Implications of the failure of nerve resection and graft to cure chronic pain produced by nerve lesions

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SUMMARY Seven patients had developed pain and abnormal sensitivity in the area supplied by a single nerve which had been injured. They were treated unsuccessfully for periods ranging from 3 to 108 months by conservative methods including neurolysis, local anaesthesia, sympathetic blocks, guanethidine, transcutaneous stimulation and analgesics. All then had the damaged nerve resected and in five cases a sural nerve graft was inserted to bridge the resected gap. The patients were then examined 20 to 72 months after the operation. In all seven cases pain and abnormal sensitivity of some intensity occurred in the same area and with the same qualitative characteristic as experienced before the operation. This operation should not be done in patients with this condition. Reasons are given to suggest that peripheral nerve damage induces changes in the central nervous system which are not reversed by treatment directed at the area of the original injury.

Patients who have suffered injury to a peripheral nerve may on rare occasions develop a highly characteristic syndrome of chronic ongoing pain and abnormal sensitivity in the area supplied by the damaged nerve.1 The symptoms of this disorder include a raised threshold to pressure and temperature stimuli with allodynia, irritation and hyperpathia. Sensations evoked by normally innocuous stimuli are often delayed and overshoot their expected intensity. Spatial or temporal summation, produced by movement or repetition of the stimulus, is particularly effective in evoking the abnormal and unpleasant sensations. Since this condition seems to be clearly related to the presence of a localised area of damage to a peripheral nerve, it is natural to direct therapy to this area.

In the seven patients to be reported, since they had resisted repeated conventional conservative therapy for long periods of time, 3-108 months, it seemed reasonable to advise surgical excision of the damaged area of nerve. In five of the seven, a sural nerve graft was inserted to bridge the gap created by the excision of the damaged nerve. This appeared justified since this operation has a high rate of success in aiding recovery from nerve lesions where pain is not the dominant symptom. With one exception all patients in which resection was carried out, this treatment must be assessed a failure because when examined 20-72 months after the operation, all had some degree of recurrence of the symptoms present before the operation. We propose that resection should not be done to damaged nerves associated with pain and abnormal sensitivity and that the failures have considerable implications as to the nature of the disorder.

Brief description of patients

Patient 1 A 58-year-old housewife injured her wrist in a fall. After 2½ months in a cast, she had pain in the wrist and the superficial radial nerve was explored twice at 5 and 7 months after the injury. Pain became very severe immediately after the second operation and 9 months later the nerve was resected and a sural bridge graft was applied.

Patient 2 A 46-year-old house painter cut through part of his median nerve falling through a window. Severe pain began on the day of the accident and the nerve was explored 5 months later. A sural graft was applied 14 months after the accident.

Patient 3 A 51-year-old housewife cut through part of her median nerve while attempting suicide. This was sutured on the day of injury. Five months later she experienced a sudden onset of severe pain after heavy...
work and the nerve was explored after 1 month and the pain subsided. Ten months after the original injury, severe pain recurred again and a graft was inserted 27 months after the injury.

Patient 4 A student radiographer had suffered a blunt injury to the plantar nerve when hit by a motorcar at the age of 16 years. Within two weeks pain and tenderness prevented walking. Her nerve was explored after two years with no effect and after four years a sural graft was applied.

Patient 5 A 45-year-old housewife noticed a tender swelling on her forearm. This was explored and proved to be a tumour of the median nerve, later diagnosed as a neurilemmoma. Immediately after this exposure of the nerve, she experienced severe pain. Three months later the tumour was excised and the gap was bridged with a sural graft.

Patient 6 A theatre nurse aged 23 yr had a contaminated blunt injury around her superficial peroneal nerve with infection and with pain developing in the area supplied by the nerve. After 5 years the nerve was explored and infection was removed but the pain was unaffected. Nine years after the injury, the nerve was resected back into apparently normal tissue, cut and ligated.

Patient 7 When aged 23 yr, a housewife had a plastic repair of a torn ankle ligament. After the operation she experienced pain and tenderness in the ankle which was re-explored. After some months she began to develop extreme sensitivity in the area of the saphenous nerve, apparently injured at the donor site from which the ligament was taken. Sixteen months after the first operation, the saphenous nerve was exposed and a neuroma was excised with 1 cm of proximal nerve.

