Multiple Crush Concept Applied to Multiple Nerves in Leprous Neuropathy

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KEYWORDS
- Leprosy • Neurolysis • Nerve compression

KEY POINTS
- A Norwegian doctor, Gerhard Henrik Armauer Hansen, in 1873, found that leprosy was caused by a bacteria. *Mycobacterium leprae* is mildly contagious and does not pass through the skin. It is inhaled.
- An orthopedic surgeon, Paul Brand, in Vellore, India, in 1948, identified a neural origin of leprosy deformity and refuted the dissolving flesh theory of leprosy.
- The World Health Organization introduced multidrug therapy in 1981: it stops leprosy spread but does not decrease disability related to its chronic nerve injury.
- An adhesion molecule was identified in 1997 that links the *M leprae* to the G domain of laminin and the Schwann cell.
- In 2004, James Wilton, DPM, and A. Lee Dellon, MD, first applied the concept of decompression of multiple sites of neurolysis along individual nerves in the upper and lower extremities to patients with leprous neuritis.

INTRODUCTION

*And the leper in whom the plaque is, his clothes shall be rent, and his head bare, and he shall put a covering upon his upper lip, and shall cry, Unclean, unclean. All the days wherein the plaque shall be in him he shall be defiled; he is unclean; he shall dwell alone; without the camp shall his habitation be.*

— *Leviticus* 13.45–46

It is most likely that doctors reading this article will never have seen even 1 person with leprosy. What is leprosy? The very first definition of it was given by God to Aaron, the brother of Moses, and it is recorded in dermatologic fashion in *Leviticus* 13.1–46. The date of this recording and clinical observations are, of course unknown. It seems
clear, however, that leprosy was considered infectious. In 1841, Gerhard Henrik Armauer Hansen was born in Bergen, Norway. Bergen was the center of Norwegian leprosy research and there were 3000 lepers in Bergen, 800 hospitalized. After medical school, Hansen, after observing these patients, did not believe the prevailing theory that the disease was inherited. Traveling in Europe, he studied the emerging science of histopathology and tissue staining. No human disease had yet been proved to be transmitted by a bacteria. When Hansen returned to Bergen in 1871, he identified rodlike structures in cells of cutaneous nodules and published his article in 1873 describing \( M \text{leprae} \). Leprosy today is known as Hansen disease. Hansen was unable to get this disease to be transmitted from one animal to another or one human to another, and therefore failed to satisfy Koch’s postulates that proved a disease was due to a bacteria. Yet this recognition within Norway led to legislation in 1877 and 1885, the Leprosy Acts that permitted lepers to live apart from their families, in precautionary isolation, resulting in the decrease in incidence of leprosy in Norway (Fig. 1).

The first use of antibiotics for “treatment” of leprosy was done by Robert Greenhill Cochrane, MD (1899–1985), a Scottish dermatologist, working in India in a leprosy “sanatorium” in Chingleput, in the southeast of the country. He also worked in Vellore, just north of Chennai (Madras). Dapsone, a sulfur derivative, was administered intra-muscularly in oil and was bacteriostatic. This became the main treatment for the next 30 years for leprosy. Cochrane would write 3 books on leprosy from 1947 to 1964.

Cochrane had a direct impact on the current approach to leprosy by inducing Paul Wilson Brand, MD (1914–2003), to come and work in Vellore. Cochrane knew Brand’s parents, who had been Christian missionaries in India, where Brand was born in 1914. When World War II ended, Brand had just finished orthopedic surgery training in the United Kingdom. His wife Margaret was an ophthalmologist. Although Cochrane described in great detail the dermatologic consequences of leprosy, Brand was struck

![Fig. 1. Typical appearance of extremities with amputations in a person with leprosy who has not had peripheral nerve surgery. This person is living in a sanctuary in Ecuador.](image-url)
by the upper extremity and lower extremity deformities. He recalled as a child in India seeing children with bones protruding from their feet but them not having any pain. As a medical student he had dissected cranial nerves and was amazed at the facial palsy present in the lepers. Charles Scott Sherrington (1857–1952), one of his teachers, a professor of physiology at the University of Oxford, went on to win the Nobel prize in 1932 for his work in neurophysiology. This exposure to Sherrington’s peripheral nerve research fascinated Brand, and he pondered the relationship between leprosy and the peripheral nerve. Brand reviewed the orthopedic literature at that time and found that nothing had been written about leprosy.\(^5\)

