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The effects of extreme cold on sensory nerves

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Summary

The effects of extreme cold on sensory nerves are discussed and a clinical application of these effects is proposed. The structural changes observed following the freezing of sensory nerves in the rat are described and correlated with the clinical results in patients with chronic facial pain treated by cryogenic peripheral nerve blockade. It is suggested that this technique offers features which are not shown by any other method for interrupting peripheral pain pathways and provides a useful alternative to existing methods of treatment for chronic pain.

Introduction

The observations of John Hunter in 1777 on the local tissue response to freezing — that tissue necrosis occurs, that there is vascular stasis, and that subsequent healing is excellent —are consistent with those of modern cryobiologists. Some 80 years later Dr James Arnott *(1)* proposed a clinical application of local freezing to destroy tumour cells, but the therapeutic application of extreme cold to biological systems has developed only over the past 20 years with the refinement of modern cryosurgical apparatus for the controlled application of extreme low temperature, based on concepts proposed by Cooper and Amoils in the 1960s *(2,3)*. The localised effect on the tissues has been termed a cryolesion and the clinical application of this technique cryosurgery, which has become established in many surgical specialties. By the formation of intracellular and extracellular ice, with the consequent disruption of tissue-fluid compartments, cell membranes, and enzyme systems and later ischaemic changes and stimulation of an immunological response, cells are destroyed.

In his experimental freezing of cocks' combs Hunter observed the analgesic effect of cold, and in modern cryosurgical practice one of the characteristic features is that postoperative pain is minimal. This is thought to be due to a combination of the modified inflammatory response which follows freezing and the local destruction of peripheral nerve endings.

It is my belief that cryosurgery has a place in the management of selected patients with facial neuralgia, and in this lecture I hope to present evidence to support this assertion obtained through histological studies in experimental animals and by the analysis of clinical results in man.

The analgesic effect of cryosurgery has been used palliatively in the management of inoperable cancers by surface freezing of the tumour, particularly those occurring on mucosal surfaces *(4,5)*. Where peripheral nerve trunks have been incidentally incorporated in the cryolesion there follows a reversible functional loss. Previous studies in animals have demonstrated that complete functional loss follows the freezing of peripheral nerves with a cryoprobe but that good recovery can be expected over a few weeks. Beazley *(6)* and Carter *et al. (7)* showed that this functional loss was associated with a second-degree type of nerve injury according to Sunderland's classification—that is, there is Wallerian degeneration with axonal disintegration and break-up of myelin sheaths but with minimal disruption of the endoneurium and other connective-tissue elements. It is important to distinguish the extended functional loss associated with peripheral degeneration following the application of extreme cold from the transient functional block associated with merely cooling the nerve. One of the characteristic

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features of the tissue response to extreme cold is the minimal degree of inflammation and subsequent fibrosis which occurs. It seems likely that this is an important factor in the early recovery of function of sensory nerves subjected to a cryolesion, axonal regeneration being facilitated by the preservation of neural connective-tissue sheaths following controlled freezing. These experimental and clinical findings suggested that the application of a cryoprobe to a peripheral nerve could be used to produce an extended, but reversible, nerve block.

Chronic pain

I would now like to consider the problem of chronic pain. In his classic book *The Management of Pain* Bonica said, 'Chronic pain is no longer a physiological sensation, which has a protective function, but a pathologic destructive phenomenon which has reached the doubtful dignity of a true disease' *(8)*. For patients with chronic pain symptomatic relief becomes the primary objective in order to allow them to return to a normal place in society. With the recognition of chronic pain as a specific disease entity and the international proliferation of pain relief units attention has focused on minimally invasive techniques to interrupt or modify pain pathways which do not impair the function of the whole organism. Recently these have included transcutaneous nerve stimulation and biofeedback techniques. Current research into pain and its pathogenesis and the recognition of endogenous pain-relieving mechanisms are beginning to provide a more scientific rationale for treatment. But at present, with frequent uncertainty of the efficacy of a particular therapeutic method, there is a great need for techniques of pain relief which do not aggravate the symptoms or produce irrevocable or undesirable sequelae for the patient.

