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J. Neuropath. + Exp Neurol. 28, 401-18 (1969)

EXPERIMENTAL LEAD NEUROPATHY: A DISEASE OF THE SUPPORTING CELLS IN THE PERIPHERAL NERVOUS SYSTEM*†

WILLIAM W. SCHLAEPFER, M.D.

(*St. Louis, Missouri*)

Experimental lead neuropathy is characterized by the coexistence of segmental demyelination and Wallerian degeneration in peripheral nerves (1–5). While the demyelinating component of these lesions clearly indicates the susceptibility of the Schwann cells in this condition, the nature and origin of the axonal damage is less clear. The occurrence of axonal degeneration in the presence of demyelination certainly raises the possibility of a causal relationship between these pathological events. Indeed, the axon has been postulated to be functionally dependent upon the Schwann cell for certain metabolites (6, 7), and nutrient materials have been shown to pass from the endoneurium into the axon (8).

Other observations, however, suggest that the pathogenesis of axonal change in experimental lead neuropathy is more complex. Previous studies of this condition have noted a poor correlation between the amounts of axonal and segmental damage (3–5). In fact, axonal degeneration has been encountered in the absence of segmental lesions among individual animals and in certain species. Furthermore, severe demyelination can be experimentally produced by diphtheria toxin (9–11), irradiation (12, 13), and spinal barbotage (14) without anatomic alteration of the associated axons.

These findings diminish the probability of a direct causal relationship between the axonal and segmental changes of experimental lead neuropathy. Conversely, the axonal damage is more likely due to additional cellular lesions which manifest themselves independent of the segmental injury. This phenomenon is, perhaps, best exemplified in the rat where axonal damage has been reported in the absence of segmental change (5). The present study has reexamined the lesions of this condition and attempted to identify additional cellular alterations which might give rise to axonal degeneration. Accordingly, ultrastructural, histochemical, and whole-mount techniques have been applied to different areas of the peripheral nervous system of rats subjected to prolonged lead intoxication.

MATERIAL AND METHODS

Eighteen male Sprague-Dawley rats weighing 200 to 250 gm were fed a 1 per cent lead acetate solution with an average daily consumption of 60 cc *per* rat. No clear-cut neurological deficits were observed during the course of the experiment, although 4 animals died from unknown causes. Pairs of the remaining rats were sacrificed after

60 cc
.01
0.6 cc Pb acetate daily.

S.g (diluent):
H_2O: 3.25
$3 H_2O$: 2.55

*From the Department of Pathology, Washington University, St. Louis, Missouri 63110

†This work was supported by grant NB 08549-01 from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health.

3.25
Tch S.g = 3.25 0.6 cc / 1.950 gm. / day 9 wk exp 56% = Pb

approximately 3, 4, 5, 6, 9, 12 and 18 months of this regime. Three rats of comparable weights were used as controls.

Under ether anesthesia, the descending thoracic aortas were perfused with 300 cc of cold Ringer's solution containing 4 per cent glutaraldehyde and 10 per cent formalin. The fixative was allowed to effuse through an incision in the inferior vena cava. After excising the sciatic and tibial nerves, the spinal columns were removed and the spinal cords exposed through a multiple bilateral laminectomy procedure. The spinal ganglia, posterior roots, and anterior roots of the lumbar and sacral regions were identified and excised with the aid of a dissecting microscope. These tissues together with segments of the lumbar spinal cord were placed in a cold solution of 10 per cent formalin and 4 per cent glutaraldehyde which was buffered with 0.1 M sodium cacodylate to pH 7.2. Following additional periods of fixation for 4 and 24 hours the tissues were washed overnight in cold 0.3 M sucrose.

Sections of sciatic and tibial nerves, and anterior and posterior spinal nerve roots were osmicated with 1 per cent $Os\text{-}O_4$, washed in sucrose, and placed on a glass slide where the individual nerve fibers were teased apart with fine eye forceps under a dissecting microscope. These preparations were embedded in gelatin and coverslipped. Unosmicated tissues which had been fixed for 4 hours were teased in a similar manner and transferred to a small beaker in which they were incubated in Gomori acid phosphatase medium (15) for 2 and 4 hours at room temperature. After a 5 minutes wash in 2 per cent acetic acid and a sulfide conversion with 1 per cent NH_4S, these teased fibers were placed on a glass slide, embedded in gelatin, and coverslipped. Longitudinal and transverse frozen sections of peripheral nerve were tested for acid phosphatase activity under identical conditions. Longitudinal frozen sections of nerve were stained with Oil Red O and hematoxylin. Other tissues were dehydrated, embedded in paraffin, and stained by the hematoxylin and eosin, Nissl, Masson, PAS, Luxol Fast Blue and Bodian silver impregnation technics.

Minced tissues from peripheral nerves, ganglia and anterior horns of the lumbar cord were post-fixed in 1 per cent buffered $Os\text{-}O_4$, dehydrated through an alcohol series and propylene oxide, and embedded in Epon. Additional aldehyde-fixed tissues were processed without post-fixation. One μ sections of dorsal root ganglia were cut with an LKB microtome for phase-contrast studies. Ultrathin sections were examined with a RCA 3-G electron microscope. The sections of unosmicated tissues were examined unstained, the others were contrasted with lead citrate or uranyl acetate.

RESULTS

Spinal Ganglia: Phase contrast examination of dorsal root ganglia from the experimental animals revealed an increase of capsular cells which occurred in a circumferential manner around individual ganglion cells and focally in the intervening tissue (figs. 1, 2). The cytoplasm of these cells was unusually prominent and contained numerous dense bodies which often accumulated in the vicinity of the nucleus. These changes were frequently observed surrounding the larger ganglion cells and their emerging axons. Quantitative variations of these alterations were noted among different animals; however, the most conspicuous capsular cell changes were seen in those animals showing Wallerian degeneration in the posterior nerve roots and in the sciatic and tibial nerves. The ganglion cells showed a wide variation in size, cytoplasmic content, and nuclear arrangement (16), but no consistent pathological alterations were observed by light microscopy.