The religion of the population in Vellore was Hindu, and, therefore, Brand did not have the ability to do autopsies on people with leprosy. Brand noted,

\[ \ldots \text{frequent paralysis in areas controlled by the ulnar nerve (Fig. 2A), moderate paralysis in median nerve, and very little in the radial nerve. I could think of no logical reason why the ulnar nerve at the elbow would cause paralysis while the median nerve, one inch away, stayed healthy; or why the median nerve went dead at the wrist while none of the radial nerve muscles was paralyzed. To add to my confusion, I had sent tissue samples from shortened fingers to Vellore’s pathology professor (Fig. 2B). The reports came back as normal tissue, except for the loss of nerve endings.} \]\(^6\)

One night, in a somewhat distant forest village, a leprosy patient without relatives died, and word of this came to Brand and his team. They were able to travel through the night and complete the removal of peripheral nerves from the arms and legs of that person. Brandt wrote,

\[ \text{On one side of the body, sections of the nerves were put into bottles and labeled, on the other side I dissected out the entire length of the nerves: I wanted to see the whole nerve in relation to the bones and muscles.…. When I stood and looked, finally taking a break, I saw it. ‘Look at the nerve swellings. Do you see a pattern?’ At certain places, behind the ankle, just above the knee, and also at the wrist, the nerves swelled up to many times normal size…and were most marked just above the elbow on the ulnar nerve (Fig. 3). …We saw clearly that nerve swellings tended to occur in just a few sites…where the nerve lay close to the skin surface, and not in the deep tissues. For the first time I sensed some rationality behind the mystery of leprosy-induced paralysis.} \]\(^6\)

Brand (Fig. 4) went on to develop the concept of tendon transfers to provide function for the loss of the muscles lost to superficial nerve injury from leprosy by replacement with the “preserved” deeper muscles whose nerves were not injured by the leprosy bacteria. He published continually on this work from 1952 through 1989.\(^7–18\)

**Fig. 2.** Typical appearance of progressive neurologic deformity that results in (A) clawing and amputation in the upper extremity and (B) amputation in the lower extremity.
When Brand opened the Raymond M. Curtis Hand Center in Baltimore in 1977, it was the year that I was doing my hand surgery fellowship and focusing on peripheral nerve problems.

DRUG THERAPY DOES NOT PREVENT NEUROLOGIC IMPAIRMENT

Drug therapy stops contagion. The purpose of controlling leprosy, however, must include a reduction in the rate and severity of disability. The key to effective management of leprosy is early diagnosis and drug treatment and early recognition and management of nerve damage, combined with effective health education.

Leprosy is an infectious disease but it has many features in common with neurodegenerative disorders. It results in a chronic neurologic illness, which is progressive unless treated; frequently, it produces long-term disability and is associated with high levels of stigma (missing digits, facial disfigurement, and skin color changes).

Fig. 3. Brand’s observations about the swelling in the major superficial nerves just proximal to a joint are illustrated here from our own experience in Ecuador. (A) The swollen ulnar nerve just proximal to the elbow. (B) The swollen tibial nerve just proximal to the ankle.

Fig. 4. Paul W. Brand, MD, approximately 1990.
As leprosy has a known infective agent, *M. leprae*, there is the possibility of disease control. Multidrug treatment with the antibiotic combination rifampicin, dapsone, and clofazimine is highly effective in curing infection, with relapse rates of 1%.\(^\text{19}\) It was hoped that having effective antibiotics would permit disease control and thus the concept of “leprosy elimination” developed. “Leprosy elimination by the year 2000” was first proposed in 1986 and at the 44th World Health Assembly in 1991 modified by the addendum “as a public health problem,” defined as less than 1 case per 10,000 population.\(^\text{20}\) Many patients experience immune-mediated nerve damage, which may occur before, during, or after treatment. Field-based cohort studies have shown that at diagnosis of leprosy, at the start of multidrug therapy, many patients already have established nerve damage; rates vary from 20% in Bangladesh to 56% in Ethiopia,\(^\text{21,22}\) and these patients have a worse prognosis for disability. Anesthesia and paresis in the hands and feet put leprosy patients at risk of secondary damage from trauma and infection, which cause the highly visible deformities of leprosy. Despite multidrug therapy, in 2005 there were 500,000 new cases of leprosy in the world per year, 12% of which in children, and 200 of which in the United States: there were 12 million lepers in the world and 6000 were in the United States.\(^\text{23–25}\)

