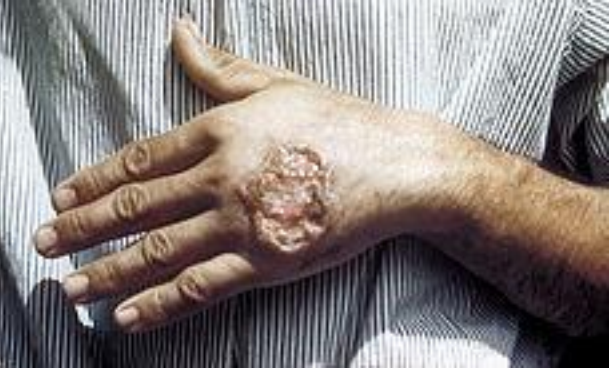
Drugs For Leishmania

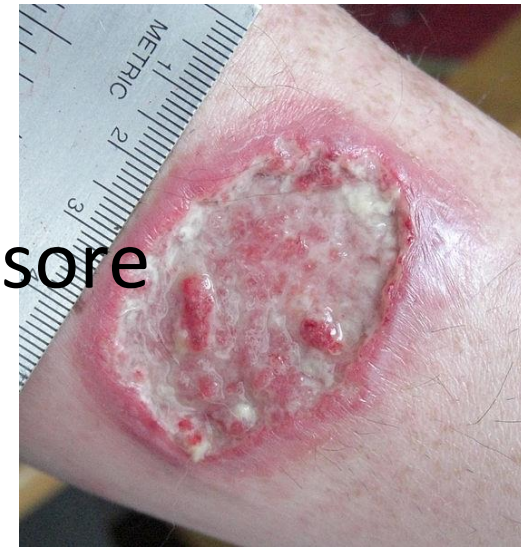


Leishmaniasis

Caused by three *Leishmania species:*

- *L.tropica* causes:

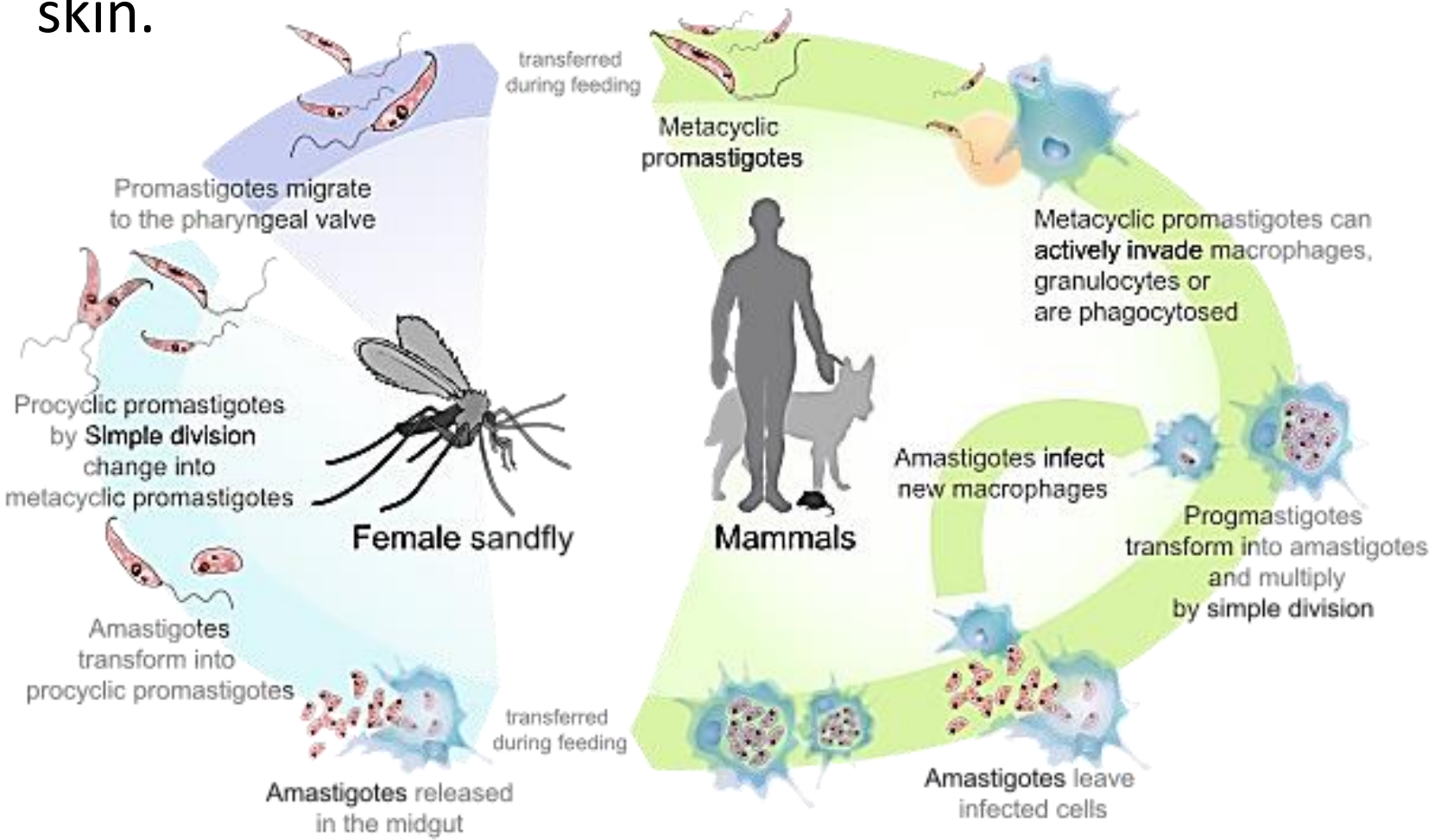
  Cutaneous leishmaniasis or oriental sore



