ULTRASTRUCTURAL STUDIES IN ALZHEIMER'S PRESENILE DEMENTIA

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An electron microscopic study of cerebral biopsy specimens from 3 cases of Alzheimer's presenile dementia has revealed several points of interest. The two major findings have to do with the neurofibrillary tangles and senile plaques which are the characteristic features of this disease. It will be shown that the former are made up of large clusters of fine neurofibrils, while plaques have as their fundamental substance a different sort of filamentous material which is structurally identical to amyloid. Also noteworthy are certain myelin distortions suggestive of primary demyelinization; and a striking, although rare, endothelial change by which lipid-like material passes through the walls of small vessels to enter the lumen.

CASE HISTORIES AND LIGHT MICROSCOPY

Case 1

A 62-year-old woman had a 7-year history of slowly progressive dementia. During the 1½ years prior to admission, she was unable to care for herself, and required nursing attention. A coarse, shaking tremor was attributed to Parkinsonism. The family history was not known.

The general physical examination was unremarkable. The patient was agitated, depressed and poorly oriented. She could not carry out simple commands, recite the alphabet or count. There were myoclonic jerks of the upper extremities. The gait was hesitant and shuffling. The face was mask-like and there was a questionable intention tremor. Muscle tone was not increased. An electroencephalogram showed a diffusely abnormal tracing. The spinal fluid protein was 47 mg. per cent, but the fluid was not otherwise remarkable. Other laboratory examinations were not unusual.

A biopsy specimen was procured from the right parieto-occipital region at craniotomy. Mental deterioration continued during the weeks after operation. Many months after operation the patient died at another hospital. Necropsy confirmed the biopsy diagnosis.

The cerebral cortex of the biopsy specimen was slightly thinner and tougher than normal. The cortical architecture was well preserved microscopically and there was only minimal gliosis. Bodian preparations revealed numerous intraneuronal, coarse neurofibrillary tangles. Many senile plaques were also found. They were composed of argentophilic fibers and granules. Core material was poorly demonstrated. The pathologic diagnosis was Alzheimer's presenile dementia.

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Case 2

A 63-year-old woman had a 1½-year history of progressive dementia beginning with inability to sign her name properly. She became particularly forgetful, got lost frequently and had difficulty in word-finding and in caring for herself. The past history and family history were not contributory.

The general physical and neurologic examinations were normal except for myoclonic jerks of the head, arms and trunk. She was fearful, disoriented and apraxic. Her memory span was very short and she was unable to perform simple calculations or to recite the alphabet. An electroencephalogram exhibited a diffusely abnormal pattern. A pneumoencephalogram revealed marked cortical atrophy.

A biopsy of the second right frontal gyrus was made at craniotomy. The patient quickly resumed her pre-operative state, and was later discharged to a state psychiatric hospital.

The cortex was thin and the leptomeninges moderately thickened. Bodian preparations showed many neurofibrillary tangles. Senile plaques could not be demonstrated. There was mild neuronal loss. Gliosis was slight in both cortex and white matter. The pathologic diagnosis was Alzheimer's presenile dementia.

Case 3

A 52-year-old woman had a 3-year history of progressive memory loss and increasingly repetitive speech. She became unable to do her housework and required nursing care at home during the 15 months prior to admission. There was a history of proven and suspected Alzheimer's disease among several relatives on the maternal side and 3 of 4 siblings.

The physical examination was not contributory. The affect was inappropriate and labile. Severe loss of recent memory, very short attention span and marked expressive aphasia were noted. The gait was broad-based. Muscle tone was uniformly increased, and there was suggestive cog-wheel rigidity at the wrists and elbows. Reflexes were normal. Sensory examination was not possible. An electroencephalogram exhibited a mild, diffusely abnormal pattern, but all other laboratory tests were unremarkable.

Biopsy was made in the second right prefontal gyrus at craniotomy. Following a short period of confusion and low fever, the patient returned to her pre-operative state and was later discharged to another institution. She died several months later, and necropsy confirmed the diagnosis which had been made on the biopsy specimen.

The cortex in the specimen was thin and exhibited moderate gliosis. The cortical layers were still apparent, but the architecture was not well preserved. Neurofibrillary tangles were rare and not very dense. There were, however, many senile plaques, which were seen as circular zones of very finely granular material with a few argentophilic rods, fibers and granules. Microglial nuclei were prominent within these plaques. The remaining neurons contained much lipofuscin which stained in positive manner with the periodic acid-Schiff and Sudan IV stains. The diagnosis was Alzheimer's disease.

Methods

The procedures have been detailed previously [1] and need only be summarized here. The biopsy specimen was removed from the nondominant hemisphere at craniotomy where a full-sized bone flap was turned. Hemostasis was secured only after removal of the tissue. The specimen weighed less than 1 gm., and was quickly divided into 3 portions. That for light microscopy was fixed in cold formalin. Bodian, Heidenhain, gallocyanin, Congo red, and periodic acid-Schiff stains were carried out on paraffin-embedded material. Sudan, Spielmeyer, acid phosphatase [2,3] and thiamine pyrophosphatase [4] preparations were made from frozen sections. The last two were for the purpose of demonstrating lysosomes and Golgi apparatus respectively. Tissue for chemical and metabolic studies (results to be reported elsewhere) was chilled in Tris

buffer. The material for electron microscopy was fixed in veronal-buffered osmic acid[5] with sucrose,[6] dehydrated in alcohol and embedded in methacrylate, Epon[7] and Araldite.[8] The thin sections were stained with lead hydroxide[9] alone or in combination with uranyl acetate.[10] The electron micrographs were taken with a Siemens Elmiskop I. The studies were based on examination of 152 blocks of tissue. More than 1,300 micrographs were made.

Electron Microscopy

Plaques

The senile plaque of Alzheimer's disease as seen with the electron microscope, had 4 major components: (a) central fibrillar core; (b) cellular perikarya; (c) axons and dendrites filled with an excess of neurofibrils; (d) cell processes filled with dense bodies.

The central core of the plaque was a stellate mass (Figs. 1 to 5) of interwoven fibrils, each 70 to 90 Å wide. The individual fibrils (Fig. 6) had a triple density indicating a hollow center. The light, central portion was about ⅓ the total thickness. Periodicity in the longitudinal dimension was lacking. There were no formed elements between the fibrils, nor was there a ground substance of appreciable density. The fibrils were often grouped into bundles, but there were no membranes segregating these bundles and, furthermore, single fibrils often passed from one bundle to the next in both cross and longitudinal sections. There was a tendency to directional orientation of the fibrils within many bundles, but this was imperfect as indicated by their interweaving. In addition, some orientation of the bundles was noted; they generally radiated outward from the center of the plaque. Collagen was not present.

While the central fibrils and bundles were clearly extracellular (Figs. 5 and 6), those toward the periphery of the plaque were found in intimate relationship to nuclei and cellular organelles. The involved cells had deeply and irregularly indented borders facing the central core. Masses of the extracellular fibrils fitted loosely into these indentations, but were, in these regions, separated from intracellular material by the plasma membrane (Fig. 7). They were at times within 200 mμ of the nuclear membrane. The convoluted plasma membrane in these areas was often unsharp and incomplete.

Bundles of fibrils appeared less commonly to be intracytoplasmic and to be without any direct continuity with extracellular material (Figs. 8 and 9). These cells had elongated, irregular nuclei, very similar to those of the cells involved as described above. The cytoplasm contained moderate numbers of free ribosomes and was usually of medium density. There was little ergastoplasm. The bundles of poorly oriented fibrils dominated a portion of the cell body. A boundary membrane only partly surrounded the bundles. In some areas the fibrils seemed not to

be separated from the cytoplasm. Continuities with the membranes of ergastoplasm or the Golgi apparatus could not be distinguished.

Many enlarged axons and dendrites (Fig. 10) containing abnormal numbers of neurofilaments were arranged in a haphazard fashion about the periphery of the core of the plaque. These filaments were closely packed within the neuronal processes, with some tendency to spare that part of the cytoplasm immediately under the plasma membrane. The long axis of most of the neurofibrils lay in the long axis of the cell process, but some took a spiral course. The filaments varied in diameter from 100 to 200 Å, and in some regions appeared to be twisted at irregular intervals of 30 to several hundred mμ (Figs. 11 and 12). They were of the same appearance whether in myelinated or unmyelinated processes.

In many of the neuronal processes there were variable numbers of small, round, dense bodies (Figs. 1 to 4 and 13). These measured about 0.5 μ, with a diameter range of 0.3 to 1.0 μ. They were much more common in unmyelinated processes than in sheathed axons. When there were only a few of the dense bodies, they were found at the periphery of the process, while groups of neurofilaments filled most of it. However, many dendrites were nearly filled by dozens of these small bodies. Between them there were usually a few filaments, which still permitted the cell processes to be identified as neuronal extensions. These swollen dendrites or axons were most common in and around the plaques where they occurred in clusters. Scattered throughout the cortex were occasional single dendrites containing similar organelles. It was apparent at higher magnification that the dense bodies were at least partly composed of membranes. A few thin layers often surrounded a more homogeneous, very dark core. Less commonly the bodies were made up of many membranes, which sometimes displayed a very considerable regularity of spacing. This periodicity varied widely between 45 and 100 Å.

There were moderately increased numbers of glial cell processes at the periphery of the plaque and to a lesser extent throughout the cortex. The glial cellular extensions contained loose clusters of non-interwoven, solid fibrils which were 60 to 70 Å wide. The astrocyte perikarya were moderately enlarged and also contained groups of similar fibrils (Fig. 14). Glial fibrils were not found outside a plasma membrane. The astrocytes often contained lipid aggregates closely resembling lipofuscin but usually with several small vacuoles in the less dense component.

Neurofibrillary Change of Alzheimer

Our observations relating to the neurofibrillary tangles in the first 2 cases have already been reported.[11] Case 3 has added more data, but

has not changed the conclusions. The tangles, therefore, will be treated only briefly here.

In the thin sections used for electron microscopy, neurofibrils were quite sparse within normal neuronal perikarya. The fibrils were of two general types: those measuring about 100 Å (90 to 125 Å) in width and resembling axonal filaments, and those about 200 Å (180 to 210 Å) wide and resembling dendritic tubules. Both types (Figs. 11 and 12) had a triple density as seen in longitudinal section, with dense edges and light cores. Some seemed to twist, in that they were intermittently narrowed. In cross section the neurofilaments were occasionally found as circlets, but were more often seen as short, curved elements with the familiar dense-light-dense structure. They were essentially similar to the filaments found within neuronal processes involved in senile plaques.

Neurofibrillary tangles were made up of similar elements which were present in greatly increased numbers and were arranged in large bundles (Figs. 15 and 16). There was little or no interweaving among the neurofilaments within a bundle. These groups of fibrils often occupied the greater portion of the neuronal cytoplasm and displaced the mitochondria, lysosomes, ergastoplasm and Golgi apparatus (Figs. 17 and 18). The filaments within a bundle were quite uniformly oriented, and were for the most part of the 100 Å variety. Continuities between the filaments and the normal cellular organelles were not found.

Many lipofuscin bodies (Fig. 19) were present in most large neurons, but the amount of lipofuscin could not be correlated either negatively or positively with abnormal neurofibrillary bundles. The lipofuscin was composed of dense, homogeneous, granular or membranous material closely associated with lighter, very homogeneous matter. A unit membrane surrounded each of these compound bodies.

