ETIO-PATHOGENESIS AND PATHOLOGY OF LEPROSY

- Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by *Mycobacterium leprae*, a microorganism that has a predilection for the skin and nerves. Though nonfatal, leprosy is one of the most common causes of nontraumatic peripheral neuropathy worldwide.

- *Mycobacterium leprae*, the causative agent of leprosy, was discovered by G. H. Armauer Hansen in Norway in 1873.

Mycobacterium leprae

- *M. leprae*, an acid-fast bacillus is a major human pathogen. In addition to humans, leprosy has been observed in nine-banded armadillo and three species of primates. The bacterium can also be grown in the laboratory by injection into the footpads of mice.
- Mycobacteria are known for their notoriously slow growth. With the doubling time of 14 days, *M. leprae* has not yet been successfully cultured in vitro

M. lepromatosis

- *M. lepromatosis* is a newly identified mycobacterium which is described to cause disseminated leprosy whose significance is still not clearly understood.

Transmission

- Two exit routes of *M. leprae* from the human body often described are the skin and the nasal mucosa. Lepromatous cases show large numbers of organisms deep in the dermis.
- Fairly large numbers of *M. leprae* were found in the superficial keratin layer of the skin of lepromatous leprosy patients, suggesting that the organism could exit along with the sebaceous secretions.

Transmission

- While the lepra bacillus of Hansen is generally conceded to be the specific cause of the disease.
- The skin and the upper respiratory tract are most likely, recent research increasingly favours the respiratory route.
- The theory of direct hereditary transmission is practically disproved.
- The precise manner in which leprosy is acquired is as yet unsettled.

Incubation Period

- Measuring the incubation period in leprosy was difficult because of the lack of adequate immunological tools and slow onset of the disease.
- The minimum incubation period reported is as short as a few weeks and this is based on the very occasional occurrence of leprosy among young infants.
- The maximum incubation period reported is as long as 30 years, or over, as observed among war veterans known to have been exposed for short periods in endemic areas but otherwise living in nonendemic areas.
- It is generally agreed that the average incubation period is between three and ten years.

Risk Factors

- Those living in endemic areas with poor conditions such as inadequate bedding, contaminated water, and insufficient diet, or other diseases that compromise immune function are at highest risk for acquiring *M. leprae* infection.
- People that live in close contact with patients who have untreated, active, predominately multibacillary leprosy and people living in countries with endemic leprosy are at an increased risk of infection.

HIV and Leprosy

- Unlike TB, HIV infection has not been reported to increase susceptibility to leprosy, impact on immune response to *M. leprae*, or to have a significant effect on the pathogenesis of neural or skin lesions to date.
- On the contrary, initiation of antiretroviral treatment has been reported to be associated with activation of subclinical *M. leprae* infection and exacerbation of existing leprosy lesions likely as part of immune reconstitution inflammatory syndrome.

Leprosy during pregnancy and puerperium

- Depression of Cell mediated immunity (CMI)
  - Sub-clinical disease may become overt
  - Established disease may worsens
  - Deterioration of nerve function
- Regaining of CMI - First six months of puerperium
  - Increased incidence of lepra reaction
- New born
  - Weigh less than baby of healthy mothers
  - High risk of getting infected with leprosy

Genetic Determinants of Host Response

- Human genetic factors influence the acquisition of leprosy and the clinical course of disease.
- Single-nucleotide polymorphism (SNP) association studies showed a low lymphotoxin-α (LTA)-producing allele as a major genetic risk factor for early onset leprosy.

Genetic Determinants

- Other Single-nucleotide polymorphism SNPs to be associated with disease and/or the development of reactions in several genes, such as vitamin D receptor (VDR), TNF-α, IL-10, IFN-γ, HLA genes, and TLR1 .

