Collateral sprouting of cutaneous nerves in man

Ciaran Healy,1 Pamela M. LeQuesne1 and Bruce Lynn2

1The Reta Lila Weston Institute of Neurological Studies and 2Department of Physiology, University College London Medical School, London, UK

Correspondence to: Ciaran Healy MD, Department of Plastic and Reconstructive Surgery, St Thomas’ Hospital, Lambeth Palace Road, London SE1 7EH

Summary
Cutaneous nerve collateral sprouting was studied in 20 adults in whom a forearm cutaneous nerve had been resected from the upper arm, such that any recovery of cutaneous nerve function could not be accounted for by nerve regeneration. Ten patients entered the study immediately following surgery and the remainder at intervals thereafter, permitting a longitudinal study covering a 27-month period. Modality-specific stimuli were used to study light touch, sharp pain, cooling, warming and heat pain sensation. Efferent sympathetic C fibre function was determined by measuring sweating in response to total body heating. Though the patients described considerable subjective reduction in the sensory defect within 2 months, by 10–15 months the objective sensory tests showed encroachment at the margin by only 6 mm (P < 0.05) for light touch, 7 mm (P < 0.01) for sharp pain and 11.5 mm (P < 0.001) for heat pain, with no significant change for warming or cooling. By 24 months, recovery of sweating was evident within the zone of persistent sensory loss, for ≥3 cm beyond the initial light touch margin (P < 0.005). This finding has important clinical implications as it calls into question the reliance placed on the recovery of sweating as evidence of nerve regeneration.

Keywords: cutaneous nerve injury; sweating (recovery of); sensory recovery; collateral sprouting

Introduction
Cutaneous nerve division results in loss of afferent and efferent function in the skin supplied by it, recovery of which may occur through axonal regeneration between the severed ends (Ramón y Cajal, 1959) when they are within the critical gap distance (Lundborg et al., 1982) or across a suitable conduit (Mackinnon et al., 1984; Lundborg, 1988). An alternative possible mechanism of cutaneous nerve function recovery is through the expansion of adjacent intact nerves into denervated skin by collateral sprouting (Oppenheim, 1911). This has been shown in animals to be distinct from the more profuse expansive regenerative reinnervation (Kinnman et al., 1989) which arises from adjacent nerves which are themselves recovering from damage (Wiesenfeld-Hallin et al., 1989). Following cutaneous nerve division and repair, axonal regeneration, expansive regenerative reinnervation and collateral sprouting may occur simultaneously, making it difficult to discern the relative contribution that each mechanism makes to functional recovery. Animal studies of cutaneous nerve collateral sprouting have been carried out following clearly defined and reproducible nerve lesions using histological, electrophysiological and behavioural methods. It has been shown to occur in Aβ low threshold mechanoreceptor fibres in the salamander, leech and neonatal rat, though it is limited to nociceptor Aδ high threshold mechanoreceptor, polymodal nociceptor C and sudomotor C fibres in adult mammals. The clinical relevance of these animal studies has yet to be shown, as the extent of collateral sprouting of cutaneous nerves in man is unclear. Previous clinical studies, largely restricted to behavioural methods, have frequently been hampered by studying subjects with ill defined nerve injuries in which a subsequent contribution to functional recovery through regeneration cannot be ruled out. Failure to ascertain the exact extent of the initial cutaneous nerve functional deficit has hindered the subsequent assessment of the timing, rate and extent of recovery. The aims of our clinical study were to establish, following the resection of a cutaneous nerve and in the absence of regeneration, (i) whether adjacent intact cutaneous nerves undergo functional collateral sprouting and (ii) the timing and extent of any such sprouting in different nerve fibre groups.

Material and methods
Patients
Patients undergoing procedures involving resection, under general anaesthesia, of a 20 cm forearm cutaneous nerve graft from the upper arm were approached for participation in this study, which was approved by the ethics committees.
Fig. 1 (A) The area of heat pain sensory deficit after excision of 20 cm of the medial cutaneous nerve of the forearm. The deficit lies on the ulnar volar aspect of the forearm. (B) The area of heat pain sensory deficit after excision of 20 cm of the posterior cutaneous nerve of the forearm. The deficit lies on the dorsal aspect of the forearm.

