

# **Skin Pharmacology**

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# Adverse Effects of Dermatologic Preparations

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

# Topical Antibacterial Agents

- **Gram-positive bacteria**
  - **Bacitracin**
  - **Gramicidin**
  - **Fusidic acid**
  
- **Gram-negative bacteria**
  - **Polymyxin B Sulfate**
  - **Neomycin**
  - **Genatamicin**

# BACITRACIN

- Active against streptococci, pneumococci, and staphylococci
- Also , most anaerobic cocci, neisseriae, tetanus bacilli, and diphtheria bacilli are sensitive .
- MOA???

- Side effects: Toxicity???

Allergic contact dermatitis occurs frequently, and immunologic allergic contact urticaria rarely. Bacitracin is poorly absorbed through the skin, so systemic toxicity is rare.





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

# POLYMYXIN B SULFATE

- **gram-negative :Pseudomonas aeruginosa, Escherichia coli, enterobacter, and klebsiella.**
- **Proteus and serratia are resistant, as are all gram-positive organisms.**
- **Side effects: total daily dose applied to denuded skin or open wounds should not exceed 200 mg in order to reduce the likelihood of toxicity “neurotoxicity and nephrotoxicity”**
  - **Allergic contact dermatitis NOT common.**

# Fusidic acid

- acts as a bacterial protein synthesis inhibitor
- Staphylococcus species, Streptococcus species, and Corynebacterium species.
- often used topically in creams and eyedrops



# NEOMYCIN & GENTAMICIN

## Neomycin

- **Aminoglycoside antibiotics**
- **gram-negative :E coli, proteus, klebsiella, and enterobacter.**
- **SE: allergic contact dermatitis**
  
- **Gentamicin generally shows greater activity against P aeruginosa than neomycin .**
- **Gentamicin more active against staphylococci and group A  $\beta$ -hemolytic streptococci.**
- **Be careful with systemic toxicity : esp in renal failure**
- **Hospital acquired resistant**



# Acne treatment

- ✚ **One of the most common skin diseases presenting to family physicians**
- ✚ **Considerable psychological impact on the quality of life**
- ✚ **Four main factors cause acne:**
  - **Excess oil (sebum) production.**
  - **Hair follicles clogged by oil and dead skin cells.**
  - **Bacteria.**
  - **Inflammation**
- ✚ **The anaerobic bacterium *Cutibacterium acnes* (*Propionibacterium acnes*) is believed to play an important role in the pathophysiology of the common skin disease *acne vulgaris*.**

# Comedonal Lesions



# Inflammatory Lesions



# Nodulocystic Lesions







# Scaring



# *Topical Therapy (Indications)*

-  **comedonal acne**
-  **mild to moderate inflammatory acne**

# *Topical Therapy (Treatment Vehicle)*

-  **cream**    **sensitive or dry skin**
-  **lotion**    **any skin type**
-  **gel**    **oily skin**
-  **solution**    **oily skin**

# *Topical Therapy (Anti Comedonal Agents)*



**Topical Retinoids 0.025% - 0.5%**



**Azelaic acid**



**Salicylic acid**

# Topical Retinoids (Adapalene, Differin)

## ✚ Topical Retinoids 0.025% - 0.5%

- apply at night
- always apply test dose
- start at low concentrations
- avoid in pregnancy

## ✚ Side Effects:

- pustular flare
- photosensitivity
- skin irritation and erythema
- dryness and peeling

Avoid in Pregnancy





# *Azelaic Acid 20%*

- ✚ **competitive inhibitor of mitochondrial oxidoreductases and of 5 alpha-reductase, inhibiting the conversion of testosterone to 5-dehydrotestosterone. It also possesses bacteriostatic activity to both aerobic and anaerobic bacteria including Propionibacterium acnes**
- ✚ **applied twice daily**
- ✚ **Side Effects**
  - **erythema and irritation**
  - **decrease in pigmentation**

## *Salicylic Acid 0.5 - 2%*



**keratolytic. It belongs to the same class of drugs as aspirin (salicylates (**



**Can reduce swelling and redness and unplugging blocked skin pores to allow pimples to shrink**



**applied twice daily**



**skin dryness and irritation**

## ***Topical Therapy (Anti Inflammatory Agents)***

 **Benzoyl Peroxide 2.5 - 10%**

**exhibits bactericidal effects against Cutibacterium**



**apply once to twice daily**



**always apply test dose**



**avoid use at night**



**dryness of skin**

## ***Topical Therapy (Anti Inflammatory Agents)***

- + Clindamycin.**
- + Erythromycin.**
  - apply twice daily**
  - skin dryness**

### ***Combination therapy***

- + 5% Benzoyl Peroxide and 3% Erythromycin**
- + 5% Benzoyl Peroxide and 1% Clindamycin**
- + Topical antibiotics and Azelaic acid or Tretinoin**

