

## LEPROSY AFFECTS FACIAL NERVES IN A SCATTERED DISTRIBUTION FROM THE MAIN TRUNK TO ALL PERIPHERAL BRANCHES AND NEUROLYSIS IMPROVES MUSCLE FUNCTION OF THE FACE

EDVIN TURKOF, BRUCE RICHARD, OJAN ASSADIAN, BHARAT KHATRI, ERICH KNOLLE, AND SEBASTIAN LUCAS  
*Division of Plastic and Reconstructive Surgery, Department of Surgery, Division of Anesthesia B, Department of Anesthesiology, and Clinical Institute for Hygiene and Medical Microbiology of the University of Vienna, Division of Clinical Microbiology and Hospital Hygiene, Vienna General Hospital, Vienna, Austria; Green Pasture Hospital, Pokhara, Nepal; Division of Clinical Laboratory Sciences, Department of Histopathology, Guy's, King's and St. Thomas School of Medicine, London, United Kingdom*

**Abstract.** Current literature rejects nerve release in leprosy facial neuropathy and states that lesions are restricted to the peripheral zygomatic branches. Since there are approximately 500,000 patients with this disease throughout the world, we wanted to clarify the precise location of facial nerve's affection and the benefit of neurolysis. Our study showed that in patients with leprosy, the facial nerve's main trunk, the peripheral zygomatic branches, and all other branches were affected. Follow-up showed improvement in lagophthalmos and in misreinnervation, with no improvement in the control cohort. Nerve release improves muscle function in leprosy facial neuropathy, provided surgery is performed on all affected segments. Intraoperative electroneurodiagnostics is an effective tool for detecting the most proximal site of lesion and ensuring effective surgery.

### INTRODUCTION

We previously reported that leprosy facial neuropathy was located at the main trunk of the facial nerve, and that neurolysis might be considered to prevent the traditional but unsatisfactory musculofascial transfer operations.<sup>1</sup> These findings are in marked contrast to those in a landmark paper in 1966,<sup>2</sup> which reported that the disease affects only the peripheral zygomatic branches and that decompression was of no benefit. Most investigators,<sup>3–7</sup> with some exceptions,<sup>8,9</sup> have accepted the observations made in the earlier study,<sup>2</sup> despite the lack of confirmatory findings. Moreover, a recent study<sup>10</sup> has reported the exclusive involvement of the zygomatic branches. Other studies<sup>11,12</sup> have suggested “total nerve damage affects nerve segments peripheral to the predilective sites.” These reports highlight the controversy surrounding the localization of this disease.

In view of the fact that there are approximately 500,000 patients worldwide with leprosy facial neuropathy or the respective sequelae, that transfer procedures never result in normal-looking faces and that prevention of lagophthalmos-induced damage to the eye is of crucial importance, we wanted to answer the following questions: 1) where exactly does leprosy affect facial nerves, and 2) is neurolysis beneficial? The implication of these two issues led us to conduct a controlled study, an approach that has not been performed until now for leprosy facial nerves. We decided to expose the entire facial nerve and to carry out the intraoperative electrophysiologic measurements introduced in our recent study.<sup>1</sup> To determine whether sites showing more fibrosis of the interfascicular or the epifascicular epineurium were in fact the sites where fusiform swellings were accentuated or, in the case of an unremarkable macroscopic appearance, the sites where amplitudes decreased, histopathologic analysis was performed to correlate the histologic results with the macroscopic and electrophysiologic findings.

### MATERIAL AND METHODS

**Study design and statistical analysis.** This investigation was a non-crossover interventional cohort study, in which 10 patients served as both the intervention cohort on which surgery

was performed on the more affected side and the contralateral side of the same patients as the non-intervention control cohort. This approach permitted us to adjust for differences in patients and cohorts and to minimize potential confounding factors. Differences were calculated within the cohorts before and after intervention or observation, respectively. 95% Confidence intervals (95% CI) were calculated where appropriate. Because our null hypothesis stated that there is no beneficial effect on muscle function and nerve conduction after surgery, one-sided *P* values were computed by applying Fisher's exact test. A difference at the 0.05 level was considered statistically significant.

**Patients and selection criteria.** Ten patients (eight men and two women) with borderline-type leprosy (six with borderline tuberculoid leprosy, one with borderline leprosy, and three with borderline lepromatous leprosy) with bilateral facial neuropathy were enrolled in the study. Their ages ranged from 31 to 62 years (median = 45.5 years, 95% CI = 39.8–51.3), and their durations of disease ranged from two to fifteen years (median = 3.5 years, 95% CI = 1.1–6.0). Informed consent was obtained from all patients prior to the study. The research protocol was prepared according to the World Health Organization (WHO) guidelines for research in developing countries and was approved by the Nepal health Research Council. All patients had been treated according to standard WHO recommendations for multibacillary leprosy at Green Pastures Hospital in Pokhara, Nepal. The criteria for case selection were persistence of facial muscle impairment for more than six months after completion of the standard WHO Multi-Drug Therapy (MDT), and the electromyographically verified presence of residual activity in the facial muscles.

