Electron Microscopy of the Gasserian Ganglion in Trigeminal Neuralgia*

DAVID L. BEAVER, M.D.
Principal Contributor and Leader of Discussion

The pathogenesis of trigeminal neuralgia has remained an enigma. Its characteristic feature, excruciating, paroxysmal facial pain, may be produced by any number of conditions affecting the Gasserian ganglion either directly or indirectly. These include dental diseases, inflammation of the sclera, arterial compression of the trigeminal root, bone changes, cranial and intracranial tumors, and lesions in the veins of the neck or in branches of the brachial plexus.

The causes of "secondary" trigeminal neuralgia have included cerebellopontine angle tumors, lesions in the tear ducts, thrombosis of the posterior-inferior cerebellar artery, diseases of the mandibular joint, syringomyelia, chronic otitis media, tuberculous toxemia, nephritis with azotemia, indoxyluria, influenza, polyneuritis, infectious polyneuritis, encephalomyelitis, serum sickness, and lead poisoning.

In fact there is no part of the trigeminal pathway, from the shin to the cortex, where a lesion has not been described.

The general belief has been that there are no pathological changes in the trigeminal ganglion itself. Some of this legend, at least, is based upon a single ganglion removed by Victor Horsely and examined by Henry Head, who finally donated the ganglion to anatomy to be used for normal histology instruction. Although other investigators have found a variety of pathological changes in the trigeminal ganglion, their findings have never been widely accepted, due in part to the fact that even by light microscopy the normal histology of the ganglion has never been clearly defined. Electron microscopy has made the problem even more complicated, for degenerative changes due to aging or to occult ganglionic disease must be differentiated from tissue artifacts due to manipulation and to fixation. The necessity of establishing the normal ultrastructure of the ganglion became obvious to us after we had obtained our first few biopsies from patients with trigeminal neuralgia. The resulting initial studies were done first on experimental animals and subsequently on man.

For the last few years our main research interest in trigeminal neuralgia has been in relationship to a study of viral diseases of the central nervous system, particularly those viruses which produce intranuclear inclusions. The neurotropic affinity of herpes zoster is well known; and shingles involving a division of the trigeminal nerve is a classic disease entity. It has also been postulated by some investigators that trigeminal neuralgia might actually be due to a latent infection of the ganglion by a related virus, herpes simplex, the cause of the common fever blister. That this might be the case seemed borne out by experimental involvement of the ganglion and by the fact that section of the posterior root for trigeminal neuralgia frequently results in the occurrence of herpes labialis, whereas section of the anterior root does not.

Initially, we carefully saved a piece of each specimen for viral isolation, but as it became increasingly apparent that we were not dealing with a herpetic ganglionitis, this approach to the study was abandoned.

The morphological changes that we encountered in the ganglionic biopsies were so striking that we were encouraged to continue our study of the Gasserian ganglion in trigeminal neuralgia. Biopsies of Gasserian ganglia were obtained from 11 patients (nine female and two male) with classical trigeminal neuralgia of either the second or the third division of the fifth nerve, or both. Because of possible sequelae to tissue removal from the area of the ganglion supplying the ophthalmic nerve, no patients with first division involvement were included in the study. The patients ranged in age from 48 to 77 years, with an average age of 59 and a median age of 56. Symptoms had been present from 6 months to 13 years, with an average duration.

* This work was done in collaboration with Drs. Harold L. Moses and C. E. Ganote.
of 4\frac{1}{2} years. One patient had a history of trauma with subsequent scarring in the region of the zygoma before the onset of symptoms; one had an episode of transitory facial paralysis 30 years before developing pain; and one had a long history of chronic sinusitis and "migraine headaches." With the exclusion of one patient who had been in mild congestive heart failure, all of the patients were in relatively good health at the time of surgery, except for the symptoms of trigeminal neuralgia. Medical treatment had been attempted in eight patients, seven receiving diphenylhydantoin (Dilantin); and one a combination of B-12, Dilantin, and mephanesin carbamate (Tolseram). Three of the patients, however, had received no treatment before surgery.

