Dermatologic Pharmacology

Dr. Alia Shatanawi

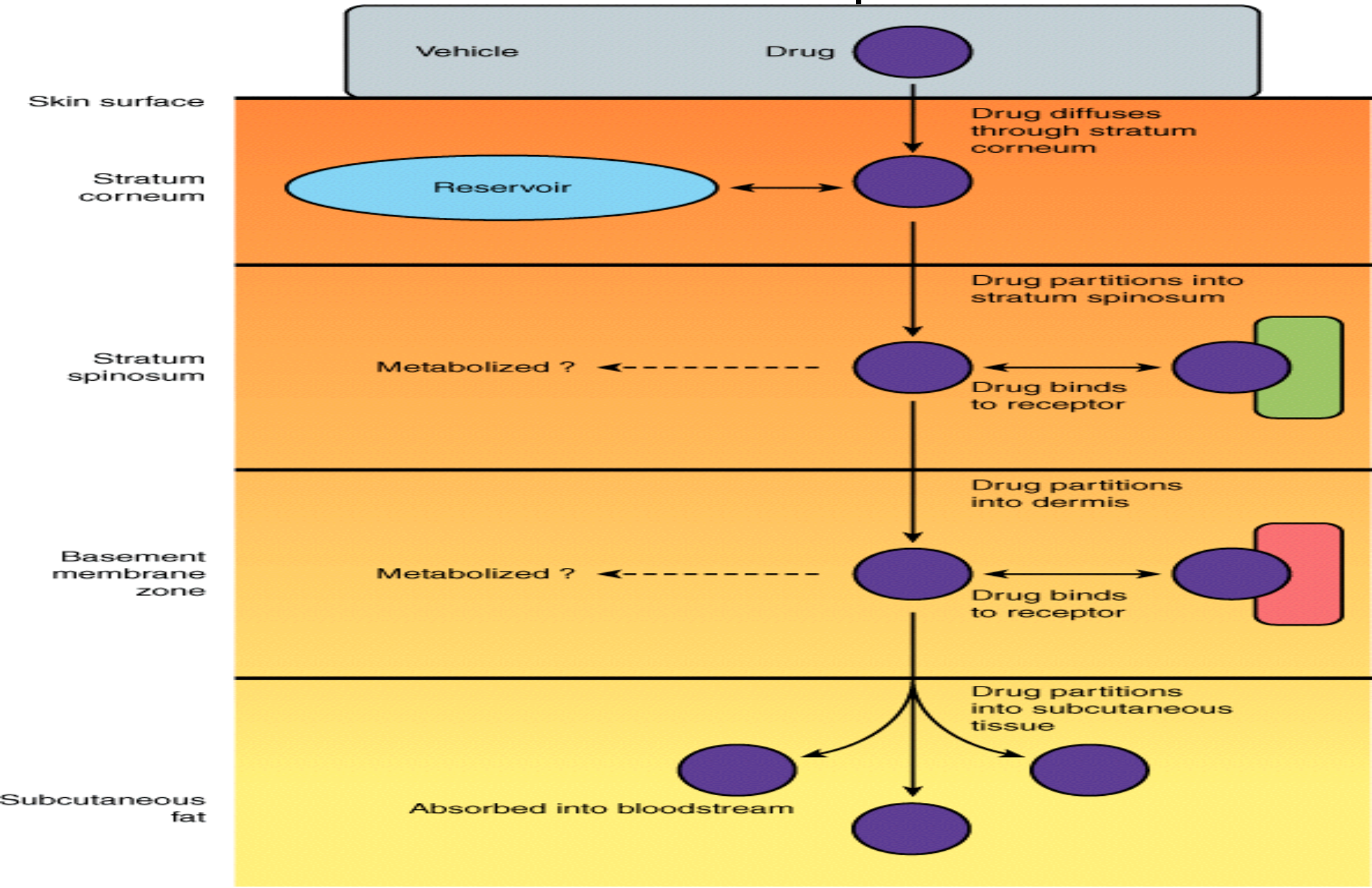
Dermatologic Pharmacology

<u>Variables affecting Pharmacologic Response:</u>

- **Regional variation in drug penetration**
- **Concentration gradient:**

  Increasing the concentration gradient increases the mass of drug transferred per unit time
- **Dosing schedule**
- **Vehicles and occlusion**

Percutaneous Absorption.



Dermatologic Formulations

- **Tinctures**
- **Wet dressings**
- **Lotions**
- **Gels**
- **Powders**
- **Pastes**
- **Creams**
- **Ointments**

Adverse Effects of Dermatologic Preparations

- **Burning or stinging sensation**
- **Drying and irritation**
- **Pruritus**
- **Erythema**
- **Sensitization**
- **Staining**
- **Superficial erosion**

Topical Antibacterial Agents

- **Bacitracin.**
- **Gramicidin.**
  - **Gram-positive bacteria.**
- **Polymyxin B:**
- **Neomycin.**
- **Gentamicin.**
  - **Gram-negative bacteria.**

Bacitracin

- Frequently used in combination with other agents (polymyxin B and neomycin)
- Form: creams, ointments, and aerosol preparations
- Usually Antiinflammatory agents added
  - (Hydrocortisone)
  - MOA??

MUPIROCIN

Mupirocin (pseudomonic acid A) is structurally unrelated to other currently available topical antibacterial agents. Most gram-positive aerobic bacteria, including methicillin-resistant *S aureus* (MRSA), are sensitive to mupirocin .

It is effective in the treatment of **impetigo** caused by *S aureus* and group A β-hemolytic streptococci. Intranasal mupirocin ointment for eliminating nasal carriage of *S aureus* may be associated with irritation of mucous membranes caused by the polyethylene glycol vehicle.

Mupirocin is not appreciably absorbed systemically after topical application to intact skin.

RETAPAMULIN

Retapamulin is a semisynthetic pleromutilin derivative effective in the treatment of uncomplicated superficial skin infection caused by group A β-hemolytic streptococci and *S aureus* , excluding MRSA.

