ELECTRON MICROSCOPIC OBSERVATIONS ON ALLERGIC ENCEPHALOMYELITIS IN THE RABBIT*, ‡

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Plates 60 to 70

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Electron microscopy has altered our concepts of the structure and formation of the myelin sheath.

It is now evident that myelin is a highly ordered multilayered membranous structure (1–6) which in the peripheral nervous system develops from and is an integral part of the Schwann cell and in the central nervous system of the oligodendroglia. Formation of a myelin sheath is dependent upon the contiguous presence of both an axon and a sheath cell. Similarly, maintenance of the myelin sheath requires the presence of both neuronal and supporting elements, and consequently, injury to either should result in loss of the myelin. Thus, an insult to either the Schwann or oligodendroglial cells should lead to a primary demyelination, whereas injury to the neuron or axon results first in degeneration of the axon and only secondarily in myelin destruction. Wallerian degeneration following section of a nerve or of a central tract is a prototype for the latter, secondary demyelination, and has been described electron microscopically for both the central and peripheral nervous systems (7, 8). Concerning the former, primary demyelination in experimental allergic encephalomyelitis, it has been suggested on the basis of silver stained preparations that the axon is preserved in early lesions, but that it has been denuded of its myelin sheath.

In view of the variety of spontaneously occurring human and animal demyelinating diseases and of the uncertainties concerning their origins, it is of interest to examine the fine structure in experimentally reproducible demyelinization. With this in mind, we have examined allergic encephalomyelitis in rabbits by electron microscopy.

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§ Sister Elizabeth Kenny Scholar in Pharmacology.

Materials and Methods

Adult albino rabbits were injected with an emulsion composed of brain and Freund's adjuvants (2 parts of the white matter from bovine brain, 1 part baylol-F, 1 part arlarcel-A, 1 part water, and 10 mg. of dried dead tubercle bacilli per ml. of the final mixture).[1] The emulsion was injected subcutaneously, 0.25 ml. into each foot-pad and 1 week later a second similar injection was made. The animals were killed by decapitation (usually 2 weeks after the second injection) at a time when paralysis of the hind limbs was marked. Specimens from a total of 4 animals were studied by electron microscopy. Control material was not obtained simultaneously since in this laboratory spinal cords and sciatic nerves of many normal rabbits have already been examined in the electron microscope by the same technics of preparation. Blocks for electron microscopy were removed from the spinal cord, dorsal and ventral roots, and sciatic nerves as rapidly as possible after killing the animal. The small excised pieces of tissue were fixed in Dalton's osmium tetroxide solution (9) for 1 hour at room temperature. They were dehydrated rapidly in gradually increasing concentrations of ethanol (10 to 100 per cent by 10 per cent increments), placed in toluene for 30 minutes (10) and then infiltrated in 7:1 butyl methyl methacrylate, and embedded in partially prepolymerized methacrylate to which 0.25 per cent benzoyl peroxide had been added as a catalyst. Polymerization was at 60°C. for 12 hours. Adjacent thick and thin sections were cut on a Porter-Blum microtome with glass knives. Thick sections (1 micron) were observed by phase microscopy or stained for light microscopy. Since the lesions of allergic encephalomyelitis were not visible in the gross, multiple blocks of spinal cord were embedded and then examined by thick sections and phase microscopy in order to find the involved areas to examine electron microscopically. Thin sections were mounted on collodion-covered copper grids and viewed in an RCA electron microscope (EMU- 2E or 3C). Original micrographs were made at 1,000 to 10,000 diameters on Cramer plates. In addition, 5 to 10 micron sections of paraffin-embedded or frozen tissue were prepared for light microscopy.

Light Microscopy:

In sections stained by Nissl, hematoxylin and eosin, or luxol fast blue–periodic acid–Schiff methods, the lesions were similar to those described by others in experimental allergic encephalomyelitis.

Meninges and dorsal root ganglia were invariably infiltrated with inflammatory cells. Perivascular accumulations of lymphocytes, plasma cells, occasional neutrophiles and mononuclear cells were especially noteworthy in the outer portions of the white matter of the lumbar spinal cord. Many of the perivascular mononuclear cells were laden with sudanophilic droplets. Scattered zones of myelin destruction were more readily discerned in osmic stained sections viewed by phase optics than by the routine myelin sheath stains. Also by phase microscopy it was evident that myelin was not only destroyed within central tracts, but also to a lesser degree in the spinal nerve roots.

Electron Microscopy:

Peripheral Nervous System.—Within the sciatic nerves the myelin of only an occasional axon (Figs. 2, 3, and 4) was damaged whereas the myelin about a

[1] Arlacel-A is an emulsifying agent, mannide mono-oleate, obtained from Atlas Powder Company, Wilmington, Delaware. Bayol-F is a mineral oil obtained from The Standard Oil Co. of New Jersey.

majority of the axons was apparently normal (Fig. 1). Such, however, was not the case in the dorsal and ventral spinal roots.

In these more proximal portions of the peripheral spinal nerves, some myelinated axons were normal but adjacent axons had been denuded of their myelin (Figs. 5 and 6). Within a single root, lesions of various stages leading up to destruction were evident. The slightest recognizable alteration, interpreted as probably representing the initial stage in pathogenesis, was an increase in volume and a vacuolization of Schwann cell cytoplasm with or without inclusions of myelin globoids secondary to disintegration of myelin (Fig. 7). Myelin destruction frequently appeared to be interrupted at a node of Ranvier (Fig. 10), sometimes resulting in essentially normal myelin on one side of the node and a naked axon with myelin debris in its surrounding Schwann cell on the opposite side. In the spinal roots numerous unmyelinated axons, one to a Schwann cell, were present. These axons were not only solitary but were too large to represent unmyelinated Remak fibers (Fig. 8). Furthermore, the surrounding Schwann cytoplasm often was vacuolated, although its nucleus was apparently normal (Figs. 5 and 8). Occasionally cross-sections of two axons shared a single Schwann cell, but in these instances, one of the axons was usually deformed or abnormally large suggesting neuroma formation with branching or bending the axon (Fig. 9). Some axons (Figs. 9 and 11) possessed a narrow rim of myelin far too thin in relation to the axonal diameter for it to be normal; these thin myelin sheaths were interpreted as evidence of remyelinization. Some of the thinly myelinated fibers were surrounded by such abnormally attenuated Schwann cytoplasm that the myelin sheath appeared to be contiguous to the basement membrane of the Schwann cell (Fig. 9). Around a few axons, in fact, their thin myelin sheaths were incomplete (Fig. 11). In some zones it thus was possible to identify normal myelinated axons, denuded axons with or without myelin debris in Schwann or phagocytic cells, and very thinly myelinated axons within the same field (Fig. 9). Rarely, an axon crowded with small mitochondria was present. Such axons were not specific or unique for allergic encephalomyelitis, but rather represented growth cones of axonal sprouts which had resulted from focal peripheral destruction of nerve fibers. Vacuolization of Schwann cytoplasm of Remak fibers also occurred, but was less marked than the changes in the Schwann cell cytoplasm of myelinated fibers (Fig. 12).

Central Nervous System.—Surrounding many vessels, both small and large, there was a thick cuff containing lymphocytes, plasma cells, rare neutrophiles and mononuclear cells many of which were distended by intracytoplasmic lipid-containing cellular debris (Figs. 13 and 22). Collagen fibrils, some of which were broader than usual, (Fig. 13), were clustered within the cellular exudate.

The perivascular inflammatory cells occupied the Virchow-Robin space about large vessels (Fig. 22) whereas about the capillaries they occupied a newly created space. Thus, about the capillaries, there now were two basement membranes outlining an interstitial space occupied by inflammatory cells, fibroblasts, and collagen fibrils. The inner margin of this new space was represented by the capillary basement membrane whereas its outer limit was marked by a newly formed or reduplicated basement mem-

brane separating the space from the adjacent neuropil (Fig. 13). Even about some capillaries not cuffed by inflammatory cells, there sometimes was a distinct interstitial space similarly lined by basement membrane on either side, whereas normally such a space would be limited to those specialized areas lacking a blood-brain barrier. Occasionally delicate bundles of collagen were identified within the neuropil, as were numerous isolated plasma cells and lymphocytes.

Mitochondria of oligodendroglia were swollen, although mitochondria of adjacent axons or cells were not (Figs. 13 and 14). Mitochondria of oligodendroglial processes distant from their cell bodies were similarly swollen (Fig. 21). Some oligodendroglial cells showed a further alteration, a delicate fibrillar component within their cytoplasm (Fig. 13). Whether or not other oligoglia had undergone some form of dissolution as a final stage of reaction could not be determined from these sections.