Group A
Ten patients, five male and five female, were examined prior to cutaneous nerve resection to confirm that there was normal sensation in the forearm. Eight of these patients were examined within the first post-operative week and the investigations were repeated in all of them during the intervals: 3–4 weeks, 2–5 months, 5–10 months and 10–15 months.

Group B
The remaining 10 patients studied were all male, by chance rather than by design. They were not examined prior to cutaneous nerve resection, as they entered the study some time after the event, though on questioning none could recall any previous sensory deficit. The experimental methods were developed and their reproducibility assessed in this group. In three of them in particular, careful measurements were made at 17–18 months and 22–27 months after nerve resection, to elucidate the later stage of the cutaneous nerve lesion’s natural history.

The duration of each formal experimental session was 6 h, regular attendance requiring considerable commitment on the part of the patients, who received no financial incentive other than reimbursement of their travelling expenses. While the compliance rate overall was satisfactory, some subjects were unable to complete the study or were unable to attend all of the experimental sessions.

Procedures
Sensory tests
These were carried out over ~2 h in a quiet room with the ambient temperature regulated to maintain the skin at 32°C. The area of sensory deficit was mapped out using a series of accurate, reproducible, modality specific stimuli. These were set at a suprathreshold level, ensuring ready perception of the stimulus when it was applied to innervated skin. They were calibrated regularly to ensure that the same stimulus was applied throughout. Accurate location of the test area in relation to cutaneous landmarks enabled the same area of skin to be tested at different time intervals.

Light touch was tested using a modified Von Frey monofilament nylon fibre which on bending produced a 50 mN force (Von Frey, 1922; Semmes et al., 1960; Levin et al., 1978). This stimulus produced a sensation of touch, but no pain. Sharp pain was tested using a pin, mounted on a nylon fibre calibrated to deliver a force of 75 mN on bending. This was sufficient to induce a sharp, painful sensation in the normally innervated skin of all the subjects studied, yet was insufficient to pierce the epidermis, so it avoided the risk of viral transmission (Lowenfels et al., 1989). Thermal sensation was tested using the computerized Middlesex Thermal Tester (Fowler et al., 1987), modified to deliver a predetermined stable thermal stimulus via a custom designed Peltier Thermode. Built by the Medical Physics Department of the Middlesex Hospital for this study, continuous computer monitoring via a thermocouple embedded within the 5×25 mm rectangular brass interface provided a constant thermal stimulus. This was delivered for 3 s on each occasion, at 5°C below skin temperature for cooling and at 5°C above skin temperature for warming. Heat pain sensation was tested using a separate brass thermode, with a thermocouple embedded at the 5×20 mm interface, heated to 65°C and applied to the skin for a duration of 1 s. The brief application of this level of noxious thermal stimulus was readily
perceived as painful in innervated skin in all of the subjects, yet did not result in damage to the local tissues. The 160 g block of brass acted as a heat reservoir, permitting the area of absent heat pain sensation to be mapped out prior to a rapid fall in the temperature of the thermode interface to <62°C.

The modality specific, supra-threshold sensory stimuli allowed ready identification of the appropriate sensory margins of the area of cutaneous nerve function deficit on each occasion. During the sensory testing, the subjects were not allowed to see the area being tested, to avoid misinterpretation of the stimuli. The forearm being studied was placed on a vacuum pillow and immobilized. Measurement of the width of the sensory deficit for each modality was made perpendicular to the long axis of the limb at up to three different widely spaced positions or levels. These levels were chosen in relation to specified cutaneous landmarks thereby ensuring that the same areas of skin was studied at each time interval. Measurement of the distance between the margins reduced the error due to variation in the exact anatomical location studied on repeat examinations. Commencing in the numb area, each stimulus was applied at 0.5 cm intervals, advancing towards the area of normal sensation. When the stimulus was perceived by the subject, the point at which it became perceptible was defined as accurately as possible by approaching it repeatedly from the direction of the numb patch. The first point where four out of five stimuli were perceived by the subject was identified for each modality of sensation and marked on the skin with water soluble ink from a felt tip pen. The ink colour used was coded for the appropriate modality of sensation.

