Evidence for a Peripheral Etiology of Trigeminal Neuralgia

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Because the paroxysmal nature of trigeminal neuralgia suggests an epileptic discharge, Kinnier Wilson\(^1\) proposed that trigeminal neuralgia was due to a paroxysmal discharge of centrally-located trigeminal neurons. This concept has met with considerable favor and is an acceptable working hypothesis, provided it is not interpreted as an argument for a central etiology. As a matter of fact the organization of the central nuclei of the fifth cranial nerve provides one of the important lines of evidence in favor of a peripheral etiology for trigeminal neuralgia.

The portion of the fifth spinal nucleus extending several millimeters below the level of the obex is primarily concerned with pain and temperature. The evidence for this in man stems from Sjögqvist’s section of the spinal tract of the trigeminal;\(^2\) it has further been shown by Hamby that an incision as far as 10 mm below the obex level gives satisfactory trigeminal analgesia.\(^3\) Thus only a small caudal portion of the nucleus, located mainly in the C-1 and C-2 segments of the spinal cord, is the major relay for pain in this system. Brodal\(^4\) demonstrated thermanalgesia of the glossopharyngeal and vagal nerves in Sjögqvist’s patients and concluded that the corresponding sensory relay must reach the spinal nucleus of the trigeminal below the obex level. Cajal\(^5\) demonstrated fibers of the ninth and tenth cranial nerves joining the spinal tract of the fifth nerve, but Ingram and Dawkins\(^6\) could not trace them below C-1 or follow them to their termination in the nucleus.

The manner of termination of the three divisions of the trigeminal nerve and of nerves 7, 9, and 10 in the subnucleus caudalis (pars spinalis)* of the fifth nerve has recently been demonstrated in considerable detail.\(^7,8,9\) Whereas all of the divisions of the trigeminal nerve are laminated throughout their course in the spinal tract and nucleus, the endings of nerves 7, 9, and 10 are diffusely distributed throughout the nucleus, intermingling with each other and with those of the trigeminal (Figs. 58 and 59). Moreover, the sensory input from the three upper cervical dorsal roots enters this nucleus and distributes terminals widely and irregularly among those of the preceding root systems. Thus, an area of dense anatomical convergence of sensory input from all the exteroceptive cranial nerves and all sensory modalities of the upper cervical roots is located in the subnucleus caudalis.

Whether such anatomical convergence is associated with physiological convergence, and if so with what root systems, has been determined only in part. Kerr and Olafson\(^10\) demonstrated that a proportion of the single units in the spinal nucleus of the trigeminus responded both to trigeminal and to cervical (C-1 and C-2) volleys in the cat. Whether this input was from primary terminals or via interneurons was not determined.

Our current interest has concerned central pathways for the spread of atypical face pain. Although our data do suggest a possible route for the bizarre spread of this type of pain, they also provide a contradictory type of evidence with regard to the location of the primary lesion in trigeminal neuralgia. We have summarized below the symptomatology and natural history of trigeminal neuralgia.

Characteristic Features of Trigeminal Neuralgia

1. Onset usually after age 40\(^11\)
2. Females affected twice as often as males\(^12,13\)
3. Right-sided involvement predominates by a ratio of 3 to 2\(^14\)
4. Trigger points present at some time in the course of the disease
5. Quality of pain superficial, intense, brief, and paroxysmal
6. Pain limited strictly to some part of the distribution of the fifth cranial nerve
7. Less than 5% start in the first division\(^15,16\)
8. Extreme rarity of combined first and third division involvement\(^17\)
9. 3% of cases ultimately bilateral
10. No neurological deficit, or one detectable only with von Frey hairs\(^18\)
11. Tendency to progression in the frequency and severity of episodes

*The term “pars spinalis” of the subnucleus caudalis is used here for that portion of the nucleus which lies in the spinal cord and is characterized by its multiple cranial and cervical root inputs and by the pronounced anatomical convergence of these systems.
12. Mechanical factors involving the root or ganglion may produce a similar syndrome. Sensory rhizotomy gives complete relief. Decompression procedure provides temporary relief. Compression procedure gives more lasting relief.

Although nerves 5, 7, 9, 10, C-1, C-2, and C-3 all feed into the same general neuron pool, fifth nerve neuralgia is about 100 times more common than ninth nerve neuralgia, while seventh and tenth nerve neuralgias are rarities. Paroxysmal neuralgia of the upper cervical roots is non-existent.

