DELAYED ACTION POTENTIALS IN THE TRIGEMINAL SYSTEM OF CATS

DISCUSSION OF THEIR POSSIBLE RELATIONSHIP TO TIC DOULOUREUX

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A. Historical Development of Therapy in Tic Douloureux. The alleviation of pain10 is one of the most important and frequent tasks undertaken by the neurosurgeon.164 Pain involving the region of the head167 occupies a major position in this field. Unfortunately, the role of the surgeon in the treatment of headache54,117 and the many varied facial neuralgias118,112,113 remains even today confused and discouraging.123 But one syndrome of great neurological interest stands out clearly separated from the rest in most instances—tic douloureux.

This term is usually associated with its most frequent and classical form, primary trigeminal neuralgia.38,42 Yet it must be remembered that occasionally other cranial nerves may be involved in what is apparently a true tic syndrome. Thus the nervus intermedius (nerve of Wrisberg) portion of the facial nerve,82,120,126,166 the glossopharyngeal nerve,1,16,145,163 and possibly also the uppermost fibers of the vagus nerve125,150 to the external auditory meatus may be involved in the tic-pain syndrome. It is not settled whether the highest cervical nerves may also rarely be the site of similar pain. Even though peripheral causalgias165,110 and the thalamic syndrome may produce severe dysesthesia to touch stimuli, the true tic syndrome does not occur outside this bulbar area where the aforementioned nerves pour their incoming general somatic afferent impulses into a common pool—the descending trigeminal tract and nucleus.32,35,166

The history of therapeutic attempts in cases of tic douloureux is long and varied.31 Unfortunately, there is still no satisfactory medical treatment. Trichlorethylene,59 vitamin B-124,45,144 and stilbamidine136,165 have been utilized, but the results generally have been disappointing. The various forms of surgical intervention for relief of pain, therefore, comprise the major portion not only of the past,111 but also of the present treatment.

Originally, the facial nerve was often attacked surgically. Then, over one

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hundred years ago, Bell demonstrated that the trigeminal, and not the facial, was the sensory nerve of the face. As peripheral neurectomies and avulsions, as well as alcohol blocks, were of only temporary benefit in most cases, the surgeon soon looked for a procedure that would offer more permanent relief.

Removal of the gasserian ganglion was perfected to a high degree by Cushing. Later Spiller and Frazier introduced posterior root section. The technique was improved to spare the motor root. Finally, only a partial sensory root section was found necessary in most cases. The surgical approach in such a craniotomy was usually performed extradurally through the temporal route with control of the middle meningeal artery. Others, such as Dandy, preferred a posterior fossa approach, which is still used by some today. Other methods of permanent destruction of the trigeminal ganglion or root have been advocated, including electrocoagulation and injection of alcohol and boiling water.

In an attempt to obviate the undesired postoperative facial anesthesia, Sjöqvist in 1938 reported his technique of trigeminal medullary tractotomy and made a major contribution to the understanding of the central connections of the trigeminal system. Walker described mesencephalic tractotomy and others improved medullary tractotomy further. These procedures, however, were considered by most either to be too major an undertaking for routine utilization, or to produce too high a percentage of dyesthesias and the Frazier operation remained the standard procedure in spite of the postoperative facial anesthesia and the risk of corneal complications in a small percentage of cases.

Then Taarnhøj in 1952 introduced a procedure for decompression of the trigeminal posterior root. This procedure was given further trial and various decompression techniques were carried out through several approaches. Apparently, some were led to believe that compression might be an underlying etiological factor since decompression seemed to help tic pain.

At the same time that Taarnhøj was decompressing the posterior root, Shelden and Pudenz were obtaining equally good results by decompressing the peripheral maxillary and mandibular branches at the foramen rotundum or ovale, also without postoperative anesthesia, and with no significant operative complications. The operative trauma to the trigeminal nerve or root seemed the most likely common factor involved in these two types of "decompression" procedures. Perhaps trauma was also an explanation of relief of pain in some of the earlier partial root sections, even when Dandy's posterior fossa approach was used. In 1955, Shelden et al. reported a series of 29 patients* treated by operative compression of the trigeminal posterior

* Drs. Shelden and Pudenz (personal communication) now have a series of over 100 patients who have had the compression procedure. The longest follow-up is 51 years. There has been a recurrence rate of approximately 9 per cent. While more recurrences are certainly to be expected as time passes, it must always be remembered that even trigeminal rhizotomy has a significant rate of recurrence.
root. The fundamental difference in this procedure, however, apparently was not appreciated by some.128

To complicate matters even further, Wyburn-Mason171,172 reported that blocking the great auricular nerve in the neck was helpful in tic douloureux.127 This was verified by the Shelden group and another cervical nerve, the great occipital,135 was also found to influence pain in the true tic syndrome.33 Thirty patients with tic had a block of the great auricular nerve, with 11 experiencing relief. In these 11 the nerve was cut or crushed. Six had recurrence of pain after a short interval of time. Although the results of blocking cervical nerves were not believed to be significant therapeutically,119 this procedure is thought to be important because of the demonstrated relationship of the upper cervical area to the mechanism of trigeminal pain.

