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Original Investigations

Abnormal Ultrastructural Appearances in Axons of Feline Pericruciate Cortex After Lateral Funiculotomy*

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Summary. Following left lateral funiculotomy, axons of cat pericruciate cortex exhibited neurofilamentous hyperplasia and complex, adaxonal, oligodendrocytic invaginations into electron-lucent or (commonly) electron-dense, degenerating axoplasm. These changes were absent from sham-operated and unoperated animals. Neurofilamentous hyperplasia was exclusively right-sided and appeared in myelinated axons 5–49 days postoperatively and in nonmyelinated axons 14–153 days after surgery. Oligoglial invaginations were present 1–49 days after surgery and were predominantly right-sided.

Intramyelinic, axo-dendritic synapses appeared in operated cats 5–10 days postoperatively. Intra-axonal accumulations of ribosomes were found also. These changes also occurred exclusively or predominantly contralateral to spinal surgery.

Other ultrastructural abnormalities, e.g., amorphous transformation of axoplasm and accumulations of dense bodies in intra-myelinic, dark cytoplasm, had a less certain relationship to lateral funiculotomy.

The axonal alterations that were limited to operated cats possibly represent a true retrograde axonal degeneration occurring at a distance from the site of axonic interruption and unaccompanied by evidence of nerve cell death.

Key words: Axons – Retrograde axonal degeneration – Motor cortex – Lateral funiculotomy – Neurofilamentous hyperplasia – Oligodendroglia.

After one-sided peripheral nerve injury axons in the ipsilateral spinal anterior horn may exhibit neurofilamentous hyperplasia and accumulations of enlarged mitochondria and ribosomes (Barron et al., 1971). Similar axonal alterations occur in lateral geniculate body after extirpation of the visual cortex (Barron and Doolin, 1968). It may be questioned whether these axonal abnormalities represent a truly retrograde axonal response to injury. Interpretation of axonal changes appearing within the lateral geniculate body after corticectomy is complicated by the concomitance of nerve fiber degeneration secondary to de-afferentation, since parent cell bodies of cortico-geniculate axons are destroyed by visual cortex extirpations. Transganglionic effects (Knyihar and Csillik, 1976) may produce alterations in the central processes of posterior root ganglion neurons after plexectomy and could conceivably account for abnormal axonic profiles in the vicinity of chromatolyzed motoneurons.

Recently we have found abnormal axons in the environs of chromatolyzed pyramidal neurons of feline pericruciate cortex. As will be brought out in the discussion, the axonal abnormalities we will describe appear to represent a truly retrograde, degenerative phenomenon. The retrograde axonal abnormalities that may follow severance of central fiber tracts have long been of interest to neuroanatomists and continue a subject of current research (Lassek, 1942; Cole and Nauta, 1970; Kalil and Schneider, 1975).

Methods

Under sodium pentobarbital anesthesia left lateral funiculotomy was performed at the second cervical (C-2) segment in adult cats using a Zeiss operating microscope employed at 6× magnification. Fifteen funiculotomized animals were sacrificed by intra-aortic perfusion with a formaldehyde-glutaraldehyde (Barron et al., 1971) sequence at survival times of 1, 3, 5, (2 aminals), 7, 10 (2 animals), 14–15 (3 animals), 22 (2 animals), 28, 49, and 153 days. The perfusion procedure resembled that described earlier (Barron et al., 1971) except that the formaldehyde concentration was 5.6% and a Holter animal perfusion pump was used in lieu of gravity perfusion. Two sham operates (laminectomy and dural incision only) surviving surgery by 5 and 14 days and two unoperated animals were killed also.

After completion of the 30–45 min perfusion, 20 ml of chilled 4% buffered glutaraldehyde solution were injected into the cisterna magna. The body was left for 2 h in a cold room at 4° C when the brain and spinal cord were removed. A parasagittal cut, extending through

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the cruciate sulcus, was made in each cerebral hemisphere 4 mm lateral to the midline. The lateral slices of each hemisphere were used for the preparation of blocks of the left and right anterior and posterior sigmoid gyri. These blocks were fixed further by immersion in cold glutaraldehyde (4° C) for 4 h and stored overnight in 0.1 M cacodylate-0.3 M sucrose, pH 7.6. Dicing, fixation in 1% osmium tetroxide for 3 h and embedment in Epon 812 followed.

