The biology of nerve injury in leprosy

DAVID M. SCOLLARD
Chief, Research Pathology, National Hansen’s Disease Programs,
LSU-SVM, Skip Bertman Dr. Baton Rouge, LA 70803, USA

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Introduction

Nerve injury is a central feature of the pathogenesis of leprosy, and the basic biological aspects have been reviewed in many textbooks.\textsuperscript{1–3} Selected aspects of current research on this subject have also been the subject of recent reviews.\textsuperscript{4,5} This review is organised to follow known steps in the pathogenesis of nerve injury in leprosy. Although most citations are to reports published within the last 10 years, older studies are included when they include important observations that have not been superseded by more recent studies. Reactions in leprosy often exacerbate nerve injury but, because additional immunological phenomena are likely to be involved in reactions, this review focuses primarily on nerve injury occurring prior to or outside of the context of reactions.

Descriptions of leprosy neuritis

In the late 1800’s, pathologists seeking to determine whether the neuropathy of leprosy was central or peripheral in origin, performed full-length dissections of peripheral nerves, i.e. from the spinal cord to the terminal ramifications of nerves in cutaneous lesions.\textsuperscript{6,7} Their reports of the macroscopic findings described an ascending neuritis of leprosy, in which inflammation was observed in the cutaneous nerves arising from the skin lesions, and in their subcutaneous trunks, extending proximally for variable distances, ultimately affecting larger nerve trunks and the branches joining them. This is the descriptive, anatomical basis of the biological mechanisms we are discussing today.

As the techniques of histology and histochemical staining developed over subsequent decades, perineural and intraneural inflammation were observed to be morphological hallmarks of this disease, and intraneural infection by \textit{M. leprae} was recognised to be a pathognomonic feature of this disease. Perineural inflammation is now known to be present in the earliest (indeterminate) lesions. This may be a more important observation than generally realised; its significance has probably been obscured observation of fuchsin-stained bacilli within delicate nerve fibres, a finding that has tantalised pathologists and dominated thinking about nerve injury in leprosy.

Correspondence to: D. M. Scollard (e-mail: dscoll1@lsu.edu)
The presence of *M. leprae* within Schwann Cells and intra-neural macrophages has been confirmed in numerous ultrastructural studies. Importantly, however, clinical studies have clearly demonstrated that non-myelinated fibres are also prominently involved in nerve injury in leprosy.9

Appreciation of the immunological basis for the diverse spectrum of clinical and histological appearances in leprosy9,10 soon led to the recognition that the well-organised granulomas in tuberculoid skin lesions were also present within cutaneous nerves and in larger nerve trunks. The destructive capability of granulomatous inflammation is well known, and has often been accepted as the basic explanation for nerve injury in TT and BT patients. Similarly, the disorganised and highly bacilliferous cutaneous infiltrates of lepromatous disease are replicated in the nerves of these patients. The mechanism of injury in lepromatous nerves, however, has been more difficult to explain since the nerves retain their basic integrity for some time and are able to maintain surprising levels of function even when heavily infected. As with cutaneous lesions, intermediate degrees of infection, and of organisation of the inflammatory infiltrate, are observed in the nerves of patients with different borderline types of leprosy. It is appropriate here to emphasise that the situation is much more diverse and complex than can be adequately represented in a 2-part, ‘pauci-bacillary/multi-bacillary’ categorisation of this disease.

The infection, host response, and functional impairment of cutaneous nerves is a very early feature of leprosy – sensory abnormalities are already present in the earliest diagnostic clinical lesions, even in small, single lesions. Nevertheless, this process is a chronic one, with a natural course of years or decades and histological evidence of nerve fibre degeneration and regeneration and collateral sprouting of axons. If not interrupted by treatment or spontaneous healing, the end results of *M. leprae* infection and the host response in nerves are demyelination, nerve fibre degeneration, and fibrosis.