In contrast to the apparently acute lesion of the oligodendroglia was the proliferative astrocytic response. Fibrous gliosis was spotty, being absent in some foci and distinct in others. Gliosis (similar to that seen in scars (11)) was formed by interlacing astrocytic processes densely packed with fibrils (Figs. 15 to 17).

In some portions of the cord no apparent abnormality could be recognized. Elsewhere, there were small or large foci characterized by demyelinization of central axons, abnormal glial cells, gitter cells laden with myelin detritus, and by infiltration of inflammatory cells (Fig. 17). Within these zones some small and large axons were totally denuded of their myelin sheaths (Fig. 15). Microglial cells or their processes partially enclosed other axons (Fig. 16). These were interpreted as stages representing active phagocytosis and removal of the lipid debris of myelin breakdown. Still other axons were surrounded by myelin sheaths in various stages of fragmentation. Some axons were totally free of myelin on one side, whereas that opposite was covered by only partially split myelin lamellae (Fig. 18). In most foci of demyelinization, relatively normal myelinated axons were present not far from demyelinated ones (Figs. 16 and 18). Axons without sheaths frequently touched other similarly unsheathed axons (Fig. 15).

Although the anterior horn cells and other smaller neurons which we observed appeared to be normal, there was definite spotty axonal destruction (Fig. 20) of the type associated with Wallerian degeneration. Detritus was present in place of the axon and was surrounded by either normal or disintegrating myelin. It also is entirely possible that some naked axons may also have undergone dissolution but we were unable to distinguish their residua.

Associated with the disruption of myelin sheaths was a proliferation of phagocytic cells, the origins of which could not always be determined. They were characterized by rounded contours and by large amounts of intracytoplasmic myelin debris (Fig. 19). Some of these cells undoubtedly arose from the invading phagocytic inflammatory cells. Others certainly were derived from the microglial cells of the cord and could readily be identified by their elongated dense nuclei, dense cytoplasm, and short thorny processes which could be seen partially surrounding a fiber in the process of losing its myelin (Fig. 16).

Occasionally axons were undergoing apparent remyelinization. They were characterized, as in the spinal roots, by an exceedingly narrow rim of myelin (Fig. 17).

DISCUSSION

Experimental allergic encephalomyelitis is a peculiarly instructive model for the study of demyelinization since its lesions bear a close resemblance to those of some human demyelinating diseases.

Addition of Freund's adjuvants (12) to injected homologous or heterologous brain has made the production of demyelinating lesions (13) more reproducible in comparison to the early experiments of Rivers, Sprunt, and Berry (14) and of Rivers and Schwentker (15) which were done without adjuvants. Waksman (16) and Kabat, Wolf, and Bezer (17) have shown that experimental allergic encephalomyelitis does not develop if the injected material is obtained from unmyelinated brains of immature animals. More recently materials partially purified chemically (16, 18–20) or isolated cytologic fractions (19, 21) have been injected in further attempts to characterize the antigenic material.

Even though the exact fraction of the injected material responsible for allergic encephalomyelitis is yet unknown, a characteristic response has been reproduced so frequently that it may be considered a pathological entity. The fine structural changes in the lesions of allergic encephalomyelitis are in distinct contrast to those of Wallerian degeneration. In the latter, dissolution of the axon is followed by fragmentation and phagocytosis of the myelin sheath and by proliferation of either Schwann cells peripherally or fibrous astrocytes centrally. In both regions lipid is removed so slowly that myelin detritus is present for long periods after complete degeneration of the axon. In contrast, allergic encephalomyelitis is characterized by destruction of the myelin sheath with residual intact axons denuded of their myelin. Although attempts to obtain the earliest recognizeable lesion have not been carried out, the frequent and extensive swelling of oligodendroglial mitochondria in the absence of such changes in other cell populations points toward an initial lesion in the oligodendroglia. Since the central myelin sheath is an integral part of the oligodendroglial cell, it is not surprising that myelin degeneration should accompany such a glial alteration. The observation that some axons were denuded on one side and not on the opposite is of considerable importance in relation to the manner in which central myelin is formed (Fig. 18), since it suggests that more than one oligodendroglial cell may be involved in formation of a single nodal unit of central myelin.

We do not know why allergic encephalomyelitis involves the oligodendroglia and the myelin primarily. Certain possibilities can, however be considered. The oligodendroglia subserve a double function in the central nervous system, forming the pathway for transport (22, 23) and forming and maintaining the myelin sheath (5, 6). Oligodendroglial cells and their processes make many perivascular contacts (Fig. 13) so that they would be among the first cells of the central nervous system exposed to circulating antibody. If oligodendroglia were altered by the antibody, as reflected in mitochondrial damage, their abnormality might be manifested by degeneration of myelin. Furthermore, since satellite oligodendroglia are related to nutrition of the neuron, some neurons or their axons might likewise undergo degeneration if their entire satellite population were diseased. This might partially explain the spotty axonal degeneration which occasionally occurs concomitantly with myelin destruction.

Demyelinization of peripheral roots has not been stressed in allergic encephalomyelitis except when the antigen was derived from peripheral nerve (24, 25), but the inflammatory reaction within the dorsal root ganglion has frequently been noted. By electron microscopy the demyelinating lesions were distinct though less marked in the roots than in the cord. It is interesting that the abnormalities of fine structure associated with minimal changes of peripheral myelin were of the Schwann cells just as in the spinal cord the changes were of the oligodendroglia. In the roots, swelling and vacuolization of Schwann cell cytoplasm preceded clear cut demyelinization. The early and definite Schwann cell alteration peripherally and the oligodendroglial mitochondrial swelling centrally are comparable, each occurring in supportive cells in which there was a dissolution of myelin. Furthermore some degree of vacuolization even occurred in Schwann cytoplasm of unmyelinated fibers (Fig. 12).

The mitochondrial multiplication in axons which Condie and Good (26) ascribed to allergic encephalomyelitis have been seen in experimental puncture wounds in the brain and following crushing or sectioning of peripheral nerves. In both of these types of injury outgrowths of axons from essentially normal neurons may occur, so that they may be equated with growth cones (Fig. 20) rather than with the specific lesion of allergic encephalomyelitis. The disruptions of mitochondrial morphology which these investigators described were present both within and without the axons and might have been related to fixation rather than to the disease process. Furthermore, this type of mitochondrial change is reminiscent of the work of Bryant *et al.* (27) on autolysis of cardiac mitochondria.

It is interesting to observe that beginning remyelinization can occur in a progressive disease of such short duration as allergic encephalomyelitis. The peripheral changes suggest that either the Schwann cells recover sufficiently to build new membrane (Figs. 3 and 4) or that the harmful immunologic environment is transient. Centrally, the fact that remyelinization occurs at all, even if in an abortive fashion, is important. Bunge (28) recently demonstrated remyelinization following a single episode of spinal fluid manipulation (barbotage) that had resulted in demyelinization and a clinical neurologic deficit. Astrocytic proliferation appears somewhat less profuse after spinal fluid barbotage than it does in allergic encephalomyelitis. However, lack of gliosis following spinal fluid barbotage is probably of less importance for remyelinization than is the fact that only a single transient insult had occurred in contrast to the prolonged metabolic derangement of allergic encephalomyelitis.

SUMMARY

Allergic encephalomyelitis was produced in rabbits by injection of white matter from bovine brain plus adjuvants. Electron microscopy revealed focal demyelinization in both the spinal roots and cord. The peripheral lesions were characterized by vacuolization of Schwann cytoplasm, destruction of the myelin sheath, and by some appearances suggesting remyelinization. In the cord there was a marked perivascular inflammatory infiltration with focal destruction of the blood-brain barrier as demonstrated by formation of an abnormal interstitial

space about capillaries. Mitochondria of oligodendroglia were strikingly swollen whereas those of other cells were morphologically normal. Axons were denuded of their myelin sheaths and the myelin detritus sequestered within gitter cells. Fibrous astrocytic gliosis occurred to some degree. Focal evidences of myelin reformation were noted centrally as well as peripherally. Allergic encephalomyelitis, as a primary demyelinating lesion, is contrasted with Wallerian degeneration in which myelin degeneration is secondary to destruction of the axon.

