A 22-year study of paroxysmal trigeminal neuralgia in 211 patients with a 3-year appraisal of the role of cryotherapy

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The scope of this investigation included a comparative study of 211 patients with paroxysmal trigeminal neuralgia (PTN) seen over 22 years (from 1959 to 1981) and the use of an open-nerve freezing technique (cryotherapy) on peripheral branches of the trigeminal nerve in 42 of these patients over 3 years (from 1978 to 1981). The study was divided into three parts. Part I was an analysis of clinical findings in all patients. Part II dealt with 33 medically uncontrolled patients and was an assessment of cryotherapy under the most adverse conditions. Part III consisted of an unselected group of 16 patients whose pain could be controlled by chemotherapy but who were not in remission. It was an assessment of cryotherapy in 9 of them as a replacement or adjuvant to chemotherapy. A total of 62 operations were performed, resulting in immediate pain relief and the gradual return of sensation in the treated nerve in all patients. The procedure had to be repeated in 6 patients early in the study to achieve this; one probable reason was inadequate freezing. The longest period of relief has been 2½ years so far; the first patient treated 3 years ago, failed to return and could not be traced. Migration of pain to smaller branches of the trigeminal nerve occurred in 16 patients from 3 to 9 months postoperatively. This was abolished by further cryotherapy in the areas of migration. It is postulated that cryotherapy acts both peripherally and centrally to produce pain relief; if the technique is correctly carried out, the results can be long lasting and may be permanent. Several reasons for suggesting this are put forward. It is concluded that cryotherapy can give unique results hitherto unachievable by other means of pain control in paroxysmal trigeminal neuralgia.
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PART I SURVEY, 1959 TO 1981

Between 1959 and 1973, 120 new patients with paroxysmal trigeminal neuralgia (PTN) attended the Department of Oral Medicine at Eastman Dental Hospital. Ninety-one additional patients were seen from 1974 to 1981. The clinical findings are illustrated in Figs. 1 and 2. In the early stages, remissions lasted for several months in 80% and for several years in 20% of the patients. In the older age group remissions, when they occurred, tended to be shorter than in the younger age group. Carbamazepine was first used in 1966 in this department and over the next 7 years was found to be effective in 84% of the patients. This figure rose to 93% when patients were given phenytoin in addition to carbamazepine. Those who failed to respond to medical treatment had to be referred elsewhere.

The blood picture was monitored every month while patients were on carbamazepine. Fig. 3 shows the persistent drop in the white blood cell count over an 84-month period in 120 patients. This figure represents the results of 10,080 white blood cell counts in this group. It was decided to stop the drug if the count fell below 3,000 per cubic millimeter, and this adds to the significance of these findings.

Other toxic effects in this group included vertigo in 33%, drowsiness in 52%, and postural hypotension in 10 cases. In one 55-year-old patient on carbamazepine therapy for 5 years diabetes developed and has rendered his PTN out of control. Skin rashes developed in five patients and therapy was discontinued (two cases) or changed to another anticonvulsant agent (three cases). These adverse reactions were reported in detail by Al-Ubaidy and Nally[1]

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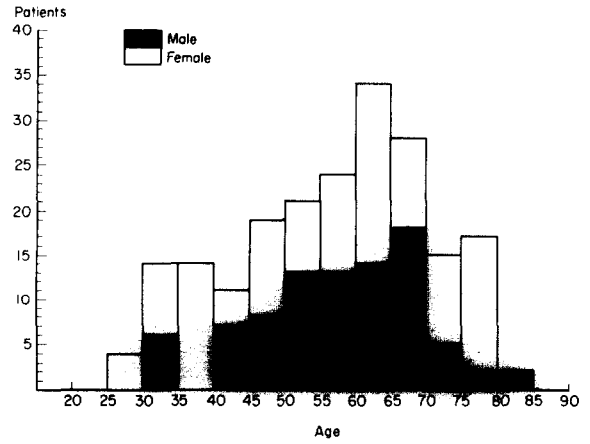

Fig. 1. Age/sex in 211 patients, 1959 to1981. (From Al-Ubaidy and Nally: Br. J. Oral Surg. 13:289, 1976.)

