ULTRASTRUCTURAL FEATURES OF THE SENSORI-MOTOR CORTEX OF THE PRIMATE

By J. J. SLOPER and T. P. S. POWELL†

Department of Human Anatomy, Oxford University, Oxford OX1 3QX, U.K.

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[Plates 1–10]

CONTENTS

The electron microscope has been used to study the normal structure of the motor cortex (area 4 of Brodmann) and area 3*b* of the somatic sensory cortex in the monkey; they have been found to be remarkably similar. The neuropil of all layers consists predominantly of axon terminals and dendritic spines together with dendritic shafts and myelinated and unmyelinated axons. Axon terminals which make synapses on to dendritic spines may also contact the shaft of the parent dendrite directly. Layer I of both cortical areas contains a plexus of myelinated axons which was shown by light microscopy and electron microscopy (e.m.) to be markedly more dense in the motor cortex than in the somatic sensory cortex, although the diameters of the myelinated axons in both areas were similar. In layers II and III there are numerous neurons among which pyramidal cells are conspicuous and between which run vertical lengths of apical dendrite; these layers contain relatively few myelinated axons compared to the deeper layers of the cortex. Layer IV, in both the motor and somatic sensory cortices, contains conspicuous stellate cell somata which receive large numbers of synapses; in the motor cortex these extend both above and below the narrow layer IV which is conventionally described. There is a considerable increase in the number of myelinated axons at and below this level in the cortex and in sections of layer IV cut parallel to the pial surface, the

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apical dendrites which run vertically through layer IV may be seen to occur in bundles of six to twelve dendrites. Layer V contains the prominent Betz cells and similar, but smaller, large pyramidal cells are present in layer V of the somatic sensory cortex. Both layers V and VI contain predominantly pyramidal and fusiform cells and these layers in the motor cortex are considerably thicker than in the somatic sensory cortex; this difference accounts for most of the difference in overall thickness between the two cortical areas. Occasional dendro-dendritic synapses have been found in the deep layers of the motor cortex and gap junctions in the deep layers of motor and somatic sensory cortices.

Subsurface cisternae in cell somata and dendrites are related to axon terminals making symmetrical synapses on to these same structures. The dense apposed membranes of the subsurface cisternae are closely apposed to the overlying plasma membrane opposite the non-synaptic part of the symmetrical axon terminal and the membranes of both the terminal and soma or dendrite may show some degree of specialization at this site. The dense regions of subsurface cisternae are specifically stained by ethanolic phosphotungstic acid, thus resembling the spine apparatus and it is suggested that the role of these structures and of cisternal organs is similar. Ethanolic phosphotungstic acid also stains cilia and nucleoli as well as the synaptic membrane complexes.

Introduction

This paper is the first of a series describing an electron microscopic study of the normal structure of the motor cortex and area 3*b* of the somatic sensory cortex of the monkey and experimental studies of their connections. The normal structure of several areas of the neocortex has already been studied: the visual cortex of the rat, cat and monkey (Colonnier 1968; Szentágothai 1969; Lund & Lund 1970; Garey 1971), the somatic sensory cortex of the cat (Jones & Powell 1970*a–c*), the parietal cortex of the rat (Peters & Kaiserman-Abramof 1970; Peters 1971) and frontal and temporal cortices of man (Cragg 1976), but the normal structure of the motor cortex has not previously been studied systematically. The motor cortex is, however, functionally distinct from these other cortical areas and there are marked differences between the sensory and motor cortical areas when seen with the light microscope. The motor cortex has also been extensively studied by physiologists and is of considerable clinical importance. The emphasis here has therefore been on the fine structure of the motor cortex (area 4 of Brodmann) and area 3*b* of the somatic sensory cortex has been studied mainly for comparison with the motor cortex and also to see if it differs markedly from the somatic sensory cortex of the cat.

The ultrastructure of the motor cortex has been found to resemble closely that of the other cortical areas described and therefore only a brief description of its general structure will be given; specific points will be described in more detail, emphasis being placed on new features and on comparison between motor and somatic sensory cortices.

Material and methods

Preparation of material for electron microscopy

All observations were made on material from the motor cortex (area 4 of Brodmann) or area 3*b* of the somatic sensory cortex of 21 young adult Rhesus monkeys (*Macaca mulatta*). Some of the material was from normal, unoperated animals, some from the normal hemisphere of experimental animals in which lesions had been placed in the thalamus of the other hemisphere and the rest was experimental material in which one or other of the afferent

pathways to the sensori-motor cortex had been selectively interrupted. The animals were deeply anaesthetized with intraperitoneal sodium pentobarbitone and then cooled with ice and alcohol to a rectal temperature of between 25 °C and 30 °C. The chest and pericardium were opened and a mixture of 0.5 ml of heparin and 0.5 ml of 1 % sodium nitrite was injected into the left ventricle. The right and left sides of the heart were opened and the animals perfused through the aorta with a buffered salt solution followed by 4 % paraformaldehyde and 1 % glutaraldehyde, both at room temperature. After 1–2 h the brain was removed and stored in fixative under refrigeration.

One millimetre thick slices were cut from the brains and care was taken to make them perpendicular both to the central sulcus and the pial surface; they were taken at various mediolateral positions along the sulcus. Blocks about 1 mm wide and running through the whole depth of the cortex were then taken from the motor cortex (area 4) and from area 3*b* of the somatic sensory cortex (Powell & Mountcastle 1959). The blocks were rinsed in 10 % sucrose in phosphate buffer, post-fixed in 2 % osmic acid in phosphate buffer and dehydrated through a graded series of alcohols; they were also block stained with uranyl acetate at the 70 % alcohol stage and embedded in Epon–Araldite.