B. Proposed Mechanisms in Tic Douloureux. In discussing mechanisms of pain in tic douloureux,97 it should always be remembered that etiology and mechanism are two different aspects of the same problem and must not be confused. The etiology of trigeminal neuralgia is unknown in most instances. In cases in which the cause of the trigeminal pain is known, for example, a neoplasm of the cerebellopontine angle, the trigeminal syndrome is usually not typical of tic douloureux, although on occasion it may be the same type of pain. In considering etiology, many vague factors such as season, heredity, trauma, unilaterality (the right side predominates,56 and only a small percentage of patients have bilateral tic pain,141 and then usually not concurrently), sex (female more than male),116 pathological conditions such as arteriosclerosis, multiple sclerosis,71 and herpes simplex11,12,24,23 have been mentioned. More specific local etiological factors have also been recorded, both peripherally and perhaps a disproportionate number more proximally involving the ganglion or the posterior root. These have included dental infections, sinusitis, dysfunction of the temporomandibular joint,20,137 basilar impression,59 vascular anomalies41 and tumors.27,69,124

Thus the preponderance of documented evidence at the present time would indicate at least the possibility of a peripheral etiology in the tic syndrome, although the majority of cases remain idiopathic. As far as the present authors are aware, a detailed serial pathological study of the central trigeminal system in any large series of cases of tic douloureux without surgery95 is not recorded. This would have to be done with the aspect of etiology specifically in mind, which was suggested as early as 1931 by Elsberg.43

Regardless of etiology, it appears at the present time that the pain in tic douloureux probably is mediated through a central mechanism. Crue et al.,33 following their observations on the results of trigeminal compression and block of the cervical nerves, attempted to summarize the clinical information relative to the mechanism of pain. While admitting a peripheral overlap,133,102,169,171,172 they felt that the central overlap, where the trigeminal descending tract was continuous with Lissauer's tract and the descending spinal nucleus was continuous with the cervical substantia gelatinosa of
Rolando, was probably the more important anatomical factor in the mechanism of the pain. The conclusion was reached that there may be an "abnormal internuncial pool" in the trigeminal bulbar system. They theorized that this central mechanism might be possible even with a peripheral etiology. There may be a fundamental difference between surgical compression of the trigeminal nerve and an "abnormality" in the nerve as far as etiology is concerned. Compression as a method of treatment in tic douloureux seems to be incompatible with the concept of compression per se as an etiological factor, although there may be different types of "compression." Possibly a peripheral pathological "irritation" could act as a causative agent. Whether such an abnormality would necessarily increase, merely change the pattern of, or probably even decrease, the sensory input "impulse frequency code" reaching the brain stem is not known at present. Such a change, however, might play a role in establishing a central abnormal focus. This concept might explain in part the trigger mechanism found in tic. It might also explain why in some rare cases of tic, and more frequently in postherpetic pain, peripheral neurectomy is ineffectual in alleviating the pain once the central focus is established.

This argument was admittedly only a hypothesis based on clinical observation with no experimental evidence to support it. Whether such an abnormal central pool must mean a central organic pathological lesion, or might be entirely functional (physiological) in response to a long-standing abnormal incoming volley of nerve impulses, was not explained. Perhaps at least an organic central "predisposition" is needed, for many individuals with severe peripheral organic trigeminal disease do not have tic, while in many patients with tic douloureux pain seems to develop only as a consequence of aging.

