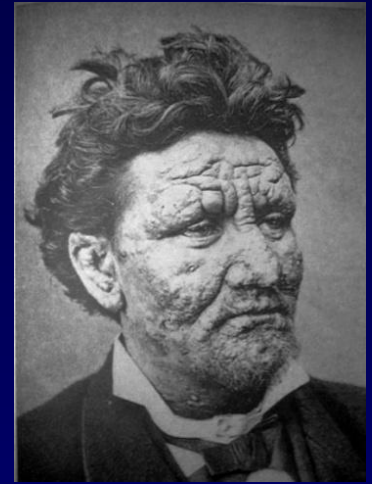


# Anti-leprotic agents



“It should be recognized that the tremendous physical and social burden caused by leprosy can not be fully expressed just in terms of statistics.”

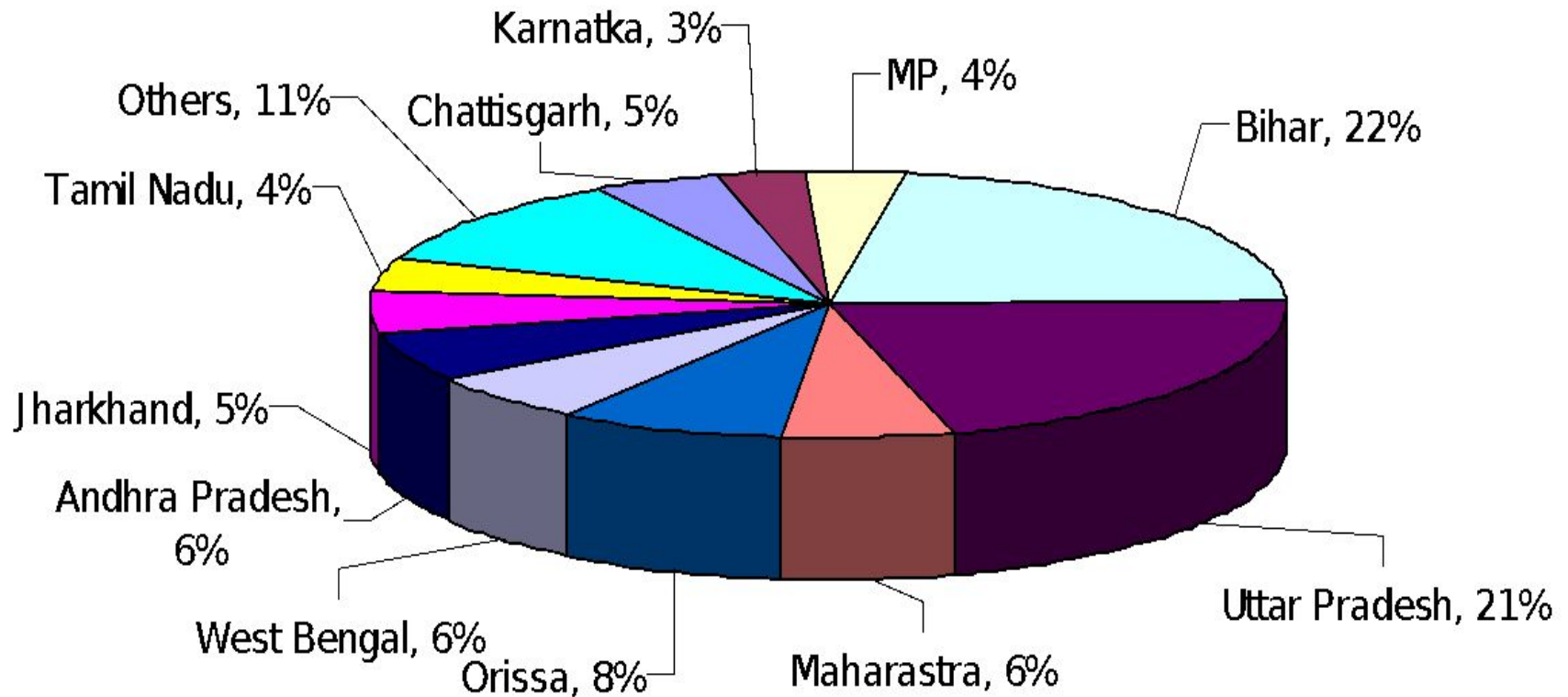
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Dept of Pharmacology  
MGM Medical College