After preparation and microscopic examination of 1 μm sections stained with alkaline toluidine blue, blocks containing large neurons (usually greater than 1000 μm^2) were trimmed appropriately and silver-gold sections were cut on an LKB ultramicrotome (Ultrotome III). "Thin" section were "stained" with lead citrate and uranyl acetate and examined in a Jeolco JEM 100 B electron microscope operated at 60 kV.

Transverse slices of Cl-4 segments of spinal cord were taken from every operated animal, embedded in paraffin and sectioned at 10 μm. The entire C2 segment was sectioned serially. The paraffin sections were stained by hematoxylin-eosin and luxol fast blue-periodic acid Schiff techniques.

Results

Except for minor intrusions on spinal gray matter and the posterior root entry zone in some animals, surgical lesions were limited to the left lateral funiculus. Different types of peculiarity in axonal ultrastructure are described separately.

1. Neurofilamentous Hyperplasia in Axons

Found only in the right sensorimotor cortex were myelinated axons exhibiting neurofilamentous hyperplasia (Figs. 1–3). These were most numerous in one of the 5-day survivals (Figs. 1–3) but examples occurred 15–49 days after operation. On three occasions filament-rich axons were invested by intramyelinic macrophages (Fig. 1) having ultrastructural characteristics of microglia. These axons sometimes had attenuated myelin sheaths (Figs. 2,3), ranged in diameter from 2.7–16.0 μm (generally 8–16.0 μm), encompassed cross-sectional areas approximating 200 μm^2 and contained lamellated dense bodies, mitochondria, (the latter often vacuolated), tubules and cisterns of smooth ER (Fig. 3), vesicular elements and glycogen granules. Paranodal regions of axons of normal animals may contain accumulations of mitochondria and lamellated dense bodies. However, dense packing of neurofilaments, closely-apposed aggregates of organelles, and obvious axonal swelling and myelin sheath attentuation successfully distinguished abnormal profiles. Conversely, the presence of many microtubules and well-preserved multivesicular bodies and prominent (but not complexly invaginated) folds of adaxonal oligoglial cytoplasm helped to characterize normal nodal regions.

Other enlarged, filament-packed neuronal processes confined to right sensorimotor cortex were unmyelinated (Figs. 4–6) and occurred 14–153 days after funiculotomy. Several contained synaptic vesicles in addition to accumulated mitochondria and glycogen granules and were apposed to dendrites (Fig. 4) or cell bodies but pre- and post-synaptic membranous specializations were not associated.

In a 14-day and a 28-day survival large unmyelinated, rounded bodies packed with dense mitchondria, filaments, and vacuoles occurred in the neuropil and had an area approximating 200–230 μm^2 (Fig. 6). These bodies lacked synaptic contacts suggesting their axonal rather than dendritic origin. Furthermore, when dendrites exhibit neurofilamentous hyperplasia during axon reaction, cell somas show a similar phenomenon (Barron, 1975) whereas in cat sensorimotor cortex axotomized neuronal perikarya seldom have even a modest increase in filamentous content (Barron and Dentinger, in prep.).

2. Axons with Adaxonal Oligoglial Invaginations

Axons invaginated by oligoglial processes (Figs. 7–9,11,12) were always myelinated and usually had electron-dense (Figs. 7,8) axoplasm containing abnormal mitochondria. Sometimes both electron-dense and electron-lucent axoplasm occurred with invaginations within the same myelin sheath (Fig. 8). Less commonly, invaginated axons had entirely electron-lucent axoplasm (Figs. 9,12) containing vesicles, vacuoles, smooth ER and, of special note, ribosomes (Figs. 12–14). Adaxonal invaginations were not associated with axons exhibiting neurofilamentous hyperplasia.