Interruption of peripheral pain pathways has become well established as a method for the relief of chronic pain over the years. Injection of local anaesthetic solutions will produce a functional block of limited duration, but for more prolonged effect neurolytics such as alcohol or phenol have been used. These agents are often painful to inject, and when used peripherally the results are often disappointing owing to neuritis of the partly destroyed nerve with consequent aggravation of symptoms. Subsequent fibrosis may be responsible for secondary neuralgia and makes repeated treatment more difficult. Surgical section or thermal coagulation produces irrevocable changes in the nerve, and neuroma formation and fibrosis may intensify symptoms. It is thus apparent that the conventional methods for interrupting peripheral pathways have severe disadvantages in the management of chronic pain. Although the methods of short duration have minimal side effects, long-acting blocks or section often precipitate undue complications. As I said earlier, clinical and experimental studies have shown that although loss of function follows the severe freezing of a nerve, with associated peripheral degeneration, there is early functional and structural recovery. It appeared, therefore, that cryogenic peripheral nerve blockade might have application in the symptomatic relief of intractable pain *(9)*.

Material and method

In considering the therapeutic application of cryogenic blockade it was necessary to evaluate the predictability and degree of degeneration following freezing and the quality of regeneration and to investigate whether the biological sequelae to freezing could be correlated with pain relief, assessed subjectively by the patient, during cryosurgery and after recovery from the cryolesion.

ANIMAL STUDIES

Young adult rats were chosen as the experimental model in which the infraorbital nerve was subjected to a cryolesion of around $-40°C$ and the sequelae were evaluated histologically by light microscopy. It was hoped that the structural changes in the rat would provide the rationale for the functional changes following the clinical application of cryogenic blockade in man and the subsequent effect upon the symptoms of pain. The cryosurgical unit used was a Spembly BMS 40 operating on the Amoils principle at a pressure of 42 kg/cm^2 (600 lb/in^2) with nitrous oxide gas as the refrigerant. The probe tip measured approximately 2 mm in diameter and the temperature was monitored with a bimetal thermocouple in the bevelled surface of a fine needle probe. The infraorbital nerves were ex-

posed through bilateral infraorbital incisions and the cryoprobe was applied to the dorsal surface of the right infraorbital nerve as close to the bone as possible. Two freeze–thaw cycles of 1 min were applied, being timed from the establishment of equilibrium in the iceball as assessed by the recording of a steady low temperature. During the thaw the temperature rose to above 0°C.

The contralateral nerve was either exposed with no further insult to serve as a control, crushed with a haemostat, or sectioned with a scalpel. The crush injury was chosen as this has been used experimentally to produce a second-degree nerve injury and would provide useful comparison with the frozen nerve. The animals were killed at intervals of up to 3 months and the extracranial part of the nerve was exposed and fixed in formol saline and then removed from the head and stained with osmium tetroxide. Transverse sections were cut above and below the site of injury.

CLINICAL STUDIES

Cryogenic peripheral nerve blockade was used in the management of 40 patients presenting to the Regional Pain Relief Unit or Department of Oral Surgery in Oxford over a 3-year period with chronic facial pain. Twenty-seven patients with pain of non-herpetic origin showed a much better response to treatment than 13 with post-herpetic neuralgia, and therefore the two diagnostic categories will be generally considered separately. In the non-herpetic group the patients had suffered pain for a mean period of 5 (1.5–12) years and in the herpetic group for a mean period of 6 (0.25–16) years. It must be stressed that all these patients had failed to respond to previous treatment for their pain which included the use of drugs, though heavy analgesics were rarely used because, although effective, they are generally unacceptable to the ambulant patient.