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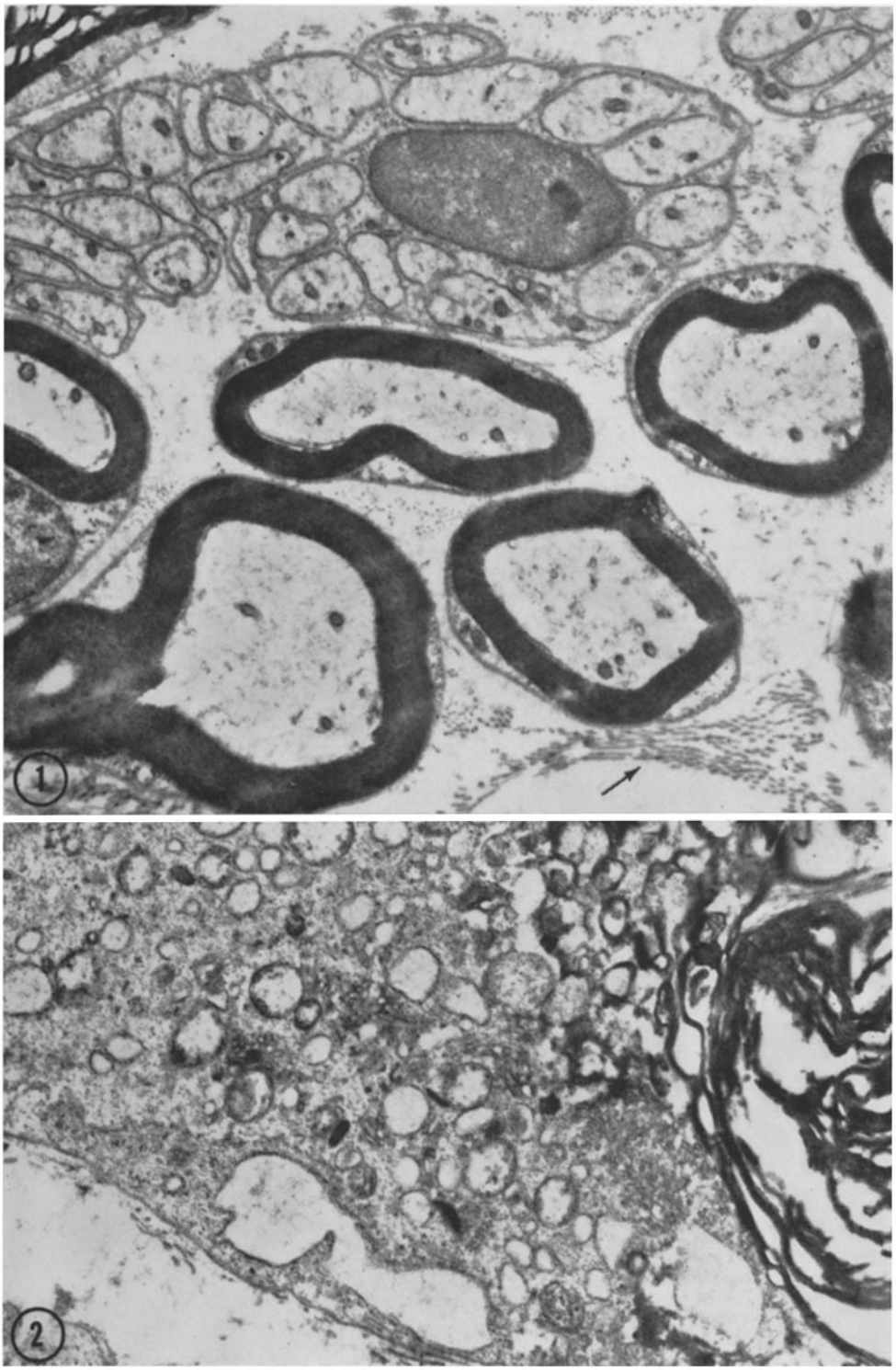
EXPLANATION OF PLATES

PLATE 60

FIG. 1. Low power electron micrograph to demonstrate normal region in the sciatic nerve of a rabbit with allergic encephalomyelitis. In the upper part of the figure is a Schwann cell containing numerous unmyelinated axons. Six myelinated axons with normal scant Schwann cell cytoplasm are present. Collagen fibrils are especially prominent at the lower right (arrow). Approximately × 8,000.

FIG. 2. This is an electron micrograph from another part of the sciatic nerve demonstrated in Fig. 1. At the right is a disintegrating myelin sheath. The remainder of the figure is comprised of vacuolated cytoplasm of the Schwann cell. The cytoplasm is distinctly more voluminous than normal and contains some lipid debris. × 10,000.

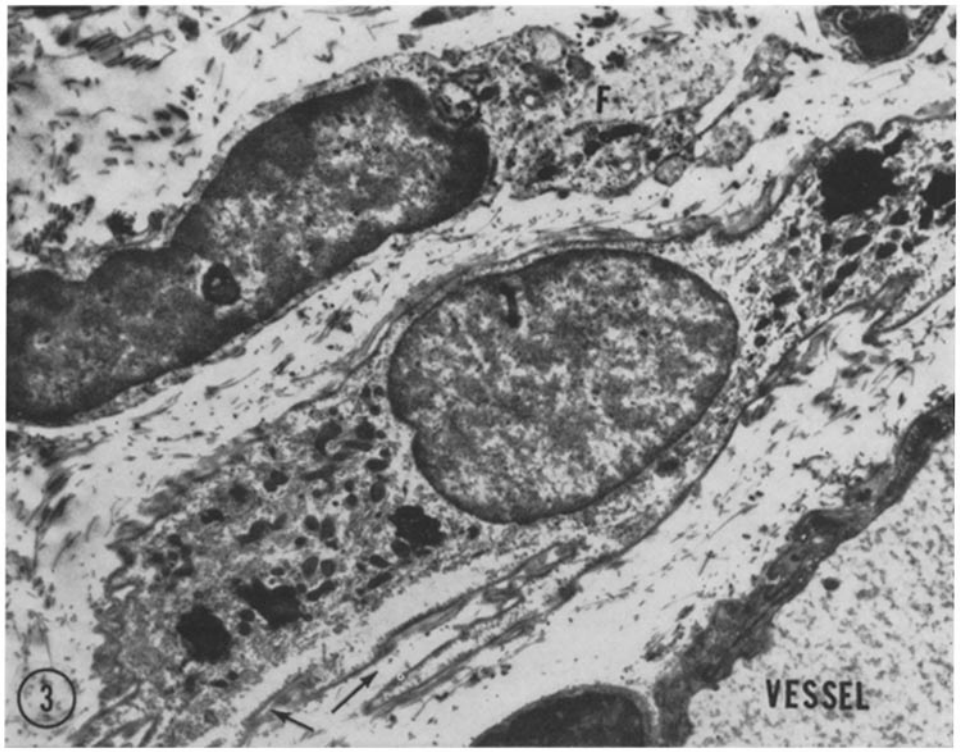


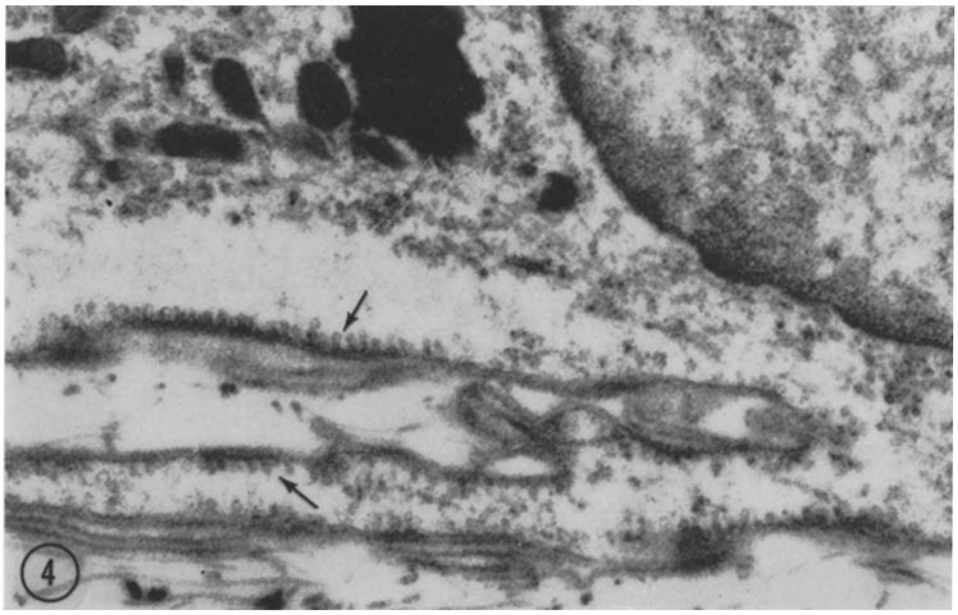
(Luse and McDougal: Allergic encephalomyelitis)

PLATE 61

FIG. 3. This section is through a reactive Schwann cell in the sciatic nerve of a rabbit with allergic encephalomyelitis. Lipid aggregates are present but at this level there is no evidence of an axon. Its cytoplasm is filled with small vesicles, mitochondria, and lipid. A basement membrane surrounds the Schwann cell. The cytoplasmic indentations (arrows) are similar to those occurring in Wallerian degeneration. A part of a blood vessel is present at the lower right and a fibroblast (*F*) at the upper left. Collagen fibrils are prominent. × 6,000.