Topical retapamulin 1% ointment is indicated for use in adult and pediatric patients, 9 months or older, for the treatment of impetigo.

Recommended treatment regimen is twice-daily application for 5 days. Retapamulin is well tolerated with only occasional local irritation of the treatment site..

POLYMYXIN B SULFATE

Polymyxin B is a peptide antibiotic effective against gram-negative organisms, including *Pseudomonas aeruginosa, Escherichia coli* , enterobacter, and klebsiella. Most strains of proteus and serratia are resistant, as are all gram-positive organisms.

NEOMYCIN & GENTAMICIN

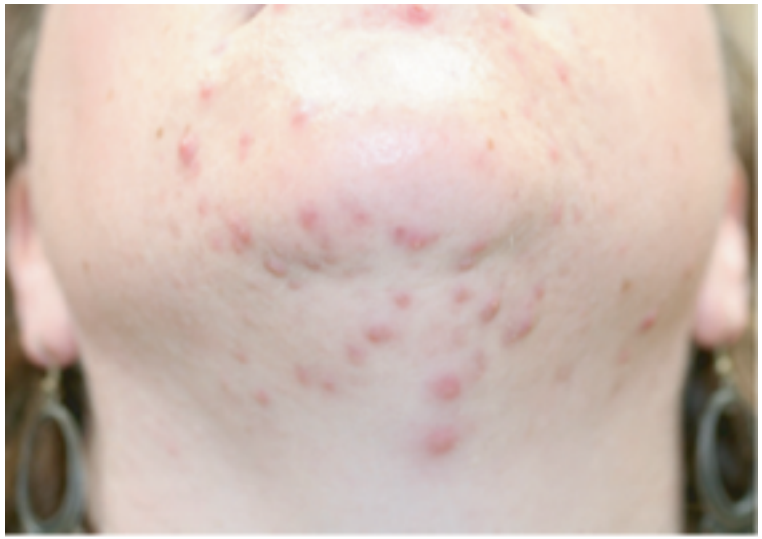
Neomycin and gentamicin are aminoglycoside antibiotics active agains gram-negative organisms, including *E coli* , proteus, klebsiella, and enterobacter.

Gentamicin generally shows greater activity against *P aeruginosa* than neomycin. Gentamicin is also more active against staphylococci and group A β-hemolytic streptococci.

Widespread topical use of gentamicin, especially in a hospital environment, should be avoided to slow the appearance of gentamicin-resistant organisms.

Topical Antibacterials in Acne

- **Clindamycin**
- **Erythromycin**
- **Metronidazole**
- **Sodium sulfacetamide**



▲ **FIGURE 15-2** Open comedones and inflammatory papules on the neck.