One micron 'thick' sections were cut from the block face perpendicular to the pial surface and stained with a mixture of methylene blue and azure II (Richardson, Jarrett & Finke 1960). By using the section as a guide, a mesa, usually of approximately 1.0×0.5 mm, was trimmed and ultrathin sections of known depth and orientation were cut, mounted on Formvar coated copper grids having a single 1×2 mm hole, and were stained with alkaline lead citrate (Reynolds 1963) and uranyl acetate (a 5 % solution in 50 % ethanol). This procedure meant that the orientation and position of any ultrathin section in relation to the cortical laminae was always known and this was of great importance in this study. The cortex was routinely studied systematically through its depth; this required three mesas per block to cover the depth of the motor cortex, and two mesas per block in the thinner somatic sensory cortex. These large sections were usually cut as short series of 10–15 serial sections, so that any profile could be followed through at least a few serial sections. Extensive use was also made of long series of up to 100 small serial sections, approximately 100 μm square, taken from selected regions of a block. In some instances blocks were trimmed so that thick sections could be cut from the side as well as the front of a block and these were used to adjust the angle at which the block was cut so that sections could be accurately taken parallel to the 'grain' of the cortex as judged by the apical dendrites. This allowed long lengths of apical dendrites and in particular axon initial segments to be studied in single or a small number of serial sections.

Sections were also cut parallel to the pial surface of the brain and to do this a thick section was first cut from the long face of a block and the block was then turned and cut parallel to the pia. The depth of any section then cut could be determined by taking further thick sections from the block perpendicular to the surface; the top edge of these thick sections, when compared to the original thick section, corresponded to the depth at which the sections cut parallel to the pia had been taken. It was thus possible to cut sections parallel to the pia at an accurately known depth in the cortex.

Phosphotungstic acid staining for electron microscopy

In addition to the routine method described above, three other techniques were used to prepare blocks for electron microscopy in order to examine specific staining of certain structures by these methods (Gray 1959; Bloom & Aghajanian 1968; Gray & Willis 1970).

(1) *Block staining with ethanolic phosphotungstic acid (ethanolic PTA)*

The blocks were dehydrated in alcohol and soaked in 1 % analar phostungstic acid in absolute alcohol for 3 h, after which they were embedded as described above. Sections were examined unstained.

(2) *Osmium ethanolic PTA*

Blocks were first postfixed in osmium tetroxide and then dehydrated in alcohol, treated with ethanolic PTA and embedded as above. Sections were examined unstained.

(3) *Control method*

Blocks were dehydrated in alcohol and embedded in Epon–Araldite. Sections were examined unstained.

Ethanolic PTA stained approximately the outermost 50 μm of the blocks used and so sections for all these three methods were taken from this region at the edge of the blocks.

For a quantitative comparison of the numbers of myelinated fibres in layer I using the electron microscope, blocks were taken from the walls of the central sulcus so as to contain in the same block the superficial layers and apposed pial surfaces of both the motor cortex and area 3*b* of the somatic sensory cortex. Ultrathin sections were cut from these so that layer I of both cortical areas was present in the same section, with the two pial surfaces being apposed. The number of myelinated axons appearing on the microscope screen at a magnification of × 6000 was noted at a point 25 μm below the surface of the brain and at 25 μm intervals below this on a line passing perpendicularly down through layer I, traverses being made alternately into the motor cortex and area 3*b*. The position and orientation of traverses were decided by plotting a map of the section studied, including the positions of the surface and the deep boundary of layer I in each area and the required coordinates for each point were read off and set on the microscope stage. Ten traverses of ten points each were made in each area in five blocks from different hemispheres. In addition to the counts, photographs were taken at a proportion of points, with final prints at a magnification of × 20 000; the external diameter of each myelinated fibre was measured to determine the size distribution of the axons in each plexus.

Normal Rhesus monkey material prepared by the Nissl method and various modifications of the Golgi technique was available for study in conjunction with electron microscopic material.

For a light microscopic comparison of the plexuses of myelinated axons in layers I of the motor and somatic sensory cortices, Weil's myelin stain was used slightly modified for frozen sections cut from glutaraldehyde-fixed material.

Results

The cortical layers

Under the electron microscope the motor cortex and area 3*b* of the somatic sensory cortex of the monkey appear remarkably similar to each other and to the somatic sensory cortex of the cat (Jones & Powell 1970*a–c*). The neuropil consists predominantly of dendritic spines and axon terminals; among these run dendrites, myelinated and unmyelinated axons and the somata of both neurons and glial cells are found at intervals. The triangular shape of pyramidal cell somata together with pyramidal apical dendrites give the cortex a definite grain so that the orientation of a section may be determined with little difficulty and the different laminae may be recognized by their differing features.

Only the occasional small neuron is found in layer I which in the motor cortex is about one and a third times the thickness of layer I in area 3*b*. It consists mostly of dendritic spines and axon terminals along with small dendrites and unmyelinated axons as in the somatic sensory cortex and most of the synapses are of the asymmetrical type although symmetrical synapses are also present. Layer I of both the motor and somatic sensory cortices also contains a plexus of small myelinated axons running parallel to the pia mater (figure 1, plate 1). In light microscopic sections stained for myelin by Weil's method, the fibre plexus in layer I of the motor cortex appears much more prominent than that in layer I of the somatic sensory cortex; this is particularly obvious in the walls of the central sulcus where the two layers I are immediately adjacent (figure 2) but is also apparent when the exposed surface of the pre-central gyrus is compared with that of the post-central gyrus. As a control, the fibre plexuses in layer I in the anterior and posterior walls of the intraparietal sulcus were carefully compared on the same sections and were found to be of approximately equal prominence; these observations were confirmed in a number of brains and over a wide range of staining density. These fibre plexuses in layer I were compared quantitatively using the electron microscope. The density of the plexus was measured by counting the number of myelinated axons appearing on the screen of the microscope at constant magnification, counts being made at equal intervals along a line running through layer I perpendicular to the pial surface of both area 4 and 3*b*. Ten sample areas were counted at 25 μm intervals in each of a total of 50 columns in both area 4 and area 3*b* using five sections from four different brains. There was considerable variation in the density of fibres between individual counts (figure 3), but the pooled results confirm previous qualitative electron microscope reports of the presence of a definite increased density of myelinated fibres in the upper third of layer I (figure 4); they show that the density in the motor cortex is approximately twice that in area 3*b*. If the total numbers of fibres in layer I are compared rather than their densities, layer I being thicker in the motor cortex, the difference is slightly more marked. At a proportion of the points counted photographs were taken at a standard magnification and the diameters of all myelinated axons on them were measured. The histograms of the distribution of fibre diameters in areas 4 and 3*b* are very similar (figure 5) as are the mean diameters, 0.71 μm for the motor cortex and 0.69 μm for area 3*b*. The difference between motor and somatic sensory cortices was therefore in the *numbers* of myelinated fibres present in layer I rather than in their sizes. There were no marked variations in axon diameters with depth from the surface in layer I.