The moderately dark, granular appearance of the invaginating cytoplasm and its resemblance to and proximity to external mesaxons (Figs. 7–9) left little doubt as to its oligodendrocytic origin. Oligoglial invaginations were observed 1–49 days postoperatively but were most numerous 5 days after funiculotomy. When invaginated axons were cut longitudinally their diameters ranged from 0.9–5.0 μm (mean 2.0 μm). In only one animal, a 5-day survival, were adaxonal invaginations present bilaterally. Otherwise they were limited to cortex contralateral to operation. In the animal with bilateral abnormality 31 blocks from the right hemisphere and 22 from the left were "thin-sectioned." The frequency of invaginated dense profiles, right: left, was 5:1. Adaxonal invaginations were not encountered in unoperated or sham-operated cats in the 126 blocks of right and left sensorimotor cortices submitted to electron microscopic survey.

3. Ribosomes in Myelinated Axons

At 5–22 days postoperatively, myelinated axons of the right sensorimotor cortex measuring 1.0 to 4.0 μm in diameter not infrequently contained single and rosette

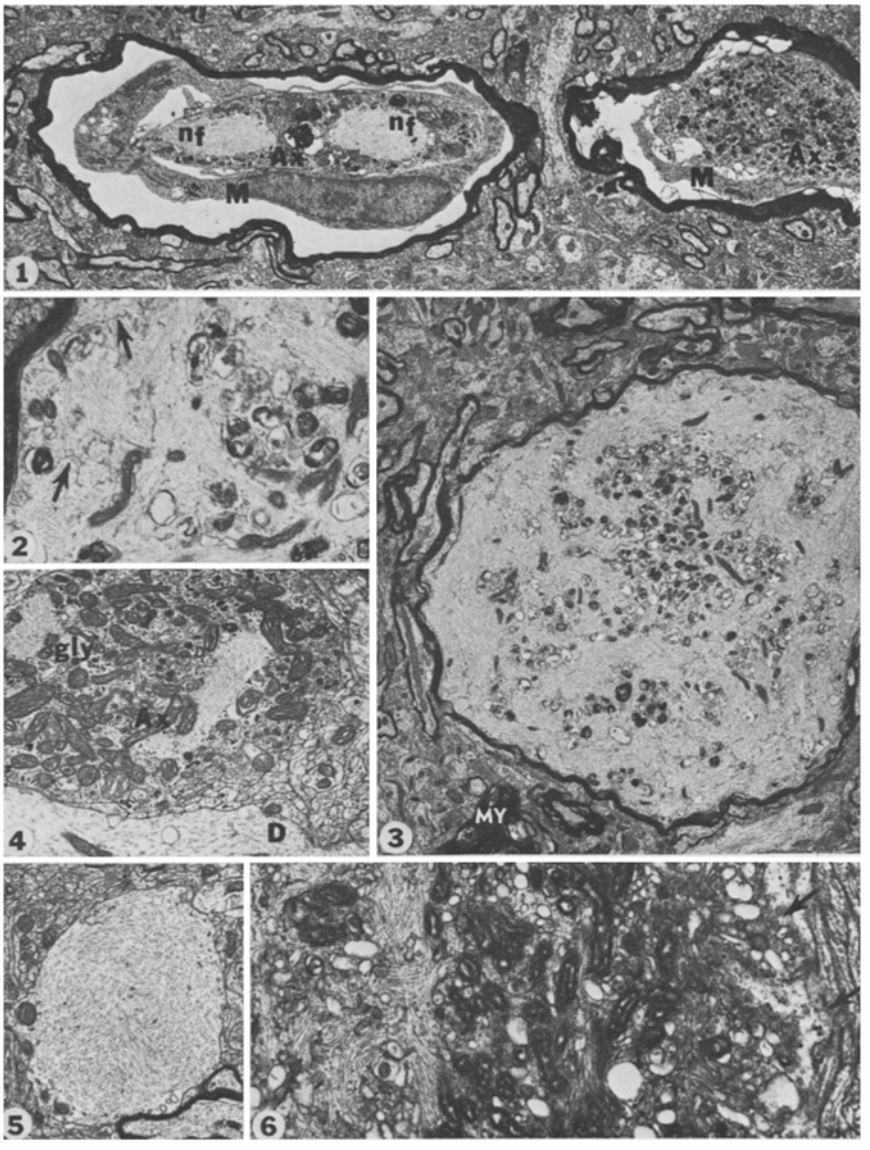

Fig. 1
All figures derive from the right pericruciate cortex of operated (left lateral funiculotomy) cats. An axon (*Ax*) containing packed neurofilaments (*nf*), dense bodies, mitochondria, etc., is enveloped by a microglial phagocyte (*M*). To the right, microglial cytoplasm (*M*) is apposed to another abnormal profile (*Ax*), doubtless a part of the same nerve fiber. 5 days survival. ×2,822

