagocyte-independent protective responses.**

Misoprostrol

- **Th1 cells mainly develop following infections by intracellular bacteria and some viruses**, whereas **Th2 cells predominate in response to infestations by gastrointestinal nematodes, granulocyte activation, and chemotaxis of inflammatory cells.**
- A randomized placebo controlled study in dogs showed a 30% improvement in the level of pruritus and skin lesions after 3 weeks of treatment with misoprostrol.

Misoprostrol

- **Indications**
- atopic dermatitis
- NSAID-associated gastric and duodenal ulceration
- **Contra-indications**
- Pregnant animals
- **Side effects**
- They are dose dependent and may include: diarrhea; abdominal pain; nausea; abortion in pregnant animals.
- **Warnings**: Pregnant women should avoid exposure to misoprostrol.

Sunscreens


VALUE SIZE
equate
Sunscreen
50
SPORT
BANANA BOAT
Light as air
BLUE LIZARD
thrive

C). Sunscreens

- Exposure of the skin to ultra-violet light causes damage that is related to the light intensity, duration of exposure and skin sensitivity.
- **Phototoxic reactions occur in skin with low levels of pigmentation which are not protected by the coat.**
- The resulting solar dermatitis varies from a mild erythematous and scaling reaction to swelling with associated cysts, bullae, folliculitis, furunculosis, and scarring.
- **Chronic light exposure may lead to the development of squamous cell carcinoma.**
- Photosensitivity reactions are caused when photodynamic agents in the skin are exposed to ultraviolet light and cause tissue damage.
- **Photodynamic agents may be generated by abnormalities of hepatic function, aberrant pigment synthesis, or may be derived from substances, ingested, injected, or absorbed through the skin.**
- The increasing levels of ultraviolet light penetration, which are now being experienced, are leading to an increasing amount of damage to the skin.

Sunscreens

- Animals that spend a lot of time outdoors and which are sparsely coated or lacking in pigmentation are especially at risk.
- Sun avoidance is the best solution but protective clothing and use of topically applied stains for example felt-tipped pen on depigmented skin are effective.
- Sunscreens which are water resistant and have a sun protection factor (SPF) of over 15 are useful and should be applied at least once daily but they do not eliminate damage totally and chronic effects may still occur.
- Pigs kept outdoors should be provided with a mud bath.

D). Anti-infective skin preparations

- They include:
- 1. Topical antibacterial skin preparations
- 2. Topical antifungal skin preparations
- 3. Preparations for minor cuts and abrasions
- An infection may be the principle cause of a skin condition or may be secondary to skin trauma or an underlying dis-order. These can include: endocrine imbalances; hypersensitivity; immunosuppression or nutritional imbalances.

1.Topical antibacterial skin prep.

- Topical treatment is often employed using topical *antibacterials, zinc sulfate, lime sulfur, and iodine* containing compounds.
- ***Dermatophilus congolensis* is susceptible to many antibacterials.**
- Antibacterials incorporated into topical preparations include: chlortetracycline; oxytetracycline, which may be effective against superficial infections caused by bacteria including: *Bacillus; Actinomyces; Clostridium; Streptococci and Staphylococci.*
- **Fusidic acid is particularly effective against infections caused by *Staphylococci; Actinomyces; Neisseria* and some *Clostridium species*.**

2. Topical antifungal skin prep.

- The success of drug therapy depends on additional management aimed at reducing and limiting infection such as careful clipping around the lesions in dogs and cats, limiting grooming, isolating the animal and using antifungal washes on the affected animal and local environment.
- **Griseofulvin and ketoconazole are used for systemic treatment of ringworm.**
- Ketoconazole is effective in *Malassezia pachydermatis* infection of the skin.
- **Itroconazole is also effective against ringworm in dogs and cats and appears to be much less hepatotoxic and associated with fewer side effects than ketoconazole.**
- Topical antifungals may be used for the treatment of ringworm, although drug toxicity, due to ingestion through self-grooming, the necessity for clipping of the fur and repeated application and limited efficacy of the preparation should be taken into account.