When Brand retired from his work in India, he became the Director of the National Leprosarium of the United States, in Carville, Louisiana. There he used a form of quantitative sensory testing with the Semmes-Weinstein monofilaments to document sensibility in many different areas of the hand and foot. He remained unenthusiastic about nerve decompression surgery in patients with leprosy.\(^\text{18}\)

**HISTORY OF PERIPHERAL NERVE SURGERY IN LEPROSY**

There is a small body of literature related to peripheral nerve surgery in leprosy. A few studies of nerve grafting for irreparable damage to the ulnar nerve, usually in the presence of abscess, were reported in the late 1970s. Nerve graft results did not give improved function.\(^\text{26–28}\)

There are many more reports of decompression of the ulnar nerve at the elbow for the treatment of pain, utilizing the whole spectrum of reported procedures with the exception of submuscular transposition.\(^\text{29–35}\) In general these studies have reported significant pain relief, with some improvement in sensation and some improvement in motor function. The claim is made that deformity is prevented when the nerve decompression is done in early cases. It is noted the electrophysiological tests do not recover to more than 80% of normal function, and often much less, even when there is good clinical and symptomatic improvement.\(^\text{35}\) Much less has been written about carpal tunnel decompression for the median nerve. In the 1 article devoted just to this nerve, of 29 patients who had a decompression, sensory recovery was seen in 90% of cases, and in 45% muscle strength improved, whereas in another 25% motor function had no further deterioration.\(^\text{35}\)

Median nerve decompression is also commented on in 1 of the studies reporting ulnar nerve results.\(^\text{34}\) Where the degree of nerve compression was graded preoperatively and clinically staged, of 3 patients with moderate degree of compression, only 1 patient improved, and 2 had no change, in contrast to 6 patients with severe compression, of whom 3 recovered normal strength and improved sensation, 2 cases were worse, and 1 was not improved. When median nerve postoperative results are compared with those after cubital tunnel decompression using this same staging paradigm, for the moderate degree of ulnar nerve compression, of 15 patients, 4 were better and 11 were not improved. For the severe degree of compression, of 17 patients, 6 were better, 5 were without change, and 6 were worse.\(^\text{35}\) Results from
Husain and colleagues\textsuperscript{34} for the ulnar decompression were also in the same area of success, although they did not clinically stage their patients’ degree of compression; although 49% had relief of pain, 11% failed to improve in terms of sensory or motor recovery, and those who had some degree of improvement were combined with those who “were prevented from getting worse to give the appearance that 89% of patients were benefited by the ulnar nerve surgery.”

Pandya’s\textsuperscript{30} report, in addition to including carpal and cubital tunnel decompression, included tarsal tunnel decompression and neurolysis of the common peroneal nerve. There are 3 other brief reports on tarsal tunnel surgery. One, using sweat production as a functional outcome measure, reported an improvement after a traditional posterior tibial nerve decompression\textsuperscript{36}; the second added an internal neurolysis of the posterior tibial nerve and a sympathectomy to restore sensation and improve ulcer healing in a single patient\textsuperscript{37}; and the third, written in French in 1976, suggests a role for neurolysis of the tibial nerve in patients with leprosy and diabetes.\textsuperscript{38}

Past approaches to nerve decompression have applied the concept of decompressing 1 nerve in 1 location at 1 operation, or, at most, 2 different nerves were decompressed, each at 1 location along the course of the nerve.