# Outline

- Leprosy
  - Cause
  - Clinical presentation
  - Diagnosis
  - Ways of transmission
- Classification of Leprosy
- Antileprotic Drugs
- Multi Drug Therapy (MDT) of Leprosy

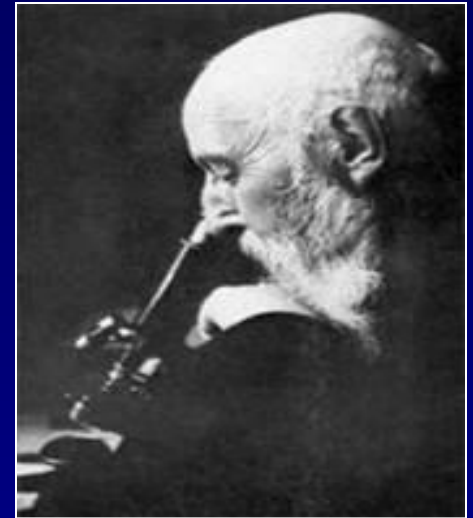
# Proportion of Leprosy Cases in India



**March 2011**

# What is leprosy?

- Leprosy is a chronic infectious disease caused by *mycobacterium leprae*, an acid-fast, rod-shaped bacillus.
- It is also known as *Hansen disease*
- The disease affects the
  - Skin
  - Peripheral nerves
  - Mucosa of upper respiratory tract
  - Eyes
- *Mycobacterium lepromatosis* in 2008



Gerhard Armauer  
Hansen(1873)

# Clinical presentation of Leprosy



Hypopigmented patches



Nerve enlargement



Neurological deficits



Nodules on the ears

# Diagnosis of Infection

- Clinical features
- Skin Smear / skin , nerve lesion biopsy
- Lepromin test : Intradermal injection of M Leprae.

# Ways of Infection

- Skin to skin
- Respiratory route
- Animals that harbor organism

# Animals that harbor M. Leprae in nature

- Armadillo



- Some types of monkeys

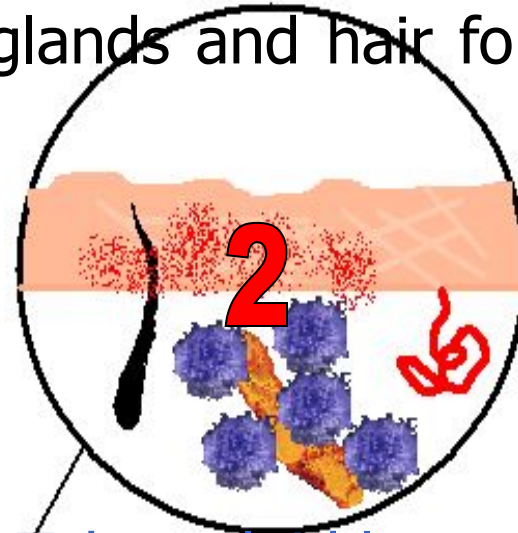
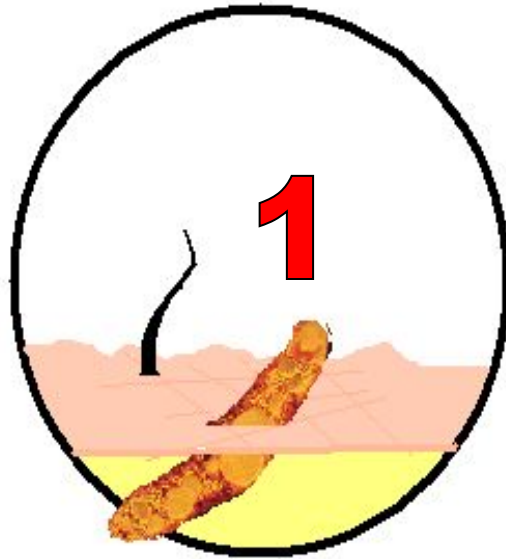


- Rabbits and Mices (foot pads)



The Immune cells attempt to seal off the infection, which can destroy sweat glands and hair follicles and the skin's sensitivity.

## **Mycobacterium Leprae enters the body**



Tuberculoid leprosy

Immune cells unable to destroy M. Leprae & the bacteria multiplies freely in the skin.