The cause of the patients pain
All seven patients had sustained injury to a single nerve: three to the median nerve and one each to the superficial radial, the plantar, the superficial peroneal and the saphenous nerves. Five were blunt injuries and two were sharp cuts of part of the nerve. In three cases pain followed within a day of the injury and the others took weeks or months before pain was fully developed. In two cases the pain followed immediately after surgical exploration of a previously damaged nerve.

Treatment of pain before graft or resection of the damaged nerve
In all seven cases, the nerve had been explored and a partial or complete exposure had freed the nerve of connective tissue. This operation failed to help and in two clearly made the situation worse. The following treatments were tried wherever applicable: (1) transcutaneous stimulation, (2) local anaesthetic blocks of the nerve, (3) local anaesthetic blocks of the sympathetic supply, (4) guanethidine blocks of the sympathetic system. Each treatment produced only a brief temporary amelioration of some of the problems even with repeated applications. In every case physiotherapy, counselling, encouragement and analgesics were unable to control the patients distress. These treatments were continued and the patients condition had developed to a steady plateau before surgery was carried out 9-108 months after the injury.

The nature of the patients
In no case were these patients involved in litigation or insurance claims related to their injury or treatment. All were making efforts to cope with their disability. Four would have been called solid and admirable citizens by the most puritanical of judges. Of the remaining three, one was a rather jolly alcoholic and two had attempted suicide for reasons unrelated to their nerve injury. No signs of secondary gain from the persistence of their pain was apparent.

The operations
The nerves were exposed and the abnormal portion resected. After stripping back the epineurium funicular grafting by means of cable grafts from sural nerve was done, using 10/0 sutures and with the aid of the operating microscope. The largest defect to be bridged was 7 cm (patient 2), the smallest 3 cm (patient 3). In the other two cases the nerve was ligated and cut proximal to the lesion.

Table

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Severity of pain

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<th>Hyperpathia</th>
<th>Localisation errors</th>
<th>Hot, abnormality</th>
<th>Cold, abnormality</th>
<th>Von Frey decrease</th>
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The signs and symptoms before and after operation (table)

All patients had been carefully and repeatedly examined before operation and a full examination was again carried out 19-72 months after the operation. The tests were done in short periods so that the patient could maintain full attention and co-operation and the test periods were spread over 1-2 days. It is not our intention here to discuss the short term aftermath of the operation since this can be extremely misleading. During this early period, a partial nerve lesion had been converted to a completely anaesthetic area, in one sense the patient may appear improved. Here we wish to report the patients' state when they had again reached a new plateau and in the graft cases when the nerve had been given the opportunity to regenerate through the graft to the periphery. In all five graft cases motor function and sensitivity returned to stable levels, suggesting that regeneration across the gap created by the surgeon had taken place, though regeneration in patient 4 was very incomplete.

1 Pain Four patients were in the same or worse pain after the operation and three were still in pain but improved in some sense. Patient 1 had the area of ongoing pain and tenderness reduced to a small area of $2 \times 2$ cm from the previous involvement of the entire superficial radial area. Patient 2 was worse with continuous burning in finger 1 and 2. Patient 3 was unchanged with steady burning and tenderness in thumb, index and palm. Patient 4 had before the operation moderate stabs and burning and tenderness on the sole of the foot. After the operation the intensity was the same or worse but the tenderness was in a smaller area and walking was slightly improved. Patient 5 had had burning and tenderness in the whole median area which was reduced after the operation to unpleasant paraesthesias and tenderness on fingers 2 and 3. On the resected patients, patient 6 had the same intensity of ongoing pain and tenderness but in a reduced area. Patient 7 had a 50% improvement of her burning and tenderness which had previously extended over the entire saphenous area but now occurred in the proximal one third of the area. It is apparent that while the area of disorder was reduced in five of seven cases, the severity of the disorder was still sufficient to make the arm or leg badly handicapped. Even in the three cases who declared themselves improved, the advance was not sufficient to justify the operation, with the possible exception of patient 1 who was pleased with the result. 