The alterations of the capsular cells were particularly apparent at the ultrastructural level. Many of the ganglion cells were enveloped by a thickened

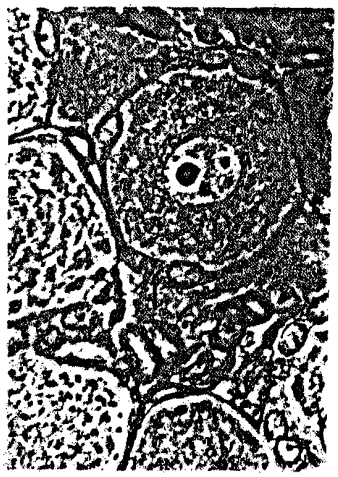

FIG. 1. Proliferation of capsular c granules (arrows) within their cytopl
FIG. 2. A ganglion cell surround dense granules (arrow). Phase contra

seam of capsular cell cytoplasm especially mitochondria, rough 3). These dense bodies consist dense granules of varying siz Further information on the na examination of aldehyde-fixed conditions, the granules within density comparable to a heav displayed variability in size ar dimensions (fig. 5). No other density in unstained tissue, inc (fig. 6).

Pathological changes within due to the characteristic va among these cells (16). Accun cells of both experimental a neurons associated with altere of neurofilaments with a d relative prominence of polyrib rated these cells from the adjo

Anterior Horn: Light and e horns of the lumbar region sl perimental and control anima cells and some focal astrocyt

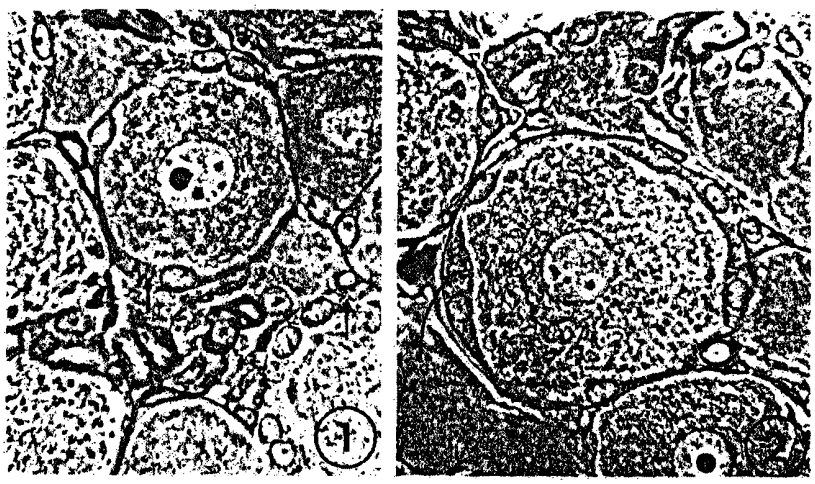

FIG. 1. Proliferation of capsular cells in dorsal root ganglion and accumulation of dense granules (arrows) within their cytoplasm. Phase contrast; × 650.

FIG. 2. A ganglion cell surrounded by a thickened seam of capsular cells containing dense granules (arrow). Phase contrast; × 800.

seam of capsular cell cytoplasm containing an increased number of organelles, especially mitochondria, rough endoplasmic reticulum and dense bodies (fig. 3). These dense bodies consisted of a homogeneous matrix in which multiple dense granules of varying sizes were randomly or peripherally distributed. Further information on the nature of these dense bodies was obtained by the examination of aldehyde-fixed, unosmicated and unstained tissue. Under these conditions, the granules within the dense bodies possessed an inherent electron density comparable to a heavy metallic material (fig. 4). The dense bodies displayed variability in size and configuration, sometimes attaining very large dimensions (fig. 5). No other tissue component manifested a similar electron density in unstained tissue, including the lipofuscin bodies of the ganglion cells (fig. 6).

Pathological changes within the ganglion cells were more difficult to assess due to the characteristic variation in the normal ultrastructural features among these cells (16). Accumulations of lipofuscin were seen in the ganglion cells of both experimental and control animals. Nevertheless, some of the neurons associated with altered capsular cells revealed an unusual prominence of neurofilaments with a decrease of rough endoplasmic reticulum and relative prominence of polyribosomes (fig. 7). A tortuous interface often separated these cells from the adjoining capsular cells.

Anterior Horn: Light and electron microscopic examination of the anterior horns of the lumbar region showed no significant difference between the experimental and control animals. Accumulations of lipofuscin in anterior horn cells and some focal astrocytic proliferation could be seen in many animals.

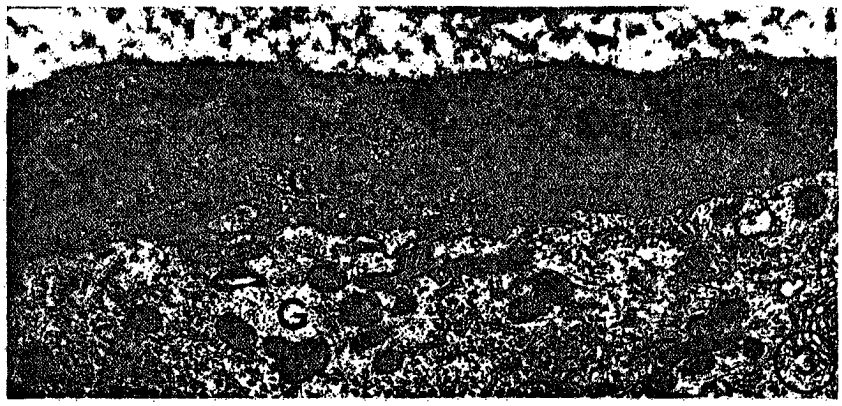

FIG. 3. A ganglion cell (G) surrounded by a thickened capsular cell (C) investment. Numerous dense bodies as well as an increase of mitochondria and ribosomes can be seen within the capsular cell; × 9,000.

No electron-dense granular material was observed in aldehyde-fixed, unosmicated, and unstained tissue.

Peripheral Nerve: In whole-mount, teased preparations of nerve, axonal or Wallerian degeneration was characterized by a linear arrangement of irregular osmiophilic droplets which traversed the segment of nerve examined (figs. 8–10). These particles of lipid debris assumed varying shapes and sizes, but were confined to longitudinally oriented, threadlike structures. A variable amount of these changes was observed in 6 of the 14 experimental animals. Although a quantitative analysis was not attempted, the Wallerian degeneration appeared most prominent in the distal tibial nerve and seemed to involve the larger myelinated fibers.

