Emerging Concept on Peripheral Nerve damage in Leprosy

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ABSTRACT

Leprosy is a chronic disease, caused by M. leprae where involvement and damage of peripheral nerves is a typical and unique feature. The presence of M. leprae has been shown in Schwan cells (SCs) of unmyelinated nerve fibers, macrophages, and Endothelial cell (EC). The presence of M. leprae in endothelial cells suggested that SCs are not the only target cells for M. leprae infection, but the organisms are also frequently seen in the EC of the endoneurial blood vessels (EBV). In the light of increasing resistance and complication of leprosy reaction, to dapsone (DDS) and rifampicin, Clofzamin (CLF) has been included as an essential component of multidrug therapy (MDT) in standard W.H.O. regimen. Interesting observations has been recorded by various investigators in LL patients, receiving continuous MDT for several years; viable bacilli were found in peripheral nerves whereas they had disappeared from the skin. In this article, we review the different recent pathway in understanding the possible and most frequent route of entry M.leprae into the nerve.

Keywords: *Leprosy, Ultrastructure, Schwann cell, Endothelial cell, M.leprae,*

INTRODUCTION

In spite of the many advances in the understanding of leprosy and its management, leprosy evokes fear in the common man and in professionals alike. In a recent survey in western countries, it was surprising to find that, when asked, people preferred to contract AIDS rather than leprosy. There is no doubt that ignorance about leprosy is the major factor in this public reaction. However, it is important to note that it is the deformities brought about by nerve damage that are largely responsible for this horror and dread of the disease; a horror and dread which appear to be almost universal. It is estimated that more than one fourth of all reported leprosy patients have disabilities, and of these nearly half are severely disabled. With over 12 million estimated leprosy patients in the world, the economic loss to the community caused by leprous neuritis must be enormous. The social and psychological effects of deformity cannot be measured.

Leprosy is a chronic disease, caused by *Mycobacterium leprae (M. leprae)*, where involvement and damage of peripheral nerves is a typical and unique feature. When leprosy is not recognized and treated at an early stage peripheral nerve damage ensues, leading to muscle weakness, paralysis, and severe deformities. Peripheral neuropathy is the most serious complication in leprosy. Selected aspects of current research on this subject have also been the subject of recent reviews [1,2]. This review is organized to follow known steps in the pathogenesis of nerve destruction in leprosy. Although most citations are two 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.

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Table1.

Type of Leprocy	Duration of Disease	Nerve biopsied	Nerve	Nerve
L	2 years	Dorsal branch of ulnar (R)	N	Present NT
T (in Reaction)	1 year	Dorsal branch of ulnar (L)	+	Present NT
L	2 years	Dorsal branch of ulnar (L)		
L	6 Months	Dorsal branch of ulnar (L)	N	Present NT
L	1 year	Superficial radial cutaneous	N	Present NT
T	2 years	Dorsal branch of ulnar (R)	+	Present NT
L	2 months	Superficial radial cutaneous (L)	N	Present NT
L	1 year	Superficial radial cutaneous (L)	+	Present NT
L	2.5 years	Superficial radial cutaneous (R)	N	Present NT
L	1 year	Superficial radial cutaneous (L)	N	Present NT
T	2 years	Dorsal branch of ulnar (R)	N	Present NT
L	1 year	Dorsal branch of ulnar (R)	N	Present NT
T	3 year			
T	1 years	Dorsal branch of ulnar (L)	N	Present NT

Note: *L=Lepromatous;*

T=Tuberculoid;

*(L)= Left; (R)=Right;*

*+=Present; - = Absent;*

 N= Could not worked out; NT=Non-tender

The Structure of the Nerve

The peripheral nerve consists of myelinated and nonmyelinated nerve fibers of various sizes. The myelinated axons are surrounded by a multilayercd myelin sheath. The Schwann cells cover the nerve fibers, and each Schwann cell contains one myelinated fiber or several nonmyelinated fibers. The Schwann cells are surrounded by loose connective tissue called the endoncurium. The sensory and motor nerve fibers are intermingled and are structurally indistinguishable. Nerve fibers are grouped and held together to form nerve fascicles by dense connective tissue and blood vessels called the perineurium. The perineurium and the blood vessels offer a barrier between the nerve parenchyma and the circulating blood and tissue fluids, and this barrier is compromised during

