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PATHOLOGICAL STUDIES OF MAREK'S DISEASE III
ELECTRON MICROSCOPIC OBSERVATION ON DEMYELINATION OF THE PERIPHERAL NERVES

Yutaka FUJIMOTO and Kōsuke OKADA

Department of Compartive Pathology
Faculty of Veterinary Medicine
Hokkaido University, Sapporo 060, Japan

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Degenerative changes of the peripheral nerves in Marek's diseases (MD) were investigated under light and electron microscopy. Three categories of demyelination were classified according to the characteristics of the lesions. Category I was considered as primary demyelination, and it was similar to experimental allergic neuritis. No morphological destruction was seen in the myelin sheath until the mononuclear cells made contact with the myelin within the neurolemma. The attacking mononuclear cells (macrophages) stripped the Schwann cell cytoplasm off the myelin sheath. Category II was considered as Wallerian-like degeneration. Category III was considered as a "hydration" of myelin sheaths due to edema. Myelinolysis, caused by a uniform separation of myelin lamellae in the region of the sub-perineurial edema, was observed independently of MD. The regenerative process, particularly remyelination, was seen in each category. It was suggested that primary demyelination of Category I was the most important phenomena in the pathogenesis of MD nerve lesions.

INTRODUCTION

Marek's disease (MD) of chickens is caused by a highly cell-associated herpesvirus[4], and is characterized by progressive paralysis of the extremities. Although there are many controversies on the pathologic nature of MD[28], we have classified the lesions of MD into two basic types: tumorous proliferation (T-type) and non tumorous response (R-type), according to the characteristics of the infiltrating cells in the affected nerves[9]. MD appears to be connected closely to nerve tissues. Some workers have been interested in the relationship between paralytic disorders and nerve lesions. Concerning the degenerative changes in affected nerves, WIGHT histologically demonstrated considerable destruction of neurites but very little cellularity in his type II lesions[39]. There are only a few reports on electron microscopic degenerative changes in the peripheral nerve lesions of MD[6,20,40]. We reported, therefore, on the ultrastructural degenerative changes in the peripheral nerves of field cases of MD at the Meeting of the Japanese Society of Veterinary Science in 1969[10] and the Japanese Pathological Society in 1973[13]. Fur-

thermore, we reported on experimental allergic neuritis (EAN) (1971[15] & 1972[12]) and Wallerian degeneration (1971[11]), and suggested that the pathogenesis of the MD nerve lesions is closely related to an allergic nature. PRINEAS & WRIGHT (1972) have also reported the fine structure of peripheral nerve lesions in field cases of MD, and have suggested a similar cell-mediated immune response.

The present paper reports on the fine structure of demyelination and regeneration not only in field cases but also in experimental cases of MD, and demyelination is classified into three categories.

MATERIALS AND METHODS

Field cases

Seventeen chickens with MD and 4 normal controls were studied. They were White Leghorn, aged from 60 to 229 days, and collected from Sapporo, Japan. Electron microscopic materials were obtained from the brachial plexus, lumbosacral plexus, spinal ganglia and vagosympathetic trunk. All chickens showed with MD clinical fowl paralysis.

Experimental cases

Ten chickens of White Leghorn (Line M), which were inoculated with MD herpesvirus infected blood (JM strain, titer ; 160 PFU/0.2 ml) at one day old, were used. The source of the JM strain of MD herpesvirus was described previously[25]. These chickens were selected from 60 chickens used in previous virological, immunological and microscopical studies[14]. Chickens of the 3rd, 8th, 12th, 14th, 16th, 23rd, 29th, 32nd, 42nd and 48th day post inoculation (PI) were used. Electron microscopic materials were obtained from the brachial plexus and the spinal ganglia. Only 2 (23rd and 42nd day PI) out of 10 showed clinical fowl paralysis.

Light microscopy

Various parts of the peripheral nerves and viscera were fixed in 10 % formalin. Paraffin sections were routinely stained with hematoxylin and eosin, and selected sections were stained with Luxol-fast blue for myelin.

Electron microscopy

Materials of the field cases were fixed in 1 % OsO_4 and embedded in MOLLENHAUER's epoxy resin mixture, as described previously[24]. On the other hand, materials of the experimental cases were fixed in 6.25 % gultaraldehyde and then refixed in 1 % OsO_4, and embedded in LUFT's Epon 812, as described previously[25]. Sections were cut with glass knives using a Porter-Blum ultramicrotome MT-1. Ultrathin sections were stained with uranyl acetate and lead citrate and observed with a JEM-7 type electron microscope. Thick sections of approximately 1 to 2 μ were stained with 1 % toluidine blue for light microscopy.

Results

Light microscopy

Seventeen chickens with MD in the field cases consisted of 3 cases of T-type, 4 of T+R-type, and 10 of R-type lesions. In the experimental cases, 6 chickens revealed T-type or T+R-type lesions from the 16th day PI, but the other 4 chickens showed no apparent lesions until the 14th day PI.

In the R-type lesions, the nerves usually showed infiltration of lymphocytes and plasma cells more or less accompanied by edema in the interneurites (fig. 1). Sometimes axonal swelling could be seen in the R-type lesions, but it was not as severe as that of the T-type lesions, as described below. Demyelination was found frequently and extended widely with the Luxol-fast blue stains and toluidine blue preparations (fig. 2). The extent of demyelination appeared to be in proportion to the extent of edema and diffuse cellular infiltration. Although the axons were apparently intact, the myelin sheaths were destroyed as globules or fragments. The demyelinated nerve fibers involved usually invaded the mononuclear cells (fig. 2). The intact fibers in the vicinity of the demyelinated zones often revealed Schwann cell hypertrophy and active formation of Büngner's band.

In the T-type lesions, the nerve fibers were individually separated by massive proliferated lymphoid cells (figs. 3 & 4). In such severely affected areas, the neural parenchyma was often completely destroyed and showed a mottled appearance (fig. 3). The axons were swollen and fragmented as club-like or massive structures, and the myelin sheaths disintegrated into acidophilic globules and fragments (fig. 3), and were often accompanied by edematous fluids within the digestion chambers. In these foci, there were infiltrations of pyknotic mononuclear cells or macrophages. Demyelinated foci usually corresponded to the massive cellular infiltrations in the Luxol-fast blue stains. Acidophilic edema fluids were seen sporadically in the interneurites.

Various degrees of degeneration and loss of nerve fibers were observed independent of any of the T-, T+R-, and R-type lesions, especially in the sub-perineurium (figs. 5 & 6). In these areas, there was conspicuous edema with infiltrations of many macrophages.

Electron microscopy

As a result of the present observation, demyelination could be classified into three categories, as described below.

Category I

The first category of the nerve lesions was considered as primary demyelination. This category of lesions was more frequently seen in the R-type lesions. Under electron microscopy, at an early stage the majority of nerve fibers appeared normal, but some of the fibers showed degenerative changes. The fibers showing degenerative changes

almost invariably had mononuclear cells within the basement membrane or neurolemma surrounding the Schwann cells. At this stage, cytoplasmic tongues from the mononuclear cell penetrated into the space between the outermost mylin lamellae and the process of Schwann cell cytoplasm (fig. 7). Mononuclear cells stripped the Schwann cell cytoplasm off the myelin sheath. Where invading cytoplasmic tongues made contact with the myelin sheath, focal disruption of several myelin lamellae occurred. The mononuclear cells showed an irregular contour in the nucleus, and the cytoplasm had large mitochondria, a poorly developed endoplasmic reticulum, and many ribosomes grouped in clusters. Their cytoplasms often revealed high electron density (fig. 9). These cells often had variable-sized vacuoles (lysosomes) in their cytoplasm. On the other hand, the macrophages had a moderate amount of smooth and rough surfaced endoplasmic reticula and numerous ribosomes. The Golgi apparatus was well developed, and characteristic phagocytic vacuoles (lysosomes) containing various sizes of myelin debris were found throughout the cytoplasm (figs. 12～15). If appeared, therefore, that the macrophage may have been transformed from the mononuclear cell; thus, this type of cell will be hereafter called "macrophage". Following focal dissolution of the myelin sheath, macrophages may invade such myelin defects and engage in phagocytic activity and the stripping process (fig. 8). A lymphocyte also appeared in the Schwann cell with disintegrated myelin lamellae (fig. 10). The cytoplasm of the lymphocyte was relatively abundant and contained a well-developed Golgi apparatus and cytoplasmic processes. At this stage, the axons were apparently still intact in spite of the disorganization of myelin lamellae (fig. 11). Finally, the macrophage completely surrounded the myelin sheath, separating it from its supporting Schwann cells (figs. 10～12). Many completely demyelinated axons were surrounded by macrophages with much myelin debris (fig. 13).

It was suggested that following the removal of the myelin sheath, the macrophages may leave the neurolemma. The reason may be that these macrophages have much phagocytosed myelin debris and high electron density in their cytoplasm, that they appear to pass through the broken basement membrane (figs. 14 & 15). In these more advanced lesions, completely demyelinated naked axons were often observed (fig. 16). Furthermore, in the advanced stages, mitosis of the Schwann cells could be seen occasionally (fig. 17). A newly formed cytoplasmic process of the Schwann cell was noted inside the remaining basement membrane. Fine, longitudinal filaments were numerously observed in the cytoplasm of this Schwann cell (fig. 18). This cytoplasmic process may correspond to Büngner's band in Wallerian degeneration[21]. A hypertrophied Schwann cell had a large, pale nucleus and a well-developed, rough-surfaced endoplasmic reticulum in the cytoplasm (figs. 15, 18 & 19). At times, early remyelination was observed in some Schwann cells (fig. 19). The axon was surrounded by several loose myelin lamellae. There were double basement membranes around the Schwann cell. The original basement membrane revealed a ruffled appearance. Collagen fibers were found between the newly formed

basement membrane of the Schwann cell and the original basement membrane (fig. 19). The neurilemmal collagen fibers appeared to increase around the remyelinated nerve fibers.

