



# Leprosy

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# Introduction

- ▶ Leprosy is associated with a stigma





# Introduction

- ▶ Leprosy in the Old Testament is not one disease
  - Original Hebrew "tsara'ath" – group of diseases
  - Translated to "lepra" in Greek – 100 BC
  - 1384 Wycliffe translated "lepra" to "leprosy" a disease seen in Europe at that time and described as a "unholy and loathsome condition"



# General

- ▶ One of the leading causes of permanent physical disability in the world
- ▶ Afflicts individuals in their most productive stage of life
- ▶ Multi-drug therapy (MDT) can eliminate leprosy as a public health problem (prevalence  $< 1/10,000$ )
- ▶ MDT can also bring about cure without disability

# Global Situation

WHO region	Registered cases 2000 (rate/10,000)	New cases detected 1999 (rate/100,000)
Africa	64490 (1.0)	55635 (8.6)
Americas	90447 (1.1)	45599 (5.7)
SE Asia	574924 (3.8)	621620 (41.3)
E Mediterranean	8785 (0.2)	5757 (1.2)
W Pacific	13771 (0.1)	9501 (0.6)
Europe	846 (negligible)	172 (negligible)
Total	753263 (1.25)	738284 (12.3)

Manson's Tropical Medicine, 21<sup>st</sup> edition, pp1065



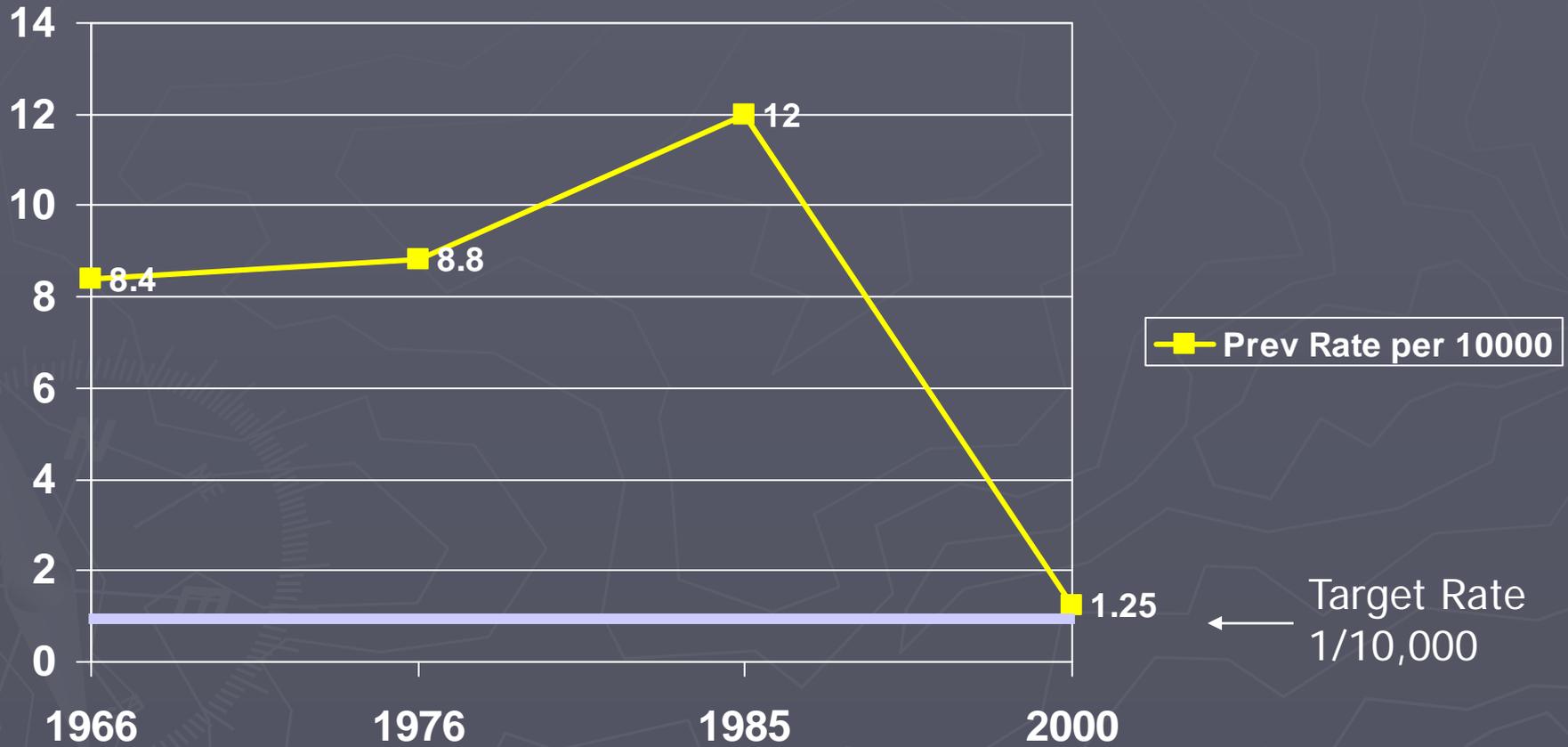
# Prevalence of Leprosy - top 11 countries