FIG. 4. This is an enlargement of the portion of the Schwann cell indicated by the arrows in Fig. 3. The basement membrane external to the plasma membrane of the cell is clear. The numerous pinocytotic vacuoles lined up inside the cell membrane (arrows), as well as the large number of vesicles in the cytoplasm, suggest a high level of metabolic activity possibly related to regeneration of myelin elsewhere in the cell. × 26,000.



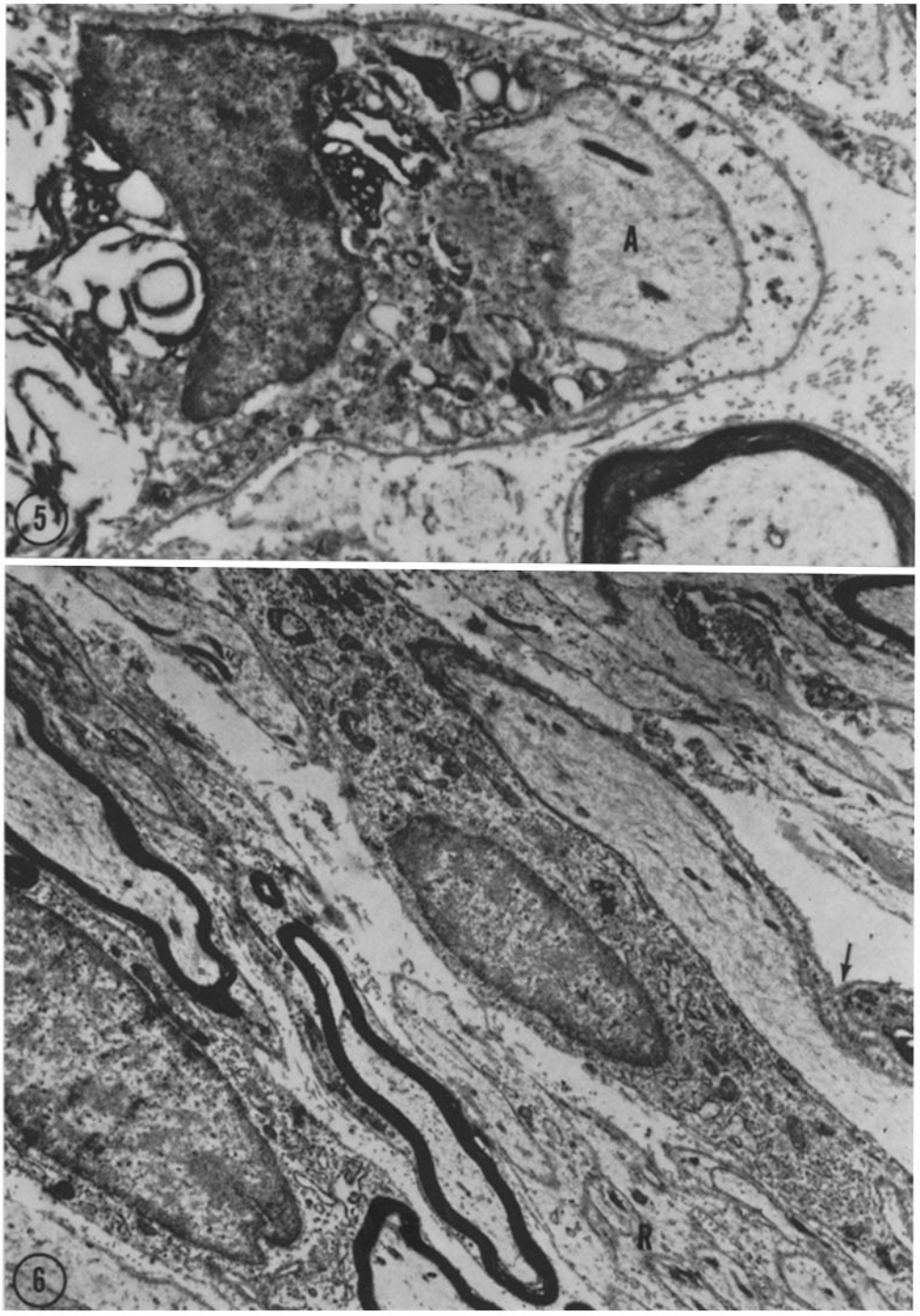


(Luse and McDougal: Allergic encephalomyelitis)

PLATE 62

FIG. 5. This is an electron micrograph of an axon in a nerve root denuded of its myelin sheath. The Schwann cytoplasm is enlarged and has engulfed the myelin debris. Both the axon (*A*) and the Schwann nucleus appear normal. × 12,000.

FIG. 6. This longitudinal section through a dorsal root shows parts of four normal myelinated axons. At the lower right are apparently normal Remak fibers (*R*), and at the upper right a demyelinated axon enclosed by a Schwann cell. No residual myelin debris is present. This section actually is at a node of Ranvier, but this is evident only at the upper surface (arrow) in this figure. × 6,000.