Category II

The second category of nerve lesions was considered as Wallerian-like degeneration. Although this category of lesions did not represent the major component of demyelination in the present MD cases, this category was often found in the T-type lesions (fig. 3). In Category I, especially, the structure of the axon was usually intact throughout the demyelinating process in the early stage. On the other hand, in Category II, axonal disintegration was more severe than myelin damage in the early stage. There were axoplasmic condensation, an accumulation of electron dense and lamellar bodies, and an increase of various-sized vacuoles and mitochondria in the axoplasm (figs. 20 & 22). The axon often revealed complete disintegration, while the myelin sheath was still preserved in the apparently normal structure (fig. 20). During the degenerative process in the nerve fibers, the myelin sheath was often broken into onion-like globules. These myelin globules were autodigested by the Schwann cell. In the endoneural space, there was much myelin debris, which may have been discharged from the Schwann cells. This myelin debris may have been phagocytosed by the macrophages in the endoneural spaces. This information suggests the preeminent role of the Schwann cells and the macrophages during degeneration of this category.

The process of regeneration was also observed in this category of the lesions. In some transverse sections of the nerve bundles, many myelinated nerve fibers with axoplasmic condensation were observed within the Schwann cell cytoplasm. Since new axon sprouts (growth cone)[23] were composed of several finger-like processes, the outer process of the growth cone entered into the Schwann cell sideways, forming several mesaxons (fig. 22). The Schwann cell surface was invaginated by the growth cone process, which formed several infoldings (mesaxon) in the Schwann cell membrane. Some of the inner processes of the growth cone also entered into the central part of the regenerating Schwann cell, which had autodigested various forms of the myelin debris (fig. 21). During the spiral turn of mesaxons around the growth cone, the infolded Schwann cell membrane may form the multilayered myelin lamellae (remyelination). The regeneration of the node of Ranvier was also observed (fig. 21).

Category III

The third category of the nerve lesions was often seen in the edematous area of the peripheral nerves of the R-type lesions (figs. 1 & 5). In the myelinated nerve fibers of the edematous region, a distinctive type of myelin breakdown occurred. This consisted of the formation of large clear spaces between the axon-Schwann interface. Some of the spaces contained edematous fluids. Inner and outer myelin lamellae had often separa-

ted from the rest of the sheath, forming some clear spaces (figs. 23 & 24). Since some clear spaces were also found at the node of Ranvier, these spaces appeared to continue into the extracellular spaces (fig. 24). In the next segment of the sheath in these lesions, demyelination was often observed. Axons were usually uninvolved in these changes, and were rarely swollen and condensed. This type of vesicular transformation and lysis of myelin lamellae may be considered as a "hydration" of myelin sheaths due to edema.

On the other hand, sub-perineurial edema was found independently of the T- or R-type lesions of MD (figs. 5 & 6). In these lesions, some outer sheaths exhibited an even separation of their lamellae. At higher magnification, it was possible to demonstrate the uniform separation of the lamellae (ca. 390 Å, fig. 25), which was composed of internal compound membrane[33]. The interlamellar space was continuous with the extracellular space via the outer measxon (fig. 25). These spaces were clearly distinguishable from the Schmidt-Lanterman cleft in the longitudinal section. Macrophages with myelin debris could often be seen in these lesions (fig. 26).

Herpesvirus particles could not be detected in any part of the peripheral nerves in either the field or experimental cases of the present investigation.

DISCUSSION

From the results of our present investigation, we classified demyelination of MD into three categories according to the characteristics of the nerve lesions.

Category I was considered as primary demyelination. The characteristics of myelin destruction observed in the present study was a direct attack by mononuclear cells on nerve fibers, which had apparently normal structures. The invading cells consisted of mononuclear cells and lymphocytes. From observing the phagocytic activity, the mononuclear cells appeared to be transformed into macrophages. After the contact of invading mononuclear cells with the myelin sheath within the neurolemma, myelin destruction occurred, while the axon remained intact. The attacking mononuclear cells were engaged in stripping the Schwann cell cytoplasm off the myelin sheath. After removal of the myelin sheath, the macrophages containing myelin debris appeared to leave from inside the neurolemma into the interneural spaces. The most outstanding feature of the demyelinating process was that the Schwann cells did not appear to participate in the phagocytic activity.

The electron microscopic findings of Category I essentially seemed to be similar to demyelination seen in EAN[18,35]. In these experiments, it was clearly apparent that the target of the mononuclear cells was myelin; phagocytosis of the Schwann cells was not observed. Histologically, SILLER (1960) first noted the analogy between the neural lesions of Experimental Allergic Encephalomyelitis (EAE) and MD. By inoculating chicken and guinea pig nerves in Freund's adjuvant, PETEK & QUAGLIO (1967) produced EAN in

chickens which was indistinguishable from WIGHT's types I and II lesions. They stressed the similarity of their EAN to the inflammatory lesions of MD and considered the possible role of the autoimmune process in the pathogenesis of MD.

We have produced similar EAN in chickens by inoculating bovine nerves in Freund's adjuvant and observed it by light[15] and electron microscopy[12]. The detailed findings of these experiments will be reported in the next issue of this series. The histological findings revealed the similarity between the EAN and R-type lesions of MD. Furthermore, electron microscopically, a pattern of myelin destruction in Category I, which is frequently seen in R-type lesions, was similar to those of EAN. Category I was, therefore, considered as primary demyelination, similar to EAN, which was due to a cell-mediated immune response.

Herpesvirus particles were not found in the peripheral neves in the present MD cases. Some workers have observed herpesvirus in the Schwann cells and lymphoid cells of the brachial plexus of a chicken with MD[22,38]. This appears to be an exceptional case because many investigators have failed to demonstrate herpesvirus particles in the peripheral nerves[6,20,31]. However, this does show the possibility that MD herpesvirus may enter the peripheral nerves and bring about myelin damage. FOSTER & MOLL (1968) speculated that the etiologic agent of MD is a neurotropic agent, and that infection of the peripheral nerves may casuse alterations of antigenicity in neural tissue, which might serve as antigens for initiating autoimmune reactions characterized by peripheral nerve tissue destruction and monocytic cell infiltration. MD herpesvirus had an external envelope derived from an altered host plasma membrane[22]. It may also be postulated that the host may become sensitized to its own peripheral myelin and liberated by a lytic virus infection or by a cross-reactivity between the viral and tissue antigens.

The virus infection occasionally provokes immune mediated myelin injury in some demyelinating diseases in man (postinfectious polyneuropathy[2]) and animals (Theiler's virus infection in SJL/J mice[5], and canine distemper[41]). PRINEAS & WRIGHT (1972) investigated the fine structure of the peripheral nerve lesions in MD and suggested that demyelination in MD is due to a cellular immune response directed at normal myelin, and that this disorder may represent a (herpes) virus-induced autoimmune demyelinating disease.

Recently, the occurrence of allergic skin reactions against myelin of peripheral nerves in MD has been reported[34]. The report indicates that in MD, the lymphocytes are sensitized against a component of the peripheral myelin. This suggests the evidence of an autoimmune response to myelin in MD.

On the other hand, humoral factors have not been necessarily accepted as the causative agents for demyelination *in vivo*, but some doubt remains as to the role of humoral agents *in vitro*[43]. Demyelination *in vitro* produced by antisera from EAE and EAN animals has been reported[3,42]. R-type lesions were usually accompanied by an

infiltration of plasma cells[9]. This finding suggests the possibility that the R-type lesions have some connection with humoral immunity. OKI et al. (1971) demonstrated anti-neural auto-antibody (IgM) in the sera from MD and EAN as an indirect proof of the appearance of antibody producing cells or cell-bound antibody connected with the nerve tissues. YONEZAWA et al. (1976) studied the details of demylinating changes by the humoral factor in a time lapse cinematographic analysis *in vitro*, and their findings suggest that the presence of cytophilic antibody in antisera is possible. This type of antibody activates the macrophages and provides the ability to attack the antigenic myelin sheaths. Therefore, a similar manner of activation of macrophages may also be seen in Category I. In order to clarify the mechanism of immunological demyelination, further study will be necessary.

Category II was regarded as Wallerian-like degeneration because the axonal destruction was much more prominent than the myelin degeneration. The Schwann cells and macrophages play an important role in the removal of myelin debris. This type of degeneration did not provide the major component of demyelination in the present MD cases. Early workers considered that the mechanical compression of the axon by massive proliferating tumor cells may subsequently bring about secondry or Wallerian degeneration[27]. With the exception of mechanical compression, it appears that there are still some factors involved in this case of degeneration.

Category III was considered as a "hydration" of myelin sheaths due to edema. One of the lesions consisted of large spaces between the myelin lamellae or underneath the myelin sheaths but was not associated with disintegration of the myelin lamellae. This type of lesions was often found in the edematous areas of the interneurites of R-type lesions. Similar lesions have been observed in cerebral edema (due to a variety of different causes[1,16,19,36]) and in the peripheral nerves of chronic EAE[32]. In addition, Theiler's virus (picornavirus), which induced demyelination of the spinal cords of mice, revealed similar vesicular disruption of the myelin[5]. Such changes may often be confused with the artifact due to fixative failure. Except for these large spaces, the intact structure of all the myelin lamellae and the appearance of reactive macrophages on the same section indicate that these changes are not due to the artifact.

On the other hand, myelinolysis by a uniform separation of myelin lamellae was seen in the region of the sub-perineurial edema, independently of MD. This type of hydration in the myelin sheath was similar to that seen in the peripheral nerve after exposure to hypotonic solutions[7,33], and that seen in severe cerebral edema after the implantation of silver nitrate[17]. In addition, such myelinolysis was also similar to that seen in the serum-induced demyelination *in vitro*[3]. Furthermore, within the EAE-affected central nervous system *in situ*, isolated fibers have also revealed a regular widening of the myelin sheath[30]. The pathogenesis of these changes and their clinical significance are not conclusive and merit further study.

Remyelination was the most common in all of the categories; furthermore, regeneration of the axon was most conspicuously seen in Category II. After the complete destruction of nerve fibers, the regeneration process was similar to that seen in each category and to the reports of many workers[21,23,31,32,39]. The elimination of disintegrated nerve components appeared to be conducted mainly by the macrophages. Schwann cell proliferation, which forms the Bünger's band, was observed in the nerve trunk. Mitosis was actually observed in the Schwann cells, and numerous fine. longitudinal filaments were found in their cytoplasm. The regenerating process was seen inside the remaining basement membrane, and the newly formed basement membranes were seen within the ruffled original basement membrane. The growth cone processes of axons[23] often invaginated into the Schwann cell cytoplasm, which still contained myelin debris in the autophagic vacuoles. The invaginated Schwann cell membranes may form the multilayered myelin lamellae by the spiral turns of the elongated mesaxon around the axon. An increase of neurilemmal collagen fibers has been observed in a report by DEUTSCH & SILLER (1961).