Data from subjects examined at the different time intervals were subjected to Student’s paired t test analysis. Variation in data recorded at different levels within subjects was similar to variation between subjects, therefore for statistical tests, data points for each level recorded in each subject have been included individually. Thus, the n values are for the total number of levels assessed over all the subjects. Regular calibration of the modality specific suprathreshold stimuli throughout the study showed them to remain constant.

### Quantification of sweating

Postganglionic cholinergic sympathetic C fibres mediate sweat gland (sudomotor) function (Uno and Montagna, 1975; Uno, 1977) which was tested in this study by inducing sympathetic activity in response to total body heating (Randall and Kimura, 1955; Sato et al., 1989). Profuse generalized sweating was induced by placing the patient in an environmental chamber at 45°C for ~20 min, thereby increasing the body core temperature above the temperature set point (Sato et al., 1989). Body core temperature was not measured, as the subjects were known to have normal general neurological function, apart from the specified peripheral nerve deficits. The density of active sweat glands was measured from the dark imprint left on bromophenol blue impregnated paper by the sweat droplets (Sakurai, 1986) after it had been applied for 20 s to the area of skin being studied. The pattern left on the paper was preserved, to prevent fading and contact damage, by covering it with a layer of clear adhesive tape. This proved effective in preserving the pattern, though in some instances an overall darkening of the paper occurred with time. Details of the anatomical location of the skin being studied were recorded on the back of the bromophenol blue paper. The dots were counted under a magnification of ×5 against a 1 cm² grid and expressed as dots per cm² at 1 cm intervals along a line perpendicular to the light touch margin. Data from different time intervals were subjected to unpaired t test analysis.

### Results

#### Subjective sensation

One patient reported an abnormal sensation other than numbness in relation to the forearm cutaneous nerve deficit. Described as a poorly defined burning sensation in the skin surrounding the numb patch in his forearm, it gradually developed within 14 days of the excision of the medial cutaneous nerve of the forearm and persisted for almost 3 months. The remaining subjects reported an initial sensation of strange numbness in the affected area of skin, as though it no longer belonged to them, the intensity of which receded within 6 months. Patients in both Groups A and B reported a reduction in their subjective impression of the size of the area of numbness, commencing within four weeks of nerve resection and continuing for up to 2 months. It was not possible to define the intensity and duration of this subjective impression accurately, as the patients themselves found it difficult to quantify and identify accurately. They were surprised at the size of the sensory deficit mapped out at the first detailed sensory testing session as it exceeded their subjective impression of it. This discrepancy became more marked with time as the subjective deficit appeared to diminish and that mapped out changed little. Four patients in Group B claimed that during the progress of the study their chronic sensory deficit was felt to have begun to reduce in extent.

### Sensory test results

#### Initial sensory deficit

The topography of the cutaneous sensory deficit was readily identified by the suprathreshold modality specific stimuli, providing a clearly defined margin for the area of sensory loss for each modality. The sensory margins of the different modalities were separate from one another, their relationship to one another remained constant throughout the study and they bore the same relationship to each other in all the subjects studied. The heat pain sensory margin was innermost (smallest sensory deficit), followed in order by those for sharp pain, light touch, cooling and warming (largest sensory deficit). The areas of heat pain sensory deficit resulting from excision of the different nerves are shown in Fig. 1A and B. After the excision of the medial cutaneous nerve to the forearm the deficit commenced proximal to the elbow on the ulnar
Table 1 Width of area of sensory deficit area for different modalities after cutaneous denervation