The attempt to get away from drug therapy is reflected by the many peripheral procedures used to interrupt pain pathways or modify pain conduction and appreciation by such methods as transcutaneous nerve stimulation or acupuncture. It is also important to realise that the patients treated by cryogenic blockade represent only 20% of the total number of patients presenting with chronic facial pain, and other methods of treatment are often employed, particularly medical management or the application of local measures such as topical anaesthesia or transcutaneous nerve stimulation. Where the pain or the trigger area appeared to be localised to a definable nerve distribution a preliminary diagnostic injection of lignocaine or bupivacaine was given so that the pain relief produced by the nerve block could be assessed by the patient and the operator. Careful note was made of the duration of relief obtained and this was correlated with the expected duration of effect of the blocking agent. It is also important to allow the patient to be able to experience sensory loss as it is well recognised that some patients complain more of facial anaesthesia than of the original pain. If the results of the block were satisfactory the relevant nerve was exposed by dissection, normally under local analgesia. The nerve was carefully mobilised from the surrounding tissues to reduce the heat sink and thereby produce the maximum effect from the cryolesion before being frozen with two 1-min freeze–thaw cycles with a fine nitrous-oxide cryoprobe.

Each freeze was timed from the establishment of thermal equilibrium in the iceball by the recording of a steady low temperature by a thermocouple in the probe tip, in the order of –60°C. The wound was then sutured and there were no problems of wound breakdown or bone sequestration following treatment. Figure 1 shows a supraorbital nerve exposed, with the cryoprobe applied. Of the 40 patients treated, 13 had 1 or 2 repeated treatments of

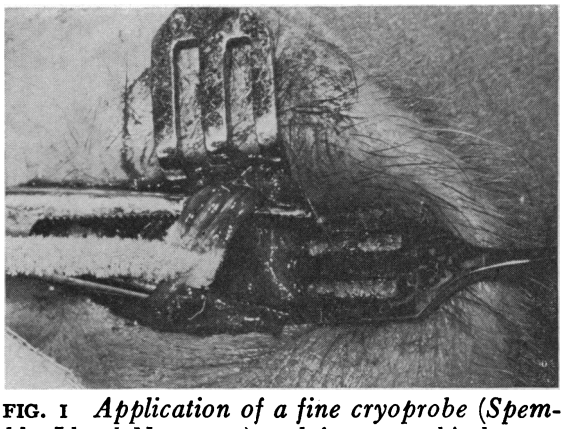


FIG. 1 *Application of a fine cryoprobe (Spembly Lloyd Neurostat) to left supraorbital nerve exposed under local analgesia.*

49 nerves, making a total of 66 patient-treatments. The results of 42 patient-treatments were finally reviewed, 24 being eliminated: 9 in which the patient failed to attend for long-term follow-up; 1 in which the patient died from carcinomatosis; 4 in which it was apparent that the wrong nerve had been blocked (this occurred owing to initial failure to appreciate the very localised action of the cryoprobe compared with the wider effect of local anaesthetic solutions, which diffuse to affect adjacent nerve trunks); and 10 in which treatment had been carried out less than 6 months before the review for this lecture. Pain relief was recorded as the period in days during which the patient stated that he was free of pain or felt that he was greatly improved. For example, converting a severe shooting pain to a background discomfort was accepted as having provided relief. Owing to the subjective nature of pain the only meaningful assessment relies on a verbal response from the patient. Sensory function was assessed by the ability of the patient to feel light touch with a cotton-wool wisp and a sharp pin-prick.

Results

ANIMAL STUDIES

The gross appearance 6 weeks after freezing was similar to that of the control and was in sharp contrast to the disordered morphology 6 weeks after section (Fig. 2).