Myelin

Large numbers of widely scattered, abnormal axons were manifest. In many of these, the axoplasm itself was morphologically intact. It displayed its usual filamentous material, mitochondria and light hyaloplasm, and it was bounded by a continuous axolemma. The myelin surrounding these apparently normal axis cylinders, however, was interrupted, bubbled and granular (Figs. 20 to 22). The lamellas were not simply spread apart and ruffled, as is seen when embedding artifacts occur. Rather, there were wide zones between lamellas, filled with dense, granular debris and small vacuoles, the latter enclosed by two or more membranes with a spacing which approximated half that of normal myelin. The granular material had a density similar to that of the major period line of myelin. These damaged areas were found in either deep

or superficial regions of the sheath, and were noted for the most part in sheaths of at least medium thickness. The lamellar destruction did not usually involve the full thickness of the myelin. It more often spared a few layers on the outside and a few adjacent to the axolemma. Nevertheless, there was unquestionable loss of myelin lamellas in these granular zones, since the total number of remaining lamellas inside the zone plus those outside the zone was less than the number of myelin layers elsewhere around the circumference of the axon.

Quite another form of axonal abnormality had essentially normal myelin while the axis cylinder filled only a small portion of the cross-section area. The rest of this space was taken up with one or a few large vacuoles (Fig. 23). These were bounded by a double membrane which had no clear connection with the myelin, and they contained only very little granular material. One layer of the double boundary membrane was sometimes broken and appeared to end in a ball or knot. The origin of these membranes or of the vacuolar contents remained uncertain. They compressed the axis cylinder into an irregular polyhedron which was not otherwise remarkable.

In a few instances, the myelin sheath was intact while the axoplasm was dense and granular. Late forms of axonal degeneration were also found. Digestion chambers and myelin whorls similar to those of wallerian degeneration [12,13] were noted (Fig. 24) in cortex and white matter. The normal myelin period of about 120 Å was maintained well after the sheath lost its continuity.

Only the superficial white matter was available for study. A moderate increase in extracellular space was noted, but it could not be determined whether this was the result of imperfect preparative methods or of a pathologic alteration. Occasional glial processes here and in the cortex contained dense lipid aggregates which were partially laminated (Fig. 25). A few of these resembled the membranous cytoplasmic bodies (Fig. 26) of Tay-Sachs disease.[14]

Vessels

Most vessels appeared to be quite normal. There were, however, numerous perithelial cells containing lipid droplets (Fig. 27). These cells were separated from the adjacent parenchyma by a basement membrane, the thickness of which varied widely. The lipid droplets contained both very dense and relatively light material. A unit membrane separated the lipid from the surrounding cytoplasm.

The endothelial cells occasionally contained lipid droplets similar to those of the perithelium. Also present here were small, irregularly outlined aggregates of closely packed, dense granules (Fig. 28). An intimate unit membrane could sometimes be distinguished at the edge of

the aggregate. This dense material was often just under the lumen plasma membrane. In a few instances the membrane was lost over a distance of 100 to 200 mμ, and the dense material, unbounded, lay in the gap extending into the adjacent lumen (Fig. 29).

A clearly related phenomenon was found with about the same frequency. In these instances, the inner (lumen) membrane was invaginated into the lumen where it formed a sphere 200 to 400 mμ in diameter (Fig. 30). It was connected to the endothelium by a narrow neck 50 to 100 mμ wide. An aggregate of the same dense, particulate material almost filled the sphere and the neck. The aggregate itself had its own unit membrane. In the lumen near the wall were occasional stemless vesicles and numerous irregular and unbounded dense aggregates which were less compact at their edges (Fig. 28).

Yet another vascular alteration was an occasional separation of the endothelial cells leaving a gap in the vascular lining so that basement membrane came into contact with lumen (Fig. 31). Residua of the cement line were apparent in the thickening of the facing endothelial plasma membranes, but an oblique fenestration up to 200 mμ wide separated these normally joined faces. Within the gap were several ovoid vesicles, each surrounded by a unit membrane. The vesicular contents varied in density but did not resemble cytoplasm. The vesicles were small, dense and indistinct within the somewhat widened, underlying basement membrane. Those nearer the lumen were larger and clearer.

The vascular abnormalities which have been described occurred primarily in thin-walled vessels 10 to 20 μ wide. They were either venules or large capillaries. The affected vessels were not scattered at random throughout the tissue but, rather, were found in several restricted areas.

Discussion

Certain differences and similarities among the pathologic elements of Alzheimer's disease may now be summarized before their implications are discussed. Plaques and tangles have many features in common, but are structurally related in a very incomplete fashion. The filamentous material of the core of the plaque is quite different from that in the tangle. The cellular elements of the plaque are probably microglial, and are also independent of the tangle. On the other hand, the enlarged dendrites and axons of the plaques are filled with neurofilaments much as are the neuronal perikarya involved in Alzheimer's change. Dendritic or axonal dense bodies are prominent in the plaque and are of neuronal origin, but are not found in the tangle.

The 4 types of filaments found in this tissue may also be enumerated: (1) Neurofilaments 100 Å wide are found in axons and are common in

neurofibrillary tangles and in abnormal dendrites. (2) Neurofilaments 200 Å wide are found in dendrites and are less common in the neuronal perikaryon. (3) Astrocytic fibrils are 60 Å wide and are solid as opposed to neurofilaments, both types of which are hollow. (4) Plaque fibrils are 90 Å wide, are interwoven and are also hollow.

The nature of senile and presenile brain changes has been much discussed. The classic concepts as well as certain histochemical information were presented in detail by Margolis.[15] The data dominating the classic concepts concerned largely the argentophilic and congophilic properties of the pathologic elements. The current ultrastructural studies permit clarification of some of the problems attending these complex phenomena.

It was Divry[16] who first noted that the senile plaque had staining reactions similar to those of amyloid. Divry and Florkin had previously suggested[17] that extraneural amyloid had a crystalloid structure despite its hyaline appearance. Recent electron microscopic studies by several groups of investigators[18–21] have demonstrated that this substance is composed of bundles of fine fibrils, but estimates of fiber diameter have varied widely from 50 to 300 Å. Ghidoni and Gueft[19] first described the hollow nature of the filament.

There is a remarkable correspondence between the image of experimentally induced splenic amyloidosis[20] and the core of the human senile plaque. The fibrils are similar; their rough orientation in bundles is similar; the stellate outline of the aggregate is similar. The combined evidence of fine structure, stain reactions and optical quality (birefringence) is so strong that we cannot doubt the identification of the core of the plaque as amyloid.

The source of this substance is uncertain, but it seems probable that it is a local cellular product, rather than a secretion from the blood. Heefner and Sorenson[20] have clearly demonstrated bundles of amyloid fibrils within the cytoplasm of splenic reticuloendothelial cells. The absence of a membrane surrounding these intracellular bundles makes it very unlikely that they have been phagocytosed. Cells in the senile plaque also contain these fibrils in their cytoplasm. The microglial cell is the counterpart in the central nervous system of the reticuloendothelial cell, and is very likely the source of amyloid material in the senile plaque. The question remains as to what stimulates these cells to produce this remarkable substance. Perhaps the stimulus comes from the abnormal neuronal components discussed below.

The aggregates of dense bodies found prominently within plaques are of unknown source and significance. Hydrated phospholipids are implicated by the structure of the membranous components. The variable periodicity and the irregular densities suggest that the chemical com-

position is inconstant. These bodies might be expected to stain positively with the periodic acid-Schiff reaction and variably with Sudan type reagents. They are distinct from the lipofuscin bodies which are found within neuronal perikarya. The latter are probably derived from lysosomes [22] and contain acid phosphatase.[23] Webster [24] has studied the early stages of wallerian degeneration in peripheral nerve and has noted focal accumulations of very similar dense bodies in distended axons distal to the experimental crush injury. He believed that they were derived from mitochondria. Regardless of their source, their prominence in the plaque implicates neuronal degeneration as playing an important role in the pathogenesis of the plaque.

The fibril-filled dendrites and axons correspond to the strongly argentophilic fibers seen in classical silver preparations. These neuronal processes have been affected by an overproduction of neurofilaments, just as have some neuronal perikarya. The closely packed, well-oriented neurofilaments contribute to the birefringence of the plaque as do the amyloid bundles.

Schmitt [25] proposed, on the basis of a series of biophysical and biochemical experiments, that a neurofibril is made up of a group of protofilaments. He believed that the latter are each a chain of 30 Å globular proteins, and that these chains are twisted in a slow helix around an empty core to form the 100 Å wide neurofilament. The electron microscopic image of filaments in our material corresponds very closely to the hypothetical model presented by Schmitt and by Davison and Taylor.[30]

Kidd [26] has more recently suggested that the triple contour of the neurofibril is due to its being made up of a pair of closely parallel, regularly twisted protofibrils. The longitudinal sections of neurofilaments could not dispute this concept, but cross sections do not reveal paired structures. There are, rather, circlets and triple density curved elements. The latter might indicate curvature of the filament in the thickness of the section.

The birefringence of the neurofibrillary tangle is undoubtedly related to the excellent orientation of the filaments within the clusters. The congophilia of the same structure is less easily explicable, for the tangle, as we have seen it, is clearly not composed of amyloid. Nevertheless, the component neurofibrils are of a width very similar to that of amyloid fibrils. Ghidoni and Gueft [19] have suggested that staining by Congo red might be based on some relationship between this diameter and the size of the dye molecules. That the dye molecules are physically arranged in an ordered fashion in the filaments is shown by the increased birefringence of a tangle stained with Congo red.

The ultrastructural aspects of wallerian degeneration in the pe-

ripheral nervous system are well known.[12,13] Similar phenomena have been found [14] in the cerebrum in Tay-Sachs disease, where secondary demyelinization is to be expected. The characteristics of primary myelin degeneration in the central nervous system have not, however, been described. Furthermore, primary demyelinization is not generally recognized in Alzheimer's disease.

Nonetheless, our micrographs clearly show intact axons surrounded by bubbled and granular myelin sheaths. They seem to indicate myelin disruption without axonal disorder and this, by definition, is primary demyelinization. The additional presence of digestion chambers with degenerative axoplasm might indicate either a later stage of the same process or a concomitant wallerian degeneration. The latter would presumably be secondary to neuronal death. These processes could account for the frequently noticed but rarely discussed shrinkage of cerebral white matter in senile and presenile dementia.

The vascular changes presented a striking picture which is without adequate precedent. Majno and Palade [27] showed gaps arising between venular endothelial cells in muscle when serotonin was injected locally. Casley-Smith [28] showed similar gaps between the lining cells of jejunal lacteals in animals fed quantities of lipid. Furthermore, vesicles, identified by isolation studies as representing chylomicrons, were found within these latter gaps. He considered these vesicles to be moving into the lumen of the lymphatics. The chylomicrons were of an appearance identical to the vesicles found in venular endothelial fenestrae in our material. Casley-Smith also described smaller dense particles, identified as lipoprotein, in caveolae on the luminal surface of the lacteal lining cells. These were invaginations into the cytoplasm, rather than, as in the tissue we have described, evaginations from cytoplasm into lumen. These granule-filled evaginations are apparently unique, and previous reference to them has not been found. Movat and Fernando [29] described dense precipitates within the lumens of sensitized mesenteric vessels one minute after exposure to antigen. However, the precipitates were unbounded, were not connected with the endothelium and were seen to move through endothelial gaps from lumen to adjacent tissue.

The central nervous system, as is well known, lacks lymphatics. Nevertheless, because of its large component of structural lipids, the brain might be called upon to transport quantities of fats in instances, for example, of destructive disease. Although catabolic cellular activity undoubtedly accounts for most lipid breakdown, it is not impossible that some large molecules would be carried to vessels by ameboid cells and then pass in aggregates through the wall to enter the lumen. It is suggested that the vesicles within the interendothelial gaps in the cere-

bral cortex in Alzheimer's disease might represent chylomicron-containing, alcohol-soluble, neutral lipids, bound in a phospholipid membrane, and that lipoproteins might make up the granules in the endothelial excrescences and intraluminal deposits. Both lipids might be catabolic products of degenerating myelin and neurons caught in the process of transport across vascular walls. These mechanisms are not to be considered specific for Alzheimer's disease, and it is expected that the vascular changes will be found in other situations in the brain and probably in other organs as well.