The preoperative medication was atropine. In all cases halothane (Fluothane) was the primary anesthetic agent; in addition, eight patients received sodium thiamylal (Surital) and succinylcholine chloride (Anecline), and three were induced with intravenous thiopental sodium (Pentothal). In each case the gross appearance of the ganglion and surrounding area was normal, except for calcification of the internal carotid artery in the region of the sella in one 73-year-old woman. Biopsies of the trigeminal ganglion were obtained with a pituitary rongeur, after section of the proximal root. Specimens were transferred from the rongeur to cottonoid saturated with normal saline and, after mincing with a razor blade, were fixed in Dalton's fluid for 1 hour at room temperature. After surgery all of the patients did well; only two of the 11 developed fever blisters.

To determine the effect of the preoperative medication, anesthesia, and surgical trauma, we operated upon Cebus monkeys in a manner similar to that used in the human patients. Some monkeys that received only atropine and halothane anesthesia were sacrificed (intentional halothane overdosage) and the ganglion removed immediately after death.

After fixation, seven human specimens and
the experimental animal ganglia were dehydrated in graded ethanol and tertiary butanol solutions; after passage through toluene and acetone the specimens were embedded in Araldite 502. Four human specimens, after similar dehydration, were embedded in a 4 to 1 mixture of butyl and methyl methacrylate for comparison. Thick sections for phase contrast microscopy were cut on a Porter-Blum microtome, and adjacent thin sections were cut with glass knives on either a Porter Blum or LKB microtome. Sections were mounted on Formvar-carbon coated grids and stained with lead acetate. The specimens were examined in an RCA EMU 3-F electron microscope, using regular, low, and high magnification pole pieces.

Under the electron microscope the ganglion cells of specimens obtained from patients with trigeminal neuralgia showed a peculiar irregular vacuolization which gave the cytoplasm a fenestrated appearance (Fig. 31). These vacuoles, which occurred in the majority of the cells in every biopsy, tended to be large and irregular in contour. They were due neither to mitochondrial swelling, as in autolysis, nor to dilatation of the Golgi apparatus (Fig. 32). In cells in which the vacuoles were relatively small, their relationship to the Nissl substance could be clearly demonstrated (Fig. 33). No significant nuclear changes were present, and except for the diffuse vacuolization, the ganglion cells were apparently unaltered.

Some of the satellite cells showed a separation of the ergastoplasmic lamellae, which also resulted in the formation of irregular vacuoles, but because of the relative paucity of rough-surfaced endoplasmic reticulum, the fenestration of satellite cells was less prominent than that of ganglion cells. Vacuolization of satellite cells and neurons appeared to occur independently, in that fenestrated ganglion cells were not necessarily surrounded by vacuolated satellite cells (Fig. 31). Except for occasional vacuolization, satellite cells were,

Fig. 32. Ganglion cell with nucleus in upper left. Note the normal-appearing mitochondria interspersed within the cytoplasm between the irregular lacunae. The Golgi apparatus is seen in the lower right; ×12,000.
morphologically at least, normal in appearance. Schwann cells, on the other hand, which are generally considered to be histologically similar to satellite cells, exhibited a variety of structural alterations (Figs. 34 and 35). For the most part these changes were limited to Schwann cells that invested myelinated fibers. Although degeneration of Schwann cells sometimes preceded the breakdown of myelin, axons usually lost their Schwann cell investment only after considerable degeneration of myelin had occurred. In fact, obvious morphological changes in Schwann cells did not always accompany myelin degeneration. In many areas, apparently-intact Schwann cells surrounded axons which were covered by a thickened, piled-up, and disorganized type of myelin sheath (Fig. 36). This increase in the amount of myelin associated with individual axons was especially noticeable within or adjacent to ganglion cell clusters where, in the normal ganglion, fibers close to neurons are usually smaller, of uniform size, and less heavily myelinated. By comparison, therefore, this increase in the thickness of the myelin sheaths was striking (Fig. 37). Under phase-contrast microscopy the axons simply appeared to be hypermyelinated; but by electron microscopy it immediately became obvious that the increased myelin surrounding these nerves was irregular, fragmented, disarranged, and in an apparent state of degeneration (Figs. 37 and 38).