Proximal sections from damaged nerves showed no differences from the controls. The distal controls clearly demonstrated the myelin sheaths (Fig. 3). At 7 days after freezing the myelin sheaths were whorled and filled in, indicating complete degeneration across the nerve bundle (Fig. 4). At 14 days degenerating myelin was still visible, but small-diameter regenerating nerves were evident (Fig. 5). By 42 days the myelin sheaths were again clearly defined, with an appearance similar to that of the control (Fig. 6). By comparison, 7 days after crush injury gross disruption was evident, but apparently normal sheaths were also present, suggesting that degeneration was subtotal across the nerve (Fig. 7). At 42 days after crush injury normal morphology appeared to be restored.

These qualitative observations of degeneration and structural recovery were confirmed by a quantitative analysis based on counts of normal myelin sheaths. Counts were made of proximal and distal sections from the nerves of rats killed at various intervals. Figure 8 shows an index of sheath counts plotted against the number of days after injury. The proximal values in all nerves were unchanged, but the distal values of both frozen and crushed nerves were markedly depressed at 7 days, to zero in the case of the frozen nerve. A return to the mean index for distal sections of control nerves, which was 3, occurred over 6 weeks.

CLINICAL STUDIES

In the total of 42 patient-treatments the median period of pain relief was 60 (0–815) days. This wide range reflects the complexity of chronic pain, both in its aetiology and in the patient response to treatment. The sensory loss was not assessed in patients with post-herpetic neuralgia as there was often residual sensory deficit from the acute infection which confused the assessment of changes due to the block.

In the 28 patients with pain of non-herpetic origin the median period of pain relief was 175