Summary

Cerebral biopsy specimens from 3 patients with Alzheimer's presenile dementia were examined by electron microscopy. Four major morphologic features were studied in detail: senile plaque, neurofibrillary tangle, myelin degeneration and endothelial modification.

The plaques had a core of amyloid fibrils. Large dendrites and axons with an excess of neurofilaments surrounded the core. Also prominent were neuronal processes which contained many laminated dense bodies. Microglia were present and seemed to be the source of the amyloid.

Alzheimer's neurofibrillary tangles were made up of great numbers of closely packed, normal neurofilaments which displaced the other cytoplasmic organelles within affected neuronal perikarya.

Myelin degeneration was often found without axonal degeneration. Wallerian degeneration was also noted.

Certain small vessels displayed endothelial fenestrations in which were several chylomicron-like vesicles. Dense particulate aggregates, possibly lipoprotein in nature, were seen to protrude from the endothelium into the lumen.

Addendum

It has been very recently learned by the authors that the third patient had familial hyperlipemia, with elevation of serum cholesterol, phospholipid and total lipid. The altered vessels were found only in the tissue from this patient. It is our opinion that the endothelial changes described here are related to the familial hyperlipemia rather than the Alzheimer's disease.

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[*Illustrations follow*]

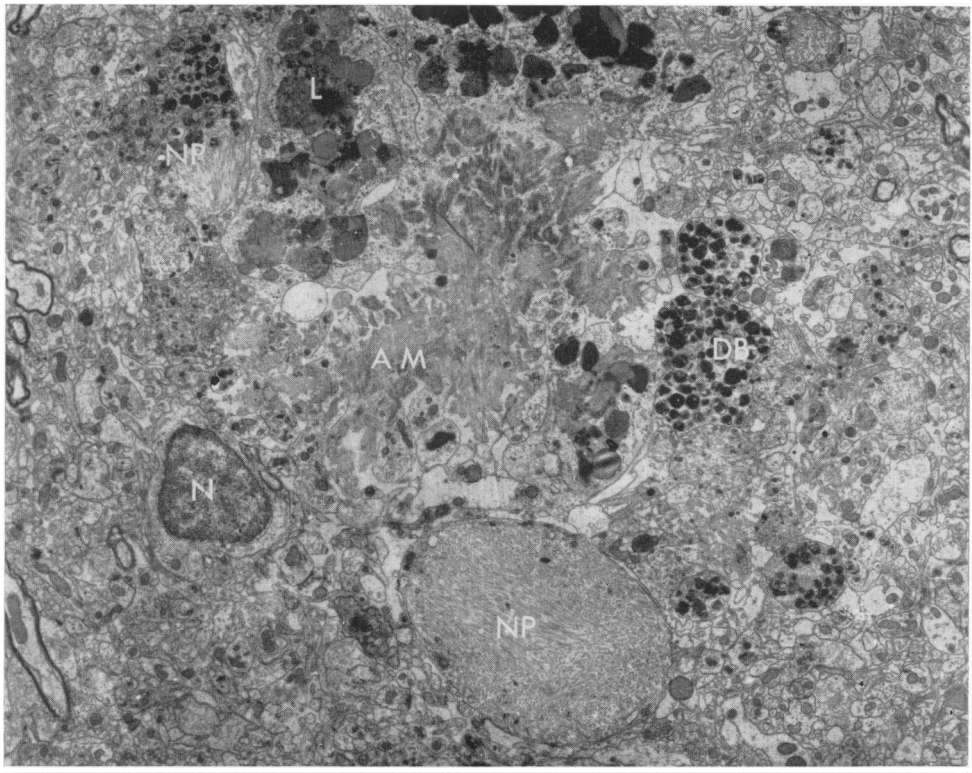
Legends for Figures

Key:

AF = astrocyte foot process	L = lipid
AM = amyloid fibrils	LF = lipofuscin
AP = fibrous process of astrocyte	LU = lumen
AX = axoplasm	M = mitochondrion
BM = basement membrane	N = nucleus
C = chylomicron-like vesicle	NF = neurofibrils
DB = dense bodies	NP = neuronal process
ES = extracellular space	P = perithelial cell
G = Golgi apparatus	R = ribosomes
GF = glial fibrils	RBC = red blood cell

FIG. 1. A senile plaque shows a central core of amyloid, large neuronal processes, dense bodies and a single cell. × 4,400.

FIG. 2. A senile plaque exhibits similar elements. The cell contains numerous lipid bodies. × 5,500.



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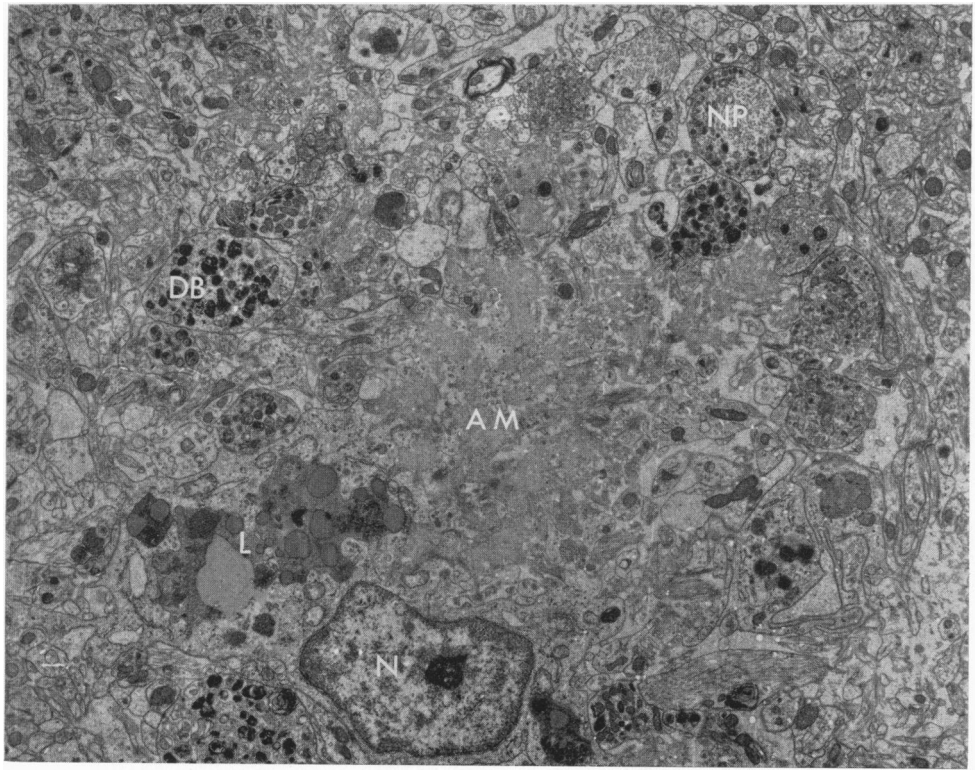

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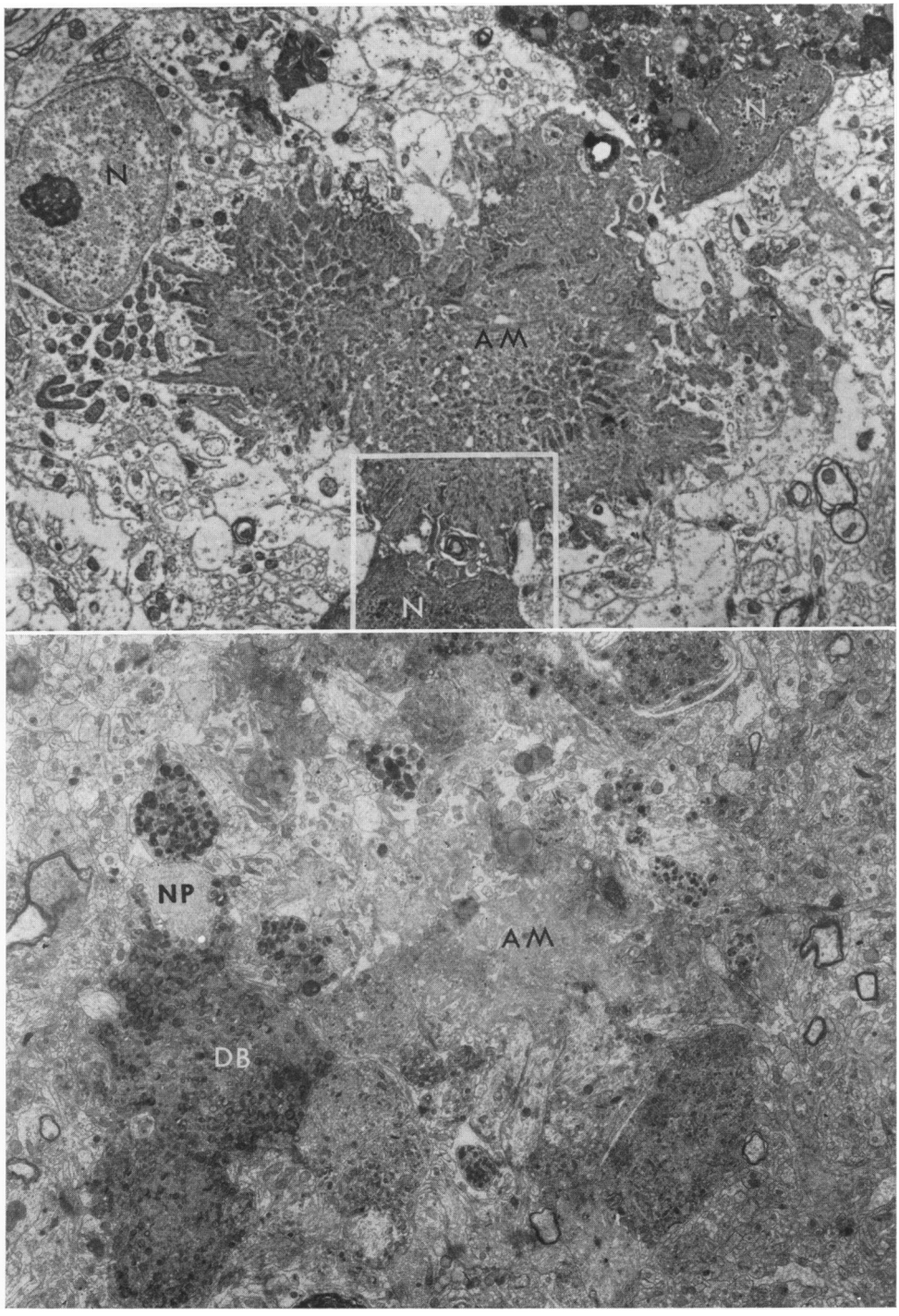

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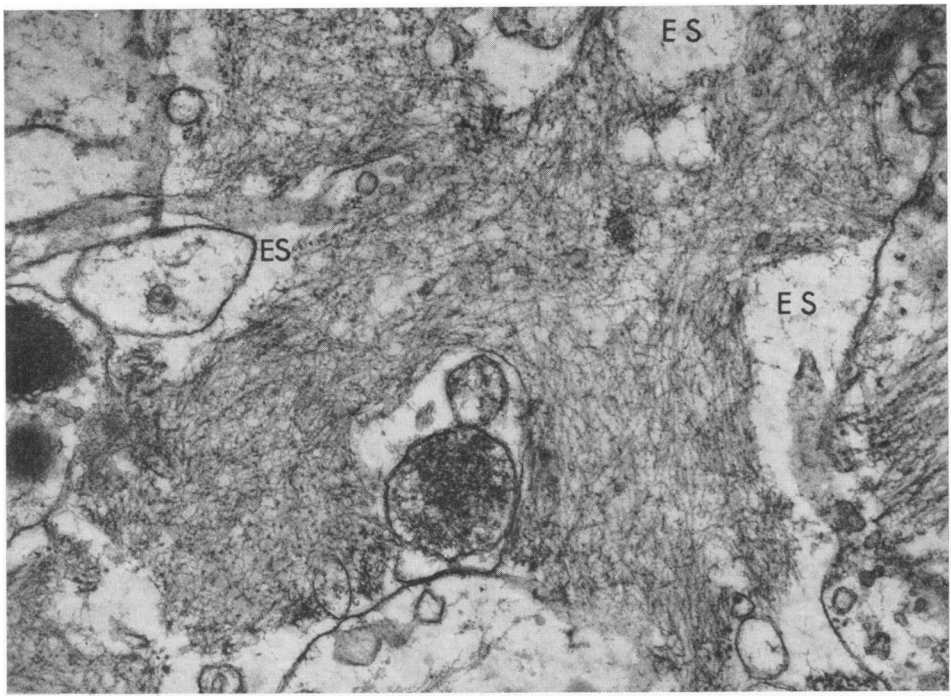
FIG. 3. A plaque has a very dense, stellate amyloid core. This material is related to the cells at left and at bottom. × 5,100.