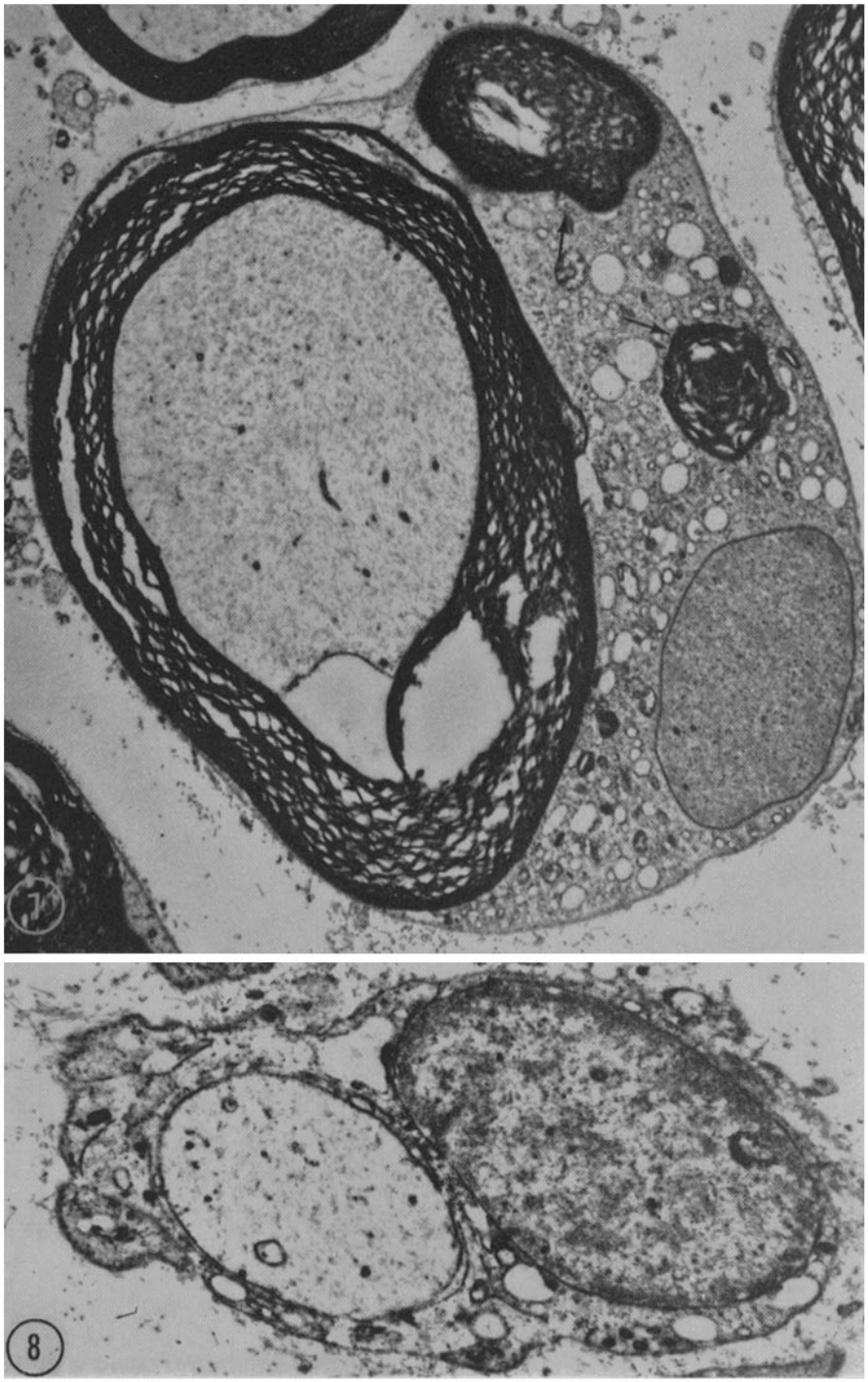


(Luse and McDougal: Allergic encephalomyelitis)

PLATE 63

FIG. 7. This low power electron micrograph demonstrates the type of abnormality of Schwann cytoplasm that was the least degree of change which we could definitely recognize. The presence of myelin globoids here (arrows) is definite evidence of myelin destruction. The vacuoles in the cytoplasm and the increase in amount of cytoplasm are distinctly abnormal. The myelin sheath itself has undergone some splitting suggesting an alteration in the forces holding the lamellae together. The axon is still essentially normal. × 8,000.

FIG. 8. This illustrates a further stage of abnormality in which the axon is totally demyelinated. Schwann cell cytoplasm is vacuolated but no myelin debris remains. × 10,000.

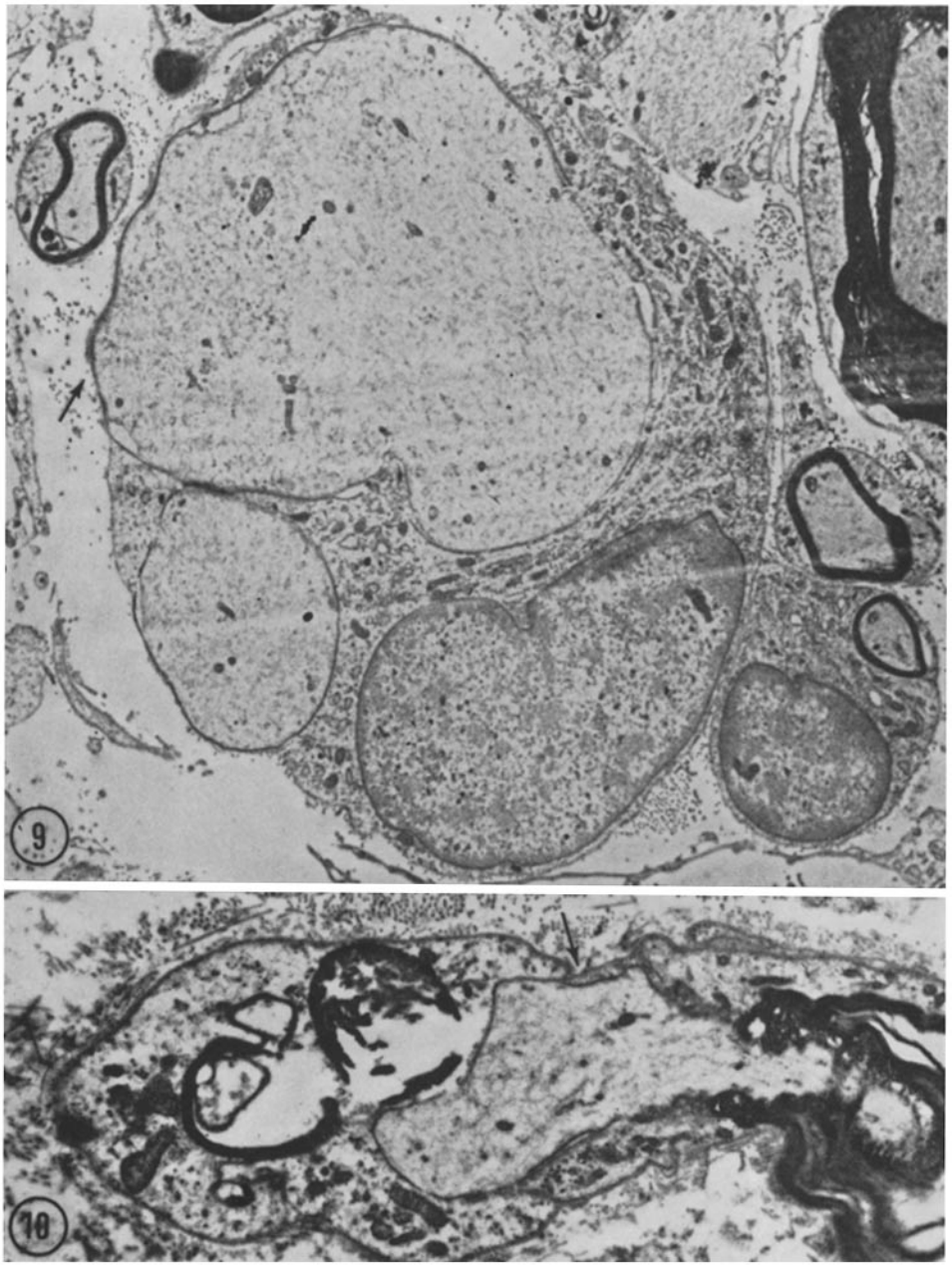


(Luse and McDougal: Allergic encephalomyelitis)

PLATE 64

FIG. 9. This electron micrograph is from a spinal cord root. It demonstrates several small and medium-sized normal myelinated axons and in the center of the figure a giant demyelinated axon. The central axon is far larger than normal and furthermore there are two axons within a single Schwann cell. This type of change has been noted in neuroma formation. The double axon may represent either a branching or a looping-back of the axon. A narrow dense rim partially surrounding these axons suggests beginning myelin formation. At the arrow the axon is surrounded only by the Schwann membrane. × 10,000.

FIG. 10. This is a demonstration of a node of Ranvier (arrow) in which the axon to the left of the node is demyelinated and to the right of the node the myelin is still present although split. × 10,000.