Evidence of segmental demyelination and remyelination was noted in 9 experimental animals. These changes were manifested by a variety of discontinuities and irregularities of the myelin sheaths along the course of individual nerve fibers. Gradations of the demyelination could be seen from a widening of the nodal myelin gap (fig. 9) to a partial or complete loss of individual myelin sheaths, and in some cases, to the preservation of only isolated segments of myelin. Remyelination of the denuded segments of nerve fibers were recognized by short and thin intercalated myelin sheaths, by a disparity in size of the adjacent myelin sheaths and by irregularly shortened lengths of successive myelin sheaths (fig. 10). No preponderance of segmental changes were noted in the proximal or distal segments of nerve.

Acid phosphatase activity was observed in the axons at nodes of Ranvier in both longitudinal frozen sections and in whole-mount, teased preparations (figs. 11, 12). A granular and dust-like component could be perceived, both of which accumulated underneath the node and spread in diminishing quantity to one or both adjacent perinodal axoplasmic regions (fig. 11). Sometimes the stain outlined the limiting axoplasmic membranes of the perinodal area (fig.

FIG. 4. Aldehyde-fixed, unosmicate
veals electron-dense particles in the c
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densities are not present in underlying

FIG. 5. Electron densities in capsul
stained tissue form circular profiles (
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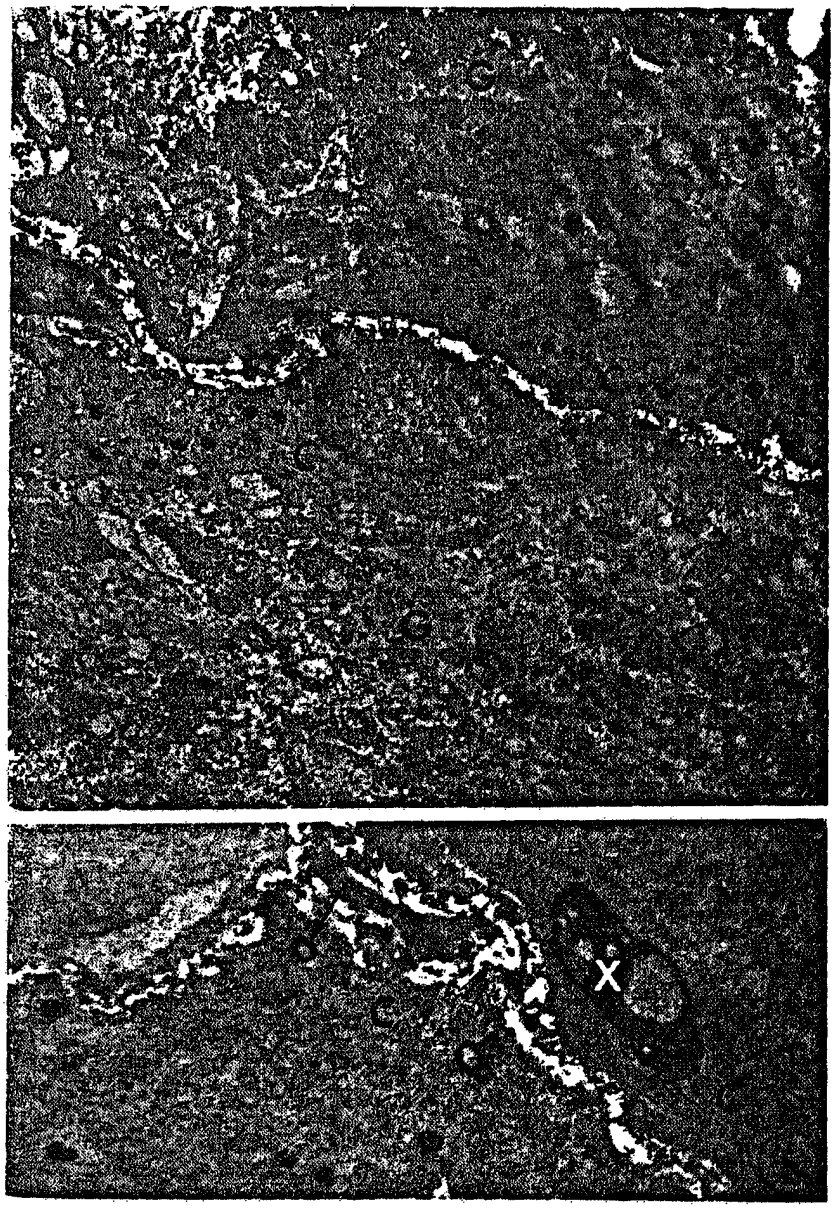


FIG. 4. Aldehyde-fixed, unosmicated and unstained section of dorsal root ganglion reveals electron-dense particles in the distribution, size and configuration of dense bodies in two adjoining capsular cells (C) separated by extracellular space (light area). Similar densities are not present in underlying ganglion cells (G); × 8,500.

FIG. 5. Electron densities in capsular cells (C) of aldehyde-fixed, unosmicated and unstained tissue form circular profiles (arrow) and, sometimes, assume very large dimensions (X); × 12,000.

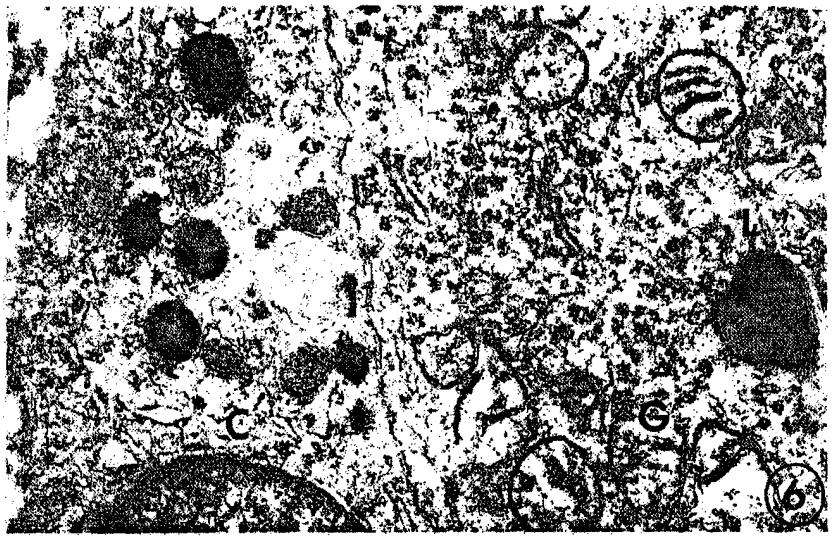


FIG. 6. Osmicated but unstained tissue reveals the dense bodies of the capsular cells (C) to consist of a homogeneous matrix in which dense granules of varying sizes are randomly or peripherally distributed. The lipofuscin body (L) of adjoining ganglion cell (G) has a different cytoarchitecture; × 28,000.