**LOCALISATION OF *M. LEPRAE* TO PERIPHERAL NERVES**

The first essential step in leprosy neuritis is the localisation of *M. leprae* to peripheral nerves. The original description of ascending inflammation was extrapolated to propose that *M. leprae* initially bind to exposed Schwann cells in the dermis, and then move proximally within the nerve, “... swimming like fish up a stream”.11 Though often repeated in periodicals and textbooks, this colorful concept is inconsistent with several basic features of the biology of *M. leprae* and of peripheral nerves; e.g., how would this non-motile mycobacterium navigate across the internodes between Schwann cells?

Recent studies of peripheral nerves in experimentally infected armadillos have suggested, rather, that *M. leprae* infect nerves from the outside-in, first aggregating in epineurial lymphatics and blood vessels and then entering the endoneurial compartment through its blood supply.12,13 This view gives new significance to old observations of substantial *M. leprae* infection of endothelial cells14 that have been largely overlooked during recent decades in which most basic studies of leprosy have focused on the unique immunological features of this disease. In addition, it is likely that the characteristic perineural inflammatory infiltrates of leprosy are the ‘footprints’ tracking the route of infection of the nerves themselves. The mechanisms responsible for the apparent selectivity of *M. leprae* for the vasculature of peripheral nerves are not known, but are topics of current research.

This view of the pathogenesis of infection of peripheral nerves raises significant implications with respect to both our understanding of the process, and to possible points of preventive or therapeutic intervention. If several steps are required for the ultimate entry of *M. leprae* into Schwann cells, then there are several potential sites of intervention – e.g.,
binding to endothelial cells, entry into endothelium, exit from endothelial cells into the endoneurium, and binding to Schwann cells – and the likelihood of developing new types of medical intervention is increased. However, if *M. leprae* enter nerves exclusively *via* the single step of direct binding to exposed Schwann cells in the dermis, then this is the only opportunity for preventive or therapeutic intervention.

**SCHWANN CELL STUDIES**

Schwann cells synthesise myelin, they become infected with *M. leprae*, and demyelination is the ultimate consequence of leprosy neuritis. These facts, considered in this sequence, have led to the hypothesis that *M. leprae* infection of SC is the direct cause of SC dysfunction which causes the demyelination in leprosy. Although this is plausible and is observed in some experimental systems, it has not yet been proved to be true in clinical lesions. As noted above, non-myelinated fibres are injured in leprosy, and *M. leprae*-infected nerves simultaneously endure many other inflammatory events that may play a major role in demyelination in leprosy. Nevertheless, this line of thinking about SC has generated the greatest range and depth of studies of possible mechanisms of nerve injury in leprosy thus far.

In patients with advanced lepromatous leprosy, both myelinated and non-myelinated SCs are infected by *M. leprae*,\textsuperscript{15,16} although some reports have suggested some preference for non-myelinating Schwann cells *in vitro*.\textsuperscript{17} *In vitro*, we have observed a similarly brisk and heavy infection of both cell types.\textsuperscript{18} Some investigators, however, have reported exclusive infection of non-myelinating cells *in vitro*.\textsuperscript{19}

**ADHESION TO SCHWANN CELLS**

Several potential mechanisms of binding of *M. leprae* to the Schwann cell have been elucidated\textsuperscript{20–22} (Table 1).

Antibodies directed against polysaccharide and lipid components of *M. leprae* inhibited adhesion to SCs, while those directed against both surface and cytoplasmic protein epitopes did not show any such effect,\textsuperscript{23} indicating that the association of *M. leprae* with SCs may be mediated by more than one of its cell surface molecules.

Recent studies have demonstrated that *M. leprae* specifically bind to alpha-Dystroglycan (alpha-DG) in the presence of the G domain of the alpha2 chain of laminin-2.\textsuperscript{20} Using alpha2 laminins as a probe, a major protein in the *M. leprae* cell wall fraction has been identified (ML-LBP21) that binds alpha2 laminins on the surface of SCs.\textsuperscript{24} Phenolic glycolipid-1

