



MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE
**DEPARTMENT OF INFECTIOUS DISEASES, EPIDEMIOLOGY,
PARASITOLOGY AND TROPICAL MEDICINE**

Lecture № 15-b

PLAGUE
LEPROSY

Assoc. Prof. Galya Gancheva, MD, PhD

LEPROSY

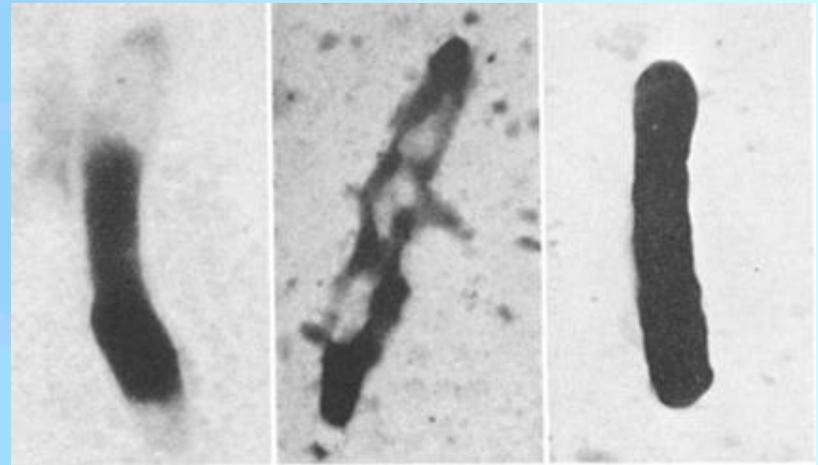
**(Hansen's disease,
hanseniasis)**

Leprosy – definition

- Leprosy is a chronic inflammatory disease of man caused by Mycobacterium leprae, which displays a wide clinical “spectrum” related to host ability to develop and to maintain specific cell-mediated immunity.
- In high-resistant “tuberculoid” leprosy, localized signs are restricted to skin and peripheral nerve, whereas low-resistant “lepromatous” leprosy is a generalized bacteraemic disease involving many systems, with widespread lesions of the skin, peripheral nerves, upper respiratory tract, the reticuloendothelial system, eyes, bone, and testes.
- Common complications include immunologically mediated inflammatory episodes (“reactions”), secondary inflammation in the anaesthetic areas that result from nerve damage, and deformity of face, hands, and feet.

Leprosy – etiology

- **M. leprae**, discovered by Hansen in Norway in 1873, is an **rod-shaped organism**, 1 to 7 μm long and 0.25 μm in width.
- **Intracellular** parasite with tropism for macrophages and Schwann cells.
- Viable bacilli stained with carbol-fuchsin appear as solid rods with rounded ends, while those with irregular stains are dead.

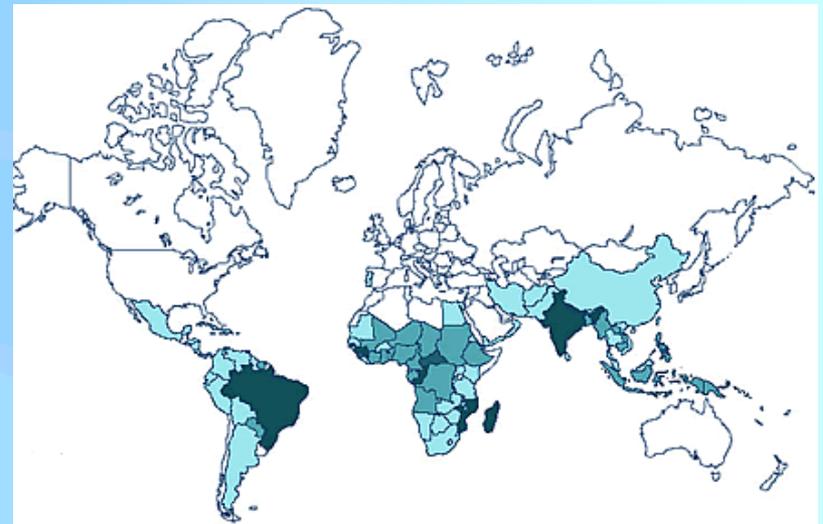


Leprosy – epidemiology

- Past governmental returns submitted to the World Health Organization produced a conservative estimate of a world total of 10.6 million leprosy patients.
- **The main source of infection in the community consists of untreated or relapsed lepromatous patients, who may shed 10^8 leprosy bacilli in 24 h in their nasal secretions.**
- M. leprae is also secreted in the breast milk of untreated lepromatous mothers, although few bacilli are excreted through intact skin.