12). In teased preparations, these deposits could be visualized at successive nodal areas along an individual nerve fiber (figs. 13–16). No generalized increase of acid phosphatase activity was present in Schwann cells without evidence of myelin breakdown. Some punctate areas of enzymatic activity could occasionally be found in the perinodal regions of Schwann cells in which there was retraction of the underlying myelin sheath. In addition, acid phosphatase activity irregularly surrounded the lipid debris which occurred in longitudinal linear arrays following Wallerian degeneration (fig. 17).

Electron microscopic examination of representative segments of peripheral nerve revealed a variable amount of alteration in the myelin sheaths. These changes were characterized by a separation and irregular folding of myelin lamellae which resulted in a marked distortion of the tubular configuration of the myelin sheath (fig. 18). Fibers with less disrupted myelin sheaths often showed an exaggeration of their Schmidt-Lantermann clefts with irregularities of the adjacent myelin lamellae (fig. 18). The terminals of myelin sheaths at nodes of Ranvier were an additional site of early disruption of the myelin lamellae. The Schwann cell cytoplasm and the axons of these fibers undergoing segmental change showed no consistent alterations, although the axons were frequently displaced and partially denuded. Some fibers appeared to be undergoing remyelination. This was characterized by a large axon surrounded by a thin myelin sheath and abundant Schwann cell cytoplasm (fig. 19).

Ultrastructural evidence of Wallerian degeneration was less frequently encountered. On rare occasions, a myelinated axon showed a loss of neurofila-

FIG. 7. Increase of neurofilaments, prominence of polyribosomes in gan tortuous membranous interface sepa (N); × 12,500.

ments and neurotubules with t material (fig. 20). The surroun partially collapsed. More often within Schwann cell cytoplasm Additional evidence of axonal a bound glycogen granules in myc neurotubular and neurofilament

Spinal Nerve Roots: This tiss whole-mount, teased preparatio

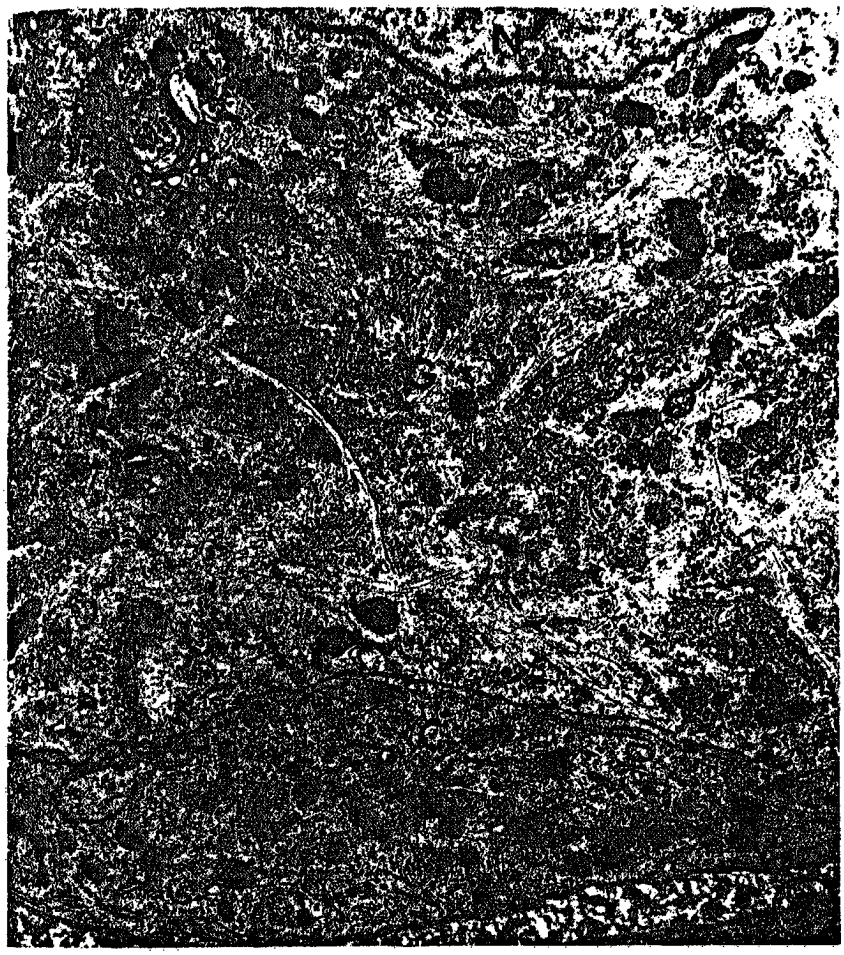


FIG. 7. Increase of neurofilaments, decrease of rough endoplasmic reticulum and relative prominence of polyribosomes in ganglion cell (G) underlying altered capsular cell (C). A tortuous membranous interface separates the neuron from the supporting cell. Nucleus (N): ×12,500.

ments and neurotubules with their replacement by an amorphous granular material (fig. 20). The surrounding myelin sheath was usually disrupted and partially collapsed. More often, however, only the myelin debris was seen within Schwann cell cytoplasm without clear-cut evidence of axonal remnants. Additional evidence of axonal alterations was seen in the form of membrane-bound glycogen granules in myelinated and unmyelinated axons (fig. 21). The neurotubular and neurofilamentous components of these axons were normal.

Spinal Nerve Roots: This tissue was less satisfactory for evaluation through whole-mount, teased preparations since considerable difficulty was encountered