With regard to Brand’s indication for peripheral nerve surgery requiring a course of steroids, it is interesting to look at 2 of the most scientifically designed studies related to the treatment of peripheral nerve problems in leprosy. In 1996, for the treatment of “early ulnar neuritis,” a randomized trial of ulnar neurolysis combined with medial epicondylectomy was compared with a full course of high-dose steroids. There were approximately 20 patients in each group, and they were followed for 2 years. There was no difference in the outcomes between the 2 groups.\textsuperscript{39} In 2003, a multicentered, randomized, double-blind, placebo-controlled trial was conducted in Nepal and Bangladesh, with 1 group getting either high-dose prednisolone, tapered over 4 months, and 1 group receiving a placebo. In this study, patients had a higher degree of nerve function impairment (NFI) then in the previous study, with duration of NFI ranging from 6 to 24 months. Of 92 patients followed for 1 year, “no demonstrable additional improvement in nerve function, or in preventing further leprosy reaction events was seen in the prednisolone group. Overall, improvement of nerve function at 12 months was seen in about 50% of patients in both groups. This result was the same for the ulnar nerve and for the posterior tibial nerve. Leprosy reactions and new NFI occurred in a third of the group, emphasizing the need to keep patients under regular surveillance during multidrug therapy, and, where possible, after completion of multidrug therapy.”\textsuperscript{40}

Summarizing the diverse, retrospective case studies in the surgical literature on leprosy from the past 25 years, it can only be inferred that traditional decompression surgery can relieve pain often, improve function in less than 50%, and have the potential to result in even worse peripheral nerve function. With regard to the only 2 high-level evidence-based studies, it could be summarized by saying that for the ulnar nerve at the elbow, steroids gave no better results than surgery, and steroids gave no better results than doing nothing; therefore, by inference, there is no demonstrated value in doing surgery in terms of functional improvement.

**A NEW CONCEPTUAL APPROACH TO NEUROLYSIS IN LEPROSY**

In 2002, as I read Brand and Yancey’s book about pain, *The Gift Nobody Wants*,\textsuperscript{6} I realized that his clinical investigative journey, concluding that peripheral nerves were the cause of the leprosy disability and noting the swelling of nerves proximal to a known anatomic site of compression, was similar to my journey trying to help
patients with progressive neurologic problems related to neuropathy, especially diabetic neuropathy. I concluded that much of the disability, termed *diabetic peripheral neuropathy*, was due to the presence of multiple nerve compressions along the course of individual nerves.\textsuperscript{41–43} The surgical solution to this puzzle was to decompress multiple sites along the course of each peripheral nerve, and this resulted in relief of pain, recovery of sensation, and, consequent to this, prevention of ulceration and amputation.\textsuperscript{44}

Would the surgical approaches developed to restore sensation and prevent ulceration and amputation in diabetics with neuropathy and nerve compression be able to help patients with leprosy and nerve compression? These approaches were based on the double crush concept that multiple sites of compression might need to be decompressed simultaneously along the course of an individual peripheral nerve.

To evaluate this, I began work in Guayaquil, Ecuador, with Wilton, a podiatric foot and ankle surgeon, from Portsmouth, New Hampshire, because he had been providing club foot care in Ecuador with the Perfect World Foundation. A team was formed to evaluate approximately 40 people at the Father Damien house in Guayaquil. The Father Damien House residents had received triple antibiotic therapy for their *M. leprae* and were no longer contagious, although they still became progressively more disabled due to what is now understood to be their peripheral nerve problems. Seiler did neurosensory testing with the pressure-specified sensory device (Table 1), and Wilton identified nerve entrapments by a positive Tinel sign. Fig. 5 shows 2 patients not chosen to be candidates for surgery and Fig. 6 shows a patient chosen for nerve decompression by that team.

Then, in September of 2004, Dellon and Wilton, with the operating nurses and anesthesiology team that Wilton organized, went back to Guayaquil and operated simultaneously on upper and lower extremities of 20 patients chosen by the first team (Fig. 7).