<table>
<thead>
<tr>
<th>Schwann cell ligand</th>
<th><em>M. leprae</em> ligand</th>
<th>Ref</th>
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<tbody>
<tr>
<td>Alpha-Dystroglycan (alpha-DG)</td>
<td>ML-LBP21</td>
<td>Rambukkana 1997; Shimoji,</td>
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<tr>
<td>- laminin</td>
<td></td>
<td>1999</td>
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<tr>
<td>Laminin-2</td>
<td>PGL-1</td>
<td>Ng 2000</td>
</tr>
<tr>
<td>Myelin P0</td>
<td>unknown</td>
<td>Suneetha, 2001</td>
</tr>
<tr>
<td>Laminin</td>
<td>Histone-like protein</td>
<td>Soares 2005</td>
</tr>
<tr>
<td>ErB2</td>
<td>unknown</td>
<td>Tapinos 2006</td>
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(PGL-1) of *M. leprae* has also been demonstrated to bind specifically to laminin-2 in the basal lamina of SC-axon units. Importantly, additional evidence clearly indicates that this mechanism of binding to the SC surface via alpha2-laminins is not unique to *M. leprae*. Other mycobacterial species, including *M. tuberculosis*, *M. cheilonae* and *M. smegmatis*, have been shown to express an alpha2-laminin-binding capacity and these species readily interact with the ST88-14 Schwannoma cell line *in vitro*. Other studies have also demonstrated the ability of myelin P0 to bind *M. leprae*, and a histone-like, laminin-binding protein (Hlp/LBP) expressed by *M. leprae* has been identified that plays a role in binding to Schwann cells and other cells. The latter protein also binds to heparin and heparan sulfate. *M. leprae* also bind to Erb2B, a SC receptor for neurigulin-1 which is a critical mediator of SC-axon interaction.

**INGESTION BY SCHWANN CELLS**

After *M. leprae* adhere to the Schwann cell surface, they are slowly ingested, as described in studies using primary denervated rat SC cultures and SC/neuron co-cultures. In *in vitro* studies of ingestion of *M. leprae* by a human Schwannoma cell line (ST88-14) demonstrated that several protein kinases were essential for ingestion, but that cAMP-dependent kinases were not involved. In these studies, acidification of vesicles containing lethally irradiated *M. leprae* proceeded normally, but acidification was minimal when live *M. leprae* were used. These findings suggest that viable *M. leprae* can interfere with normal endocytic maturation in SC.

**EFFECTS OF SCHWANN CELLS ON M. LEPRAE**

Schwann cells apparently provide an environment suitable for preservation and proliferation of *M. leprae*. Studies using highly viable suspensions of nude-mouse-derived *M. leprae* have demonstrated that viability of the bacilli in rat SC is comparable to that previously described for bacilli within macrophages *in vitro*, and that survival of this organism within Schwann cells is greater at 33°C than at 37°C, similar to its survival *in vitro* in macrophages. This survival within Schwann cells *in vitro* is consistent with the longstanding histopathological observations that *M. leprae* appear to persist and grow within Schwann cells in human nerves.

**EFFECTS OF M. LEPRAE ON SCHWANN CELLS**

Infection of SC with whole, viable *M. leprae* has not been observed to cause SC loss, and even appeared to favour SC survival rather than apoptosis (Table 2). However, human SCs express toll-like receptor 2 (TLR2) both *in vitro* and *in vivo*, and binding of an *M. leprae*-derived lipoprotein to TLR2 on SC has been reported to result in apoptosis. These investigators also identified SCs that had undergone apoptosis in biopsies of human lesions. The significance of these observations with respect to clinical nerve injury remains to be determined, since both live and dead *M. leprae* are undoubtedly present in clinical lesions.