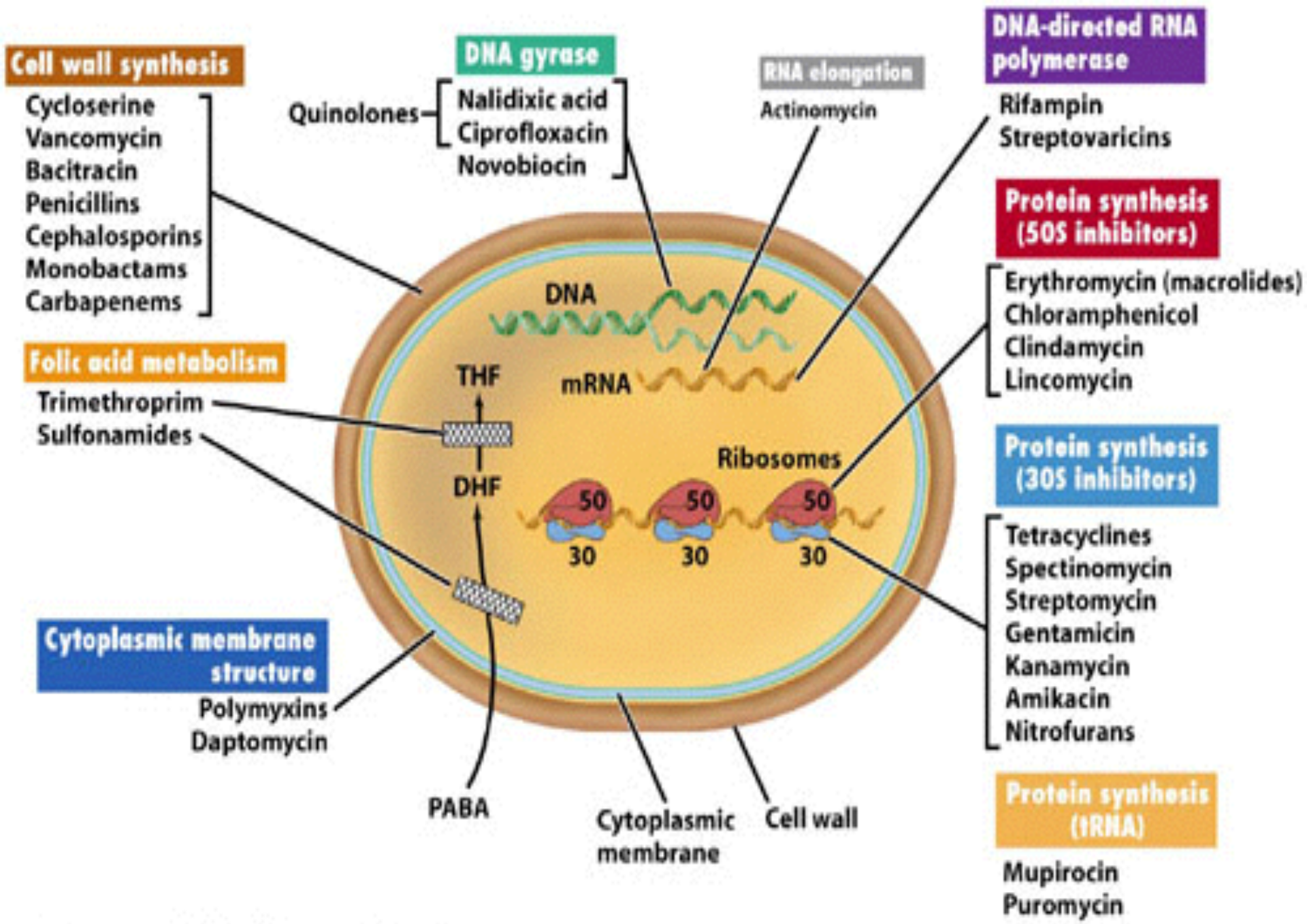


Figure 20-14 Brock Biology of Microorganisms 11/e

Clindamycin

- **10% absorbed, so, possibility of *Pseudomembranous colitis***
- The hydroalcoholic vehicle and foam formulation (Evoclin) ……may cause drying and irritation of the skin, with complaints of burning and stinging.
- The water-based gel and lotion formulations….. well tolerated and less likely to cause irritation. *Allergic contact dermatitis is uncommon*.
- Clindamycin is also available in fixed-combination topical gels with benzoyl peroxide (Acanya, BenzaClin, Duac), and with tretinoin (Ziana).

Metronidazole

- Effective in the treatment of rosacea.
- The mechanism of action is unknown, but it may relate to the inhibitory effects of metronidazole on *Demodex brevis*; This drug may act as an anti-inflammatory agent by direct effect on neutrophil cellular function
- Adverse local effects include dryness, burning, and stinging.
- Less drying formulations may be better tolerated (MetroCream, MetroLotion, and Noritate cream).
- Caution should be exercised when applying metronidazole near the eyes to avoid excessive tearing.

Metronidazole

- Metronidazole nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa
- is selectively toxic for amebae and for anaerobic organisms (including bacteria).
- Mechanism of action

Some anaerobic protozoan parasites (including amebae) possess ferrodoxin-like electron transport proteins that participate in metabolic electron removal reactions.

The nitro group of metronidazole is able to serve as an electron acceptor, forming reduced cytotoxic compounds that bind to proteins and DNA to result in cell death.

Erythromycin

- In topical preparations, erythromycin base rather than a salt is used to facilitate penetration
- One of the possible complications of topical therapy is the development of antibiotic-resistant strains of organisms, including staphylococci
- Adverse local reactions to erythromycin solution may include a burning sensation at the time of application and drying and irritation of the skin
- Erythromycin is also available in a fixed combination preparation with benzoyl peroxide (Benzamycin) for topical treatment of acne vulgaris.

Antifungal Chemotherapy

- Fungal infections are termed *mycoses* and can be divided into:

  (1) Superficial infections: affecting skin, nails, scalp or mucous membranes
  (2) Systemic infections: affecting deeper tissues and organs.

- Superficial fungal infections can be classified into the dermatomycoses and candidiasis.

- Dermatomycoses are infections of the skin, hair and nails, caused by dermatophytes. The commonest are due to *Tinea* organisms which cause various forms of “ringworm”.