Injury or infection. Several fascicles are bound together by the epineurium composed of loose connective tissue, blood vessels and lymphatics to form a nerve trunk. The number of fascicles in a nerve, such as the ulnar nerve, varies as it courses down the arm. The bundles of nerve fibers form the fascicles branch and rearrange. The fibers are so distributed in the fascicles that a third of a nerve trunk may be severed without causing demonstrable motor or sensory loss.
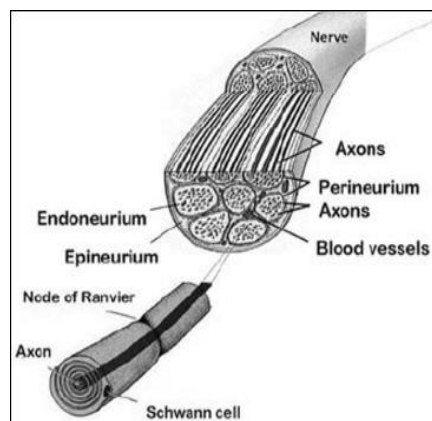

Fig1. *Schematic presentation of peripheral nerve showing various part of the nerve.*
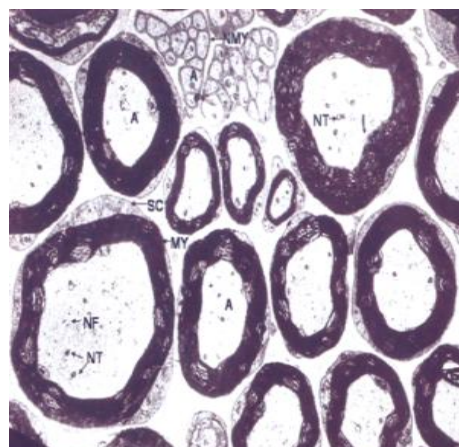
Fig2. *Ultrathin section of the normal peripheral nerves showing Myelinated (MY) and Unmylinated fibres. Neural tubules (NT) and neural filaments (NF) is also clearly seen X7000.*

Neuritis in Leprosy

Leprosy in humans is essentially a disease of the peripheral nerves. The clinical diagnosis of leprosy depends largely on the recognition of the results of nerve damage in the patient. The findings of thickened peripheral nerves, of anesthetic areas in the skin, and of paralyzed muscles in the hands, legs or face, lead to the diagnosis of leprosy. The histopathological demonstration of nerve invasion by *M.leprae* or the presence of an inflammatory granuloma in and around a nerve is mandatory to confirm the diagnosis of leprosy. The 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 described in the present article. Clinically, neuritis can be silent with no noticeable signs or symptoms or it can be very obvious and acute, accompanied by severe pain, tenderness, swelling, loss of sensation and paralysis of the muscles. At the very early stage of the disease, leprous neuritis is present without demonstrable nerve damage. However, it usually becomes chronic and progresses on to show nerve damage, typically beginning with loss of sweating, then loss of sensations and, finally, muscle paralysis.
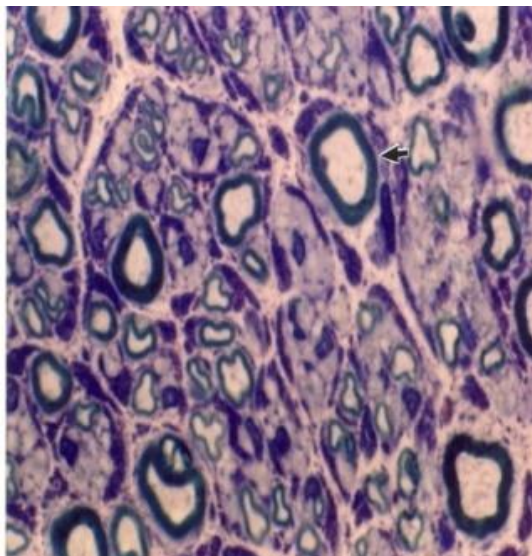
Fig3. *Semithin section showing of the normal peripheral nerves with prominent Mylinated sheath. X600.*