Frequently the axis cylinders of these nerves were also abnormally hypertrophic and tortuous (Fig. 36). When the axon was severely involved, the axis cylinder appeared folded, tangled, or plicated, so that it might be called a "plexiform microneuroma" (Fig. 39). With this myelin degeneration and axonal tortuosity, the hypertrophic axis cylinder generally assumed an eccentric position, where it was separated from the interstitial space only by a remaining lip of Schwann cell cytoplasm or

Fig. 33. Clump of vacuolated Nissl substance in the cytoplasm of a ganglion cell exhibiting minimal fenestration. The vacuoles seem to arise from the Nissl substance by dilatation of ergastoplasmic lamellae, which eventually form large irregular lacunae (compare Fig. 32); ×15,000.
FIG. 34. Various degenerative changes in the Schwann cells are illustrated here and in Fig. 35. In (a), a lipid droplet or lipofuscin-like accumulation is present in a Schwann cell surrounding an unmyelinated axon. In (b), a fragmented irregular lipid deposit is seen in the cytoplasm of a Schwann cell surrounding a myelinated axon. In (c), degenerative changes are present in the Schwann cell cytoplasm external to the myelin sheath as well as in the internal mesaxon.
FIG. 35. In (a), the internal portion of the Schwann cell shows greater involvement than the external. In (b), whorl-like deposits are present in the Schwann cell; and in (c), the degenerative changes are so severe that there is apparent disruption of the myelin.
Fig. 36. Intact Schwann cell surrounding a disorganized myelin sheath and hypertrophic tortuous axon; \( \times 7,000 \).

Fig. 37. Relatively normal sized myelinated axons (right) are seen in the vicinity of a nerve fiber which exhibits slight hypertrophy and tortuosity of the axis cylinder. Note particularly the thickness of the myelin sheath as well as its disorganized appearance; \( \times 7,000 \).
Fig. 38. Myelin sheath exhibits fragmentation and disruption, but is still surrounded by an attenuated Schwann cell and basement membrane. The axis cylinder occupies an eccentric position, but is not in direct contact with the extracellular space. Compare with Fig. 40. ×8,000.

Fig. 39. Tortuous hypertrophic axis cylinder giving the appearance of a “plexiform microneuroma.” Degenerating Schwann cell cytoplasm is discernible between the folds. Note also the extreme thinness of the myelin sheath on the lower aspect of the neuroma and the absence of myelin above. Collagen fibrils are present in the adjacent extracellular space; ×9,000.
by residual basement membrane (Fig. 38). Axonal dystopia or herniation seemed especially prone to occur at the nodes of Ranvier between the separated Schwann cells; but it was also seen internodally, accompanied by myelin disruption and Schwann cell degeneration (Fig. 38). With attenuation of the basement membrane, the naked axons lay in direct continuity with the extracellular space and collagen (Fig. 40).

All biopsies from patients with trigeminal neuralgia exhibited similar changes, which varied from one ganglion to another only in the degree of severity. Although focal demyelinization was occasionally seen in ganglia of monkeys that had been subjected to operation or killed by anesthesia, the changes were not different from those previously described in experimental animals and in man. In these studies of normal ganglia, we never saw vacuolization of nerve cells, degenerative hypermyelinization, microneuroma formation, or denudation of axis cylinders.