Leprosy – epidemiology

- The incubation period is measured in years, being longer in lepromatous than tuberculoid leprosy.
- In leprosy-endemic areas, the overall peak incidence occurs in the 20 to 35-year-old group, although that for tuberculoid leprosy usually occurs in the 5 to 19-year-old group.
- In 9 countries in Africa, Asia and Latin America – more than 1/10 000 population.
- 83% of cases are present in 6 countries: India, Brazil, Burma, Indonesia, Madagascar and Nepal.
- India account for 64% of cases world wide.



(WHO, 2005)

Leprosy – pathology and clinical manifestations

- Whatever the portal of entry of *M. leprae*, the target organ for the invading bacilli is probably the endoneurium, an immunologically protected site.
- Once leprosy bacilli have been engulfed by Schwann cells, their subsequent fate and the type of disease that ensues is decided by the speed and degree of resistance developed, and maintained, by the infected individual.
- This in turn may be related to the route (and frequency) of antigen presentation and load of antigen presented to the immune system, to variations in non-specific cell-mediated immunity, and to past exposure to other, especially environmental, mycobacteria and to BCG.

Indeterminated leprosy

- Child contacts may develop a single (rarely two or three) hypopigmented macule, 2 to 5 cm in diameter, which when fully developed shows hypo-aesthesia and decreased sweating.
- The majority of such lesions are self-limiting, fading after some months, but about a quarter may evolve to one of the determinate “spectrum” types of leprosy to be described.
- Histological changes are slight and non-specific, consisting of lymphocytic cuffing around the dermal appendages and neurovascular bundles. After careful searching, an acid-fast bacillus may eventually be found within a dermal nerve.

The spectrum of leprosy

- The spectrum of leprosy was first defined by Ridley and Jopling (1966) who proposed a 5-group system of classification according to certain immunological features.
- These included the cytology of the host cells of the monocyte-macrophage series (whether histiocytic or epithelioid), the degree of infiltration by lymphocytes, and the bacterial density.
- The five groups are, in order across the spectrum, tuberculoid (TT), borderline-tuberculoid (BT), (mid-) borderline (BB), borderline-lepromatous (BL), and lepromatous (LL).

Leprosy – clinical features (summary)

- Skin involvement:
- Commonly macules or plaques rarely papules or nodules are seen.
- In tuberculoid and BT, lesions are few, hypopigmented with raised edges, and with reduced sensation.

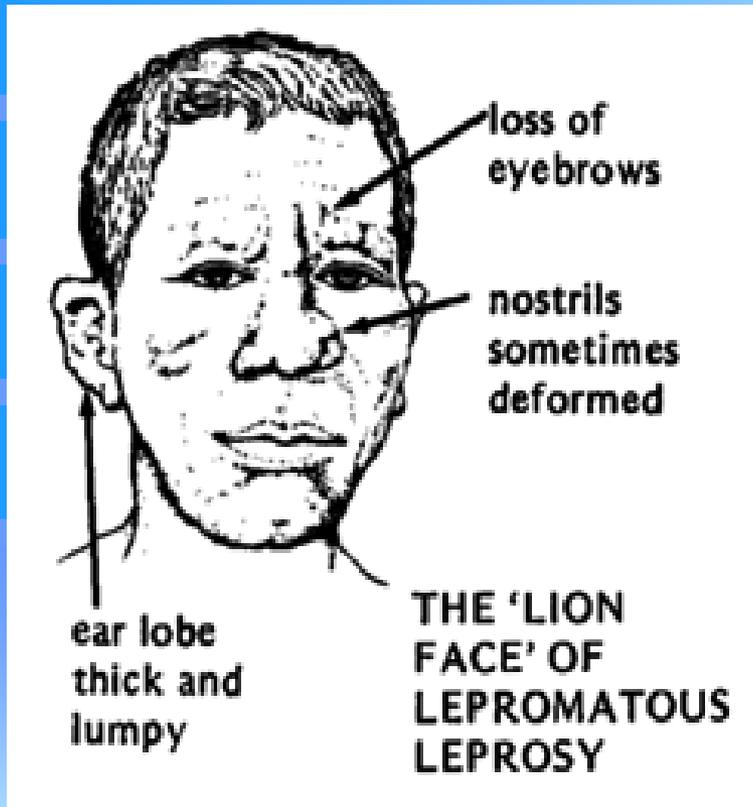


Leprosy – clinical features (summary)

- Lepromatous form, many skin lesion, symmetrical, confluent in some cases, and many of them are not hypoaesthetic.