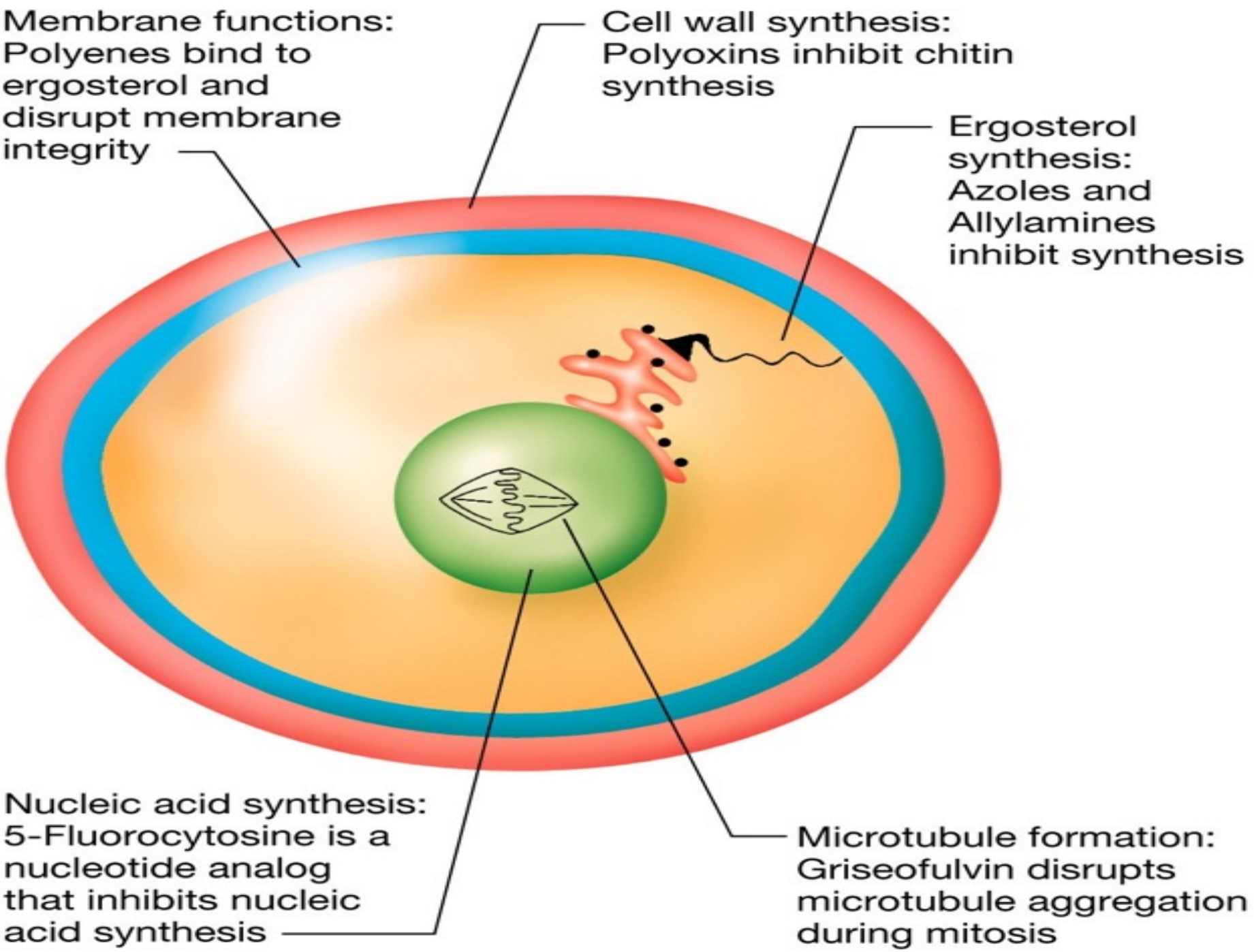
Topical Antifungal Agents

- **Azole Derivatives:**
  - **Clotrimazole**
  - **Econazole.**
  - **Ketoconazole.**
  - **Miconazole.**
  - **Oxiconazole.**
  - **Sulconazole.**
    - **Activity against dermatophytes and yeasts, including *Candida albicans*.**

Antifungal Chemotherapy

- In superficial candidiasis, the yeast-like organism infects the mucous membranes of the mouth (thrush), the vagina (vaginal thrush), or the skin (penis).

- Systemic diseases (infections) include: systemic candidiasis, cryptoccocal meningitis or endocarditis, pulmonary aspergillosis.

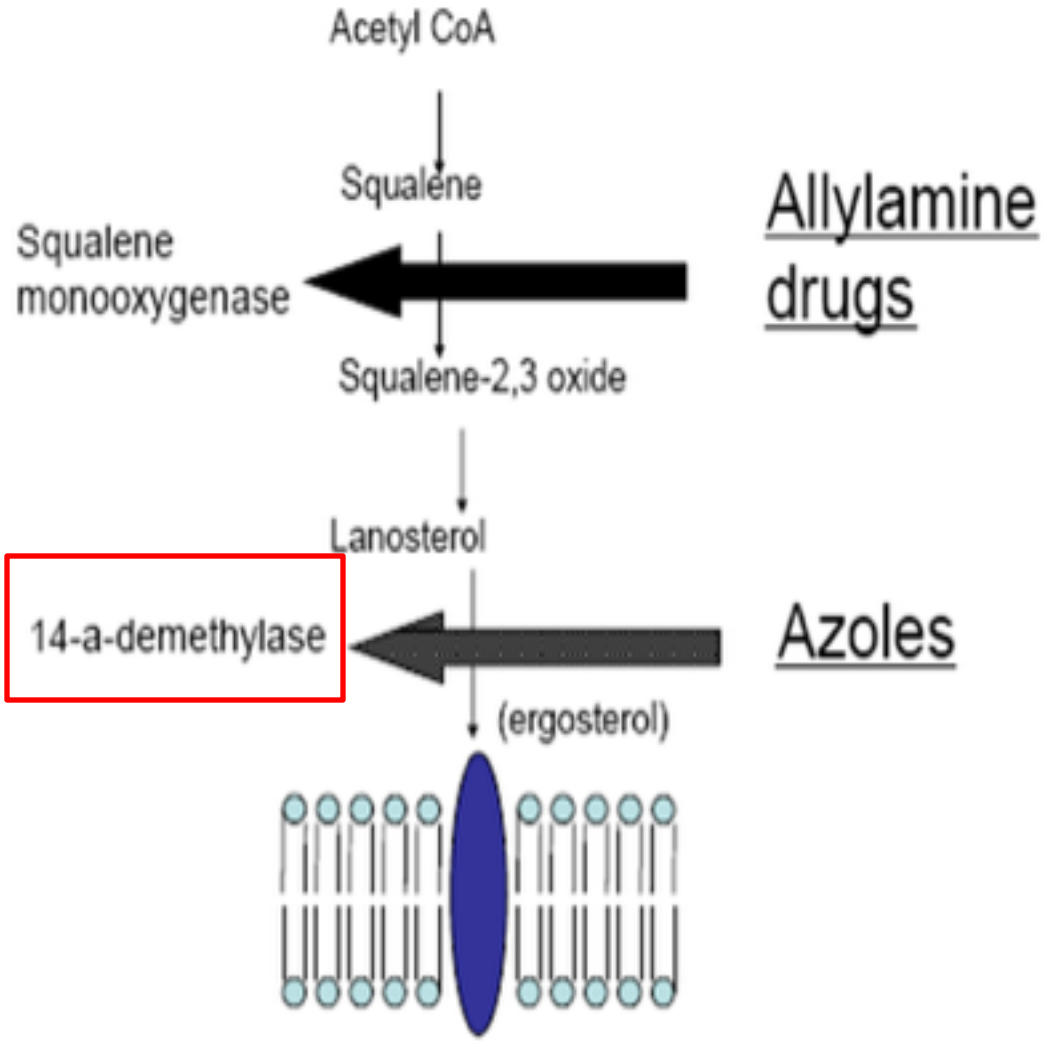

Membrane functions:
Polyenes bind to ergosterol and disrupt membrane integrity
Cell wall synthesis:
Polyoxins inhibit chitin synthesis
Ergosterol synthesis:
Azoles and Allylamines inhibit synthesis
Nucleic acid synthesis:
5-Fluorocytosine is a nucleotide analog that inhibits nucleic acid synthesis
Microtubule formation:
Griseofulvin disrupts microtubule aggregation during mitosis