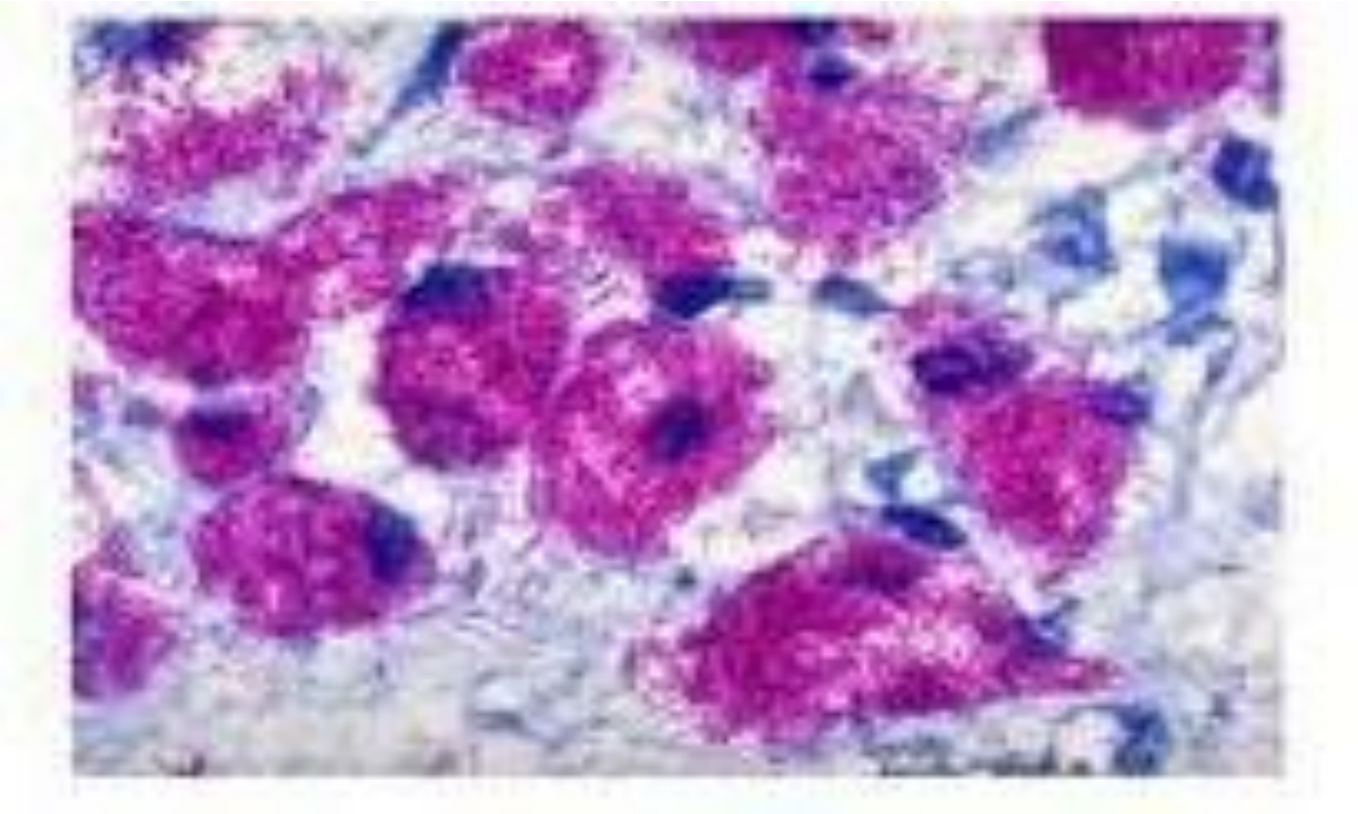
Genetic Determinants

- Linkage studies have identified polymorphic risk factors in the promoter region shared by two genes: PARK2 and PACRG.
- A study also suggests that NOD2 genetic variants are associated with susceptibility to leprosy and the development of reactions (type I and type II).