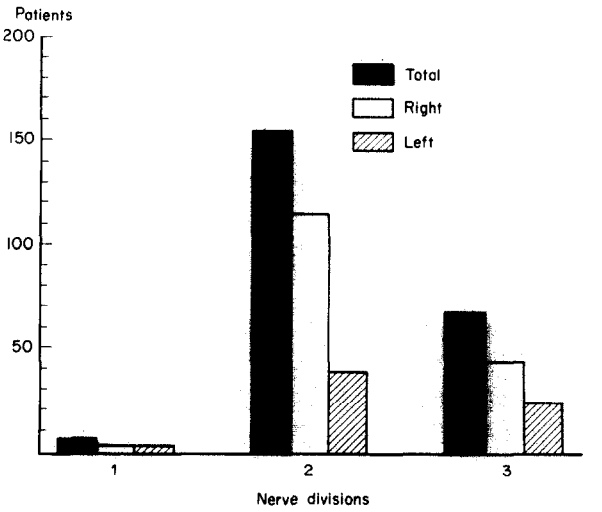

Fig. 2. Divisions in 211 patients, 1959 to 1981.

PART II. MEDICALLY UNCONTROLLED PATIENTS, 1978 TO 1981

Before 1978 a number of patients were proving difficult to manage with medical treatment and were referred elsewhere. Cryotherapy had been used in the department for treating various mucosal lesions, such as leukoplakia, since 1975. An important observation with the use of this technique was the remarkable absence of pain in the healing process. It was also noted that when a nerve (for example, the lingual) was implicated in the cryolesion, the patient would have anesthesia for several weeks but this was reversible. Because of this observation, a pilot study on the role of cryotherapy in 14 uncontrolled patients was started in March, 1978.

Nerve branches involved in PTN were identified by local anesthetic injections. For example, if a trigger zone was temporarily abolished by a mental or infraorbital block, it was decided to proceed with cryotherapy on these nerves and the effects were explained to each patient. All patients were in severe pain before the operation. Local anesthesia was employed if pain was confined to the distribution of the mental nerve, and the procedure was carried out on an outpatient basis. A general anesthetic was used if pain occurred in the infraorbital nerve, either alone or with the mental nerve, and the patient was hospitalized overnight. An intraoral approach was used. The mental nerve was exposed by an incision just above the mucogingival line extending from the first molar to the canine and a mucoperiosteal flap was raised (Fig. 4). The infraorbital foramen was approached via a Caldwell-Luc incision placed well into the lining mucosa and the nerve was exposed by blunt dissection.

The exposed nerves were frozen with a $2H_3$ cryoprobe using the BMS-40 system* in which nitrous oxide is the refrigerant. A temperature of approximately −45° C was achieved, and the duration of freezes varied from 30 seconds to 3 minutes.

The pilot study was assessed approximately 18 months later. The advantages of the technique were becoming apparent because patients either reduced or stopped medication, no one was referred for other peripheral procedures or neurosurgery, and, fortunately, sensation returned after several weeks. It was concluded that the results were sufficiently encouraging to take the study a stage further. A DFS-30 liquid nitrogen* system was purchased. It was decided that a greater number of severely affected patients would be treated with the BMS-40 or the DFS-30 system. An unselected group of control patients (Part III) would be treated at the same time.

CRYOTHERAPY RESULTS: 1978-1981

A total of 42 patients were treated. There has been no return of pain in the distribution of the 54 (out of 55) nerves controlled by cryotherapy; the first patient failed to return and cannot be traced. The first operation which had to be repeated was in September, 1978 (30-second freeze at −45° C); pain returned in May, 1979, and the procedure was redone with a 60-second freeze.

One important finding was migration of pain from the original source in 16 patients within this 3-year period. This happened from 3 to 9 months postoperatively. However, it was not as severe as the original

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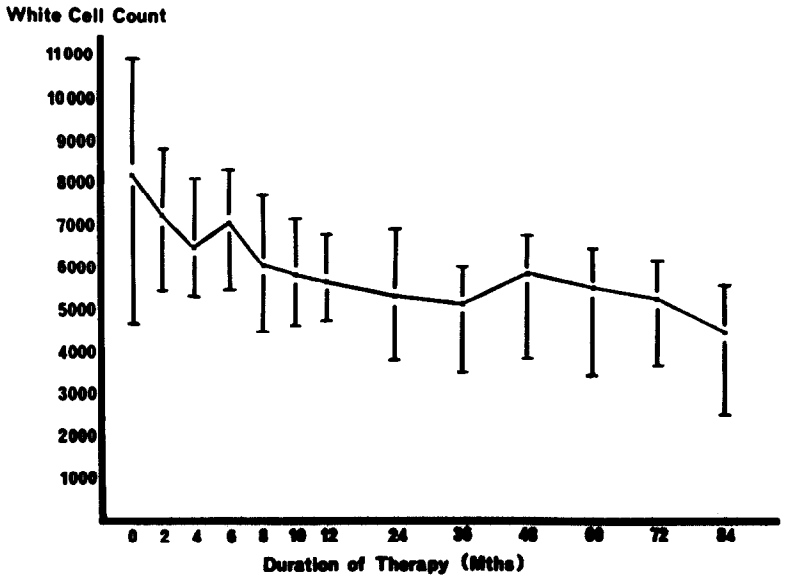