Azole Antifungal Agents

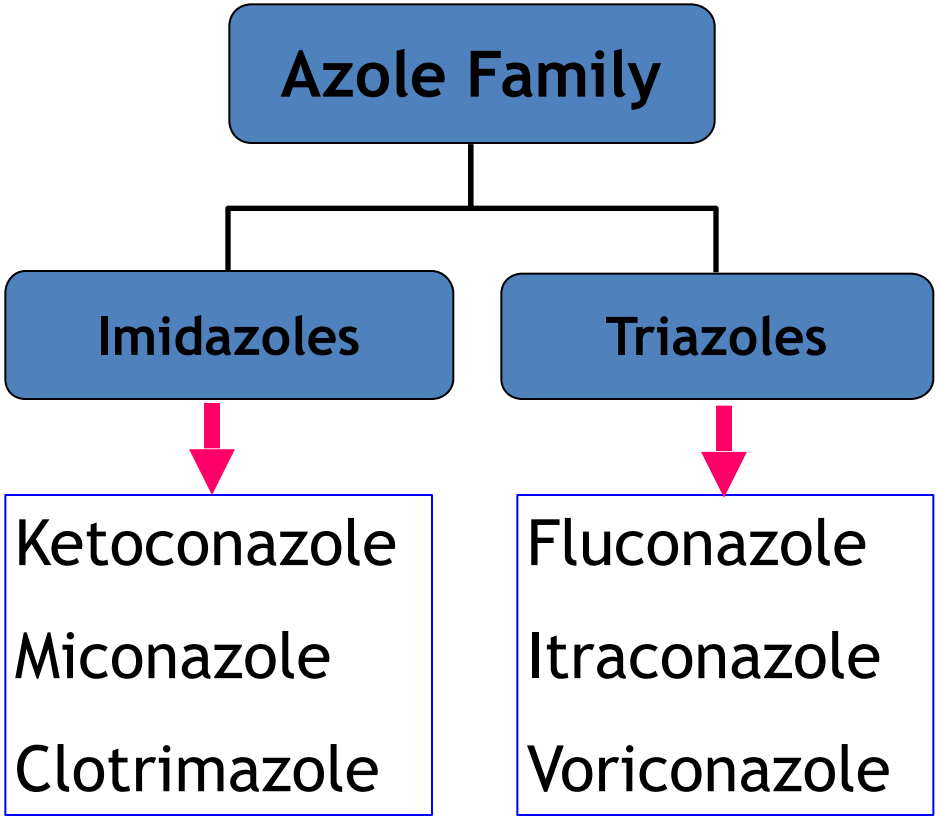
- The azole antifungal agents can be divided into two broad classes : the Imidazoles and the Triazoles.
- They share the same antifungal spectrum and the same mechanism of action.
- They are used topically and systemically, the Triazoles being less toxic and are thus the more widely prescribed.

Azole Antifungal Agents

- Inhibit fungal sterol 14-a-demethylase
- Impair the biosynthesis of the ergosterol
- Ergosterol is required for the fungal cytoplasmic membrane.
- This leads to cessation of growth.



The Azole Family

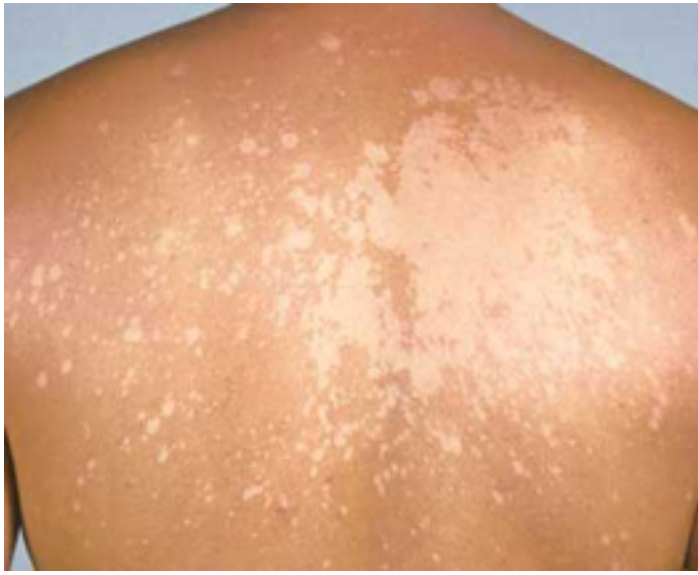


Topical Azoles

- Clotrimazole and Miconazole are used topically.

- Indications for the topical azoles include ringworm, tinea versicolor and mucocutaneous candidiasis.

- Miconazole is a potent inhibitor of warfarin metabolism (even topical application)



Other topical Antifungal Agents

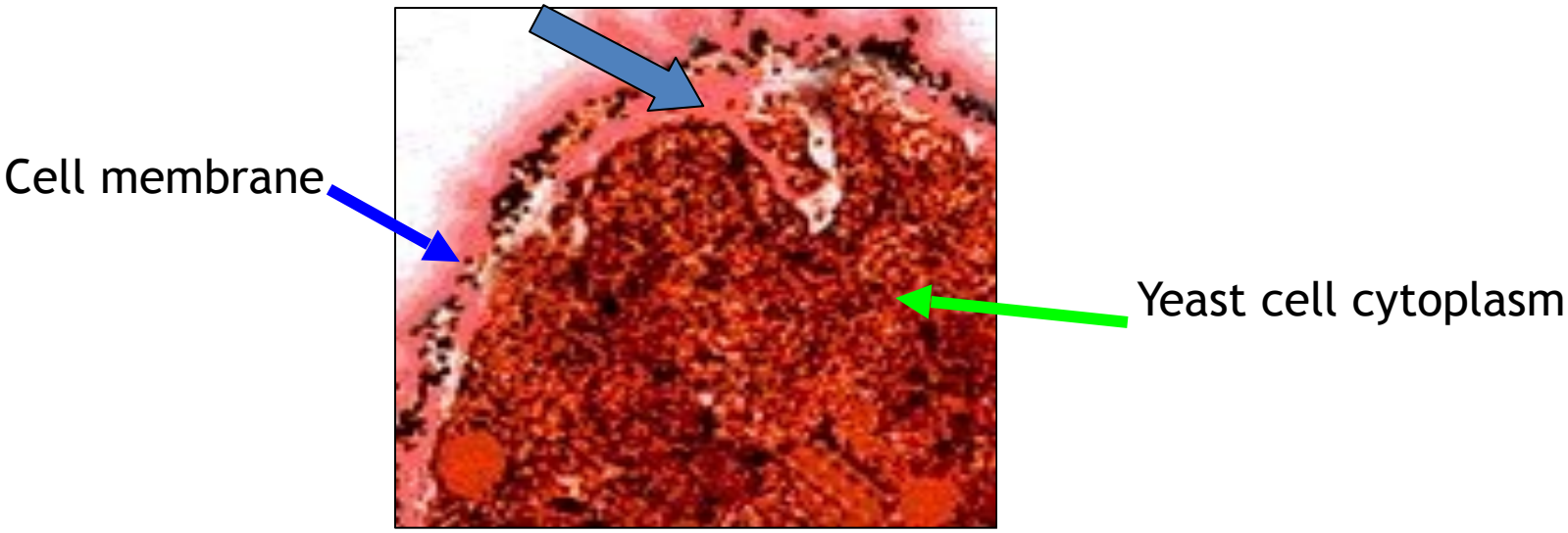
- Ciclopirox Olamine: Tinea versicolor
- Naftifine and Terbinafine: tinea pedis, tinea cruris, and tinea corporis
- Tolnaftate
- Nystatin and Amphotericin B:
  - Only for *Candida albicans*.
  - Available *as* topical preparations, oral suspension, or vaginal tablets