Layer II in the motor cortex contains a considerable density of small neurons which may occur singly or in groups of two or three. Many are typical small pyramids, some of which

may be seen to give rise to apical dendrites although their somata are less pyramidal in shape than those of larger pyramids. Other somata are frankly round or oval in outline with sparse clear cytoplasm, few dendrites and receive few synapses, but these may be of the asymmetric type. These have been identified as small stellate cells (Sloper 1973*a*; Sloper, Hiorns & Powell 1979). The apical dendrites of deeper pyramids run vertically through layer II and in sections taken parallel to the pia mater they may be seen to be uniformly distributed (figure 26, plate 7). The neuropil between the apical dendrites consists predominantly of spines and axon terminals and only a few myelinated axons are seen, some of which run vertically through the layer; the occasional one may be seen to arise from a vertical axon initial segment above and in a few cases these have been traced in continuity with pyramidal cell somata.

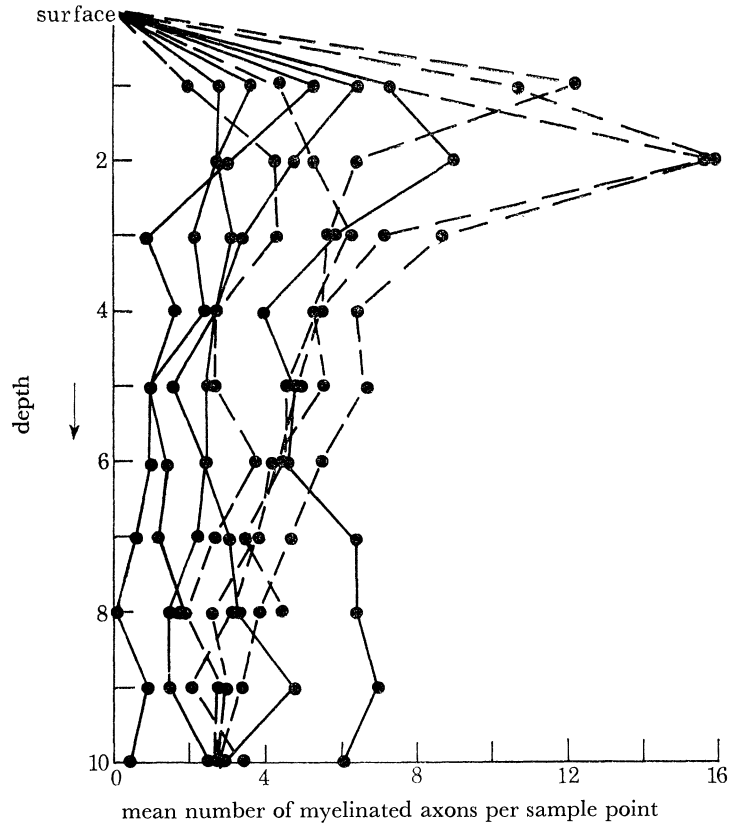
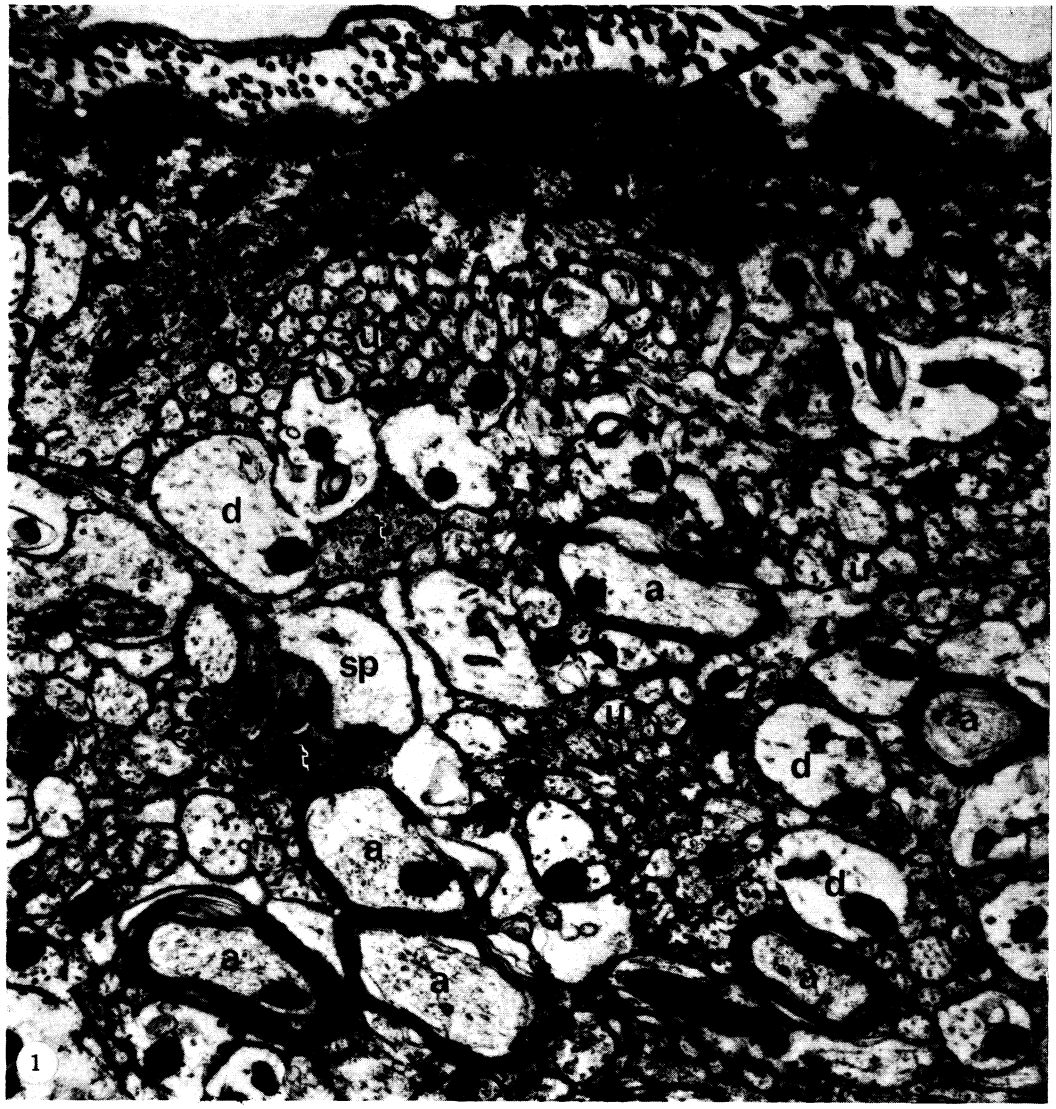