Fig4. *Ultrathin section of peripheral nerves in TT patients showing UMY Schwann cell with numerous collagen fibres being phogocytosed by SC. X8000.*

Whatever be the type of neuritis the nerve underwent, it finally gets fibrosed and hyalinized. There is perineurial fibroses, and the nerve parenchyma is completely replaced by hyalinized fibrous tissue. Hardly any inflammatory cells are seen. Occasionally, one or a few acid-fast organisms are found incarcerated in the "fibrous coffin." These organisms are often solid-staining, viable-looking bacilli. It is possible that they may serve as a nucleus for relapse. At this point I would like to state that in leprous neuritis the axons, their myelin sheaths, and their Schwann cells are destroyed and replaced by fibrous tissue. There are no Schwann tubes left behind for regrowing nerve fibers, if any, to grow into and, therefore, nerves destroyed due to leprous granuloma are permanently destroyed.

Neuritis and nerve damage are not synonymous. Nerve damage can also occur due to some other causes. In common practice, the clinical diagnosis of neuritis is made only when there is pain or tenderness, or swelling of a nerve, or a sensation of pinprick and tingling localized to that part of the skin supplied by the nerve. It is important to remember that in leprosy, as we define the disease now, there is always neuritis. The presence of *M. leprae* within Schwann Cells and intra-neural macrophages has been confirmed in numerous ultrastructural studies [3]. Importantly, however, clinical studies have clearly demonstrated that non-myelinated fibres are also prominently involved in nerve injury in leprosy [4]. Appreciation of the immunological basis for the diverse spectrum of clinical and histological appearances in leprosy [5,6] 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 tuberculoid types (TT) and borderline types (BT) patients[7,8]. Similarly, the disorganized 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 [9]. In cutaneous lesions, intermediate degrees of infection, and of organization of the inflammatory infiltrate, are observed in the nerves of patients with different borderline types of leprosy. It is appropriate here to emphasis that the situation is much more diverse and complex than can be adequately represented in as pauci-bacillary and multi-bacillary categorization 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.

Localization of *M.Leprae* in Peripheral Nerve

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" [10]. The presence of *M. leprae* has been shown in Schwann cells of unmyelinated nerve fibers, macrophages, and EC. [11,12] demonstrated *M. leprae* in endothelial cells and suggested that Schwann cells are not the only target cells for *M. Leprae* infection, but the organisms is also frequently seen in the endothelial cells of the endoneurial blood vessels [13]. The endoneurial blood vessels supply the nutrients to the nerves for

maintaining the metabolic activity of Schwann cells and are essential for proper functions of the nerve [14,15]. Thus, invasion of *M. leprae* in endothelial cells of endoneurial blood vessels could be an essential event in the initiation of nerve damage in leprosy [16]. Additionally, the 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 [17]. This view gives new significance to old observations of substantial *M. leprae* infection of endothelial cells 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 [18,19] . In addition, it is likely that the characteristic perineurial 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.

Fig5. *Ultrastructure of SC showing well developed nucleus, disrupted myelinated sheath and nemerious bacilli in center of SC.X15000.*
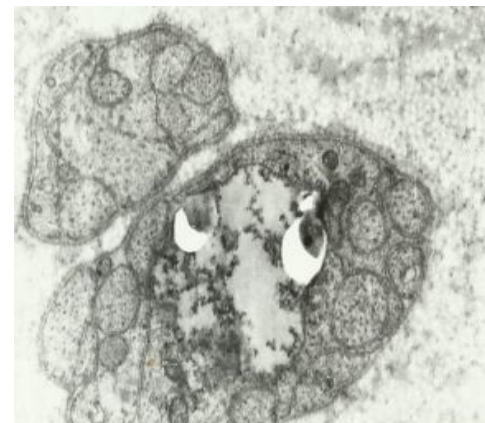
Fig6. *Showing two bacilli in the SC with prominent axon with degenerated portion of the SC by clumping of neural filaments and neural tubules. X15000.*

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 by *M. leprae* into Schwann cells, then there are several potential sites of intervention like as 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.

