A NEW OPERATION FOR THE PREVENTION
AND TREATMENT OF AMPUTATION NEUROMAS

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A stump neuroma is caused by the disorganised growth of axon cylinders into proliferating granulation tissue, but this is stopped by an undamaged epineural sleeve. We report experiments in the rat in which the epineural sleeve of the stump of the sciatic nerve was freed from nerve fascicles for about 5 mm and then sealed with a synthetic tissue adhesive. Neuroma formation was largely prevented in comparison with the results of other methods.

This new technique has been used to treat 68 painful neuromas in 36 patients. All but three of the patients were cured or improved and none were made worse.

A neuroma often remains symptom-free, but if it is put under tension or pressure, severe pain may develop; sometimes the pain comes on without any recognisable cause. Research on the aetiology of the pain has been concentrated on the morphological characteristics of the neuroma (Mathews and Osterholm 1972; Wall and Gutnik 1974; Wall and Devor 1978; Blumberg and Jänig 1981; Wall 1981; Wiesenfeld and Hallin 1981). It is considered that insufficient blood supply, isolation of the regenerating nerve fibres, artificial synapses, and most important, the presence of free fascicles, are possible causes of pain sensation.

Several authors have reported free nerve fascicles exiting from painful neuromas (Evans et al. 1968; Sunderland 1968; Tupper and Booth 1976). These fascicles could well be vulnerable to external stimulation and it is believed that these unprotected nerve fibres play a major role in producing neuroma pain.

Many clinical investigations and animal experiments have aimed to discover ways of inhibiting the growth of a neuroma: more than 150 methods have been described in the literature (Snyder and Knowles 1965). Sunderland (1968) considered that undamaged perineurium presented an impenetrable barrier for regenerating fascicles, and it is known that if a severed nerve can be completely reconstructed, no neuroma will develop. Tupper and Booth (1976) excised newly-grown fascicles and re-sutured the epineurium. Recurrence after this led to re-exploration: single nerve fibres had grown through ligatures which had not been tight enough. Dietrich, Michaelis and Kühnlein (1974) reported experiments in which nerve endings were covered by Histoacryl (butyl-2-cyanoacrylate; Braun, West Germany) in order to prevent neuroma formation. The results however, were as discouraging as those following the application of a silicone cover.

We aimed to test whether watertight closure of the perineurium could prevent neuroma formation. Because neither a double ligature nor a purse-string suture could be certain to achieve this, we used a tissue glue.

MATERIALS AND METHODS

Our animal experiments were performed using an operating microscope, on the sciatic nerves of 40 female Sprague-Dawley rats, weighing 175 ± 15 g. A section was removed from both sciatic nerves and the proximal stump was managed in one of five ways, giving 16 nerves in each treatment group.

In the first group, the epineurium was pushed back for about 5 to 8 mm, and single fascicles were pulled forward and shortened. The epineural sleeve was then pulled forward again to cover the nerve stump completely and sealed with a drop of Histoacryl glue (Fig. 1). In the second group, the cut nerves were marked and left untreated. In the third group, the severed ends were closed with Histoacryl glue without further preparation (Dietrich et al. 1974). The fourth group had simple ligation of the nerve stump as the only method of treatment (Chavannaz 1940). In the fifth group, the epineurium was prepared as described for Group 1, but no Histoacryl was used and the stump was ligated instead (Tupper and Booth 1976). All animals were killed 12
weeks after the initial operation. The nerve stumps were photographed and then evaluated by light microscopy and electron microscopy.

We later applied these experimental methods to the clinical treatment of selected patients.

RESULTS

A summary of the animal experiments is given in Table I.

All the proximal stumps which were left untreated (Group 2) formed neuromas of various sizes. After simple ligature of the nerve stump (Group 4), all 16 nerve endings formed a large neuroma. The histology of these showed multiple nerve fascicles sprouting both terminally and laterally, taken to be due to contusion of the coverings of the nerve (Fig. 2).

Of the 16 carefully prepared nerve endings in which the epineurium had been ligated over shortened fascicles (Group 5), nine were failures; several nerve fascicles had succeeded in growing beyond the ligature on the neuroma (Figs 3a and b). Of the 16 nerve endings sealed by Histoacryl glue without careful preparation of the epineurium (Group 3), 11 showed neuroma formation. Histology showed that the tissue glue had crumbled or had been pushed aside. The free nerve endings were swollen and some fascicles had prevented the capsule of

### Table I. Results of animal experiments

<table>
<thead>
<tr>
<th>Group</th>
<th>Method of operation</th>
<th>Number of nerves</th>
<th>Neuroma formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Histoacryl within epineurial tube</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>No treatment</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>Capping with Histoacryl</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Ligation of the nerve stump</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>Ligation of the epineurial tube</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>

### Table II. Clinical series

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of Patients</th>
<th>Number of Neuromas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finger</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Arm</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Forearm</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Thigh</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Calf</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

Figure 2 – Neuroma formed after ligation of the nerve stump. Figure 3a – Neuroma formed after ligation of the epineural sleeve. Figure 3b – Micrograph showing continued axonal growth (Bodian × 25).