FIGURE 3. Graph showing results of individual counts of the density of myelinated axons against depth in the motor and somatic sensory cortices. These show that the plexus is much more apparent on some sections than others. ---, Area 4; ——, area 3*b*. Interval between sample points = 25 μm.

Layer III in the motor cortex is a little thicker than in the somatic sensory cortex and may be identified by its medium and large pyramidal cells. Their somata are more obviously pyramidal in shape than those of layer II and give rise to apical dendrites passing vertically upwards and axon initial segments passing vertically downwards. These somata are frequently accompanied by a satellite glial cell. Many apical dendrites pass through layer III from below and because of their similarity to the dendrites of mitral cells in the olfactory bulb, which are myelinated in the monkey (Pinching 1971), a careful search was made to see whether pyramidal apical dendrites were ever myelinated. None was found to be truly myelinated but in a few cases in experimental material an empty myelin sheath had become flattened and



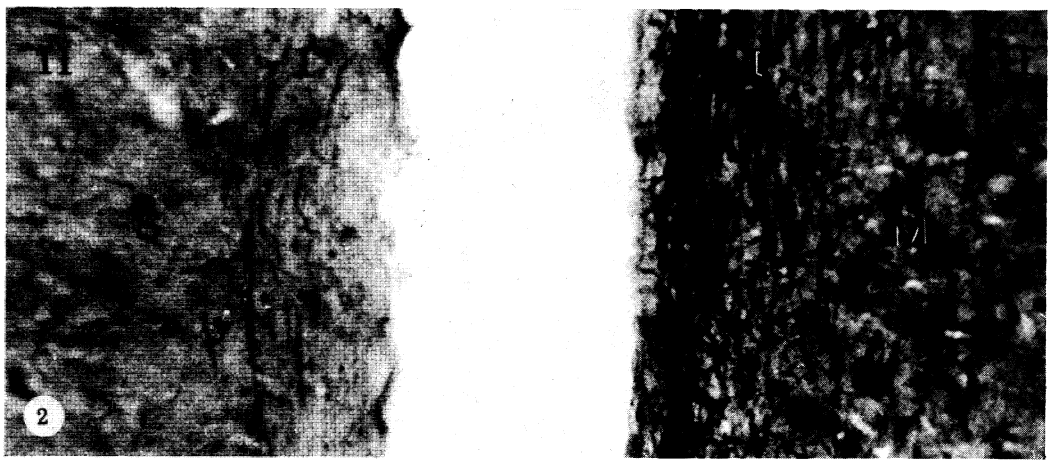


FIGURE 1. Electron micrograph showing the superficial part of layer I of the motor cortex with the pial surface at the top. Note the myelinated axons (a) which form part of the plexus of myelinated axons in this layer. There are also many small unmyelinated axons (u) in addition to a spine (sp), small dendrites (d) and axon terminals (t). (Magn. × 20000.)

FIGURE 2. Light micrograph showing the superficial parts of both somatic sensory cortex (area 3*b*) (S) and motor cortex (M) in the walls of the central sulcus, stained by Weil's method to show myelinated axons. Note the marked difference in density of staining of the fibre plexuses in the two cortical areas which were immediately adjacent on the same section as shown. (Magn. × 150.)