FIG. 4. Another plaque exhibits especially prominent aggregates of dense bodies. × 4,900.



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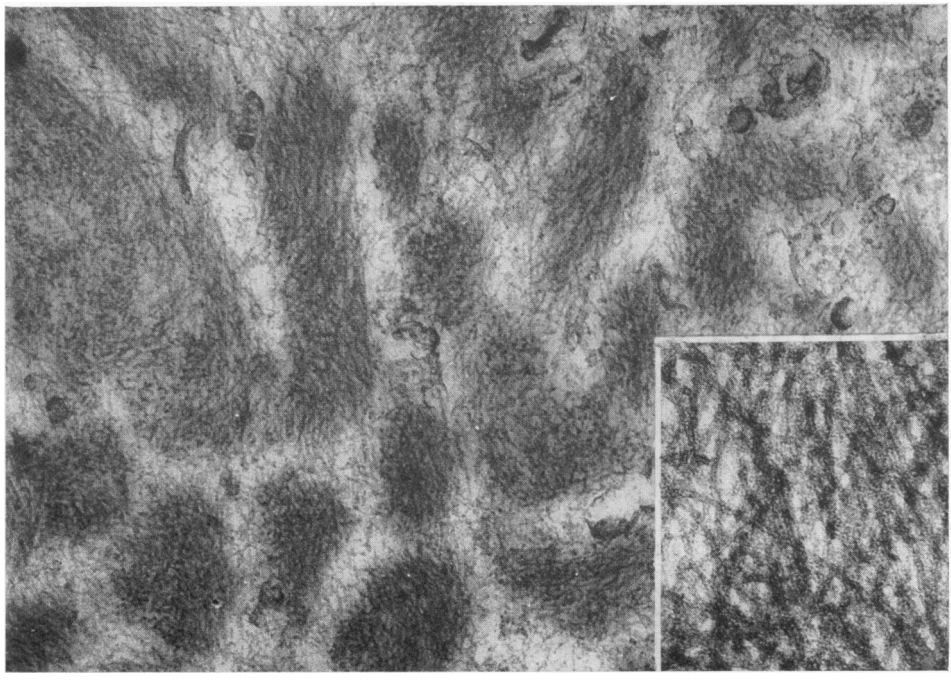

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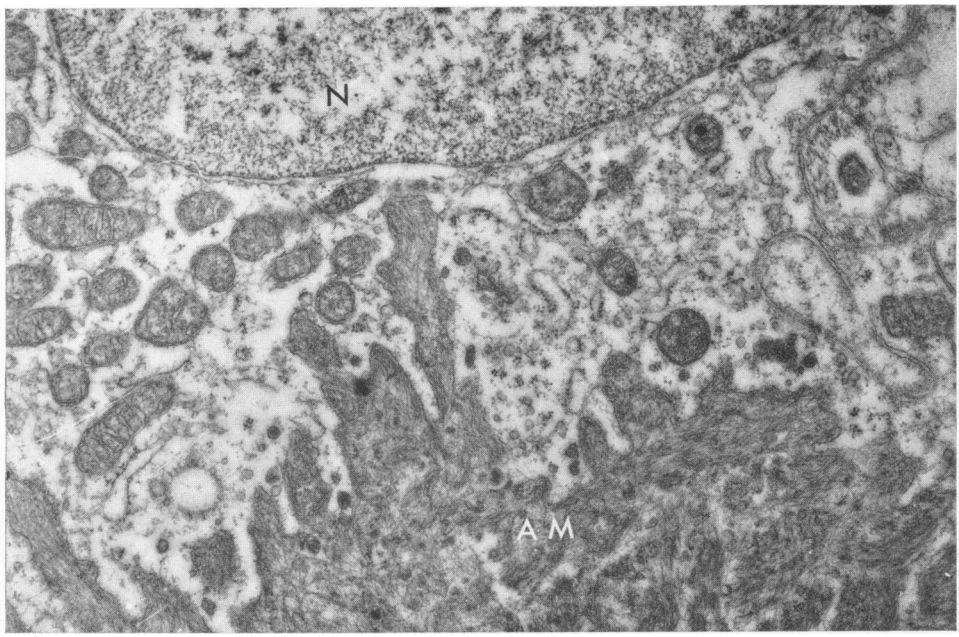
FIG. 5. Extracellular amyloid lacks a boundary membrane in apposition to the several circumscribed cell processes. × 39,000.

FIG. 6. A portion of the amyloid core from Figure 5. In the bundles are interwoven but oriented fibers. × 51,000. The inset demonstrates the hollow structure of the amyloid filaments. × 120,000.



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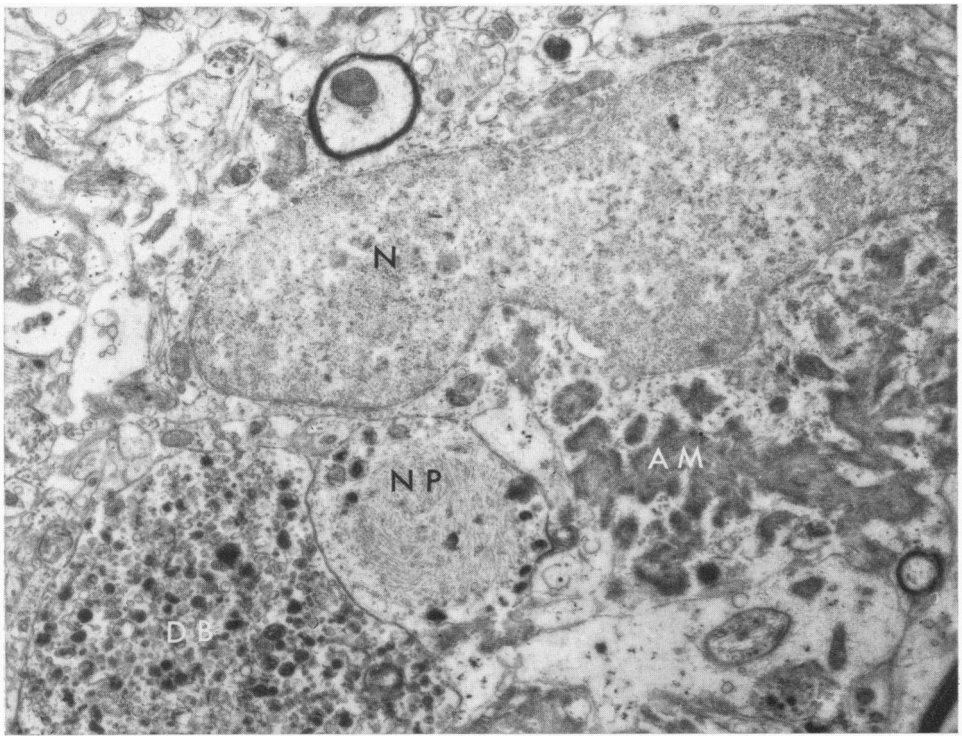

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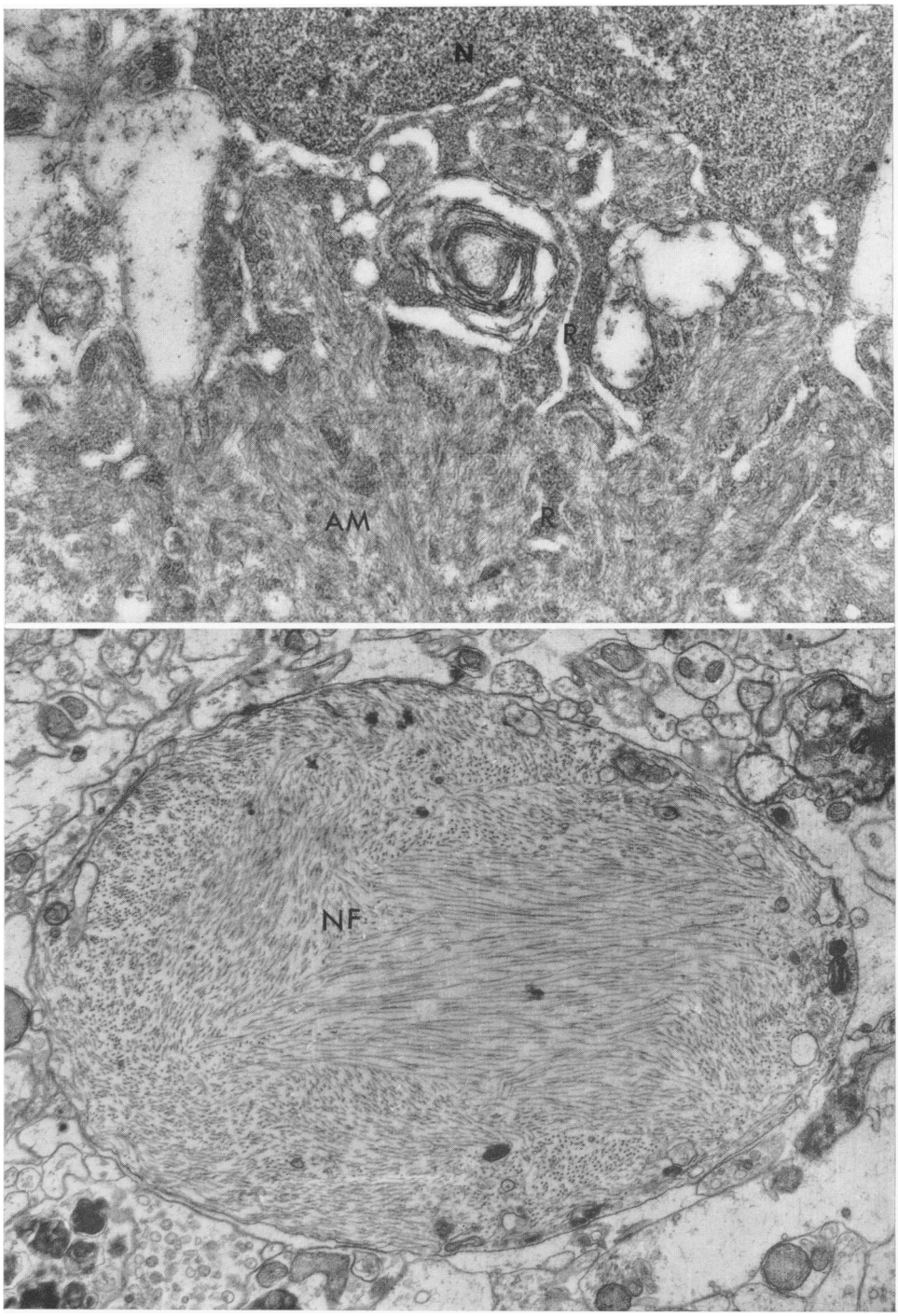
FIG. 7. A detail from the left of Figure 3. The amyloid bundles lie in deep indentations of the cell and are partially separated from the cytoplasm by an incomplete membrane. × 19,000.