Country	Registered cases 2000	Prevalence / 10000	New cases during 1999	Detection rate / 100000
India	495073	5.0	537956	54.3
Brazil	78068	4.3	42055	25.9
Myanmar	28404	5.9	30479	62.9
Indonesia	23156	1.1	17477	8.3
Nepal	13572	5.7	18693	78.7
Madagascar	7865	4.7	8704	51.6
Ethiopia	7764	1.3	4457	7.4
Mozambique	7403	3.9	5488	28.7
D.R. Congo	5031	1.0	4221	8.6
Tanzania	4701	1.4	5081	15.4
Guinea	1559	2.0	2475	32.0
Total	672596	4.1	677086	41.7





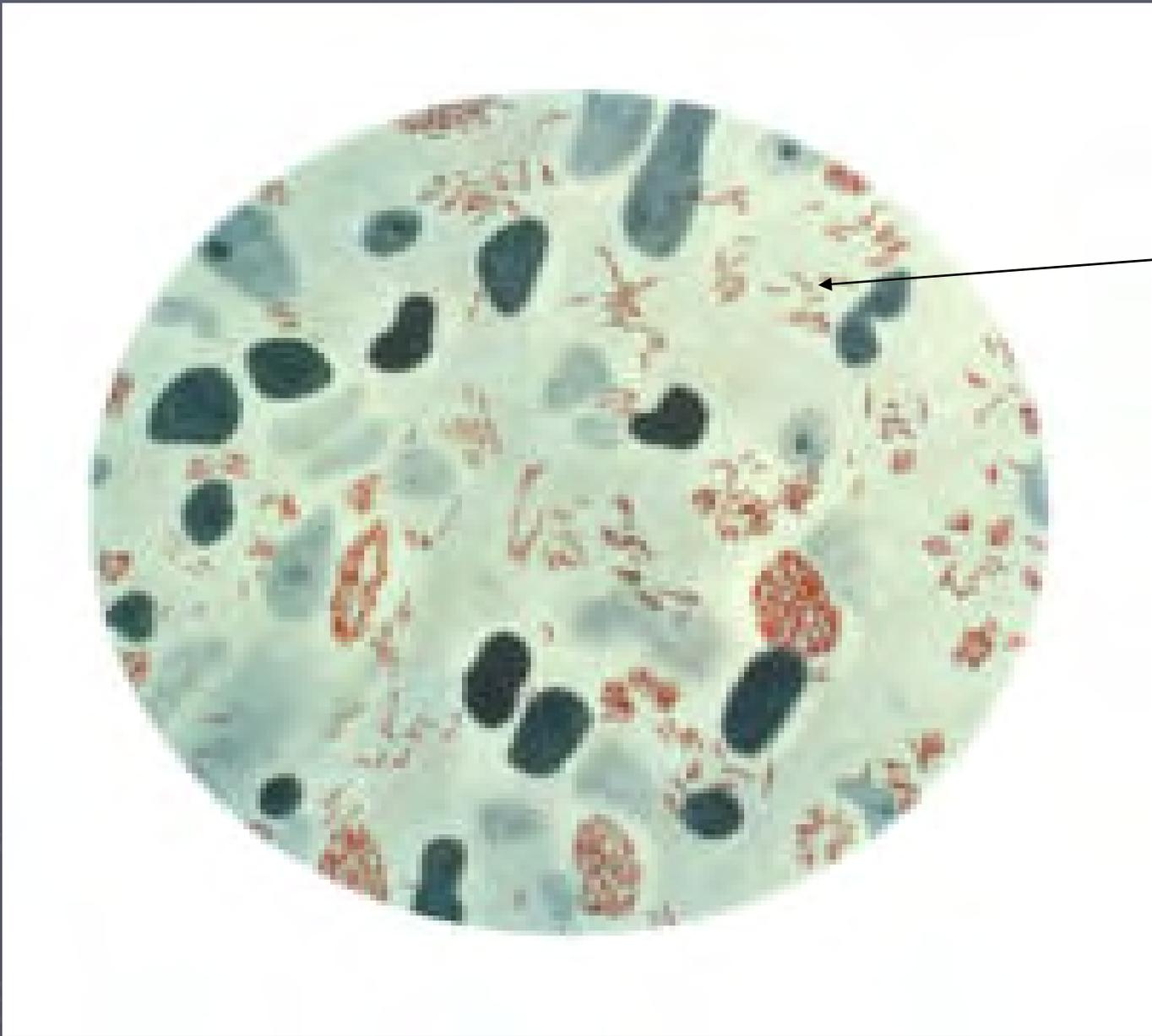
# Registered Cases





# Organism

- ▶ Mycobacterium leprae – acid fast bacillus
- ▶ Primarily found in masses within macrophages
- ▶ Intra and extra-cellular globi



Leprosy bacilli

# Transmission

- ▶ Two portals of exit
  - Skin
  - Nasal mucosa
    - ▶ Majority of lepromatous patients have bacilli in nasal secretions from blowing the nose
    - ▶ Can yield as many as 10 million viable organisms per day
- ▶ MDT renders a person non-infective after a few doses