Antifungal Antibiotics

- Amphotericin and Nystatin are polyene macrolide antibiotics that function by binding to fungal cytoplasmic membranes.
- Thus, they interfere with membrane permeability and transport functions.
- One significant outcome is the loss of cellular K+.
- The polyene macrolides are very poorly absorbed orally and they are reluctant to pass through mucous membranes.

Polyene Antifungals: Amphotericine B & Nystatin

- **Mechanism of action:** Polyene antifungal drugs bind to the fungal cell membrane component ergosterol, leading to increased fungal cell membrane permeability and the loss of intracellular constituents.



Amphotericin B

- A polyene antifungal drug produced by the actinomycete Streptomyces.
- Amphotericin has a lesser affinity for the mammalian cell membrane component cholesterol, but this interaction does account for most adverse toxic effects associated with this drug.
- Amphotericin B is most commonly used to treat serious disseminated yeast and dimorphic fungal infections in immuno-compromised hospitalized patients.
- Amphoteracin B can be given IV

Amphotericin B

- **Side effects:**
  - Fever, chills, and tachypnea commonly occur shortly after the initial intravenous doses of amphotericin B
  - Other side effects include anaemia, hypokalaemia, liver damage, thrombocytopenia and anaphylatic reactions.
  - **In short, its a very toxic drug.**

- Main toxicity of Amphotericin is renal.
- 80% of patients get reduction in kidney function which generally recovers after treatment.

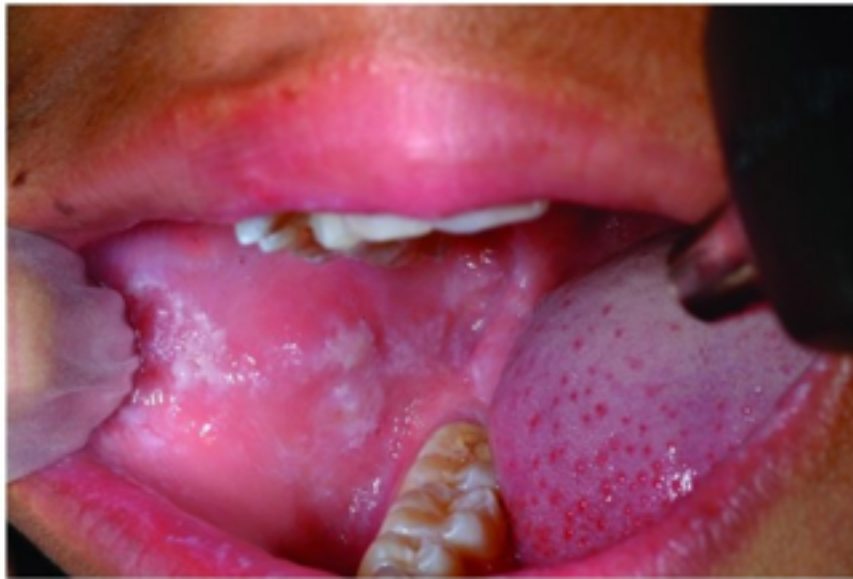
- Nephrotoxicity is the most common and the most serious long-term toxicity of amphotericin B administration

Nystatin

- **Nystatin** is limited to the topical treatment of superficial infections caused by C. albicans.

- Infections commonly treated by this drug include oral candidiasis (thrush), mild esophageal candidiasis and vaginitis.

- Too toxic for systemic use



Oral Antifungal Agents

- **Azole Derivatives:**
  - **Fluconazole.**
  - **Itraconazole.**
  - **Ketoconazole.**
    - **Affect the permeability of fungal cell membrane through alteration of sterol synthesis.**
    - **Effective in systemic mycosis, mucocutaneous candidiasis, and other cutaneous infections.**
    - **Might have systemic side effects: hepatitis and liver enzyme elevations, and interactions.**

Oral Antifungal Agents

- **Azole Derivatives.**
- **Griseofulvin:**
  - **Effective against *epidermophyton*, *microsporum*, *and trichophton*.**
  - **Requires prolonged treatment:**
    - **4-6 weeks for the scalp.**
    - **6 months for fingernails.**
    - **8-18 months for toenails.**
    - **Has many side effects.**
- **Terbinafine:**
  - **Recommended for *onchomycosis*** (ringworm of the nail)
    - **6 weeks for fingernails.**
    - **12 weeks for toenails.**

Topical Antiviral Agents

- **Acyclovir.**
- **Valacyclovir.**
- **Penciclovir.**
- **Famciclovir.**
  - **Synthetic guanine analogs with inhibitory activity against herpes viruses.**
  - **Ointments and creams are useful for recurrent orolabial herpes simplex infection**

Immunomodulators

- **Imiquimod:**
  - **For external genital and perianal warts. (**condyloma acuminatum)
  - **Actinic keratosis on the face and scalp.**
  - **Primary basal cell carcinoma.**
  - **Stimulates peripheral mononuclear cells to release interferon- ά and to stimulate macrophages to produce interleukins-1,-6, and -8 and tumor necrosis factor-ά.**
- **Tacrolimus.**
- **Pimecrolimus.**
  - **Useful for atopic dermatitis.**
  - **Inhibit T-lymphocyte activation and prevent release of inflammatory cytokines and mast cell mediators**