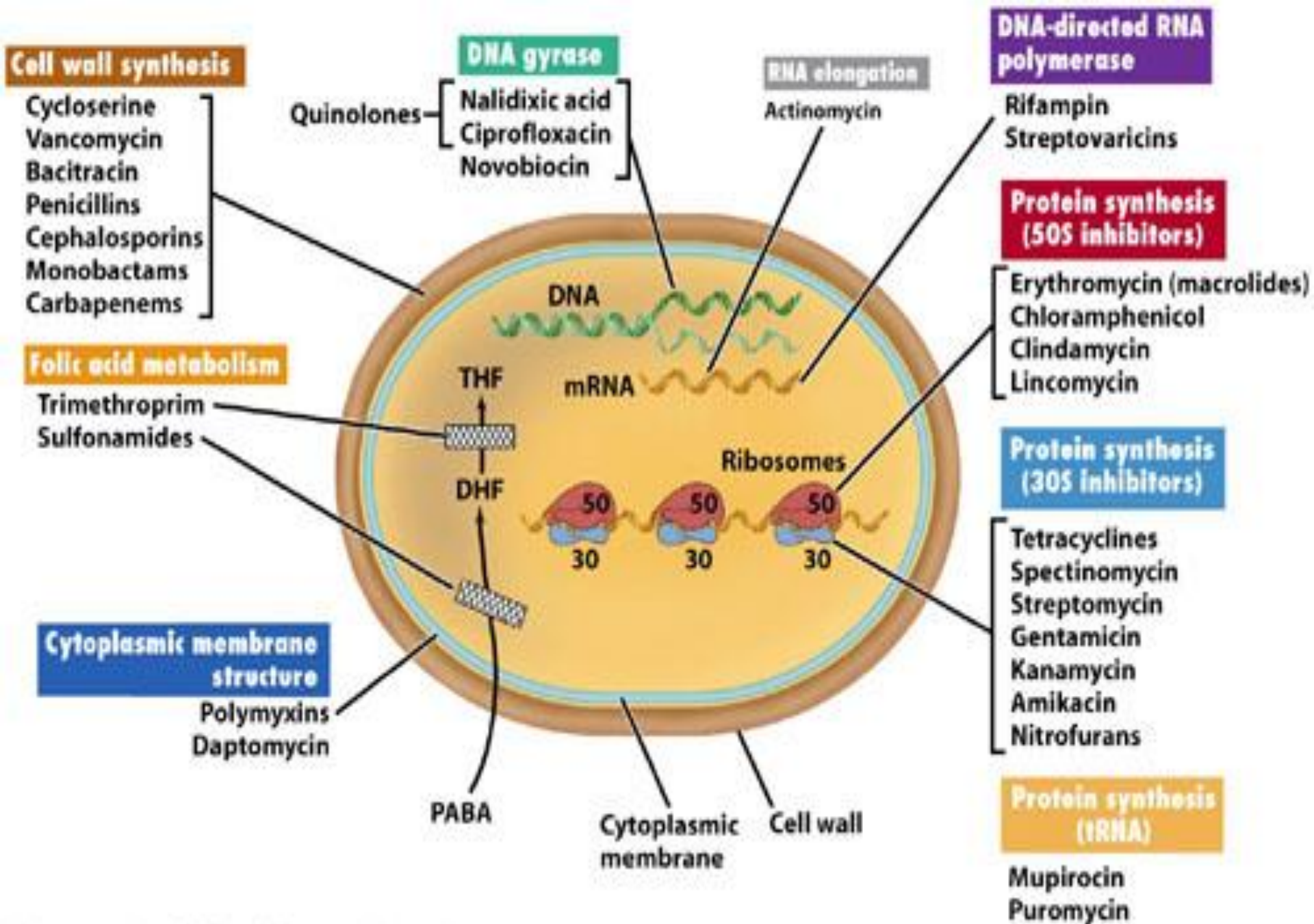


Figure 20-14 Brock Biology of Microorganisms 11/e  
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# Clindamycin

- **%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.)

# 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
- 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 .
- Rosacea: common skin condition that causes blushing or flushing and visible blood vessels in your face. It may also produce small, pus-filled bumps. These signs and symptoms may flare up for weeks to months and then go away for a while





# Metronidazole

- 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 .
  - ✚ Caution should be exercised when applying metronidazole near the eyes to avoid excessive tearing.