**Preoperative investigations.** The functional status of the facial muscles and the misreinnervation characteristics were assessed in each patient the day before surgery. Preoperative electrophysiological investigations consisted of a routine nerve conduction velocity (NCV) study of both facial nerves with surface electrodes above the orbicularis muscle and electromyography of the orbicularis oris, the orbicularis oculi, and the frontalis muscles of both sides in each patient (the operated and the contralateral non-operated side) (Compass-

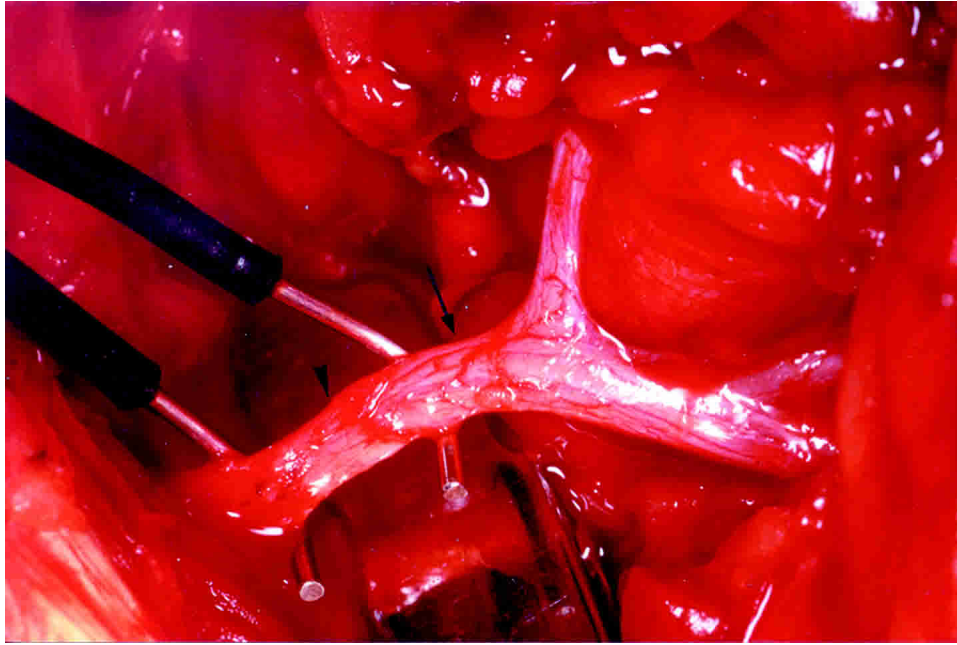


FIGURE 1. Main trunk of the right facial nerve of patient 4. **Left:** centrally, towards the stylomastoid foramen; **right:** towards the first main bifurcation. A bipolar silver wire electrode undermines the nerve. The **arrow** points to the side where curve 4 of Figure 2 was recorded (most strongly affected site in the main trunk); the **arrowhead** points to the side where curve 1 of Figure 2 was recorded (most proximal site of lesion). The distal hook of the bipolar electrode (the right one) is located where curve 3 (see Figure 3) has been recorded, while curve 2 has been recorded a small increment proximally (left) from this side halfway to the **arrowhead**. Note that the switch from the healthy site (**arrowhead**) to the most strongly affected site (**arrow**) occurred within a segment of less than 2 cm within a macroscopically unremarkable nerve segment with no indication of epineuriotomy. This highlights the effectiveness of the method for detecting the proximal extent of the disease and ensuring effective surgery.

Port-a-Book; Nicolett Biomedical, Madison, WI). All preoperative, intraoperative, and postoperative electrophysiologic measurements were performed with the same electromyographic machine and by the same investigator. Lagophthalmos was assessed by gentle closure and by full voluntary activity tight closure. The remaining gap was measured in millimeters.

**Nerve stimulation.** The technical problems encountered during the previous study<sup>1</sup> (overloading of the preamplifier, i.e., measuring becomes impossible due to the recording of too high electrical loads) prompted us to develop a new technique for the intraoperative electrophysiologic test. Facial nerves were stimulated transcranially in the cisternal region with two unipolar needle electrodes placed subcutaneously in the patient's ipsilateral temporo-parietal region.

**Nerve exposure, intraoperative electroneurodiagnostics (IOE), and neurolysis.** The patients were anesthetized with an infusion of propofol and intermittent doses of fentanyl. Facial nerves were exposed by superficial parotidectomy. Patients were then fully relaxed with norcuronium to exclude registration of any volume-conducted muscle action potentials. A Digitimer D-185 electrical stimulator (Digitimer, Ltd., Hertfordshire, United Kingdom) was activated (range = 180–350 V) to evoke efferent nerve compound action potentials (NCAPs), which were registered with a bipolar electrode (sterling silver wire coated with rhodium, diameter = 1 mm, length = 5 cm), placed on the main trunk of the facial nerve, and recorded to the electromyograph. With repeated stimulations and recordings, the electrode was moved distally and proximally in small increments of approximately 5 mm (Figure 1). Decreased amplitude was regarded as an indication of nerve damage, and elevated amplitude was regarded as a sign

of a healthy segment (Figure 2). The site at which the amplitude reached a maximum with no further increase when moving centrally along the nerve was regarded as the most proximal site of lesion.<sup>1,13,14</sup> Epineuriotomy was begun at this point regardless of the macroscopic appearance. The exposed fascicles were inspected through an operating microscope. If the interfascicular epineurium was fibrosed, epineuriotomy was extended distally until fascicles regained a healthy ap-

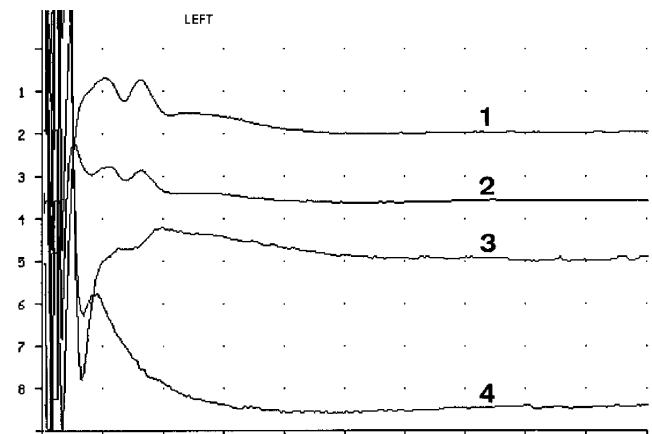


FIGURE 2. Readings for patient 4 on intraoperative transcranial electrical stimulation of the facial nerve with two needle electrodes placed subcutaneously above the ipsilateral temporal region. Recording site: the main trunk; curve 1: see **arrowhead** in Figure 1; curve 2: halfway between arrowhead and the distal hook of the electrode in Figure 1; curve 3: recorded at the electrode position shown in Figure 1; curve 4: see **arrow** in Figure 1. Curves were plotted in increments of approximately 5 mm; electromyograph: Nicolett Compass Port-a-book; stimulator: Digitimer D 185; time = 1 ms; gain = 200  $\mu$ V.

pearance. All fibrosed nerve segments underwent microsurgical interfascicular neurolysis.