Ectoparasiticides

- **Permethrin:**
  - **Toxic to P*ediculus humanus*, *Pthirus pubis*, *and Sarcoptes scabiei***
  - **Pediculosis:cream applied for 10 minutes and then rinsed off with warm water.**
  - **Scabies: cream applied for the whole body for 8-14 hours.**
- **Lindane (Hexachlorocyclohexane):**
  - **10% absorbed and concentrated in fatty tissues.**
  - **Can cause neurotoxicity and hematoxicity**
- **Crotamiton:** drug that is used both as a scabicidal (for treating scabies) and as a general antipruritic
- **Sulfur.**
- **Malathion.**

Agents affecting Pigmentation

- **Hydroquinone:** topical application skin whitening to reduce the color of skin
- **Monobenzone**

Monobenzone may be toxic to melanocytes resulting in permanent depigmentation.

- **Mequinol**
  - Topical hydroquinone and mequinol usually result in temporary lightening.
- Reduce hyperpigmentation of skin by inhibiting the enzyme tyrosinase which will interfere with biosynthesis of melanin

Agents affecting Pigmentation

- **Trioxsalen.**
- **Methoxsalen.**
  - **Are psoralens used for the repigmentation of depigmented macules of vitiligo.**
  - **Must be photoactivated by long-wave-length ultraviolet light (320-400nm) to produce a beneficial effect.**
  - **They intercalate with DNA.**
  - **Can cause cataract and skin cancer.**

Sunscreens and Sunshades

- **Sunscreens absorb UV light.**
  - **Examples are para amino benzoic acid (PABA) and its esters.**
- **Sunshades are opaque materials that reflect light, like titanium dioxide.**
- **Useful in polymorphous light eruption, lupus erythematosus, and drug –induced photosensitivity.**

Acne Preparations

- **Retinoic Acid and Derivatives:**
  - **Retinoic Acid.**
  - **Adapalene.**
  - **Tazarotene.**

Acne Preparations

- **Retinoic Acid and Derivatives:**
  - **Retinoic Acid(Tretinoin): is the acid form of Vitamin A. Stabilizes lysosomes, increases RNA polymerase activity, increases PGE_2, cAMP, and cGMP levels, and increases the incorporation of thymidine into DNA.**
  - **Decreases cohesion between epidermal cells and increases epidermal cell turnover. This will result in expulsion of open comedones and the transformation of closed comedones into open ones.**
  - **Also, promotes dermal collagen synthesis, new blood vessel formation, and thickening of the epidermis, which helps diminish fine lines and wrinkles.**
  - **Can cause erythema and dryness.**
  - **Tumerogenic in animals**

Acne Preparations

- **<u>Isotretinoin(Accutane):</u>**
  - **Restricted for severe cystic acne resistant to standard treatment.**
  - **Inhibits sebaceous gland size and function.**
  - **Given orally:** 1–2 mg/kg, given in two divided doses daily for 4–5 months
  - **Toxic: dryness, itching, headache, corneal opacities, pseudotumor cerebri, inflammatory bowel disease, anorexia, alopecia, and muscle and joint pains. Also lipid abnormalities.**
  - **Teratogenicity**

Acne Preparations

- **Benzoyl Peroxide:**
  - Penetrates the stratum corneum or follicular openings and converted to benzoic acid within the epidermis and dermis.
  - Has antimicrobial activity against *P. acnes* and peeling and comedolytic effects.
  - Can be combined with erythromycin or clindamycin.
  - Can cause bleaching of hair or colored fabrics.
- **Azelaic Acid:**
  - Has antimicrobial activity.

Drugs for Psoriasis

- **Acitretin:**
  - **Related to isotretinoin.**
  - **Given orally.**
  - **Hepatotoxic and teratogenic.**
  - **Patients should not become pregnant for 3 years after stopping treatment, and also should not donate blood.**

Drugs for Psoriasis

- **Tazarotene:**
  - Topical.
  - Anti-inflammatory and antiproliferative actions.
  - Teratogenic. Also, can cause burning, stinging, peeling, erythema, and localized edema of skin.
- **Calcipotiene:**
  - Synthetic vitamin D_3 derivative

Drugs for Psoriasis

- **Biologic Agents:**
  - **Alefacept:**
    - Immunosuppressive dimer fusion protein of CD2 linked to the Fc portion of human IgG_1.
  - **Efalizumab:**
    - Recombinant humanized IgG_1 monoclonal antibody.
    - Withdrawn :progressive multifocal leukoencephalopathy (PML),
    - Can cause thrombocytopenia.
  - **Etanercept:**
    - Dimeric fusion protein of TNF receptor linked to the Fc portion of human IgG_1.

Anti-inflammatory Agents

- **Topical Corticosteroids:**
  - **Hydrocortisone.**
  - **Prednisolone and Methylprednisolone.**
  - **Dexamethasone and Betamethasone.**
  - **Triamcinolone.**
  - **Fluocinonide.**

Anti-inflammatory Agents

- **Topical Cortcosteroids:**
  - **Dermatologic disorders very responsive to steroids:**
    - **Atopic dermatitis.**
    - **Seborrheic dermatitis.**
    - **Lichen simplex chronicus.**
    - **Pruritus ani.**
    - **Allergic contact dermatitis.**
    - **Eczematous dermatitis.**
    - **Psoriasis**

Anti-inflammatory Agents

- **Topical Cortcosteroids:**
  - **Adverse Effects:**
    - **Suppression of pituitary-adrenal axis.**
    - **Systemic effects.**
    - **Skin atrophy.**
    - **Erythema.**
    - **Pustules.**
    - **Acne.**
    - **Infections.**
    - **Hypopigmentation.**
    - **Allergic contact dermatitis.**

Anti-inflammatory Agents

- **Topical Cortcosteroids.**
- **Tar compounds:**
  - **Mainly for psoriasis, dermatitis, and lichen simplex chronicus**
  - **Can cause irritant folliculitis, phototoxicity, and allergic contact dermatitis.**

