Nerve repair by denatured muscle autografts promotes sustained sensory recovery in leprosy

The success of multi-drug therapy has improved the management of leprosy but it is still a major cause of neuropathy worldwide. Motor and sensory loss impair the ability to work, and with ulceration and mutilation contribute to social exclusion. Localised damage to a nerve trunk (Fig. 1) occurs in 20% to 30% of patients, with lesions appearing specifically where nerves pass through fibroosseous tunnels, usually the median at the wrist, the ulnar at the elbow, the lateral popliteal at the neck of the fibula and the posterior tibial in the tarsal tunnel. Acute neuritis on confrontation of six months of effective drug treatment may respond to antileprosy drugs, steroids or surgical decompression, but many patients develop complete motor and sensory paralysis. Motor function can be improved by tendon transfers, but there is no standard technique to allow for the recovery of sensation. Nerve excision and grafting has previously been unsuccessful.

Muscle grafts have been used successfully to repair nerves in animal models after traumatic nerve damage, in an experimental model of leprosy and in damaged human digital nerves. The senior author (JHP) has previously described the use of muscle grafts in 12 mixed peripheral nerves in ten patients with leprosy.

We present the results of a larger study with longer follow-up of up to 14 years.

**Patients and Methods**

Between 1989 and 1994, 38 patients underwent 48 nerve repairs (11 median and 37 posterior tibial) at the Sacred Heart Leprosy Centre in India. Three patients died of unrelated causes during the study and one was lost to follow-up. The results of the remaining 34 patients and 41 grafts (11 median and 30 posterior tibial) are presented.

Ethical approval was obtained from the hospital ethics committee and all patients gave informed consent. The criteria for inclusion were complete motor and sensory loss in the hands and feet of 18 months duration, complete sensory loss in a nerve trunk at the ankle, absence of ulceration at operation and no recent steroid therapy. The exclusion criteria were the presence of any sensory modality of the hands and feet, any motor activity on voluntary motor testing (VMT), ongoing steroid therapy, incomplete anti-leprosy drug therapy and ulceration.

**Operative technique.** The operations were carried out under spinal or axillary block with 1% Xylocaine (Astra Zeneca UK Ltd, Luton, United Kingdom) and magnifying loupes (Carl Zeiss, Jena, Germany)

A total of 38 patients with leprosy and localised nerve damage (11 median at the wrist and 37 posterior tibial at the ankle) were treated by 48 freeze-thawed skeletal muscle autografts ranging between 2.5 cm and 14 cm in length. Sensory recovery was noted in 34 patients (89%) and was maintained during a mean period of follow-up of 12.6 years (4 to 14). After grafting the median nerve all patients remained free of ulcers and blisters, ten demonstrated perception of texture and eight recognised weighted pins. In the posterior tibial nerve group, 24 of 30 repairs (80%) resulted in improved healing of the ulcers and 26 (87%) demonstrated discrimination of texture. Quality of life and hand and foot questionnaires showed improvement; the activities of daily living scores improved in six of seven after operations on the hand, and in 14 of 22 after procedures on the foot. Another benefit was subjective improvement in the opposite limb, probably because of the protective effect of better function in the operated side. This study demonstrates that nerve/muscle interposition grafting in leprosy results in consistent sensory recovery and high levels of patient satisfaction. Ten of 11 patients with hand operations and 22 of 25 with procedures to the foot showed sensory recovery in at least one modality.
Zeiss Ltd, Welwyn Garden City, United Kingdom) (× 4 to × 6) were used. The damaged nerve was exposed by a longitudinal incision over the wrist or behind the medial malleolus, and after limited mobilisation, isolated with rubber slings. In one-third of cases, a fusiform swelling of the diseased nerve was seen (Fig. 1). In the others, the thickened abnormal nerve with its firmer consistency was identified by palpation. The abnormal nerve segment and scarred tissue was resected. The emergence of the contents of the perineurium from the cut ends indicated a healthy nerve. The quality of the nerve at the cut ends was assessed visually. The diameter and length of the gap was measured. A length of sartorius muscle was obtained. The graft should be at least twice the length of the nerve gap to allow for shrinkage during the freeze/thaw process.

The muscle was stretched over a sterile wooden board by minimal traction on stay sutures. The whole graft was evenly sprayed with an aerosol of dichlorodifluormethane, which freezes at -30˚C. Turning the muscle during the procedure ensured complete freezing with special attention paid to the ends of the graft. Thawing of the muscle and further denaturing by osmosis was by immersion in sterile distilled water. The freeze-thaw process takes between five and ten minutes. The graft was cut to a thickness of 1 mm to 2 mm greater than the diameter of the nerve ends. The nerve end was enveloped in muscle and sutured in place using 8/0 polyamide or polypropylene sutures (Fig. 2). Approximately four or five sutures were necessary for each end. To allow for shrinkage, the final length of the graft was not decided until one of the ends was sutured in place. Wound drainage was usually not necessary. A light compression bandage and a plaster cast was used for three to four weeks to prevent stretching of the graft. Strenuous activities which might cause tension at the repair site were avoided in the first six weeks after treatment.