Topical antifungal skin preparations

- Topical enilconazole, clotrimazole and ketoconazole are effective for *Malassezia pachydermatis* infection.
- **However, the treatment of choice is a shampoo containing chlorhexidine and miconazole (shampoo containing selenium sulfide may also be effective).**
- Topical enilconazole or miconazole may be used in conjunction with systemic griseofulvin for the treatment of ringworm. Povidone iodine is also used as a fungicide.
- **Natamycin is a polyene antifungal antibacterial, which may be used for topical treatment and also for disinfection of the ringworm-contaminated environment and horse tackle (accessories worn by horses in the course of their use as domesticated animal).**
- A vaccine is available for immunization against ringworm in cattle

3.Prep. For minor cuts and abrasions

- **These preparations are used to treat minor skin infections and abrasions, and to prevent infection following surgery or when dehorning.**
- **They are applied as necessary in the form of dusting powder, ointments or sprays.**
- **Preparations containing benzoic acid, cresol or phenols should not be used on cats (Cats have significantly lower tolerance to the preparations).**

E). Keratolytics and Keratoplastic Agents

- Keratolytic agents promote shedding of cornified cells from the stratum corneum, keratoplastic agents slow the rate of proliferation of keratinocytes, allowing them to develop and function more normally.
- Primary keratinization dis-orders are skin diseases in which excessive scale formation occurs in epidermal structures including the hair follicle and inter-follicular epidermis.
- They manifest as blocked follicles (comedones), superficial scale (dry, waxy or greasy seborrhea), and follicular casts.
- Secondary superficial bacteria and yeast (*Malassezia pachydermatis*) infections commonly occur.
- Treatment of primary keratinization disorders may involve the use of topical or systemic substances.
- Topical treatments include keratolytic shampoos and antimicrobials.

Fig. 4. (a) Teenage Black male with lamellar ichthyosis. Note plate-like dark scales, most visible on face and arms. Note no sparing of flexures. (b) Close-up of face of same patient. Ectropion was very mild in this patient but is usually a problem in lamellar ichthyosis. (c) Lower legs of same patient. Note larger scales nearer to ankles. No sparing of flexures covers entire top and bottom of the foot.

Keratolytics and Keratoplastic Agents: Isotretinoin

- **Indications**
- Primary keratinization dis-orders
- **Side effects**
- Keratoconjuctivitis sicca
- Joint and leg pain
- Mild elevation of serum alanine-aminotransferase, cholesterol and triglyceride concentrations
- Inhibition of spermatogenesis
- Possible extended teratogenic effect as a result of tissue storage for long periods.
- **Warnings**: Monitor changes in haematology, blood chemistry, urine and tear production, teratogenic in humans

Tretinoin: Tretinoin is used to treat acne or other skin diseases as determined by your doctor. It works partly by keeping skin pores clear. One of the tretinoin creams is used to treat fine wrinkles, dark spots, or rough skin on the face caused by the damaging rays of the sun.

Indications

- Primary keratinization disorders
- **Side effects**
- Occasional allergic or irritant reaction
- **Warning**: Gloves should be worn when applying the preparations; should not be applied by pregnant women.
- . *Available preparations include:*
- **POM Retin A (Janseen-Cilag) UK**
- *Cream*, tretinoin, 0.025%
- *Gel*, tretinoin 0.01%, 0.025%
- *Lotion*, tretinoin, 0.025%.

F). Wound management

- **1. Skin cleansers and disinfectants**

Background

- wounds occur frequently and need to be assessed and treated similarly to wounds in humans.
- The objective of any wound management regimen is to heal the wound in the shortest time possible and with minimum pain, discomfort and scarring for the patient.
- Open wounds such as abrasions, lacerations, avulsions, ballistic, penetrating, hernias and excised or surgical wounds are most common and are characterized by a break in the skin.
- Closed wounds include contusions, bruises, ruptures and sprains.

1.Skin cleansers and Disinfectants

- Alcohol (70%) is commonly used for its solvent properties for the removal of superficial contamination.
- Cetrimide, Chlorhexidine, and Povidone-iodine are used for skin dis-infection.
- Contaminated wounds should be thoroughly lavaged with isotonic solutions such as sodium chloride 0.9% solution (Normal saline) or ringer's solution.
- If the wound is less than three hours old, antibacterials in the lavage solution will decrease the occurrence of wound infection.
- After three hours, antibacterials in lavage are no more effective than lavage alone.

G). Preparations for the ear

Ear cleansers and sebolytics

- A significant proportion of otic disorders will improve with flushing and cleansing of the ear canal to remove wax and debris.
- Preparations are available using solvents such as propylene glycol, squalane or xylene and incorporating benzoic acid, acetic acid, boric acid and salicylic acid.
- **Indications**
- Ear cleansing.