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Explanation of plates

Plate I

Fig. 1 R-type lesion

Vacuolization, demyelination and axoplasmic swelling (↑) are seen. Lumbosacral plexus Chicken 615 Field case Hematoxylin-eosin-stain (H-E) × 640

Fig. 2 R-type lesion

Demyelinated nerve fibers involve invading mononuclear cells (↑). Lumbosacral plexus Chicken 632 Field case Epon embedded section Toluidine blue stain × 640

Figs. 8~11 & 13~18 were taken from the block of this section

Fig. 3 T-type lesion

The neural payenchyma is completely destroyed and shows mottled appearance. Vacuolization and demyelination are prominent. Brachial plexus Chicken 644 Field case H-E × 390

Fig. 4 T-type lesion

Degenerations of nerve fibers are seen. N: nerve cell Cervical spinal ganglion Chicken 765 Experimental case (23rd day PI) Epon embedded section Toluidine blue stain × 640

Figs. 20 & 21 were taken from the block of this section

Fig. 5 R-type lesion and sub-perineurial edema

Numerous macrophages are seen in the sub-perineurial area Brachial plexus Chicken 623 Field case H-E × 160

Fig. 6 Sub-perineurial edema

A weakly stained myelin sheath (↑) Brachial plexus Chicken 626 Field case Epon embedded section Toluidine blue stain × 640

Figs. 19 & 26 were taken from the block of this section

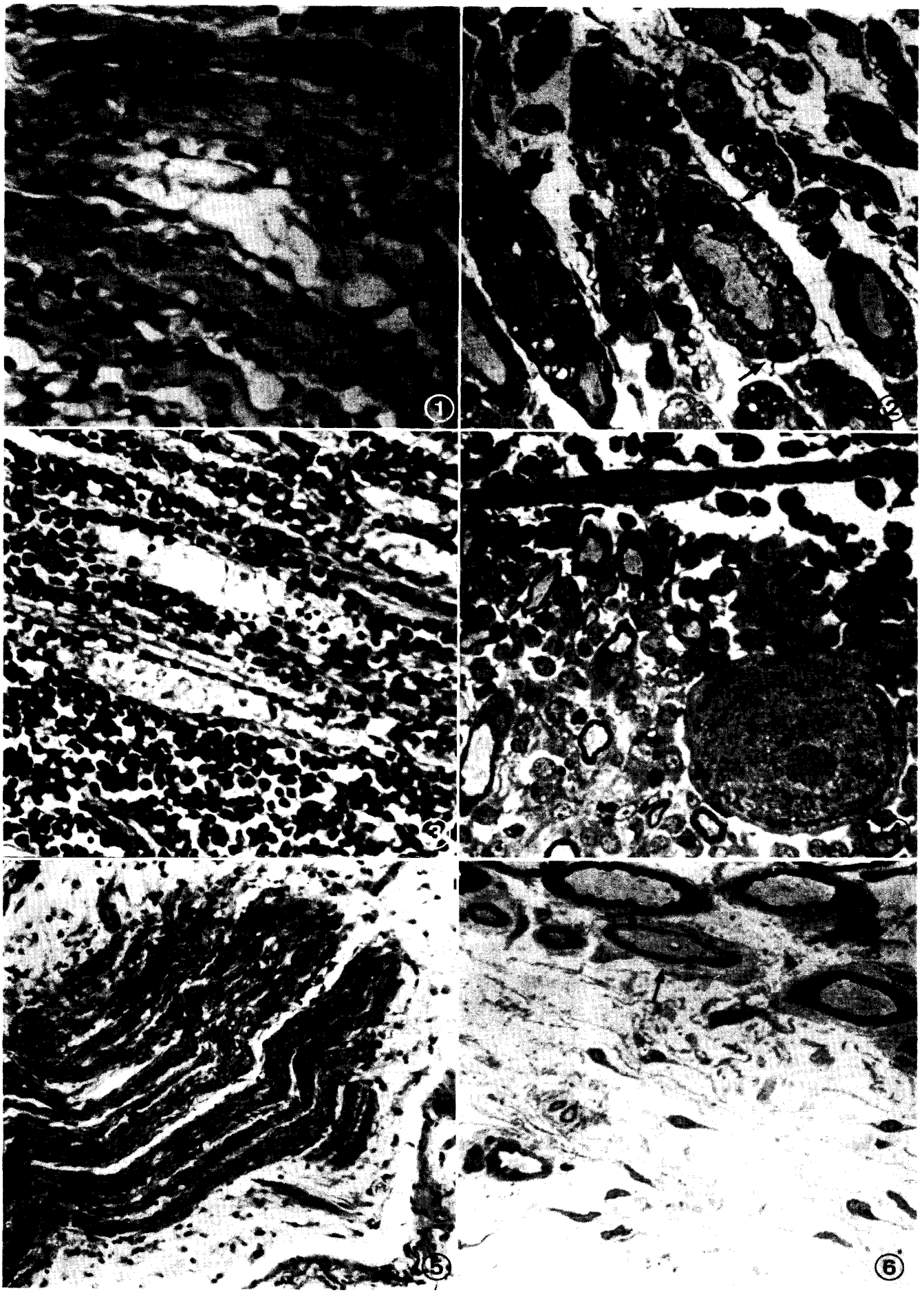
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PLATE II

Fig. 7 Category I T-type lesion

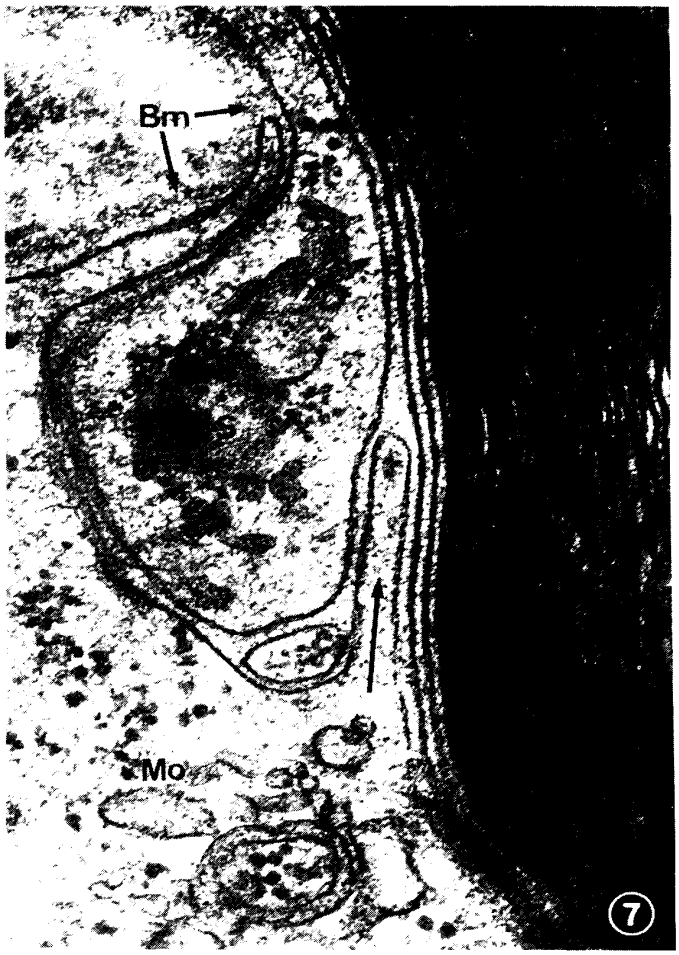
Cytoplasmic tongue (↑) from a mononuclear cell (Mo) is engaging in stripping Schwann cell cytoplasm (S) off the myelin sheath. Note the normal appearance of the myelin sheath. Bm: basement membrane Cervical spinal ganglion Chicken 766 Experimental case (29th day PI) × 6,4000

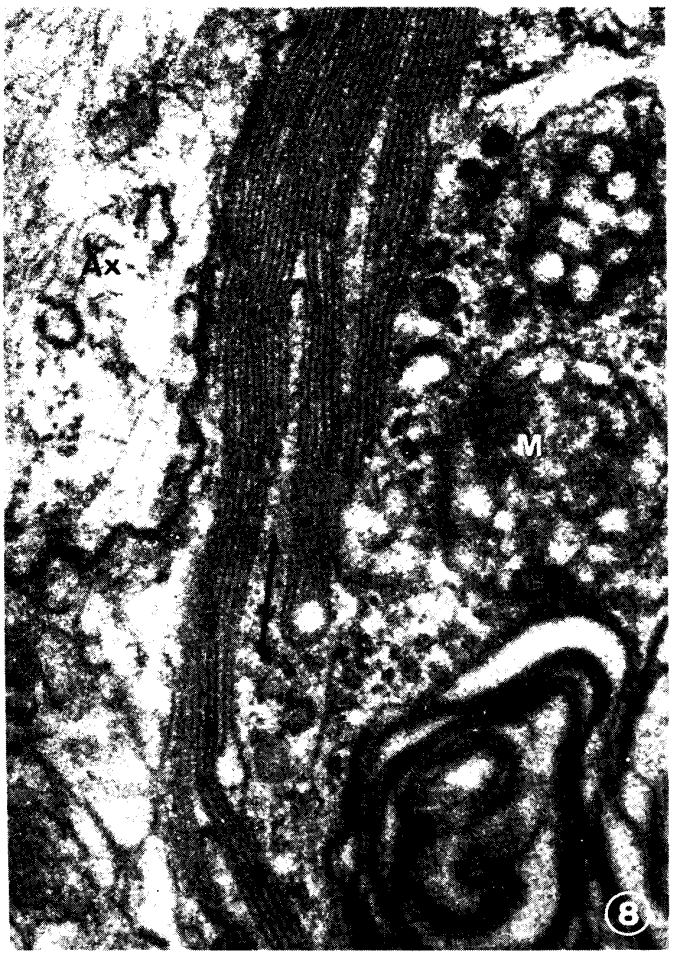
Fig. 8 Category I R-type lesion

Meylin lamellae are peeled off the sheath by cytoplasmic tongue (↑) from a macrophage (M) in an advanced stage. Ax: axon Lumbosacral plexus Chicken 632 Field case × 24,500