FIG. 8. This cell has many unbounded amyloid bundles in its cytoplasm. A neuronal process with many neurofibrils and a large aggregate of dense bodies lie nearby. × 11,000.



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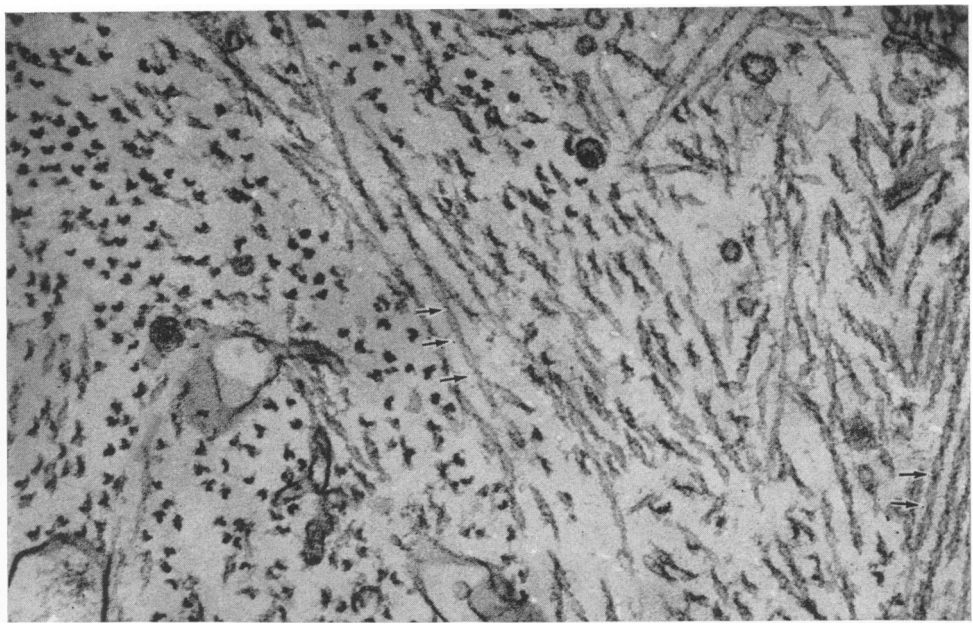
10

FIG. 9. A detail from bottom of Figure 3. The basophilic cytoplasm extends in tongues among the masses of amyloid. × 25,000.

FIG. 10. A distended neuronal process is filled with neurofibrils. This is a detail from Figure 1. × 12,000.

11



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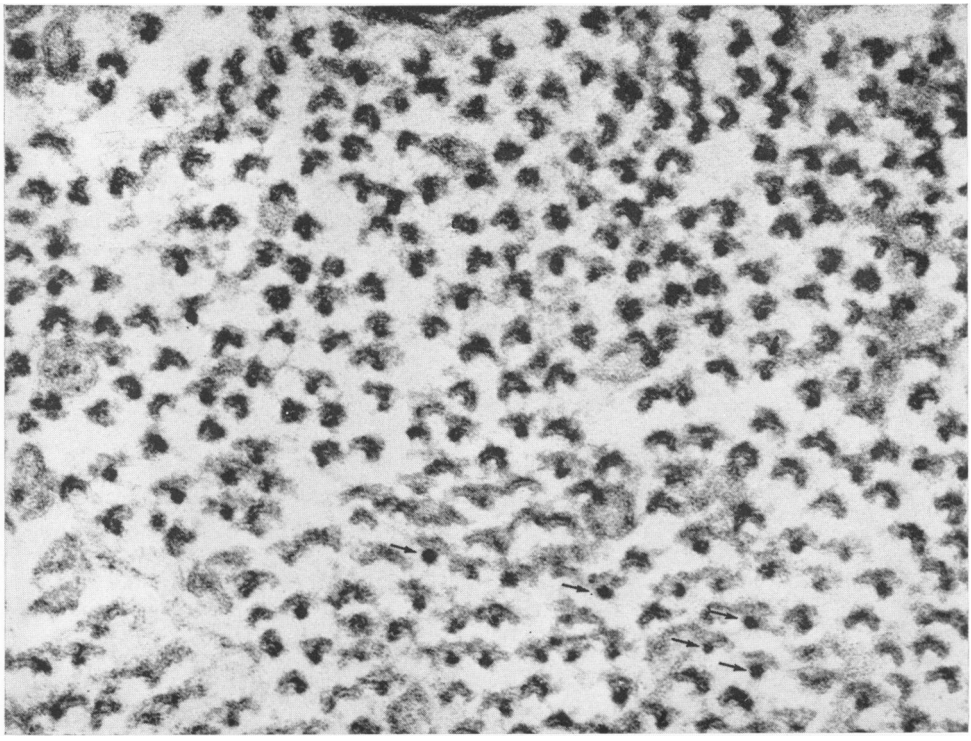
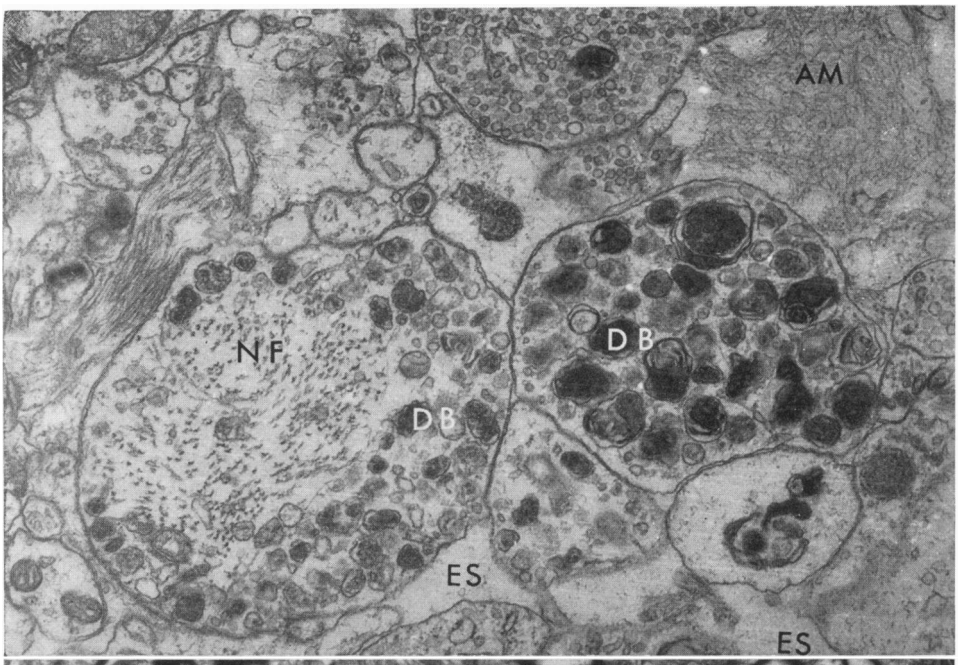


FIG. 11. Numbers of neurofilaments appear in longitudinal sections at the right, and in cross section at the left. The former show intermittent narrowing (arrows) which might indicate twists. × 57,000.

FIG. 12. Neurofilaments cut in cross section. Most have curved, triple density outline, but some (arrows) have circular profiles. × 140,000.



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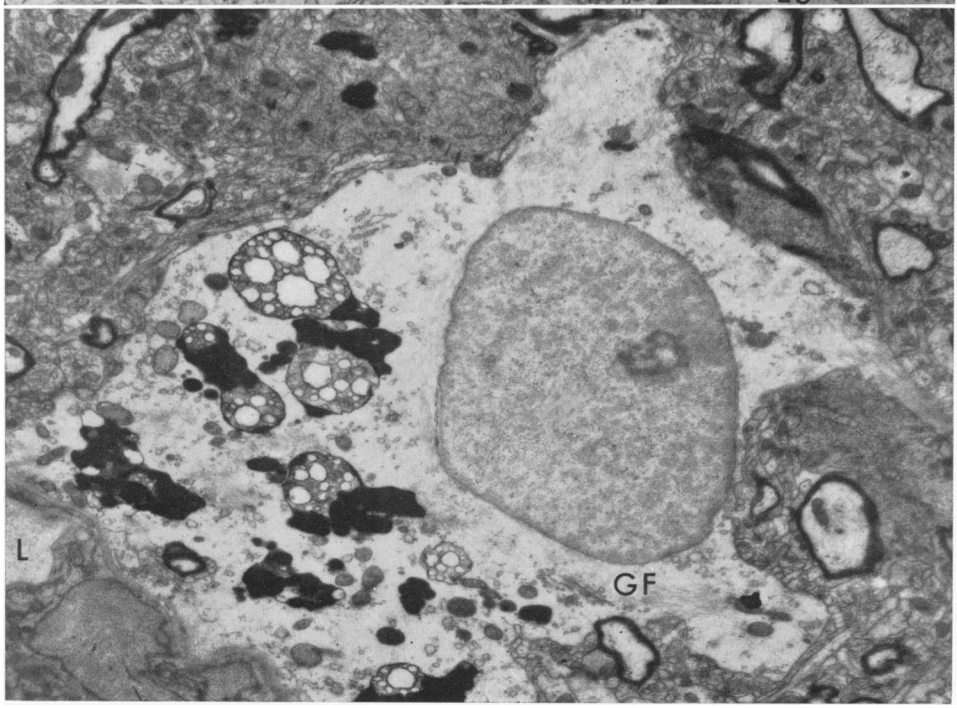

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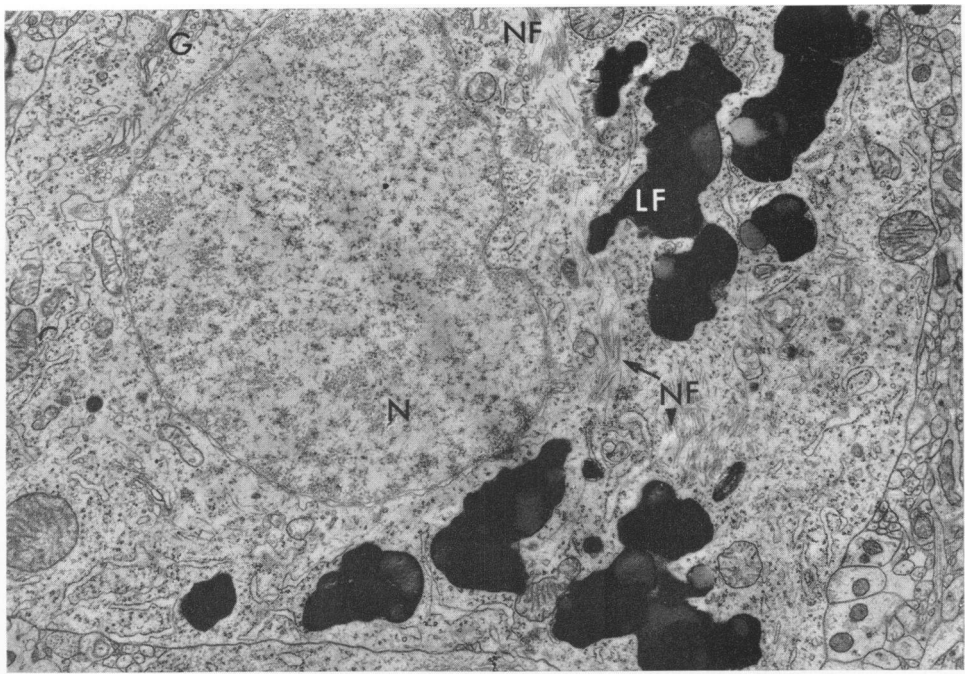
FIG. 13. The cell process on the left contains neurofilaments and peripheral dense bodies. Immediately to the right is a cell process filled with partially laminated dense bodies. Extracellular amyloid is present at top right. Extracellular space is apparent. × 22,000.

