Short-term, Multi-drug Chemotherapy of Leprosy and Type I Reaction

TO THE EDITOR:

From an extensive experience in the management of borderline leprosy, I consider the following a most important communication that needs urgent and wide dissemination.

The aim of all leprosy treatment is to ultimately prevent deformity and disability. The major cause of deformity and disability in leprosy is nerve damage. Therefore, our first goal in treatment is to prevent nerve pathology.

Prevention of nerve damage. Injury to nerves is the most important component of the pathology of leprosy, yet in a majority of cases it is not of significance. In indeterminate and simple tuberculoid leprosy it never occurs at all. At the other end of the spectrum in true lepromatous leprosy there will be no disability due to nerve damage if the disease is treated with multi-drug therapy at an early stage and treatment is continued correctly.

This then leaves borderline leprosy as the area of the spectrum where there is grave danger of disability. I want to stress the point that in BT, BB and BL leprosy the vital need of the patient is to suppress the unwanted inflammation of hypersensitivity. Only when that is controlled should we look to the treatment of the underlying disease. There are several articles by Crawford ([2,3,5]) that bring out an important point. He states that there are two types of nerve damage: one that is associated with edema of the extremities which is a purely sensory form of polyneuritis; the other related to involvement of the superficial peripheral nerves, which he terms a mononeuritis, or a mononeuritis multiplex. He stresses the importance of recognizing the edema of hands, feet and face, concluding that this is a type of reaction occurring in BT leprosy only. But it must be recognized that it occurs in BL as well.

I believe this is just where many are making a major mistake in management. Since it is recognized as BL type of disease, it is assumed that therefore any reaction is a Type II response to antigen. Out of our experience with the use of thalidomide in these cases I have been forced to conclude that a part of what is seen in BL is actually Type I reaction. Thalidomide has no effect in this reaction, and frequently patients are left with problems after the thalidomide has cared for the Type II complications. This is usually a residual neuritis which will take a long course of relatively low dose corticosteroids to control. But it does respond well to this. The same is true of peripheral edema and also the tenosinovitis of leprosy. Neither will be affected by thalidomide, but both respond dramatically to corticosteroids. I really wonder if neuritis is in fact a part of Type II reaction. I do not know how to determine this, but it does not respond to thalidomide, which is dramatic in its effect on all other aspects of Type II reaction. Crawford states that the nerve damage of paucibacillary leprosy is early, acute and severe, and therefore must be on an allergic or auto-immune basis ([4]). He even goes so far as to say that the skin lesions of tuberculoid leprosy are secondary due to nerve injury. In actual fact the skin lesions in BT or TT leprosy are simply a "sarcoid" response to foreign material. Histologically, when we see *Mycobacterium leprae* or damaged nerves, then we say the lesion is due to leprosy; otherwise we cannot distinguish the pathology from other granulomatous responses. In a recent Letter to the Editor in the INTERNATIONAL JOURNAL OF LEPROSY, Dr. McDougall ([7]) replying to Dr. Crawford states that the mention of nerve damage associated with peripheral edema is "something new concerning the pathogenesis of leprosy." But I propose that it is simply something hitherto unrecognized. Potentially this reaction is an important cause of very disabling and permanent nerve damage. Very frequently it takes place so quickly that we do not see the patient until it is too late to prevent the damage.

A recent summary of the immunopathology in leprosy by Hill-Smith ([6]) concludes that the major factor in the causation of nerve damage is not the pathogen, but rather the host response. Although no auto-an-

tibody to nerve tissue has been specifically incriminated ([10]) certainly the many peculiar immune abnormalities in leprosy make this more than likely.

Chatterjee ([1]) supports our views in an editorial discussing the significance of immunologic considerations in determining the treatment of leprosy, when he asks just what does the patient require in order to prevent disability? And he asks specifically "would these cases (that threaten neural damage) do better if they are not treated with dapsone but only their hypersensitivity state treated with anti-inflammatory agents to prevent neuritis . . . ?"

In our experience all effective antileprosy drugs aggravate the hypersensitivity with the exception of clofazimine, which is found to be anti-inflammatory as well as antibacterial. The bacteriostatic drugs, such as the sulfonamides and the thiourea group are less effective and result in much less reactional response.

Multi-drug, short-term chemotherapy. From many sources we now hear recommendations for short course intensive treatment of all cases of leprosy. Most of these courses include both dapsone and rifampin. On a theoretical basis this seems reasonable. I only mention one of these suggestions by Pattyn, *et al.* ([8]). They propose that if one eradicates the bacilli rapidly, one will also rapidly get rid of the cause of the hypersensitivity. But I contend that this state of hypersensitivity is like a forest fire that is started by a single match, but then continues to burn quite out of control. In just this way in borderline leprosy auto-immune responses set up a Type I reaction no longer dependent upon the etiological agent.

Our very preliminary trial reported in 1975 ([9]) demonstrated without question the potential damage that can take place when rifampin is used in treating BT leprosy. We had assumed that to eradicate the bacilli quickly would reduce the immunologic potential, but there must be some factor here which is yet unexplained. I fear our warning about this has not been noted or else forgotten. More recently, we have had more unfortunate experiences with rifampin. This has been when it was used as a second drug in BL patients. It is very hard to determine where it will be damaging, but there are three signs that give warning. One is the peripheral edema stressed by Crawford. Another is the tenosynovitis of leprosy. A third is spontaneous ulceration in a Type I reactional lesion. All these are strong indications for high dosage and prolonged corticosteroid treatment. Also if the smears are not very strongly positive, I question if rifampin should be used. Certainly one is on far safer ground to simply give clofazimine, or even streptomycin as a second drug. I am quite convinced that either of these can be used with less danger of inciting reaction, and they are also effective bacteriocides. It is important that rifampin be used only in highly bacilliferous patients in order to avoid untoward Type I reactions that may lead to permanent nerve damage. In highly bacilliferous patients it causes very few side effects, with perhaps only a slight increase in Type II reaction.

Just one final point that must be raised about the widespread introduction of multidrug treatment. We are associated with a large outpatient control scheme and have found it almost impossible to implement correct treatment due to logistical constraints simply attempting to use dapsone alone. I cannot see how we could possibly attain staff and patient cooperation if we attempted to introduce a more complicated treatment scheme. I am sure the problems would be insuperable. But this aspect of the problem still takes second place to the medical contraindications of multi-drug therapy of all cases irrespective of type.

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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-