Fig. 9 Category I R-type lesion

A mononuclear cell, which appeared to transform into a macrophage, can be seen within the basement membrane (↑). The myelin lamellae are disintegrated and are separated from the axon. Lumbosacral plexus Chicken 632 Field case × 8,250


Bm
Mo
7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M
8

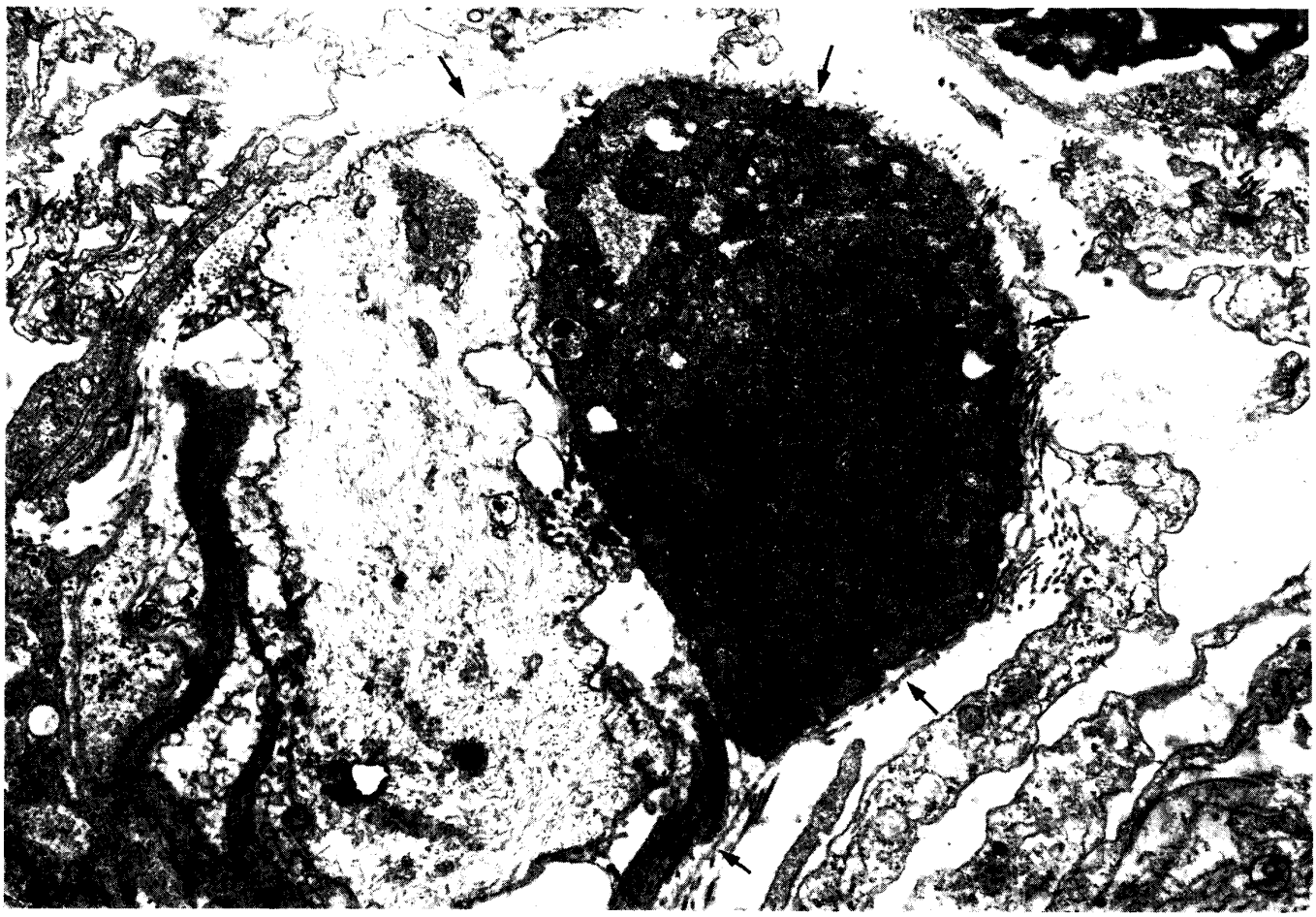


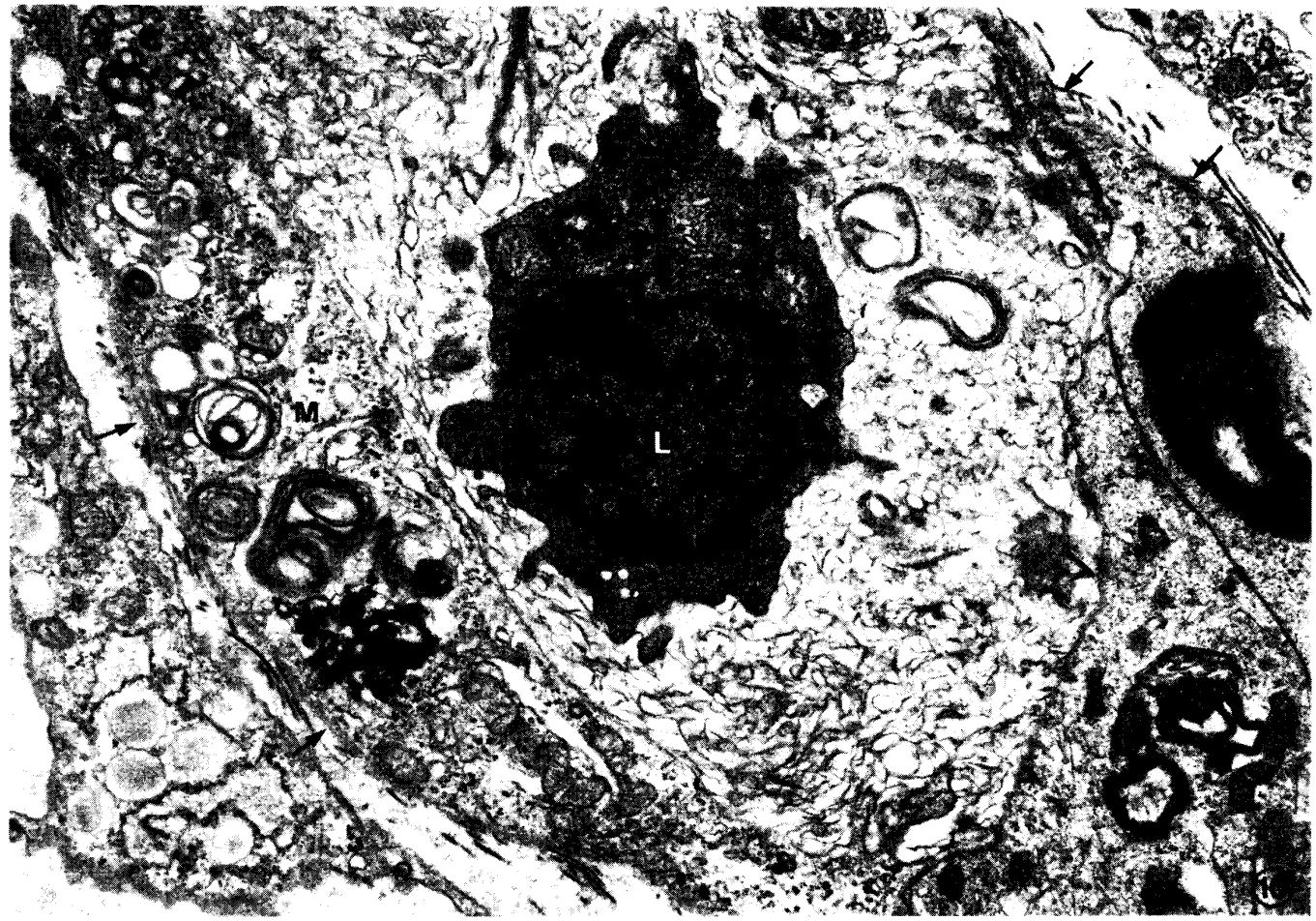
PLATE III

Fig. 10 Category I R-type lesion

A lymphocyte (L) can be seen in the Schwann cell with disintegrated myelin lamellae. Macrophages are surrounding the Schwann cell with altered myelin sheath. M: macrophage ↑: basement membrane Lumbosacral plexus Chicken 632 Field case × 8,000

Fig. 11 Category I R-type lesion

Myelin sheath shows disintegration. Axon is apparently normal, but contour of axolemma reveals waved appearance (↑). M: macrophage Lumbosacral plexus Chicken 632 Field case × 8,000