*M. leprae* appears to have no effect on intact, mature Schwann cell/axon units, but did alter Schwann cell expression of a small number of genes examined in a preliminary study (GFAP, TGFβ1, NCAM, ICAM, N-Cadherin and L1). Ingestion of lethally-irradiated *M. leprae* by the ST88-14 Schwannoma cell line induced activation of the transcription factor NF-kB, a function that was modulated by thalidomide. Further evaluation of the effect of *M. leprae* infection on primary human Schwann cells, a microarray analysis of approximately 15,000 genes has now been performed and significant changes (up- or down-regulation) have
Table 2. Changes Reported in SC function after binding/ingestion of *M. leprae*

<table>
<thead>
<tr>
<th>SC function</th>
<th><em>M. leprae</em></th>
<th>System</th>
<th>Ref</th>
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<tbody>
<tr>
<td>Inhibition of acidification of normal encodytic maturation in SC</td>
<td>Live</td>
<td>Human Schwannoma (ST88-14) cell line</td>
<td>Alves <em>et al.</em>, 2004</td>
</tr>
<tr>
<td>Up-regulation of GFAP gene transcription</td>
<td>Live</td>
<td>Rat SC</td>
<td>Hagge 2002</td>
</tr>
<tr>
<td>Up-regulation of NCAM gene transcription</td>
<td>Live</td>
<td>Rat SC</td>
<td>Hagge 2002</td>
</tr>
<tr>
<td>Down-regulation of N-Cadherin gene transcription</td>
<td>Live</td>
<td>Rat SC</td>
<td>Hagge 2002</td>
</tr>
<tr>
<td>Selective participation of protein kinases in internalization of <em>M. leprae</em> in SC</td>
<td>Live and Dead</td>
<td>Human Schwannoma (ST88-14) cell line</td>
<td>Alves <em>et al.</em>, 2004</td>
</tr>
<tr>
<td>Antigen presentation</td>
<td>Dead</td>
<td>Murine SC</td>
<td>Steinhoff, 1988; Ford <em>et al.</em>, 1993</td>
</tr>
<tr>
<td>Reduction in apoptosis</td>
<td>Live</td>
<td>Rat SC</td>
<td>Rambukkana <em>et al.</em>, 2002</td>
</tr>
<tr>
<td>Activation of NF-κB after ingestion of <em>M. leprae</em></td>
<td>Dead</td>
<td>Human Schwannoma (ST88-14) cell line</td>
<td>Pereira <em>et al.</em>, 2005</td>
</tr>
<tr>
<td>Apoptosis after binding <em>M. leprae</em>-derived lipoprotein to SC Toll-Like Receptor 2</td>
<td>Lipoprotein of <em>M. leprae</em></td>
<td>Human Schwannoma (ST88-14) cell line</td>
<td>Oliveira <em>et al.</em>, 2003; Soares de Lima <em>et al.</em>, 2005</td>
</tr>
<tr>
<td>Lack of demyelination</td>
<td>Live (33°C)</td>
<td>Rat SC</td>
<td>Hagge 2002</td>
</tr>
<tr>
<td>Demyelination</td>
<td>Live (37°C)</td>
<td>Rat SC</td>
<td>Rambukkana <em>et al.</em>, 2002</td>
</tr>
<tr>
<td>Erk1 &amp; Erk2 phosphorylation &amp; demyelination</td>
<td>Live</td>
<td>Rat &amp; Human SC; RAG mice</td>
<td>Tapinos 2006</td>
</tr>
</tbody>
</table>
been observed in several hundred genes (Diana Williams, personal communication). Additional analysis and verification of these findings are in progress.

Using a rat SC/axon co-culture system, Rambukkana and colleagues have reported rapid demyelination following adherence of *M. leprae* to SCs in the absence of immune cells, interpreted to be a contact-dependent mechanism dependent on PGL1, a component of the *M. leprae* cell wall.17 Similar findings in T and B cell deficient (Rag1−/−) mice, led these authors to conclude that attachment of *M. leprae* to the myelinated SC surface is sufficient to induce rapid demyelination of these cells thus suggesting a mechanism for demyelination of nerves in leprosy (For review see ref. 19). These conclusions, however, are at considerable odds with well documented clinical and histopathological observations. Notably, patients with untreated lepromatous leprosy may have billions of bacilli in their bodies but they do not have widespread demyelination.

The effects of *M. leprae* on SC have been the subject of many other studies in vitro. Notably, however, optimal conditions (highly viable bacilli and cooler cultivation temperatures) were not used in earlier studies of this interaction, possibly contributing to a variety of conflicting reports in the literature. Current studies of various cell types in vitro have indicated that ingestion of dead *M. leprae* – but not live organisms – will trigger apoptosis (R. Lahiri, personal communication). The relevance of these findings to clinical nerve injury is still uncertain.