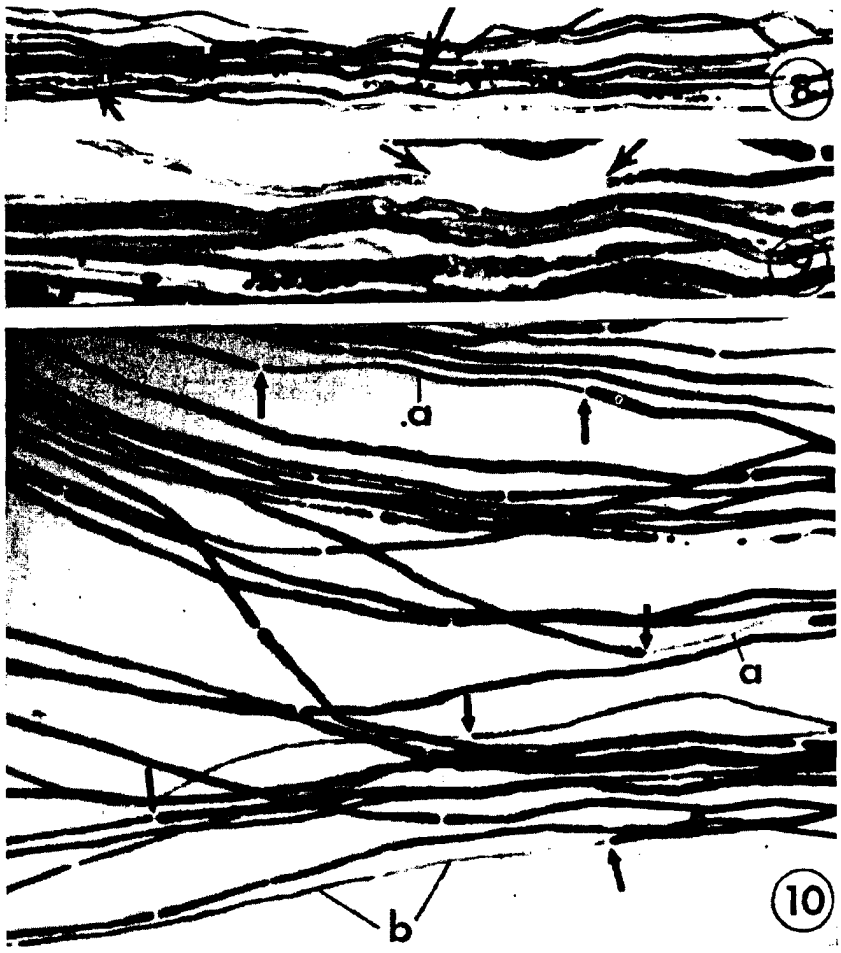
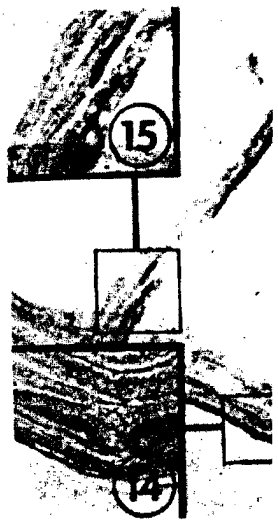


FIG. 8. Whole-mount, teased preparation of tibial nerve showing linear arrangement of osmiophilic droplets in fiber undergoing Wallerian degeneration (arrows); × 100.

FIG. 9. Segmental loss of myelin sheath along a nerve fiber in tibial nerve (arrows). This change begins at nodes of Ranvier; × 220.

FIG. 10. Short "intercalated" myelin sheaths (a) and a series of shortened myelin sheaths (b) along nerve fibers of tibial nerve. Remyelinated segments can be recognized by the unequal calibre of adjoining myelin sheaths at nodes of Ranvier (arrows); × 125.

in the separation of the individual nerve fibers without breakage and disruption. However, in addition to these preparatory artifacts, similar characteristic features of Wallerian and segmental change could be recognized in these fibers. A linear arrangement of osmiophilic droplets was seen in the posterior nerve roots of 3 rats. No clear-cut Wallerian degeneration, however, was noted in the other posterior roots or in any of the anterior spinal nerve roots.



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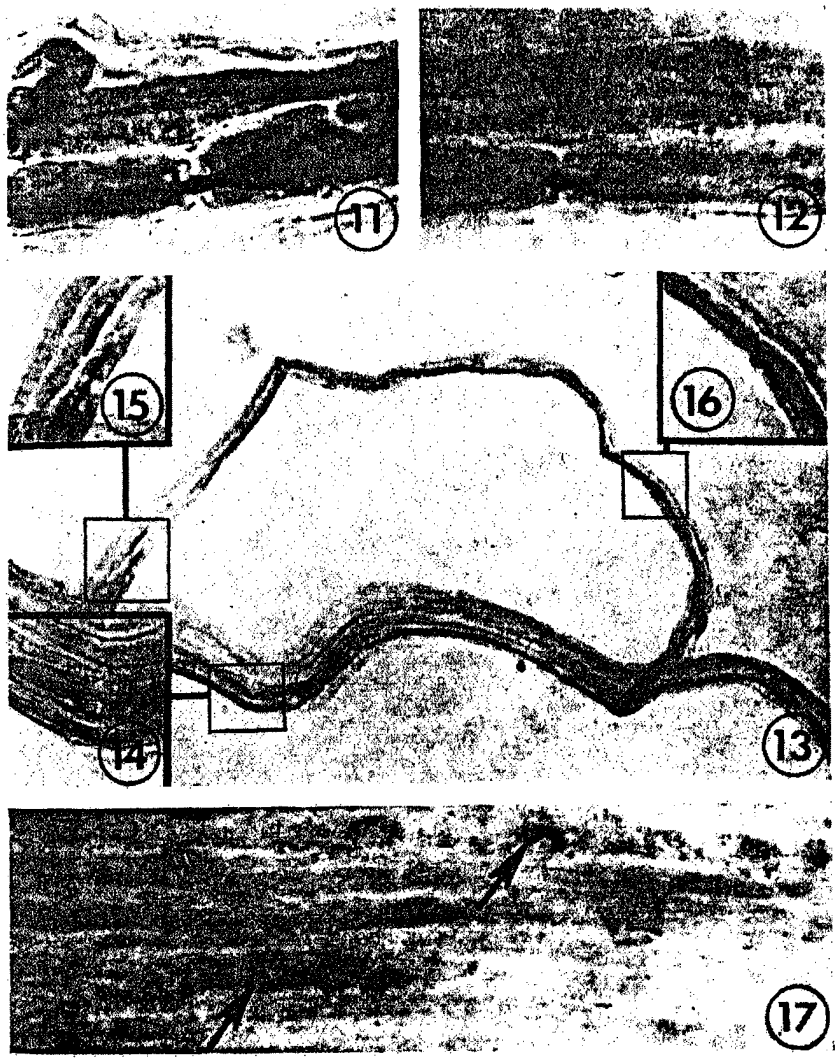

FIGS. 11 and 12. Whole-mount, teased preparations of tibial nerve displaying acid phosphatase activity in the nodal axoplasm with unilateral spread into the adjacent axoplasm; × 700.