# Viability of *M. leprae*

- ▶ 36 hours to 9 days
- ▶ Contaminated fomites and clothing could be a source of infection



# Portal of Entry

- ▶ Skin
- ▶ Upper respiratory tract – most likely route
- ▶ Others?
  - Breast Milk
  - Placental



# In vitro culture

- ▶ No substantiated in vitro culture of the bacillus



# In vivo culture

- ▶ Mouse footpad culture is the standard
- ▶ Use of the footpad culture method
  - Culture diagnosis of patients
  - Minimum concentration of treatment drugs
  - Sensitivity to new drugs
  - Drug resistance in patients

# Nine banded Armadillo

- ▶ The armadillo can be infected with leprosy
- ▶ Has a primitive immune system and low body temperature
- ▶ IV inoculation produces disseminated disease
- ▶ Main source of leprosy research





# Other animals

- ▶ Chimpanzee in Sierra Leone
- ▶ Mangabey monkey in West Africa



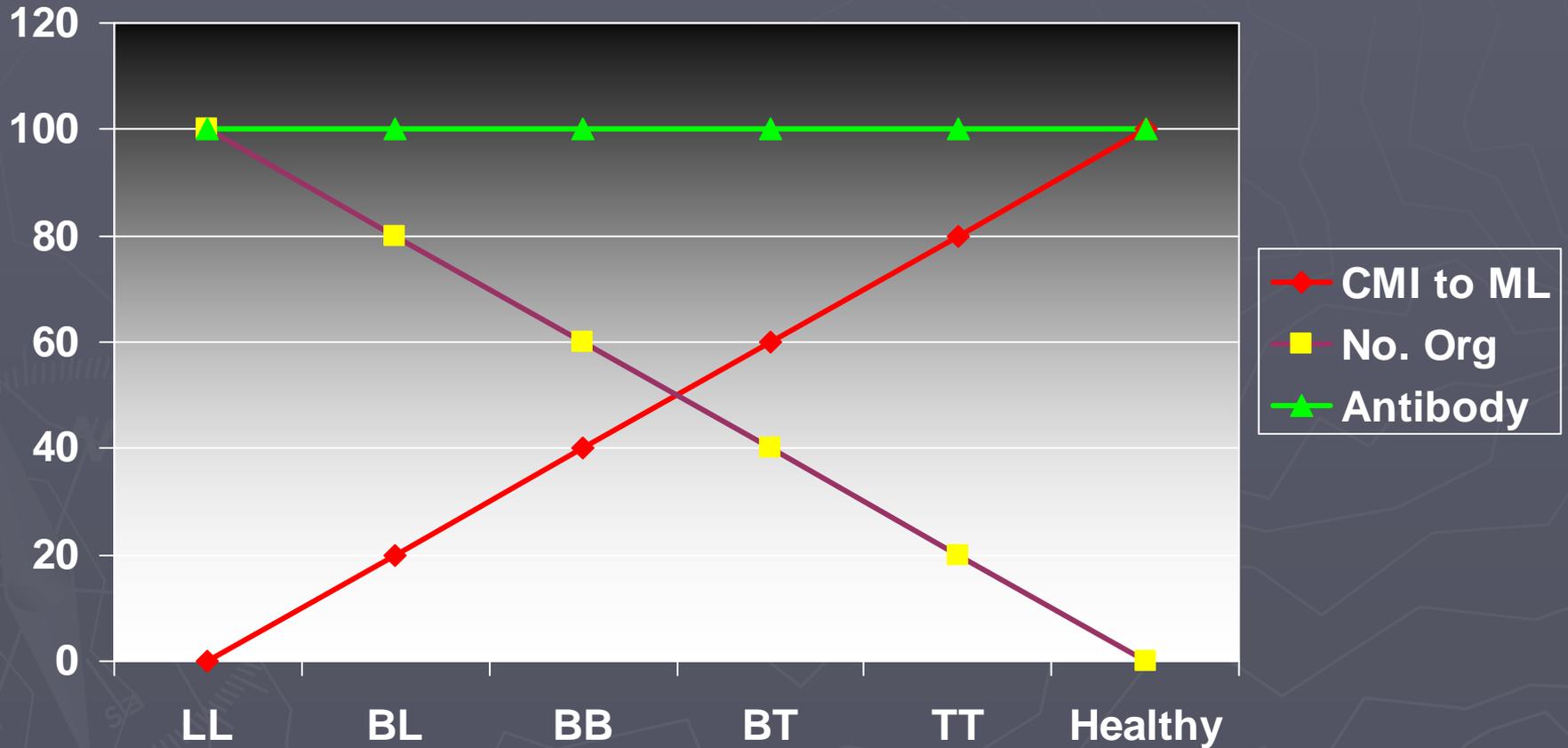
# Family tree

- ▶ M. leprae has the longest doubling time of all known bacteria – extreme case of reductive evolution
- ▶ Less than half the genome contains functional genes eliminating many important metabolic activities
- ▶ There are 1500 genes common to TB and M leprae
- ▶ TB and M leprae derived from a common ancestor and likely had gene pools of similar size
- ▶ Many of the genes of M leprae have been lost.