Then King, Meagher and Barnett made an outstanding contribution. They produced a tic-like syndrome in cats, similar to the causalgias of Kennard, by injecting 0.02 to 0.03 cc. of an alumina gel suspension into the area of the descending spinal tract of the fifth nerve. King and Meagher had previously reported an unusual late electrical potential in the trigeminal system. This delayed response reportedly was centrifugal and followed the afferent volley by several milliseconds when the infra-orbital nerve was stimulated. Although there was no proven direct correlation between this delayed potential and tic douloureux, these authors reported two significant findings. This late potential was of greater amplitude in the abnormal cat preparations, and trauma to the region of the trigeminal ganglion seemed not only to decrease or abolish this late potential, but also to abolish the tic-like syndrome. Certainly, this delayed potential deserved further investigation. A late trigeminal potential had been recorded previously, but King's work forms the basis on which the present investigation was undertaken. Specifically, answers to four separate aspects of the problem were sought. They are given below and the findings pertinent to each are presented and discussed separately.
DELAYED POTENTIALS IN TRIGEMINAL SYSTEM

MATERIALS AND METHODS

Twenty-one normal adult cats of both sexes were utilized for the present study. The animals were anesthetized with ether, both carotid arteries were ligated and a tracheotomy was performed. They were then fixed in a Johnson-Horsley-Clarke stereotactic apparatus and decerebrated and decerebellated. All of the brain above the level of the superior colliculi was removed. Intravenous injection of Flaxedil was then given and ether anesthesia was discontinued, and the animal was maintained on artificial respiration. In all animals, the infra-orbital nerve on at least one side was exposed. In over half of the animals either the facial or great auricular nerves or both were also exposed peripherally. In 4 animals, a cervical laminectomy was also carried out, exposing the spinal cord at the 5th and 6th cervical level. All exposed tissues were covered with warm mineral oil and the temperature of the animals was maintained at the normal level. Sufficient time was allowed for the effects of ether to wear off before recording was begun.

Peripheral stimulation was carried out by using either bipolar needle electrodes or hook electrodes. Central stimulation was performed using either monopolar needle electrodes with tips in the 20 to 50 μ range or concentric bipolar 23 gauge needle electrodes. Monophasic stimuli of either 0.1 or 0.01 msec. duration were delivered from Grass stimulators and isolation units. Varying voltage and frequency parameters were employed.

Recording electrodes were monopolar or bipolar hooks or needles peripherally, and monopolar needle electrodes centrally. The recording leads were led into a dual-channel oscilloscope and photographs were taken with a 35 mm. camera.

RESULTS

A. Confirmation of the Delayed Trigeminal Response and Its Direction of Propagation. The responses of the trigeminal nerve were the same as those described by King and Meagher. On stimulating the infra-orbital nerve, both an initial afferent spike and a later wave could be seen (Fig. 1A). The afferent spike reached the recording electrode on the maxillary nerve intracranially at the foramen rotundum in approximately 0.4 msec., and the posterior root about 0.6 msec. The delayed response appeared at about 2 msec. and had a threshold higher than that required to evoke the afferent spike, but an amplitude less than that of the initial afferent volley. The delayed potential was found in all three peripheral divisions of the tri-

Fig. 1A. Stimulation of infra-orbital nerve (0.68 volts). Top sweep was recorded from posterior root of trigeminal nerve; bottom sweep was recorded from intracranial portion of maxillary nerve at foramen rotundum (8 msec. time line). Note that the afferent spike follows almost immediately after shock artifact. Also note time lapse between afferent spike and multipeaked delayed potential. Throughout all illustrations a downward deflection represents negativity and an upward deflection positivity.
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Fig. 1B. Stimulation of infra-orbital nerve. Top sweep recorded activity from region of entering trigeminal fibers within the pons (see lesion produced at this site in photograph—Klüver stain). This represented the point of maximum amplitude of the delayed wave within the brain stem, although it could be followed both upwards and downwards along the trigeminal tract.

Bottom sweep is a simultaneous control recording from maxillary nerve at foramen rotundum.

geminal nerve as well as in the ganglion, posterior root and medulla following infra-orbital stimulation (Fig. 1B). No electrical activity was detected in the contralateral trigeminal nerve. It was also verified that stimulation of any of the three peripheral branches of the trigeminal nerve, the ganglion itself, or the posterior root produced the delayed wave. The threshold for the late wave was very low on several occasions, being obtained with a stimulus of about 0.25 volt. This seemed to depend on the individual preparation.

King believed that the late wave was centrifugal because it was abolished by section of the posterior root and because the latency time was less at the posterior root than in the peripheral 2nd division. The latency times as
illustrated were not measured readily, however, and another explanation was possible. Perhaps the first afferent volley initiated a fast reflex discharge down the facial or other motor nerve and the delayed trigeminal wave was merely an afferent "echo" of some slight imperceptible "movement" in the face. Thus, section of the posterior root might abolish the late wave by preventing the initiating afferent volley from reaching the medullary trigeminal-facial reflex pathways.

It was hoped that simultaneous recording with a dual-channel oscilloscope would permit latency times to be compared more precisely. When this was done, the latency times did seem slightly longer in the infra-orbital nerve and at the foramen rotundum than in the posterior root, but the differences in time were very slight and the difference in wave form of the late potential in the posterior root made even direct comparison difficult to evaluate (Fig. 1).