Fig. 3. Drop in white blood counts in 120 patients, 1966 to 1973.

pain and could be controlled with smaller doses of carbamazepine. Pain migrated to the long buccal nerve in 12 patients (out of 32) who had mental nerve freezes, to the posterior superior dental nerves in 5 patients, and to the greater and lesser palatine nerves in 1 (out of 30) who had infraorbital nerve freezes. Long buccal or other nerve involvement was proved by using local anesthetic infiltrations into the areas supplied by these nerves. Because of this, and because access to these nerves was initially thought to be more difficult for open nerve freezing, an attempt to abolish pain by injecting absolute alcohol was made in 7 (out of 16) patients. Only 2 patients experienced satisfactory pain relief; the other 5 had to continue on small doses of carbamazepine.

Recently 4 of those patients whose pain migrated have had the mucosa, in which a trigger zone could be identified, frozen for 2 minutes at −100° C. So far, this has relieved the pain in the long buccal nerves but not in the posterior superior dental nerves. More recently, accurate localization and open nerve freezing of the long buccal, posterior superior dental, and greater and lesser palatine nerves has been carried out and pain that had migrated to these branches has been abolished.

PART III. MEDICALLY CONTROLLED PATIENTS

Out of a total of 91 patients (Part I, survey 1974 to 1981), 16 were allocated at random to Part III. This consisted of a group whose pain could be controlled (or almost controlled) on 800 mg (or less) or carbamazepine daily but who were not in remission. This state was assessed on the grounds that a certain dose

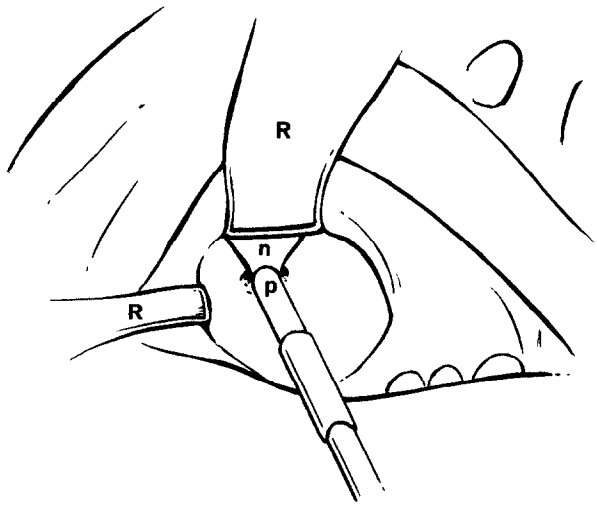

Fig. 4. Infraorbital nerve exposure and probe in position. *n*, Nerve. *p* Probe. *R* Retractor.

of carbamazepine had to be maintained, and any attempt at reduction brought about a return of pain. It was an assessment of cryotherapy as a replacement or as an adjuvant to chemotherapy. Sixteen patients were offered cryotherapy, and 9 accepted. The other 7 refused and elected to continue on chemotherapy.

The results of cryotherapy in Part III showed that, out of 9 patients, complete pain relief occurred in 7 within this 3-year period, and carbamazepine was no longer required. Of the remaining 2 patients, 1 developed long buccal nerve pain after a mental nerve freeze which was completely controlled postop-