Lepromatous leprosy

## **Pathophysiology**

# Difference

| <b>Tuberculoid</b>                               | <b>Lepromatous</b>                                                                |
|--------------------------------------------------|-----------------------------------------------------------------------------------|
| Anaesthetic patch                                | Diffuse skin and mucous membrane infiltration, nodules                            |
| CMI is normal                                    | CMI absent                                                                        |
| Lepromin test positive                           | Lepromin test negative                                                            |
| Bacilli rarely found in biopsies                 | Bacilli found in biopsies                                                         |
| Prolonged remissions with periodic exacerbations | Progress to anesthesia of distal parts, atrophy, ulceration, absorption of digits |

# Classification of Leprosy

## Paucibacillary leprosy (PBL)

- Indeterminate (I)
- Borderline tuberculoid (BT)
- Tuberculoid(T)

## Multibacillary leprosy (MBL)

- Borderline(BB)
- Borderline lepromatous (BL)
- Lepromatous(L)

# Goals of Treatment

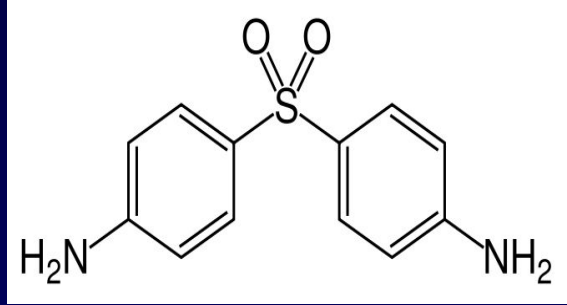
Major goals of treatments are:

1. Early detection of patients
2. Appropriate treatment
3. Adequate care for the prevention of disabilities and rehabilitation:  
specific, paralytic & anaesthetic

# Classification

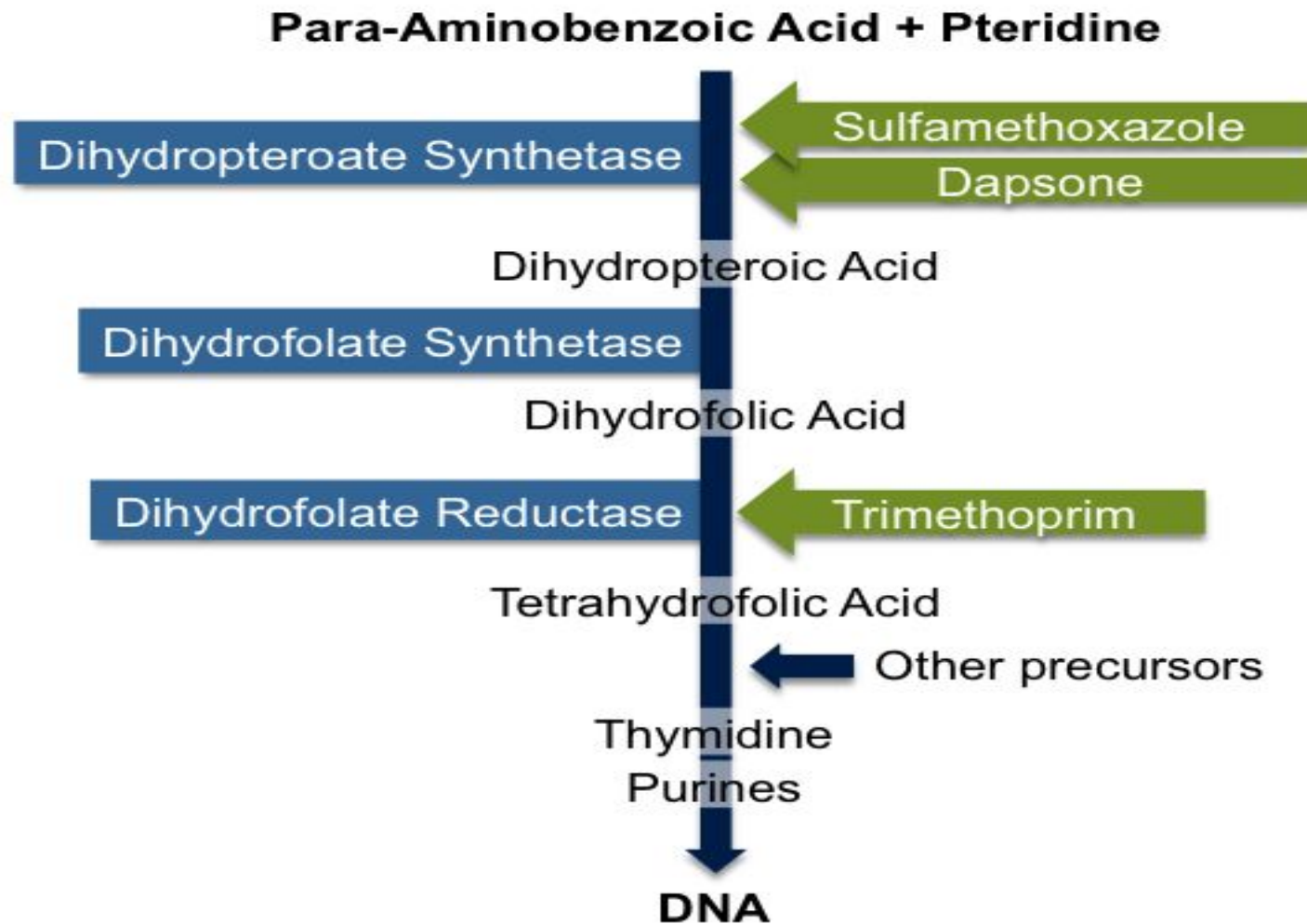
- Sulfone : Dapsone
- Phenazine derivatives : Clofazimine
- Antitubercular drugs : Rifampin,  
Ethionamide
- Antibiotics : Ofloxacin,  
Minocycline,  
Clarithromycin