**Histopathology.** Biopsy specimens of the epifascicular and interfascicular epineurium were taken from the main trunk, the zygomatic branches, and arbitrarily from other remarkable and unremarkable segments, fixed in formalin, processed, and embedded in paraffin. Multiple sections were stained with hematoxylin and eosin, van Gieson stain (for collagen), Wade-Fite stain (for leprosy bacilli), and S100 stain (immunocytochemistry for Schwann cells). In patients 5, 9, and 10, two biopsies had been taken from the main trunk.

**Postoperative investigations.** Clinical and electrophysiologic investigations were performed by the same investigator 3, 6, 12, and 24 months after surgery in patients 1–6 and 3, 6, and 12 months after surgery in patients 7–10.

## RESULTS

**Intraoperative morphology.** Branching classifications<sup>15</sup> ranged from Ia to IVb. Nerve exposure revealed an unexpected variety within all nerve segments. The main trunk was unremarkable in five patients, thickened (fusiform swelling) in three patients, and thin in two patients. The peripheral zygomatic branches were thickened in all but one patient. One patient had a normal-looking nerve throughout and another patient had only remarkable zygomatic branches. In seven patients, various segments of the nerve branches showed thickened portions (fusiform swellings) and by normal-looking portions, which sometimes thickened again distally (skip or scattered lesions). These scattered segments were irregular; i.e., any part of the exposed nerve could be affected (Figures 3–5 and Table 1).

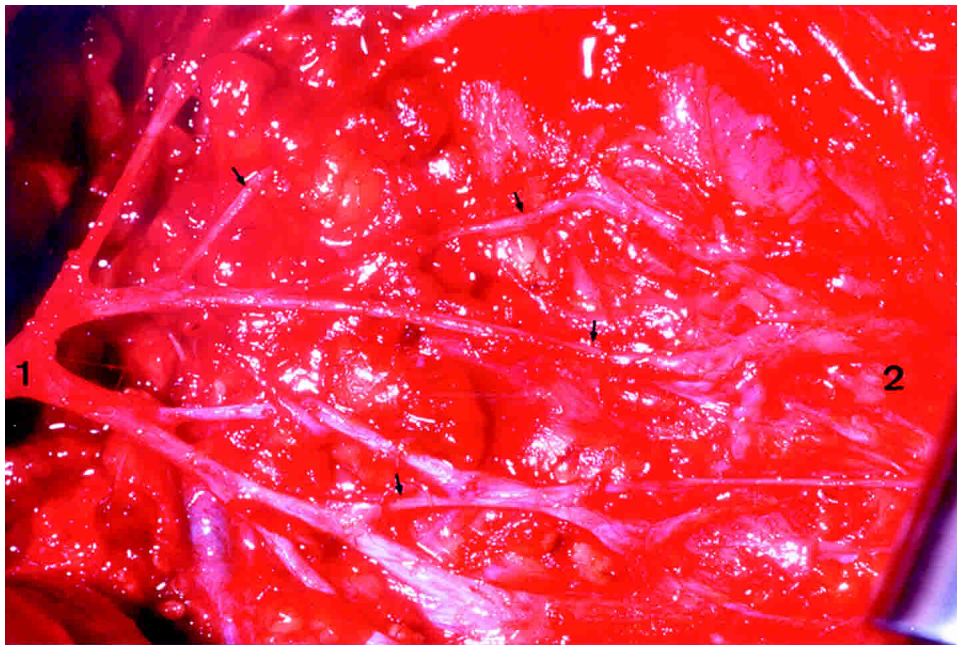
The epifascicular epineurium was thickened in the main

trunk in nine patients; in seven patients, fascicles were either fibrosed and darkened, and in three patients, the fascicles were just darkened. Fibrosis diminished proximally towards the stylomastoid foramen, where in all but one patient (patient 9) no fibrosis was present. These findings were always consistent with the intraoperative measurements (increase in amplitudes). Distally towards the main bifurcation, fascicles became more fibrotic and/or darker in all patients. At scattered distances further distally, these pathologic changes ended abruptly. Epineuriotomy extended peripherally following the affected fascicles.