# Epidemiology

- ▶ Transmission = close contact with leprosy patients
  - Cebu – 6.2/1000/year
  - South India – 55.8/1000/year
- ▶ Upper respiratory route most likely
- ▶ Other factors for clinical expression;
  - Genetics
  - Route of entry
  - Malnutrition
  - Prior exposure to other mycobacterial organisms

# Leprosy an Immune Disease





# Epidemiology - Age at onset

- ▶ Mainly young adults
- ▶ Range of infections from 3 weeks old to 141 years old



# Epidemiology - Gender

- ▶ Males affected more than females – 2:1 ratio
- ▶ In many parts of Africa there is an equal gender distribution
- ▶ In Uganda, Nigeria, Malawi, Gambia, Burkina Faso, Zambia, Thailand, and Japan there is a female predominance



# Epidemiology - Incubation period

- ▶ Few weeks to 30 years +
- ▶ The average – 3-5 years



# Epidemiology – Sub Clinical Infection

- ▶ Sub-clinical infection is far more common than overt disease
- ▶ The factors influencing the onset of disease may be different from those associated with infection



# Epidemiology – Household contacts

- ▶ Household contacts of leprosy patients are at greater risk of developing leprosy disease vs non-household contacts
- ▶ Household contacts contribute only a limited proportion of all new cases



# Epidemiology - HIV

- ▶ No association of HIV and leprosy

# Epidemiology - BCG

- ▶ BCG seems to provide some protection against leprosy
  - Field trials – Malawi, Myanmar, Papua New Guinea, Uganda, Venezuela, India
  - Protective efficacy – 20-30% Myanmar, 50% Venezuela, 80% in Uganda
  - Greater effect if vaccinated < 15 yo
  - Booster doses seems to increase protection
  - Addition of killed *M leprae* organisms does not increase protection
  - Use of BCG may be contributing to the decline of leprosy worldwide



# Epidemiology - Disability

- ▶ 2 million worldwide with leprosy disability
- ▶ Men
- ▶ Multibacillary forms
- ▶ Age
- ▶ Duration of disease
- ▶ Significantly reduced with MDT

# Epidemiology - Lepromin

- ▶ This skin test is still used as an indicator of CMI response to the organism
- ▶ Limited use in diagnosis or indicator of protective immunity
- ▶ Use killed organisms
  - Fernandez reaction – 48 hours
  - Mitsuda
    - ▶ Delayed CMI response (3-4 weeks)
    - ▶  $\geq 5$  mm – tuberculoid
    - ▶ 3-5 mm – borderline
    - ▶ 0-2 mm - lepromatous



# Epidemiology - Mortality

- ▶ Rarely the immediate cause of death
- ▶ Indian and Philippines lepromatous patients had a 4X and non-lepromatous patients have a 2X increased mortality vs the general population

# Clinical - General

- ▶ Majority of people significantly exposed experience infection but develop no signs or symptoms
- ▶ Onset is quite variable and progression is usually insidious
  - Skin lesions – hypopigmented or erythematous patch with anesthesia, single, multiple or diffuse
  - Spontaneous healing is common in childhood and some communities
  - Unlike TB there is an absence of toxicity with large numbers of organisms present
  - At any stage sudden exanthems may be seen associated with fever
  - Chronic onset is so gradual and insidious that it is usually far advanced on presentation
  - Acute onset (less common) presents often with multiple lesions that spread rapidly and contain numerous bacilli, often associated with another stressor