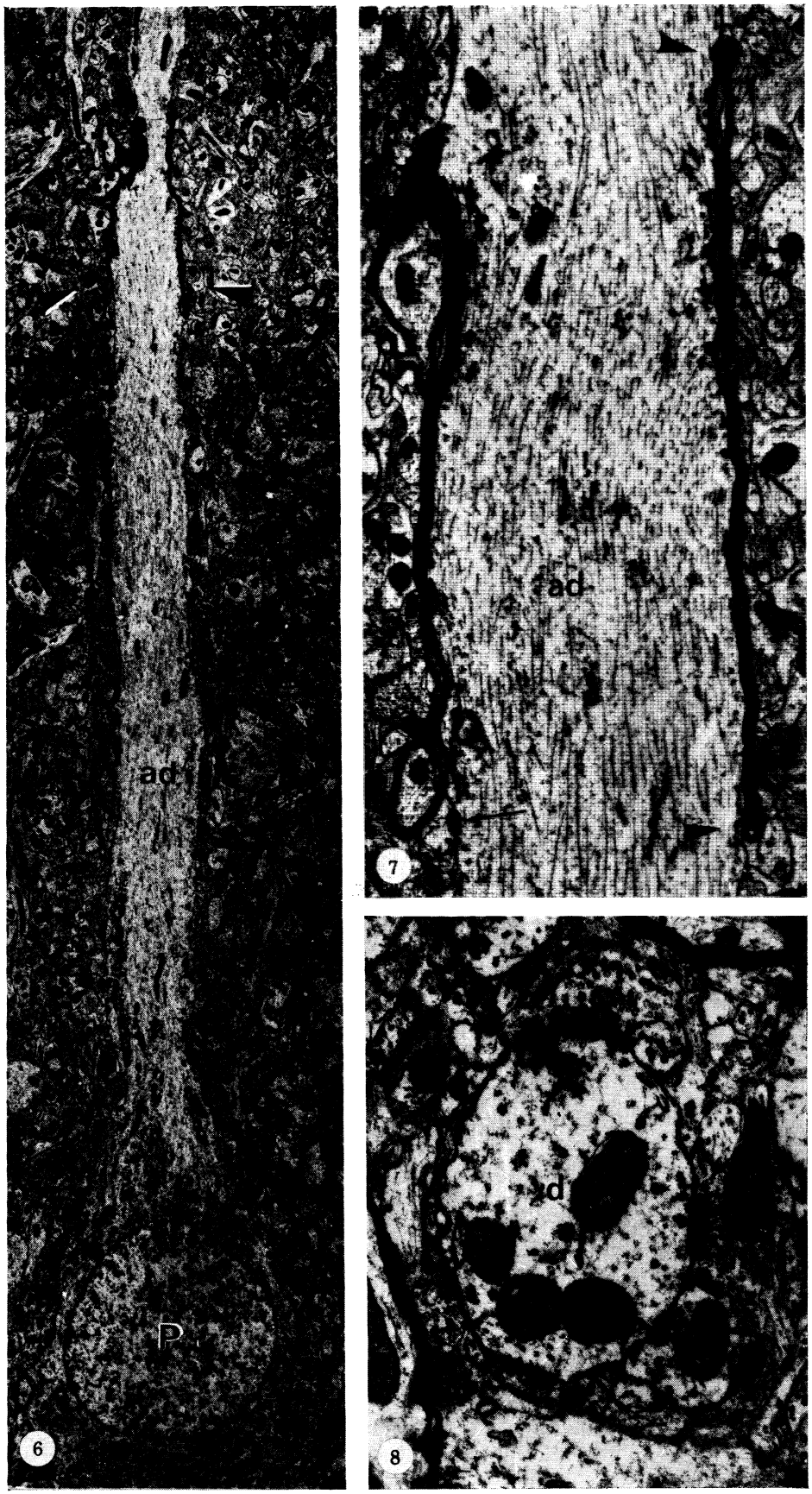
(*Facing p.* 128)

Description of plate 2

Figure 6. Medium sized pyramidal cell (P) from layer III of the motor cortex with a long length of its apical dendrite (ad) cut in continuity with the cell soma. An empty myelin sheath has become wrapped round the apical dendrite (arrowheads) giving the appearance of myelination. (Magn. × 3900.)

Figure 7. Enlargement of the apical dendrite wrapped in myelin, from a serial section. Unlike a true myelin sheath, this myelin doubles back on itself at its limits (arrowheads). Note the synapse received by the dendrite (arrow). (Magn. × 15000.)

Figure 8. Varicose dendrite (d) of the type receiving a high density of synapses from layer III of motor cortex. (Magn. × 29000.)



FIGURES 6–8. For description see opposite.