Infectious Agent

- Leprosy is cause by infection with an intercellular pathogen known as *Mycobacterium leprae*.
- *M. leprae* is a strongly acid-fast, rod-shaped bacterium. It has parallel sides and rounded ends, measuring 1-8 microns in length and 0.2-0.5 micron in diameter, and closely resembles the tubercle bacillus.

Acid fast staining showing *M. lerpae* bacilli



- Besides humans, the only known reservoir is the armadillo. It is thought that they are a good host for *Mycobacterium leprae* because of their low body temperature.

Picture of a Nine banded Armadillo

Vector

- It is uncertain whether or not insects can act as a vector for *M. leprae*.

Pathogenesis:

M. Leprae

Enters → **Transient Bacillemia**

Schwann cells, cooler places (Cutaneous nerves & Peripheral nerves trunks of limbs and face)

Strong Immunological Response ↔ **Weak immunological Response**

Nerves only: **Pure Neural Leprosy**

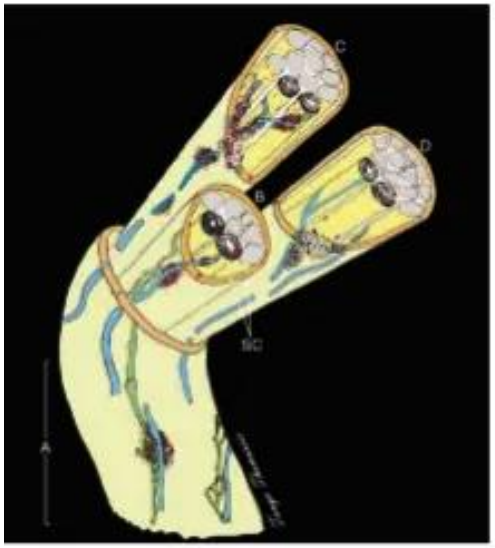
Escape to skin: **Skin lesions appear**

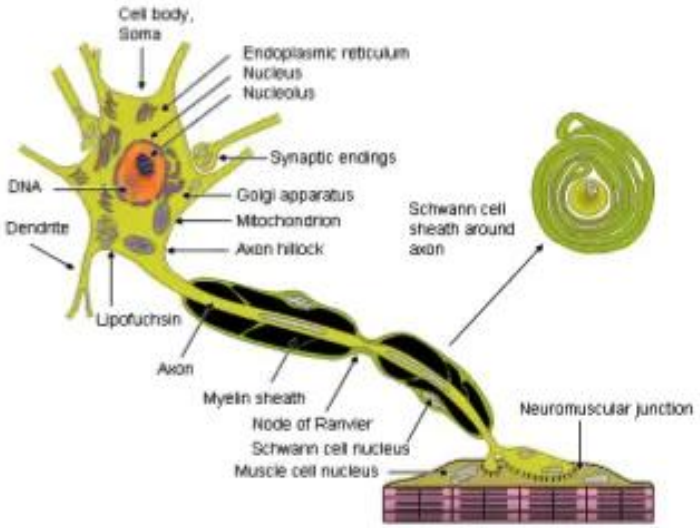
Lesions may heal spontaneously

M. Leprae multiply in Schwann cells or

Engulfed Histiocytes – wandering Macrophages

Affect other organs in the body





- **Entry Through Blood Vessels**
- **Inflammatory Response**
- **Demyelination**