Site and Extent of Nerve Involvement

The nerves involved in leprosy are of two types: first, the autonomic and sensory nerves in skin lesions which supply the structures in the dermis and subcutaneous tissue and, second, the portions of nerve trunks such as the ulnar, median, radial, common peroneal, posterior tibial and facial nerves which are subcutaneously placed and which supply specific areas of the skin and certain groups of muscles. The extent and degree of the loss of sensation and paralysis varies considerably depending on the disease classification, its spread, its duration, and the reactional episodes. In tuberculoid groups the lesions are localized and patchy, and in the patches only the superficial sensations may be lost. When nerve trunks are involved, it involves one or a few of them, but then the deep sensations and muscle functions supplied by them are impaired. On the other hand, in lepromatous groups the disease is extensive. The involvement of the skin is generalized and can affect virtually the entire skin except that of the axillae, the groin, and the perineum. The scalp and the midline of the back are relatively spared. Many, if not all, of the nerve trunks are affected to a lesser or greater degree. There are borderline lepromatous patients who present with every nerve trunk of the extremities and face paralyzed.

It is important to know that in leprosy during the early stage of the disease only the nerves present in the skin lesions are affected, and there are losses of superficial sensations and autonomic functions of that localized part of the skin. In the more advanced stage, one or more nerve trunks with mixed nerve fibers can become infected and damaged, producing loss of all sensations in

the distribution of the nerve trunk, superficial and deep, and muscle paralysis. Loss of muscle function alone is not reported in leprosy; paralysis of muscles always coexists with the loss of cutaneous sensation. (PGL-1) of *M. leprae* has also been demonstrated to bind specifically to laminin-2 in the basal lamina of SC-axon units [20]. Importantly, additional evidence clearly indicates that this mechanism of binding to the SC surface via alpha2-laminins is not unique to *M. leprae*. [21,22]. 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 P_0 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.[23] 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. [22,23,24].

Mode of Entry of *M.Leprae* into Schwann Cell of the Peripheral Nerve

M. leprae can enter the nerve by four different pathways. It was suggested that *M. leprae* enter the body through naked nerve filaments in the epidermis and spread centripetally along the axon [25]. The upward movement of the bacilli along the axonal flow was compared to fish swimming against the stream. Intra-axonal bacilli have been shown by several workers in electron-microscopic studies, but it is a rare occurrence.

The second suggestion was that *M. leprae,* on entering the skin, are phagocytosed by Schwann cells in the upper dermis. Thus protected from the cells of the immune system, they multiply inside the Schwann cells and travel along the nerve from one Schwann cell to another by contiguity. Many workers consider that *M. leprae* has a special predilection for Schwann cells and it remains as an important host cell of *M. leprae*. [26].The third possibility is that macrophages in the upper dermis initially take up the bacilli and these bacilli-laden cells aggregate around skin adncxal structures, including nerve bundles. Bacilli released from these macrophages are ingested by perincurial cells, which pass them on to Schwann cells, or the macrophages containing the bacilli infiltrate

the perineurium and invade the nerve. In thymectomized irradiated mice, or in athymic, nude mice infected with *M. leprae,* nerve involvement follows the formation of dermal lepromatous granulomas which grow to a fair size before there is evidence of nerve invasion by the bacilli. Bacilli-packed macrophages invade the perineurium and then enter the nerve parenchyma [27].