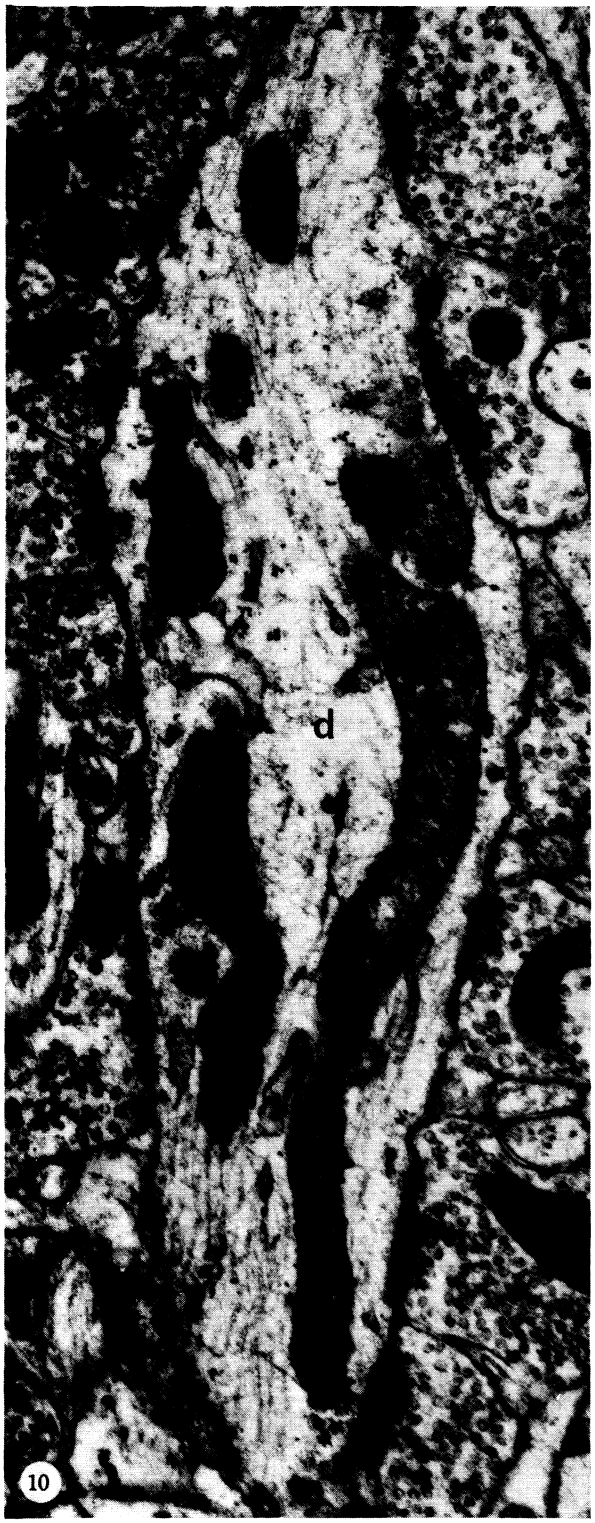


FIGURE 9. Example of the type of varicose dendrite (d) having a markedly varicose shape, clear cytoplasm and a moderate density of synapses. Layer I of motor cortex. (Magn. × 32000.)

FIGURE 10. Example of the type of varicose dendrite having a less obviously varicose shape but containing a high density of organelles and receiving many synapses. Layer III of motor cortex. (Magn. × 29000.)

applied to an apical dendrite to give the appearance of a myelinated segment of dendrite in a single section (figures 6 and 7, plate 2). However at the ends of the myelin the sheath was folded back on itself instead of having true end feet and serial sections confirmed that this was not true myelination. Layer III also contained varicose dendrites. These tended either to have a markedly varicose shape with empty looking cytoplasm and to receive a moderate number of synapses of both types (figure 9, plate 3) or else to receive a very high density of synapses and to contain a lot of organelles but to have a much less markedly varicose shape (figures 8 and 10). The latter type of dendrite was more frequent in the deep part of layer III. The neuropil of layer III is dominated by dendritic spines which receive synapses from axon terminals. Most of these are asymmetric and are from axon terminals of the small dark type, but a proportion of the synapses is symmetrical and is made by rather paler axon terminals.

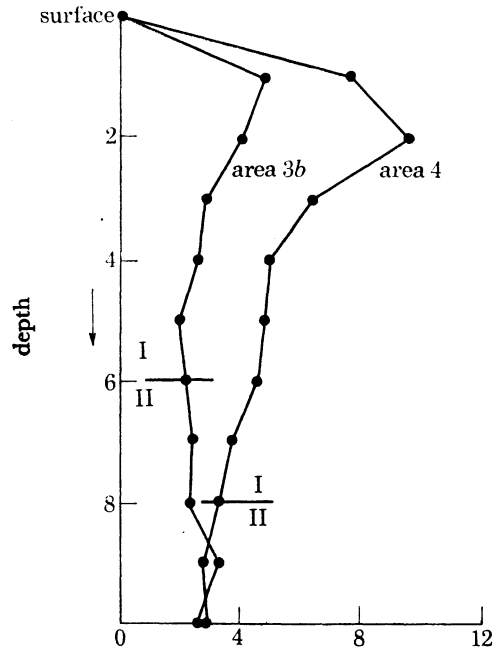


FIGURE 4. Graph showing the pooled results of the layer I fibre counts and showing the overall greater density of the fibre plexus in the motor cortex. Interval between sample points = 25 μm.

Dendritic spines receive one or two asymmetric synapses or an asymmetric and a symmetrical synapse (figure 11, plate 4) but no dendritic spine was found to receive only a symmetrical synapse. A few examples were found of spines which received synapses from three axon terminals or had unusual configurations (figures 12 and 13). It was not uncommon, both here and in other layers, for a single axon terminal of either the asymmetric or symmetrical type to make a synapse both on to a spine and on to the shaft of the dendrite giving rise to that spine by way of a separate membrane specialization (figures 14 and 15), but serial sections were often required to demonstrate this. Spines were also found occasionally on neuronal somata in several laminae (figures 16, 17 and 20, plate 5). On pyramidal somata these have received symmetrical synapses, but no clearly asymmetric synapses and a terminal making a synapse on to a somatic spine may also make a synapse directly on to the parent cell soma (figure 20). In several laminae a rare but distinct type of axon terminal was found which had a remarkably

varicose, but uniform shape; occasionally more than one varicosity could be traced in continuity (figures 18 and 19). These terminals contained round vesicles with a high proportion of large dense cored vesicles and made asymmetric synapses.

With the light microscope, layer IV in the motor cortex is usually described as a narrow strip containing rather more small cells situated between the Betz cells of the upper part of layer V and the large pyramids in the lower part of layer III. Under the electron microscope layer IV in the motor cortex has no obvious boundaries. There is an increase in the number of myelinated axons in the region of its upper border and some sections show a dense plexus