Insight Into B Lymphocytes & Plasma Cells

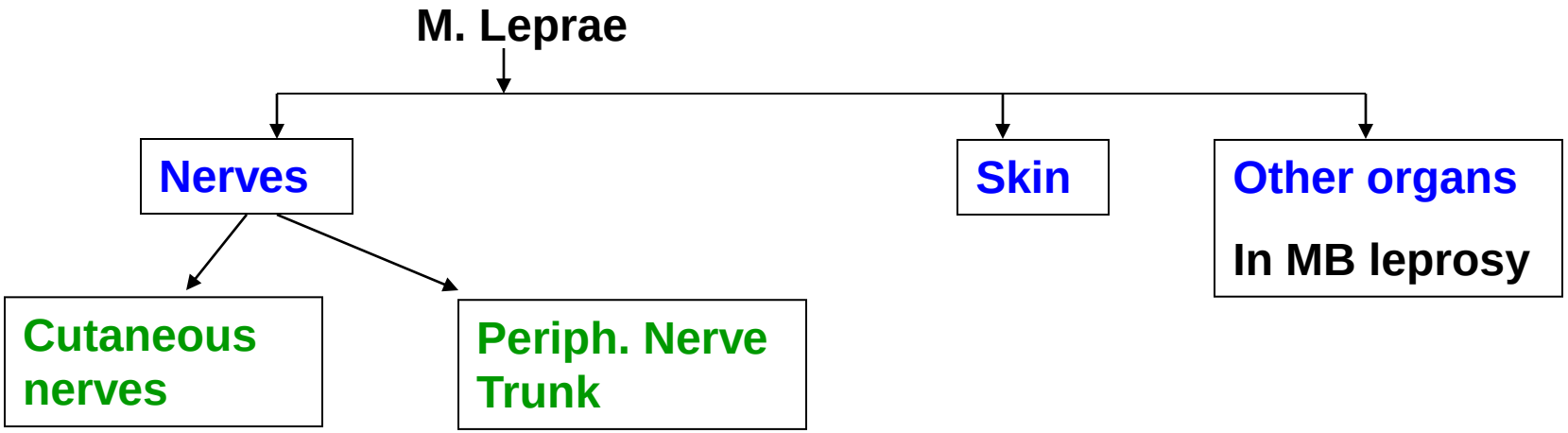
- Schwann cells (SCs) are a major target for infection by *M. leprae* leading to injury of the nerve, demyelination, and consequent disability.
- Binding of *M. leprae* to SCs induces demyelination and loss of axonal conductance.
- Several studies have been performed on the involvement of T cells in leprosy and more recently have focused on genetic factors and innate immune response.

- The clinical demonstration of the disease is determined by the quality of host immune response.
- Th1-type immune response helps to kill the bacteria, but hosts are encroached upon when Th2-type response is predominant.
- The bacteria have affinity to the peripheral nerves and are likely to cause neuropathy. M. leprae/laminin-alpha2 complexes bind to alpha/beta dystroglycan complexes expressed on the Schwann cell surface.

- It has been shown that *M. leprae* can invade SCs by a specific laminin-binding protein of 21 kDa in addition to PGL-1.
- PGL-1, a major unique glycoconjugate on the *M. leprae* surface, binds laminin-2, which explains the predilection of the bacterium for peripheral nerves.
- *Mycobacterium leprae*-induced demyelination is a result of direct bacterial ligation to neuregulin receptor, ErbB2 and Erk1/2 activation, and subsequent MAP kinase signaling and proliferation.

- Macrophages are one of the most abundant host cells to come in contact with mycobacteria.
- Phagocytosis of *M. leprae* by monocyte-derived macrophages can be mediated by complement receptors CR1 (CD35), CR3 (CD11b/CD18), and CR4 (CD11c/CD18) and is regulated by protein kinase.

Pathogenesis contd



- Loss of
- Sensation
- Secretions of Cutan. glands
- Vasomotor function
- Hair follicles

- Sensory loss
- Weak/ Paralysed Muscles
- Loss of sweating / hairs

- Macule
- Papule
- Nodule
- Infiltration

- Face
- Eyes
- Testes
- Kidney
- Bone

TYPE 1 (REVERSAL) REACTIONS

- A T1R is characterised by the development of acute inflammation in skin lesions or nerves or both. Borderline leprosy is a strong risk factor for the occurrence of T1Rs 4 but individuals with polar forms of leprosy may also experience T1Rs.