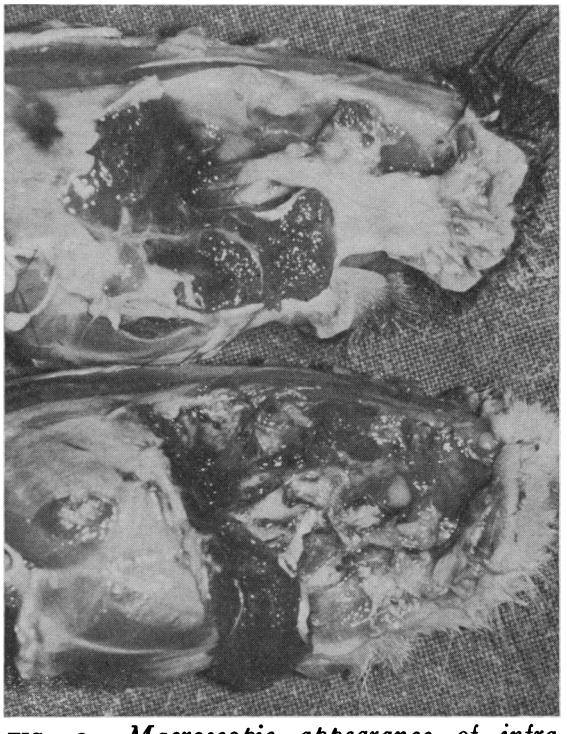
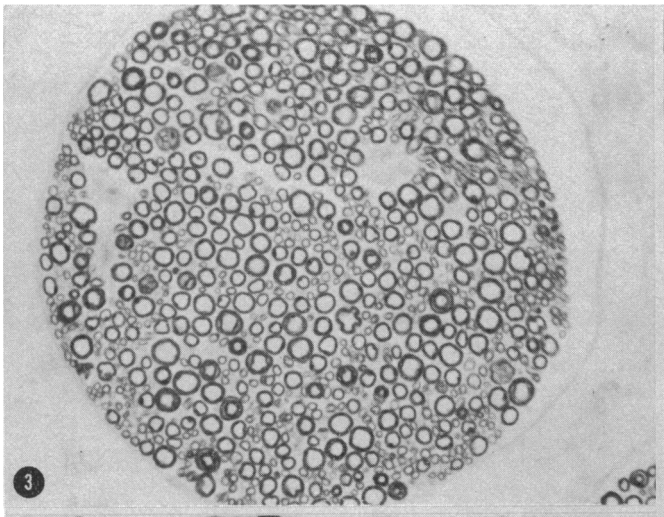
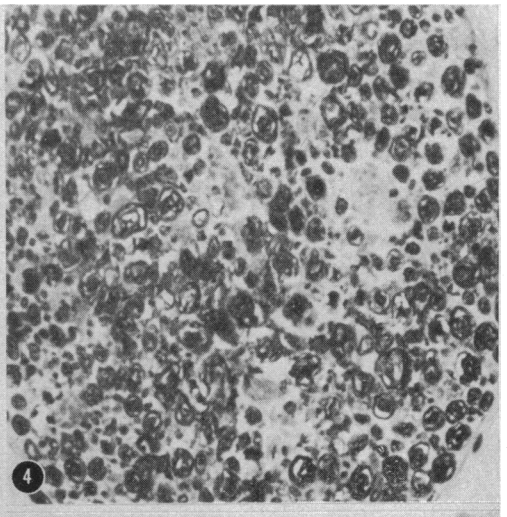
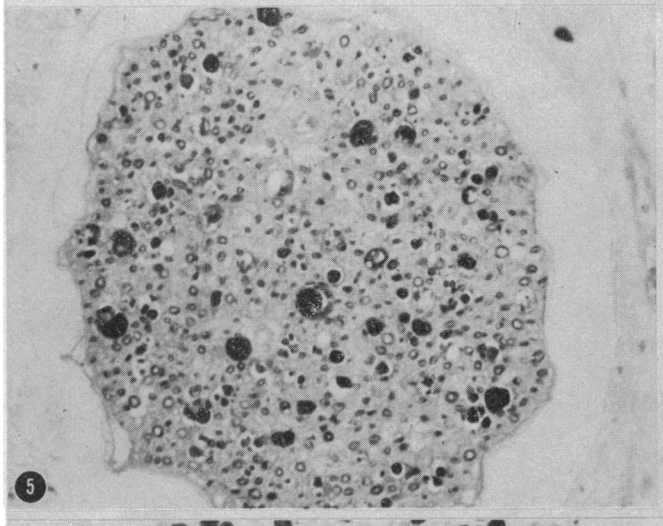
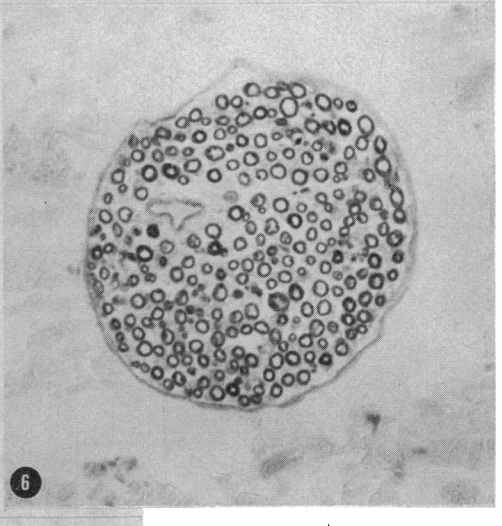