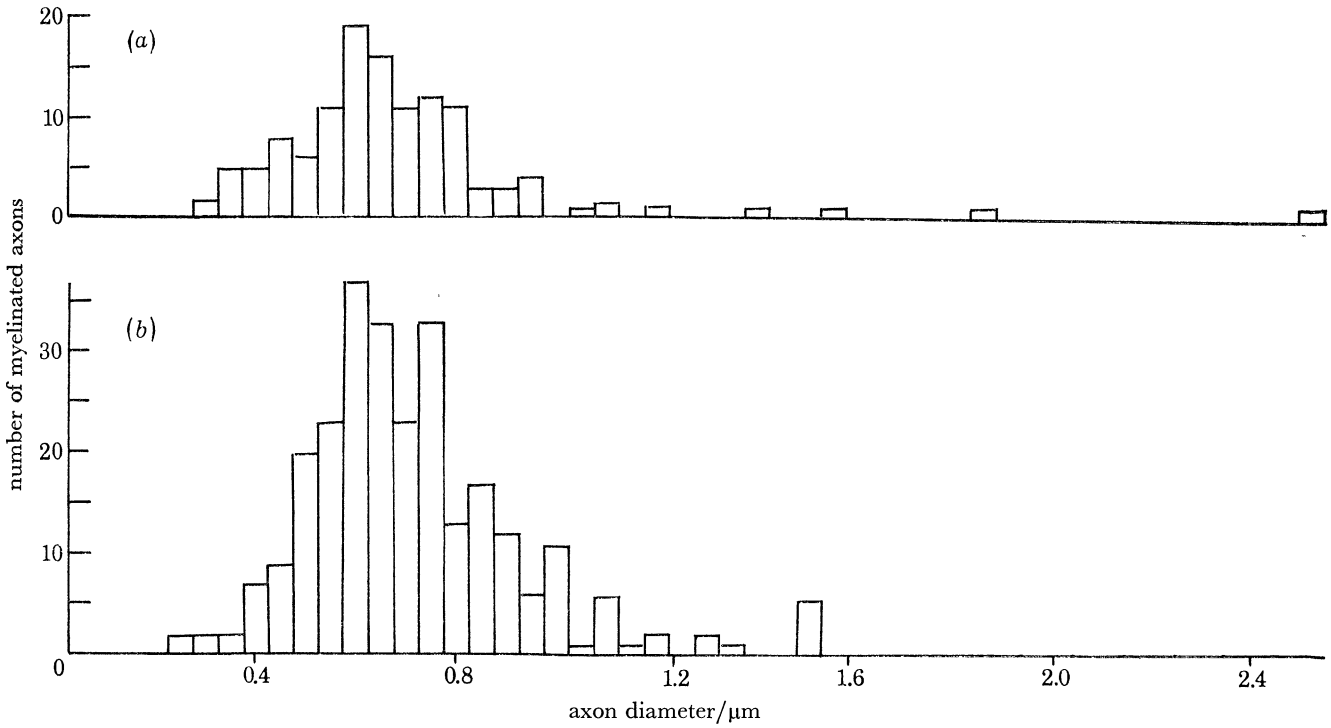


FIGURE 5. Histograms comparing the size distribution of the myelinated axons in layer I of (*a*) the somatic sensory cortex (area 3*b*) and (*b*) the motor cortex (area 4). Mean diameter of area 3*b* axons determined from 124 fibres = 0·69 μm. Mean diameter of area 4 axons determined from 269 fibres = 0·71 μm.

of unmyelinated axons in this region as in the somatic sensory cortex. Myelinated axons may be seen to give off branches at nodes of Ranvier (figure 21, plate 6) particularly in the deeper cortical layers and in the somatic sensory cortex pale axons making several 'en passage' symmetrical synapses are not infrequently seen (figure 22); these are rare in motor cortex. Large stellate cells appear prominent in layer IV as are the varicose dendrites of the type studded with synapses but both cells and dendrites extend well up into layer III and down through layer V. Small stellate cells also occur in layer IV but quantitatively in both motor and somatic sensory cortices of the monkey, the majority of neurons in layer IV are small pyramids although their presence is not conspicuous. In area 3*b* the large stellate cells appear to be more restricted to layer IV than in the motor cortex. Layer IV in both motor and somatic sensory cortices contains large pale axon terminals with round vesicles making asymmetric synapses which are often multiple in a single section. An occasional finding has been a structure consisting of bundles of parallel, densely staining fibrils, usually in dendrites (figures 23–25).

Their significance is unclear but one example appeared to be in continuity with a mitochondrion. Apical dendrites pass up through layer IV from deep pyramids and in sections cut parallel to the pia in motor cortex these are seen to occur in bundles of about six to twelve (figures 27 and 28, plate 7). These bundles extend up into the lower part of layer III and appear to be more prominent in some parts of the motor cortex than others.

The motor cortex of the monkey is between one and a half and two times the thickness of area 3*b* of the somatic sensory cortex; most of this difference is accounted for by the greater thickness of layers V and VI in the motor cortex. Layer V is characterized by the Betz cells which occur mainly in its upper part and may occur in groups of two or three. Very large examples of the large type of stellate cell are also found in layer V and may be as much as 30 μm in diameter. They are less common than Betz cells but are often found close to them. Most of the neurons in layer V are pyramidal but in the deeper part and in layer VI many neurons are fusiform in shape and often have large dendrites emerging from their upper and lower poles. Large stellate cells are prominent in the upper part of layer V and small stellate cells are found in layers V and VI. Dendrites of the varicose type studded with synapses are also frequent in layer V, although both these and large stellate somata appear to be more prominent in some parts of layers IV and V than in others. In both layers dendrites of this type may make gap junctions with other dendrites, usually of the same type, or with large stellate somata (Sloper 1972) and gap junctions are also occasionally found in the lower part of layer III. In the deep layers of the motor cortex the occasional dendrite is also found which makes a dendro-dendritic synapse (Sloper 1971). These synapses have symmetrical membrane thickenings and small groups of synaptic vesicles. The presynaptic dendrites are varicose in shape and receive a number of both asymmetric and symmetrical synapses. Myelinated axons are frequent in layer V; many run vertically through it and it is not infrequent for several of these vertical axons to occur together (figure 29, plate 8). Toward the bottom of the cortex, myelinated axons become even more frequent until the neuropil of layer VI merges into the white matter.