True trigeminal neuralgia, by definition, has to be a diagnosis of exclusion, that is, typical pain is present in the absence of demonstrable ganglionic disease. As with all idiopathic classifications of disease, the validity of such a diagnosis depends not only upon the limitations of the methods and techniques employed, but also upon the definition of what is meant by “normal.” Unfortunately, there is often a difference in perspective between the pathological and the anatomical points of view. An anatomist may consider a tissue normal if the changes present are found in a certain percentage of patients in a particular age group. A pathologist would find such a concept untenable, for it fails to take into account latent, subclinical, or occult disease, and relegates many degenerative diseases to a state of normality. In ganglia of all species, focal degen-

Fig. 40. Thick, disorganized myelin sheath exhibiting a loss of Schwann cell investment and focal attenuation or absence of the Schwann cell basement membrane. The eccentric axis cylinder lies in direct contact with the extracellular collagen; \( \times 6,000 \).
operative changes are the rule rather than the exception, and numerous pathological processes occur without any manifestations of overt disease. Thus, if a totally disease-free ganglion is to be the \textit{sine qua non} for the diagnosis of primary trigeminal neuralgia, few, if any, cases could qualify. The problem, therefore, is not whether changes are present in trigeminal neuralgia but, rather, whether the ganglionic abnormalities are of sufficient degree and individuality to be diagnostic of the disease and whether they can be related to the etiology, pathogenesis, or symptomatology.

The changes which we observed are probably the same as those described almost 40 years ago by Lignac and Van der Bruggen, namely, vacuolization of nerve cells, demyelination, and piling up of myelin. Without the aid of an electron microscope, however, it would be impossible to differentiate these alterations from those seen in autolysis and in non-specific focal degeneration due to age or to occult disease.

In our material, the vacuolization of the ganglion cells was a prominent and a constant feature. Yet, it is difficult to ascribe any particular significance to a phenomenon which could be due to a rapid intracellular fluid shift and which could conceivably occur within a matter of seconds or minutes. In all other respects, the ganglion cells appear normal. If ganglia are put on cottonoids or sponges moistened with tapwater, vacuolization will occur after a few minutes, but the vacuoles, as in autolysis, seem to result primarily from swollen mitochondria, although the endoplasmic reticulum is occasionally involved. In autolysis, the vacuolization is due almost entirely to mitochondrial swelling, and the Nissl substance is rarely involved. Nor does operative trauma seem to be a factor; it did not affect the simian ganglia which, due to the inexperience of the neurosurgical resident in operating on monkeys, were removed much more traumatically than any of the human specimens. Neither the preoperative medication nor the anesthetic agent seemed to make any difference.

We found a similar vacuolization of the ganglion cells, however, in one autopsy of a patient who did not have trigeminal neuralgia (Fig. 41); abnormalities of the myelin and axis cylinders were not present. The patient, a 39-year-old man, died about 3 days follow-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{Vacuolated ganglion cell in autopsy specimen from a digitalized patient who died 3 days following an acute myocardial infarction. No abnormalities were present in the axis cylinders and myelin; $\times$15,000.}
\end{figure}
ing an acute myocardial infarction. He had been rather heavily digitalized. Tic-like symptoms have been reported as a manifestation of digitalis intoxication; and in some experimental animals, at least, digitalis has also been reported to cause neuronal vacuolization. We are investigating this possibility further; three guinea pigs are being given increasing daily doses of digoxin (0.025 to 0.200 mg) intraperitoneally for 6 to 12 weeks. Although these studies are incomplete, no ganglionic vacuolization has, as yet, been observed (Fig. 42).

Since vacuolization of the nerve cells, including those in the trigeminal ganglion, has been reported in some species and also occurs in autolysis, these observations, which were made by other investigators by light microscopy, cannot be evaluated at the present time. Although vacuolization of the Nissl substance was a constant feature in our material, this, too, is difficult to evaluate. It seems unlikely that the vacuoles could be due to a long-standing disease process or to a severely damaged neuron, for hypesthesia and anesthesia, not pain, should have been the final result.

However, the changes observed within the myelin sheaths and axons might very well be capable of producing pain. The pain associated with post-traumatic, postoperative, and postamputation neuromata is well documented. In trigeminal neuralgia, not only is there the formation of "plexiform micro-neuromata," but also axis cylinders are frequently in contact with the extracellular space and collagen. Whether this is the mechanism by which pain is produced, cannot, of course, be ascertained, but the findings offer a possible explanation as to why decompression operations might have some therapeutic value, since internal pressure on abnormal formations within the ganglion would at least be reduced. The apparent disappearance of symptoms by simple decompression has heretofore been inexplicable and is one of the main arguments for considering trigeminal neuralgia a psychiatric disease.