The fourth possibility, and the one which is perhaps the most frequent route of entry into the nerve, is through the bloodstream via the intraneural capillaries. Evidence of bacillemia is seen in all forms of leprosy. Therefore, organisms could easily be transported into the nerve by the bloodstream. Minimal injury to a nerve may increase the stickiness of the endothelial cells of intraneural capillaries and also may compromise the blood-nerve barrier. Schwann cells will actively phagocytes *M. leprae* brought into the nerve through the blood circulation. Perivascular intraneural granuloma is not an uncommon finding in tuberculoid neuritis (unpublished personal observation).
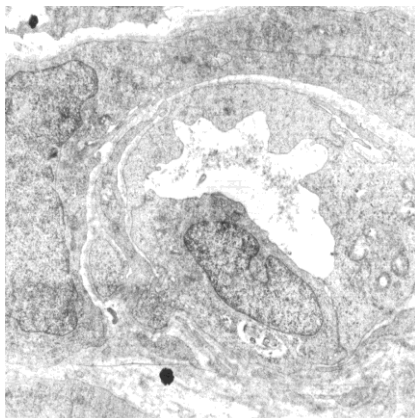
Fig7. *Ultrastructure of TT nerve showing endonurial blood vessels with numerous mitochondria and other cellular organells. The lumen is being narrower with prominent nucleus. X15000.*

Fig8. *Endonurial blood vessels showing lumen is completely closed with enlarged nucleus.The septum of the EC is clearly visible. X15000.*
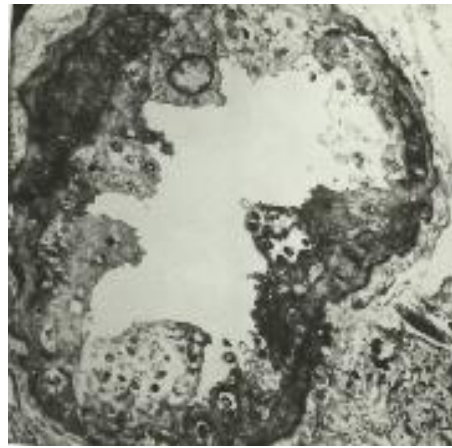
Fig9. *Endoneurial blood vessels showing small nucleus, lumen is open & numerous bacilli in endothelial. The cell was clearly depicted by releasing bacilli from endothelial cells. X20000.*

Schwann cells synthesize 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*, although some reports have suggested some preference for non-myelinating Schwann cells in vitro. In vitro, was observed a similarly brisk and heavy infection of both cell types. Some investigators, however, have reported exclusive infection of non-myelinating cells in vitro. Several potential mechanisms of binding of *M. leprae* to the Schwann cell have been elucidated.[22] 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, indicating that the association of *M. leprae* with SCs may be mediated by more than one of its cell surface molecules [28]. 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. 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, Phenolic glycolipid-1 [29,30,31].

M.Leprae And Immunologic Processes of Schwann Cells

Infection of SC with whole, viable *M. leprae* has not been observed to cause SC loss and even appeared to favor SC survival rather than apoptosis. 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 [32]. 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. TGFb1, 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 [33]. To further evaluate 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 been observed in several hundred genes. 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 [34]. Similar findings in T and B cell deficient (Rag1 $2/2$) 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. 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 [35].

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. 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*. Cultured SC appear to be able to process and present *M. leprae* antigens to CD4 þ T cells [36]. The infected Schwann cells were highly susceptible to killing by CD4 þ 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(þ) T cells, and are efficiently killed by these activated T cells.

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] TNFa, for example, have 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, TNFa may act synergistically with other cytokines to initiate apoptosis of SC. [39]. In addition, pro-inflammatory cytokines themselves may contribute to demyelination [40,41]. 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 [42,43]. 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 [44]. 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 [45].

Nerve Degeneration

In detailed evaluations of human leprosy-affected nerves, [46] noted, in addition to segmental demyelination, evidence of paranodal demyelination and atrophy, evident as a reduction in axon caliber. Segmental demyelination may be associated with local inflammation, whereas the pathogenesis of the atrophic lesions is not as evident [47]. 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 [48]. This was seen in nerves with minimal inflammation as well as in those with more extensive inflammation. Hypophosphorylated neurofilament proteins are more susceptible to proteolyic degradation, and loss of these proteins may explain the observed reduction in axonal calibre. Dephosphorylation of neurofilament proteins has been recognized 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.