M
L

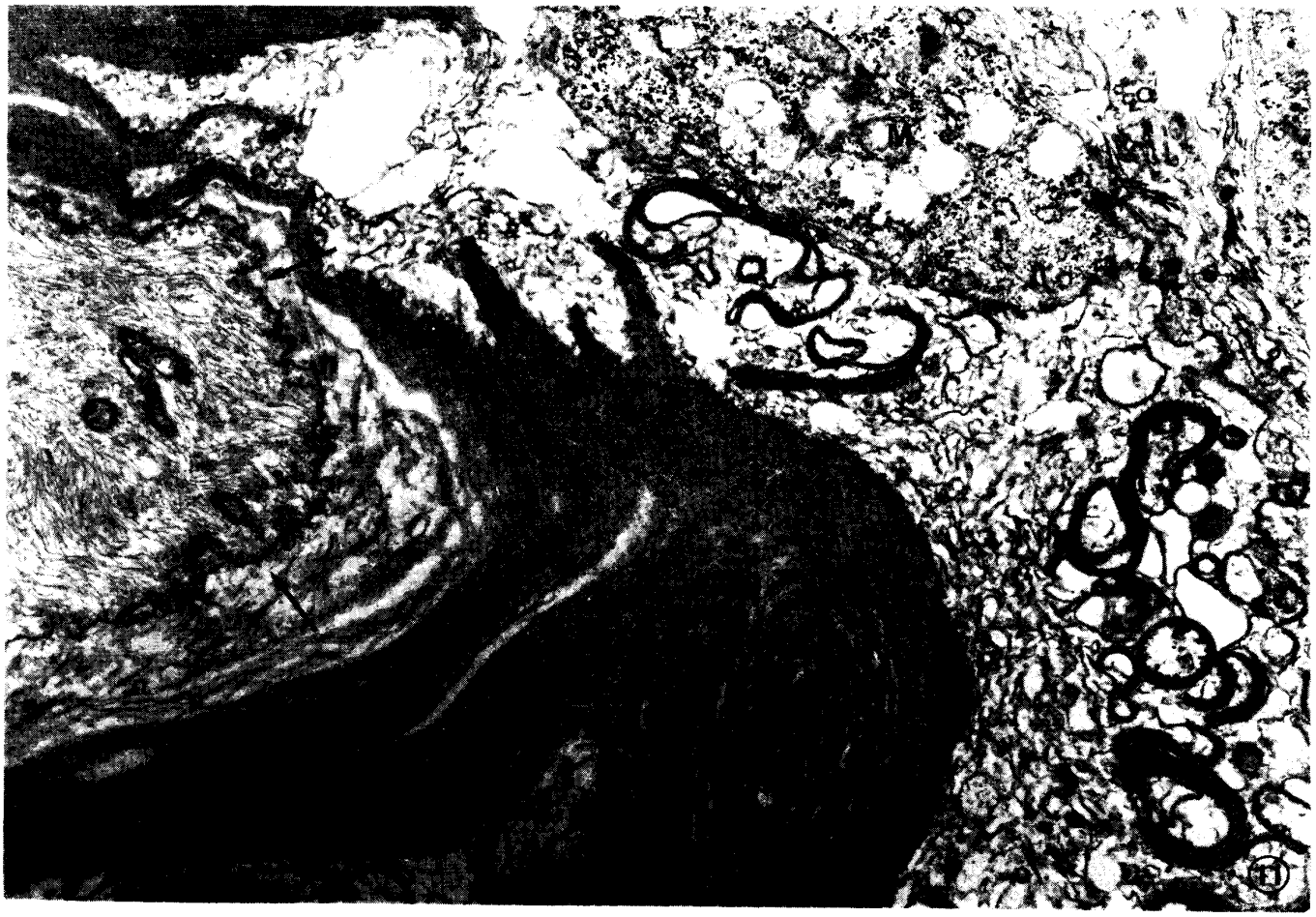

M

PLATE IV

Fig. 12 Category I T-type lesion

A macrophage (M) containing myelin debris surrounds a completely demyelinated axon. The Schwann cell cytoplasm (S) has been pushed to the periphery and can be seen as two islands of cytoplasm connected by superficial myelin lamella (↑). Cervical spinal ganglion Chicken 766 Experimental case (29th day PI) × 15,750

Fig. 13 Category I R-type lesion

A macrophage (M) containing myelin debris completely surrounds a naked axon with a long cytoplasmic process (↑). Lumbosacral plexus Chicken 632 Field case × 5,500

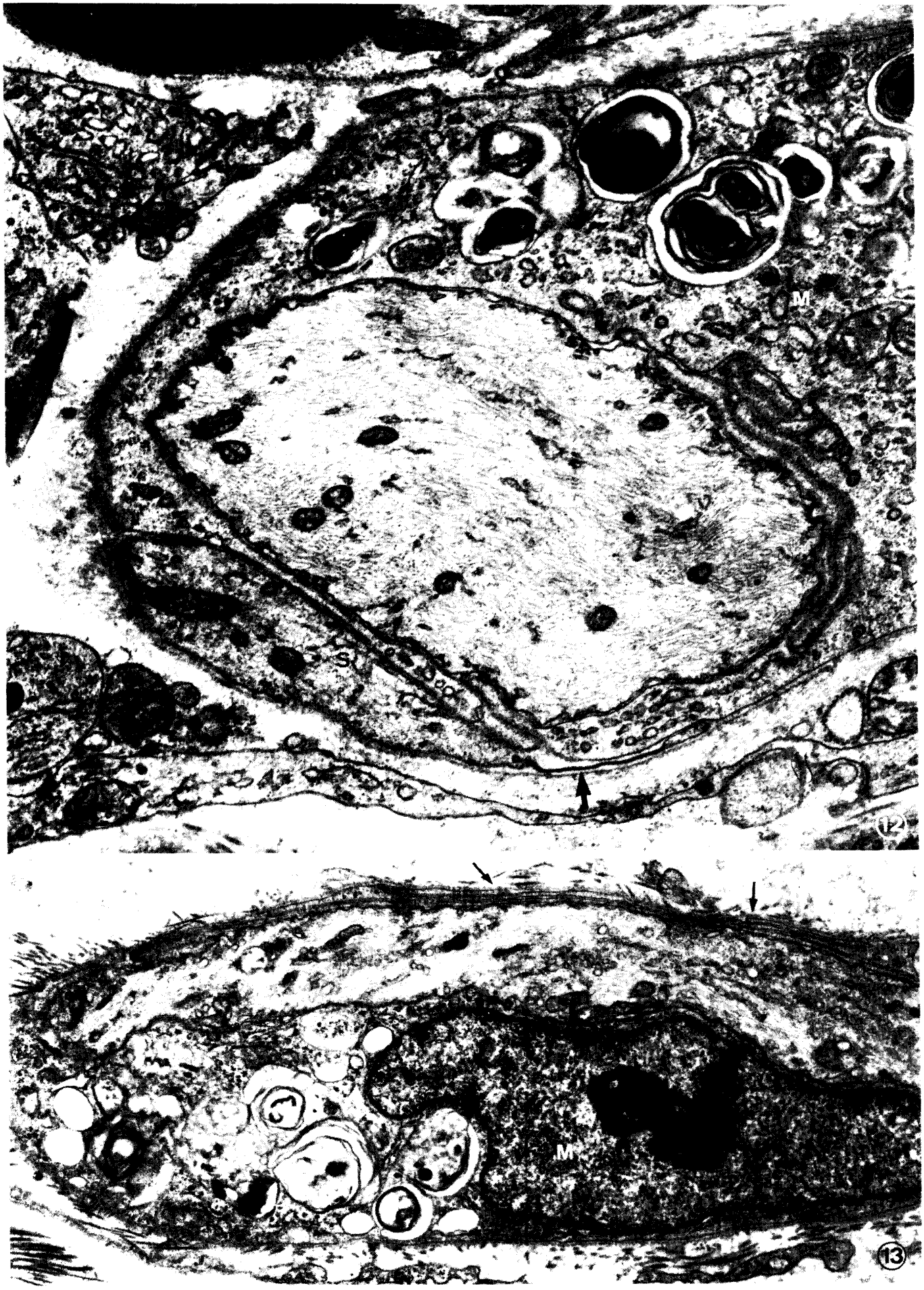

M
12
M
13

PLATE V

Fig. 14 Category I R-type lesion

Process of a macraphage (M) is penetrating from the basement membrane of a Schwann cell between two arrows. Lumbosacral plexus Chicken 632 Field case × 12,250

Fig. 15 Category I R-type lesion

A macrophage (M) containing myelin debris is leaving from the rent of the basement membrane between two arrows. Note long slender cytoplasmic processes of macrophoge. S: hypertrophied Schwann cell Lumbosacral plexus Chicken 632 Field case × 9,250