Fig. 59 indicates the density of the several root systems converging in the subnucleus caudalis at C-1 and C-2. It is difficult to conceive how a lesion or pathophysiological factor located in this area could have so specific an affinity for trigeminal interneurons. Also, this lesion would have to involve the second or third division neurons leaving the adjacent first division neurons unaffected. It would have to affect women twice as often as men and the right side more frequently than the left. Other improbable considerations of this type might include the remarkable and variable relief of pain by decompression, or compression of the ganglion and sensory root. Although the sensory input has not been markedly affected, one possible location for a central lesion has ceased to discharge paroxysmally. It is also probably significant that there is no well-documented case of syringomyelia, tumor, or infarction involving the spinal nucleus and associated with the clinical syndrome of trigeminal neuralgia.

Experimental efforts to produce trigeminal neuralgia in animals have been made, particularly by King and Barnett, who injected alumina gel into the spinal nucleus of the fifth nerve in cats. They produced a syndrome of dysesthesia of the face consisting of overreac-
tion to tactile stimulation, but were careful to avoid claiming that they had produced trigeminal neuralgia. They stated only that it was tempting to postulate a central mechanism for the paroxysmal pain. Their conservative and cautious comments should be noted. It is also of interest to remember that Kennard also produced sensory overreaction by injecting alumina gel into the cervical spinal cord of the cat. The problem of determining pain responses in animals is fraught with difficulties. However, the demonstration of a typical trigger point in an experimental animal would be of great value and perhaps not so difficult to determine in view of the very characteristic response which occurs in patients.

Evidence of this sort makes it difficult for us to accept a central etiology for trigeminal neuralgia. On the other hand, there is much to support the idea of a peripheral origin.

It has been shown on repeated occasions that certain types of pathological changes which impinge on the posterior root and occasionally on the ganglion are capable of producing a syndrome which, particularly in the early stages, may be indistinguishable from trigeminal neuralgia. Among these are cholesteatomas, small acoustic neurinomas, and vascular malformations or arterial loops in the cerebellopontine angle. That they do in fact bear an etiological relationship to the complaint would appear to be well borne out by the lasting relief obtained when they are removed. As Olivecrona pointed out, for paroxysmal pain to be produced, the lesion must be slow-growing and small. Although large lesions produce much more distortion, they do not produce tic pain. Why this should be has not been explained.

The fact that a peripheral lesion has often been demonstrated suggests that some mechanical factor can be found in every case of trigeminal neuralgia. Furthermore, since the
lesions are known to be small, a minor vascular abnormality, a small hyperostosis, or a dural constriction could be responsible. Much of the difficulty concerns the subjective evaluation of an apparently insignificant lesion. We have confirmed the pronounced pathological changes demonstrated in the trigeminal ganglion by Beaver, et al., and extended them to the immediately adjacent posterior rootlets. It does not seem reasonable to assume that the minor lesions which appear to have produced trigeminal neuralgia could also have produced the significant changes in myelin described. It seems more likely that an underlying degenerative process in the ganglion and root, related probably to aging, has been aggravated by an otherwise negligible mechanical factor. The frequency with which vascular lesions are incriminated suggests that a pulsatile contact may be particularly significant.

**Review of Lesions**

Let us now review some of the more commonly described peripheral types of lesions which have been proposed as the cause of trigeminal neuralgia. If it is to be accepted as a true cause, a peripheral lesion should account for the majority of the features of trigeminal neuralgia and not conflict seriously with any one of them.

**Teeth.** The teeth have often been indicated as a likely factor in the genesis of trigeminal neuralgia since they are frequently involved in various processes and since primary neuralgia of the second and third divisions is far more frequent than first division neuralgia. Although trigger points are common on the gums, teeth themselves are never trigger points. Trigeminal neuralgia almost never occurs in the younger age groups, which are particularly affected by caries, while it often has its onset in individuals who have been edentulous for years. Finally, this cause cannot apply to first division trigeminal neuralgia.

**Vibrissae.** The possibility that the vibrissae which are present in lower mammals might have left involuted remnants in man which would be a source of neuralgia is interesting and compatible with the rostral distribution of trigger points, but fails to account for the trigger points so commonly found within the mouth.

**Virus disease.** The frequent occurrence of perioral herpetic vesicles following trigeminal rhizotomy has suggested the possibility of a virus as the cause of trigeminal neuralgia. This subject has been investigated by Carton and Kilbourne, who found herpes simplex virus in the vesicles from the patients but could not demonstrate them in the ganglion. Dr. Beaver pointed out that he has examined the fluid from the herpes vesicles by electron microscopy and found no virus particles, but he also emphasized the difficulties in identifications. Further efforts to demonstrate a virus in the ganglion by culture technique would be desirable. No evidence of viral particles or inflammatory infiltrates has been found in the ganglion or in the posterior root in electron microscopic studies reported to date. The predominance of primary first and second division neuralgias can be used as an argument in favor of this concept, in view of the relatively septic nature of the oral cavity, but the predominance in middle age, in females, and of the right side is hard to reconcile with viral etiology. Nevertheless, a virus might be responsible for the pathological changes which have been described, while the clinical syndrome itself might be due to an additional structural defect.