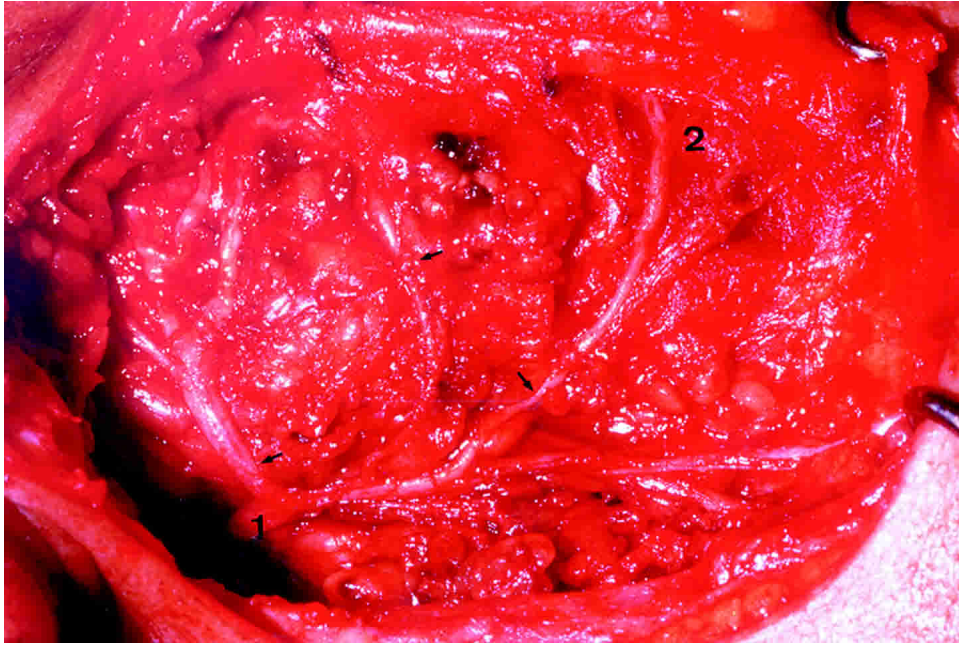
The peripheral zygomatic branches had a thickened epifascicular epineurium in all patients and fibrosed and darkened fascicles in nine patients. The other affected branches identified as such by their fusiform swellings had a thickened epifascicular epineurium in nine patients and concomitantly fibrosed fascicles in eight patients. One patient had darkened fascicles only. Microscopic interfascicular neurolysis was performed on all fibrosed fascicles, while epineuriotomy remained the only surgical treatment on just darkened unfibrosed segments. Patient 9 did not undergo radical surgery because we did not open the stylomastoid foramen and therefore did not reach unfibrosed segments.

**Histopathologic findings.** Histopathology confirmed the presence of fibrosis characteristic of a post-inflammatory process in all 10 patients. In patients 5, 9, and 10 (two biopsies from the nerve's main trunk), the specimens closer to the main bifurcation were more fibrotic, thus confirming the IOE measurements. Patient 3 showed florid granulomatous leprosy neuritis with no acid-fast bacilli.

**Intraoperative electroneurodiagnostics.** The NCAPs were recorded from the exposed nerve in all but one patient (patient 1) in whom the severity of the lesion prevented any



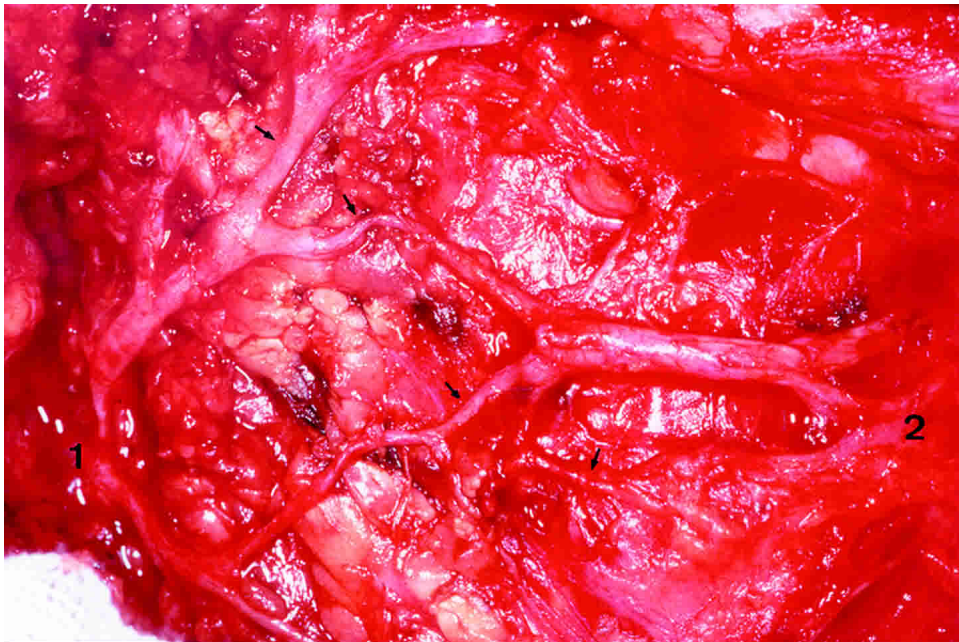
FIGURES 3. Irregularity and scatter in leprosy facial neuropathy (patients 3, 8, and 9). **Left:** proximally towards the stylomastoid foramen; **right:** distally towards the zygomatic branches; **1** = main trunk at the site of the first main bifurcation; **2** = peripheral zygomatic branches; **arrows** = sites of the nerves followed distally by thickened segments. This macroscopic evidence of skip lesions conflicts with existing theories as to how *Mycobacterium leprae* invades human nerves.



FIGURES 4. Irregularity and scatter in leprosy facial neuropathy (patients 3, 8, and 9). **Left:** proximally towards the stylomastoid foramen; **right:** distally towards the zygomatic branches; **1** = main trunk at the site of the first main bifurcation; **2** = peripheral zygomatic branches; **arrows** = sites of the nerves followed distally by thickened segments. This macroscopic evidence of skip lesions conflicts with existing theories as to how *Mycobacterium leprae* invades human nerves.

recording. The most proximal site of lesion was found to be 1–4 cm distally from the stylomastoid foramen (Table 2). Measurements indicated a lesion proximal from the stylomastoid foramen in patient 9. The most severely affected site of the main trunk was the area of the first bifurcation in six

patients; it was found 2 and 3 cm proximally in two patients, and in short distance distally in one patient. Amplitudes at the stylomastoid foramen ranged from 30  $\mu$ V to 1.9 mV and latencies ranged from 1.1 to 1.3 ms, thus confirming that the site of stimulation was the cisternal nerve exit.<sup>16,17</sup> Supramaximal



FIGURES 5. Irregularity and scatter in leprosy facial neuropathy (patients 3, 8, and 9). **Left:** proximally towards the stylomastoid foramen; **right:** distally towards the zygomatic branches; **1** = main trunk at the site of the first main bifurcation; **2** = peripheral zygomatic branches; **arrows** = sites of the nerves followed distally by thickened segments. This macroscopic evidence of skip lesions conflicts with existing theories as to how *Mycobacterium leprae* invades human nerves.

