The Immunopathology of Nerve Damage in Leprosy

TO THE EDITOR:

We read with great interest the review on this subject by Dr. Hill-Smith in Vol. 49 No. 2 of the JOURNAL (pp. 223–227).

It seems now that one must make a clear distinction between cutaneous or sensory nerve damage and damage affecting motor or major nerve trunks whenever discussing the immunology of leprosy neuropathy. This point has for a long time been neglected, and this has led to the currently poorly understood immunopathology of nerve damage in leprosy. It is possibly due to the fact that motor nerve involvement is more important clinically, but one must not forget that sensory loss contributes quite a lot to the mutilations in leprosy.

Sensory nerve damage occurs early in patients with non-lepromatous leprosy (non-LL) where *Mycobacterium leprae* are scanty or absent ([2]) and the cutaneous nerves harboring these bacilli seem to be healthy and not involved in the inflammatory process ([9]). Lepromatous leprosy patients (LL) on the other hand harbor large numbers of *M. leprae* but develop sensory loss late in the disease when the numbers of the bacilli are comparatively few. Furthermore, this process can be very rapid and preceded by edema of the limbs ([2]). The pattern is of glove and stocking type, and thus predominantly distal, and often occurs without accompanying motor loss ([2]). In non-LL patients, sensory loss can occur limited to the hypopigmented skin lesion which is also often hairless.

Since *M. leprae* are virtually non-toxic ([4]) and the inflammatory response is not always correlated to the presence of *M. leprae* or its antigens *in situ*, it is not unreasonable to assume that the triad of hypopigmentation, cutaneous sensory nerve damage, and hair loss are related to an autoimmune response and not to *M. leprae* per se. This has long been suspected ([2]) and, in fact, experiments have shown that an autoimmune delayed type hypersensitivity reaction to the non-myelin component of human sensory nerves reproduces the triad ([3]). One can then postulate that the inflammatory response seen in areas where no *M. leprae* or its antigens are demonstrable is attacking a host structure. If the structure is a sensory receptor, then secondary degeneration or damage in named cutaneous nerves, *e.g.*, radial cutaneous and sural nerves, can occur even in the absence of both *M. leprae* or inflammatory cells as has been reported ([6]). This is so since it has been shown that during development a nerve has to make contact with the periphery for the survival of the nerve cell, and that peripheral receptors are important in this process perhaps by secreting factors that maintain the integrity of the nerve cell ([7]).

An immune response directly attacking peripheral nerves and causing motor nerve damage has been produced in animals ([8]) and has been proposed as a model for human Guillain-Barré syndrome. The antigen initiating this experimental neuritis has been shown to reside in the myelin basic protein, P_2 ([5]). We have searched for both antibodies and cell-mediated immune responses to this protein in leprosy patients and found none. It seems, therefore, that a direct autoimmune attack on myelin proteins is not involved in the neuropathy of major nerve trunks in leprosy. An immune attack to-

wards intraneural antigens can, however, lead to nerve damage ([10]). Since *M. leprae* or its antigens can be found intraneurally, it is possible that this mechanism is relevant in leprosy. We have sensitized a rabbit with *M. leprae* and then injected *M. leprae* sonicate into the sciatic nerve. Histologically the nerve damage seen in the injected nerve was strikingly similar to that of human nerves during reversal reaction. Whole intraneural *M. leprae* per se may not cause nerve damage, but intraneural antigens of *M. leprae* in the face of systemic delayed type hypersensitivity to them can certainly lead to a neuropathy.

In summary then, we feel that there are two completely different mechanisms involved in leprosy neuropathy. One is an autoimmune granulomatous reaction secondary to interactions between *M. leprae* and Schwann cells of unmyelinated cutaneous fibers. This reaction leads to loss of pigment and hair as well as sensory loss. The other one is a consequence of delayed type hypersensitivity to intraneural *M. leprae* antigens and affects motor or major peripheral nerve trunks. The distinction of the two mechanisms offers a more rational approach to the understanding of the immunopathology of nerve damage in leprosy and also in other diseases like diabetic neuropathy.

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