# Dapsone



- It was discovered by German chemists Fromm and Wittmann in 1908
- **Structure:** Diamino diphenyl sulfone (DDS)
- Cheapest, most active and most commonly used member
- Leprostatic at low doses
- **MAO:** Folate antagonist

# Dapsone: Mechanism of action



# Dapsone



- Resistance to dapsone is increasing
  - Primary (2.5-40 %) resistance
  - Secondary resistance (20%)
- Pharmacokinetics:
  - Poor penetration in CSF
  - Protein binding: 70 %
  - Concentrated in skin (muscle, liver, kidney)
  - Retention in tissues and entero-hepatic circulation
  - T<sub>1/2</sub>: 24 h

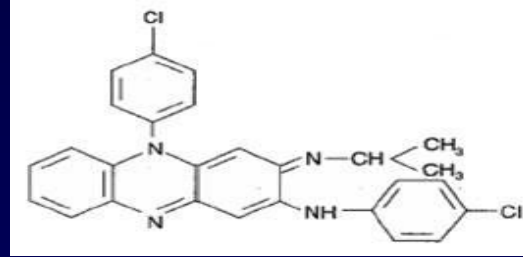
# Dapsone

- ADR:
  - Hemolysis of RBCs
  - Nausea & vomiting
  - Fever, allergic dermatitis, methemoglobinemia, & phototoxicity
  - Hepatitis and agranulocytosis
  - Lepra reaction :
    - Lesions enlarge, malaise, Neuritis (Type 1)
    - Erythema nodosum leprosum, fever (Type 2)

# Dapsone

- ADR:
  - **Sulfone syndrome:** fever, malaise, lymph node enlargement, dermatitis, skin rash, hepatitis
- Uses:
  - Leprosy
  - Chloroquine resistant malaria
  - Pneumocystis pneumonia
  - Acne
- Preparations
  - 25, 50 and 100 mg tab, 5 % gel

# Clofazimine



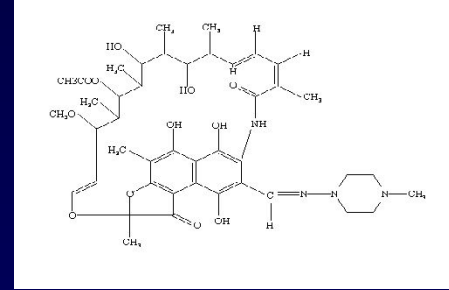
- Dye, synthesized by Dr. Vincent Barry, 1954 (B663)
- Leprostatic and anti-inflammatory activity
- MAO: interfere with template formation of DNA in *M. leprae*, accum. of lysophospholipids
- Dapsone resistant *M. leprae* respond to Clofazimine
- PK: Oral absorption (40-70 %), CSF conc. poor
  - Accumulates in fat
  - T 1/2 70 days

# Clofazimine



- ADR:
  - Reddish black discoloration of skin
  - Discoloration of hair and body secretions
  - Dryness of skin and itching
  - Conjunctival pigmentation
  - GIT: Enteritis , loose stools, abdominal pain
- Uses:
  - MDT for MAC, leprosy, Lepra reaction
- Preparations
  - 50 and 100 mg capsule