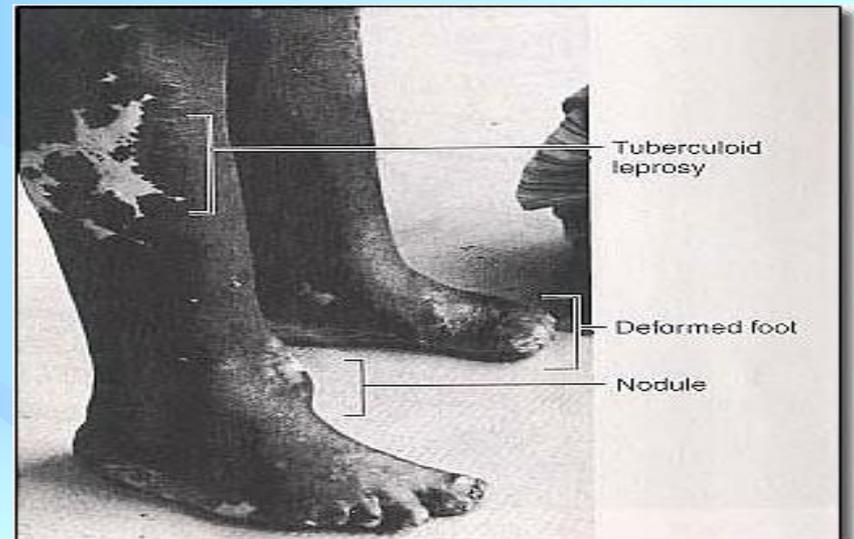


Leprosy – clinical features (summary)



Leprosy – clinical features (summary)

- Peripheral nerve trunk damage:
 - Posterior tibial, ulnar, median, lateral popliteal and facial.
 - Involved nerves are enlarged, and with regional sensory and motor loss.
- Small dermal sensory and autonomic nerves:
 - Hypoaesthesia – in TT and BT.
 - Glove and stocking – in lepromatous form.
- Pure neuritic leprosy.



Leprosy – clinical features (summary)

- Eye involvement:
 - Blindness – nerve damage and direct invasion.
 - Lagophthalmus – orbicularis oculi – zygomatic and temporal branches of facial nerve.
 - Corneal ulceration – anaesthesia – ophthalmic branch of trigeminal nerve.



Leprosy – clinical features (summary)

- Systemic features:
 - Nasal mucosa – cartilage – saddle shape.
 - Bone destruction – osteomyelitis.
 - Testicular atrophy – loss of testosterone.
 - Renal involvement and amyloidosis.



Clinical forms – tuberculoid leprosy (TT)

- When a high degree of cell-mediated immunity is developed, the infection remains very localized and asymmetrical. Only a small number of skin lesions develop, usually one to three, although the cutaneous sensory nerve supplying the skin of the lesion is frequently thickened.
- Typically, a tuberculoid skin lesion is large and annular, with a sharply raised outer edge and thin, erythematous rim that slopes gradually to a hypopigmented, flattened centre. In profile, it resembles a saucer the right way up.

Clinical forms – tuberculoid leprosy (TT)

- The surface is dry with loss of sweating, sometimes scaly, and usually with a diminished number of hairs; established lesions are always markedly anaesthetic, save for some situated in the midline of the face or forehead.
- Sometimes the lesion is a plaque or a hypopigmented macule.
- The nerves of predilection are little involved, either none or only one being enlarged; rarely, however, symptoms and signs may be purely neural, related to a single thickened nerve.

Clinical forms – tuberculoid leprosy (TT)

- Histological examination of the active edge of the skin lesion reveals a tuberculoid granuloma, consisting of whorls of epithelioid cells enclosed by lymphocytes, surrounding neurovascular elements and extending up to the epidermis without leaving the papillary zone clear.