FIG. 14. This enlarged astrocyte is adjacent to a vessel (lower left) and contains bundles of glial fibrils and several vesiculated lipid bodies. The neuropil is compact. × 9,300.

15



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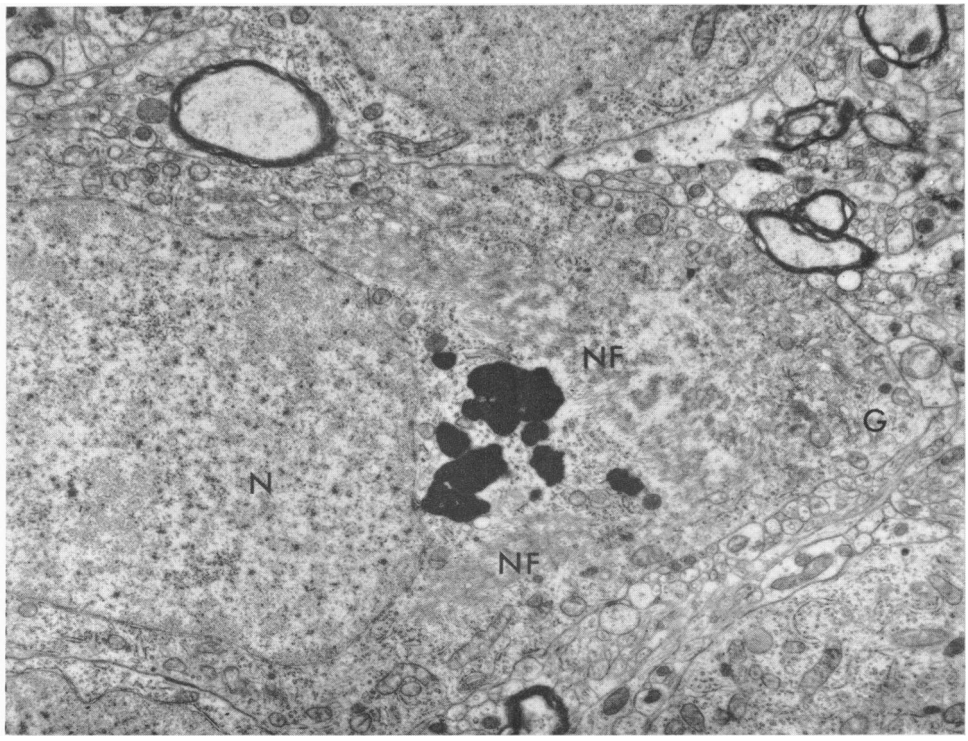
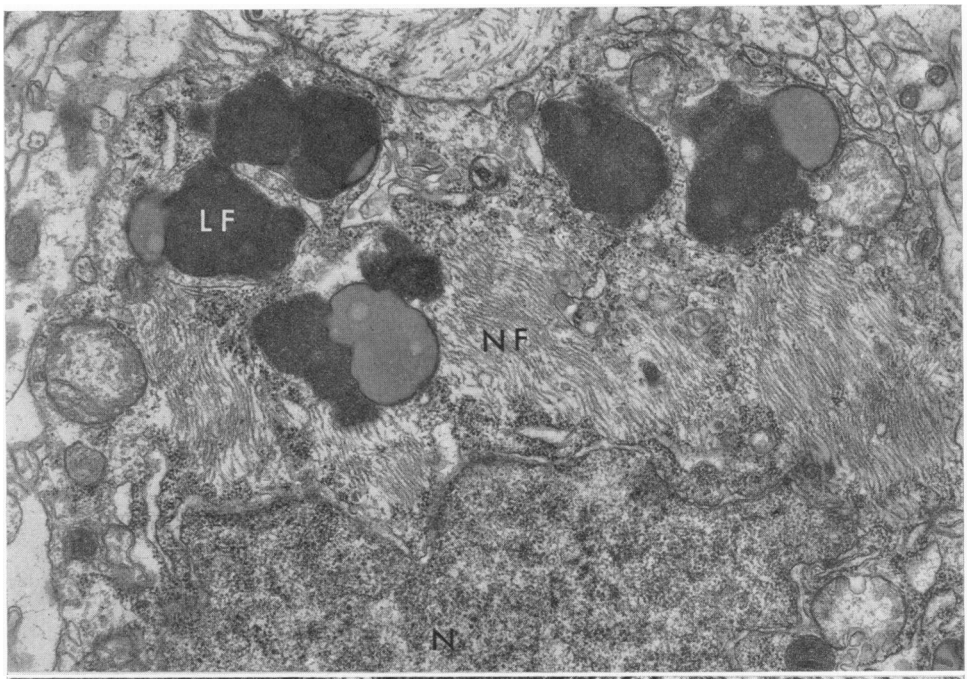


FIG. 15. Medium-sized neuron contains a moderate number of lipofuscin bodies. Neurofibrillary aggregates are mildly increased above normal. × 11,000.

FIG. 16. A neuron displays a moderately severe tangle of neurofibrils. × 9,600.



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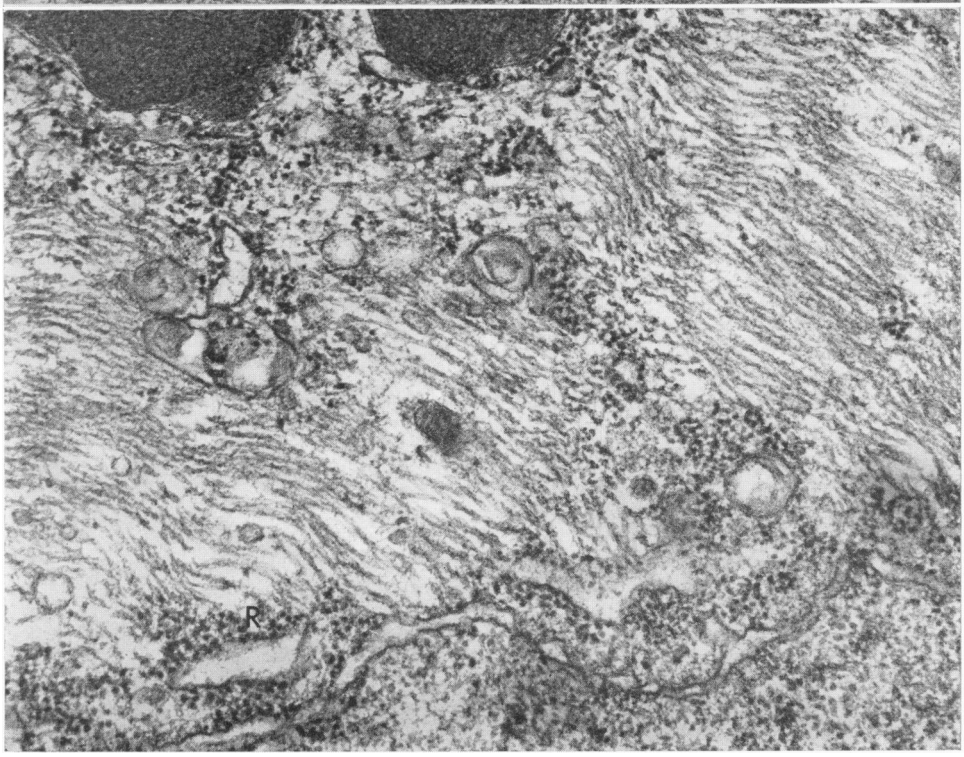
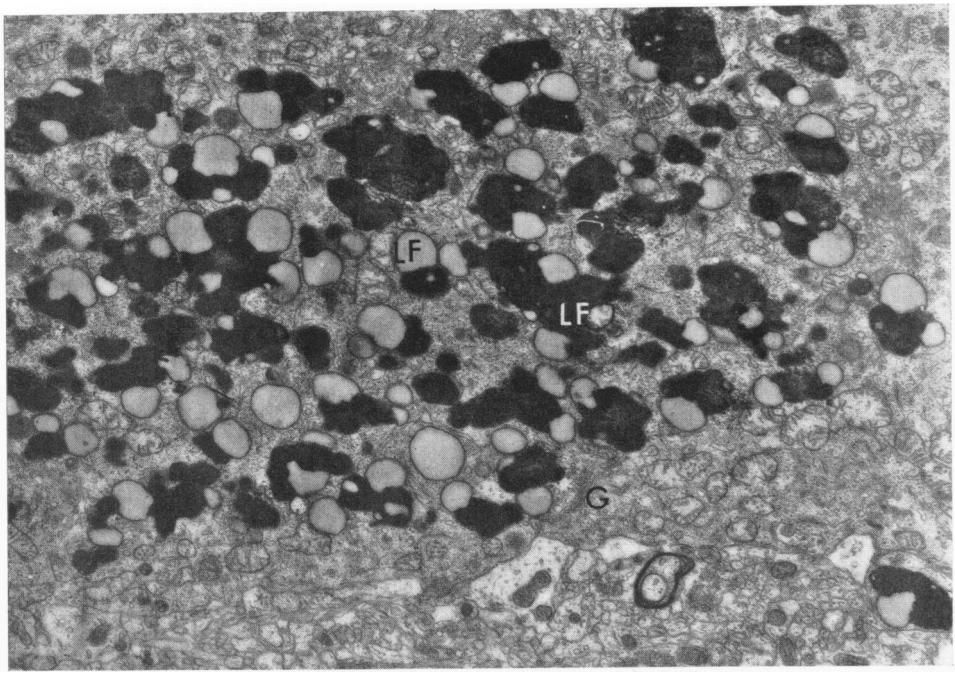


18

FIG. 17. Most of the cytoplasm of this smaller neuron has been displaced by the extensive neurofibrillary tangle. × 18,000.

FIG. 18. Higher magnification of Figure 17. × 47,000.