Detailed protocols for examination were developed for pre- and post-operative sensory and motor assessment. Patients were seated comfortably in a quiet, well-lit room, with their eyes shut. Rests were taken frequently. No direct questions in relation to sensory changes were asked. The areas of the hand and foot were mapped numerically, enabling the accurate recording of areas of recovery. The comments of the patient and examiner were recorded simultaneously.

The following tests were used: 1) touch and pressure, using graded monofilaments of 10 g, 20 g and 300 g; 2) pain using sliding weighted pins of 5 g, 10 g, and 20 g; 3) vibration, using a biothesiometer (Arnold R Howel Ltd, Newbury, Ohio); 4) texture for hands using graded sand papers with an abrasive rating of 240, 180, 100 and 50 and for feet by walking on wooden trays filled with sand, stones and microcellular rubber, respectively, embedded in concrete to prevent auditory simulii and covered so that patients could not see the underlying material; 5) skin and ambient temperature, using an electronic thermometer; 6) temperature perception, using hot (90˚C) and cold (4˚C) water; 7) sweat function, using the ninhydrin sweat test; 8) motor function, according to VMT/Medical Research Council (MRC) grading and 9) pre- and post-operative photographs, radiographs and nerve conduction studies.
A total of 29 patients completed questionnaires on their quality of life. They were asked general queries as to their activities of daily living, and others specific to the hand or foot, as appropriate, relating to the use of the limb, their ability to work and the frequency of injury or ulceration. The questions were direct, with a five-part scale (a = much improved through to c = no change and e = much worse).

The questionnaires were administered to both groups. The hand surgery group were intended to act as controls for foot surgery patients and vice versa. Those who underwent both hand and foot surgery were allocated to the treatment group. Since many patients had unilateral surgery, the opposite limb was compared with the operated side as a second control.

Results
Median nerve repairs. A total of 11 patients, with a mean age of 26.8 years (14 to 42), had median nerve muscle grafts. Four of these also had tendon transfers, two prior to grafting and two at the same time. The length of the initial period of recovery varied between one and two years, after which all patients were free of ulcers and blisters until their final assessment. Ten patients could differentiate between grades of sandpaper, nine perceived a 300 g filament and four a 10 g filament over part of the palm and fingers. Eight patients perceived a 20 g pin and three a five g pin. Four patients felt heat using warmed test tubes. Vibration sense showed progressive improvement but there was no correlation with any of the sensory modalities which recovered in these patients. Nerve blocks were performed in selected patients with grafts of 4 cm, 8 cm and 14 cm which showed a loss of the sensation that had been regained at operation, and a lack of overlap, indicating that nerve recovery had occurred within the graft. Comparison of the pre- and post-operative photographic and radiological assessment of the hands showed maintenance of bone and soft-tissue architecture in all but one patient. Nerve conduction studies were performed before and after operation in selected patients. However, electrodes placed proximal and distal to the grafts did not show any significant electrical activity, probably because of the small numbers of regenerated nerve fibres. Skin temperature and sweat tests were also inconclusive.

After operation, the patients noted recovery of protective sensation and increased function. They found an increased ability to feel and hold light and heavy objects, enabling them to return to work or undertake domestic activities more efficiently. Only one did not experience any subjective improvement in sensory function. The number of patients was too small to identify any correlation of the results with the type and duration of disease, the degree of paralysis, the length of the graft or the histological quality of the nerve stumps.

Posterior tibial nerve repairs. A total of 25 patients with a mean age of 27 years (15 to 50) had posterior tibial grafts, of which five were bilateral. Of the 30 repairs, 26 showed recovered perception of at least one walking surface and 16 could differentiate two or more surfaces. In 25 of the 30 legs there was ulceration pre-operatively. There was improvement in 24, with total healing in 20 and partial healing in four. A further four reported continuing deterioration and two were unable to comment. In ten patients, the ulcers became painful, thereby providing protective function before healing. The assessment of sensation revealed patchy responses, with 7 of 30 limbs perceiving 300 g filaments, indicating a return of crude touch. Three perceived 20 g pins. There was no evidence of overlap from the territory of the saphenous or sural nerves. Vibration sense improved but not as well as after repair to the median nerves. Temperature perception did not recover in any patient. Sweat tests and nerve conduction studies were inconclusive.

The patient’s most commonly noted recovery of their ability to feel ordinary walking surfaces and discriminate between stones and thorns. They were also aware that for the first time they were wearing footwear and noted the absence or reduction in ulceration and/or pain in the ulcers. Histology. All nerve segments which were removed were subjected to paraffin staining and immunohistochemistry. There was extensive damage to the myelinated nerve fibres, with a residual nerve fibre count in the proximal stumps of between 5% and 10%. There was no difference in the population of nerve fibres between the proximal, middle and distal parts of the removed segment. The residual nerve fibres were arranged in regenerating units, signifying the potential for regrowth. At all levels there were moderate to severe degrees of scarring. This comprised varying degrees of chronic lymphocytic inflammation and granulomata. There were dormant or dead mycobacteria in some borderline lepromatous nerves.