Clinical forms – borderline tuberculoid leprosy (BT)

- The skin lesions, which may be very few to moderate in number, resemble those of TT leprosy, although they are usually smaller in size, or else small "satellite" lesions may be present near the periphery of the larger lesions (Fig. 1).
- Sharp-edged papules may also occasionally appear.
- Cutaneous sensory nerves are occasionally enlarged, whereas asymmetrical enlargement of the peripheral nerves of predilection is common, although caseation only rarely occurs; sometimes the symptoms and signs may be purely neural, related to one or more thickened nerves, although such patients occasionally develop visible skin lesions after commencing on effective chemotherapy. BT leprosy is often associated with deformity of one or both hands and/or feet. A patient may present with burns or infection of anaesthetic fingers or with a plantar ulcer in an anaesthetic foot. Lagophthalmos may result in exposure keratitis.

Borderline tuberculoid leprosy (BT) – fig.1

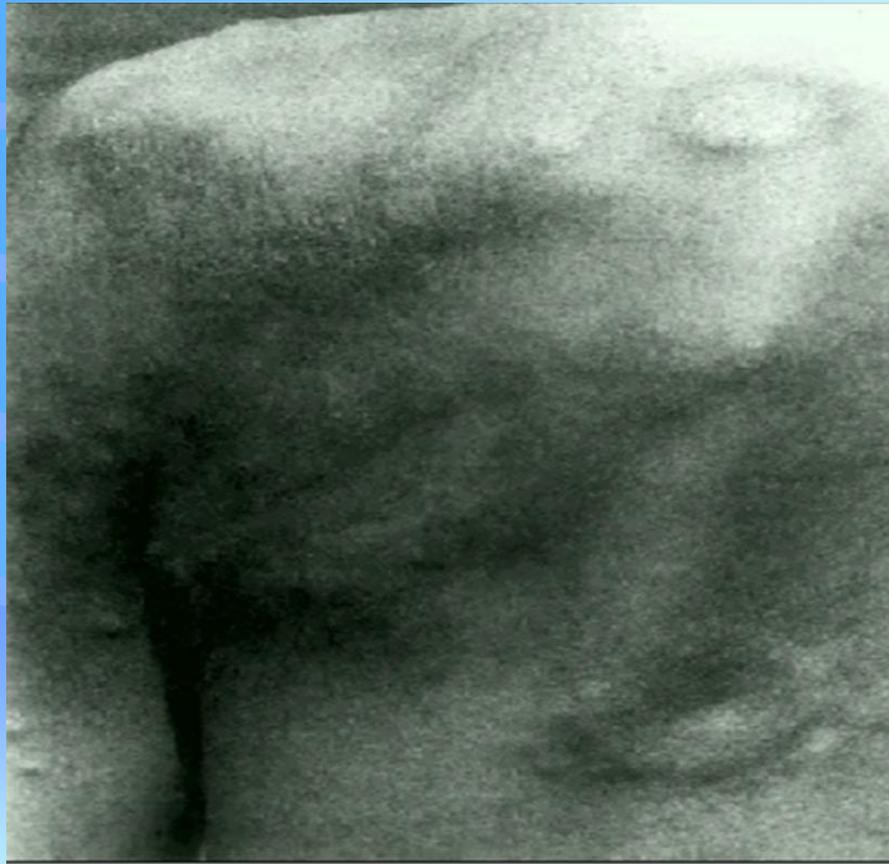


Active tuberculoid annular lesions showing the sharp outer edge, thin, raised, erythematous, dry rim, and the broad, hypopigmented, dry centre with slight hair loss.

Borderline leprosy (BB)

- The skin lesions are rather numerous, though asymmetrical, vary markedly in size, and are erythematous or hypo- or hyperpigmented.
- Papules and plaques may occur, but **the most characteristic lesion is annular with a broad rim** (Fig.2).
- The outer edge is often flattish and irregular; it rises to a thick inner edge overlooking a sharply “punched-out”, hypopigmented, anaesthetic centre.