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean width±SE (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Light touch</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Week</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9.6±0.78</td>
</tr>
<tr>
<td>4</td>
<td>9.4±0.89</td>
</tr>
<tr>
<td>(n)¹</td>
<td>(16)</td>
</tr>
<tr>
<td>Months</td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>9.0±0.77</td>
</tr>
<tr>
<td>1-2</td>
<td>9.0±0.88</td>
</tr>
<tr>
<td>2-5</td>
<td>8.6±0.80</td>
</tr>
<tr>
<td>5-10</td>
<td>8.5±0.84</td>
</tr>
<tr>
<td>10-15</td>
<td>7.8±0.81*</td>
</tr>
<tr>
<td>(n)²</td>
<td>(13)</td>
</tr>
<tr>
<td>Months</td>
<td></td>
</tr>
<tr>
<td>17-18</td>
<td>7.9±0.85</td>
</tr>
<tr>
<td>22-27</td>
<td>8.3±1.02</td>
</tr>
<tr>
<td>(n)³</td>
<td>(7)</td>
</tr>
</tbody>
</table>

Mean widths are shown in cm ± SE. The n-values represent the total number of independent measurements (at different levels) in eight⁴, five¹ and three³ patients, as indicated. Statistical analysis was carried out using a paired Student's t test within each of the three main time groups. Between the periods 0–1 months and 10–15 months the reductions in the mean widths represent an encroachment of the sensory margin for light touch by 6 mm (*p < 0.05), for sharp pain by 7 mm (**p < 0.01) and for heat pain by 11.5 mm (***p < 0.001), with no significant alterations in warming or cooling sensation.

Fig. 2 The mean widths of the areas showing sensory deficits for light touch (LT), sharp pain (SP), heat pain (HP), warming (W) and cooling (C) following cutaneous denervation are compared in the time intervals shown. The standard errors and statistical significance of the changes are shown in Table 1.

aspect of the arm, gradually spreading out as far as the mid-forearm. From here it gradually narrowed to its termination at the wrist (Fig. 1A). The heat pain sensory deficit resulting from excision of the posterior cutaneous nerve of the forearm commenced at the elbow on the postero-radial aspect of the arm and extended onto the posterior aspect of the forearm, reaching it's widest point immediately distal to the elbow. From here it gradually narrowed as it passed along the forearm to terminate at the junction of its middle and distal thirds (Fig. 1B).

Early sensory tests
No significant change was found for any sensory modality when eight patients in Group A were tested during the first and fourth weeks and results compared (Table 1 and Fig. 2). Thus data collected from all Group A subjects within the first 4 weeks could be compared with those from later time intervals, up to 10–15 months, without erroneously concealing any early significant change in the extent of the sensory defect.

Intermediate sensory tests
The time intervals within which the intermediate data were grouped were: 0–1, 1–2, 2–5, 5–10 and 10–15 months. Five patients were studied in all of these time intervals and the data analysis was confined to them. Where more than one series of tests were carried out in a given time block, the mean of the values recorded was taken as that representing the value within that time interval. By taking each of the levels separately for five different subjects, 13 readings for the time intervals up to 15 months were available for analysis of the change for light touch and sharp pain sensation. Eleven readings for the same time intervals were available for heat pain, cold and warm sensation. The results are shown in Table 1 and Fig. 2.

There was a gradual reduction in the mean width of the light touch sensory deficit from 2 to 15 months, but this only reached statistical significance at the 10–15-month interval. This represented a 6 mm (P < 0.05) movement of the sensory margin for light touch by 10–15 months. There was a statistically significant reduction in the mean width of the sharp pain sensory deficit at 2–5 months and 10–15 months, the latter representing a 7 mm (P < 0.01) movement of the sensory margin. Whereas no significant change was detected for cooling or for warming at any of the time intervals, by 2–5 months a statistically significant reduction in the mean width of the sensory deficit for heat pain occurred, increasing in subsequent intervals. By the 10–15-month interval this
Collateral sprouting of cutaneous nerves

Table 2 The recovery of sweat gland function following cutaneous denervation

<table>
<thead>
<tr>
<th>Months</th>
<th>n</th>
<th>Mean sweat dots per cm² at given distances outside the LT deficit area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>+2 cm</td>
</tr>
<tr>
<td>0–6</td>
<td>10</td>
<td>105</td>
</tr>
<tr>
<td>6–12</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>12–27</td>
<td>8</td>
<td>99</td>
</tr>
</tbody>
</table>