TABLE 1  
Intraoperative morphology and histopathologic findings in the 10 patients studied\*

Patient	Macroscopy				Microscopy				Histopathology			
	Branching classification	Aspect of main trunk at first bifurcation	Aspect of zygomatic branches	Aspect of affected segments of all other branches	Aspect of main trunk		Aspect of zygomatic branches		Aspect of affected segments of other branches		Correlation of fibrosis with decrease in amplitude (++) or thickness of fusiform swelling (%)	Special findings
					Epineurium	Fascicles	Epineurium	Fascicles	Epineurium	Fascicles		
1	Ia	Thin	Thick	Thin	Normal	Normal	Thick	Fibrosis	Normal	Normal	Yes +	—
2	IIIa	Normal	Normal	Normal	Thick	Thick	Thick	Dark	Thick	Dark	Yes +	—
3	Iva	Slightly thick	Thick	Skip lesion	Thick	Thick	Thick	Fibrosis	Thick	Fibrosis	Yes +	—
4	IIIc	Normal	Thick	Skip lesion	Thick	Thick	Thick	Dark	Thick	Fibrosis	Yes +	—
5	Ivb	Thick	Thick	Thick all over	Thick	Thick	Thick	Fibrosis	Thick	Fibrosis	Yes ++	—
6	Iva	Normal	Thick	Skip lesions	Slightly thick	Fibrosis	Slightly thick	Fibrosis	Slightly thick	Fibrosis	Yes +	—
7	Ia	Normal	Thick	Skip lesions	Slightly thick	Fibrosis	Thick	Fibrosis	Thick	Fibrosis	Yes +	—
8	Iib	Slightly thick	Thick	Skip lesions	Thick	Thick	Thick	Fibrosis	Thick	Fibrosis	Yes +	—
9	Ivb	Normal	Thick	Skip lesions	Thick	Thick	Thick	Fibrosis	Thick	Fibrosis	Yes ++	—
10	Ivb	Thin	Thick	Skip lesions	Thick	Thick	Thick	Fibrosis	Thick	Fibrosis	Yes ++	—

\* Macroscopy = aspect of the nerve observed with the naked eye; Microscopy = aspect of the nerve through the operating microscope. In seven patients the main trunk appeared normal, in seven cases skip lesions were macroscopically detectable, and in all but one patient fibrosis of the fascicles were irregularly present on all segments of the nerve. These observations strongly suggest that the existing opinion about the localization of the disease and the theory as to how *Mycobacterium leprae* invades peripheral nerves needs revision.

stimulus was achieved with 180–350 V. The preamplifier did not overload on any occasion.

**Routine NCV study.** Changes in NCV and amplitude were regarded as significant if they increased or decreased by  $\geq 10\%$ . The NCV improved (i.e., latency decreased) significantly after surgery in six patients ( $P = 0.005$ ) and in two patients in the non-intervention cohort ( $P = 0.237$ ). Amplitudes of the intervention cohort improved (i.e., increased) significant in seven patients and deteriorated in one patient (patient 9) ( $P = 0.002$ ). In the control cohort, one patient improved, seven patients deteriorated, and two patients showed no changes ( $P = 0.500$ ).

**Long-term clinical results.** Patients 1–6 had their follow-up examinations two years after intervention and patients 7–10 had their examinations after one year (Tables 3 and 4). Misreinnervation significantly disappeared in the intervention cohort (five patients;  $P = 0.016$ ), but never disappeared in the non-intervention cohort. The risorius muscle improved significantly in the intervention cohort (five patients;  $P = 0.016$ ), but there was just one insignificant improvement in the non-intervention cohort. Muscle function of the frontalis muscle did not change significantly in both cohorts. Although it improved in two patients who underwent surgery (patients 2 and 7), it worsened in one (patient 3).

**Lagophthalmos.** For tight eye closure, no significant change could be observed in both cohorts: one improvement (patient 6) and two deteriorations (patient 3: silent neuritis, patient 9: incomplete surgery) in the intervention cohort, and one deterioration (patient 9) in the non-intervention cohort. In contrast, significant improvement was seen for gentle eye closure in five patients in the intervention cohort ( $P = 0.016$ ), the status remained unchanged in three patients, and the status deteriorated in two (patients 3 and 9). No change occurred for gentle eye closure in the non-intervention cohort. It should be noted that deterioration of lagophthalmos and other muscle functions occurred in the surgical cohort in these two patients, on whom radical surgery could not be carried out (see Histopathologic findings, patient 3 and Intraoperative morphology, patient 9).

TABLE 2  
Findings of intraoperative electroneurodiagnostics in the 10 patients studied\*

Patient	Latency at the stylomastoid foramen (ms)	Localization of the most proximal lesion site (cm distally from the stylomastoid foramen)	Localization of most strongly affected site in the main trunk	Amplitude at the most proximal lesion site ( $\mu\text{V}$ )
1		Recording impossible	Recording impossible	
2	1.2	1	3 cm proximal from bifurcation	50
3	1.1	3	At bifurcation	480
4	1.2	2	At bifurcation	220
5	1.2	2	At bifurcation	85
6	1.1	4	Just after bifurcation	180
7	1.2	2	At bifurcation	1,900
8	1.2	1	At bifurcation	210
9	1.2	Fallopian's channel?	At bifurcation	30
10	1.3	1	2 cm proximal from bifurcation	400

\* Results are intraoperative electrophysiologic measurements by transcranial electric stimulation of the facial nerve at the cisternal region with recording from the nerve surface at the main trunk. The consistency of the latency values at the stylomastoid foramen shows the preciseness and specificity of the technique.