Borderline tuberculoid leprosy (BT) – fig.2



Borderline annular lesions on the shoulder and back: the rim is broad, the edge irregular, and the 'punched-out' centre

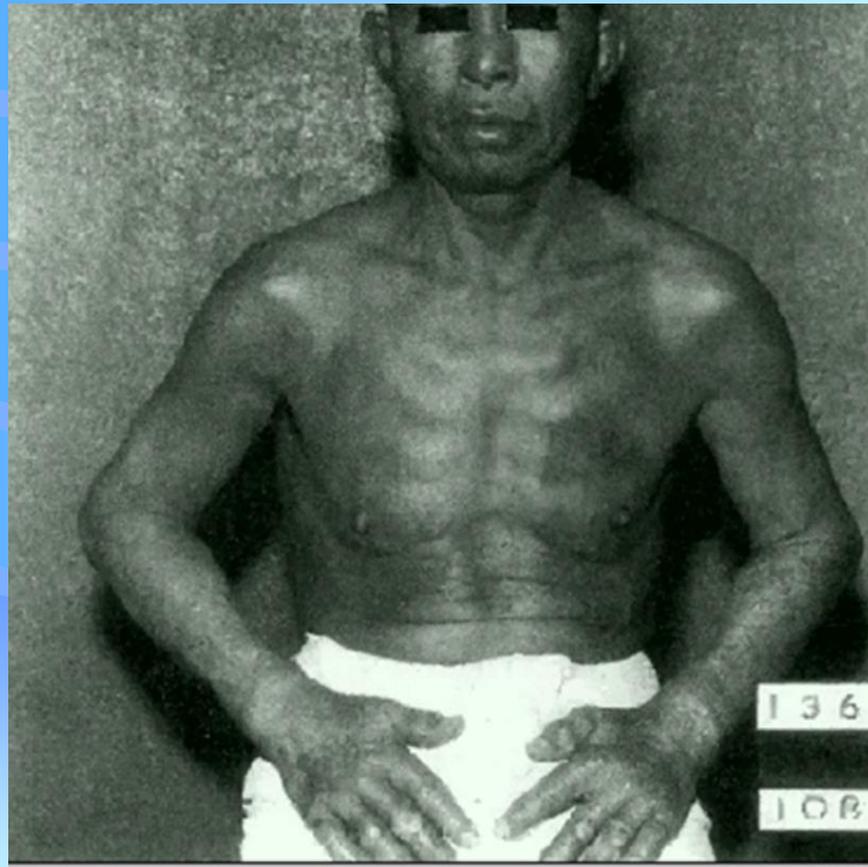
Lepromatous leprosy (LL)

- The early manifestations are dermal, never neural. At this stage the skin lesions consist of very numerous, small, symmetrical, vague-edged, hypopigmented macules with erythematous, smooth, shiny surfaces that are neither anaesthetic nor anhydrotic, and small papules with indefinite edges.
- The nerves of predilection may show little thickening, though in more advanced cases they are symmetrically enlarged.
- Thickening of the nasal mucosa often occurs early, eventually giving rise to nasal blockage and blood-streaked discharge.

Lepromatous leprosy (LL)

- With time, plaques and nodules develop, and the skin progressively thickens as the lepromatous infiltrate increases; the lines on the face coarsen and deepen, giving a “leonine facies”, and the ear lobes enlarge.
- Nodules may occur in the mucosa of the palate, and on the nasal septum, and even on the sclera.
- The lips often swell, and the eyebrows and eyelashes become scanty and are lost (Figs. 3 and 4).

Lepromatous leprosy (LL) – fig.3



Active, untreated lepromatous leprosy, showing generalized infiltration of the skin, swelling of fingers and lips, and thinning of eyebrows

Lepromatous leprosy (LL) – fig.4



Leonine facies in advanced untreated lepromatous leprosy, with gross thickening of the ear lobes.

Lepromatous leprosy (LL)

- Iritis and keratitis are common.
- The nasal cartilage and bones may be gradually destroyed, resulting in saddle-nose deformity.
- Lepromatous laryngitis may cause hoarseness or stridor.
- Oedema of the extremities sometimes occurs, and the skin of the lower part of the legs often becomes firm and waxy in appearance and ulcerates easily.
- The lymph nodes are often enlarged, especially the epitrochlear and axillary, and testicular involvement may lead to atrophy and occasionally to gynaecomastia.
- In the absence of treatment, the dermal nerves are gradually destroyed, leading to a progressive pseudo “glove-and-stocking” anaesthesia; light touch, pain and temperature sensation are eventually lost over most of the body except the hairy scalp, axillae, perineum, and groins, but position sense is well preserved.
- Histologically, the dermis is massively and diffusely infiltrated with foamy histiocytes full of leprosy bacilli and globi-containing Virchow giant cells. In contrast, bacilli are only rarely found either in the epidermis.