Figs. 2 and 3
Expanded axons are filled with neurofilaments, mitchondria, lamellated dense bodies, vacuoles, and profiles of smooth endoplasmic reticulum (arrows, Fig. **2**). Unravelled myelin of another degenerating axonal profile is present (*MY*) in Fig. **3**. 5 days survival. ×11,288 and ×3,604

Fig. 4
Unmyelinated axonal profile (*Ax*) contains neurofilaments, glycogen granules (*gly*), and mitochondria with dark membranes and electron-lucent matrix. A dendrite (*D*) is closely apposed. 22 days survival. ×9,180

Fig. 5
An unmyelinated, presumably axonic profile, is packed with neurofilaments. 153 days survival. ×6,562

Fig. 6
Part of a large, rounded, unmyelinated structure, presumedly axonal, contains electron-dense mitochondria, vesicles and vacuoles. Note lack of a clear limiting membrane peripherally (arrows). 22 days survival. ×15,232

ribosomes (Figs. 10, 12–14) in association with clusters of large mitochondria (Fig. 10) or complex oligoglial invaginations (Figs. 12–14). Adjacent cisterns of ER were granulated only rarely. We observed but one myelinated axons of an unoperated animal which contained ribosomal rosettes and large (0.7–1.0 × 2.5–3.0 μm) mitochondria.

4. Axons with Amorphous Axoplasm

Expanded myelinated axons having a structureless or very finely granular axoplasm were found bilaterally in unoperated, sham-operated and funiculotomized cats. In the last they were sometimes very large, especially on the right side (Fig. 15) where major and minor axes of 10–14 and 6–8 μm were encountered. They contained vacuoles and vesicles of varied appearance (Figs. 15, 16); focal concentrations of mitochondria (Fig. 15) normal-appearing or vacuolated; tubules of smooth ER (Fig. 16); multivesicular bodies and rounded aggregates of electron-dense particles (Fig. 15). Twice a single strand of adnexal oligoglial cytoplasm sequestered normal-appearing axoplasm at the periphery of the amorphous material but complex oligoglial invaginations were not associated.

5. Other Findings

Myelinated profiles containing synaptic complexes (Fig. 17) occurred in 5–10 day survivals and were confined to the right side. Redundant loops of myelin were larger in the right pericruciate cortex and measured 12–25 μm in length.

In *both* operated and unoperated cats we encountered attenuated myelin sheaths around an eccentrically-placed, relatively small axon. Between the