19



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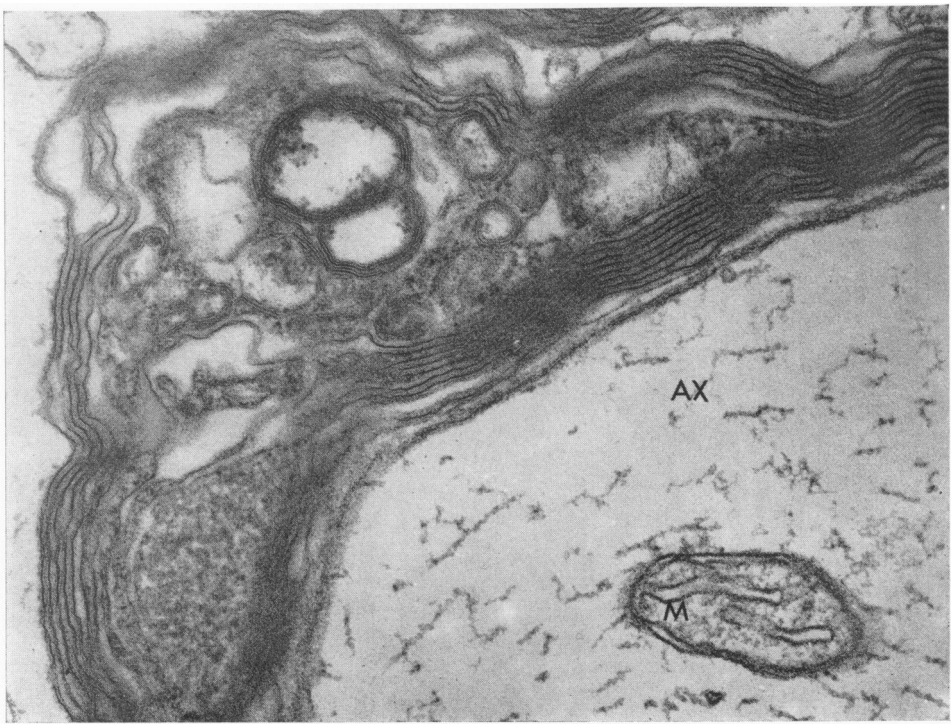
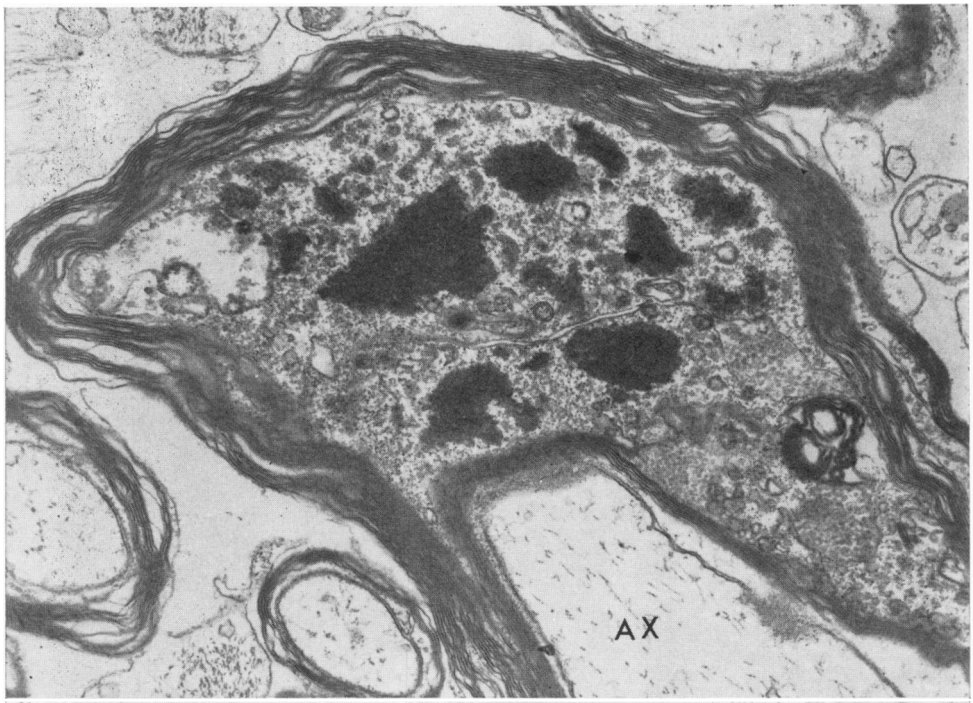


FIG. 19. A neuron contains a great many lipofuscin bodies, but its neurofibrillary content is not remarkable. × 9,000.

FIG. 20. Abnormal myelin with lamellar and granular degeneration surrounds a normal axon. × 76,000.



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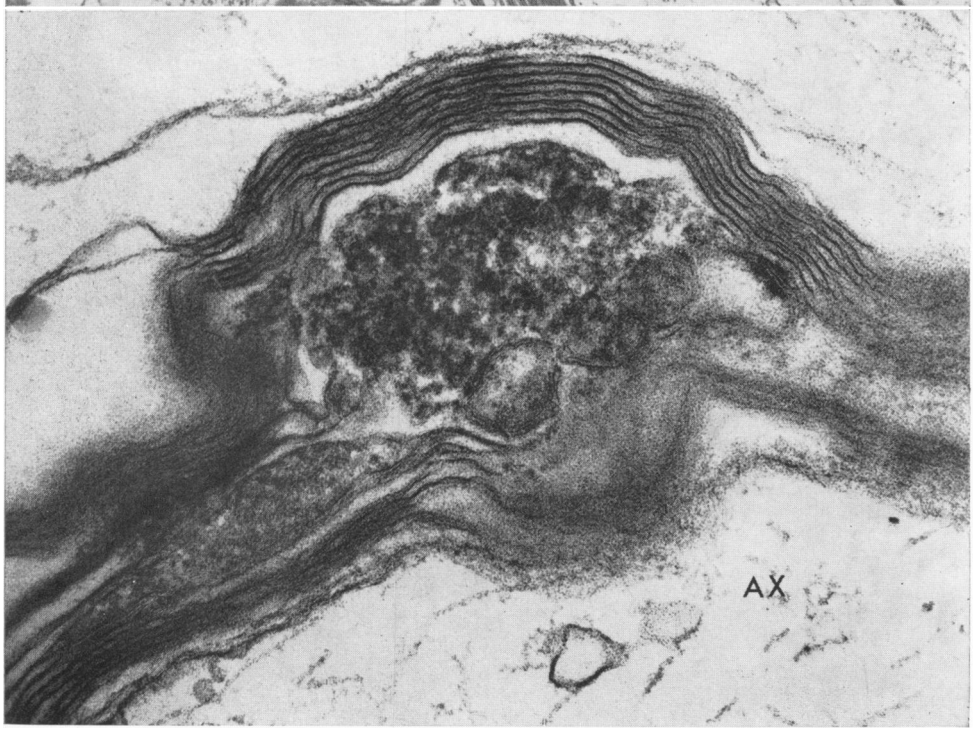

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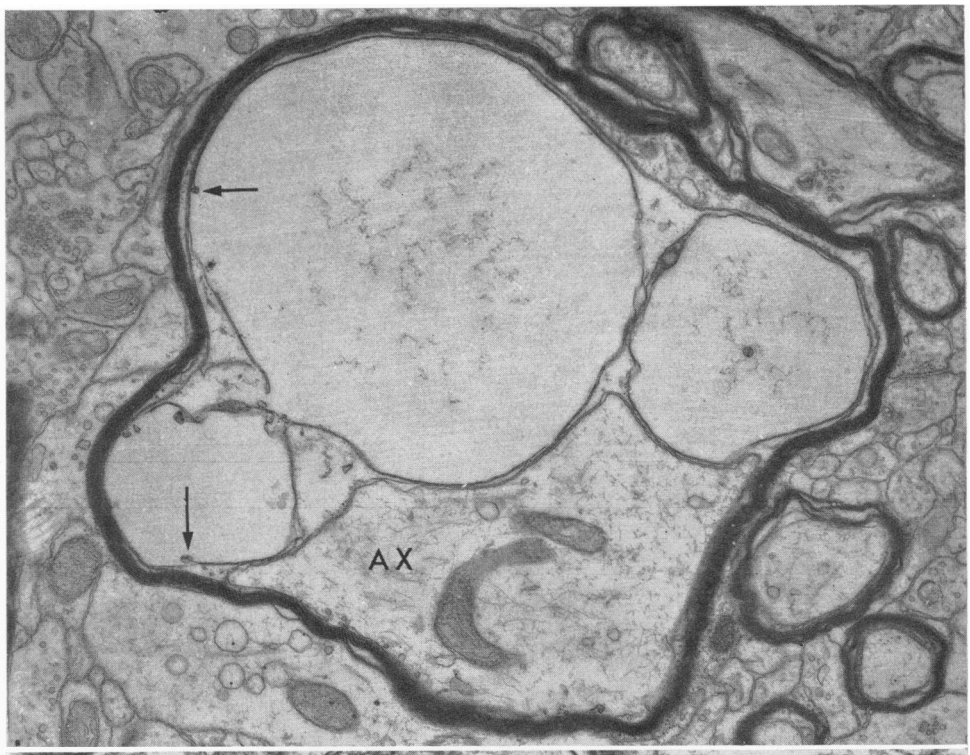
FIG. 21. Severe but focal granular degeneration of myelin is associated with an intact axis cylinder. × 27,000.

FIG. 22. Granular myelin degeneration in the presence of a normal axon. × 86,000.

23



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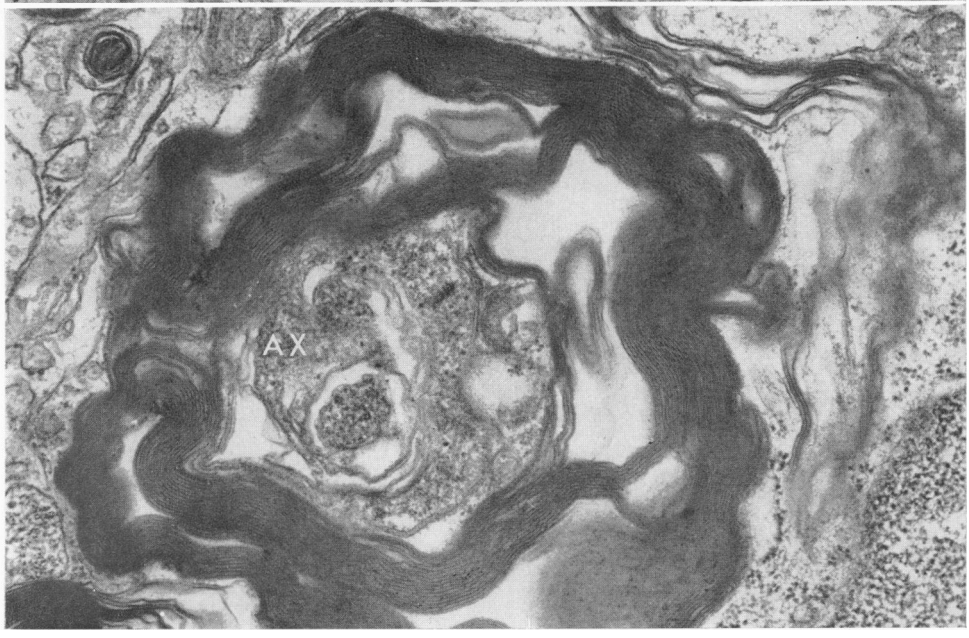
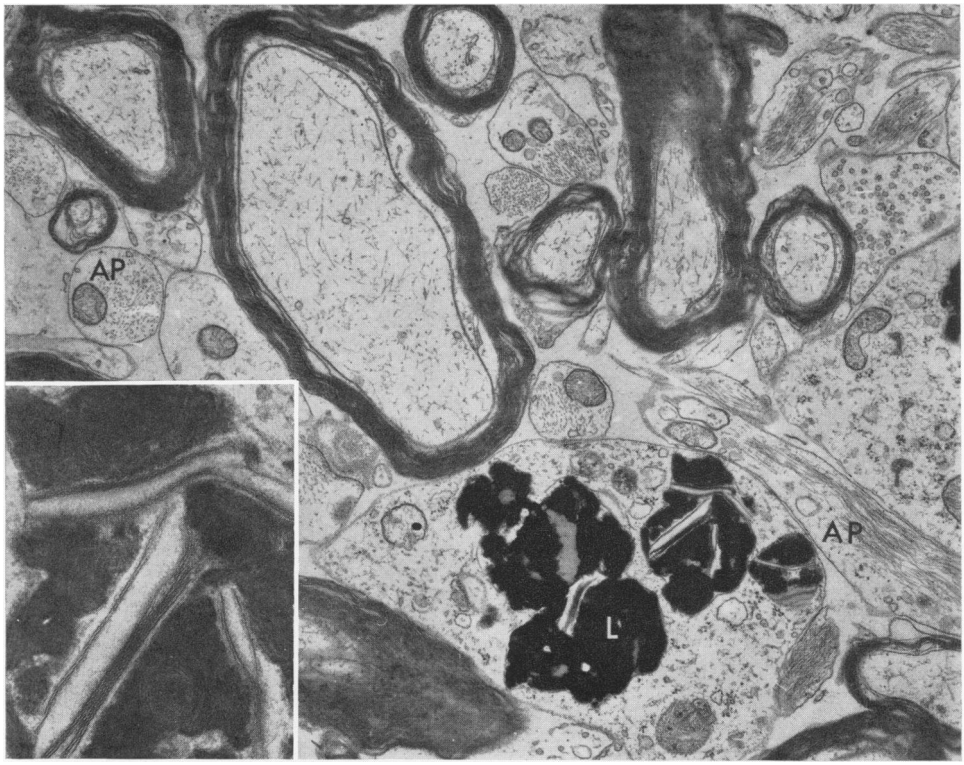


FIG. 23. This myelin sheath is normal. Several large vacuoles compress the otherwise unremarkable axis cylinder. The abnormal vacuoles are bounded by membranes which are occasionally broken and knotted (arrows). × 25,000.