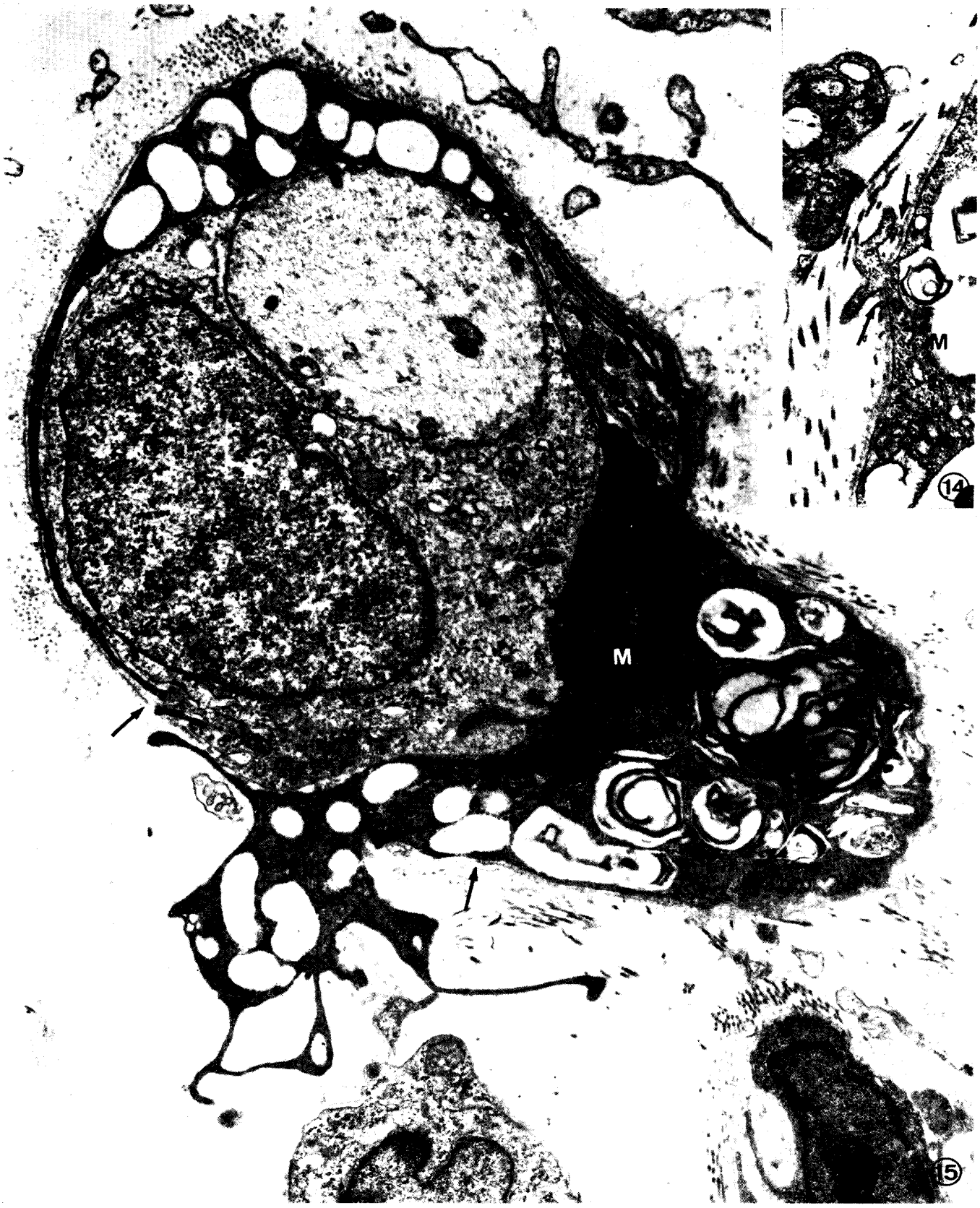
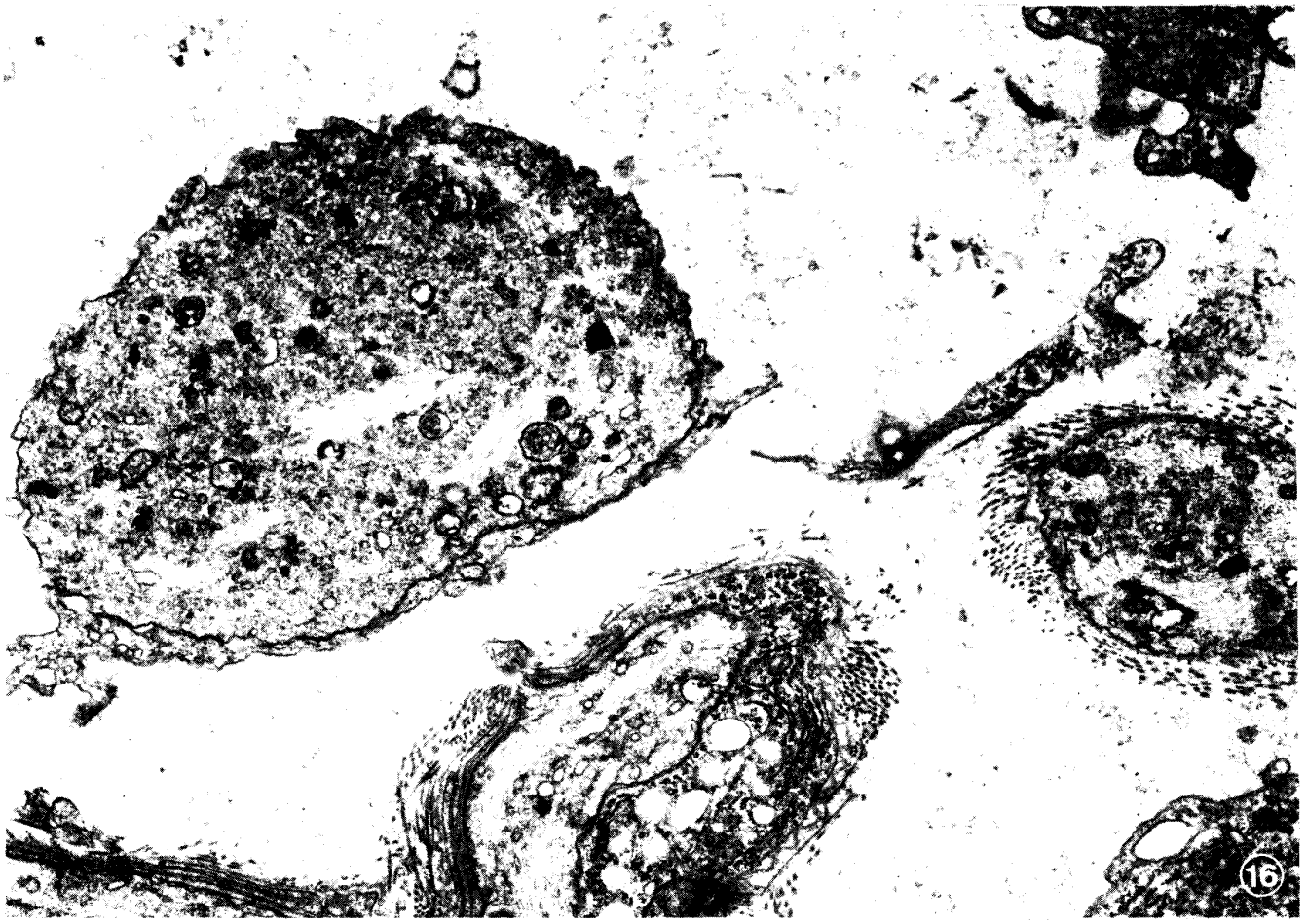

M
M
14
15

PLATE VI

Fig. 16 Category I R-type lesion
Two naked axons are seen. Lumbosacral plexus Chicken 632 Field case × 8,000

Fig. 17 Category I (remyelination) R-type lesion
Mitosis (anaphase) of Schwann cell in the demyelinated nerve fiber. M: cytoplasm of macrophage Lumbosacral plexus Chicken 632 Field case × 8,000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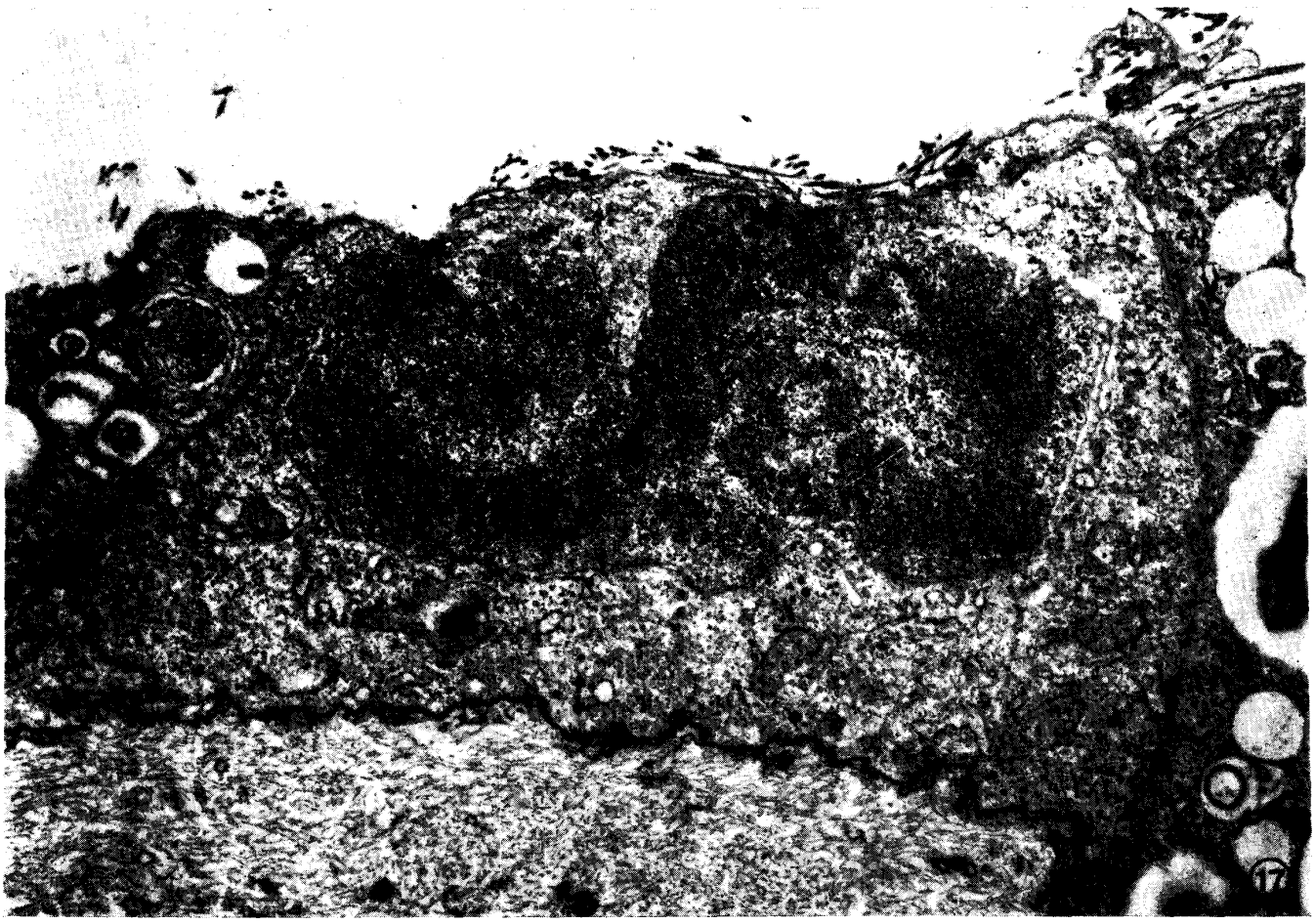