Sweat gland function was assessed in an environmental chamber at 45°C and the active sweat gland density measured using bromophenol blue impregnated paper. It was expressed as sweat dots per cm² at 1 cm intervals along a line perpendicular to the light touch (LT) sensory margin on each occasion. Positive/negative distances indicate positions outside/inside the area of LT deficit; n = total number of subjects examined within each time interval. Student's t test analysis of the sweat gland data in the area of persistent sensory loss (at −3 cm) showed a statistically significant change (P < 0.005) between the 0–6 month and 12–27 month intervals.

Sweat gland reinnervation

Immediately, pilocarpine electrophoresis was used to assess sweat gland re-innervation, but it proved unreliable as the period of persistent sweat gland pilocarpine sensitivity following denervation overlapped with their re-innervation. This was substituted by whole body heating at 45°C in the environmental chamber, the active sweat gland density being measured by the sweat dot count on bromophenol blue impregnated paper. Control values for maximal active sweat gland density ranged from 125 to 160 cm² (mean = 146). These were obtained from normally innervated contralateral forearm skin during nine separate observations in three patients and showed little variation within subjects, in keeping with previous reports (Kuno, 1956). As the environmental chamber was introduced when the study was in progress, the appropriate data for patients entered prior to this are incomplete. In analysing the data available it was therefore not possible to limit the analysis to subjects who had been studied at every time interval, as was done for sensory function. The mean of each set of readings from the different time intervals was therefore used to look at the change in sudomotor function in response to total body heating. In order that the sudomotor function in the numb area could be compared between individual patients it was expressed in relation to the location of the light touch sensory margin of the denervated area, as first measured for each individual (Table 2 and Fig. 3). During the 0–6-month interval the mean sweat count 2 cm outside the light touch sensory margin was 105 cm², decreasing progressively at each centimetre interval towards the centre of the denervated area in all subjects. Within the area of persistent sensory loss there was a steady encroachment of recovery in sweat gland activity/density, e.g. rising from 5 cm² at 0–6 months to 54 cm² at 12–24 months (P < 0.005) 3 cm inside the light touch sensory margin. These findings show that following excision of the cutaneous nerve sweat gland function was absent within the area of sensory loss. With time, it was seen to recover at the margin of the denervated area. This recovery of sweat gland function advances with time into the zone of persistent sensory loss. The extent to which this occurred was variable, at 12–24 months ranging from 0 to >100 cm² (mean = 54) 3 cm inside the light touch sensory margin.

Discussion

Early clinical studies of cutaneous reinnervation following nerve injury (Rivers and Head, 1908; Pollock, 1920; Pollock and Davies, 1933) were directed at assessing the regenerative capacity of cutaneous nerves and did not refer to collateral sprouting as such, though evidence of it can be inferred. It has since been investigated extensively in animals and to a lesser extent in man, the latter studies being hampered by uncertainty regarding the nature of the nerve lesions, variations in their anatomical locations and the extent of the areas involved. The present study involved 20 adult subjects in whom an extensive area of cutaneous denervation was created by resecting a forearm cutaneous nerve. Recovery of cutaneous nerve function within the denervated area could only be accounted for by collateral sprouting as regeneration could not occur across the resulting inter-stump nerve gap in the absence of a nerve graft conduit (Lundborg, 1982).