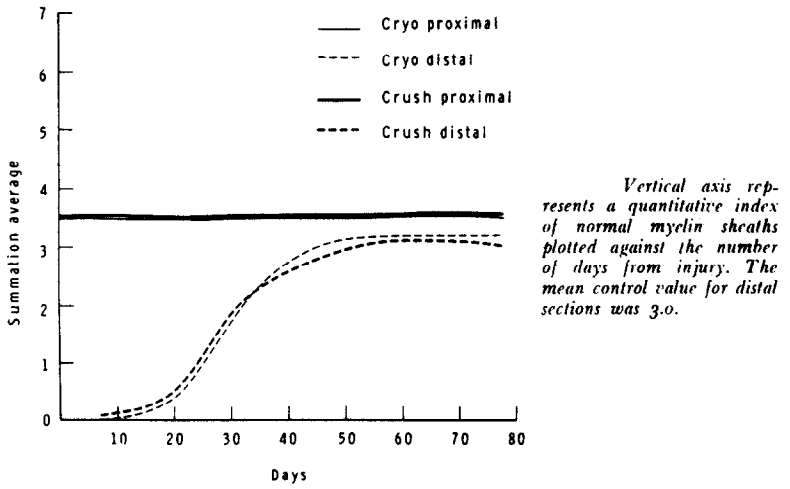

Fig. 5. Myelin sheath counts after cryotherapy and crush injuries in a mixed peripheral nerve. (After Barnard: Ann. R. Coll. Surg. Engl. 62:180, 1980.)

eratively with 400 mg carbamazepine daily; the patient required 800 mg daily preoperatively. The other developed pain in the posterior superior dental nerve after an infraorbital nerve freeze and was controlled on 200 mg carbamazepine daily; 600 mg daily was required preoperatively. Complete pain relief has now been achieved by further cryotherapy in the area of the pain migration.

Questionnaire

All patients were asked to complete a questionnaire. In answer to the questions "Do you think the freezing operation on the nerve causing the neuralgia has helped you?" and "If the pain comes back would you agree to have the same operation carried out again?" 41 patients (out of 42) said "Yes" to each question. Patient No. 41 failed to return.

Recommendations in management of PTN

When the results of cryotherapy are analyzed, it will be seen to be effective in medically uncontrolled and medically controlled patients. Pain relief has been maintained over a 3-year period so far; the long-term benefits have yet to be assessed but may be permanent. Cryotherapy is easily repeated and is eminently suitable for elderly patients. Nerve freezing for less than 2 minutes at −45° C may not be sufficient to produce lasting pain relief. Therefore, the best results will probably be achieved with a temperature of −100° C or lower for three 2-minute freezes, with a 5-minute defrost between freezes. If pain migrates to small, relatively inaccessible branches, an oral mucosal freeze of 2 minutes on the trigger zone appears to be more effecitve than the injection of absolute alcohol. However, exposure of these branches and open nerve freezing is probably a better procedure. Gradual reduction of carbamazepine postoperatively is recommended to prevent withdrawal features. This is particularly important if patients have been on high doses for long periods.

Patients should also be advised to ignore the change from anesthesia to paresthesia ("pins and needles") which begins to occur about 4 weeks postoperatively and lasts several weeks; it is caused by nerve recovery. If they are not warned about this, some may think that the pain is coming back. The possibility of pain migration should also be explained in detail.

Finally, and perhaps most important, cryotherapy may replace long-term medication which carries with it well-recognized overt and cryptic hazards. Although central neurosurgical procedures, such as controlled thermocoagulation and retrogasserian rhizotomy, are also effective in producing pain relief, they are potentially more hazardous than cryotherapy. The resulting permanent reduction in or loss of sensation may even mask the signs and symptoms of late or secondary involvement by space-occupying lesions in any part of the trigeminal pathways.

DISCUSSION

While the cause of PTN remains unknown, it is currently suspected that a combination of degenerative changes in the gasserian ganglion and mechanical compression by a prominent petrous ridge or an aberrant branch of the superior cerebellar artery may be involved in the production of pain.[2] These factors may produce demyelination which, in turn,

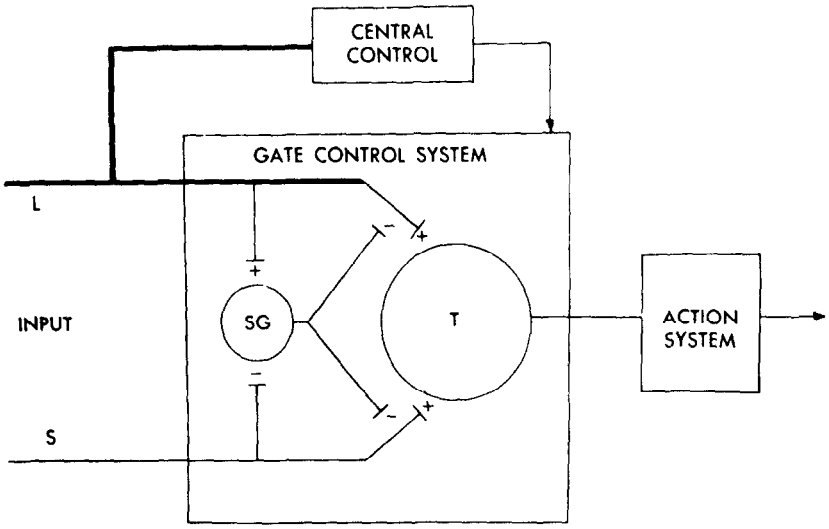

Fig. 6. Diagram of gate control theory. (After Melzack and Wall: Science 150:971, 1965.)