- *L. brazeliensis* causes: Mucocutaneous leishmaniasis
- *L. Donovani* causes: Visceral leishmaniasis

The Parasite

- Is transmitted from animals to humans by the bite of infected sand fly.
- Diagnosed by the presence of parasite in biopsy from skin.



Sodium Stibogluconate (Pentostam)

- Drug of choice for all forms of leishmaniasis.
- Pentavalent antimonial
- Binds to SH groups on proteins.
- Typical preparations contain 30% to 34% pentavalent antimony by weight
- Dose: 20 mg/kg per day
- Resistance is increasing, especially in India.

- MOA: Unknown, Production of oxygen free radicals

Sodium Stibogluconate

- Not absorbed orally

- Given IV/ IM for 20 days for cutaneous leishmaniasis
- 28 days for visceral and mucocutaneous disease.

- Distributed in extravascular compartment.
- Partially metabolized
- Excreted in urine

Adverse effects

- GIT upset
- Fever, headache, arthralgia , rash.
- IMI----(local pain & sterile abscess).
- QT prolongation.
- Hemolytic anaemia

Amphotericin

- Antifungal agent.
- Alternative therapy for visceral leishmaniasis, especially in areas with high resistance.
- **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

Miltefosine

- An alkylphosphocholine analog
- 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

- Not absorbed orally
- Given IV/ IM.
- Accumulative drug & eliminated slowly in urine (elimination half-life 12 days).
- Not effectively cross blood brain barrier
- Can be inhaled as a nebulized powder.

Pentamidine

Leishmaniasis:

Alternative to sodium stibogluconate for visceral leishmaniasis

Pneumocystis jiroveci:

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

Trypanosomiasis:

For early hemolymphatic stage.

Pentamidine

Adverse Effects:

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

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.**

Trichogenic and Antitrichogenic Agents

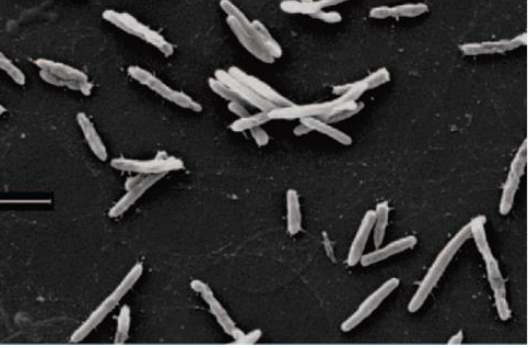
- **Minoxidil (Rogaine):**
  - **Designed as an antihypertensive agent.**
  - **Effective in reversing the progressive miniaturization of terminal scalp hairs associated with androgenic alopecia.**
  - **Vertex balding is more responsive than frontal balding.**