Credit to Tom Rey, Univ of Iowa

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# Case Definition

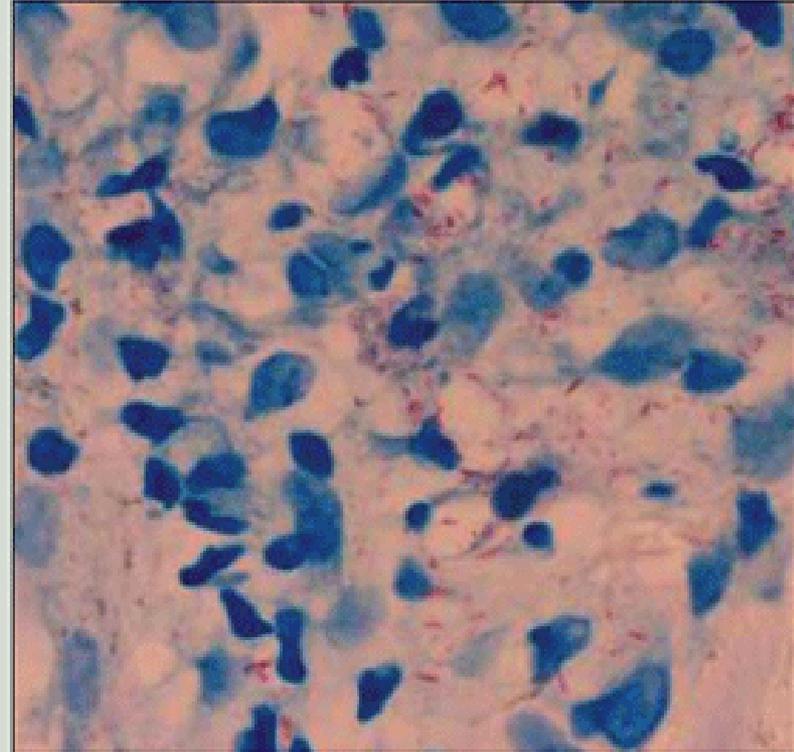
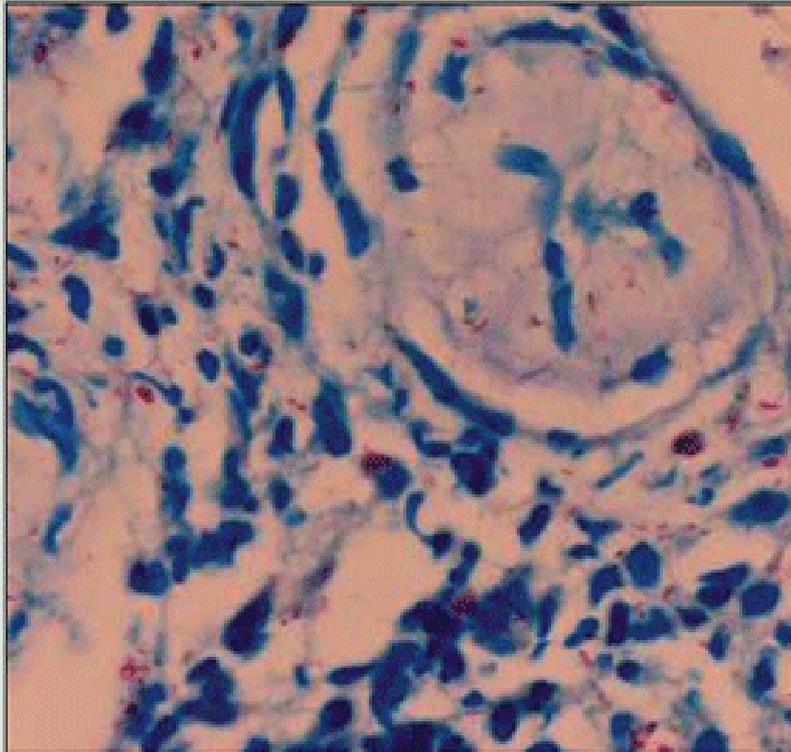
- ▶ Hypopigmented or erythematous skin lesion(s) associated with loss of sensation
- ▶ Involvement of the peripheral nerves with loss of sensation and weakness of the muscles of the hands, feet or face
- ▶ Positive skin smear for leprosy bacilli

Must have at least one of the above to meet the case definition

# Ridley-Jopling Classification

Sign or Test	Type of Leprosy				
	TT	BT	BB-BL	LL	Indeterminate
No of lesions	Usually single	Single or few	Several or many	Very many	Vague hypopigmented or ery macules
Size of lesions	Variable	Variable	Variable	Small	Variable
Surface of lesions	Very dry, scaly	Dry	Shiny	Shiny	Variable
Hair in lesions	Absent	Moderately diminished	Slightly diminished	Non-affected	Variable
Sensation	Completely lost	Moderate-marked loss	Slight-moderate loss	No loss early	Variable
AFB in smears	None	None or scanty	Several – many	Very many plus globi	None or scanty
Nasal AFB	None	None	None (scanty rarely)	Very many plus globi	Negative or scanty
Lepromin test	+++	+ or ++	Negative	Negative	Negative or +