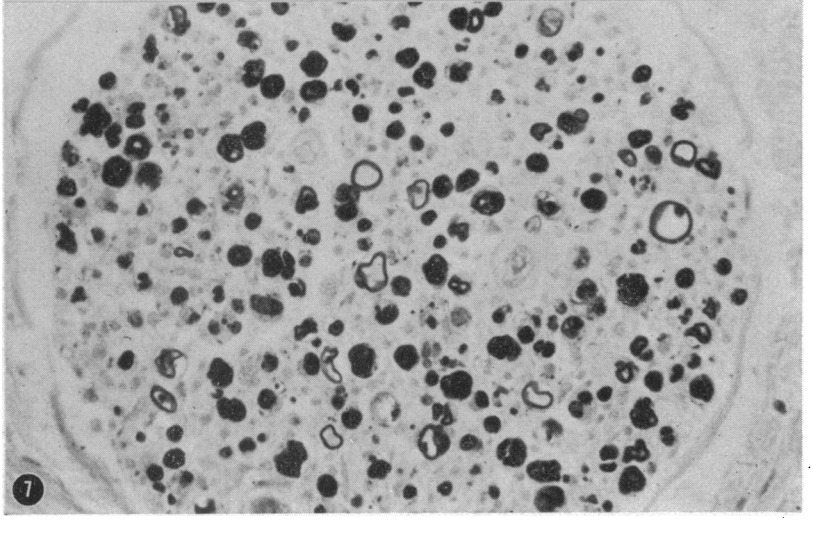
FIG. 2 *Macroscopic appearance of infra-orbital nerves 42 days after cryosurgery (above) and nerve section (below).*











Infraorbital nerve, rat. Transverse section from distal part of nerve. Osmium tetroxide × 200.

FIG. 3 *Control.*

FIG. 4 *7 days after freezing.*

FIG. 5 *14 days after freezing.*

FIG. 6 *42 days after freezing.*

FIG. 7 *7 days after crush injury.*

(0–815) days, but the median period of sensory loss was only 60 (0–117) days. In the post-herpetic group (14 patients) the median duration of pain relief was 42 (0–119) days. It is interesting to consider the results in the non-herpetic group by diagnostic category. In 8 patients with tic douloureux the median duration of pain relief was 235 (62–815) days, and in 11 patients with post-surgical neuralgia it was 273 (35–808) days. In both these groups sensory function returned in approximately 2 months. One patient with post-traumatic neuralgia subsequent to a fractured frontal bone who was included in the series had no relief, and sensory loss could not be accurately assessed owing to the residual paraesthesiae from the original injury. As might be expected, 8 patients with atypical facial neuralgia had a poor result generally, with a median duration of pain relief of 10 (0–623) days, though with the unpredictable response in this condition—probably related to the variable and ill-understood aetiology—1 patient had good relief for almost 2 years. The quality of pain relief for the periods already indicated was assessed as follows: in the non-herpetic group 11% had no improvement, 29% had marked improvement, and 60% were free of pain; in contrast, in the post-herpetic group 21% had no improvement, 64% had marked improvement, and 15% were pain-free. Summarising the results: in the non-herpetic group 71% had relief for longer than 6 weeks and 50% for longer than 6 months, the longest period of pain relief being 2 years 2 months; in the post-herpetic group 63% had relief for longer than 6 weeks and only 1 patient (7%) for just over 6 months.

Case reports

1) A 67-year-old pensioner had suffered from tic douloureux for 15 years. He had a trigger over the right cheek and the pain had been only intermittently controlled with carbamazepine as unpleasant side effects had limited the dose which could be tolerated. A diagnostic right infraorbital lignocaine block abolished the trigger and the nerve was frozen. He had normal sensory return at 3 months but has remained pain-free for 2 years and 3 months.

2) A 70-year-old widow had a 3-year history of tic douloureux with a lingual trigger which made her terrified of eating and speaking. Her pain had been poorly controlled by carbamazepine. Cryogenic blockade of the right lingual nerve gave her 9 months complete relief of pain. When this returned she sought a repeat treatment, which gave her relief for a further 9 months. After each treatment normal sensation returned over 3 months. This treatment has now been repeated for the third time at the patient's request.