FIG. 24. A later stage of axonal degeneration. The axoplasm is dense and granular; the myelin is broken and crumpled although still laminated. × 33,000.



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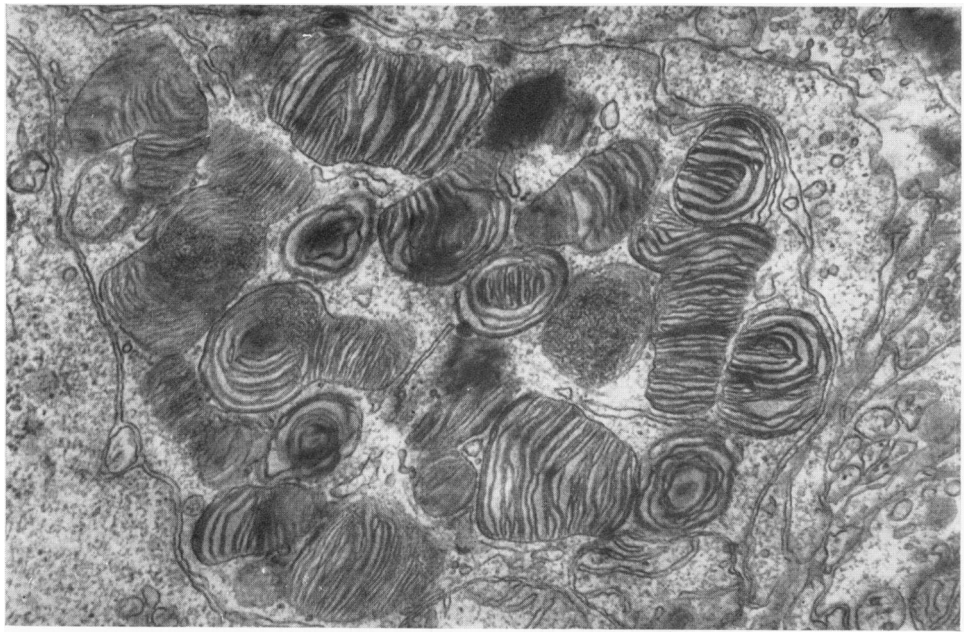
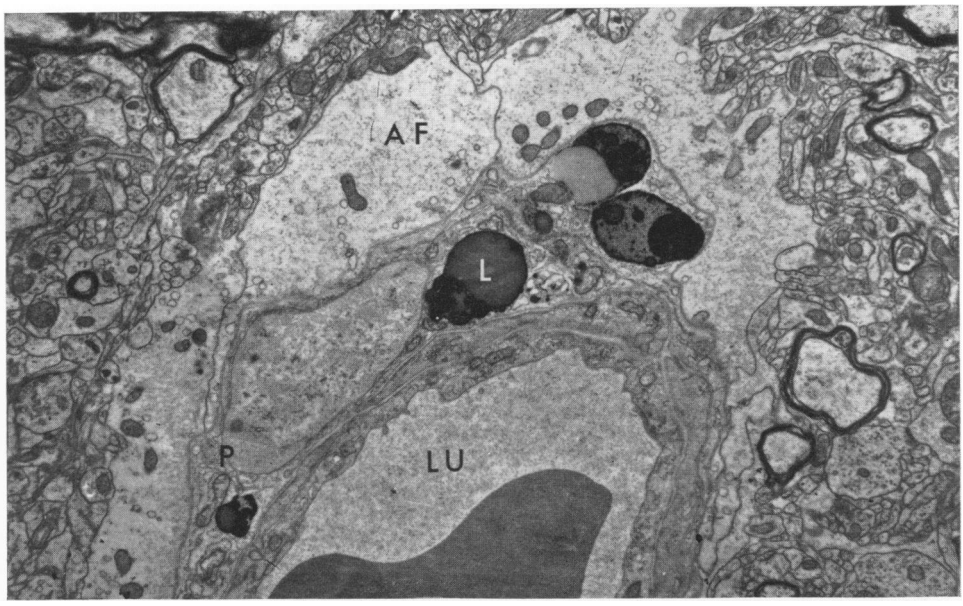


26

FIG. 25. Glial processes in the white matter occasionally contain dense lipid. × 16,000. The inset reveals its partially lamellated structure. × 60,000.

FIG. 26. Occasional aggregates of lamellar lipid bodies are found. These closely resemble the membranous cytoplasmic bodies of Tay-Sachs disease. × 34,000.

27



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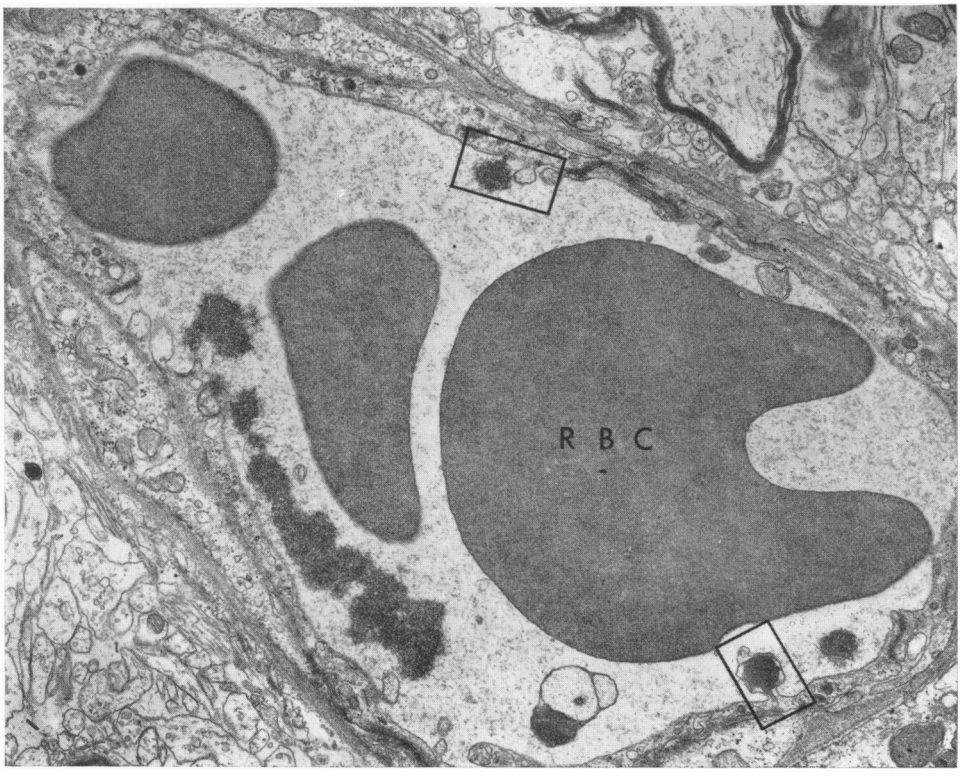
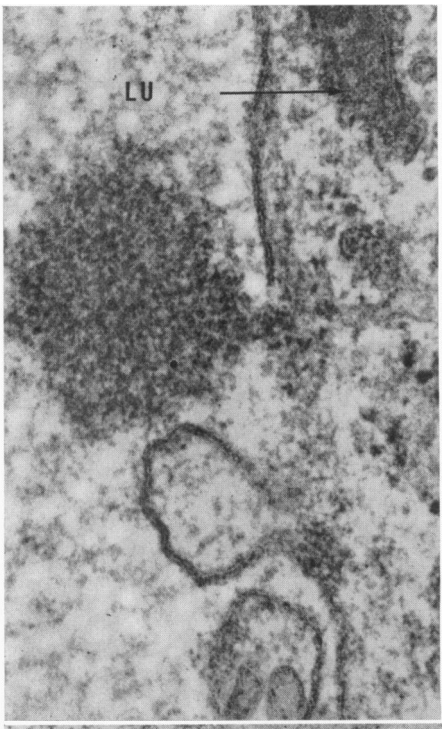


FIG. 27. Several astrocytic foot processes closely surround the upper aspect of this vessel. A perithelial cell contains several lipid droplets. × 9,700.

FIG. 28. A small vessel contains numerous dense, unbounded aggregates in its lumen. The endothelium displays an excrescence at the bottom and a membrane-gap at the top. Each contains dense particulate material similar to that in the lumen. × 13,000.



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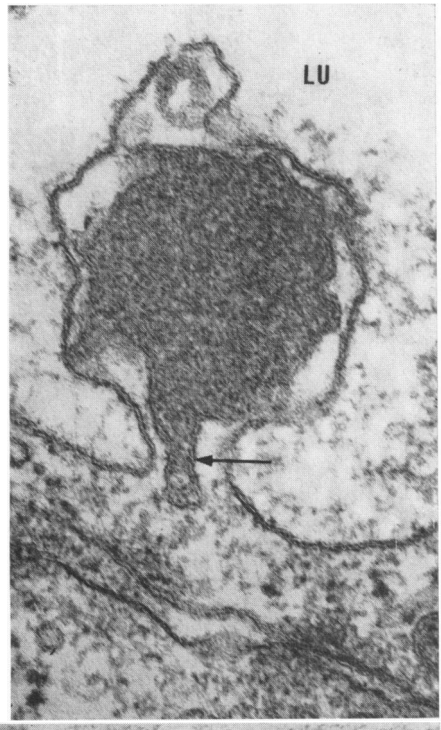

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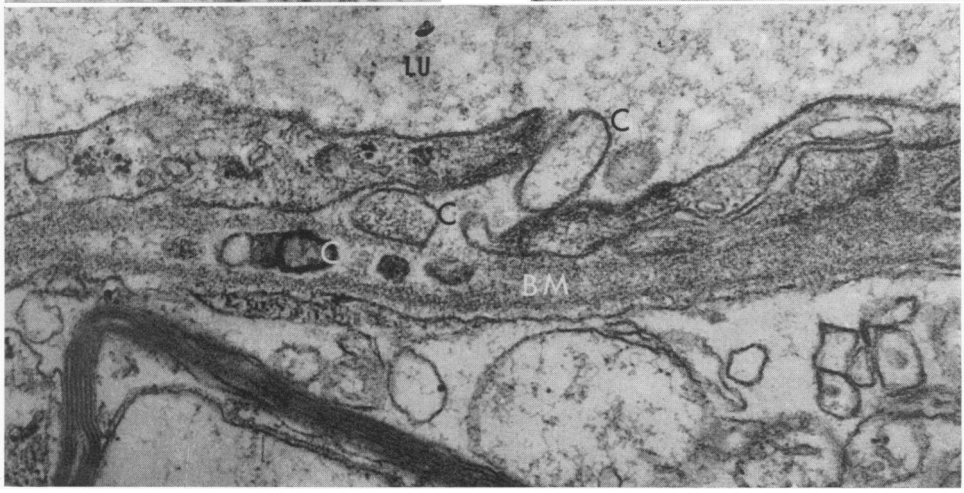

31

FIG. 29. Detail from top of Figure 28. The lumen is to the left, the endothelium at the right. The lumen membrane is invaginated into the lumen at the bottom and is broken in the middle. Dense material appears in the endothelial cytoplasm (arrow) and protrudes from the endothelium into the lumen through the break. × 95,000.

FIG. 30. Detail from bottom of Figure 28. The endothelial excrescence extends upward into the lumen. It is bounded by the lumen membrane. Dense material fills the evagination and is itself partly surrounded by a unit membrane (arrow). × 95,000.

FIG. 31. The endothelial cells lining this vessel are separated by a gap in which are several vesicles resembling chylomicrons. These seem to extend from the basement membrane into the lumen. × 43,000.