2 Allodynia This is the production of an unpleasant sensation by a stimulus which is felt as innocuous when applied to normal skin. This was present before and after operation in all seven cases when cotton wool was moved lightly over the affected area.

3 Irradiation All seven patients reported before the operation that a light stimulus applied to one point provoked a shooting sensation which spread away from the actual stimulus point. After the operation all but one of the cases still reported this phenomenon.

4 Hyperpathia This refers to the temporal sequence of the response. There is a delay. A single stimulus may evoke no reaction but if it is repeated or slowly moved it produces a steadily mounting sensation which rises to unbearable levels and takes some time to wear off. All seven patients showed this response before the operation and only patient 1 improved in this respect afterwards.

5 Localisation One of us has developed a localisation test.1 1 The patient wears red goggles, standard points are marked in red ink which the patient is unable to see. When stimulating the goggles are temporarily closed with a flap. The response is marked under visual control by the patient with a black felt pen. Pairs of red and black dots now show the actual and sensed location of the stimulus. Four of the postoperative patients were making very large errors of localisation in the affected area while three were not. It is of interest that the three capable of fairly accurate localisation were the three who reported some improvement of their pain state.

6 Response to a hot stimulus In this simple test, a 2 cm diameter test tube filled with water, which feels tolerably hot on the examiner's palm is rested gently on the affected area and the patient is asked to report what he feels. The answers are most instructive in telling one about the state of the patients ability to analyse stimuli. Patient 1 before operation first reported the tube as warm but then after a few seconds delay cried out and withdrew the hand: "overshoot". After the operation which produced some pain relief the tube evoked only paraesthesias and some feeling of warmth. Patient 2 who was not helped by the operation had pre-operative delay and painful overshoot and post-operatively had only delayed prolonged paraesthesias. Patients 3 and 4 lost the unpleasant overshoot. Patients 5, 6 and 7 were unchanged with delay and overshoot both before and after operation.

7 Response to a cold stimulus Here a 2 cm test tube containing crushed ice is gently rested on the affected area. This test too produces a series of abnormal reports depending on the severity of the disorder. At first contact the patient may be unable to state if the tube is hot or cold. Then after a delay they may report paraesthesias followed by a welling up of a feeling of cold which overshoots to severe pain. Patient 1 showed only an inability to detect cold preoperatively and some paraesthesias after the graft. Patient 2 had delay, radiation and overshoot before and after. Patient 3 preoperatively correctly identified the temperature but the effect was eventually painful while postoperatively it was felt as intensely cold. Patient 4 retained a simple inability to feel cold. Patient 5 preoperatively made mistaken hot or cold identifications before but was correct after operation. Patient 6 felt the tube as icy cold and unpleasant before but only as paraesthesias afterwards. Patient 7 changed from reporting a delayed painful overshoot to feeling paraesthesias. It is of interest that this test evidently produces fewer explosive reactions than a hot tube and is sensitive to small post-operative changes.
since six of the seven patients showed weaker abnormalities postoperatively.

(8) Von Frey hair stimulation The abnormal area of skin was compared with the normal zone on the other side with a graded series of nylon bristles (Semmes-Weinstein series). The threshold was tested by moving up in strength from subliminal touches to just sensed stimuli and then tested again by moving down from easily detected stimuli until the patient failed to respond. In the six patients tested both before and after operation all had a raised threshold before operation and afterwards three were the same, two were worse, and one was improved. As part of the syndrome with allodynia, irradiation and hyperpathia with its features of delay, summation and overshoot, it is not surprising that repeated testing of the same point produces a lowering of threshold with the onset of unpleasant paraesthesias, or with frank pain if intermittent repeated stimuli are delivered.

(9) Direction of movement We had found on examining patients with sensory deficits as a result of dorsal spinal cord lesions that they were unable to detect a surprisingly simple aspect of cutaneous stimulation. A finger is rested on the skin and gently moved toward or away from the patient or left or right and the patient is asked to declare the direction. Of five patients tested in this way postoperatively, three could succeed in this measure and two failed. The one patient tested both before and after operation, patient 3, was unable to sense direction before but could do so after the operation.