Consequently, another series of experiments was carried out to verify the centrifugal direction of this late response. It was found that section of the 7th and motor 5th nerves did not change the late wave in the trigeminal nerve. Section of all three divisions of the trigeminal nerve intracranially, if it was done very carefully, also did not diminish the late potential seen in the ganglion when the posterior root was stimulated. Section of the posterior root, however, immediately abolished the delayed potential when the infra-orbital nerve was stimulated. Thus, the centrifugal (or recurrent) nature of the late response described by King and Meagher was confirmed.

It was verified that even minor trauma, such as stripping the dura mater overlying the ganglion, prevented the demonstration of the delayed wave. Pressure on the posterior ganglion or root with a cotton pledget in a manner similar to that done in a Shelden compression procedure abolished the recurrent delayed potential at the foramen rotundum (Fig. 2). The initial afferent volley was still transmitted to the posterior root and medulla, and appeared unchanged grossly. However, if the stimulating voltage was increased, the delayed wave was again obtained central to the point of compression, but not peripherally. Thus there appeared to be a change of conduction at the site of compression which affected the axons carrying the recurrent impulses. The afferent spike must also have been changed in some manner as it no longer produced the late response at the same intensity of stimulus. With increased voltage the delayed wave was seen central to the site of compression, but did not seem able to pass the point of compression on its course toward the periphery.

B. Relationship of the Trigeminal and the Facial Nerves. Reflexes involving the trigeminal nerve and the cranial motor nerves, such as the oculocardiac and wink reflexes, have been known for a long time. Recently Green, De Groot and Sutin, using electrophysiological techniques, have demonstrated the connections between the 5th and the 7th, 10th, 11th and 12th cranial nerves.

In the present study, recording electrodes were placed on the 7th nerve peripherally and centrally at the internal auditory meatus. Stimulation of
the ipsilateral infra-orbital nerve revealed a quick response in the 7th nerve, followed by a delayed potential concurrent with the delayed potential in the trigeminal system (Fig. 3A). The short latency time (approximately 1 msec.) between the shock artifact and the initial discharge down the 7th cranial nerve seems to indicate very few synapses in this reflex connection. Indeed, it would seem to be monosynaptic. The delayed potential could also be found in the 7th nerve upon medullary stimulation in the region of the descending tract of the trigeminal nerve. Surprisingly, stimulation of the 7th nerve at the internal acoustic meatus also produced the delayed potential in the trigeminal nerve, the medulla in the region of the descending trigeminal system, and down the great auricular nerve (Fig. 3B). The contralateral 7th-nerve connections were not tested.

C. Relations of Trigeminal and Great Auricular Nerves. Response is also found in the great auricular nerve, as illustrated in Fig. 4. Following stimulation of the ipsilateral infra-orbital nerve there is no initial afferent volley but a late potential, after a delay of approximately 8 msec., passes peripherally down the great auricular nerve in the neck. This response in the great

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Fig. 2. Sweep a: Maxillary nerve response at foramen rotundum following 0.6 volt stimulation of infra-orbital nerve.

Sweep b: When the posterior root of the trigeminal nerve is compressed gently with a cotton pledget the delayed response is no longer seen while the afferent spike remains.

Sweep c: A 30-minute wait and increasing the stimulus to 15 volts did not bring back the late potential. However, in the posterior root on the proximal side of the compression the afferent spike was always present and on increasing the stimulus to 4 volts the delayed wave was obtained again.

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Fig. 3A. Response in maxillary division of trigeminal nerve at foramen rotundum (top sweep) and a simultaneous record from facial nerve (bottom sweep) following stimulation of ipsilateral infra-orbital nerve (8 msec. time line). Note fast spike and later potential found in both nerves.
auricular nerve is seen only with a stimulus of higher voltage than that necessary to produce the delayed wave in the trigeminal nerve. The delayed potential in the great auricular nerve also is abolished by compression of the trigeminal nerve, suggesting that the compression also blocks some component of the afferent volley. The contralateral great auricular nerve was not examined adequately.

That the trigeminal, facial and great auricular nerves are related can therefore be inferred from the demonstration of the delayed potential in these structures. Stimulation of the 5th nerve produces this late wave in all three nerves, but stimulation of the facial or of the great auricular nerves also produces a late wave down the other two. None of the other (lower brain stem) cranial nerves were examined, but it would seem likely that they are also intimately connected, and study of the figures of Green, De
FIG. 3C. All records from infra-orbital nerve.
(a) Stimulation of ipsilateral 7th nerve between medulla and internal auditory meatus.
(b) Stimulation of medulla 22 msec. prior to stimulation of 7th nerve blocks infra-orbital response
to stimulation of 7th nerve.
(c) Stimulation of medulla oblongata alone.
(d) Stimulation of 7th nerve 22 msec. prior to stimulation of medulla alters response previously
evoked by medullary stimulation.