FIG. 13. Accumulations of acid phosphatase activity at three successive nodes of Ranvier along a single nerve fiber of the tibial nerve; × 100.

FIGS. 14, 15 and 16. Higher magnifications of nodal areas in Figure 13. The same direction of unilateral spread of enzymatic activity into adjacent axoplasm occurs at each node; × 350.

FIG. 17. Acid phosphatase activity within the linear arrays of lipid debris following Wallerian degeneration (arrows). Frozen section; × 450.

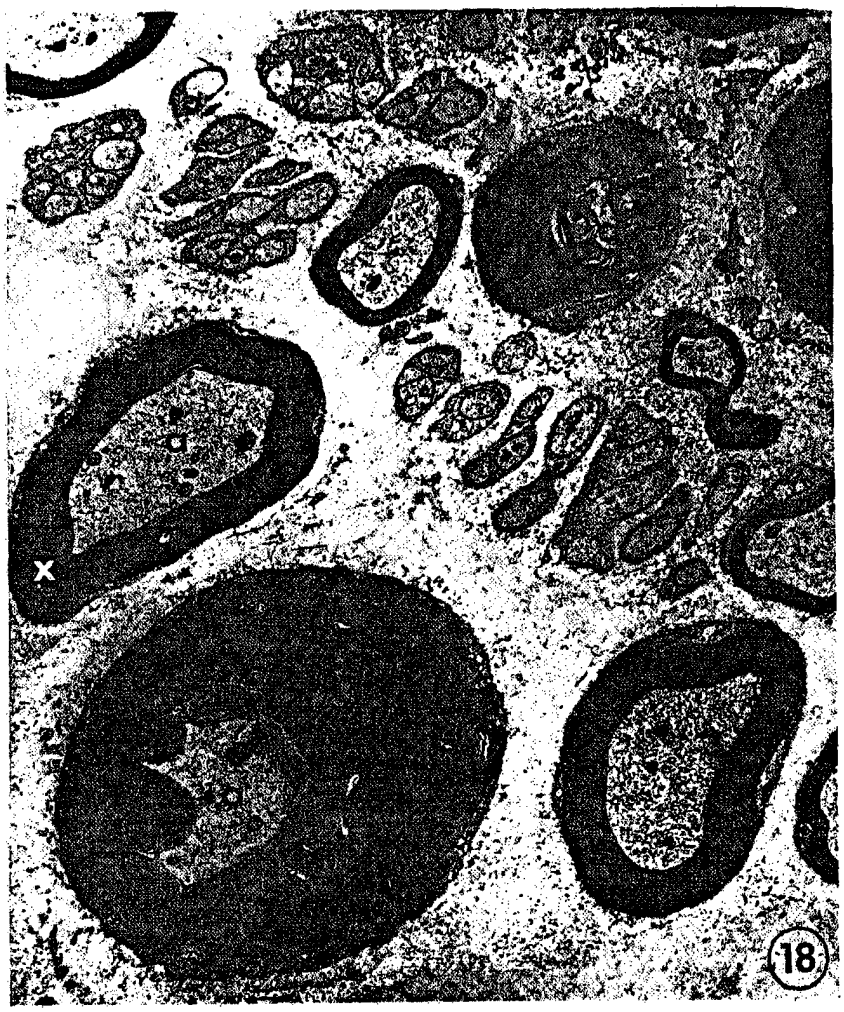

FIG. 18. Distortions in the tubular configuration of myelin sheaths in sciatic nerve. Irregularities of myelin lamellae are also present adjacent to exaggerated Schmidt-Lantermann cleft (x). The axons (a) of these fibers appear intact; × 5,000.

Evidence of segmental demyelination, on the other hand, was noted in both the anterior and posterior spinal nerve roots of 7 rats.

DISCUSSION

An experimental polyneuropathy has been produced in adult rats by the prolonged oral administration of lead acetate. Peripheral nerve alterations in these animals were characterized by the presence of Wallerian degeneration and segmental demyelination, a combination of changes which had been previ-

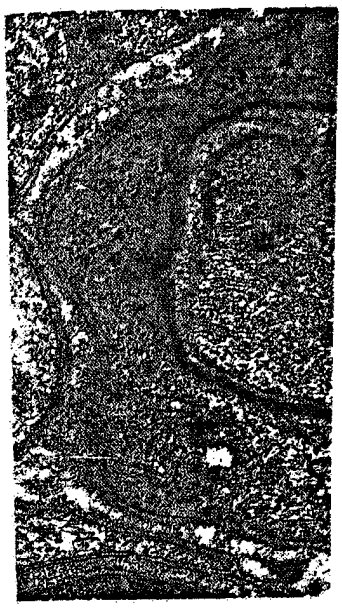

FIG. 19. Axon (A) of tibial nerve

FIG. 20. Granular disintegration disruption and partial collapse of s

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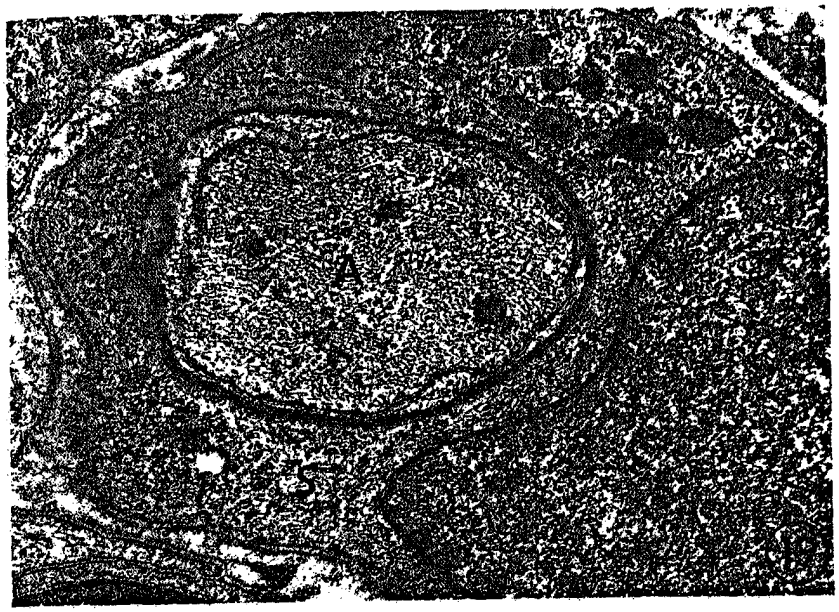

FIG. 19. Axon (A) of tibial nerve being remyelinated by Schwann cell (S); × 20,000.