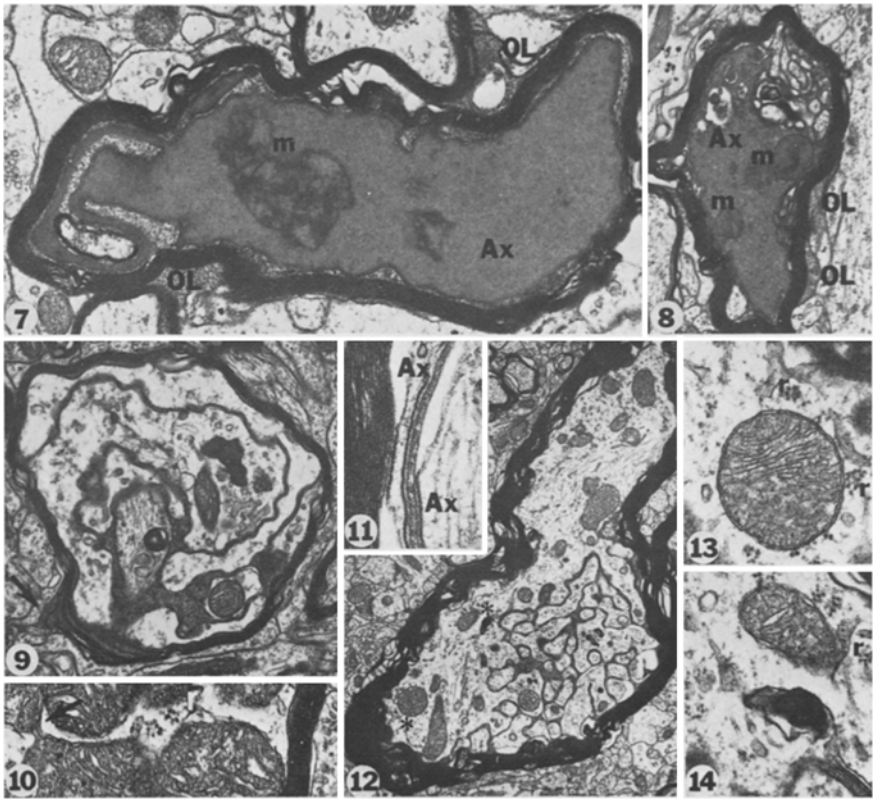

Fig. 7
Five days postoperatively dense axoplasm (*Ax*) with degenerating mitochondrion (*m*) is surrounded by intramyelinic oligodendroglial cytoplasm resembling that of oligodendroglial processes (*OL*) external to the myelin sheath. ×21,080

Fig. 8
Note oligoglial cytoplasm (*OL*) external to myelin sheath containing degenerating dense axoplasm (*Ax*) with abnormal mitochondria (*m*). Note also relatively lucent axoplasm (see upper right corner of profile) invaginated by thin, dark, oligoglial processes. 5 days postoperatively ×12,920

Fig. 9
Electron-lucent axoplasm invaginated and compartmentalized by processes of oligoglial cytoplasm. Oligoglial cytoplasm external to the myelin sheath (arrow) is similar to that of internal invaginations. 5 days survival ×12,920

Fig. 10. Within a myelinated axon of anterior sigmoid gyrus 15 days after funiculotomy note large mitochondria and rosette ribosomes (*r*). Note narrow waist connecting 2 mitochondria at arrow. ×27,472

Fig. 11. A tongue of oligoglial cytoplasm with axoplasm (*Ax*) on either side. 5 days postoperative. ×42,840

Fig. 12. Complex network of adaxonal oligodendroglial cytoplasm invaginates myelinated axon of 22 day survival. The areas of axoplasm marked by asterisks are enlarged in Figs. 13, 14. ×6,120

Fig. 13. Enlargement of portion of Fig. 12. Note particles having size, electron-density, and rosette arrangement of ribosomes (*r*). ×21,880

Fig. 14. Another enlargement of an area of Fig. 12 to show ribosome-like (*r*) particles. ×27,880

myelin and the axon dark, structureless cytoplasm was interposed and was packed with vacuoles and dense bodies (Figs. 18,19). The latter had often a lamellar structure.

Only a few electron-dense boutons were seen. These were confined to right sensorimotor cortex of funiculotomized cats.

Discussion

1. General Comment on Retrograde Changes in Proximal Stumps of Severed Central Axons

Following severance of central axons, the fate of the proximal stump varies. (1) The proximal stump may undergo dissolution (indirect Wallerian degeneration of van Gehuchten, 1903) when death of the parent perikaryon is associated (Grant and Westman, 1969; Aldskogius, 1974). Indirect Wallerian degeneration proceeds in a cellulifugal, spatio-temporal sequence beginning at the cell body (van Gehuchten, 1903; Grant and Westman, 1969; Aldskogius, 1974) and is encountered specially in immature animals (reviewed in Aldskogius, 1974). (2) In some systems, proximal stumps of interrupted central axons persist almost indefinitely (Cole and Nauta, 1970) though they and their parent cell bodies atrophy. (3) The central stump may degenerate *only in its distal part*. Thus Kalil and Schneider (1975) reported that, following severance of the medullary pyramid in the hamster, a retrograde degeneration ensued which began in the most caudal part of the central stump and proceeded slowly rostrally though not effectively extending beyond pontine levels even 14 months after the lesion. Severe shrinkage, but not loss, of layer V pyramidal neurons of sensorimotor cortex was associated (Kalil and Schneider, 1975).