In animal studies evidence of collateral sprouting of nerve fibres mediating light touch/pressure sensation has been confined to the salamander, the leech (Diamond et al., 1976; Blackshaw et al., 1982) and rodent neonates (Diamond and Jackson, 1978; Jackson and Diamond, 1984; Kinnman and Aldskogius, 1986; Wiesenfeld-Hallin et al., 1989). This evidence suggests that comparison of adult studies with children, in which extensive recovery has been reported (Leonard, 1973), may be invalid. Light touch sensation was found to recover over a distance of 0.6 cm (P < 0.05) in the present study, a small change in clinical terms relative to the
extent of the sensory deficit. While this is consistent with some adult clinical studies (Livingston, 1947; Robinson, 1983, 1988; Hoffert et al., 1984; Nunely et al., 1989), others have failed to detect such recovery (Pollock and Davies; 1933; Inbal et al., 1987). Robinson (1983) reported indirect evidence of <1 cm of recovery following trigeminal sensory root section and (1988) a significant reduction in the total area of light sensory loss within 6 months of inferior alveolar nerve resection. Though the distance over which the latter sensory margin advanced was not reported it appeared to be no more then 1 cm in the accompanying photographs. Though the nerve deficits studied differed in type and anatomical location from those in the present study, the magnitude of collateral sprouting of light touch conveying fibres appears to be similar.

Collateral sprouting of sharp pain conducting Aδ fibres has been shown consistently in adult animal studies (Devor et al., 1979; Brenowitz and Devor, 1981; Greenfield and Devor, 1981; Markus et al., 1984; Nixon et al., 1984; Pomeranz et al., 1984; Bisby and Keen, 1986; Kinnman and Aldskogius, 1986; Diamond et al., 1987; Owen et al., 1989). In the present study the sharp pain (pinprick) sensory margin encroached by 0.7 cm (P < 0.01) in contrast with previous clinical reports of extensive early pin prick sensory recovery (Rivers and Head, 1908; Pollock and Davies, 1933; Livingston, 1947; Hoffert et al., 1984; Inbal et al., 1987; Nunely et al., 1989). The pin-prick stimulus strength used by Rivers and Head and by Inbal et al. was significantly greater than was used in the present study and may have stimulated subcutaneous intact sensory nerves, giving an erroneous impression of extensive sharp pain sensory recovery. As with light touch sensory recovery, Robinson (1983, 1988) has reported collateral sprouting of sharp pain conducting fibres, of a similar magnitude to the present study, following trigeminal sensory root section and inferior alveolar nerve resection.

Collateral sprouting of polymodal nociceptor C fibres in animals (Robinson, 1984, 1988; Brenan, 1986; Diamond et al., 1987; Doucette and Diamond, 1987; Pertovaara, 1988; Kinnman et al., 1989; Wiesenfeld-Hallin et al., 1989) and extensive early encroachment of dull pain sensation following cutaneous nerve division in man (Rivers and Head, 1908; Inbal et al., 1987) has been reported. This is in keeping with the findings of the present study in which the greatest sensory recovery occurred at the heat pain (noxious thermal) sensory margin which encroached by 11.5 mm (P < 0.001) into the denervated area. However, the degree to which heat pain sensation recovered relative to sharp pain in the present study is contrary to that found in the rat and mouse (Diamond et al., 1987).

No statistically significant evidence of functional collateral sprouting involving warming or cooling conducting fibres
was found in the present study, in keeping with previous clinical reports (Robinson, 1988). Rivers and Head (1908) found that the margin of absent cold sensation lay between that of pin prick and light touch following cutaneous denervation, otherwise the relative locations of the margins for the different sensory modalities in their study were similar to those in the present study. The difference may be explained by the type of cooling stimulus used in the two studies. Rivers and Head applied a metal tube filled with ice to the skin whereas in the present study a cooling stimulus of only 5°C below skin temperature was used. The former cooling stimulus may have spread further in the skin than the latter, giving an impression of a smaller area of anaesthesia to cooling. Alternatively the very low cooling temperature stimulus may have stimulated nociceptive fibres, giving an erroneous impression of the margin for the area of cooling sensory loss.