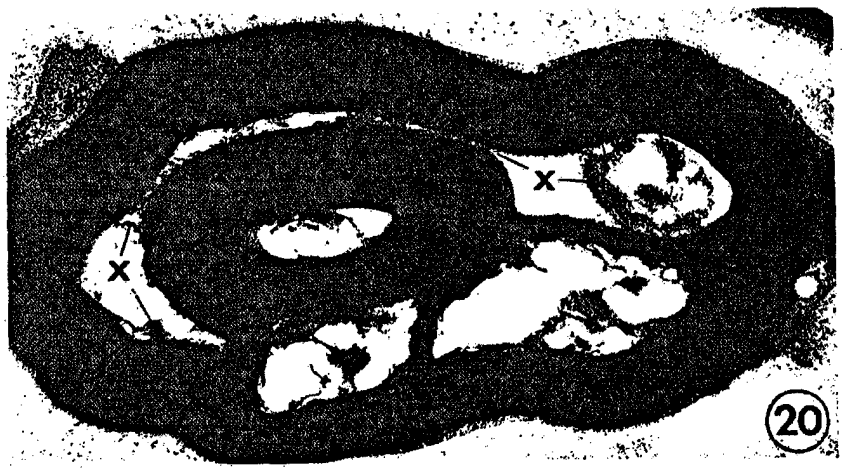

FIG. 20. Granular disintegration (x) of axoplasm in nerve fiber from tibial nerve with disruption and partial collapse of surrounding myelin sheath; × 20,000.

ously reported in other species with lead neuropathy (1–5). The absence of demonstrable lesions in several animals may have reflected differences in individual susceptibility, variations in the amount of lead ingested or metabolized, or the relative resistance of the rat to experimental lead neuropathy (5). These and other quantitative aspects of lead neuropathy were not explored

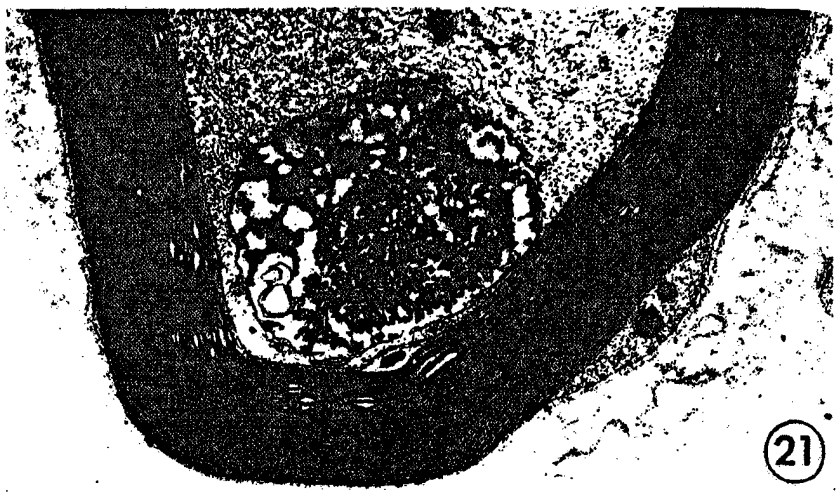

FIG. 21. Membrane-bound glycogen particle in myelinated axon of sciatic nerve; × 13,500.

in the present study. Instead, attention was directed towards the nature of tissue changes in the peripheral nervous system under these conditions.

The appreciation of pathological alterations in peripheral nerves was considerably enhanced by the use of whole-mount, teased preparations. This technique enabled a relatively large sample of material to be surveyed for the characteristic myelin sheath changes brought about by different pathological processes. Focal alterations of varying severity were detected which might be overlooked in routine histological preparations and not included in the limited material subject to ultrastructural examination. Demyelinating and remyelinating phenomena result in a variety of disruptive patterns in the sequence of myelin sheaths along an individual nerve fiber (5, 10, 11, 17). Many of these features were observed in the present study including a widening of nodal interspaces, a loss of individual myelin sheaths, and the appearance of thin intercalated myelin sheaths. Discrepancies in the lengths of successive myelin sheaths were also noted and could be differentiated from the uniform shortening of internodes which arise along regenerated fibers (18, 19). Wallerian degeneration was readily recognized and differentiated by a characteristic linear arrangement of irregular osmiophilic droplets which traversed the examined segment of nerve.

The nerve fiber alterations observed in whole-mount preparations were corroborated by the findings at the ultrastructural level. Separation of myelin lamellae and deformations in the tubular configurations of myelin sheaths were evidence of a segmental injury and resembled changes noted in other demyelinating conditions (13, 14, 20, 21, 22). Further elaboration on the ultrastructural features of the demyelinating lesion in this condition has recently been reported (23). The predilection of these alterations for the

perinodal regions indicates a pa
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perinodal regions indicates a particular vulnerability of this area and accounts for the early internodal widening observed in whole-mount preparations (20). A progressive disruption of the myelin sheath leads to an eventual denudation and displacement of the axon. Even under these conditions, the axons of these fibers remained intact and showed no evidence of secondary degeneration.

Other nerve fibers showed the changes characteristic of a primary axonal degeneration; namely, a granular disintegration of the neurofilaments with or without collapse of the surrounding myelin sheath. Similar changes have been encountered in the distal stumps of transsected nerves (24–27) and in INH neuropathy (28). The paucity of these changes in the electron microscopic findings may reflect the relatively transitory nature of this process in a chronic degenerative disease. Perhaps the membrane-bound accumulations of glycogen-like particles in the axon of myelinated and unmyelinated fibers reflect a more chronic derangement of the axon. These changes have also been observed within the peripheral nerves in experimental INH neuropathy (28), in tetanus toxin poisoning (29), and following x-irradiation (30).

Further evidence of axonal injury in lead neuropathy was obtained by histochemical studies. Enzymatic alterations appeared as an early axonal change, and were characterized by an accumulation of acid phosphatase activity in the axons of myelinated fibers at their nodes of Ranvier. By a technical modification of the teased preparations, these foci could be observed at successive nodal areas along a single nerve fiber. This uniform reactivity of successive nodal areas of an individual nerve fiber is most likely a response to a generalized affliction of the axon. It should be noted that the myelin sheaths surrounding these segments of nerve fibers did not show evidence of demyelination.