TYPE 1 (REVERSAL) REACTIONS

- T1Rs are frequently recurrent and this can lead to further nerve damage. Skin lesions become acutely inflamed and oedematous and may ulcerate.
- Oedema of the hands, feet and face can also be a feature of a reaction but systemic symptoms are unusual.

TYPE 1 (REVERSAL) REACTIONS

- Acute neuritis if not treated rapidly and adequately leads to permanent loss of nerve function causing peripheral sensory and/or motor neuropathy.
- Skin lesions develop scaling in the chronic phase of T1R and may then mimic psoriasis, dermatophyte infections and cutaneous T-cell lymphoma.

PATHOLOGY OF TYPE 1 (REVERSAL) REACTIONS

- T1Rs are delayed hypersensitivity reactions. The dermatopathological features of acute T1R are oedema, increased number of lymphocytes in the dermis and loss of normal granuloma organisation. As time passes there is an increase in the number of Langhans' giant cells.

- M. leprae antigens have been demonstrated in the nerves and skin of patients experiencing T1Rs, localised to Schwann cells and macrophages.
- M. leprae infection may lead to the expression of MHC II on the surface of the cells. This may give rise to antigen presentation which triggers CD4 lymphocyte killing of the infected cell which is mediated by cytokines such as tumour necrosis factor (TNF).

- T1Rs appear to be mediated via Th1 lymphocytes and cells from reactional lesions express the pro-inflammatory cytokines interferon gamma (IFN-γ) and interleukin 12 (IL-12).

ERYTHEMA NODOSUM LEPROSUM / T2Rs

- ENL or type 2 reaction is a serious, difficult to manage immunological complication of borderline lepromatous (BL) and lepromatous leprosy (LL). The majority of patients with ENL go on to develop several episodes over many years, as multiple acute episodes or chronic ENL.

ERYTHEMA NODOSUM LEPROSUM / T2Rs

- The cutaneous manifestation of ENL is widespread crops of erythematous, inflamed nodules and papules, which may be superficial or deep.

ERYTHEMA NODOSUM LEPROSUM / T2Rs

- Ulcerated, necrotic, pustular and bullous forms have also been reported. Some nodules may persist as a chronic painful panniculitis leading to fibrosis and scarring.

PATHOLOGY OF T2Rs

- The inflammatory infiltrate in ENL is situated in the dermis and the subcutis. The predominant cell type is the neutrophil. Eosinophils and mast cells may also be present.
- Skin biopsies performed show fewer neutrophils and increasing numbers of lymphocytes, plasma cells and histiocytes, representing a chronic inflammatory infiltrate.

PATHOLOGY OF T2Rs

- Immune complexes are important in the pathogenesis of ENL as demonstrated by the presence of complexes of complement and M. leprae antigen in cutaneous lesions.

PATHOLOGY OF T2Rs

- There is evidence of a cell mediated immune response in the pathogenesis of ENL. The major T cell subtype in ENL is the CD4+ cell in contrast to lepromatous leprosy where CD8+ cells predominate.
- TNF and IL-6 have been shown to be present in skin lesions of ENL.

PRESENTATION OF LEPROSY

Pathogenesis: Skin Lesions

Leprosy Lesions	Exclude Leprosy
•One/ Few/ Many •Small/ Large •Hypo- pigmented / reddish/ pale / coppery •Ill defined / well defined margins •Dry/ wrinkled / granular to shiny soft succulent •Sweating +/- •Hairs – sparse/ fragile / absent •Macule/ Papule/ nodular	•Present since birth •Black / dark red / De-pigmented •Itches •Appears disappears suddenly •Painful •Scaly •Shows any seasonal variation

Nerve involvement

Stage I

- Thickening of nerve trunk
- Pain & tingling along the nerve trunk
- Tenderness along the course of nerve trunk
- No evidence of loss of nerve function