**Compression of the posterior root** as it passes through the dural foramen or its angulation over a tilted petrous ridge are often cited. Yet it is difficult to understand why the first division is spared in 95% of cases, whereas all three divisions are intimately associated at these points. It would seem that a much more random involvement of the various divisions would occur and that first and third division combinations might be seen with some frequency, yet this almost never happens. With the data now available, it seems unlikely that a lesion placed at the petrous ridge or central to it could lead to distal degenerative changes since the usual direction of myelin degeneration is away from the cell body and not toward it. However, it may well be that changes are present throughout the whole of the primary neuron and that an abnormality at the petrous ridge might act simply as an irritative factor in the production of paroxysmal pain. This possibility, however, means that two pathological factors must be present for the production of tic douloureux, one of which is a primary, severe, degenerative change and the
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other a precipitating, extrinsic, structural abnormality.

Traction. Olivecrona noted that downward sagging of the contents of the posterior fossa was a relatively frequent occurrence in individuals of advancing years and suggested that traction on the sensory root of the trigeminal against the petrous ridge might be the cause of the neuralgia. This meets with the same difficulties discussed in connection with the petrous ridge etiology plus the additional problem of accounting for the rarity of bilateral involvement in a phenomenon that is no doubt symmetrical.

Internal carotid. We have proposed another possibility, namely, that the internal carotid artery which lies directly beneath the trigeminal ganglion and adjacent posterior rootlets (the pars triangularis or fan-shaped plexiform portion of the root as it leaves the ganglion) might play a significant role. We have shown that quite often the bony roof of the carotid canal is replaced by a thin layer of connective tissue so that intimate contact can be established between the ventral surface of the ganglion and the underlying carotid artery. Furthermore, this relationship is true only for the second and third divisions, since the first division is to be found in the wall of the cavernous sinus where the carotid is surrounded by venous blood and the opportunity for contact is much less pronounced. This would account for the predominance of the primary involvement of the second and third divisions and the relative rarity of first division symptoms. In cadavers in which the carotid canal defect is present, a pulsatile flow of saline injected into the carotid artery in the neck can be readily palpated through the ganglion when it is exposed on the floor of the middle fossa. This light pulsatile contact suggests an imitative mechanism comparable to that in which small vascular abnormalities apparently cause neuralgia pain.

In a further effort to establish the validity of this suggestion, we carried out studies to determine the areas of skin served by the neurons on the ventral aspect of the ganglion, that is to say, those neurons which lie close to the internal carotid artery. A study employing steel microelectrodes and physiological stimulation of the face of cat and monkeys was the most successful. In this study the tabulation of data was done separately by Dr. Walter Lysak to avoid the possibility of unintended bias. It was found that the ventral ganglion cells had receptive fields distributed around the most rostral areas of the face, the lips, the nose, and the eyebrows. This observation correlates surprisingly well with the distribution of trigger points in a series of patients studied by Kugelberg and Lindblom as illustrated in Fig. 60.

The trigger area is often extremely small; a single hair may be all that is required to trigger an intense paroxysm of pain. These small zones are comparable in size to the small receptive fields seen in the most rostral distribution of the trigeminal nerve as are apical receptive fields seen in the rest of the body. In most instances the only clinical evidence of a disturbed function is the trigger point, which suggests that only a few fibers or single units of the peripheral division are involved. Thus, the term second division or third division neuralgia is in the strict sense a misnomer because, in fact, only a very minor part of the division is involved. At times the trigger is not a point but more diffuse, a trigger zone, as described by Kugelberg and Lindblom. It seems likely that the trigger point is extremely sensitive so that it can be activated from a considerable distance (as often happens in electrophysiological studies); on the other hand, numerous adjacent fibers may supply a single area and in some manner fire together.

It is interesting that the adequate stimulus starts as touch but is received as pain. A discussion of current views on the conduction of noxious stimuli is beyond our present scope. It is sometimes suggested that the tactile stimulus short-circuits into the pain pathway. We suggest that when a tactile stimulus triggers pain, it need not necessarily be the tactile afferent fiber that is firing, but that adjacent involved fibers of any modality may have such a low threshold that they discharge repetitively, at a distance from the site of application of the stimulus. A hair might thus act simply as a lever to activate a nearby fiber unrelated except by proximity to the hair follicle network. However, the intensity of the stimulus must be low, as in light brushing or tickling; pain or firm pressure will not evoke the response. Thus, it is not only low threshold
response in damaged or irritated fibers, but also the modality of the stimulus that is a primary factor.