Given that excellent surgeons had attempted to decompress nerves in patients with leprosy in the past, what could we add to improve the chance of success? The double crush concept applied to leprosy suggested that the host response to *M. leprae* occurred at locations where the nerve was superficial and where there were known sites of nerve compression. The conclusion was to decompress each nerve at each site in which it could be decompressed in that extremity. For the ulnar nerve, the decompression had to be at the elbow and at the wrist, and the decompression at the wrist had to include the motor branch of the ulnar nerve (Fig. 8). For the median nerve, the decompression had to be at the wrist and also, if possible, in the forearm. In the absence of specifically finding evidence of the pronator syndrome, the approach

<table>
<thead>
<tr>
<th>Peripheral Nerve</th>
<th>Number of Nerves Tested</th>
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<tbody>
<tr>
<td>Median</td>
<td>29</td>
</tr>
<tr>
<td>Ulnar</td>
<td>40</td>
</tr>
<tr>
<td>Radial sensory</td>
<td>2</td>
</tr>
<tr>
<td>Peroneal</td>
<td>30</td>
</tr>
<tr>
<td>Tibial</td>
<td>18</td>
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<tr>
<td>Sural</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
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used to the ulnar nerve decompression, the submuscular transposition by the musculo-fascial lengthening technique, demonstrating the best long-term results, would decompress the median nerve at the elbow by lengthening the superficial head of the pronator and incising the lacertus fibrosus (Fig. 9).

Fig. 5. Two patients whose degrees of paralysis, amputation, and sensory loss were too advanced to be included for surgery. (A) Note amputated fingers. (B) Note neurosensory testing with the pressure-specified sensory device demonstrated absent static 2-point discrimination and even 1-point discrimination. Neither of these patients had a positive Tinel sign.

Fig. 6. This patient had neurosensory testing consistent with moderate degree of nerve compression and had a positive Tinel sign. Therefore, this patient was a candidate for nerve decompression.
Fig. 7. Operating room organization for 2-team approach to nerve decompression in patient with leprosy. Doctor with hand up indicating V for victory is the anesthesiologist at the head of the operating table. Wilton, foreground, is operating on the right leg, and Dellon, back of head to camera, in center of photograph, is operating on the right arm.

Fig. 8. Surgical approach at wrist. The median nerve has been decompressed in the carpal tunnel and Guyon canal is opened to decompress the ulnar nerve. Clamp demonstrates the hypertrophic ulnar motor branch after incising the hypothenar muscle fascia at the hook of the hamate.

Fig. 9. Surgical approach at elbow. Musculofascial technique for submuscular transposition of ulnar nerve at elbow shows (A) the muscle flaps that have been created, with ulnar nerve lying above, on muscle, and (B) muscle flaps transposed and lengthened, permitting finger and ulnar nerve to lie beneath. This approach also decompresses the proximal median nerve.
The radial nerve at the elbow lies deep to muscles and would likely not be invaded by *M. leprae*, but superficial sensory branch should be decompressed in the forearm (Fig. 10).

For the tibial nerve, its branches in the medial and lateral plantar and calcaneal tunnels are decompressed (Fig. 11).

For the peroneal nerve, it would be decompressed at both the fibular neck and over the dorsum of the foot and, if there were a positive Tinel sign, over the superficial peroneal nerve in the leg.

Internal neurolysis was done as indicated, based on intraoperative findings of firmness, intraneural fibrosis, and loss of perineurial markings (Fig. 12).

**RESULTS IN THE EARLY SERIES OF PATIENTS**

Twelve patients had the surgical approach shown in Table 2, with surgical decompression of 3 nerves in an arm and 3 nerves in a leg done simultaneously. They each received intravenous cephalosporin prior to inflating the tourniquets, and they continued oral cephalosporin for 1 week postoperatively. There were no surgical complications. There were no anesthesia complications. As indicated from Table 2, there was a wide range of impairment preoperatively in these patients. They were each kept the first night in the hospital and were returned to the Father Damien House the day after the surgery. On examining them the day after surgery, many who did not have fixed joint deformities in the hand (clawing) could already straighten their fingers and make a better fist. One patient is shown as an example of early recovery of sensibility in the foot after extensive neurolysis of the posterior tibial nerve and its branches (Fig. 13) and another as an example of early recovery of motor function (Fig. 14).

The mid-November 2004, 2-month follow-up was remarkable for no wound infections. Two patients who lived far away were not back for follow-up. Of the remaining 10 patients, 7 said they had better sensation in the hand and foot that were operated on than they had before surgery, and they had better feeling in these operated extremities than they did in the nonoperated extremities. Three patients noted no improvement. No patient was worse. The results were recorded by Dr. Martinez and submitted by e-mail in the form of a chart for each patient by e-mail.