Erythema nodosum leprosum

- Erythema nodosum leprosum occurs only at the lepromatous end of the leprosy spectrum, and up to 50 per cent of treated LL patients, and the occasional untreated LL or treated BL, suffer from one or more episodes of this type of reaction.
- Over the course of a few hours, a crop of painful, erythematous papules develops, typically on the extensor surfaces of the limbs, but in severe attacks over much of the body except the scalp (Fig. 5).
- In BL patients, most papules erupt in juicy plaques or nodules in which the concentration of leprosy bacilli is highest.

Erythema nodosum leprosum – fig.5



Erythema nodosum leprosum (ENL) on the forehead of a patient with early lepromatous leprosy. The papules (and nodules) are firm and tender, with rather indefinite edges. In dark-skinned patients the ENL lesions are often easier to feel than to see, especially over the extensor surfaces of the arms and thighs.

Leprosy – haematology and immunology

- In LL and BL leprosy, mild normochromic anaemia may occur. This may become more marked in chronic erythema nodosum leprosum, during episodes of which a polymorphonuclear leucocytosis is also usually present.
- Reversal of the albumin:globulin ratio occurs in many LL and some BL patients, and IgG is almost always raised, although IgM and IgA are more variable. Such patients often give false-positive tests for syphilis, and long-standing LL patients may also give positive tests for thyroglobulin antibodies, LE cells, antinuclear factor, and cryoglobulin.

Leprosy – diagnosis and differential diagnosis

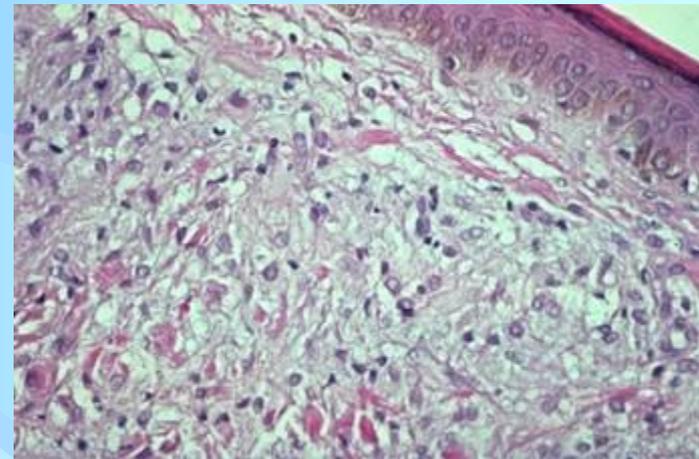
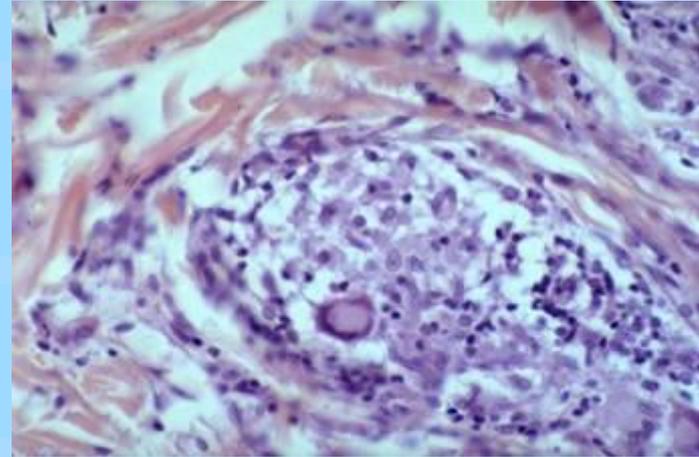
- The diagnosis of leprosy should always be considered in any patient with skin or peripheral-nerve lesions who has resided in an endemic area.
- It should especially be suspected when skin or nasal symptoms persist despite routine treatment, in idiopathic foot drop, in unusual presentations of arthritis and erythema nodosum, in chronic plantar ulceration, and in painless burns or injuries to the hands and feet.

Leprosy – diagnosis and differential diagnosis

- Skin lesions should be tested for anaesthesia, peripheral nerves systematically palpated for thickening, and skin smears taken from both ear lobes and up to four typical skin lesions.
- The anaesthesia of TT and BT leprosy differentiates tuberculoid lesions from vitiligo, mycotic skin infections, lupus erythematosus, and psoriasis, as well as from lupus vulgaris and sarcoidosis; histological examination of the two last conditions will reveal the presence of normal cutaneous nerves in the otherwise very similar granuloma.