**IMMUNE RESPONSES AND SCHWANN CELLS**

The immune response may also be directed at *M. leprae*-infected Schwann cells. Human Schwann Cells express MHC II molecules after infection with *M. leprae*.33,34 Cultured SC appear to be able to process and present *M. leprae* antigens to CD4+ T cells.35,36 The infected Schwann cells were highly susceptible to killing by CD4+ cytotoxic T cell clones derived from leprosy patients. Long-term cultures of human SC also express MHC class I and II, ICAM-1, and CD80 surface molecules involved in antigen presentation. These cells process and present *M. leprae*, and some of its protein and peptide antigens to MHC class II-restricted CD4(+) T cells, and are efficiently killed by these activated T cells.

**OTHER INFLAMMATORY AND IMMUNOLOGIC PROCESSES**

The nerve infected with *M. leprae* may also be seriously affected by concurrent immunological/inflammatory events. Intraneural macrophages, especially, are capable of secreting a wide array of cytokines and chemokines, some of which may be deleterious.37 TNFα, for example, has been shown to be present in leprosy nerve lesions in comparable degree to its presence in skin lesions, in both in reactive and non-reactional lesions.38 In some circumstances, for example, TNFα may act synergistically with other cytokines to initiate apoptosis of SC.39

In addition, pro-inflammatory cytokines themselves may contribute to demyelination.40 The major toxic effector molecule known to kill *M. leprae* is nitric oxide (NO), and NO has been demonstrated in the inflammatory infiltrates of nerves in leprosy lesions.41 Nitrotyrosine, an end product of the metabolism of NO, has also been observed in nerves in BL lesions, and this molecule has been associated with lipid peroxidation of myelin leading to demyelination of nerves in other diseases.42 In association with the active inflammation of leprosy neuritis reduced immuno-staining for neurofilaments, Nerve Growth Factor receptor, and other neural components has been described.43
Very interestingly, Rook and colleagues have proposed that the nerve damage itself may interrupt normal neuroendocrine feedback that can limit inflammation, thus enabling the local inflammation to persist. Consistent with the hypothesis, downregulation of gene expression for the enzymes that convert cortisone to cortisol has indeed been observed in skin lesions at the onset of Type 1 reactions. Thus, nerves may not only be the targets of inflammation in leprosy, directly or indirectly, but their destruction may enhance the intensity or duration of the inflammatory processes themselves.

A pronounced polyclonal antibody response is observed in many leprosy patients, especially lepromatous ones, and the possibility that some of these antibodies react with components of peripheral nerve has been suggested by several investigators. Antibodies to *M. leprae* proteins homologous to myelin P have been demonstrated in leprosy, and similarities of this molecule to some *M. leprae* proteins have prompted suggestions that molecular mimicry could be the basis for mechanisms of immunological injury to nerves in leprosy. Another recent study noted a decline in antibodies to nerve growth factor after treatment of chronic leprosy neuritis with Cyclosporine A. However, none of these studies has convincingly demonstrated that the antibodies reported are actually responsible for nerve injury. The issue of antibody-mediated nerve injury in leprosy remains unresolved.

**Axonal Injury**

In detailed evaluations of human leprosy-affected nerves, Shetty and colleagues noted, in addition to segmental demyelination, evidence of paranodal demyelination and atrophy, evident as a reduction in axon calibre. Segmental demyelination may be associated with local inflammation, whereas the pathogenesis of the atrophic lesions is not as evident.

In subsequent studies of nerve biopsies from leprosy patients, they have observed abnormalities phosphorylation of neurofilament proteins in nerves from treated and untreated patients with different types of leprosy. This was seen in nerves with minimal inflammation as well as in those with more extensive inflammation. Hypophosphorylated neurofilament proteins are more susceptible to proteolytic degradation, and loss of these proteins may explain the observed reduction in axonal calibre. Dephosphorylation of neurofilament proteins has been recognised in a variety of other neurological disorders, but the mechanisms responsible in them, as in leprosy, are poorly understood. This is an area of research in the neuropathology of leprosy that has received too little attention, and hopefully it will be pursued further.