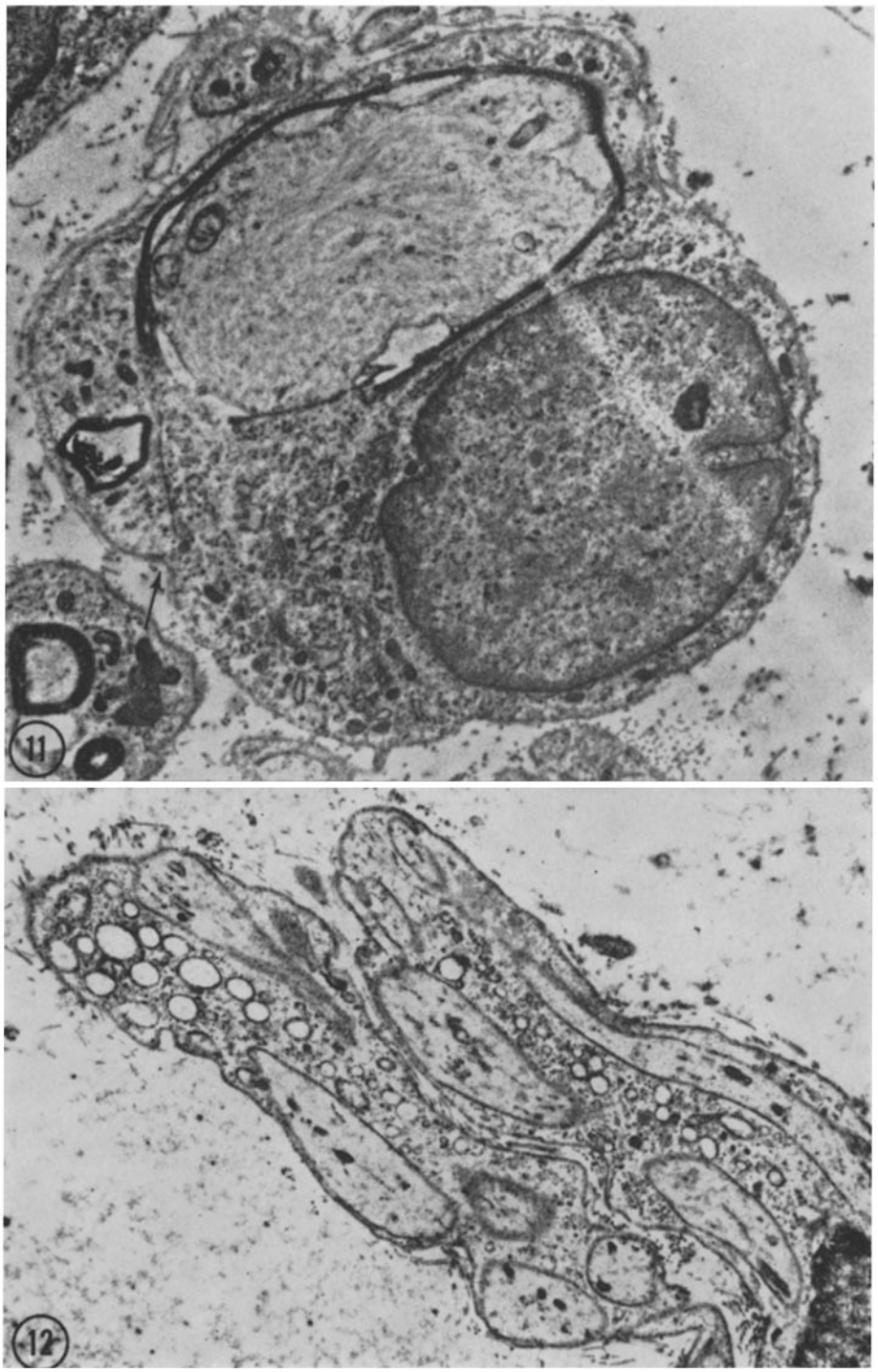


(Luse and McDougal: Allergic encephalomyelitis)

PLATE 65

FIG. 11. In this micrograph a partially remyelinated axon is present. The mesaxon is evident at the arrow, lower left. Schwann cell cytoplasm is increased in amount and filled with numerous vesicles. The myelin sheath is incomplete, only partially surrounding the axon, being absent at the lower left. × 12,000.

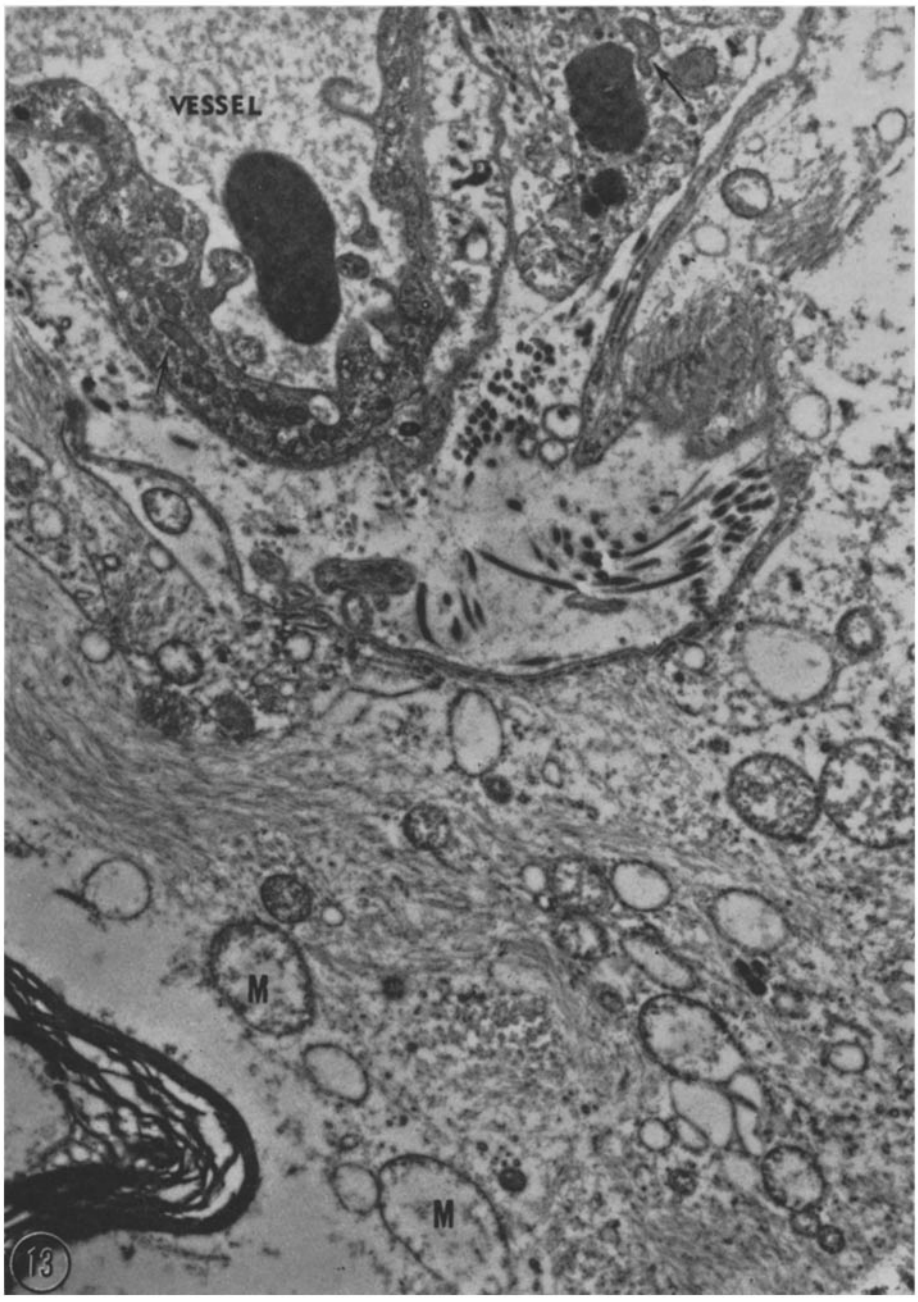
FIG. 12. In this figure there is part of a bundle of unmyelinated Remak fibers in a Schwann cell (dorsal root). The Schwann cytoplasm is filled with vesicles, which is an unusual finding in those containing unmyelinated axons. This raises the possibility that the Schwann cytoplasm of unmyelinated axons also responds to the harmful antibody to at least a limited degree. × 8,000.



(Luse and McDougal: Allergic encephalomyelitis)

PLATE 66

FIG. 13. This is an electron micrograph from the spinal cord of a rabbit with allergic encephalomyelitis. At the upper left is a capillary containing a RBC. This capillary is surrounded by a basement membrane outlined extracellular space containing a lipid filled macrophage and collagen fibrils. Part of an oligodendroglial cell abuts upon the outer basement membrane. It has abnormal fibrils in the cytoplasm and many of the mitochondria (*M*) are swollen. Note the normal mitochondria of the macrophage and endothelium (arrows). × 12,000.