17

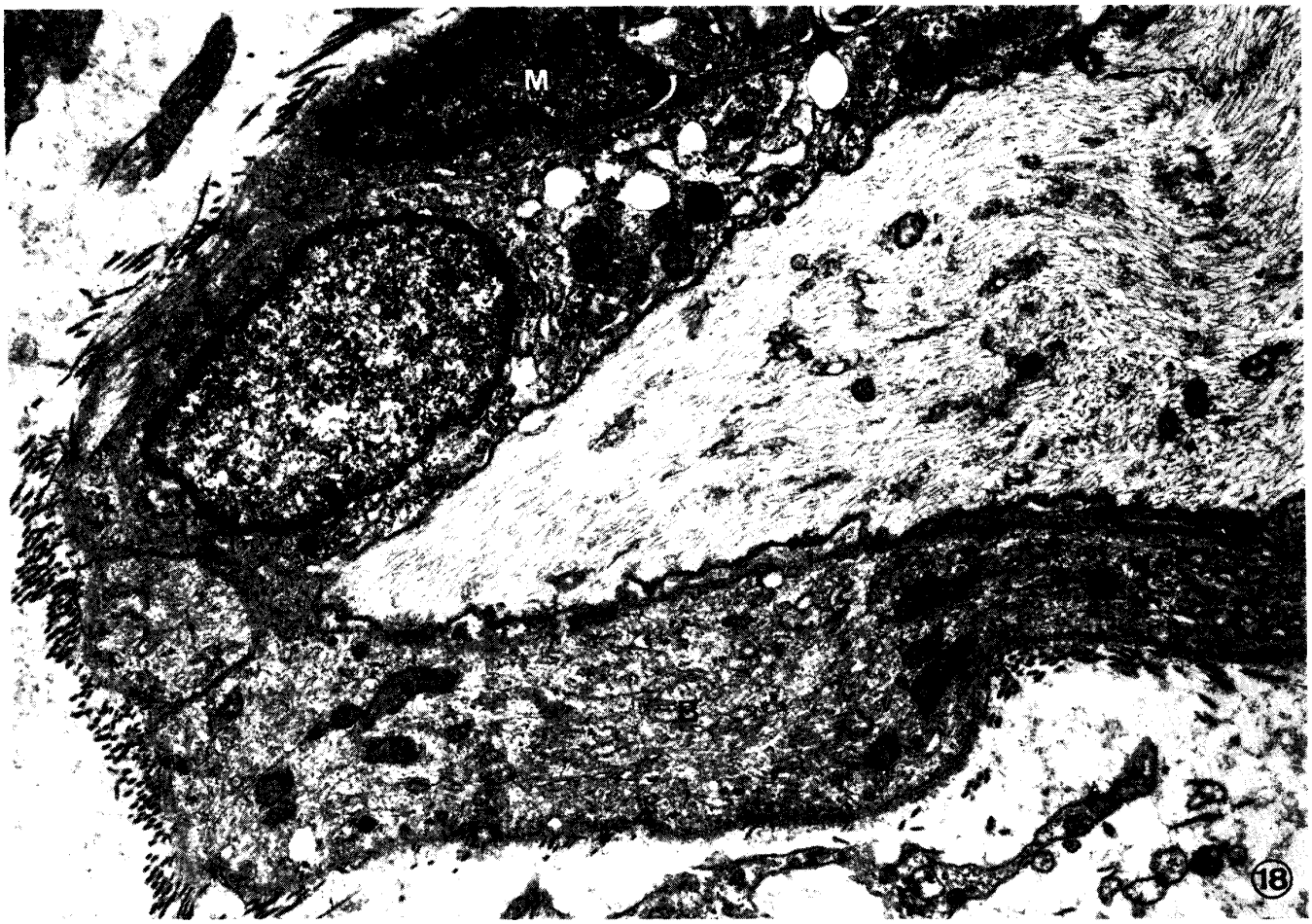
PLATE VII

Fig. 18 Category I (remyelination) R-type lension

Büngner's band (B) formation New cytoplasmic processes of Schwann cell are seen within the basement membrance. S: hypertrophied Schwann cell M: macrophage Lumbosacral plexus Chicken 632 Field case × 7,750

Fig. 19 Category I (remyelination) R-type lesion

An axon is surrounded by several loose myelin lamellae (remyelination) in the hypertrophied Schwann cell (S). Collagen fibers are seen between the newly formed basement membrane (↑) of the Schwann cell and the original basement membrane with ruffled appearance (↑↑). Ax: axon Brachial plexus Chicken 626 Field case × 15,500


M
18

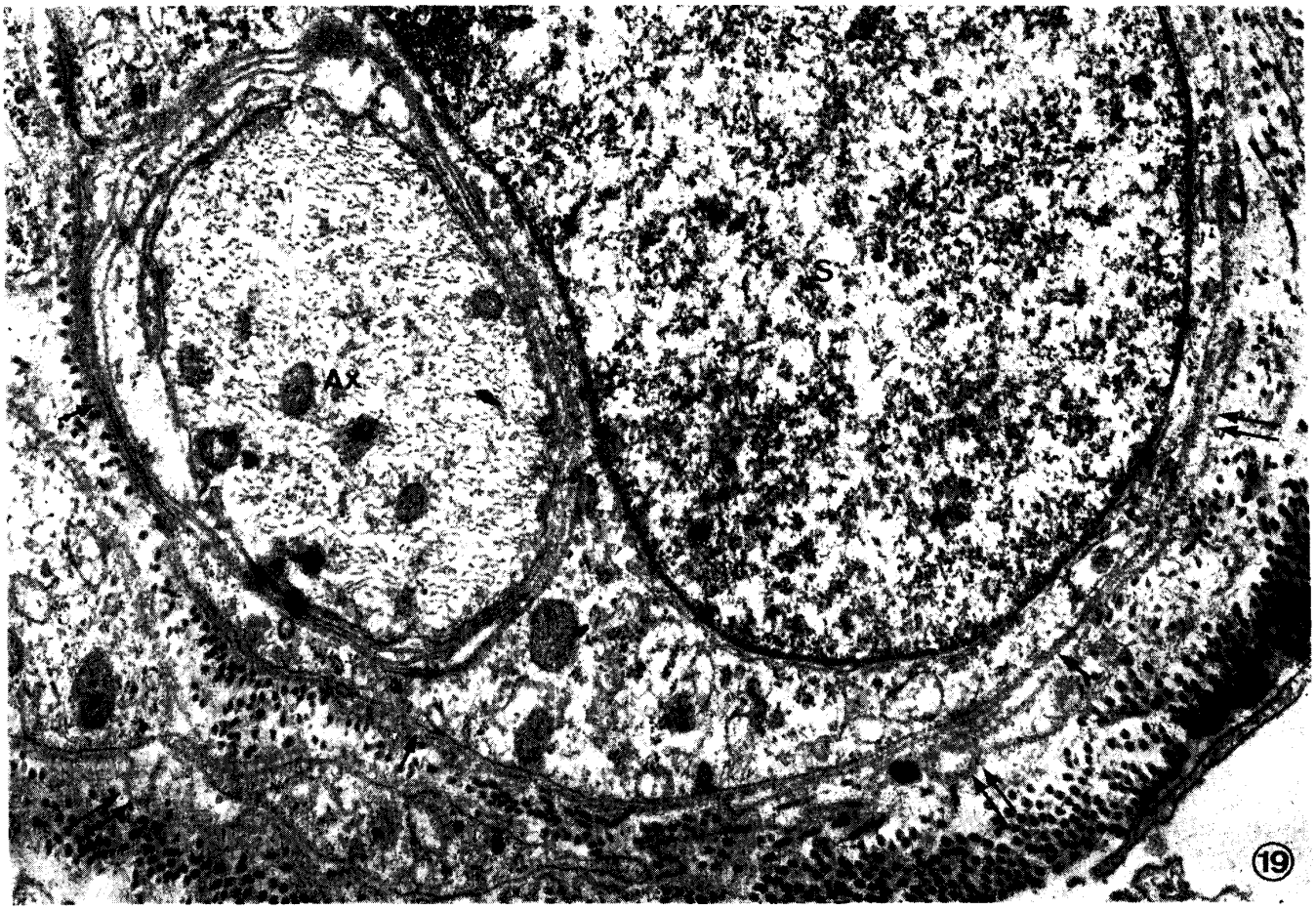

S
Ax
19

PLATE VIII

Fig. 20 Category II T-type lesion

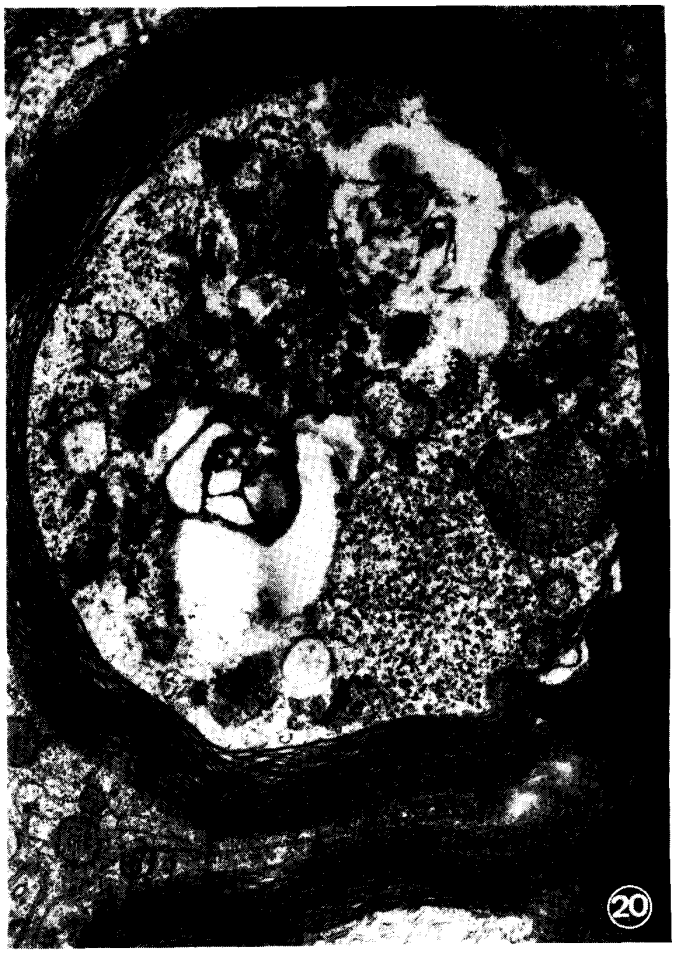
An axon reveals complete destruction, whereas the myelin sheath is apparently normal. Cervical spinal ganglion Chicken 615 Field case × 11,000

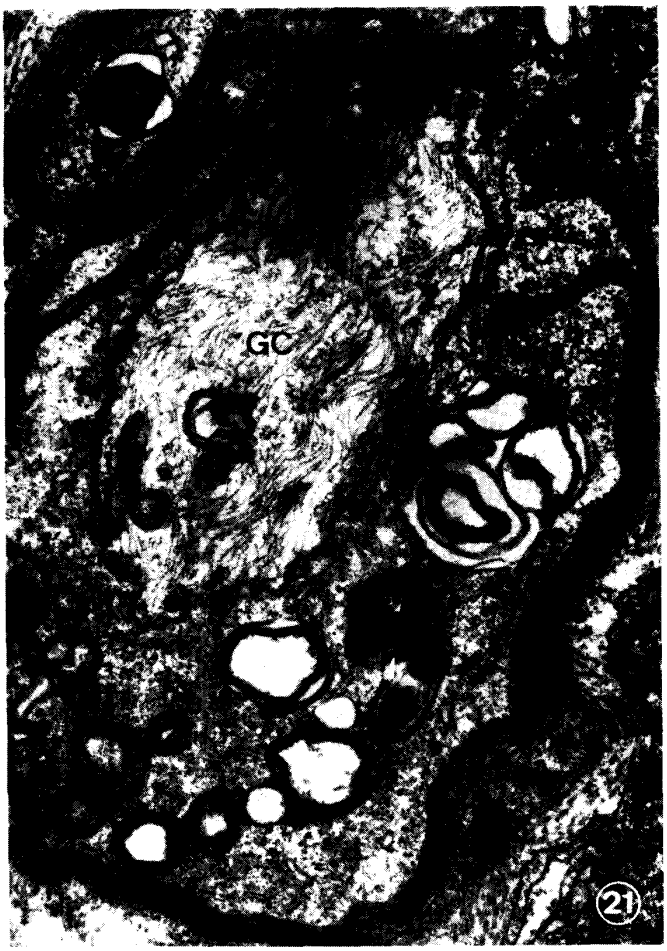
Fig. 21 Category II T-type lesion

A new axon sprout (growth cone: GC) invaginates into the central part of regenerating Schwann cell which autodigested myelin debris. A new inner mesaxon (↑) is found in connection with the axolemma of the growth cone. Remyelination at a tangential section of the node of Ranvier can be seen. Cervical spinal ganglion Chicken 615 Field case × 11,000