**Demyelination and Wallerian Degeneration**

In advanced leprosy lesions, various investigators have reported that segmental demyelination predominated in lepromatous lesions, while Wallerian degeneration predominated in tuberculoid ones. Details concerning the actual duration of these lesions are not known, and it is possible that the severity of the inflammation of nerves, rather than the immunological responses, may be responsible for these differences. That is, when the immunologically-induced inflammation of nerves is sufficiently severe, acute nerve injury occurs, followed by Wallerian degeneration, regardless of the type of immunological response.

Segmental demyelination in leprosy-affected nerves was confirmed in studies of teased nerve fibres. Does demyelination occur prior to the development of intra-neural and peri-neural inflammation? Shetty and colleagues have reported that demyelination is present in some fibres even in very early nerve lesions, and *in vitro* studies have now demonstrated...
that direct M. leprae binding of the ErbB2 receptor and thus induced rapid demyelination.\textsuperscript{28} In this \textit{in vitro} system these investigators have now identified two pathways proceeding to rapid demyelination that are of great interest from a cell biology perspective. The relevance of these findings to leprosy, however, remains uncertain. The specificity of these effects has not been reported – do other mycobacteria also bind to these receptors and trigger demyelination? In addition, the very rapid onset of demyelination (5 minutes in some experiments) is difficult to reconcile with longstanding clinical experience in leprosy.

**EXPERIMENTAL MODELS**

Biopsy of human nerves is not feasible in most circumstances, for obvious ethical reasons. This has greatly limited our ability to understand the mechanisms of nerve injury in leprosy.

Full-length dissection of major peripheral nerve trunks in the nine-banded armadillo (\textit{Dasypus novemcinctus}), similar to the initial human dissections of the later 1800’s, have demonstrated that this is a remarkably good animal model of leprosy neuritis.\textsuperscript{13,58} After intravenous inoculation of \textit{M. leprae}, and without any manipulations to direct bacilli to nerves, nerves are naturally infected in a manner recapitulating human infection: armadillo nerve lesions are focal, more numerous and more severe distally than proximally, characterised by interstitial inflammation, and infection of Schwann Cells and intra-neural macrophages. As noted above, epineurial infection is also prominent in this model, and exploration of this phenomenon has led to current studies of the role of blood vessels and endothelial cells in the infection of nerves. The armadillo genome has been sequenced (http://www.ncbi.nlm.nih.gov/BLAST, \textit{Dasypus novemcinctus} WGS), and as molecular probes and specific antibodies become available they are likely to revolutionise the study of leprosy neuritis in this model. Functional studies in this model are lacking thus far, but preliminary work on this is now underway.

The immunologically intact mouse is not susceptible to \textit{M. leprae}, except for the limited multiplication observed in the footpad. Notably, even extensive multiplication of bacilli in the footpads of normal or nude (nu/-nu-) mice is not reproducibly accompanied by infection of peripheral nerves (personal observations, unpublished). Nevertheless, the mouse is an extraordinary model for the study of immunological and inflammatory phenomena, and diligent efforts have therefore been made to elicit neuritis in mouse models by the inoculation of \textit{M. leprae} into major nerves. In these studies, however, \textit{M. leprae} did not establish an ongoing infection,\textsuperscript{59} nor did the inocula elicit characteristic evidence of leprous neuritis. It appears, therefore, that the mouse is not a suitable model for this process in general, although some of the many types of mutant mice now available might be employed to explore specific mechanisms suggested by studies of human or armadillo neuritis.