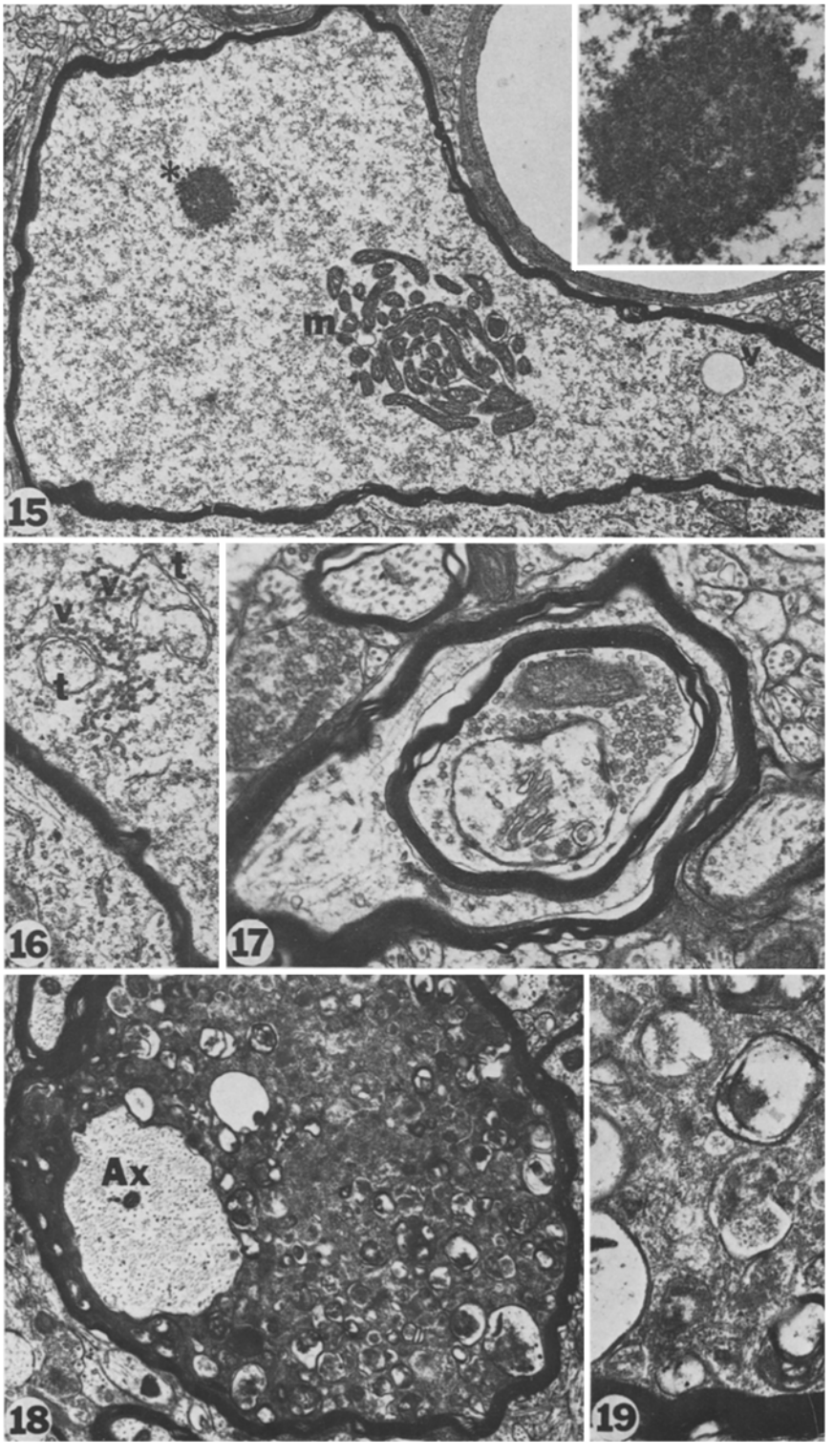

Fig. 15
Expanded myelinated axon of 5 day survival contains a cluster of mitochondria (*m*) within amorphous axoplasm, a vacuole (*v*) and a cluster of dark particulate material (*) composed (inset, upper right) of granules and vesicles. ×10,094 and (inset) ×35,226