**FIGURE 3**



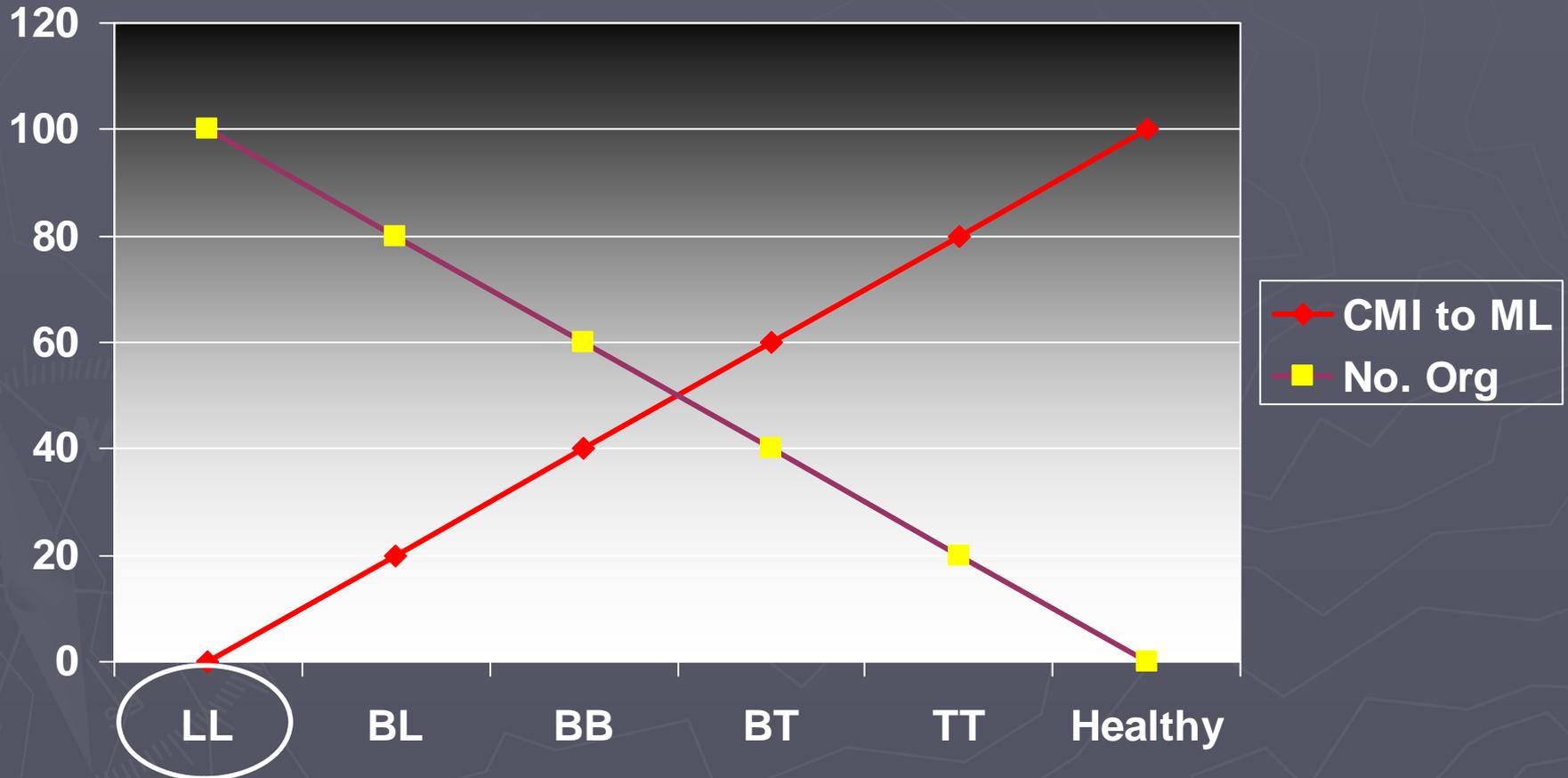
Fite stain of the biopsy specimen under oil immersion at 100x magnification shows numerous acid-fast bacilli and that organisms have infiltrated a nerve. Note the foamy histiocyte in the image at right.



Hematoxylin-eosin stain of the biopsy specimen under oil immersion at 100x magnification reveals a superficial and mid-perivascular infiltrate dominated by lymphocytes without spongiosis.