(10) The painfree period This averaged 6 months (3, 7, 6, 5 months) in the grafted patients with the exception of patient 1 who developed a small hyperesthetic area over the scar after 1 month. They were not all seen immediately when the pain recurred, but when examined the hyperpathic response could be obtained in the regenerated area in all. Of interest is the fact that they all volunteered that when the pain recurred accidental contact in the area supplied by the grafted nerve was very unpleasant.

(11) The area denervated by removal of the sural nerve The five grafted patients had all received an iatrogenic complete nerve lesion of their sural nerve. Examination showed that three still had an area on the lateral foot of raised threshold to touch stimuli but in no case were there any abnormal sensations or complaints of pain.

Discussion

We report here seven patients who had all suffered partial injury to a single nerve and who all showed a consistent pattern of complaint: ongoing pain and extreme sensitivity in the distribution of the damaged nerve. On examination all showed a raised threshold on von Frey hair testing, allodynia, irradiation and hyperpathia with abnormal reactions to hot and cold stimuli. An attempt was made to cure their pain by nerve resection in all seven cases and by sural grafting to reconnect the nerve in five cases. The long term results were poor. In only one patient (patient 1) the result can be described as a qualified success, but this was a relatively minor cutaneous nerve. In the other grafted cases, all major nerves, the results were so abysmal that the operation should not have been done. There is no doubt that the sural grafts were successful in the sense that nerve regeneration has occurred across the graft and sensitivity was re-established in the cut nerve's distribution. One must stress that conclusions can only be based on long term follow up, here over 19 months. In the period after the operation during which regeneration is in progress, the formerly sensitive skin is anaesthetic and the patient may report this as relief even if the ongoing pain continues. Not only can we not recommend this operation but we must also point out that the onset of the severe pain in two of the patients had immediately followed the simple surgical exploration of a previously damaged nerve. The limited and marginal improvements can be largely attributed to the decreased area of sensitivity which were reported by five of the seven. However, in the remaining sensitive area, the nature of complaint and the abnormal findings on sensory examination duplicated those experienced before operation. Allodynia continued in all seven with irradiation in all but one. The hyperpathic response remained in six patients. The abnormal responses to a hot stimulus were unchanged in three cases, decreased in three and improved in one. This powerful tendency for recurrence of severe disorder after resection and graft has implications for the nature of the disease which we will now discuss.

The syndrome of ongoing pain with tenderness after nerve injury has been well known since Mitchell. However, all agree that it is a rare phenomenon so that the frequency of causalgia which is the extreme type of the syndrome discussed here ranges from 2-5% in military casualties with peripheral nerve lesions. There have been many hypothetical explanations for the rarity of occurrence, variously attributed to (1) the peculiarity of the injury, (2) the peculiarity of the nerve or, (3) the peculiarity of the patient. Our results bear on these hypotheses. It will be realised that these patients suffered two sequential lesions of the same nerve, the first was the original damage and might be claimed to contain some special element which left the nerve in a pain generating state. However, it must be emphasised that the nature of the first injury varied very widely in these patients. The second injury was carried out by the surgeon 3-108 months after the first and was of a different type: the nerve was dissected free well proximal to the
original lesions and cleanly cut across. This type of lesion is normally produced in nerve repair and does not give rise to this complication. Therefore it is likely that there was something special about the first injury and that the maintenance of the chronic state has a different and distant mechanism, no longer related to the site of injury. We will return to this possibility. It might more reasonably be proposed that these particular patients have some general disorder which causes them to react badly to nerve damage. Inbal et al. have shown that the Wistar type of rat develops a vigorous ongoing discharge in sectioned nerves. These animals also show a marked tendency to attack the areas made anaesthetic by the nerve lesion. However, the closely related Lewis strain of rat develops neither a discharge from the cut ends of nerves nor does it show abnormal behaviour. In five of our seven patients, one could consider the section of the sural nerve which was necessary to obtain tissue for the graft as being a control lesion to test the patients reaction to nerve lesions. In no case did the patients show unusual responses to the sural nerve lesion in spite of the fact that this nerve can on occasions be the source of the pain-tenderness syndrome following nerve injury.