Keratolytic and Destructive Agents

- **Salicylic acid:**
  - **Solubilizes cell surface proteins resulting in desquamation of keratotic debris.**
  - **Keratolytic in 3-6% concentration, but destructive in higher concentrations.**
  - **Locally, can cause urticaria, anaphylactic and erythema multiforme reactions, irritation, inflammation, and ulceration.**

Keratolytic and Destructive Agents

- **Propylene Glycole:**
  - **Usually used as a vehicle for organic compounds.**
  - **Used alone as a keratolytic agent in concentrations of 40%- 70%, with plastic occlusion, or in gel with 6% salicylic acid.**
  - **Minimally absorbed, oxidized in liver to lactic acid and pyruvic acid.**
  - **Develops an osmotic gradient through the stratum corneum, thereby increasing hydration of the outer layers of skin.**

Keratolytic and Destructive Agents

- **Urea:**
  - **Has a humectant activity, i.e. softening and moisturizing effect on the stratum corneum.**
  - **Increases water content as a result of its hygroscopic characteristics.**
  - **Decreases the unpleasant oily feel of dermatologic preparations._**
  - **When absorbed, it is excreted in urine.**

Keratolytic and Destructive Agents

- **Flurouracil:**
  - **Antimetabolite that resembles uracil and inhibits thymidylate synthetase, thus interferes with DNA and may be RNA synthesis.**
  - **Used in multiple actinic keratosis.**

Keratolytic and Destructive Agents

- **Nonsteroidal Anti-inflammatory Drugs:**
  - **3% gel formulation diclofenac.**

- **Aminolevulinic Acid:**
  - **Used in actinic keratosis.**
  - **After topical application(20%) and exposure to light, produces a cytotoxic superoxide and hydroxyl radicals**

Antipruritic Agents

- **Doxepine:**
  - **Potent H_1 and H_2 - receptor antagonist.**
  - **Can cause drowsiness and anticholinergic effects.**
- **Pramoxine:**
  - **Is a topical local anesthetic agent.**

Trichogenic and Antitrichogenic Agents

- **<u>Minoxidil (Rogaine):</u>**
  - **Designed as an antihypertensive agent.**
  - **Effective in reversing the progressive miniaturization of terminal scalp hairs associated with androgenic alopecia.**
  - **Vertex balding is more responsive than frontal balding.**

Trichogenic and Antitrichogenic Agents

- **Minoxidil.**
- **Finasteride (Propecia):**
  - **5ά-reductase inhibitor which blocks the conversion of testosterone to dihydrotestosterne.**
  - **Oral tablets.**
  - **Can cause decreased libido, ejaculation disorders, and erectile dysfunction.**

Trichogenic and Antitrichogenic Agents

- **Minoxidil.**
- **Finasteride.**
- **Eflornithine:**
  - **Is an irreversible inhibitor of ornithine decarboxylase, therefore, inhibits polyamine synthesis. Polyamines are important in cell division and hair growth.**
  - **Effective in reducing facial hair growth in 30% of women when used for 6 months.**

Drugs for Leishmania

Caused by three *Leishmania species*:

***L.tropica* causes: Cutaneous leishmaniasis or oriental sore.**

***L. brazeliensis* causes: Mucocutaneous leishmaniasis.**

***L. Donovani* causes: Visceral leishmaniasis**

Sodium Stibogluconate

Pentravalent antimonial

Binds to SH groups on proteins.

Typical preparations contain 30% to 34% pentavalent antimony by weight as well as *m*-chlorocresol added as a preservative.

Also, inhibits phosphofructokinase

Local, IM or slow IV, irritant.

Given for 20-28 days.

Drug of choice for all forms of leishmaniasis.

Resistance is increasing, especially in India.

Cough, V, D, myalgia, arthralgia, ECG changes, Rash, Pruritus.

Amphotericin

- **Antifungal agent, difficult to use, and toxic.**
- **Alternative therapy for visceral leishmaniasis, especially in areas with high resistance.**

Miltefosine

- **For visceral leishmaniasis.**
- **Given orally, for 28 days.**
- **Causes V & D, hepatotoxicity, nephrotoxicity, and it is teratogenic.**

Pentamidine

- **Inhibits DNA replication.**
- **Also, DHF reductase inhibitor**

- **Given IM or IV injection and Inhalation**
- **Binds avidly to tissues, not the CNS.**

Pentamidine

Leishmaniasis:

Alternative to Na stibogluconate

Pneumocystis jiroveci:

Treatment and prophylaxis of patients who cannot tolerate or fail other drugs.

Trypanosomiasis:

For early hemolymphatic stage.

Pentamidine

- **<u>Adverse Effects:</u>**
- **Rapid Infusion: Hypotension, tachycardia, dizziness.**
- **Pain at the injection site.**
- **Others: Pancreatic, Renal, and Hepatic toxicity.**

Antilepromatous Drugs

- **<u>Dapsone and Sulphones:</u>**
  - **Related to sulphonamides.**
  - **Inhibit folate synthesis.**
  - **Resistance develops.**
  - **Combined with Rifampin and Clofazimine.**
  - **Also used for *Pn. Jeroveci* in AIDS patients.**
  - **Well absorbed and distributed.**
  - **Retained in the skin, muscle, liver and kidney.**

Antilepromatous Drugs

- **Dapsone and Sulphones:**
  - Hemolysis, particularly in G-6-PD deficiency.
  - GIT intolerance
  - Fever, Pruritus, Rashes.
  - Erythema Nodosum Leprosum:

    suppressed by steroids or thalidomide.

Antilepromatous Drugs

- **Rifampin:**
  - **Discussed with antituberculous drugs.**
- **Clofazimine:**
  - **Binds to DNA.**
  - **Stored widely in RES and skin.**
  - **Released slowly from storage sites, $t_{1/2}$ = 2 months.**
  - **Given for sulphone- resistant or intolerant cases.**
  - **Causes skin discoloration (red-brown to black) and**

    GIT intolerance.