Fig. 16
Myelinated axon similar to Fig. 15 containing smooth tubular profiles (*t*) and dark vesicles (*v*). 5 days postoperative. ×13,596

Fig. 17
Within a myelinated axon is a myelin-invested axodendritic synapse. 10-day survival. ×23,690

Figs. 18 and 19
Eccentrically-placed (Fig. 18) normal-appearing axon (*Ax*) seems compressed by intramyelinic oligoglial cytoplasm containing numerous dense and vacuolar membranous (Fig. 19) profiles. 28 days post-funiculotomy. ×10,609 and ×32,239

An axonal reaction leading to death of neurons of pericruciate cortex and indirect Wallerian degeneration of their axons does not account for the numerous abnormal axons occurring in our material ar a relatively great distance from the lesion and within a few days of it. We have not observed evidence of nerve cell death in cat sensorimotor cortex after lateral funiculotomy despite extensive study by light and electron microscopy (Barron and Dentinger, in preparation). Similarly, Lassek (1942), who studied Betz cells in cat

and monkey after high cervical hemisections, did not discover indication of death of Betz cells after axotomy.

Lateral funiculotomy interrupts axons of cortical neurons located outside the sigmoid gyri. If these cells were to die during axon reaction and if they normally sent collateral axons to pericruciate cortex, our finding of axonal degeneration in pericruciate tissue should be explained. We know of no evidence that supports this possibility nor have we seen indication of it.

There are no direct spino-cortical fibers and prograde or direct Wallerian degeneration cannot be invoked in explication of our findings. It seems unlikely in the extreme that degenerating fibers in pericruciate cortex could be the result of a transneuronal degeneration following upon interruption of spinothalamocortical projections. Furthermore, axonal alterations due to interruption of spinothalamic fibers and a transneuronal effect would be expected to occur ipsilateral to the side of cord surgery. Involvement of the posterior funiculi in our operated material was absent or inconsequential, thus virtually eliminating this source of any putative transneuronal changes.

We are led to suggest that the abnormal cortical axons described in this paper derived from collaterals of layer V pyramidal neurons or from main stem axons distal to collateral branches. There is a reduction in numbers of axon collaterals of cortical pyramids after undercutting of the cerebral cortex and interruption of their axons (Rutledge et al., 1969). Swelling of axons of undercut cortex occurs and may involve collateral branches (Cajal, 1928; Rutledge et al., 1969). Electron microscopic investigation of the medullary pyramids of cats subjected to high cervical lateral funiculotomy may help to determine where, in the course of corticospinal axons and their branches, the retrograde axonal degeneration we describe begins.

2. Types of Axonal Alteration

a. Neurofilamentous Hyperplasia. Axonal profiles, myelinated and unmyelinated, and boutons may swell and may develop increased numbers of neurofilaments and other organelles during the retrograde changes that affect lateral geniculate body, lateral cervical nucleus, spinal lateral motor cell columns and red nucleus following interruption distally of the axons of neuronal perikarya located within these structures (Barron and Doolin, 1968; Grant and Westman, 1969; Barron et al., 1971; Barron et al., 1975). Neurofilamentous hyperplasia lacks etiopathogenetic specificity, however, since similar axonal alterations occur in a variety of pathologic circumstances, such as in the proximal stumps of severed axons adjacent to the site of an injury, vitamin E deficiency, senility (medullary sensory nuclei), and other conditions (Lampert, 1967; Jellinger, 1973).