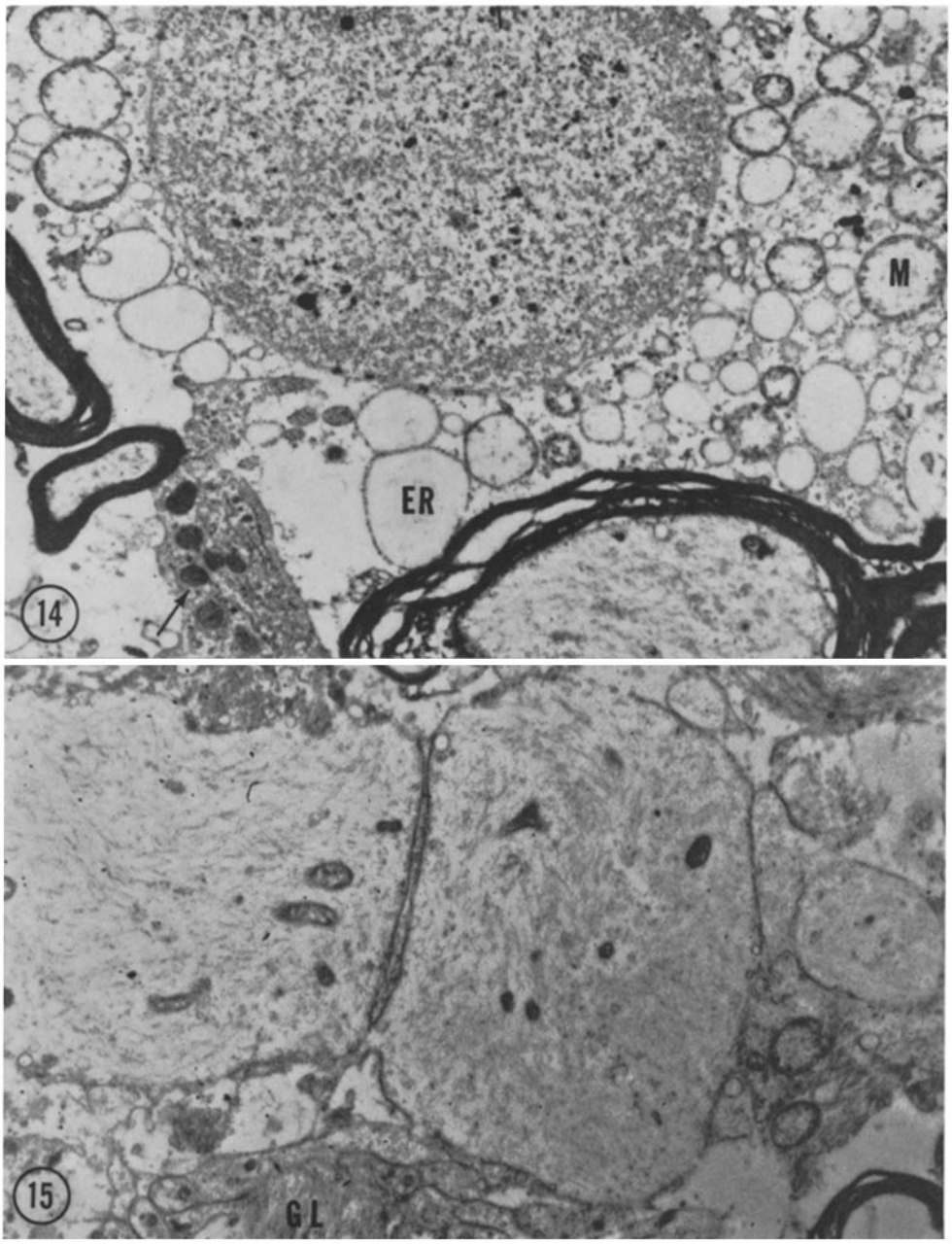


(Luse and McDougal: Allergic encephalomyelitis)

PLATE 67

FIG. 14. This micrograph illustrates another oligodendroglial cell in the spinal cord of a rabbit with allergic encephalomyelitis. The nucleus is relatively normal. The cytoplasm contains swollen ergastoplasmic sacs (*ER*) and swollen mitochondria (*M*). The mitochondria in an axon and in an inflammatory cell are normal (arrow). × 10,000.

FIG. 15. Two demyelinated axons in the spinal cord are practically touching each other. No myelin or myelin debris remain. The mitochondria are normal. Dense astrocytic gliosis partially surrounds these axons (*GL*). × 15,000.

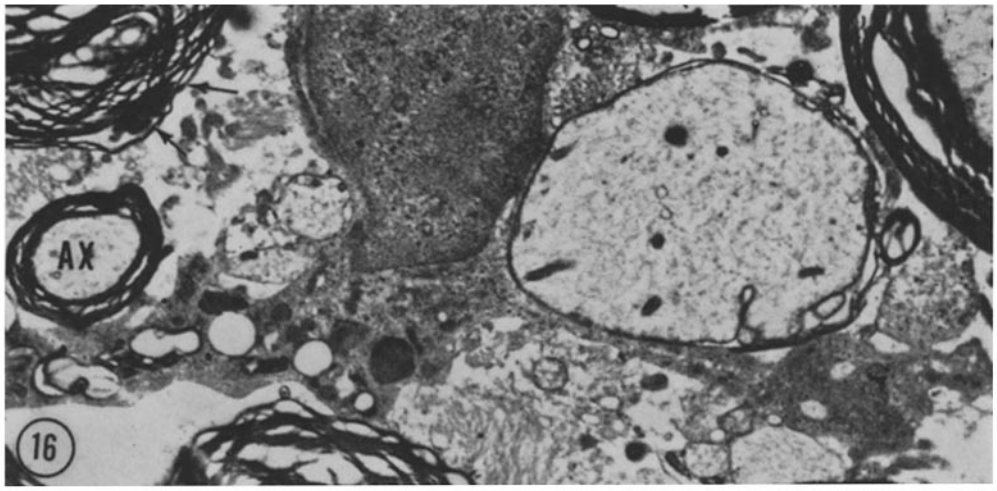


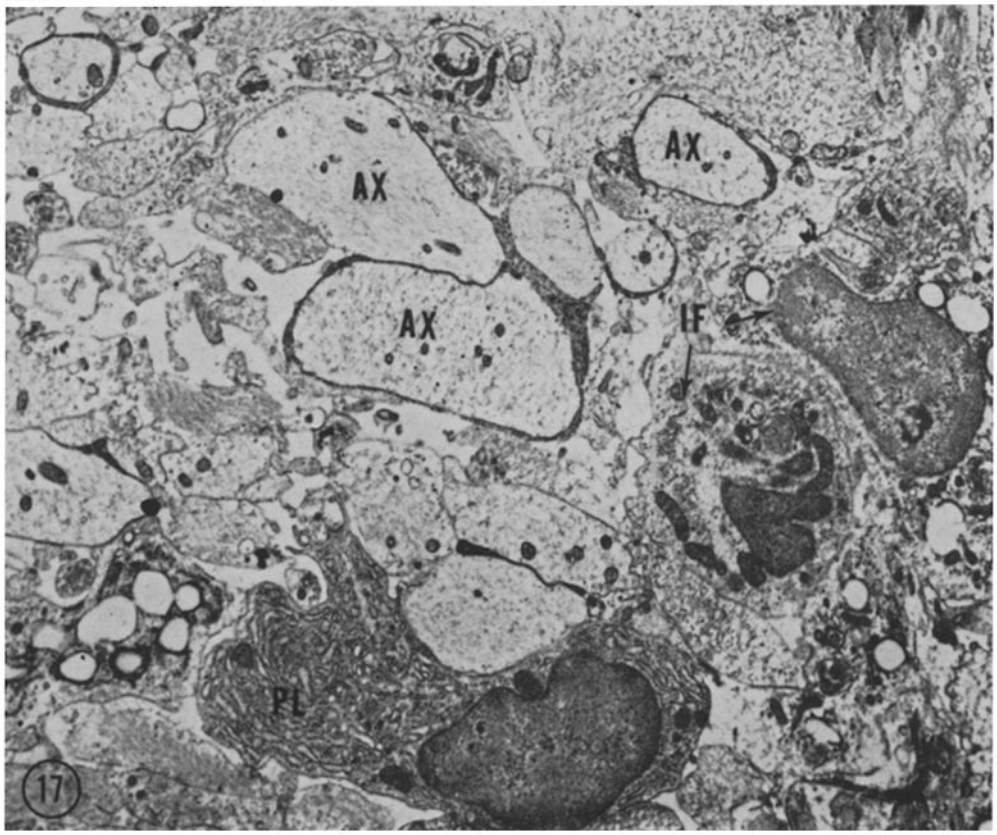
(Luse and McDougal: Allergic encephalomyelitis)

PLATE 68

FIG. 16. Electron micrograph of allergic encephalomyelitis, spinal cord. Myelin debris is present at the upper left. A single axon with almost normal myelin is present at (*AX*). A microglial cell nucleus is in the upper center of the field. Its cytoplasm partially surrounds a large axon which is apparently undergoing demyelinization. Myelin debris (arrows) is evident in the microglial cytoplasm. × 10,000.

FIG. 17. This electron micrograph of the spinal cord shows a region in which there is a plasma cell (*PL*), and other inflammatory cells (*IF*). Many unmyelinated axons are present (*AX*), several of which are apparently being remyelinated. × 8,000.