Fig. 22 Category II T-type lesion

In the transverse section of nerve bundle, myelinated nerve fibers with axonal condensation (Ax) are seen within the Schwann cell cytoplasm. The axonal condensation consisted of an accumulation of swollen mitochondria and electron dense bodies. A growth cone (GC) enters into the outer part of the Schwann cell sideways forming several mesaxons. Cervical spinal ganglion Chicken 765 Experimental case (23rd day PI) × 22,000




GC

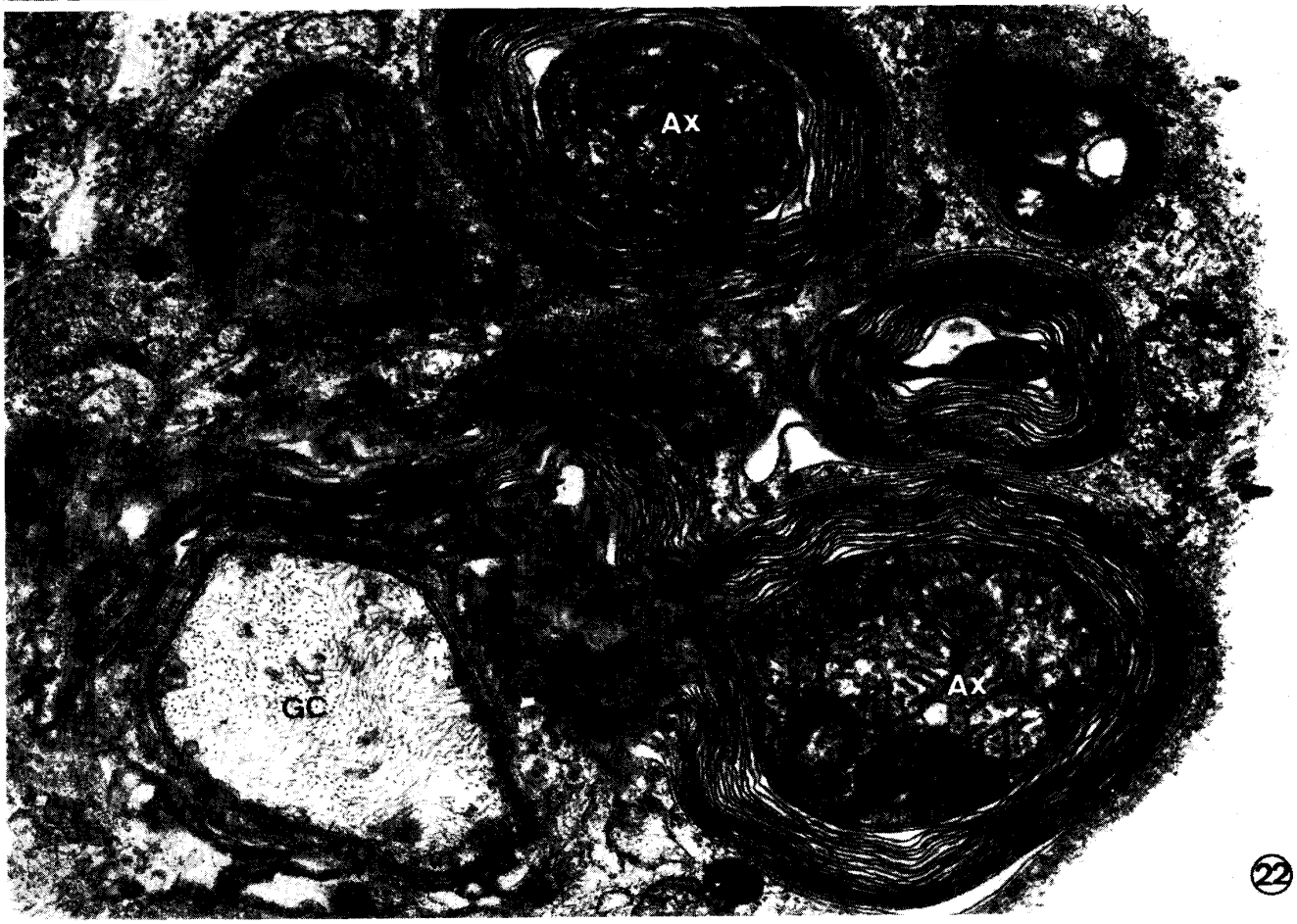

Ax
GC
Ax

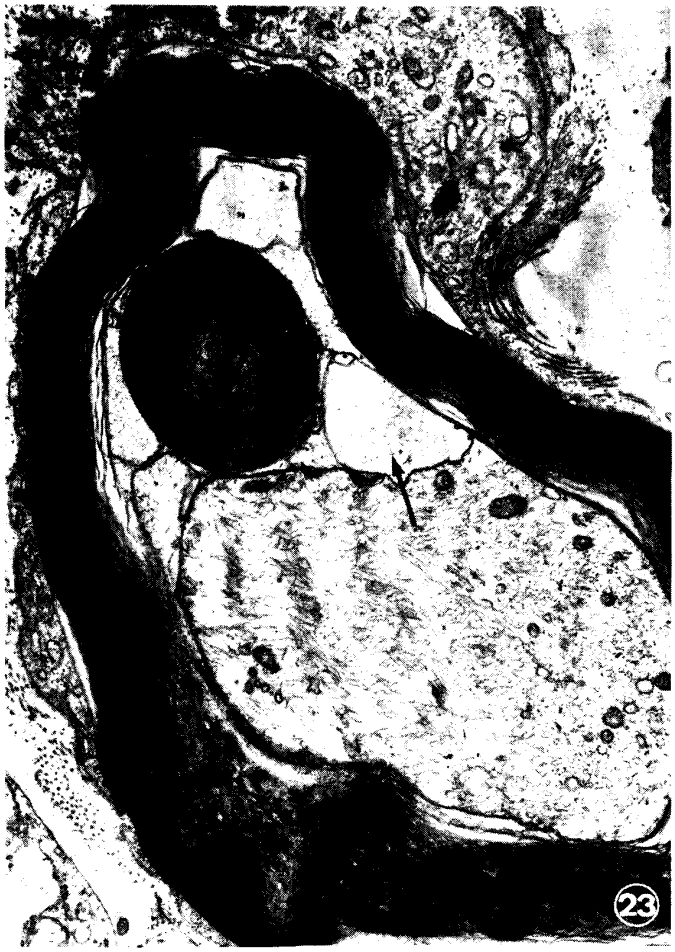
PLATE IX

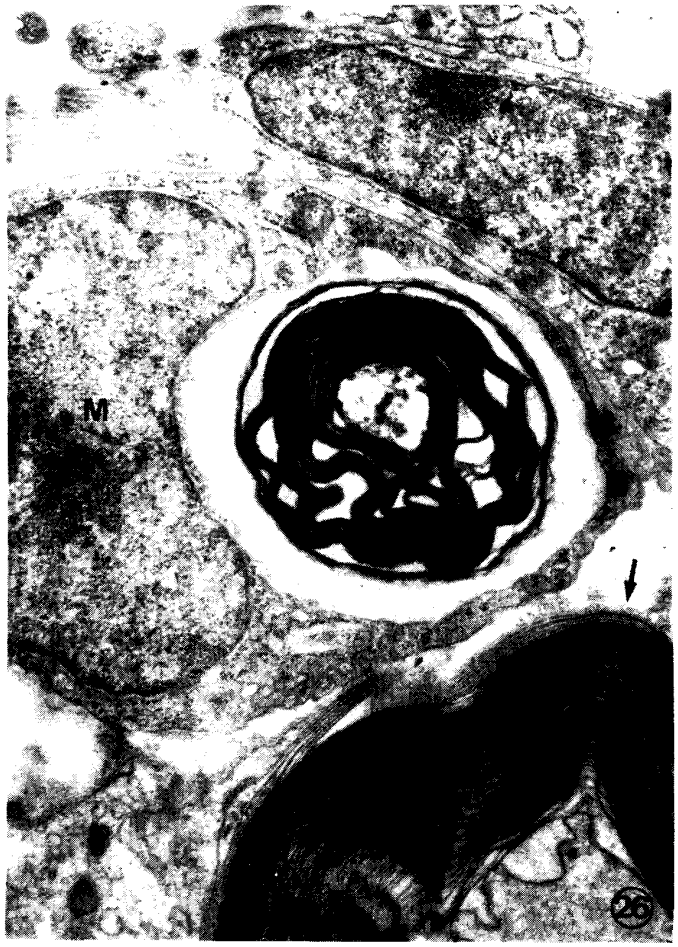
Fig. 23 Category III R-type lesion (interneural edema)
Several large clear spaces (↑) and invagination of myelin sheath are seen between axon-Schwann interface. Brachial plexus Chicken 622 Field case × 5,625

Fig. 24 Category III R-type lesion (interneural edema)
Longitudinal section of node of Ranvier The upper part of the axon involves complete demylination. The lower part of the axon is swollen. Clear spaces (↑) are seen between axon-Schwann interface and initial part of the node. Invagination of myelin sheath is also seen. Brachial plexus Chicken 623 Field case × 6,875

Fig. 25 Sub-perineurial edema
In the outer myelin sheath, even separation of the lamellae (internal compound membrane) can be seen. The interlamellar space is continuous with the extracellular space via the outer mesaxon (↑). Lumbosacral plexus Chicken 623 Field case × 46,000

Fig. 26 Sub-perineurial edema
A macrophage (M) containing myelin debris is seen near the myelinated nerve fibers with myelinolysis. Even separation of the lamellae (↑) is seen in the outer myelin sheath and clear spaces are also found between axon-Schwann interface. Brachial plexus Chicken 626 Field case × 10,250




M