Trichogenic and Antitrichogenic Agents

- **Minoxidil.**
- **Finasteride (Propecia):**
  - **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.**

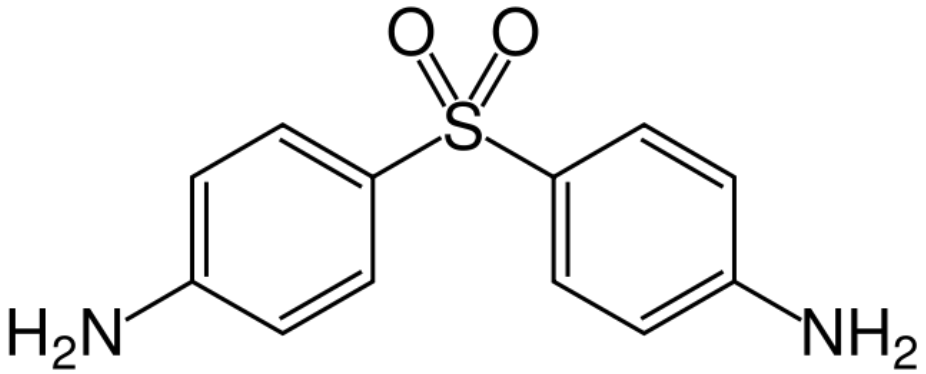


Leprosy

- A chronic disease caused by the bacteria Mycobacterium leprae and Mycobacterium lepromatosis
- a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract, skin lesions are the primary external sign

1941: Discovery of Dapsone

- Targets dihydropteroate synthase (DHPS)
- Inhibits nucleic acid synthesis



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

- **<u>Dapsone and Sulphones:</u>**
  - **Hemolysis, particularly in G-6-PD deficiency.**
  - **GIT intolerance**
  - **Fever, Pruritus, Rashes.**

Erythema Nodosum Leprosum

Inflammation of the fat cells under the skin (panniculitis)

suppressed by :

- **Steroids**
- **Thalidomide**
- **Chochicine**

1960's: Rifampicin and Clofazimine Discovered

- **Rifampicin (Rifampin):** Inhibit RNA synthesis

- **Clofazimine:**

  Anti-inflammatory

Rifampin

- ***Stretomyces miditerranei.***
- **Mycobacteria, enterococci and chlamydia**
- **Binds to the beta subunit of bacterial DNA-dependant RNA polymerase and therefore inhibits RNA synthesis.**
- **Rifampin does not affect mammalian polymerases**

Rifampin

- **Bactericidal**
- **Well distributed.**
- **Well absorbed, highly bound to proteins**
- **Hepatic metabolism and exhibits enterohepatic recirculation.**

Uses of Rifampin

- **TB**
- **Leprosy**
- **Meningococcal Carrier State**
- **Prophylaxis in *H.influenzae.***
- **Serious Staph osteomyelitis and valve endocarditis.**

Rifampin: side effects

GI disturbances : nausea, vomiting

- Nervous system symptoms: headache, dizziness, and fatigue.
- Hepatitis is a major adverse effect, and the risk is highest in patients with underlying liver diseases and in slow isoniazid acetylators; the rate of hepatotoxicity is increased if isoniazid and rifampin are combined
- Induce hepatic cytochrome P-450 enzymes, leading to an increased metabolism of many drugs

Rifampin

- Hypersensitivity reactions, such as pruritus, cutaneous vasculitis, and thrombocytopenia, are seen in some patients
- An immune-mediated systemic flu-like syndrome with thrombocytopenia also has been described.
- Rifampin imparts a harmless red-orange color to urine, feces, saliva, sweat, tears, and contact lenses.
- Absorption is impaired if rifampin is given concurrently with aminosalicylic acid or is taken immediately after a meal.

Antilepromatous 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.

1981: WHO Proposes Multi-Drug Therapy (MDT)

- Combination of DAPSONE, RIFAMPICIN, and CLOFAZIMINE

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