# Leprosy an Immune Disease



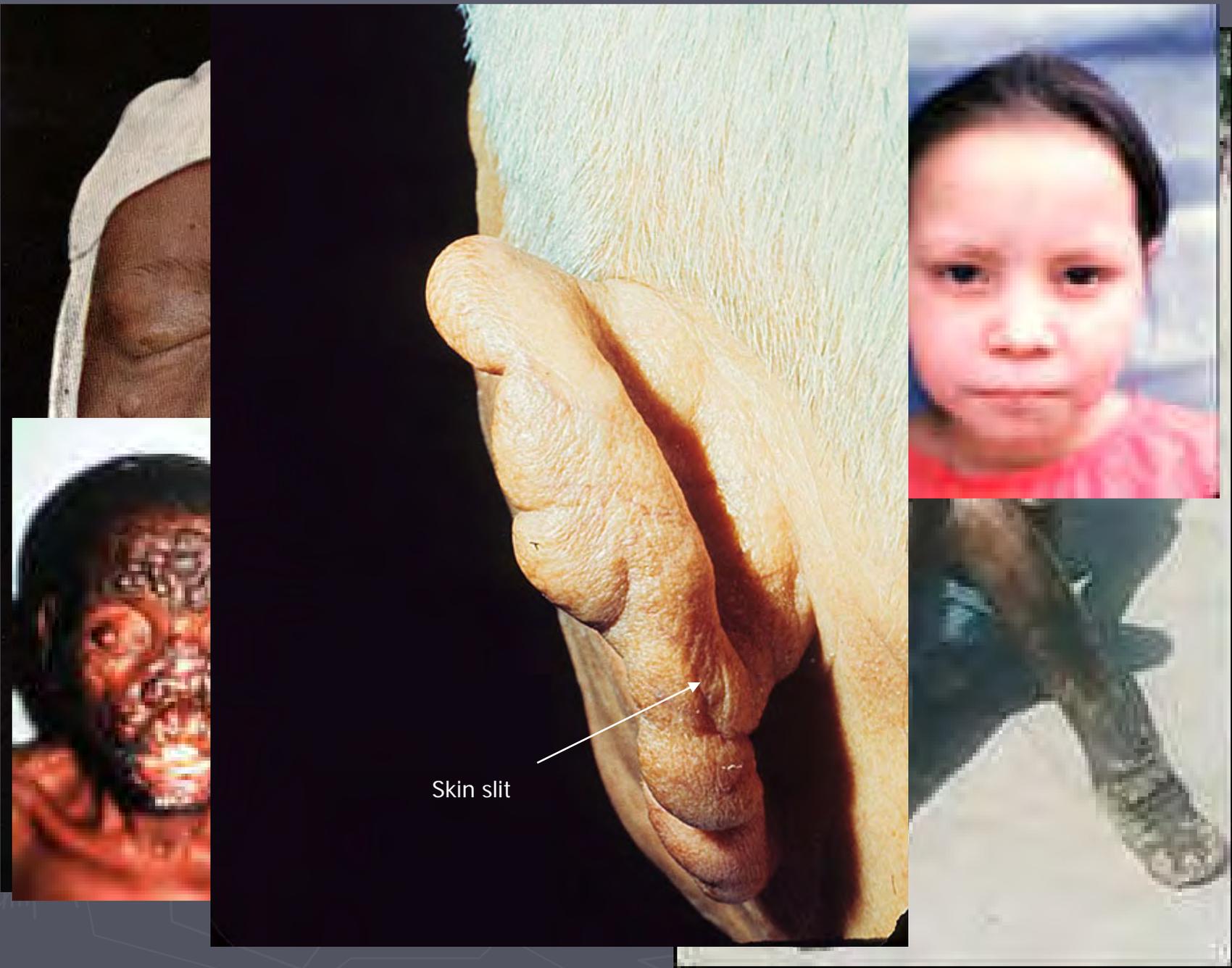


# Lepromatous Leprosy

- ▶ Wide dissemination
  - Skin
  - Nerves
  - Reticuloendothelial system
  - Eyes
  - Testes
  - Bones
  - Mucous membranes
  - Mouth
  - Nose
  - Pharynx
  - Trachea

# Lepromatous Leprosy - Skin

- ▶ Multiple, symmetric macules (flat), plaques (elevated), papules and nodules
- ▶ Macules are usually the first seen most commonly seen on the face, buttocks and extremities
- ▶ Macules may be erythematous in light skin and faintly hypopigmented in dark skin
- ▶ Plaques are elevated and do not appear on the palms and soles
- ▶ Papules and nodules occur as the disease advances and favor the face, ears and buttocks
- ▶ Leonine facies – enhanced wrinkles, loss of eyebrows
- ▶ Nodules and plaques may ulcerate on legs when associated with lymphedema
- ▶ Pure Diffuse – skin of the whole body becomes infiltrated and resembles scleroderma, also can be associated with Lucio's phenomena



Skin slit



# Lepromatous Leprosy – Nerve Involvement

- ▶ The nerves are not involved without the skin
- ▶ Nerves are damaged later in LL
- ▶ Sensory loss is predominant
- ▶ Nerve thickening is symmetric (great auricular, supraclavicular, ulnar, antebrachial in the forearm, radial and median at the wrist, femoral cutaneous, common peroneals, superficial peroneal at the front of the ankles, posterior tibial below the internal malleolus)
- ▶ Sensory disturbance – paresthesia, hyperesthesiae, hyperalgesia, anesthesia (light touch, temperature, pain)





# Other tissues involved with LL

- ▶ Nails of fingers and toes – dry, lusterless, narrowed, longitudinally ridged
- ▶ Mucous membranes
  - Nose – discharge, blocked airway, swollen mucosa, nodules / ulcers on the septum, septal perforation (saddle nose)
  - Mouth – nodules / ulcerations on lips, tongue, palate
  - Larynx – nodules / ulcerations, altered voice, stidor
  - Glottis – edema, obstruction



# Other tissues involved with LL

## ▶ Eye

- Corneal changes
- Iridocyclitis
  - ▶ Acute
  - ▶ Insidious
- Cataracts



# Other tissues involved with LL

- ▶ Musculoskeletal system
  - Skull, arms and legs
  - Multiple factors
    - ▶ Bacilli invading bones – cysts and perostitis
    - ▶ Neurotrophic changes – localized to the phalanges
    - ▶ Repeat trauma
    - ▶ Disuse atrophy
    - ▶ Secondary infections
    - ▶ Generalized osteoporosis



# Other tissues involved with LL

- ▶ Reticuloendothelial system (RES)
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Lymphedema of the lower legs - elephantiasis
- ▶ Testes – testicular atrophy
- ▶ Kidneys – glomerulonephritis, interstitial nephritis, pyelonephritis, renal amyloidosis

# Leprosy an Immune Disease





# Tuberculoid Leprosy

- ▶ Good immune response
- ▶ May be neural or neural and dermal
- ▶ Localized

# Tuberculoid Leprosy

## ► Neural Disease

- Thickened nerves
- Sensory and motor involvement
- Motor changes affect the face, intrinsic muscles of the hand and dorsiflexors of the feet
- Abscesses along affected nerves can be seen
- Eye can be involved due to damage to the facial nerve