causes a short-circuiting of fibers, so that innocuous tactile stimuli to the face may cause abnormal discharge of pain. Effective drugs are now available to control PTN in the majority of patients, but they usually have to be maintained for long periods (sometimes indefinitely) and the cryptic effects, such as hepatotoxicity, should not be overlooked.

The results of various peripheral procedures, such as injection of neurolytic agents and neurectomy, have often proved disappointing. The injection of phenol or alcohol probably produces only partial nerve destruction which aggravates the pain, and later intraneural scarring and fibrosis may result in secondary neuralgia. After neurectomy or electrocoagulation, neuroma formation and fibrosis may cause the pain to return.

The multiplicity of neurosurgical procedures undertaken in the past is disconcerting, although obviously each technique has its advocates. Guidetti and associates,[3] when discussing modern trends in surgical management, reported that they had treated 560 patients between 1955 and 1978. They concluded that only two procedures should now be undertaken—retrogasserian rhizotomy or controlled thermocoagulation of the trigeminal ganglion and rootlets. In their experience, the other techniques showed too high a number of relapses and others were potentially too hazardous to justify their use. The results of retrogasserian rhizotomy were reported in 175 patients, and "success was achieved in 173." In a follow-up which averaged 10 years, pain returned in 12 patients.

The results of thermocoagulation were reported in 167 patients with PTN, and pain relief occurred in 166. They were able to preserve some touch sensation in 158 patients. In a follow-up period averaging 2 years, pain has returned in 6 patients who have undergone repeat thermocoagulation. Barnard[4] treated 8 patients with PTN by cryotherapy, and pain relief ranged from 62 to 815 days (mean, 235 days). Sensation returned to the treated area after several weeks.

MECHANISMS OF CRYOTHERAPY

Peripheral

Experimental work in animals has shown that a cryolesion will produce a second-degree nerve injury with complete degeneration distal to the lesion.[4] The effect is reversible, however, and recovery occurs in 42 days with a remarkable absence of fibrosis and scar formation. However, when one compares the nerve sheath counts in the controls with those in the nerve recovered from cryotherapy in the experiments, it is seen that the sheath counts did not reach the level of the controls (Fig. 5). Although Barnard made no comment on this, it probably does indicate that the cryolesion will result in selective nerve-fiber destruction and the results of cryotherapy in patients may be directly related to these findings. It is probable that the fibers that are most vulnerable are pain fibers, since they are of a smaller diameter than the majority of fibers in a mixed peripheral nerve.

Central

If we assume that an irritable focus has become established centrally, for as yet unknown reasons, then a consideration of the whole problem of pain modulation is important to permit a better under-

standing of the clinical management of patients and not just the application of the cryoprobe to the affected nerve. From clinical observation, we can appreciate that even though the same noxious stimulus is present, the response that the recognition of pain produces and the emotional reaction to it are separate issues. The time-honored concept of a cause-and-effect relationship is too simple when one considers the following situations which apply particularly to patients with paroxysms of pain from PTN. We know that pain can return and even be aggravated after surgical sectioning of peripheral nerves as well as their central connections. The cause-and-effect concept would imply that all pain must be abolished by simply blocking the afferent pain nerve fibers. This does not always happen. The intensity of pain in PTN is not necessarily related to the intensity of the stimulus. For example, light touch, even the movement of a hair follicle on the face, can trigger excruciating pain, whereas deep hard pressure in the same area may produce a minimal response or none at all. These responses cannot be explained on the basis of pathologic changes in end organs or peripheral receptors, because none has been demonstrated and, besides, the responses can vary enormously throughout one day.

It was also observed in this study that the trigger zones, once abolished by cryotherapy, would sometimes migrate to other areas of the trigeminal nerve. Another paradoxical feature was the discrepancy in time between the stimulation of a trigger zone and the start of paroxysmal pain in some patients. A delay of up to 60 seconds or more was noticed not infrequently. Again, this fact is not compatible with the known velocity of nerve impulses.