While it appears that trigeminal neuralgia can result from various types of peripheral lesions, the relatively stereotyped pattern that emerges from large series of cases suggests that a considerable proportion of cases are due to a single etiological agent. Rather than summarize these recurrent features again, the reader is referred to our list on p. 168. The internal carotid would fit these postulates relatively satisfactorily but not even such highly suggestive correlations can be taken as proof of etiology.

We emphasize that we are not proposing that the carotid pulsation causes triggering of the paroxysm; neither do the vascular anomalies of the cerebellopontine angle. Our thesis is that the carotid acts as a traumatic agent impinging on the ganglion and root and thus promotes a more severe breakdown of myelin sheaths in older individuals; these are the same individuals who may already have pronounced localized changes in myelin. Or the carotid pulsation may act simply as an additional irritative factor in a primarily degenerative disease of the nerve.

Hypertension and arteriosclerosis, which are often mentioned, appear to have little bearing on the etiology of the syndrome. These data make it easier to account for the characteristic course of trigeminal neuralgia. The typical course consists of weeks during which several episodes of pain occur daily, followed by relatively long remissions with a tendency to progressive increase in frequency, duration, and intensity of the episodes. The pathological findings are apparently widespread in some individuals and less so in others. It seems probable, in view of the clinical progression, that the pathological process is a progressive one also. The basis for short-circuiting of impulses from one axon to
another as suggested first by Dott is certainly present, since the proliferative degenerative change in the myelin sheaths often exposes the axon to the interstitial tissue.\(^6,9^6\)

**Summary of Hypothesis**

We offer the following tentative working hypothesis to account for the peculiarities of trigeminal neuralgia. In the course of the degenerative process, short-circuiting may occur when the demyelinated surfaces of two adjacent axons closely approximate each other. In addition, close association of a demyelinated large axon with the degenerating unmyelinated axons, which have lost their Schwann cells but otherwise remain intact, may also be a mechanism by which myelinated fibers may cause firing in unmyelinated fibers.

This short-circuit situation would persist as long as the two axons remained viable. However, we have seen that a number of axons disappear completely, leaving as their only trace an accumulation of proliferated myelin. When one of the axons degenerates in this manner, the short-circuiting phenomenon would naturally cease and with it the episodes of paroxysmal pain. Exacerbations of the pathological process may lead to a relatively rapid breakdown of myelin, the simultaneous appearance of several trigger points, and more severe paroxysms of pain.

The favorable effects of compression and decompression are not yet understood. It is possible that both procedures inflict enough trauma on the already partially degenerated nerve fibers so that all these fibers succumb; there will then be no more paroxysms of pain until the demyelinating process involves groups of axons. While there is considerable risk in speculations of this nature, the hypotheses are suggested on the basis of observed facts, with the intent of providing a basis for further investigation of peripheral mechanisms.

The clinical manifestations of trigeminal neuralgia can be neither peripheral nor central in origin. The trigeminal system, from its most peripheral receptors in the skin to the termination of its pathways in the central nervous system, is involved as a whole during the painful paroxysm. The evidence now appears to be overwhelmingly in favor of a peripheral etiology and pathology. The effect of this peripheral abnormality on the central mechanisms in the spinal nucleus of the fifth nerve has never been recorded instrumentally. We can assume, however, that a paroxysmal or seizure type of discharge of these neurons occurs during the painful paroxysm. The “seizure” is then followed by a more or less prolonged period of inhibition corresponding to the refractory period of the trigger point. This phenomenon is almost certainly on a central basis, in view of the extremely short refractory period of primary neurons. Phenomena such as temporal and spatial summation and surround inhibition, all of which are significant factors in trigeminal neuralgia, can only be manifestations of central nervous system mechanisms and never of ganglion cells and their processes. These, important as they are, are nevertheless responses to the peripheral changes in trigeminal neuralgia.

What the central nervous system “sees” coming into it from the periphery, whether it be a disordered input along the trigeminal sensory system in tic douloureux or along somatic sensory roots in painful conditions of peripheral etiology elsewhere, results in the phenomenon of pain, the central nervous system’s response to noxious input. Trigeminal neuralgia, however, differs from somatic pain mainly in that there is a trigger point and that the pain is paroxysmal.

It may be worth re-emphasizing that compression of the spinal roots, as in herniated discs, never results in “tic” pain. It remains to be determined whether this difference is due to a specific type of lesion in the periphery occurring only in trigeminal and glossopharyngeal nerves, or to a significant difference in the structure and function of the central nuclei of the trigeminal nerve.