The apparent piling up of myelin which occurs in trigeminal neuralgia can be best evaluated in sites where ganglion cells are present, namely, in the interneuronal and juxtaganglionic areas. In areas devoid of ganglion cell clusters, the nerve fibers tend to be more heavily myelinated and the myelin sheaths are irregular, so that focal myelin

Fig. 42. Ganglion cell from trigeminal ganglion of a guinea pig which received 2.05 mg. digoxin over a period of 6 weeks; X13,000.
Fig. 43. Trigeminal ganglion from 23-year-old female who died during an acute exacerbation of multiple sclerosis. Note degenerative hypermyelination and axonal hypertrophy and tortuosity; ×5,000.

degeneration in these areas could be misinterpreted. In trigeminal neuralgia, however, there is an apparent increase in the amount of myelin, accompanied by myelin degeneration, in areas where the nerves are not usually heavily myelinated.

Although degenerative changes occur in occasional Schwann cells in the absence of any noticeable myelin alterations, Schwann cell investments frequently remain, even after a considerable amount of myelin has been destroyed. In contrast to Wallerian degeneration, which involves both the axoplasm and the myelin, trigeminal neuralgia does not involve the axis cylinders. A somewhat similar process has been called "segmental demyelinating neuropathy," and is a cardinal feature of postinfectious encephalomyelitis, acute idiopathic polyneuropathy (Guillain-Barré syndrome), diphtheritic neuritis, combined system disease in pernicious anemia, and multiple sclerosis.

The association of multiple sclerosis with trigeminal neuralgia is an interesting relationship, well documented in the literature. In three different series reporting trigeminal neuralgia in a total of 2,905 patients, nearly 4% also had multiple sclerosis; moreover, trigeminal neuralgia is occasionally the first manifestation of multiple sclerosis.

Recently we examined by electron microscopy the trigeminal ganglion from a 22-year-old woman who died during an acute attack of multiple sclerosis. Three months before her death she had had a transient attack of unilateral facial numbness, but since she was admitted in a moribund condition, no further history was obtainable. By light microscopy, the ganglion on the affected side showed a small focal infiltration of sparsely-scattered chronically inflamed cells. By electron microscopy, however, the most interesting changes were in the myelinated axons. There was degenerative hypermyelination, demyelination, and tortuosity of the axis cylinders, approaching in severity that seen in trigeminal neuralgia (Figs. 43 and 44). Although there was no vacuolization of the ganglion cells, the morphologic resemblance of the axonal changes observed in multiple sclerosis to those in trigeminal neuralgia was striking.

We are still far from explaining the initiating factor or factors of trigeminal neuralgia.
In view of our findings, however, we can hypothesize that any disease process capable of producing segmental demyelinization might cause pain providing the ganglion cells themselves remain intact and if accompanied by denuded axis cylinders or a neuromatous response to injury. Since most diseases that affect the trigeminal ganglion result in the destruction of ganglion cells, hypesthesia and anesthesia could be expected rather than pain.

In summary, the electron microscope pictures trigeminal neuralgia as a disease characterized by vacuolated but intact ganglion cells, degenerative hypermyelinization, segmental demyelination with denudation of axis cylinders, and microneuroma formation. This morphological situation could produce the clinical evidence of a sensory disturbance. The paroxysmal nature of the pain may be inherent in the function of the ganglion itself, or it may be related to fluid shifts, vascular disturbances, central connections, or to peripheral injury or stimuli. The presence of microneuromata within the ganglion, depending on their relationship to peripheral sensory nerves, might also explain the frequency of precisely-located trigger points. In any event, even though the basic etiology of trigeminal neuralgia is obscure and the mechanism of pain hypothetical, the concept that there are no associated pathological changes in the Gasserian ganglion itself is no longer tenable.