Our findings of relatively small objective sensory changes contrast with the patients' subjective impressions of significant sensory recovery; this may be explained in terms of plastic adaptation of the primary somatosensory cortex. Reported in mammals (Kalaska and Pomeranz, 1979; Rasmussen, 1982; Merzenich et al., 1983a, b) and humans (Yang et al., 1994), within 16 weeks of afferent nerve ablation the associated cortical cells receive new functional input from neighbouring intact nerves, creating the impression of an encroachment of the adjacent intact sensory margin into the area of cutaneous sensory loss. The time scale is consistent with that of the subjective alteration in the area of cutaneous sensory loss reported in the present study. Plasticity within the mammalian spinal cord has been shown in the dorsal horn (Basbaum and Wall, 1976) and dorsal column nuclei (Devor and Wall, 1978) resulting from either immediate unmasking of pre-existing silent synapses by removal of inhibiting input (Basbaum and Wall, 1976; Dostrovsky et al., 1976; Devor and Wall, 1978; Metzler and Marks, 1979) or later collateral sprouting of intact axons (Raisman and Fields, 1973; Goldberger and Murray, 1974; Cotman and Nadler, 1978; Tsukahara, 1978). We found no sensory recovery within the first 4 weeks, suggesting that in humans the unmasking of pre-existing synaptic activity following de-afferentation is of little functional importance. Long-term functional changes brought about in the rat spinal cord by peripheral nerve injury are confined to the original projections of intact adjacent nerves (Williams et al., 1991). Together with the results presented here, this implies that the neural plasticity which attributes sensory information to a denervated receptive field takes place mainly in the brain rather than in the spinal cord or in the periphery.

Phantom limb sensations and paraesthesia are common sequelae of traumatic nerve loss (Haber, 1956; Carlen et al., 1978), though only one patient in this study complained of discomfort relating to the loss of the cutaneous nerve extending beyond the immediate post operative period. The axillary nerve palsy, for which his medial cutaneous forearm nerve was resected as a nerve graft, was the sequela of a brachial plexus traction injury, a mechanism known to give rise to phantom sensation. The remaining subjects denied phantom sensations or paraesthesia in the distribution of the resected nerves which were removed with surgical precision, under general anaesthesia and with adequate post-operative pain control. This is in contrast with the frequency of paraesthesia, hypersensitivity and cold intolerance as sequelae of traumatic cutaneous nerve lesions (Sunderland, 1978; Mackinnon and Dellon, 1988). The presence of pain prior to or during the occurrence of a peripheral nerve deficit may permit pain pathways to become established which may be difficult or impossible to eradicate after the event (Melzack and Wall, 1965).

Our findings of extensive functional reinnervation of adult sweat glands through sudomotor C fibre collateral sprouting are in agreement with reports in children (Leonard, 1973) and mice (Kennedy and Sakuta, 1984; Kennedy et al., 1986). Following cutaneous nerve resection the density of functioning sweat glands was considerably below normal within the sensory defect margin (see Fig. 3). Recovery of sweating was evident by 6–12 months and continued during the 12–24-month interval, when the density of active sweat glands rose significantly from the 0–6-month interval to reach 54 cm⁻² (P < 0.005) within the area of persistent sensory loss. Clinical reliance on the detection of sweating as an objective indicator of sensory recovery following nerve injury and repair (Guttmann and List, 1928; Guttmann, 1931; Klar, 1955; Moborg, 1958; Smith and Mott 1986) is called into question by this evidence of collateral sprouting of sudomotor C fibres leading to the return of sweating within the area of persistent sensory loss. Our evidence may help to explain why some have found the return of sweating unreliable (Seddon et al., 1943; Öne, 1962).

The specificity of cutaneous nerve fibre afferent and efferent function (Vallbo et al., 1979) permits identification of the different nerve fibre types involved in collateral sprouting. Light touch sensation is conveyed by low threshold mechanoreceptor Aβ fibres, sharp pain by high threshold mechanoreceptor Aδ fibres (Hallin and Torebjörk, 1976), cooling by Aδ fibres (Hensel, 1981), warming by C fibres (Konietzny and Hensel, 1977) and heat pain (noxious thermal) sensation by polymodal nociceptor C fibres (Perl, 1984). A group of heat sensitive Aδ nociceptor fibres described in human (Adriaensen et al., 1983) and primate skin (Campbell et al., 1979) may mediate the short latency 'first pain' induced by cutaneous noxious thermal stimuli (Dubner and Bennett, 1983). The possibility that our noxious thermal stimulus was stimulating Aδ rather than polymodal nociceptor C fibres must be considered. The noxious thermal threshold is higher for Aδ than C fibres, at least in normal nerves (Adriaensen et al., 1983). The subjective quality of the noxious thermal stimulus reported by the patients was consistent with C fibre stimulation rather than the sharp 'first' pain of Aδ fibre stimulation, suggesting that the changing margin was more likely to be due to polymodal nociceptor C than Aδ fibre collateral sprouting.