Subjective assessment. The questionnaires included 14 items, six relating to aspects of daily living and eight to specific limb function/sensitivity.

Of the seven hand patients who completed the questionnaire, one showed minor deterioration in two modalities (washing and caring for themselves) with no change in other areas. The others all showed mild or marked improvement in most or all aspects of daily life. Thus, six of seven patients benefited by seeing improvement. Relating to specific function, all patients reported improvement in at least one aspect; 80% of responses reported positive improvement, 5% reported deterioration. Of the 22 foot patients who completed the questionnaire, 14 had overall improvement, one had deteriorated, and seven noticed no change in daily living. Relating to specific found, six found deterioration in one or more aspects of function and 18 improvement in one or more. Over the range of questions 50% of responses reported improvement, and 9% deterioration.

Overall 29 patients who received operations completed the questionnaire; in daily living one showed minor deterioration, eight showed no change and 20 showed improve-
ment. In limb function, across the questions asked, 63% of responses reported an improvement.

We asked the same questions relating to function in the non-operated limbs. For hand surgery patients, 35% responses described improvement in the non-operated hand, 38% of responses in patients with foot operations reported positive improvement in hand function, 6% reported deterioration in both.

Discussion

We describe restoration of sensory function in patients with leprosy using muscle grafts for nerve repair, a relatively inexpensive procedure that can be performed under regional anaesthesia.

The best results followed repair of the median nerve. There may have been less sensory nerve damage and ulceration in the palm than in the sole of the foot, and the distance for regenerating nerve fibres to grow is shorter.

The healing and prevention of ulcers, and the improvement in textural recognition by both hands and feet were the most promising outcomes for these patients. Sensory recovery was often patchy, in some cases returning two to four years after operation. It is likely that, because only limited numbers of healthy sensory nerve endings remain, time is necessary to form connections and allow central and peripheral adaptative mechanisms to translate into useful sensory function.14

In advanced leprosy, there is extensive destruction of sensory nerve endings. It is no surprise, therefore, that objective assessment with monofilaments and weighted pins elicit only limited responses. In traumatic nerve damage of this extent and duration, surgery to promote sensory recovery would rarely be considered. The fact that conventional objective tests showed limited results should not be seen as a weakness of this study because functional recovery is the goal after nerve repair, particularly in patients who often have had complete loss of sensation and lack of protective sensation for many years.16 Even minor improvement in sensory recovery will be of major benefit, similar to the partial recovery of sight in the blind. Partial recovery of texture recognition allows patients to recognise uneven walking surfaces, thereby avoiding injuries.17 Evidence of useful functional recovery in our patients was through textural assessments of the hand and foot, improved ulcer healing, a better quality of life, improvement in hand and foot function and the patients’ comments. The usefulness of this novel technique is demonstrated further by improved performance of occupational and domestic activities. For example, a glass bottle manufacturer dropped no bottles after recovery and others ceased to burn themselves when cooking.

Along with marked improvement in the operated side there was a lesser but noticeable subjective improvement in the non-operated hands and feet. This unexpected benefit is probably because a patient who has recovered sensory function in one limb is able to use it preferentially thus protecting the opposite side. A general sense of improved well-being may explain other positive outcomes. We originally intended the non-operated limbs to act as controls. Clearly this is not valid and therefore, statistical analysis is inconclusive. Similar observations were made by Yoon et al18 in a group of patients with bilateral carpal tunnel syndrome undergoing unilateral operation. Whereas contralateral improvement in 15 of 20 patients was seen, nerve conduction studies showed this subjective improvement was not matched by physiological changes. Their explanation for the contralateral improvement was similar to ours, namely lessening of the load on the untreated hand.

To patients, disability and deformity represent ongoing disease even in the absence of infection. Studies on patient satisfaction show a major failure in identifying their needs. Patient-centred outcomes cannot be ignored, as shown by evidence of differences in perspectives of the clinicians and the patients on the effects of treatment.16,19

The mechanism of nerve regeneration through muscle is by replacement of scarred nerve and inflammatory infiltrate by the loose collagen framework pathway in the denatured muscle graft. The trauma of nerve transection causing release of nerve growth factors further stimulates nerve regeneration.20

Our study shows that nerve-muscle grafts for the median and posterior tibial nerves are successful in providing sustained high quality sensory recognition and patient satisfaction, and should be offered as part of standard treatment. Previous studies with short term follow-up after muscle graft repairs in Indian and Ethiopian patients have shown similar patterns of sensory recovery.21,22 For maximum benefit, operations should be performed soon after conventional medical treatment and nerve decompression has failed to restore sensation, ideally within two years, and could be combined with tendon transfer operations. Patients should be warned to expect a slow rate of recovery. The use of fibrin glue will simplify the operation, thus allowing its use in less well-equipped centres.

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Supplementary Material

A further opinion by Professor Birch and supplementary tables showing the clinical details of patients with median and posterior tibial nerve repairs and the results following median and posterior tibial, nerve-muscle graft operation are available with the electronic version of this article on our website at www.jbjs.org.uk
References