# Systemic therapy






## Indications:

- **Moderate inflammatory acne non-responsive to topical therapy**
- **nodulocystic acne**

## *Systemic therapy*

-  **Oral Antibiotics**
-  **Isotretinoin**
-  **Hormonal Therapy**

*Oral Antibiotics (used for 3-6 months)*

-  **Tetracycline 500mg X BD**
-  **Doxycycline 100mg X BD**
-  **Minocycline 100mg X OD**
-  **Eythromycin 500mg X BD**
-  **combined with topical therapy**

## *Isotretinoin (Accutane) indicated in*



**severe nodulocystic acne**










**non responsive acne**



**severe psychological distress**

## *Isotretinoin (RoAccutane) side effects*

-  **teratogenic**
-  **mucosal dryness**
-  **photosensitivity**
-  **arthralgias**
-  **alteration of liver enzymes**
-  **hypertriglyceridemia and hypercholesterolemia**
  
-  **Tumerogenic in animals**

## *Isotretinoin (RoAccutane)*

- ✚ **Retinoic Acid( Tretinoin):** is the acid form of Vitamin A. Stabilizes lysosomes, increases RNA polymerase activity, increases PGE<sub>2</sub>, 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.

# 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<sub>3</sub> derivative



# New Drugs for Psoriasis

## Apremilast(Otezla)

- psoriasis and psoriatic arthritis .
- It may also be useful for other immune system-related inflammatory diseases .
- The drug acts as a selective inhibitor of the enzyme phosphodiesterase 4 (PDE4) and inhibits spontaneous production of TNF-alpha from human rheumatoid synovial cells.

# Apremilast

## Side Effects

– diarrhea

–nausea.

–stomach pain.

–vomiting.

–headache.

–sore throat, cough, and fever.

–sneezing, runny nose, and nasal congestion.e-to-severe psoriasis demonstrating superior efficacy to apremilast

# New Drugs for Psoriasis

## Deucravacitinib (Sotyktu)

- A new oral treatment option for adults with plaque psoriasis.
- moderate-to-severe plaque psoriasis
- It is a once-daily oral medication with its clinical trials in moderate-to-severe psoriasis demonstrating superior efficacy to apremilast
- MOA: Allosteric inhibitor of TYK2
- Side effects:runny nose, congestion, or sore throat, sore on mouth, lips, gums, tongue or roof of mouth, acne.

New Drugs for Psoriasis  
**Roflumilast (Zorvye) cream**

Selective, long-acting inhibitor of the enzyme phosphodiesterase-4 (PDE-4). It has anti-inflammatory effects.

– chronic plaque psoriasis

– an effective topical therapy for use on all psoriasis-affected areas including body, face, and intertriginous areas



## New Drugs for Psoriasis

### **Tapinarof (Vtama)**

**Tapinarof (Vtama)** is a topical (on the skin) medication used to treat plaque psoriasis in adults.

- MOA: immune modulation, skin-barrier normalization, and antioxidant activity.
- It's convenient to use because it's only applied once daily

# Drugs for Psoriasis

- **Biologic Agents:**

- **Etanercept:**

- Dimeric fusion protein of TNF receptor linked to the Fc portion of human IgG<sub>1</sub>
- approved for the treatment of psoriasis, psoriatic arthritis, and ankylosing spondylitis in adults

# Anti-inflammatory Agents

- **Topical Corticosteroids:**

- Hydrocortisone.
- Prednisolone and Methylprednisolone.
- Dexamethasone and Betamethasone.
- Triamcinolone.
- Fluocinonide.

# Anti-inflammatory Agents

- **Topical Corticosteroids:**
  - **Absorption:**
    - **1% of hydrocortisone applied to the ventral forearm.**
    - **0.14 times of hydrocortisone applied to the plantar foot.**
    - **0.83 times of hydrocortisone applied to the palm.**
    - **3.5 times of hydrocortisone applied to the scalp.**
    - **6 times of hydrocortisone applied to the forehead.**
    - **9 times of hydrocortisone applied to the vulvar skin.**



# Anti-inflammatory Agents

- **Topical Corticosteroids:**
  - **Absorption:**
    - Absorption increased with inflammation.
    - Increasing the concentration does not proportionally increase the absorption.
    - Can be given by intralesional injection.

# 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 Corticosteroids:**

- **Adverse Effects:**

- Suppression of pituitary-adrenal axis.
- Systemic effects.
- Skin atrophy.
- Erythema.
- Pustules.
- Acne.
- Infections.
- Hypopigmentation.
- Allergic contact dermatitis.

# Agents affecting Pigmentation

- Hydroquinone.
- Monobenzone.
- Monobenzone may be toxic to melanocytes resulting in permanent depigmentation.
- Mequinol
  - 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.

# Trichogenic and Antitrichogenic Agents

- **Minoxidil (Rogaine):**
  - 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:(**
  - **5 $\alpha$ -reductase inhibitor which blocks the conversion of testosterone to dihydrotestosterone.**
  - **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. braziliensis* causes: Mucocutaneous leishmaniasis.

*L. Donovanii* causes: Visceral leishmaniasis

# Sodium Stibogluconate

**Pentavalent 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 hemolympathic stage.

# Pentamidine

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

# Antilepromatous Drugs

- **Dapsone and Sulphones:**

- 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.