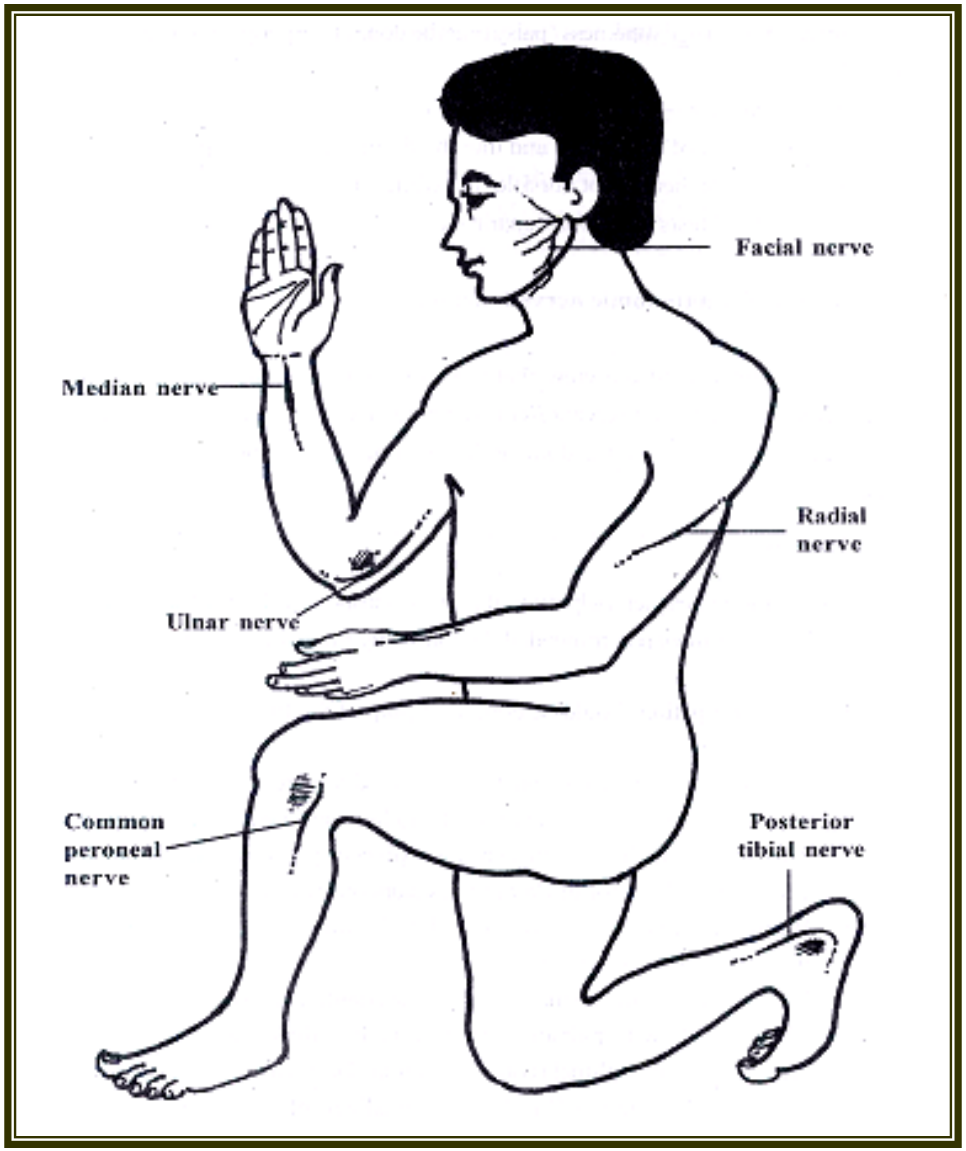
Stage II

- Incomplete / complete paralysis of recent origin
- Loss of sweating
- Loss of sensibility
- Muscle weakness/ Paralysis

Stage III

- Complete Nerve Paralysis for 1 year/ more
- Recovery of Nerve function not possible

Commonly affected Nerves



Thank you