Neuropathy in Leprosy

- Autonomic neuropathy – an early sign?
- Silent neuropathy
- Late onset Neuritis/ neuropathy
- Neuropathic pain
- Acute and Chronic Neuritis
Reactions and Neuritis in Leprosy: Clinician’s perspective

Reactions and Neuritis in Leprosy: Basic Science Perspective
Steps in the Pathogenesis of Nerve Injury in Leprosy

- Localization of M. leprae to nerves
- Schwann Cell infection
- Inflammation
- Demyelination

Localization of *M. leprae* to Peripheral Nerves

"Primary Binding to Schwann Cells"
Khanolkar, 1964

Entry via blood vessels
Scollard, 1999

Perineural Inflammation
Schwann Cell Infection

Both Non-Myelinating and Myelinating Schwann Cells are infected by *M. leprae* in vivo and in vitro.
**M. leprae & Schwann Cells**

- *M. leprae* binds to many SC molecules, including $\alpha$-dystroglycan-laminin, Myelin P$_0$, and ErbB2
- *M. leprae* are taken up into vesicles within SC, and appear to inhibit acidification
- *M. leprae* prefer cooler growth temperature in SC in vitro

**Effects of SC on M. leprae**

SC appear to be good host cells for *M. leprae.*

Studies of *M. leprae* responses to host cells are only beginning.
Micro-array studies of Gene Expression in Schwann Cells --

- Primary human SC in vitro
- Live *M. leprae*
- mRNA collected 24 hr after infection
- Hybridized to full human genome array (approx 16,000 genes)
- Hundreds of genes up-regulated
- Hundreds of genes down-regulated
- Analysis of genes and pathways in progress

Immune Responses and Schwann Cells

- Expression of MHC II
  Narayanan 1990; Cowley, 1990
- Antigen Presentation
  Steinhoff, 1991

- SC as targets for CD4+ cells
  Spierings, 2001

- Immune reactivity of SC in reactions???
Other Inflammatory & Immunological Processes

• Intraneural macrophages and lymphocytes; edema

• Cytokines – e.g. TNF
  Khanolkar-Young 1995

Fig. 4. Cytokine TNF-α mRNA in leprosy lesions as determined by in situ hybridization (a) and immunocytochemistry (b). The results show the percentage of positive cells in skin (■) and nerve lesions (□) of reactional and non-reactional leprosy biopsies. Bars represent mean value ± s.e.m.
Other Inflammatory & Immunological Processes

- Intraneural macrophages and lymphocytes & edema
  Khanolkar-Young 1995
- Cytokines – e.g. TNF
  Khanolkar-Young 1995
- Neuroendocrine feedback?
  Rook, 2002

“Gene expression of 11beta-HSD type 2, which converts cortisol to cortisone, is down-regulated in skin from T1R lesions”. Andersson, 2007

Demyelination – the final common pathway of neuropathy in leprosy

- Segmental demyelination
  Teased nerve studies, Swift, 1974
Demyelination – the final common pathway of neuropathy in leprosy

- Segmental demyelination
- Teased nerve studies, Swift, 1974

Paranodal demyelination & axonal atrophy

Save 2004

Contact demyelination

Rambukkana; Tapinos 2006
**Experimental Model:** Armadillo

**Pathogenesis of Leprosy Neuropathy**

Localization → SC Binding → Ingestion → SC-M. leprae toxicity → Axonal atrophy → Inflammation → Demyelination

**Mechanisms of Nerve Injury**
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http://www.hrsa.gov/hansens
M. leprae
Infection of Armadillo Nerves

Intra-neural M. leprae and Inflammation
Lt post. tibial nerve

Inflammation
AFB

Nerve segment (cm)

Image of histological sections showing nerve tissue and inflammation.