The mutual interference of responses in the infra-orbital nerve resulting from stimulation in the
medulla and 7th nerve suggests that both stimulation points resulted in activation of a common system
of neurons.

See photograph for location of medullary bipolar electrode in area of trigeminal tract at level of 7th
nerve genu. A lesion marks the site at the recording electrode (vertically above arrow). Klüver stain.
Groot and Sutin\textsuperscript{65} reveals potentials in the vagus nerve (their Fig. 3D) similar to the delayed response considered here.

In an attempt to determine whether the trigeminal late response is present even lower than the great auricular, laminectomy was performed on 4 animals and the 5th and 6th cervical areas were examined. After trigeminal

\textbf{Fig. 4A.} (a) Stimulation of infra-orbital nerve with 6 volts at 0.1 msec. pulse duration. Top sweep is recorded from ipsilateral great auricular nerve; bottom sweep is recorded from maxillary nerve at foramen rotundum. (b) Recording from great auricular nerve alone. Calibration line in both records represents amplitude of 50 microvolts. Top sweep in a is same gain as in b. Time line is 8 msec. Note long delay of about 9 to 10 msec. between shock artifact and delayed potential in great auricular nerve.

\textbf{Fig. 4B.} Top sweep records response from facial nerve upon ipsilateral infra-orbital stimulation. It shows a fast spike followed by a delayed potential. Bottom sweep is a simultaneous recording from great auricular nerve, showing no fast spike and an even later multipeaked delayed wave, which in this instance is negative.
stimulation, delayed potentials were found in both the dorsal roots and dorsal columns, not only ipsilateral, but contralateral (Fig. 5). Interpretation in the few animals tested was made difficult by the finding that even a minimal trigeminal stimulus produced a widespread bilateral reflex contrac-

![Fig. 5A. Potentials from ipsilateral great auricular nerve (bottom sweep) and simultaneously in C4 dorsal root (top sweep) upon stimulation of 2nd division of trigeminal nerve (8 msec. time line).](image)

![Fig. 5B. (A) Shows potential obtained from contralateral C5 dorsal nerve root upon infra-orbital stimulation. (B) Record from a second recording electrode on ipsilateral maxillary nerve at foramen rotundum. (C) Simultaneous recording of both A and B (8 msec. time line).](image)
tion of the cervical as well as the facial muscles unless substantial neuromuscular blockade was obtained by increased doses of Flaxedil. Even then a definite small muscular contraction can often be produced by a single stimulus to the infra-orbital nerve if this is preceded by a tetanic series of stimuli. This produces an enhanced delayed response in the trigeminal as well as in the great auricular nerve. Examination of the ventral horns at the 5th and 6th cervical levels revealed marked activity following trigeminal stimulation (Fig. 6). Thus activity of the dorsal root and dorsal column might be a secondary segmental pattern reflecting movement induced by the motor root. That such trigeminocervical motor connections exist has long been known. Hooker and Humphrey have shown the character and anatomical connections of this response, one of the earliest of all human reflexes.

D. Observations Concerning the Nature of the Delayed Potential. There appear to be two possible explanations of this centrifugal late wave. It may be either an efferent potential or an antidromic impulse in sensory fibers analogous to the reflex phenomenon of the dorsal root.

At the present time we do not have enough evidence to substantiate with any certainty either viewpoint concerning the nature of the late potential. Below are listed several observations related to this question.

a) The form of the late response in the trigeminal system is relatively

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**Fig. 6.** Response obtained from ventral horn at about C5 level after stimulation of infra-orbital nerve. Stimulation of ventral horn, however, elicited no activity back in trigeminal system. Note how much faster this appears than the dorsal root potential seen in Fig. 5B, record A.

Photograph on right shows recording site in ventral horn, which is marked by a lesion which may be seen on the reader's left. Klüver stain.
constant. Recording peripheral to the ganglion, there is found a series of sharp spikes of decreasing amplitude. Recording in the posterior root, the amplitude is greater and more uniform, and at times it appears similar to that seen within the medulla.

It does not seem possible to explain the separate peaks, usually three, on the basis of differences in rates of fiber conduction. If this were so, a similar dissociation might be expected in the original afferent volley. Whether the delayed response is efferent or antidromic, it reflects bursts of neural activity which may be masked in the posterior root by activity within the medulla or possibly impulses in the motor root of the 5th nerve.