Schwann Cells have been used extensively in studies \textit{in vitro}, reviewed above. Rat Schwann cells and neurons have usually been employed in these studies because neurobiologists have developed standardised techniques for the isolation and cultivation of these cells from murine species. However, mice and rats are not susceptible to infection nor to localised nerve lesions. Results from these models must therefore be interpreted very cautiously. Human Schwann cell lines are now available and these would appear to be superior to murine cells for studies of the effects of \textit{M. leprae}. Studies of the possible role of endothelial cells and macrophages \textit{in vitro} may also contribute to understanding of the pathogenesis of leprosy neuritis, and such studies should also employ human cells whenever possible.
As also emphasised above, recent microbiological studies of *M. leprae* clearly demonstrate that this organism is highly susceptible to freezing and thawing, and survives longer in tissue culture at 33°C than at 37°C. Moreover, some results now indicate that apoptosis is much more likely to be initiated by dead *M. leprae* than by live bacilli, in a variety of cell types (Lahiri, personal communication). These findings strongly suggest that future studies *in vitro* should be planned and conducted under conditions of optimal survival of *M. leprae*, or should specifically compare responses to living vs. dead bacilli.

**Summary**

The steps in the pathogenesis of nerve injury in leprosy are depicted in Figure 1.

Localisation of *M. leprae* to nerve, Schwann cell infection & responses, as yet unknown mechanisms of injury, axonal atrophy, and finally demyelination. These steps, and the mechanisms responsible for them, occur quickly in the course of this disease (as noted, even the earliest diagnostic lesions have sensory abnormalities), but they are also chronic processes that may contribute to progressive nerve injury over a period of many years unless interrupted by treatment, and even after cure of the infection in some patients.

A common feature throughout this pathogenesis is inflammation – within and around the nerve. Inflammation is not only defined by its chemical mediators such as cytokines and chemokines, but by one of the most basic phenomena of inflammation – edema. The extent to which edema might contribute to nerve injury in leprosy has not been reviewed because it has not been studied in nerves affected by leprosy, although clinically, surgeons who perform neurolysis are convinced that they are decompressing nerves sustaining injury due to increased (edematous?) pressure. Inflammation in and around nerves is undoubtedly driven, in part, by the immunological responses in each of the portions of the immunologic spectrum

**Pathogenesis of leprosy neuropathy**

**Mechanisms of nerve injury**

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**Figure 1.** The ‘steps’ in the pathogenesis of nerve injury in leprosy that have been reviewed are depicted here, as a working draft: Localization of *M. leprae* to nerve, Schwann cell infection and responses, axonal atrophy, and finally demyelination. It is likely that other, unknown mechanisms are yet to be discovered, as indicated. Mechanistically, although specific abnormalities have been described in Schwann cell function, a common feature throughout most of these steps is inflammation – within and around the nerve, accompanied by the edema characteristic of inflammation. Inflammation in and around nerves is undoubtedly driven, in part, by the immune responses in each of the areas of the immunological spectrum of leprosy, but some inflammatory phenomena may be non-specific inflammation related to infection and foreign material (i.e., mycobacterial components). Few if any fixed associations can be made between the steps outlined in this conceptual framework of events; even the sequence of events, as depicted here, is uncertain. Considerable additional data is needed to determine the sequence and connections between these processes and their underlying mechanisms.
of leprosy, but some inflammatory phenomena may be non-specific inflammation related to infection and foreign material (i.e., mycobacterial components).

Few if any fixed associations can be made between the steps outlined in this conceptual framework of events; even the depicted sequence of these events is uncertain. Considerable additional data is needed to determine the connections between these processes and their underlying mechanisms. Additionally, although much emphasis is given to myelinated fibres (and demyelination) in studies of the biology of leprosy neuropathy, the small, sensory fibres in the skin are not myelinated. Additional studies of mechanisms of injury to these nerves is required. The results of all of these studies can be reasonably expected to identify new points for clinical intervention in – and possibly the prevention of – nerve injury in leprosy.

References


35 Ford AL, Britton WJ, Armati PJ. Schwann cells are able to present exogenous mycobacterial hsp70 to antigen-specific T lymphocytes. *J Neuroimmunol*, 1993; 43: 151–159.


Kamala AN, Antia NH, Shetty VP. Study of the involvement of the sciatic nerve following inoculation with *M. leprae* and other mycobacteria in the mouse foot pad. *Int J Lepr Other Mycobact Dis*, 1984; 52: 506–514.