

Editorial

Nerve damage *is* leprosy. ‘Leprosy would be a rather innocent skin disease were it not for the nerve damage and subsequent loss of sensation and muscle power and secondary ulcerations and deformities, which make the leprosy patient an outcast from society’.¹ It is this that makes it a ‘disease apart’ in many people’s minds.² It is poignant that the author of the last quote, Paul Brand, only died in July of this year.³ It was he, more than any other, who recognized the link between nerve damage and the secondary deformities which characterize the disease unless it is treated early with effective chemotherapy.

Considering the central place that nerve damage occupies in leprosy and in the personal and social consequences of the disease, it is perhaps surprising how little prominence its recognition and treatment is given in many elimination campaigns where the emphasis is very much on MDT alone.⁴ Even more surprising are the gaps that still exist in our current state of knowledge about the prevention and management of nerve damage. This issue contains some important papers, which, taken as a whole, seem to pose more questions than provide answers. It is important that research continues into nerve damage, for it is likely to be many decades before the incidence of leprosy has fallen so low that we dare to forget about the problem.

TRIPOD (TRials In Prevention Of Disability) is a triad of multi-centre, randomized, double-blind, placebo-controlled clinical trials designed to investigate the prevention and treatment of nerve damage in leprosy by using corticosteroid therapy. This type of study is rare in the leprosy field. The results of two arms of the trials are presented in this issue, as is another paper using the TRIPOD data to investigate the safety of corticosteroids. (The results of the final arm of TRIPOD are being finalized and will be published in the near future.)

In this issue, the TRIPOD 2 paper, by Van Brakel *et al.*, asks whether the treatment of very early sensory changes detectable only with monofilaments (but not the ballpoint pen) improves outcome in terms of recovery of touch sensibility. The answer is that it does not, and neither does it reduce the risk of leprosy reactions or nerve function impairment (NFI) beyond the initial 4-month treatment phase. The TRIPOD 3 paper (Richardus *et al.*) considers whether corticosteroid treatment offered to patients whose NFI was present for longer than 6 months would recover function. Again the answer is negative, and confirms the current practice not to treat long-standing NFI with prednisolone.

A finding common to both of the TRIPOD papers is the frequency of spontaneous recovery of nerve function. Van Brakel found that early NFI recovered spontaneously in 75% of nerves at 12 months in the placebo group, and Richardus found improvement in nerve function in 51% of his placebo group. Spontaneous recovery of nerve function has been documented before, but not in the context of a randomized control trial.

The third paper, by Richardus *et al.*, considers the safety of corticosteroids in the standard regimens used in TRIPOD, and provides reassurance for those involved in the field treatment of NFI using corticosteroids. The relative risk for minor adverse events in the prednisolone

group was 1.6, and there was no excess risk for major adverse events. The overall message seems to be that prednisolone is safe, but has definite limits to its usefulness that have now been more clearly defined.

Ben Naafs' paper, 'Treatment duration of reversal reaction: a reappraisal. Back to the past', strikes a different note. It is a personal paper by a single (distinguished) author, and argues that the current trend for relatively short, fixed regimens of corticosteroids for leprosy reactions should be seriously reconsidered in view of a body of evidence which he presents. He suggests that we should be treating reactions for much longer, and that if we did, patients would benefit. His 'counter-culture' view underlines the fact that there is still no consensus about the best way to use prednisolone.

A large retrospective cohort study from Brazil forms the next offering (de Oliveira *et al.*). The cohort of 5230 new patients detected in Rondonia State between 1996 and 1999 was studied for the dynamics of impairment during treatment. While the results are broadly in line with those determined by other studies, this paper gives a strong message that 'reactions and impairments in Hansen's disease will continue to occur in large numbers, requiring the development of adequate infrastructures and sustainable services to detect and manage problems . . . during and after MDT'. Nerve damage cannot be ignored.

The Bangladesh Acute Nerve Damage Study (BANDS) has already provided a wealth of data relating to the epidemiology, risk factors and response to treatment of acute NFI in leprosy (see references in Nicholls' paper). Peter Nicholls and his co-authors have studied delay in presentation as an indicator for nerve function status and treatment outcome, using data from BANDS. They found, perhaps not surprisingly, that delay in presentation was associated with increased signs of NFI at registration. Delay was a risk factor for any event of NFI during follow-up, and a risk factor for the development of recurrent NFI. They suggest that 6 months should be set as the definition of delay and that it should be incorporated as an indicator for use in reporting and evaluating the effectiveness of a control programme.

A fascinating small study from Rosenberg *et al.*, in the Netherlands, looks at 14 patients and tracks the development of late NFI after completion of treatment in the absence of relapse, ENL or reversal reaction. They found two groups of patients, one of which developed a subacute multiple mononeuropathy and another a slowly progressive multiple neuropathy. The first group had a partial response to steroids, the latter not at all. The authors postulate an immunological mechanism for the first group, but are unclear about the aetiology of the NFI in the second group. It has been recognized for some time that another mechanism of NFI probably exists, distinct from an immunological reaction.⁵ This paper confirms that likelihood and brings us back to the question: what is it?

Husain's electrophysiological studies of ulnar and median nerves in PB leprosy shows how, in the absence of clinical signs of NFI, widespread nerve damage is detectable by EMG. He found that amongst patients who have apparently full recovery of function after steroid therapy or nerve decompression, there is incomplete recovery of electrophysiological function. The authors suggest that low-dose prednisolone could be administered along with MDT to all PB cases for 6 months, to prevent a 'spurt in immunological functions' leading to clinically detectable nerve damage. However, the TRIPOD 2 paper in this Special Issue suggests that this would not be effective.

Finally, Brandsma and Van Brakel propose a much-needed overhaul of the WHO Disability grading system. Those working with leprosy sufferers will be familiar with the many deficiencies of the current system. In particular, their proposal that sensory impairment (WHO anaesthesia) be defined as the inability to feel the chosen sensory testing instrument

(ballpoint pen or monofilament) on two or more test sites is very welcome, since it standardizes what is now rather variable practice. It would be very good indeed to see their clarifications adopted by the WHO Expert Committee and universally adopted.

In conclusion, then, what important themes emerge from the papers published in this issue? The first one is surely about corticosteroids: useful though they are in modulating the immune response, they clearly have their limitations. In addition, there is no consensus about the best way to use them, as Ben Naafs reminds us. A second, converse but related theme is the phenomenon of frequent spontaneous recovery of nerve function, which TRIPOD has documented with randomized rigour. The absence of randomized controlled trials in evaluating the effectiveness of steroids in treating nerve damage is a serious gap in our knowledge that TRIPOD has unexpectedly exposed.

References

- ¹ Naafs B. Leprosy reactions. *Quad Coop San*, 1992; **12**: 67–72 (quoted by Van Brakel WH, Khawas IB in *Lepr Rev*, 1994; **65**: 204–221).
- ² Brand PW. Deformity in leprosy. In: *Leprosy in theory and practice*, 2nd edn. John Wright & Sons, Bristol, 1964, p. 448.
- ³ Nash JE. Obituary—Paul Wilson Brand. *Lepr Rev*, 2003; **74**: 284–285.
- ⁴ Lockwood DNJ. Leprosy elimination: virtual phenomenon or reality? *BMJ*, 2002; **324**: 1516–1518.
- ⁵ Van Brakel WH, Khawas IB. Silent neuropathy in leprosy: an epidemiological description. *Lepr Rev*, 1994; **65**: 350–360.

RICHARD CROFT
(Guest Editor)