A 1-year follow-up mission returned in 2005, led by Wilton and Scott Nickerson, an orthopedic surgeon not involved in the initial surgery; they went to do the...

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**Fig. 10.** Surgical approach to radial nerve in forearm. Fascia has been divided. Hand is to the right, and elbow is to the left. Note proximal normal size of nerve, and distally, at exit from fascia, there is enlargement of nerve at site of entrapment.
Fig. 11. Surgical approach to the tibial nerve at the ankle. (A) After releasing the tarsal tunnel itself, an internal neurolysis of medial and lateral plantar nerves was done because of the presence of intraneural fibrosis. (B) After release of the medial and lateral plantar tunnels and excision of septum between medial and lateral plantar tunnels to create 1 large tunnel, note that surgeon’s finger extends into the plantar aspect of the foot.

Fig. 12. Examples of internal neurolysis in upper extremity. (A) Excision of epineurium and intraneural neurolysis of median nerve at wrist. (B) Excision of epineurium and intraneural neurolysis of the ulnar nerve at elbow.

Table 2
Documentation and staging of peripheral nerve dysfunction with the pressure-specified sensory device

<table>
<thead>
<tr>
<th>Peripheral Nerve</th>
<th>(Mild–Moderate)</th>
<th>(Severe)</th>
<th>(Anesthetic)</th>
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<tbody>
<tr>
<td>Median</td>
<td>41%</td>
<td>24%</td>
<td>35%</td>
</tr>
<tr>
<td>Ulnar</td>
<td>35%</td>
<td>37%</td>
<td>28%</td>
</tr>
<tr>
<td>Peroneal</td>
<td>10%</td>
<td>13%</td>
<td>77%</td>
</tr>
<tr>
<td>Tibial</td>
<td>11%</td>
<td>16%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Fig. 13. Patient smiling while having the operated foot tickled, indicating improved sensation 1 day (24 hours) after neurolysis of the tibial nerve and its branches in the 4 medial ankle tunnels. He had severe sensory loss prior to surgery.
postoperative physical examinations. Postoperative neurosensory testing was also done. Overall, of the 12 patients operated on, 6 were in the excellent category (Fig. 15) and 4 were in the good category, with only 2 patients not improved. No one was worse. The entire follow-up team is noted in Fig. 16.

Subsequent missions have accounted for approximately 150 patients having had approximately 700 nerve surgeries. Future challenges include designing a prospective

Fig. 14. Patient with improved motor function 24 hours after having neurolysis of the common peroneal nerve at the knee. (A) immediately preoperatively, inability to extend big toe and dorsiflex ankle; (B) immediately postoperatively, after neurolysis of common peroneal nerve at the knee, note ability now to extend big toe and dorsiflex the ankle.

Fig. 15. Improved hand function after neurolysis of median and ulnar nerve at both the wrist and elbow regions. (A) Preoperatively, note clawing and wasting of first dorsal interosseous muscle. Postoperatively at 1-year follow-up, note (B) reversal of clawing, (C) ability to pinch, and (D) ability to write.
study with appropriate outcomes and implementation of this surgical strategy on a worldwide scale.

REFERENCES

1. Available at: www.telecom.net.et/ahri/hansen.html.

Fig. 16. In 2005, a team returned to Ecuador to do a 1-year evaluation of the first group of leprosy patients to have this surgery. Seated on the floor, from the left are Sister Annie Credidio, BVM, Damien House Director; Shannon Wilton and Rosemary Wayes, who did neurosensory testing for Wilton; and David Seiler, MBA, who did the neurosensory testing for Dellon. In the second row, seated, are Anne Nickerson, a local host; James Wilton, who led the team; a local host, Dale Montgomery, from the Perfect World Foundation, which sponsored the team; and David Nickerson and his father Scott Nickerson, MD, an orthopedic surgeon, who, uninvolved in the first surgery itself, did the postoperative physical examinations. Martinez is the physician at the Damien House. Standing in the third row is Martinez, the Damien House physician. Shannon Wilton and Anne and David Nickerson served as translators.