TABLE 3  
Baseline data and follow-up results of the intervention cohort in the 10 patients studied\*

Patient	Clinical results following lateral parotidectomy and microsurgical interfascicular neurectomy										Conventional electrophysiologic measurements Routine motor nerve conduction velocity study with surface electrodes on the orbicularis oris muscle								
	Frontalis		Risortius		Misreinnervation		Lagophthalmos (gentle)		Lagophthalmos (tight)		Latency (ms)		Amplitude (mV)		Result				
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After					
1	Paralysis	Same	Weak	Better	No	Same	4	2	Better	1	0	Same	6.30	4.10	Better	0.19	0.21	Better	
2	Weak	Better	Weak	Better	Yes	Same	5	2	Better	1	0	Same	6.20	3.60	Better	0.01	2.30	Better	
3	Normal	Worse	Weak	Worse	Yes	Better	6	9	Worse	5	9	Worse	4.10	3.60	Same	0.50	1.60	Better	
4	Normal	Same	Weak	Better	Yes	Better	10	7	Better	5	6	Same	3.40	2.80	Better	2.10	2.40	Better	
5	Normal	Same	Normal	Same	No	Same	5	6	Same	3	2	Same	5.30	3.80	Better	0.37	0.60	Better	
6	Normal	Same	Weak	Same	No	Same	3	3	Same	2	0	Better	3.70	3.90	Same	0.39	0.77	Better	
7	Weak	Better	Weak	Better	Yes	Better	5	6	Same	3	3	Same	3.00	4.20	Worse	1.10	1.00	Same	
8	Normal	Same	Weak	Better	Yes	Better	10	6	Better	4	3	Same	4.80	3.30	Better	0.57	0.53	Same	
9	Normal	Same	Normal	Worse	Yes	Better	4	6	Worse	1	3	Worse	5.70	6.60	Worse	1.20	0.10	Worse	
10	Normal	Same	Weak	Same	No	Same	5	3	Better	4	3	Same	6.80	7.00	Same	0.70	1.20	Better	
Median													5.05	3.85		0.53	0.89		
SD±													1.33±	1.39±		0.61±	0.81±		
95% CI													4.17-6.11	3.32-4.59		0.20-1.40	0.45-1.78		
Fisher's exact test P value	0.237		0.016†		0.016†				0.016†		0.500				0.005†				0.002†

\* Results are clinical and electrophysiologic findings following microsurgical interfascicular neurectomy of the entire extracranial nerve in 10 leprosy patients. Lagophthalmos for gentle closure and misreinnervation both improved significantly in five patients with no improvement of all of these functions at the control side. Furthermore, latency improved in six patients and amplitudes improved in seven patients (both significantly) on the operated side, with just two and one, respectively (non-significant) improvements on the control side. Surgery could not have been successful in two patients because in one (patient 3), histopathologic studies showed an unexpected fluid granulomatous leprosy neuritis (silent neuritis), and in another (patient 9), intraoperative electrodiagnostics showed that the lesion extended further proximally within the Fallopian's channel, which was not opened, thus rendering the intervention incomplete. These observations strongly suggest that the existing opinion about the lack of surgical benefit after one or two years of failed recovery following multi-drug therapy and about the rejection of microsurgical, interfascicular neurectomy needs revision. CI = confidence interval.

TABLE 4  
Baseline data and follow-up results of the non-intervention cohort in the 10 patients studied\*

Patient	Clinical assessment										Conventional electrophysiologic measurements Routine motor nerve conduction velocity study with surface electrodes on the orbicularis oris muscle								
	Frontalis		Risortius		Misreinnervation		Lagophthalmos (gentle)		Lagophthalmos (tight)		Latency (ms)		Amplitude (mV)		Result				
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After					
1	Normal	Same	Weak	Same	No	Same	3	2	Same	0	0	Same	3.30	2.50	Better	1.90	0.84	Worse	
2	Normal	Same	Normal	Same	Yes	Same	0	0	Same	0	0	Same	3.70	3.70	Same	1.90	0.84	Worse	
3	Normal	Same	Normal	Same	Yes	Same	0	0	Same	0	0	Same	3.20	3.50	Worse	1.10	1.40	Better	
4	Normal	Same	Normal	Same	Yes	Same	4	4	Same	0	0	Same	3.20	3.10	Same	2.60	0.66	Worse	
5	Normal	Same	Normal	Same	No	Same	1	0	Same	0	0	Same	4.40	4.60	Same	0.73	0.39	Worse	
6	Normal	Same	Normal	Same	No	Same	3	3	Same	1	1	Same	2.60	3.40	Worse	1.40	1.50	Same	
7	Weak	Same	Weak	Better	Yes	Same	0	0	Same	0	0	Same	3.00	2.90	Same	2.80	0.99	Worse	
8	Normal	Same	Weak	Same	Yes	Same	7	7	Same	3	5	Worse	4.70	2.30	Better	0.90	0.60	Worse	
9	Normal	Same	Normal	Same	Yes	Same	5	5	Same	2	2	Same	5.20	5.00	Same	0.39	0.40	Same	
10	Normal	Same	Normal	Worse	No	Same	0	0	Same	0	0	Same	5.50	6.00	Same	3.10	2.40	Worse	
Median													3.50	3.45		1.65	0.84		
SD±													1.00	1.17		0.93	0.62		
95% CI													2.17-5.65	2.52-4.73		0.96-2.84	0.32-2.21		
Fisher's exact test P value	1.000		0.500		1.000		1.000		1.000		1.000				0.237				0.500

\* Results are clinical and electrophysiologic findings after two years (patients 1-6) and one year (patients 7-10) of follow-up without surgical intervention. No improvement was observed for lagophthalmos and misreinnervation, with two and one (non-significant), improvements for latency and amplitude, respectively. CI = confidence interval.