It is not possible to state that only specific fibers carry the late potential. When it is found, it seems relatively constant in form, but it has been observed that the needle electrode often may have to be moved within the nerve to record the wave optimally. Under the conditions of this experiment, we would expect an entire filament of the infra-orbital nerve to be stimulated with the type of stimulus used. At times the stimulating electrodes also have to be repositioned to obtain a maximal late response. It must be reiterated that this is at present only an impression. Histological studies investigating degeneration in the trigeminal system following a surgical compression procedure in cats are under way at the present time and will be reported at a later date.

b) The late electrical response fails to follow rapid repetitive stimuli. At the beginning of our experiments a frequency of 1 per sec. was used for convenience, but it was soon found that an even slower frequency resulted in an increased amplitude of the late wave. At 10 per sec., the delayed response was always decidedly attenuated or abolished (Fig. 7). This was also true of the other nerves in which the delayed response was demonstrated (Fig. 3).

c) In 2 animals, a second electrode was used to stimulate (150/sec.) the medullary reticular formation during the same time that a single stimulus was being delivered to the infra-orbital nerve. It failed to modify the delayed response, although stimulation of reticular formation has been reported to alter evoked activity in the trigeminal system.\textsuperscript{131}

d) In 1 animal, the cortex was left in place and stimulation of the sensory motor cortex failed to influence the trigeminal late potential provoked by the usual infra-orbital stimulation.

e) Barbiturates were not used as anesthetics, as it had been thought that perhaps the delayed wave was a reflection of activity in the reticular substance of the medulla. Subsequently, the effects of intravenous administration of Nembutal were tested in 3 animals while the delayed wave was being demonstrated. The delayed wave was greatly reduced in 1 animal and abolished in the other 2 within a very few minutes.

f) The effect of asphyxia was also examined. The delayed wave was abolished within 1 min. after cessation of artificial respiration (Fig. 8). The afferent spike could still be demonstrated for 30 min. after the heart ceased to beat.
Fig. 7. Top sweep in both records was taken from trigeminal posterior root near medulla; bottom sweep was taken from maxillary nerve at foramen rotundum. (1) Single shock stimulation. (2) Repetitive stimulation at 20/sec. The delayed potential was markedly attenuated in record 2 by repetitive stimuli. This simultaneous recording from posterior root of 5th nerve and maxillary nerve at foramen rotundum illustrates the difficulty in determining the precise time of onset of the centrifugal delayed wave which at first glance would appear to occur later in the recording nearest the brain stem.

g) One of the most interesting findings concerning the delayed potential was the demonstration of a marked post-tetanic potentiation. This was an inconstant finding and the variable factor is not known. Even when large doses of Flaxedil were given and all muscular movement was ruled out, at times decided potentiation of the delayed wave followed the attenuation which occurred with a short burst of stimuli of as low frequency as 10 per sec. (Fig. 9). This was produced by stimulation of, and recorded in, the trigeminal, facial and great auricular nerves. It is, of course, interesting to hypothesize regarding a possible correlation between this experimental

Fig. 8. (a) Response at maxillary nerve at foramen rotundum following stimulation of infra-orbital nerve. (b) Shows effects of hypoxia 1 min. later after having discontinued artificial respiration. The late wave is quickly reduced.
This record illustrates post-tetanic potentiation in facial nerve. The stimulating electrode was placed on 7th nerve at internal auditory meatus. The recording electrode was placed on 7th nerve peripherally in the face.

(A) An efferent volley immediately followed the shock artifact. After a longer delay there was a very small delayed potential. Tetanic stimulation at 10 per sec. abolished late wave but did not alter initial spike (B).

(C and D) Records taken 2 and 3 sec. after cessation of tetanic burst. Note marked potentiation of late potential, which presumably reflects an increase in central activity.

finding and the pain potentiated clinically by a touch stimulus in patients with tic douloureux. However, any such conjecture at the present time is highly speculative at best. But it would seem to be a finding that deserves further investigation.

DISCUSSION

A. The Delayed Response. The centrifugal propagation of the delayed wave within the trigeminal system as reported by King et al. has been confirmed. Volleys with a latency comparable to the delayed wave in the trigeminal system have also been seen in the facial and great auricular nerves and upper cervical dorsal roots. It would appear that a similar late volley occurs in the vagus nerve in addition to the reflex discharge that trigeminal stimulation evokes in nerves VII, X, XI and XII. Thus it seems that all of the cranial nerves that contribute afferents to the descending trigeminal tract show a delayed wave. This suggests that ephaptic signal transmissions within the descending tracts of the trigeminal system may be a factor in the production of the delayed response.