In a more subtle fashion, these patients had also received a second type of control nerve injury. In each case, the original injury had produced a partial nerve lesion. The surgical cut produced a complete transection of the entire nerve thus involving both fibres involved in the original injury and their neighbours which had escaped. When regeneration proceeded, they duplicated their original disorder only in the original region while the surgery had produced anaesthesia followed by recovery by regeneration in a wider area. Thus the nerve fibres damaged for the first time by the surgical operation did not produce the pain-sensitivity syndrome while those fibres involved in both the first injury and in the surgery continued to evoke abnormal sensations.

It is apparent that these patients did not have a generalised tendency to produce the condition from all their nerves. There is an unwarranted custom of some doctors to dismiss as psychiatric problems those patients who have the misfortune to fail to respond to conventional treatment. This is particularly likely in patients with a well localised and apparently “simple” origin of their distress. We do not accept this easy way out as an explanation of the pain of our patients particularly of the four who were continuing active work and successful private lives, avoiding their tender areas and coping with their pains. Furthermore these patients unlike psychiatric patients did respond to therapies such as local nerve block, transcutaneous stimulation and sympathetic blocks but for periods too brief for useful therapy. Evidently some aspect of the damaged nerve or its central connections was in a highly abnormal and stable state.

The source of the patient’s pain and disordered sensitivity is normally assumed to be in the area of damage. This natural conclusion is supported by animal experiments as well as by the obvious presence of localised injury and localised signs and symptoms in the patient. If a rat sciatic nerve is damaged, there is an immediate short lived injury discharge followed by the slow development of the following properties: (1) ongoing discharge from the cut end, (2) the development of mechanical sensitivity, (3) the development of extreme sensitivity to nor-adrenaline. These three new properties increase over the first two weeks and then die down to a steady level by about one month. After one month there is the appearance in a small minority of fibres of epaphic transmission of impulses between fibres. If a similar combination of changes occurs in man, they do not explain why the pain after nerve injury is such a rare phenomenon. Therefore additional factors must be involved for an adequate explanation of the patients condition. There is no doubt that impulses from the periphery play a role for several reasons. The patients discomfort is temporarily allievated by peripheral local anaesthesia and made worse by peripheral stimulation. Furthermore in the grafted cases recurrence of pain seems to take place synchronously with the reappearance of peripheral sensitivity. However, these peripheral mechanisms do not explain two crucial aspects of the disorder. Why is it that the ongoing pain often recurs in the original area after complete transection of the nerve which denervates a larger area than the disordered one and why is it that the pain and abnormal sensitivity is so accurately duplicated after regeneration?

An alternative explanation is that whatever the mechanism of the primary injury is that gives rise to an abnormal or disbalanced input, the disorder is gradually transferred from the site of injury to more central structures. Rapid switches of receptive field following afferent lesions have been observed in single cells in dorsal column nuclei, in ventral posterior lateral nucleus of thalamus, and in somatosensory cortex. No such changes have been seen yet in spinal cord but here there are a series of chronic changes which could be highly relevant to the maintenance of abnormal response. Within one week of rat sciatic section, there are the following changes in the spinal cord: (1) a disappearance of substance P, somatostatin and cholecystokinin and acid phosphatase from the central terminals of the
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cut unmyelinated afferents,14 (2) morphological changes in the terminals of C fibres,15 (3) the disappearance of dorsal root potentials evoked by the cut nerve,16 (4) the disappearance of central inhibitions normally evoked by the cut nerve,17 (5) the appearance of novel receptive fields in the cells which have lost their normal afferent input.13 At a later stage there is a degeneration of some of the dorsal root ganglion cells whose axons are cut peripherally.17 We thus have widespread evidence from animals that peripheral nerve damage induces both rapid and chronic changes in the reaction of cells in the central nervous system. It is therefore not unreasonable to suggest that these patients had transferred the source of their abnormal processing of nerve impulses from the periphery to the centre. The failure of the operations could then be explained as being due to an attack on structures no longer responsible for the disorder.

References

7 Wall PD, Gutnick M. Ongoing activity in peripheral nerves: the physiology and pharmacology of impulses originating from a neuroma. Exp Neurol 1974;43:580-93.