# Rifampicin



- **Source:** *Streptomyces mediterranei*
- **AMS:** *M. tuberculosis*, *S. aureus*, *N. meningitidis*, *H. influenza*, *E. Coli*, *Klebsiella*, *Pseudomonas*, *Proteus*
- **MAO:** Inhibits DNA dependent RNA synthesis
- **PK:** well absorbed, penetrates cavities & meninges
  - Enzyme inducer (corticosteroids, OCP, sulfonylureas, warfarin)

# Rifampicin

- **ADR:** Hepatitis, urine & secretions orange red
  - Respiratory, cutaneous , Flu, Abdominal syndrome
- **Uses:** Leprosy
  - Meningitis (H. influenza)
  - Brucellosis comb with doxycycline
- **Preparation:** 150, 300, 450 , 600 mg capsule



## Ethionamide

- Hepatotoxic , reserved drug

## Antibiotics

- Ofloxacin
  - Alternative to rifampicin
  - Hastens the bacteriological and clinical response (99.9 % bacilli in 22 days)
  - Alternate MDT, Dose: 400mg/day
- Clarithromycin
  - Less bactericidal than Rifampicin
  - Alternate MDT, Dose 500 mg/day
- Minocycline
  - High lipophilicity
  - Alternate MDT ,Dose: 100 mg/day

# Monotherapy of Leprosy

- National Leprosy Control Programme in 1955
- Dapsone 100 mg daily (5 days/week)
  - PBL: 4-5 years
  - MBL: 8-12 years
- Threatened the efficacy of monotherapy
  - Emergence of Dapsone resistance in 1964
  - Relapse rate 20%
  - Primary dapsone resistant cases increased

# Multi Drug Therapy of leprosy

- WHO in 1981
  - Microbial persisters
  - Dapsone resistance strains
- Included under the National Leprosy Eradication Programme (NLEP) in 1982
- PBL: Dapsone + Rifampicin for 6-12 months
- MBL: Dapsone + Rifampicin + Clofazimine for 2 years
- Fixed duration therapy : WHO (1994) whether disease inactivity/skin smear negativity attained or not

# Multi Drug Therapy

|                    | <b>Multibacillary</b>                                            | <b>Paucibacillary</b>             |
|--------------------|------------------------------------------------------------------|-----------------------------------|
| <b>Rifampicin</b>  | <b>600 mg/month supervised</b>                                   | <b>600 mg/month supervised</b>    |
| <b>Dapsone</b>     | 100 mg/daily<br>self administered                                | 100 mg/daily<br>self administered |
| <b>Clofazimine</b> | <b>300 mg/month Supervised</b><br>50 mg/day<br>Self administered |                                   |
| <b>Duration</b>    | 12 months                                                        | 6 months                          |

**Single Lesion:** ROM regimen- Rifampicin 600 mg  
+ Ofloxacin 400 mg + Minocycline 100 mg

# Multi Drug Therapy



PB adult blister pack

## PB adult treatment:

### Once a month: Day 1

- 2 capsules of rifampicin (300 mg X 2)
- 1 tablet of dapsone (100 mg)

### Once a day: Days 2–28

- 1 tablet of dapsone (100 mg)

**Full course:** 6 blister packs



MB adult blister pack

## MB adult treatment:

### Once a month: Day 1

- 2 capsules of rifampicin (300 mg X 2)
- 3 capsules of clofazimine (100mg X 3)
- 1 tablet of dapsone (100 mg)

### Once a day: Days 2–28

- 1 capsule of clofazimine (50 mg)
- 1 tablet of dapsone (100 mg)

**Full course:** 12 blister packs

# ADVANTAGES OF MDT

- Highly effective in curing the disease(12 Vs 2 million)
  - Interrupts transmission of infection
- Reduces the period of treatment
- Well accepted by patients
- Prevents development of drug resistance
- Reduces risk of relapse (0.7 % MBL Vs 1.1% PBL)
- Prevents disabilities
- Improves community attitude

# Alternative Regimens

- Clofazimine 50 mg + any two of Ofloxacin 400 mg/Minocycline 100 mg/Clarithromycin 500 mg daily for 6 months
- Followed by Clofazimine 50 mg + any one of Ofloxacin 400 mg/minocycline 100 mg daily for 18 months
- Rifampicin 600 mg + Sparfloxacin 200 mg + Clarithromycin 500 mg + minocycline 100 mg for 12 weeks