B. Relation of Trigeminal and Facial Nerves. The relation of the 7th nerve to tic douloureux has long been the subject of speculation. Not only the sensory component of Hunt, but the peripheral motor branches (which may contain deep proprioceptive fibers) seem to be involved. Dandy
Fig. 9B. Post-tetanic potentiation in infra-orbital nerve following a tetanic burst of stimuli to trigeminal posterior root. Top tracing was a pretetanus recording while bottom tracing was taken 4 sec. following the 100/sec. tetanic stimulus.

Fig. 9C. Tetanic stimuli to posterior root of 5th nerve also caused a potentiation in response recorded from great auricular nerve in this cat preparation. Top line is again pretetanus; bottom line post-tetanic. Note also decreased latency time. Tetanic stimulus frequency was 100/sec.

pointed out that facial neurectomy continued to be performed for tic pain long after Bell classified it as the motor nerve of the face. Instead of wondering how the surgeons could have continued to perform such an obviously nonhelpful procedure, we must consider whether cutting the peripheral 7th nerve might not be of aid. A review of the older literature produced no satisfactory statistics on this point, but Cushing in 1920 stated that cutting the facial nerve helped by placing at rest the areas from which the pain could be triggered. Many patients with true tic pain also demonstrate facial twitches, and Cushing described a “painful tic convulsif.” In the older literature there is often little distinction between the motor and sensory components.

Recently one of us (B.C.) tried a local block of the 7th nerve in an elderly woman with tic pain and trigger zones in the 2nd and 3rd trigeminal divisions. Although local block at the stylomastoid foramen has been reported with no mention of complication, the nerve was blocked more peripherally to avoid risk of a more lasting Bell's palsy from edema. The branches of the lower 7th nerve were blocked with 5 cc. of 1 per cent procaine just anterior to the parotid gland. A good lower facial paralysis was obtained with no subjective or objective sensory loss on the face, tongue or ear. Both the tic pain and the trigger zones were definitely reduced but not abolished. Because this type of response so closely paralleled that often
seen in block of the great auricular nerve for tic pain.\textsuperscript{33} it was thought that perhaps the fibers of the cervical nerve included in the facial nerve might have been responsible for the effect observed. Therefore, the great auricular nerve in the neck was also blocked; no further effect was produced on the tic pain, although the usual area of the lower ear became anesthetized.

It would be of interest to try local blocks of the 7th nerve at the foramen in patients with tic douloureux, but in view of the psychological effects of even a temporary facial paralysis, especially before planned surgical treatment, such experimentation has not seemed indicated.

C. \textit{Relationship of the Trigeminal and Great Auricular Nerves.} The relationship of the trigeminal system to the cervical region of the spinal cord\textsuperscript{44} has long been known anatomically.\textsuperscript{128} More of the physiological connections are now being reported. Although the spinal tract of the 5th nerve is supposedly largely composed of pain and temperature fibers,\textsuperscript{57,122} impulses resulting from a touch stimulus have been traced as far as the upper cord.\textsuperscript{72} Our entire concept of peripheral sensation may have to be modified in view of the work of Weddell and his group.\textsuperscript{123,162} von Frey's application of Müller's laws of specific nervous energies to the four primary modalities of common sensibility no longer seems sufficient.\textsuperscript{68} Regarding the problem of skin sensory discrimination, Granit\textsuperscript{61} stated, "It must be admitted that at the moment histology still is far in advance of physiology." Exteroceptive touch and pain are not simply mediated by different nerve endings, but are a complex pattern\textsuperscript{61} of the peripheral area stimulated (with overlap factors), intensity of stimulus, length of time the stimulus acts, varying rate of fiber conduction\textsuperscript{66} and temporal\textsuperscript{9} and spatial variables at the central endings as well. The spatial connections of the trigeminal nerve extend well into the cervical cord and it is now fairly well established that in the human adult the highest division of the trigeminal nerve not only lies most ventrally, but extends farthest caudally.\textsuperscript{30,106} It may be within the realm of possibility that impulses from a single afferent neurone may well convey information of different modalities. Thus in the trigeminal system the axones dividing as they enter the pons may have the impulses going to the main nucleus, ending up associated with the conscious interpretation of touch, while the impulse that descends in the trigeminal tract may subserve the sensation of pain. The physiological aspects of the touch and pain fibers have been thoroughly discussed by King\textsuperscript{91} who reported the trigeminal late potential as low as the 2nd cervical segment.