### Table III. Results in 36 patients

<table>
<thead>
<tr>
<th></th>
<th>Complete relief</th>
<th>Improved</th>
<th>Unchanged</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroma pain</td>
<td>28</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Phantom pain</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

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Figure 4 – Neuroma formed after simple capping of the nerve stump with tissue glue. Figure 5 – After sealing with Histoacryl the nerve stump is smooth and non-adherent.

A micrograph at 12 weeks after sealing with Histoacryl shows the newly formed capsule. On the right are remnants of the Histoacryl glue (H), and the newly formed capsule shows two cell layers (K1/K2). The nerve fibres (N) are arranged in parallel rows and there is no neuroma formation (Haematoxylin and eosin × 200).

Electron micrograph showing collagen-rich connective tissue in a cross section of the external layer of the newly formed capsule. The connective tissue cells show the characteristics of a synthesising (SP) and a proliferating perineural cell (PP) (× 2000).

The neuroma from being adherent to the surrounding tissues (Fig. 4). Of the 16 nerve endings sealed interneurally with Histoacryl (Group 1), only two showed some proliferation and regrowth of the fascicles next to the adhesive. These failures were due to technical faults, in one case because the epineurium had been perforated by a hypodermic needle. The other 14 nerves treated in this way showed no neuroma formation, and the tissue glue had not caused necrosis or infection. There were no signs of adverse tissue reaction or rejection (Fig. 5).

Light microscopy showed the acrylate spaces as empty honeycombed cystic structures containing only small parts of the artificial substance. The boundary of the cavity was a thick connective tissue capsule in several layers and formed from perineural and epineural connective tissue. The inner layer was mainly cellular, containing fibrocytes, fibroblasts, phagocytes and histiocytes, while in the outer layer collagen fibres dominated. The capsule contained numerous blood vessels and adipose tissue.

Between the fascicles and the fibrous capsule, there was a further layer of connective tissue which in longitudinal section appeared as an arcade originating from the perineurium on both sides. It closed off the epineural space and the free endings of the nerve fascicles. This layer contained few cells and very little foreign material (Fig. 6). The barrier function of the perineurium was well demonstrated by this newly-formed connective tissue layer. The nerve fibres immediately adherent to the tissue glue were seen to be arranged in parallel rows, and some interfascicular oedema could also be seen. In cross section, myelinated axons predominated. Electron microscopic examination of the stump showed that the newly formed capsule under the tissue glue contained numerous collagen fibres as well as proliferating perineural cells (Fig. 7).

The animal experiments using this new method had all shown that the morphological features of neuroma formation could be eliminated.

Clinical experience. The results of our animal investigations encouraged us to use the method for selected patients. Over a three-and-a-half year period 36 patients, aged 22 to 68 years (mean 44.5), with 68 limb neuromas were treated. All patients had stump pain and had tried conservative treatment including local infiltration and transcutaneous nerve stimulation. Thirteen of the 36 had had unsuccessful operations including further resection of nerve (six), ligation (three), silicone capping (two) and implantation of the neuroma into bone (two). The sites involved are given in Table II.

There were no postoperative complications and patients have been followed up for seven to 43 months (average 17 months). With the exception of three patients, all 36 were improved or pain-free (Table III). It was noticeable that the function of the amputation stump improved as a result of pain relief. There were no trophic...
disturbances, evidence of incompatibility to the injected glue, or any inflammatory response.

DISCUSSION

Our experiments aimed to discover how to prevent the continuous growth of axons described by Sunderland (1968). Numerous attempts to prevent the formation of a neuroma have failed because of technical problems (Krüger 1916; Chapple 1917; Corner 1918a, b; Chavannaz 1940; Munro and Mallory 1959). Both Tupper and Booth (1976) and Battista and Cravioto (1981) tried to overcome these problems by using an operating microscope, but the methods they used were not entirely satisfactory. Neither a ligature nor a purse-string suture, closed off the epineurium completely. With either method, the small gaps which remained open were large enough for regenerating fascicles to grow through and form a neuroma.

We used a tissue glue, because the technique was simple and the seal was complete. Swanson, Boeve and Lumsden (1977) showed that it was insufficient just to cover the nerve end with tissue glue, or with a silicone cap. We therefore prepared the epineurium carefully, shortened the fascicles and sealed off the prepared tube of epineurium with tissue adhesive. This closed the nerve end completely. Deep to the adhesive plug, perineural cells proliferated and formed a tight connective tissue capsule which effectively prevented further growth of regenerating axons, even after resorption of the adhesive.

Our technique appears to fulfil the criteria set out by Sunderland, and “prevent the escape of regenerating axons into the neighbouring connective tissue where their disorderly growth is responsible for the formation of the neuroma”. Our clinical experience confirms that the small amount of tissue adhesive we used was tolerated with no side effects. We saw no neuroma recurrence and believe that our technically simple method effectively stops the disorganised growth of regenerating axons without causing necrosis or scarring due to constricting sutures.

The authors would like to thank Mr D. H. Brown, FRCS(C), for his help in preparing the manuscript.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

REFERENCES