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 [49]. 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. In this 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 is difficult to reconcile with longstanding clinical experience in leprosy.

Management of Neuritis

Silent Neuritis

In all leprosy patients with active disease, neuritis is always present, and most of the time it is asymptomatic or "silent." Therefore, in the management of neuritis a careful documentation of sensory and motor functions should be done at regular intervals to assess the progress of the disease and the benefits of the treatment. The most important step to prevent nerve damage or to arrest the damage that has already taken place is to sec that the patient gets regular antileprosy chemotherapy. In the lepromatous group, where nerve destruction is mainly due to the presence and multiplication of *M. leprae,* the sooner the intraneural bacilli are killed the sooner further nerve damage is prevented. In patients of all leprosy types with thickened nerves, if there is evidence of progressive nerve paralysis despite administration of regular antileprosy drugs, a course of corticosteroid therapy is indicated, even if there are no symptoms such as nerve pain and tenderness.

Acute Neuritis

During acute neuritis patients complain of pain and tenderness of nerve trunks localized to the sites of predilection. They may also experience hyperesthesia, feeling of pinpricks and tingling in the skin areas supplied by the nerve. The pain is caused by the sudden swelling of the nerve due to intraneural edema and cellular infiltration producing stretching of perineurium and cpineurium. Acute neuritis can be seen

during the ordinary course of the disease, but it is more often present during times of ENL and during exacerbation reactions in bordcrline-tuberculoid disease. In addition to treating the general symptoms that accompany neuritis, the nerve should be put at rest with an appropriate splint or a comfortable sling. Prevention of movement of the swollen nerve through narrow passages will frequently alleviate the pain. In addition, steroid therapy which suppresses edema and hypersensitivity reaction should be administered. Prednisone, up to a dose of 60 mg daily in divided doses, may be given to start with and it may be reduced weekly to less than 10 mg daily in 4 to 6 weeks. If successive documentation of the sensory and motor functions done weekly shows progressive loss in spite of corticosteroid treatment, it is necessary to relieve the intraneural pressure by surgery. At the site of the swelling, the nerve is exposed and the cpincurial sheath is incised longitudinally, taking care not to cut the blood vessels. In ulnar nerve swelling, the epicondyle may be excised or the nerve may be transposed in front of the epicondyle and buried in the muscles. In tuberculoid leprosy the nerve may have a localized cold abscess, containing caseous material, which should be excised. It is important to continue antileprosy therapy together with the anti-inflammatory drugs during the reactive episodes. In recent years, there have been several instances of neuritis due to dapsone (DDS) toxicity. Therefore neuritis caused by DDS should be carefully differentiated from leprous neuritis. DDS toxicity affects only motor nerve fibers. The drug should be discontinued in such patients.

CONCLUSION

Nerve damage is an ever-present serious complication of all forms of leprosy. We now understand much of its pathology and some of its pathogenesis. Its pathogenesis are closely linked with the reactive phase of leprosy about which we know very little. We should explore the possibility of producing ENL in the now available animal models such as the nude mouse, the armadillo, and the mangabay monkey. In experimental armadillo leprosy

there is no evidence of nerve damage; whereas in the primate model we observed the nerve damage characteristic of leprosy. Studies using these three experimental animal models to probe the unanswered questions about nerve damage are long overdue. In closing, I would like to repeat that in leprosy there is always neuritis, in some instances even after pronouncement of medical cures.

SUMMARY

The 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 decompressed nerves sustaining injury due to increased (edematous?) pressure. Inflammation in and around the nerves is undoubtedly driven, in part, by the immunological responses in each of the portions of the immunologic 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 depicted sequence of these events is uncertain. Considerable additional data are 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. An additional study 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 preventionof nerve injury in leprosy.

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