There are many other examples of varying responses to pain stimuli. These include battlefield injuries and patients who have undergone frontal lobotomy, but a consideration of central mechanisms involved, such as the production of endorphins and altered brain chemistry, is outside the scope of the present study. However, the "gate-control theory" first proposed by Melzack and Wall[5] probably has a particular relevance to the modulation of pain in PTN and possibly helps to explain certain central mechanisms that may occur after cryotherapy of a mixed peripheral nerve, such as the trigeminal nerve.

The theory proposed by Melzack and Wall is based on a controlling system in the central nervous system that can modify sensory stimuli before it will be recognized as pain and lead to a response. They suggested that the "gate" was located in the substantia gelatinosa of the spinal cord. We know that there is a substantia gelatinosa in the nucleus caudalis of the spinal tract of the trigeminal nerve, and it is here that the first synapses of the pain afferent system are present. Therefore, the gate-controlling mechanism may be located in this area, in which afferent trigeminal nerve impulses can be modulated. The basis of the theory is that pain perception can be influenced in the synapse of the primary sensory neurones. It is suggested that modulation of synaptic activity is dependent upon neurones other than those smaller fibers traditionally considered to carry the sensation of pain centrally. These neurones are of a large diameter with a high conduction velocity, and are also activated by noxious stimuli. Stimulation of a mixed peripheral nerve, such as the infraorbital, relays impulses centrally in large- and small-diameter fibers. These impulses synapse with a second or T cell and the substantia gelatinosa (SG) (Fig. 6). The T cell, also called the first central transmission cell, is activated by the large and small fibers. As a result, the T cell impulses travel centrally to give rise to pain perception, localization, and the autonomic, emotional, and voluntary responses of the patient (action system).

However, T cell activity can vary and probably depends on the influence of the SG cell. It is suggested that the large fibers initially activate the T cells but are rapidly inhibited because of a negative-feedback mechanism arising more centrally. On the contrary, the small-fiber activity is maintained by a positive-feedback mechanism.

It is postulated, therefore, that the central effect of cryotherapy is that the cryolesion initially produces total blockage of large- and small-fiber input, thereby completely "closing the gate." Large fibers are known to regenerate in several weeks, and so the patient will experience a gradual return of sensation. Small fibers probably do not recover, and pain fibers are known to be of small diameter. Therefore, cryotherapy, by a process of selective nerve-fiber destruction, may produce a state in which the T cells can no longer be influenced by small-fiber activity. This state could be a permanent one because smaller nerve fibers are unmyelinated.

One principle from this theory seems to work in practice; stimulation of large diameter in excess of small fibers can clinically mask pain. For example, it has been noticed that firm pressure on the upper lip just prior to needle penetration will often reduce or prevent the perception of pain. Even vigorous massage of a trigger zone in PTN may abolish paroxysms for a time. This theory can be considered in relation to PTN because it implies that anything that will inhibit large-fiber activity and allow small-fiber

activity to predominate should result in "an open gate" situation, whereby the action system is flooded with pain reception unimpeded and the characteristic responses occur. Light and electron microscopy studies have shown degenerative changes of large fibers in the trigeminal nerve in patients who had PTN.[6,7] These changes included demyelination and microneuromas between the gasserian ganglion and the brain stem. One result could be a decrease of large-fiber activity into the gate-control system in PTN. Even though mild degenerative changes can be found in controls, it is probably increased in PTN, and multiple sclerosis is a recognized complication in PTN. It has been shown that it is the large myelinated fibers that are mainly destroyed in multiple sclerosis and is the reverse of what probably results from cryotherapy.

Finally, in an important study of postsurgical experimental trigeminal neuropathy, Gregg[8] has shown that sectioning branches of the trigeminal nerve distal to the gasserian ganglion resulted in ganglion-cell degeneration and noticeable changes in the centrally projecting fibers. The cell bodies of large fibers degenerated and fibrosis occurred in the ganglion. It was particularly noticeable that large ganglion cells were more extensively damaged when compared with the small cells, and the greatest destruction was in the main sensory nucleus where the large fibers predominate.

It would seem logical to conclude that if such changes follow surgical manipulation of the peripheral branches of the trigeminal nerve, as can occur after difficult dental extractions, it could be conjectured that an imbalance between large- and small-fiber activity will occur and "an open gate" situation could result in the development of PTN in some persons. Cryotherapy of the trigeminal nerve could merely reverse this imbalance.

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