The absolute amount of cutaneous nerve collateral
sprouting occurring in humans may be similar to that in animals, rather than the relative amount in proportion to body surface area. If this is the case, in terms of relative size cutaneous nerve collateral sprouting in humans would be less clinically significant or functionally useful than in smaller animals. Our study has shown that it is limited in the range of nerve fibre types involved and in the area of skin which they can reinnervate. The mechanisms by which it is controlled are therefore of clinical interest, as their manipulation may be of therapeutic value (Nixon et al., 1984). Animal studies to elucidate these factors have postulated production of a nerve growth-promoting substance produced by denervated target tissue (Aguilar et al., 1973; Diamond et al., 1976; Diamond, 1979; Diamond and Jackson 1980; Diamond, 1982), possibly endogenous β nerve growth factor (Diamond et al., 1987; Owen et al., 1989), regenerating nerve–target contact inhibition mediated by fast axoplasmic transport (Aguilar et al., 1973; Diamond et al., 1976; Diamond, 1979; Diamond and Jackson 1980; Diamond, 1982), resulting in withdrawal of the collateral sprouting fibres induced by a mutual growth inhibitory factor produced by the regenerating nerve fibres (Devor et al., 1979). While elucidation of the control mechanisms behind cutaneous nerve collateral sprouting in man was beyond its scope, the design of our study could be modified for such elucidation, and to assess the efficacy of neurotrophic factors as therapeutic agents.

In summary, this clinical study found that collateral sprouting of cutaneous nerves resulted in encroachment of the sensory margin by 6 mm for light touch (P < 0.05), 7 mm for sharp pain (P < 0.01) and 11.5 mm (P < 0.001) for heat pain, with no significant alteration for warming or cooling. The subjects’ erroneous impression of considerable early recession in the area of numbness may explained by central nervous system plasticity. Collateral sprouting of sudomotor C fibres resulted in the return of sweating in the absence of sensory recovery, underlining the validity of the return of sweating as an objective indicator of sensory function recovery following cutaneous nerve injury.

Acknowledgements

We wish to thank Mr R. Birch, Professor R. Saunders, Professor M. Hobbs, Mr B. Morgan and Mr N. Waterhouse for permission to include their patients in this study and Mr T. Gajree for his technical assistance. While carrying out this work C.H. was a Sir Jules Thorn Research Fellow. The support of the Sir Jules Thorn Charitable Trust is gratefully acknowledged.

References


Aguilar CE, Bisby MA, Cooper E, Diamond J. Evidence that axoplasmic transport of trophic factors is involved in the regulation of peripheral nerve fields in salamanders. J Physiol (Lond) 1973; 234: 449–64.


Brenowitz GL, Devor M. Reinnervation of rat glabrous hindpaw skin by collateral sprouts following denervation by sciatic nerve section [abstract]. Anat Rec 1981; 199: 37A.


Diamond J, Jackson PC. Do cutaneous nerves sprout in the mammal? J Physiol (Lond) 1978; 280: 52P–53P.


Dostrovsky JD, Millar J, Wall PD. The immediate shift of afferent...
Collateral sprouting of cutaneous nerves


Merzenich MM, Kaas JH, Wall JT, Sur M, Nelson RJ, Felleman DJ. Progression of change following median nerve section in the


Pollock LJ. Nerve overlap as related to the relatively early return of pain sense following injury to the peripheral nerves. J Comp Neurol 1920; 32: 357-78.


Received July 4, 1996. Accepted August 5, 1996