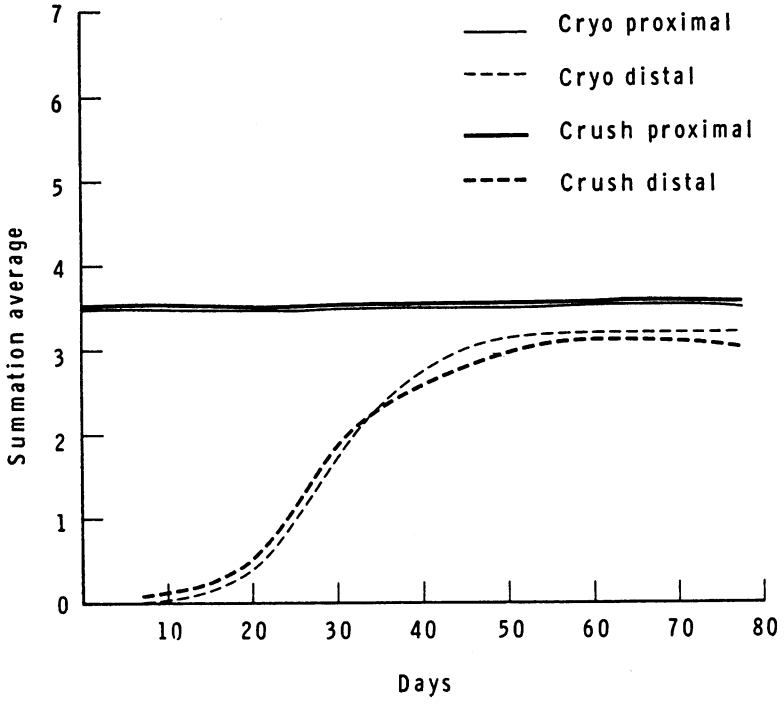


FIG. 8 *Vertical axis represents a quantitative index of normal myelin sheaths plotted against the number of days from injury. The mean control value for distal sections was 3.0.*

3) A 76-year-old voluntary hospital worker had shooting pains over the right side of the head following a muscle graft at mastoid surgery 2 years previously. Examination revealed an exquisitely tender focus over the right auriculotemporal nerve. This was exposed and the nerve was found to be expanded at this point, giving the clinical impression of a neuroma. The expanded part of the nerve was frozen and she has remained pain-free for 11 months.

4) A 71-year-old pensioner had suffered from post-herpetic neuralgia over the distribution of the left supraorbital nerve for 3 years. His pain was considerably reduced by a lignocaine block of this nerve, and it was exposed and frozen. Although there was some altered sensation before treatment, after cryogenic blockade the area of distribution of the left supraorbital nerve was completely anaesthetic, indicating a technically successful block. In spite of this he had pain relief for only a few hours, and when reviewed a week later there were areas of hyperaesthetic skin within the distribution of the apparently anaesthetised nerve, a clinical phenomenon of this condition described by Harris as long ago as 1926. Cutaneous sensation returned to the pre-treatment level in 3 months and his pain is now partly controlled by combined antidepressant–anticonvulsant therapy.

Discussion

Bradley *(10)* found that if the anatomical continuity of a nerve is destroyed, then regeneration is likely to be poor or absent. This observation was supported by the gross examination of the sectioned nerves in this experiment. After freezing, however, the gross normal morphology of the nerve was unaltered. Microscopically it was evident that degeneration proceeded distal to the site of cryoinjury to a peripheral nerve, but there was no apparent change proximal to the site of injury. It was further apparent that this degeneration was consistent and complete across the whole nerve bundle, in contrast to the findings subsequent to a crush injury, in which some fibres were spared. Thus it would appear that cryosurgery provides a method of producing a consistent and complete degeneration but without disruption of anatomical architecture, which can be expected to be associated with a total functional block.