**Clinical significance of the achieved functional improvements.** Five patients who benefited from the disappearance of missinnervation unanimously reported on their significant improvement of life quality due to the lack of the stigmatizing and disturbing synknesia and dysknesia of the facial muscles. Patient 2 reported that he was able to close his eyes during sleep.

## DISCUSSION

The present observations show that our hypothesis on the complementarity of the two study approaches<sup>1,2</sup> was partially correct. Neither our group<sup>1</sup> nor Antia and others<sup>2</sup> were mistaken in the sense that leprosy affects facial nerves at the main trunk<sup>1</sup> and at the peripheral zygomatic branches.<sup>2</sup> However, the two studies were not just complementary, but primarily incomplete, because they both failed to show that any segment of the extracranial nerve can be affected. This detail was unknown until now, but nevertheless is essential if incomplete surgery is to be avoided.

Furthermore, the presence of scattered (skip) lesions conflicts with existing theories on how *Mycobacterium leprae* invade human nerves. It is widely assumed that sensory nerve endings are the pathway for the bacteria into peripheral nerves, and that *M. leprae* subsequently migrate centrally to lodge at the predilective sites because of presumed mechanical (osteofibrotic channels) and/or thermal reasons (vicinity to the lower temperature of skin).<sup>11,18</sup> However, there is no mechanical obstacle below the parotid gland, and the intensive vascularization of the face argues against the theory of hypothermia.

Karat and others<sup>19</sup> have shown that the livers of leprosy patients show granulomas containing *M. leprae*. This early evidence of an hematogenous spread of the bacilli was confirmed in 1972 by Drutz and others,<sup>20</sup> who demonstrated frequent bacillæmia in leprosy patients. Recently,<sup>21</sup> the presence of *M. leprae* in epineural and perineural blood vessels was also shown. We believe that the irregular and skip nerve lesions can better be explained by a hematogenous pathway of nerve involvement than by a centripetal migration because *M. leprae* has no obvious reason to stop arbitrarily and to continue its way again centrally with no identifiable pattern. Our observations demand a revision of the current opinion on the localization of the disease, and reconsideration of the theory as to how *M. leprae* invade peripheral nerves. A recent publication with similar findings on leprosy tibial nerves strengthens this demand.<sup>22</sup>

The innovative placement of the electrodes at the temporo-parietal region prevented involvement of the entire motor cortex, which had been unavoidable with the technique previously used.<sup>1</sup> This more selective positioning of the electrodes permitted supramaximal stimulations with markedly lower intensities (180–350 V) compared with the earlier technique (550–750 V). Keeping the trigger artifact sufficiently low in this way made it possible to avoid overloading of the preamplifier and to ensure successful measurements in all patients despite the small distance between stimulation and recording site. Technical and diagnostic limitations of IOE have been reported elsewhere.<sup>1,13,23</sup>

In all cases, surgery and histopathology confirmed the presence of affected fascicles at the electrophysiologically detected sites of lesions, and fibrosis was accentuated where

decreased amplitudes were recorded. Measurements permitted detection of lesion-sites in unremarkable trunks in seven patients. These facts underline the value of IOE, since surgeons do not perform epineuriotomy on normal-looking nerves. Measurements therefore ensured effective intervention. We would like to emphasize that the described intraoperative electroneurodiagnostic technique has most probably been applied for the first time worldwide. The reproducibility of the results has been repeatedly verified during surgery since each measurement was repeated at least 4–5 times, especially due to the unexpected results and their consequences. Nevertheless, we believe that this technique can be easily performed by any electro-physiologist in cooperation with a peripheral nerves surgeon.

The functional outcome of neurolysis in leprosy facial nerves has been investigated within a controlled study. Our results demonstrated that surgery significantly improves lagophthalmos (gentle closure of eye), misreinnervation, and other muscle function of the face. These clinical results were confirmed by the results of the routine NCV-studies, which showed significant improvement of latency and amplitude in the operation cohort, with unchanged latencies and worsened amplitudes in the non-intervention cohort.

Previous reports have shown that nerve regeneration persists for years in leprosy.<sup>14,20</sup> These observations demonstrate that the potential for recovery remains for a long time. Surgery could therefore promote regeneration, even if performed late. In view of the present results achieved on long lasting affected patients, we reject the International Federation of Anti-Leprosy Association's (ILEP) claim<sup>24</sup> that surgery offers no benefit after one or two years of failed recovery following MDT treatment.

Interfascicular neurolysis did not harm our patients. This surgical approach is also rejected by the ILEP<sup>24</sup> because of the fear that the blood supply to the nerve will be endangered. However, it is important to remember that nerve grafts also survive by diffusion alone, and there is no reason to assume that this characteristic does not apply to a released nerve, provided that the wound bed is sufficiently well vascularized,<sup>25</sup> which is the case in the facial nerves.

Received April 28, 2002. Accepted for publication August 5, 2002.

**Acknowledgments:** We thank Dr. G. Cruccu (Rome, Italy) who helped us develop the new stimulation technique, and Professor Suresh Tambwekar (Bombay, India) for his suggestions, which led to the implementation of the study. We also thank Professor T. Lion (Vienna) and Professor M. Rotter (Vienna) for carefully revising the manuscript.

**Financial support:** The study was supported by the Medical School of Vienna, Austria, Zeneca, Inc., EMS (Nicolett), Inc., Smith-Kline Beecham, Inc., Novartis, Inc., KCI-Medicus Inc., Immuno, Inc., and an International Nepal Fellowship.