Recently one of us (B.C.) has had occasion to do several arteriograms under local anesthesia. The cervical nerves were blocked unilaterally at the level of the transverse processes of the higher cervical vertebrae with either 1 per cent xylocaine or procaine. There did not seem to be any possibility of local spread to involve the trigeminal system. Yet, while the area of anesthesia did not extend above the usual line along the jaw, there was definite, decreased sensation subjectively to touch and pinprick over the entire ipsilateral face and head. This had also been observed previously in
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blocking the great auricular nerve. A patient was found who after such a cervical nerve block had a hemihypesthesia of the entire ipsilateral half of the body. Since this could not be explained by any known peripheral overlap or systemic reaction, it was dismissed as probably ascribable to suggestion. In reviewing the literature, Hunt in 1909 described this condition in discussing the sensory function of the facial nerve and reported that Frankl-Hochwart in 1891 and later Donath had reported such a finding. The question must now be asked whether this does not coincide with knowledge concerning the central modulation of afferent impulses. Perhaps the pattern of inflow of impulses over the cervical sensory nerves (as well as the chorda tympani) maintains some type of activity centrally in the spinal cord or lower brain stem which modulates the passage of afferent trigeminal impulses or the ascending spinal impulses from below on their way to the thalamus. How this fits in with the newer concepts of the function of the reticular formation and the ascending extralemniscal sensory system must remain mere speculation for the present. It should, however, be verifiable experimentally.

D. General Nature of Delayed Responses. In recent years, much has been learned concerning efferent modulation of peripheral afferent systems. These now include muscle spindles, the retina, the cochlea, the olfactory bulb, and peripheral nerves. Even touch receptors may be under some efferent control. The effects of attention and habituation of afferent impulses have been well demonstrated. Corticotrigeminal connections are known to exist.

Some investigators contend that the trigeminal nerve contains efferent fibers, probably parasympathetic in nature. That the late trigeminal wave is not specific in the cat with its vibrissae was shown by King and his coworkers who reported the wave present also in monkeys. The question was raised whether the trigeminal delayed wave was present peripherally even in the free nerve endings. Our initial attempts to record potentials from the cornea or tooth root pulp have not been satisfactory technically.

The other explanation of the delayed wave as a dorsal root reflex seems to fit as far as latency times and wave form are concerned. But King reported that a decreased temperature did not bring about the expected increase in the late wave. If the delayed impulse is antidromic, is it merely a meaningless epiphenomenon reflecting neural activity around the central afferent endings, or does it have some physiological significance? Does the longer acting centrifugal potential affect the excitability of the peripheral receptor?

In view of the effect of barbiturates and asphyxiation on the reticular delayed response, the following observations may be of interest. One of us (B.C.) has observed the effects of phenobarbital, Dilantin, and chlorpromazine on a small group of patients with tic douloureux in an attempt to block the hypothecated sensory epileptogenic focus. Although the effect of sedation may have improved the patients' mood, no demonstrable change
was noted in the basic syndrome. But one patient with thalamic pain after a stroke was helped clinically by Dilantin. (More recently, Dilantin in larger doses has been reported by others to have been of value in a small series of tic patients.) Mephenesin was not tried either experimentally or clinically in patients.

That the trigeminal system contributes important afferent fibers to the reticular activating system is shown by the fact that after bilateral extirpation of the gasserian ganglion an "encéphale isolé" preparation will sleep like a "cerveau isolé." Recent histological investigations by the Scheibelst give further support to intimate connection of the trigeminal and reticular systems.

SUMMARY AND CONCLUSIONS

1. The historical development of therapy for tic douloureux has been reviewed and some of the mechanisms that have been proposed to explain this disease are discussed.

2. The delayed response in the trigeminal system following peripheral trigeminal stimulation and its centrifugal direction of conduction has been confirmed. The question of the antidromic versus the efferent nature of this response has not been settled conclusively.

3. By using the delayed potential, a relationship has been demonstrated between the central connections of the trigeminal, facial and great auricular nerves.

4. The delayed wave showed attenuation to repeated stimuli at a low-frequency and an inconstant post-tetanic potentiation. However, since the phenomenon of post-tetanic potentiation has not been investigated in a sufficiently large number of animals, conclusions regarding this aspect of the results must be regarded as preliminary and will require subsequent verification.

5. Barbiturates and asphyxia quickly abolished the delayed response.

6. There is still no direct evidence to correlate any change in this delayed trigeminal wave with the clinical syndrome of tic douloureux in the human. The delayed wave, however, is abolished in normal cats by minimal compression to the trigeminal system in a manner similar to the Shelden procedure for tic douloureux in the human.

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