Leprosy – histologic diagnosis

- In TT: Noncaseating granuloma, bacilli are few or absent, dermal nerve involvement, with normal skin organs.
- In LL: Diffuse granulomatous reaction, foamy macrophages, more common around blood vessels and nerves.



Leprosy – treatment

- **Dapsone** (4,4'-diaminodiphenyl-sulphone, DDS)
- This drug is as cheap as aspirin and may be given by mouth or parenterally. Clinical improvement is detected from about 3 months after starting dapsone in LL and BL patients (often earlier in TT, BT, and BB leprosy) and from around this time bacilli from nose and skin will no longer infect normal mice; the morphological index (MI) reaches zero by 6 months, although the bacterial index (BI) takes many years (2 in BB, 4-5 in BL, and 8-11 in LL) to become smear negative.
- The recommended standard adult dose is 100 mg/day (1-2 mg/kg body weight) by mouth. This dosage gives a peak blood level about 500 times the serum minimal inhibitory concentration (MIC), which explains why drug resistance was seldom seen in the early days of dapsone chemotherapy.

Leprosy – treatment

- **Rifampicin (rifampin)**
- This is so rapidly bactericidal that a single dose of 600 to 1200 mg renders an LL patient a minimal public health risk within a few days, bacilli obtained from the skin 3 days after the dose usually failing to multiply in the foot-pads of mice.
- Clinical improvement begins within 7 to 14 days of starting rifampicin and the MI falls to zero within 6 weeks.
- The recommended dosage is 10 to 15mg/kg body weight, that is 600 mg to those weighing 35 kg or over, preferably given on an empty stomach. Rifampicin may be given daily or, because of the prolonged generation time of M. leprae, monthly; monthly rifampicin (600 mg originally given on two consecutive days every 4 weeks).

Leprosy – treatment

- **Clofazimine**

In the dosage of 100 to 200 mg daily it kills leprosy bacilli at about the same speed as dapsone. Various intermittent dosages, from 100 mg three times a week to 600 mg on two consecutive days every 4 weeks, are also effective but give a slightly slower rate of kill.

Leprosy – treatment

- **Prothionamide and ethionamide**
- A dose of 375 mg of either drug gives a peak blood concentration about 40 times the MIC.
- Resistance to ethionamide has been reported after 5 to 8 years of monotherapy. Prothionamide has been more widely used, usually in the dosage of 350 mg daily, but only in combined chemotherapy.

Leprosy – treatment

- Three new drugs, or groups of drugs, have been identified, which achieve a 10^4 kill of *M. leprae* within 1 to 3 months.
- Among the 4-fluoroquinolones, ofloxacin has been shown to give such a kill in 3 months in mice, and ofloxacin (400 mg daily) and pefloxacin (800 mg daily) have given a similar kill in 1 month in a pilot study in man.
- Sparfloxacin is likely to be as least as effective.
- **Ciprofloxacin is ineffective against *M. leprae*.**

Leprosy – treatment

- **Minocycline**, the only fat-soluble tetracycline, has also been shown to be highly bactericidal in mice, and in the dosage of 100 mg daily in a pilot study in man, achieved a 10^4 kill within 3 months.
- There is increasing evidence that the erythromycin derivative, clarithromycin, in the dosage 500 mg daily in man, is also highly bactericidal, and from its mode of action on ribosomal enzymes it may be synergistic with minocycline.

Leprosy – prognosis

- With early diagnosis and correct treatment, the prognosis is now excellent.
- Patients who fail to care for anaesthetic limbs may develop increasing deformity, and amputation may become necessary for chronic osteomyelitis.
- Iridocyclitis may cause impairment of vision or blindness and cataract is common in LL patients.

Leprosy – prophylaxis

- Immunoprophylaxis:
 - BCG offer variable protection against leprosy (34-80%) in different countries, adding heat – killed *M. leprae* increases the protective effect to 64%.
 - Endemicity of leprosy, background saprophytic mycobacterial flora, and the age at vaccine may affect the response to vaccination.
 - Vaccination may precipitate TT leprosy in apparently healthy contacts, thus immunoprophylaxis is best carried out at an early age.
- Chemoprophylaxis:
 - Rifampicin, to close contact of a case, and can be give to children under the age 12 years (15mg/kg monthly for 6 months).

Leprosy – prophylaxis

- Vaccination with BCG gives some protection, both in children and in whole populations.

**THANKS
FOR YOUR ATTENTION!**