CORRESPONDENCE

This department is for the publication of informal communications that are of interest because they are informative and stimulating, and for the discussion of controversial matters. The mandate of this JOURNAL is to disseminate information relating to leprosy in particular and also other mycobacterial diseases. Dissident comment or interpretation on published research is of course valid, but personality attacks on individuals would seem unnecessary. Political comments, valid or not, also are unwelcome. They might result in interference with the distribution of the JOURNAL and thus interfere with its prime purpose.

Nerve Damage in Leprosy

TO THE EDITOR:

A proper understanding of the mechanism of nerve damage in leprosy is extremely important in the treatment, prevention, and modulation of nerve damage.

The immunohistopathological classification of leprosy is based mainly on the histopathology of skin and not of nerve. While some workers have shown concordance between skin and nerve pathology ([10]), others disagree ([15]). The lack of a suitable animal model for nerve damage in leprosy and the fact that nerve biopsy is more difficult than skin biopsy and needs surgical skill for choosing a correct nerve funicle for biopsy have limited the study of pathogenesis in the nerve.

A number of important questions relating to peripheral nerve involvement in leprosy have been addressed in the past. The mechanism of entry and dissemination of *Mycobacterium leprae* in the nerve, the interaction between the invader and the various neural constituents, and the type and pattern of degeneration of nerve fibers have been dealt with by various workers. Unfortunately, the views on the mechanism of nerve damage remain diverse and unclarified.

Intra-axonal transport ([8]), portal of entry ([16]), and Schwannian relay ([6]) of *M. leprae* have been proposed. The cause of nerve pathology has been attributed to ischemia and mechanical trauma by some investigators ([3]). By and large, in tuberculoid neuropathy nerve damage is related directly or indirectly to cellular infiltrate and edema or granuloma formation. In lepromatous leprosy, nerve destruction is associated with the presence of *M. leprae* ([6, 7]), chiefly a process of slow fibrosis.

A multidisciplinary, correlative, clinical, electrophysiological and ultrastructural study on the index branch of the radial cutaneous (IRC) nerve in a group of early leprosy cases along the spectrum and in familial contacts of lepromatous leprosy patients was initiated by Antia and his colleagues ([1]). The similarity between the nerve lesions in humans and in the sciatic nerves of *M. leprae*-inoculated mice was established and extended to longitudinally monitor the nerve damage ([1]). The use of such an approach led to the demonstration of diffuse peripheral neuropathy with significant endoneural changes in clinically uninvolved nerves of leprosy patients as well as in contacts. There is evidence that nerve pathology may be present at a very early stage of the disease or in leprosy contacts without any clinical symptoms. In general, similar changes were seen in both the tuberculoid and lepromatous types of leprosy, suggesting a common mechanism of nerve damage at least in the early stages. This gives support to the view that early pathology may be caused by a humoral factor or by locally produced antigens found in both types of leprosy.

Morphological evidence also suggests that there is abnormal Schwann cell-axon interaction and disturbance in Schwann cell metabolism ([13]).

The nerve tissue culture model was also employed to investigate Schwann cell-*M. leprae* interaction. Light and ultrastructural

studies of both short- and long-term, *M. leprae*-infected, dorsal root ganglion cultures revealed that *M. leprae* were absent in the neuronal cell bodies and axons, thus confirming the *in vivo* observation that these were not the favorable sites for *M. leprae* maintenance and multiplication. It was also shown that DNA synthesis is inhibited in Schwann cells infected with *M. leprae*, while protein synthesis as measured by ^{3}H-leucine incorporation remains unaltered. In addition, the entry of *M. leprae* into Schwann cells was viability dependent, and a lipid moiety on the Schwann-cell membrane was probably responsible for facilitating this entry ([9]).

Peripheral nerves under normal circumstances possess two major protective barriers, i.e., the blood–nerve barrier and the perineural barrier. The involvement of blood vessels and the perineurium has been recorded in human leprosy. It is obvious that the blood vessel and the perineurial functions will be impaired in a highly inflamed nerve. However, what is not clear is whether it is the cause or the consequence of nerve pathology in leprosy. Functional studies carried out in the experimental mouse model reveal that the blood vessel and the perineural barriers are not impaired even when the surrounding endoneurial cells are quite heavily bacillated ([4], and Shetty, *et al.*, unpublished observation).

An extensive qualitative and quantitative study on the perineural changes in human nerve lesions carried out by us reveals some interesting observations. There was no abnormality in the perineural cell tight junctions in early nerve lesions or in moderately involved nerves. However, there was significant thickening of the perineurium due to multiple factors. In tuberculoid lesions it was mainly due to connective tissue increase; in lepromatous nerves there was a two- to fourfold increase in the number of perineurial layers around the fascicles. Thickened or multilayered but otherwise normal-looking perineurium, if it has lost its normal properties of semipermeability and elasticity, could adversely affect the intraneurial milieu or even affect penetration of drugs.

Another important aspect of nerve damage is to understand if and how a damaged nerve can repair itself following treatment, and whether antileprosy and anti-inflammatory treatments can ensure protection from further damage to the nerve. Information available so far is purely on the basis of clinical follow up. The study by Radhakrishna and Nair ([11]) revealed that the deformity rate increases with increased duration of regular treatment. This has been attributed to probable dapsone (DDS) neurotoxicity by these workers. Motor neuropathy associated with overdosing of sulfone appears to be the prime feature of DDS toxicity in humans ([12]).

In a study of nerve biopsies obtained from leprosy patients who were on antileprosy treatment for as short a time as a few months to as long as over 20 years, we observed a high antigenic load (as demonstrated by anti-BCG antibody using the peroxidase-anti-peroxidase technique) in the nerve, even after prolonged (>20 years) treatment in lepromatous patients and in untreated, active tuberculoid lesions ([2]). In the same study it was observed that in active tuberculoid nerve lesions, where standard carbol fuchsin stain had failed to reveal any acid-fast organisms, osmiophilic, electron-dense bacilli were seen in the Schwann cells at the ultrastructural level. This gives support to the view that degraded bacterial antigen and a non-acid-fast stage in the life cycle of *M. leprae* ([5]) may contribute to the continuing nerve damage following treatment.

Light and ultrastructural studies of treated leprous nerves reveal that the regenerative, especially remyelinating, capacity of a leprous nerve is very poor and deteriorates with time in spite of regular treatment. There were axonal atrophic changes and increased fibrosis in these nerves. However, none of the nerves studied from patients under treatment (>6 months) revealed active degeneration of nerve fibers, which is reported in cases of DDS neuropathy ([14]). There are apparently other factors to be considered. Immobilization of certain functional properties of neural elements by the continued presence of bacterial antigen and the presence of a thickened/multilayered perineurium acting as a nonpermeable membrane needed to be considered as the reasons for the lack of regeneration and atrophic changes in the nerve fibers.

Therefore, is the treatment of patients with antileprosy drugs, as far as nerve damage is concerned, only helping in the formation of scar tissue? If so, restoration of the dying nerve's function needs to be considered as a separate entity from the antimycobacterial treatment in relation to leprous neuritis.

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