These nodal concentrations of enzymatic activity not only heralded an early damage to these fibers, but also indicated a specific vulnerability and reactivity of the nodal region of axoplasm under pathological conditions. Nodal accumulations of acid phosphatase activity were observed in the distal stumps of transsected nerves within 2 hours following injury (31). The aggregations of sundry vesicles, dense bodies and mitochondria in the nodal areas of axoplasm in the earliest stages of Wallerian degeneration (32, 33) may be related to these enzymatic changes. Similar axoplasmic accumulations of organelles have been reported in experimental lead neuropathy (23).

The participation of hydrolytic enzymatic activity in the earliest phase of segmental injury could be differentiated from the axonal nodal reactions and was evidenced by the presence of acid phosphatase activity in the perinodal regions of Schwann cells adjacent to retracted elements of myelin sheaths. This increase of acid phosphatase activity appeared to coincide with the morphological evidence of myelin sheath disruption and breakdown. An increase of acid phosphatase activity has been reported to precede the detection of segmental demyelination in diphtheritic neuropathy (34). The presence of acid phosphatase activity in the vicinity of myelin debris within Schwann cells and macrophages is in accord with the presumed degradative nature of the

processes occuring at these sites. Myelin debris resulting from Wallerian degeneration has been shown to undergo a chemical decomposition following an initial latent period (35).

Examination of the anterior horn cells and the dorsal root ganglia was undertaken in search of additional cellular changes which might relate to the peripheral axonal degeneration in this condition. While no alterations were detected in the anterior horns of the lumbar spinal cord, prominent cellular changes were found in the dorsal root ganglia, especially in those animals showing peripheral axonal degeneration. These changes appeared to primarily involve the capsular cells and consisted of their proliferation and accumulation of dense bodies within their cytoplasm. While a proliferative response of the capsular cells is known to occur following chromatolysis (36, 37) and in other conditions associated with neuronal damage (38), the aggregation of numerous dense bodies within these cells has not been noted to follow neuronal injury. Furthermore, the particulate material within these dense bodies had the electron density characteristics of a heavy metallic substance, compatible with lead, in osmicated and unstained tissue. Similar cytoplasmic dense bodies have been observed in the renal proximal tubular cells (39), another site of selective susceptibility to lead toxicity. These findings suggest the possibility of a direct intervention of lead in the metabolism of the capsular cells.

Metabolic alterations of the capsular cells might be expected to result in degenerative changes in the associated neurons or in their distal cell processes. Tissue culture studies have shown that the viability of the ganglion cell is dependent upon a capsular cell investment (40, 41). Accordingly, some of the sensory neurons associated with altered capsular cells did show a prominence of neurofilaments and a paucity of endoplasmic reticulum. Similar increases of the neurofilamentous component of these neurons have been observed in the aftermath of neuronal injury (36, 37, 42). These changes may be related to alterations in axonal transport of material from neuronal cell bodies. Movements of this nature are believed to be dependent upon the integrity of the neurotubules (43). Substances which disrupt cytoplasmic movements and the neurotubules also produce aggregates of neurofilaments (44).

A disruption in the normal axonal transport within sensory nerve fibers might also explain the preponderance of axonal degeneration in the distal segments of nerve. Similar changes have been noted in other peripheral neuropathies and have led to the concept of a "dying back" phenomenon (45). The relative sparing of the cell bodies and the proximal axons in this process can obscure the precise identification of the injured neurons. Nevertheless, the cellular alterations of the dorsal root ganglia and the axonal degeneration within the posterior spinal nerve roots attest to the presence of a sensory neuronal degeneration in the present study.

The combination of a sensory neuronal degeneration and a segmental demyelination in lead neuropathy may be explained by a common metabolic lesion to the supporting satellite and Schwann cells of the peripheral nervous system. A mutual vulnerability of these supportive cellular elements may be

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another indication of their biological similarity. Not only do these cells provide a continuous monocellular investment for the neuron and axon, but they also selectively contain butyryl cholinesterase (46) and reveal a membranous nucleoside phosphatase at the critical cellular interface adjoining the adjacent neuronal element (47). Furthermore, their common embryological origin (48) and similar ultrastructural features (49, 50) indicate a close kinship. It is, therefore, not surprising that both cell types show an initial vulnerability to x-irradiation (13, 51, 52) and respond in a proliferative manner following loss or damage of the associated neuronal element (36–38, 53).

A mutual involvement of the satellite and Schwann cells in a common disorder may account for the presence of Wallerian and segmental change which has been observed in human neuropathies in the absence of a local inflammatory or destructive process (54). Diabetic neuropathy reveals this pattern of alteration in the peripheral nerves (55) and a focal proliferation of capsular cells in the dorsal root ganglia (56). A similar combination of increased capsular cells and segmental demyelination has been seen in hypertrophic neuritis (57, 58). However, in these conditions, a variable involvement of the supporting cellular elements as well as the chronicity of the pathological processes may obscure the appreciation of the overall pathological events, especially when the examination is limited to an isolated segment of peripheral nerve.

SUMMARY

An experimental lead neuropathy was produced by the administration of a 1 per cent lead acetate solution to 200 to 250 gm. rats for periods ranging from 3 to 18 months. Examination of peripheral nerves, spinal nerve roots, and spinal ganglia of these animals with ultrastructural, histochemical, and whole-mount techniques revealed prominent changes in the supporting cellular elements. Pathological alterations of the Schwann cells were manifested by widespread segmental demyelination and remyelination in the peripheral nerves and spinal nerve roots. A selective involvement of the capsular cells in the spinal ganglia was characterized by a proliferation of these cells and an accumulation of numerous dense bodies within their cytoplasm. These dense bodies contained a particulate material which had the electron density characteristics of a heavy metallic substance, compatible with lead, in unosmicated and unstained tissue. An increase of neurofilaments and a relative paucity of endoplasmic reticulum was seen in some associated sensory ganglion cells. More striking neuronal alteration, however, occurred in the distal peripheral nerves and in the posterior nerve roots in the form of Wallerian degeneration. The accumulation of acid phosphatase activity in the nodal axoplasm of some peripheral nerve fibers appeared as an early form of axonal injury and attested to a special reactivity of the nodal region.

The coexistence of segmental demyelination and Wallerian degeneration in the peripheral nerves of lead neuropathy has been postulated to result from a common metabolic lesion of the supporting Schwann and capsular cells. This

same pattern of pathological changes has been noted in some human polyneuropathies and may reflect a similar pathogenesis.

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