**Authors' addresses:** Edvin Turkof, Abteilung für Plastische Chirurgie, Universitätsklinik für Chirurgie, AKH Wien, Währinger Gürtel 18-20, A-1090 Vienna, Austria, Telephone: 43-1-40400-5620, Fax: 43-1-409-1057, E-mail: edvin@turkof.com. Bruce Richard and Bharat Khatri, Green Pasture Hospital, Pokhara, Nepal. Ojan Assadian, Division for Clinical Microbiology, Clinical Institute of Hygiene and Medical Microbiology of the University of Vienna, Vienna General Hospital, Vienna, Austria. Erich Knolle, Division of Anesthesia B, Department of Anesthesiology, Vienna General Hospital, Vienna, Austria. Sebastian Lucas, Department of Histopathology, Division of Clinical Laboratory Sciences, Guy's, King's and St. Thomas School of Medicine, London, United Kingdom.

## REFERENCES

1. Turkof E, Tambwekar S, Kamal S, El-Dahrawi M, Mansukhani K, Soliman H, Ciovica R, Mayr N, 1998. Leprosy affects facial nerves at the main trunk: neurolysis can possibly avoid transfer procedures. *Plast Reconstr Surg* 102: 1565-1573.
2. Antia NH, Divekar SC, Dastur DK, 1966. The facial nerve in leprosy. I. Clinical and operative aspects. *Int J Lepr Other Mycobact Dis* 34: 103-117.
3. Job CK, Desikan KV, 1968. Pathologic changes and their distribution in peripheral nerves in lepromatous leprosy. *Int J Lepr Other Mycobact Dis* 36: 257-270.
4. Selby RC, 1974. Neurosurgical aspects of leprosy. *Surg Neurol* 2: 165-177.
5. Malaviya GN, Ramu G, 1981. Loss of taste and somatic sensations over the tongue in leprosy facial palsy - a case report. *Lepr India* 53: 656-659.
6. Reichart PA, Srisuwan S, Metah D, 1982. Lesions of the facial and trigeminal nerve in leprosy. An evaluation of 43 cases. *Int J Oral Surg* 11: 14-20.
7. Hogeweg M, Kiran KU, Suneetha S, 1991. The significance of facial patches and type I reaction for the development of facial nerve damage in leprosy. A retrospective study among 1,226 paucibacillary leprosy patients. *Lepr Rev* 62: 143-149.
8. Lubbers WJ, Schipper A, Hogeweg M, de Soldenhoff R, 1994. Paralysis of facial muscles in leprosy patients with lagophthalmos. *Int J Lepr Other Mycobact Dis* 62: 220-224.
9. Ranney DA, Furness MA, Santhanakrishnan CK, 1973. Misreinnervation in leprosy neuritis affecting the facial nerve. *Lepr Rev* 43: 151-158.
10. Anonymous, 1995. Leprosy. Report of a Meeting of Physicians and Scientists at the All India Institute of Medical Sciences, New Delhi. *Lancet* 345: 697-703
11. Miko TL, Le Maitre C, Kinfu Y, 1993. Damage and regeneration of peripheral nerves in advanced treated leprosy. *Lancet* 342: 521-525.
12. Miko TL, Gschmeissner SE, Le Maitre C, Kinfu Y, Kazen R, Pereira JH, 1993. Regeneration at the predilective damage sites of nerve trunks in treated leprosy. *Lepr Rev* 64: 330-337.
13. Turkof E, Tambwekar S, Mansukhani K, Millesi H, Mayr N, 1994. Intraoperative spinal root stimulation to detect most proximal site of leprosy ulnar neuritis. *Lancet* 343: 1604-1605.
14. Chaco J, Magora A, Zauberman H, Landau Y, 1968. An electromyographic study of lagophthalmos in leprosy. *Int J Lepr Other Mycobact Dis* 36: 288-295.
15. Katz AD, Catalano P, 1987. The clinical significance of the various anastomotic branches of the facial nerve. Report of 100 patients. *Arch Otolaryngol Head Neck Surg* 113: 959-962.
16. Rimpilainen I, Pyykko I, Blomstedt G, Kuurne T, Karma P, 1993. The site of impulse generation in transcranial magnetic stimulation of the facial nerve. *Acta Otolaryngol(Stockh)* 113: 339-344.
17. Benecke R, Meyer BU, Schonle P, Conrad B, 1988. Transcranial magnetic stimulation of the human brain: responses in muscles supplied by cranial nerves. *Exp Brain Res* 71: 623-632.
18. Antia NH, Enna CD, Daver MB, 1992. Prevalence, pathogenesis, and pathology. Mookerjee SK, ed. *The Surgical Management of Deformities in Leprosy*. Bombay: Oxford University Press, 24-25.
19. Karat AB, Job CK, Rao PSS, 1971. Liver in leprosy: histological and biochemical findings. *BMJ* 1: 307-310.
20. Drutz DJ, Chen TS, Lu WH, 1972. The continuous bacteremia of lepromatous leprosy. *N Engl J Med* 287: 159-164.
21. Scollard DM, McCormick G, Allen JL, 1999. Localization of *Mycobacterium leprae* to endothelial cells of epineurial and perineurial blood vessels and lymphatics. *Am J Pathol* 154: 1611-1620.
22. Richard B, Khatri B, Knolle E, Lucas S, Turkof E, 2001. Leprosy affects the tibial nerves diffusely from the middle of the thigh to the sole of the foot, including skip lesions. *Plast Reconstr Surg* 107: 1717-1724.
23. Turkof E, Tambwekar S, Mansukhani K, Millesi H, Mayr N, 1995. Intraoperative electroneurodiagnostics to detect a second granuloma in the cubital area of median nerves affected by leprosy: a new approach to prevent incomplete surgery. *Int J Lepr Other Mycobact Dis* 63: 409-416.
24. Anonymous, 1999. *Guidelines for Identifying Patients for Referral for Surgery*. London: International Federation of Anti-Leprosy Associations.
25. Millesi H, 1992 *Chirurgie der Peripheren Nerven*. Wien, Austria: Verlag Urban & Schwarzenberg, 20-26