In this experimental series in the rat orderly structural regeneration occurred in about 6 weeks after freezing, but in other situations this period can be expected to be related to the distance of the cryolesion from the periphery of the nerve. The clinical results showed that the application of extreme cold to terminal branches of the trigeminal nerve was followed by an extended but reversible nerve block with recovery of normal sensation in 2–4 months. The experimental findings in rats indicate that this is associated with Wallerian degeneration and regeneration of axons along the intact nerve sheaths. No patients suffered aggravation of their symptoms, which is probably due to the predictable degeneration and the modified tissue response to cryosurgery. In his book *Neuritis and Neuralgia* Harris *(11)* observed that when the inflammatory response and subsequent fibrosis are suppressed the incidence of secondary neuritis and neuralgia is likely to be reduced. Later Sunderland *(12)* demonstrated that when the endoneurium remains intact, as is the case after cryosurgery, neuroma formation does not occur and this may also contribute to the absence of causalgic pain following cryogenic nerve blockade. The relation between the nerve block and subjective experience of pain relief is less predictable. In 64% of patients with pain of non-herpetic origin the period of pain relief exceeded the period of sensory loss. Treatment appeared particularly successful in the patients with tic douloureux and post-surgical neuralgia, in 85% of whom the period of pain relief exceeded that of sensory loss.

The reason for this was not clear, but it may be due to the breakdown of an established pain cycle involving central and peripheral pathways. Ashby *(13)* reported that prolonged pain relief may follow the brief interruption of a pain cycle by a lignocaine block. It may be that the extended blockade produced by cryosurgery is an extension of this phenomenon. Also encouraging was the good response in post-surgical neuralgia when a clinically identified neuroma was frozen. These lesions have a high incidence of recurrence after excision, with a return of pain. The effect of cryosurgery on these lesions needs to be further studied. In the post-herpetic group the response was poor in spite of earlier relief from a local anaesthetic injection. Post-herpetic neuralgia is a distressing condition which has proved to be extremely refractory to the many forms of treatment which have been advocated over the years. Although the results of cryogenic blockade were disappointing in this group, they do support the earlier findings of White *(14)*, who suggested that when pain

relief followed a peripheral nerve block subsequent neurectomy was likely to give prolonged relief in a few patients, even though the site of viral damage was thought to be more proximal on the afferent pathway.

Owing to its multifactorial aetiology no single method of treatment will produce a good result in all patients with chronic pain, but if any method produces good results in a few patients it should be considered. Because of the reversibility of cryogenic blockade, with no long-term undesirable sequelae, the method may be more readily applied even when the outcome is uncertain and therefore it may be used as a diagnostic, prognostic, or therapeutic block.

The clinical results of cryogenic blockade which I have presented suggest that all fibre types are damaged by severe freezing. Earlier experimental studies suggest that a selective destruction of large myelinated fibres, sparing small unmyelinated fibres, would follow mild freezing. This is undesirable and, considering the gate control theory of Melzack and Wall *(15)*, might be expected to intensify pain by reducing large-fibre activity and opening the gate. Therefore cryogenic blockade must utilise extreme low temperature adequate to produce pan-necrosis and include small pain fibres.

Conclusion

It would appear that cryogenic peripheral nerve blockade offers features which are not shared by any other method in that a complete nerve block is produced which recovers within 2–3 months and which does not aggravate symptoms or precipitate other unpleasant side effects. This has particular application in the management of chronic facial pain and may result in relief of pain for a long period. When pain relief is undramatic the reversibility of the technique is an advantage. The technique is being applied to other areas of chronic pain with encouraging results *(16)*.

This technique does not, of course, offer a panacea in the management of intractable pain, but for many of these patients there is at present no single satisfactory method of treatment and the technique has provided a useful alternative to existing methods of therapy.

With John Hunter's constant search for ways to reduce his patients' suffering it is fitting that his early observations on the biological effects of cold are still being developed, with the aid of modern technology, in an attempt to help the surgeon in his task of relieving pain.

My thanks are due to Professor David Poswillo for his encouragement to me to begin this project and his support and guidance throughout. I am grateful to Dr John Lloyd for allowing me access to the Oxford Regional Pain Relief Unit, to Mr Peter Barton and Dr John Rayne for their helpful criticism in the preparation of this lecture, and to Spembly Ltd for technical assistance.

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