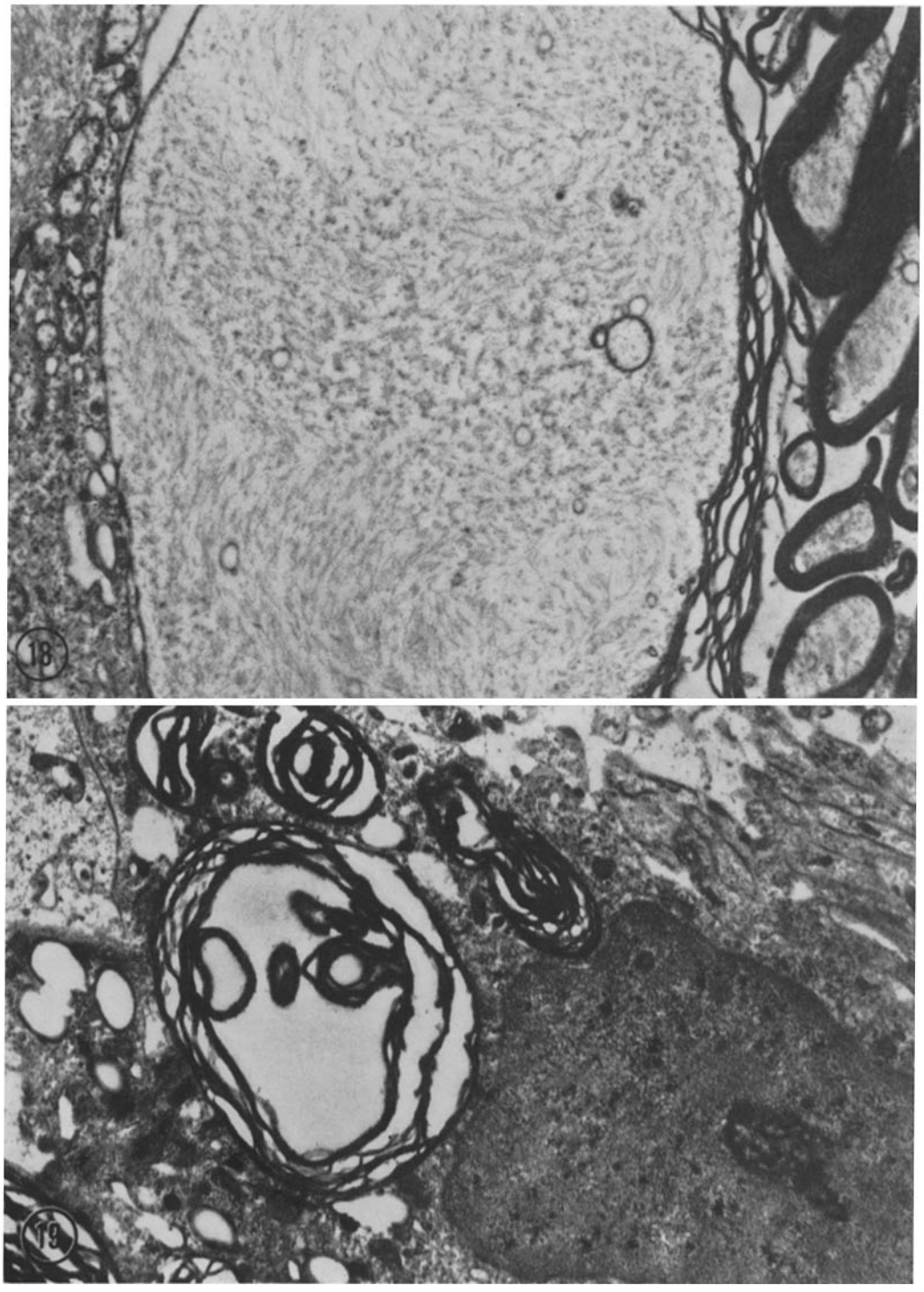


(Luse and McDougal: Allergic encephalomyelitis)

PLATE 69

FIG. 18. This electron micrograph is of a large axon (spinal cord) which has totally lost its myelin sheath on the left but still retains a distorted myelin sheath on the right. The axons on the right have normal myelin. × 10,000.

FIG. 19. A gitter cell almost completely fills this field. The density of the nucleus points to the microglial origin of this particular cell. The cytoplasm is filled with myelin detritus. × 8,000.



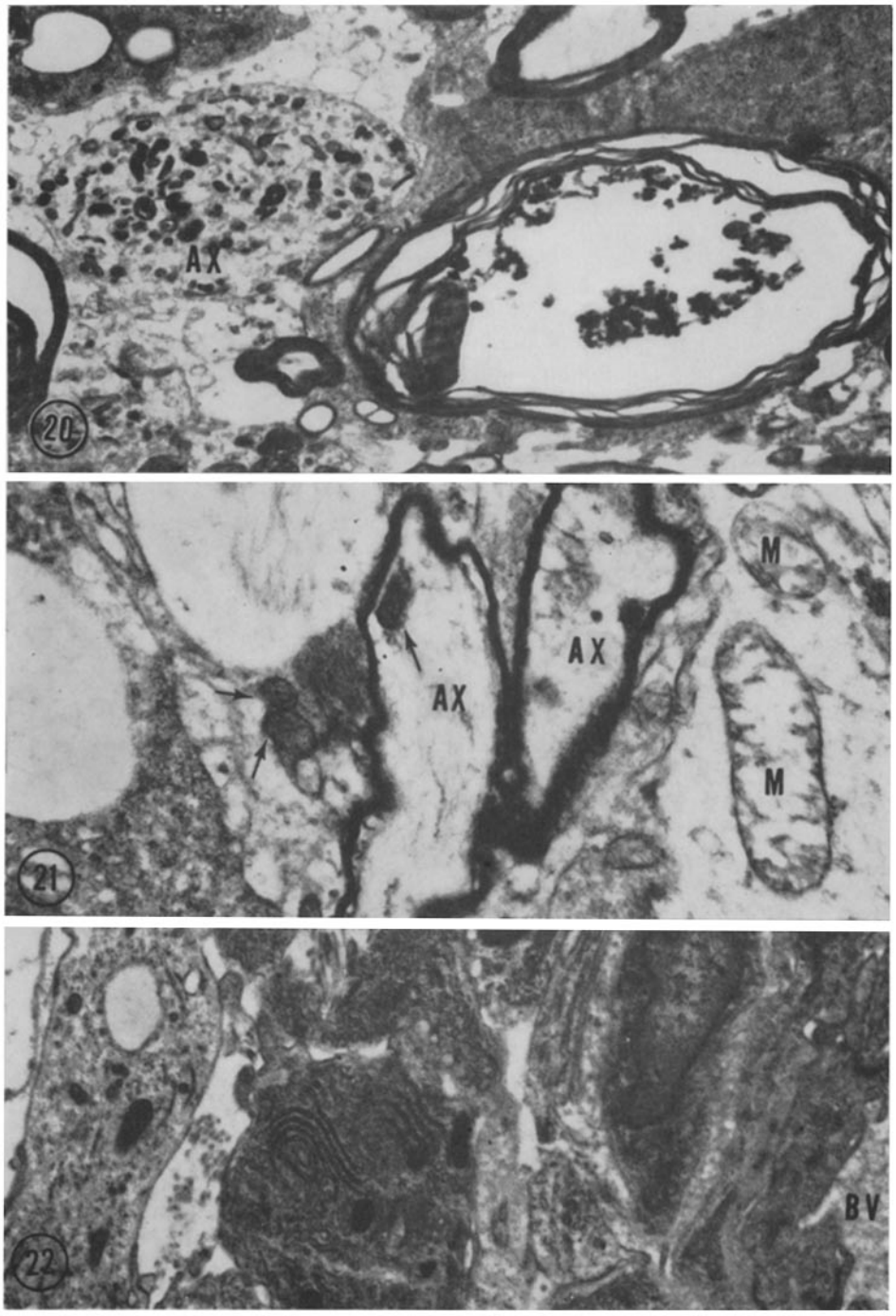
(Luse and McDougal: Allergic encephalomyelitis)

PLATE 70

FIG. 20. This section from the spinal cord shows myelin debris in a gitter cell, upper left and beneath it an axon "growth cone" (*AX*) with numerous small mitochondria. On the right is a myelin sheath surrounding degenerated axon that suggests Wallerian degeneration. × 10,000.

FIG. 21. A section through the neuropil of the spinal cord. Two myelinated axons are present (*AX*). Normal mitochondria are evident at the arrows. At the right are two abnormal swollen mitochondria (*M*) in an oligodendroglial process. × 15,000.

FIG. 22. A section through the cuff of inflammatory cells around a vessel (*BV*) in the spinal cord. × 10,000.



(Luse and McDougal: Allergic encephalomyelitis)