b. Oligodendroglial Invaginations within Myelinated Nerve Fibers. Spencer and Thomas (1974) consider invaginating adaxonal sheaths of cytoplasm to accomplish in both peripheral and central nervous systems the sequestration and phagocytosis of abnormal axonal organelles. The process is part of the constant removal, renewal and remodeling that characterizes living tissue and may be exaggerated in pathologic circumstances. However, Spencer and Thomas rarely observed "oligodendroglial cell/axon networks" in normal central nervous system and neither Balentine (1977) nor ourselves, as yet, have encountered them in normals. Interestingly, Spencer and Thomas found maximal development of interdigitating adaxonal sheath cell networks under conditions of centripetal axonal degeneration ("dying-back") in both peripheral and central nervous systems. Despite the established association of interdigitating adaxonal sheath cell networks with "dying back" (Spencer and Thomas, 1974) and retrograde axonal atrophy or degeneration, it is apparent that this, like other forms of axonal abnormality, does not have etiopathogenic specificity and may occur with intoxications (Blakemore, 1972; Blakemore, Palmer and Noel, 1972; Balentine, 1977) and prograde Wallerian degeneration (McMahan, 1967).

c. Other Ultrastructural Abnormalities in Axons. There is biochemical evidence both for an autochthonous, RNA-directed, extramitochondrial, protein-synthesizing machinery intrinsic to axons (reviewed in Frankel and Koenig, 1977) and for axoplasmic transport of ribosomal RNA (Bondy et al., 1977). In reports of ultrastructural studies, Barron and Doolin (1968) and Barron et al. (1971) illustrated ribosomes in myelinated axons of lateral geniculate body and cervical anterior horn of cat after, respectively, visual corticectomy and brachial plexectomy. Zelena (1970) described ribosome-like particles in myelinated axons of normal rat posterior root ganglia and noted their concentration in the initial segment. Dimova and Markov (1976) encountered ribosomes around clusters of large mitochondria within initial segments of regenerating axons of rat hypoglossal nerve. That the accumulations of ribosomes we now describe in axons of sensorimotor cortex of funiculotomized cats have some meaningful relationship to distal axotomy seems likely since ribosomes were seen on only one occasion in a cortical axon of an unoperated animal.

Myelinated axons containing amorphous axoplasm (e.g. Fig. 15) are of uncertain significance. They were largest contralateral to surgery. We are not aware of publications where entirely similar myelinated profiles are illustrated. Altered axons and axon terminals,

especially the latter, may be encountered, however, in the central nervous system of normal cats and rats (Rustioni and Sotelo, 1974; Sotelo and Palay, 1971). The altered profiles may be indicative of a continuing turnover and remodeling of axonic processes and terminals (Sotelo and Palay, 1971). Such a normal process of degeneration and renewal might be exaggerated under pathologic circumstances.

The presence of axo-dendritic synapses within myelin sheaths has been reported during transneuronal atrophy (Colonnier and Guillery, 1964) and retrograde degeneration (Barron and Doolin, 1968) of lateral geniculate body. This abnormality appeared in the present work only in the sensorimotor cortex opposite to lateral funiculotomy. Possibly retraction of axons with their termini and attached synaptic dendrites accounts for these peculiar profiles.

Broad rings (Figs. 18, 19) of oligodendroglial cytoplasm filled with lamellated dense inclusions and surrounding small, well-preserved, but seemingly compressed axons were observed in unoperated animals and may represent a type of spontaneously occurring cellular degeneration.

3. *Miscellaneous Comment*

The work reported here prompted a review of more than 2,000 electron micrographs collected during a study of axon reaction in cat red nucleus (Barron et al., 1975). Five examples of complex oligoglial invaginations were found. All occurred on the side opposite a unilateral, high cervical rubrospinal tractotomy.

The great preponderance of axonal abnormality in pericruciate cortex contralateral to funiculotomy agrees with the observation that Betz cell alterations are virtually exclusive to the hemisphere opposite the side of spinal surgery (Barron and Dentinger, unpublished; Lassek, 1942). Injection of horseradish peroxidase into cat lateral funiculus results almost solely in labeling of pyramidal neurons on the side opposite the injection (Berrevoets and Kuypers, 1975).

Brodal and Walberg (1952) claimed the presence of *ascending* fibers in the pyramidal of the cat. They found degenerating, argyrophilic fibers in sensorimotor cortex after cervical lateral funiculotomy. Their findings may possibly be interpreted as due to a retrograde axonal response which we now describe at an ultrastructural level.

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