# Tuberculoid Leprosy

## ► Dermal Disease

- Macules and plaques
- Asymmetric
- Face, extensor surfaces of limbs, back, buttocks





# Borderline Leprosy

- ▶ Not strictly localized like TT or as widespread as LL
- ▶ Nerve involvement can always be demonstrated and often preceded skin lesions
- ▶ Nerves are thickened and show sensory and motor involvement





# Indeterminate Leprosy

- ▶ Early phase and has not yet committed to either TT or LL
- ▶ Single macule, uncharacteristic histology, absence of bacilli





# Antileprosy Medications

## ▶ Standard

- Rifampicin (rifampin, rifadin, rimactane)
- Clofazamine
- Dapsone (4,4' diaminodiphenylsulfone)

## ▶ Special situations

- Ofloxacin
- Minocycline
- Clarithromycin

# Standard MDT regimens

- ▶ **Multibacillary – Rx for 12 months (US 1-3 years)**
  - Rifampicin: 600 mg once / month, supervised
  - Dapsone: 100 mg once / month, self administered
  - Clofazamine: 300 mg once / month, supervised + 50 mg daily, self administered
- ▶ **Paucibacillary – Rx for 6 months (US 1 year)**
  - Rifampicin: 600 mg once / month, supervised
  - Dapsone: 100 mg daily, self administered

Pregnancy and Lactation – Leprosy is exacerbated in pregnancy therefore the above regimens are recommended unchanged for pregnancy and lactation. Some of the medications are excreted in small quantities in breast milk but no adverse reactions have been noted.

HIV patients respond to standard MDT



# Pediatric Doses

- ▶ Dapsone – 1 mg /kg
- ▶ Rifampin – 10 mg / kg
- ▶ Clofazamine – 1 mg / kg

# Special Situations

- ▶ Single lesion paucibacillary leprosy
  - Single dose therapy (ROM)
    - ▶ Rifampicin 600 mg
    - ▶ Ofloxacin 400 mg
    - ▶ Minocycline 100 mg
    - ▶ Marginally less effective than standard MDT for paucibacillary disease
- ▶ Can't take Rifampicin
  - Treat for 24 months
    - ▶ Clofazamine 50 mg / day +
    - ▶ Two of the following / day (Ofloxacin 100 mg, Minocycline 100 mg, or Clarithromycin 500 mg) for 6 months then
    - ▶ Daily Clofazamine 50 mg + either Minocycline 100 mg or Ofloxacin 400 mg for 18 months

# Special Situations

- ▶ Multibacillary patients Refusing Clofazamine
  - Standard MDT but replacing Clofazamine by Ofloxacin 400 mg daily or Minocycline 100 mg daily for 12 months
  - 24 month regimen (ROM) of Rifampicin 600 mg / month, Ofloxacin 400 mg / month and Minocycline 100 mg / month



# Special Situations

## ▶ Can't take Dapsone

- With multibacillary disease just stop the Dapsone and continue the other meds (rifampicin and clofazamine)
- With paucibacillary disease substitute clofazamine for dapsone



# Reactions

- ▶ Lepra reactions – immune mediated inflammation
- ▶ 5% of PB and 20% of MB patients
- ▶ Two major types
  - Reversal (type 1)
  - ENL (erythema nodosum leprosum) (type 2)
- ▶ ENL less common with MDT



# Reversal Type 1

- ▶ Lesion changes – Erythema, edema, pain, tenderness over nerves
- ▶ High risk of nerve damage
- ▶ Treat – Steroids (1 mg / kg / day, max 40-60 mg of prednisolone)
- ▶ Taper off steroids over a 12 week period

# ENL type 2

- ▶ Varies in severity duration and organ involvement
- ▶ Rapid onset of erythematous nodules, fever, joint inflammation, iridocyclitis, ulceration of the skin, glomerulonephritis and amyloidosis
- ▶ Mild ENL Rx – Aspirin
- ▶ Severe ENL with neuritis – Rx with prednisolone as for Type 1 reactions
- ▶ Clofazamine may be useful when withdrawing steroids (dose 300 mg / day divided doses)
- ▶ Iridocyclitis – add topical steroids to regimen







# Lepra Reaction – Program Recommendations

- ▶ Patients taught to recognize Lepra reactions and report promptly
- ▶ Clinicians able to diagnose and promptly treat reactions
- ▶ Adequate stocks of medications to treat reactions
- ▶ Continue MDT without interruption during a lepra reaction



# Relapse

- ▶ 0.1% relapse rate
- ▶ All *M leprae* from relapse patients remain susceptible to rifampicin and clofazamine and respond favorably to a second course of MDT



# Strategies for eliminating Leprosy as a public health problem

- ▶ Identification of endemic districts
- ▶ MDT services integrated into general health facilities
- ▶ Monitoring the elimination at the district level
- ▶ Promoting community action
- ▶ Social marketing / advocacy
- ▶ Remotivating the research community
- ▶ Prevention of disabilities and rehabilitation