Subsurface cisternae

Subsurface cisternae are a well recognized feature of neurons and their structure in the motor cortex corresponds to previous descriptions (Rosenbluth 1962*b*; Siegesmund 1968; Jones & Powell 1970*a*). They are found both in neuronal somata and in dendrites. As in the somatic sensory cortex they show a considerable variation in structure from a simple dense area of fused membrane which often opens into a sac of endoplasmic reticulum (figures 30–33, plate 9) to a complex structure of alternating fused membranes and sacs (figure 35). In the motor cortex those subsurface cisternae having a single area of dense fused membrane may often be found with it closely applied to the plasma membrane of a cell soma or dendrite opposite a symmetrical axon terminal (figures 30–33). These terminals frequently make a symmetrical synapse with the cell or dendrite in the same section but the synaptic membrane complex occupies only a part of the area over which the symmetrical terminal is apposed to the cell or dendrite and the fused membranes of the subsurface cistern are found opposite a different part of the symmetrical axon terminal and are thus separate from the synaptic complex. However, opposite the subsurface cistern the membranes of both dendrite or soma and terminal are also usually thickened, this being distinct and separate from the synaptic membrane thickening, and in most examples there is granular, electron dense material in the extracellular

cleft opposite the cistern and between the fused membranes of the cistern and the adjacent plasma membrane. These membrane specializations opposite the cisternae therefore appear identical to a synaptic membrane complex of the symmetrical type but the cistern is attached below the 'postsynaptic' component, synaptic vesicles are not aggregated opposite the structure and the membrane thickenings are not always as prominent as those of a synapse. Such membrane specializations have not been seen between a subsurface cistern and any other adjacent profile. Subsurface cisternae related to symmetrical axon terminals occur in both pyramidal and stellate cells. Pyramidal somata receive only symmetrical synapses but large stellate somata receive synapses of both types and so all identifiable synapses on to a series of large stellate somata selected at random were recorded and the presence or absence of a subsurface cistern opposite the terminal was noted to see whether the relationship was specific to symmetrical type axon terminals. Of 290 synapses recorded, 120 were symmetrical and of these 18 (15 %) had associated subsurface cisternae whereas none of the 170 terminals giving rise to asymmetric synapses were related to a subsurface cistern. The fused membranes of these cisternae may extend beyond the specialized region opposite a symmetrical axon terminal and in some examples in single sections they may be found opposite other components of the neuropil; extensive study of serial sections would be required to determine whether all cisternae of this type are related to symmetrical axon terminals in adjacent sections. The fused membranes of these subsurface cisternae may often be seen to be connected to the endoplasmic reticulum of the cell soma and may also be closely related to a mitochondrion (figures 30 and 31).

Vesicles

It is not unusual for the plasma membranes of neuronal profiles in the sensori-motor cortex to show small coated pits and these have been described in various sites as part of the process

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Description of plate 4

Figure 11. Dendritic spine (sp) from layer II of motor cortex which contains a spine apparatus (s) and receives an asymmetric synapse from a terminal (t_1), containing round vesicles and a symmetrical synapse from a terminal containing flattened synaptic vesicles (t_2). (Magn. × 53000.)

Figures 12 and 13. Serial sections of a double headed dendritic spine (sp) cut in continuity with its parent dendrite. It contains a spine apparatus (s) and the upper head received synapses from 3 axon terminal profiles (t_1–t_3). That from t_1 is clearly of the asymmetric type (single arrowhead) and that from t_2 of the symmetrical type (two arrowheads). (Magn. × 29000.)

Figure 14. Axon terminal (t_1) which makes asymmetric synapses (single arrowhead) on to both a spine and the shaft of its parent dendrite. The spine also receives a synapse from a second axon terminal t_2. (Magn. × 44000.)

Figure 15. Axon terminal t_2 which makes symmetrical synapses (two arrowheads) with a spine and the shaft of its parent dendrite. The spine also receives an asymmetric synapse (single arrowhead) from terminal t_1. (Magn. × 44000.)

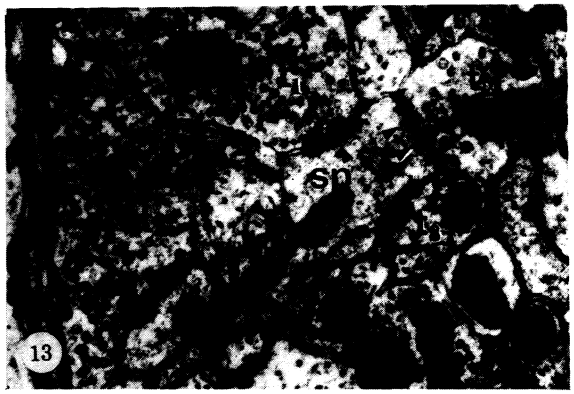
Description of plate 5

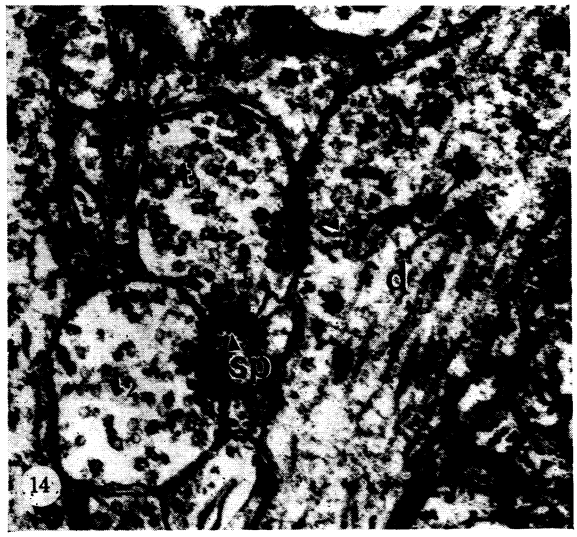
Figure 16. Somatic spine (single arrowhead) on the soma of a pyramidal cell (P) from layer III of the motor cortex. (Magn. × 9000.)

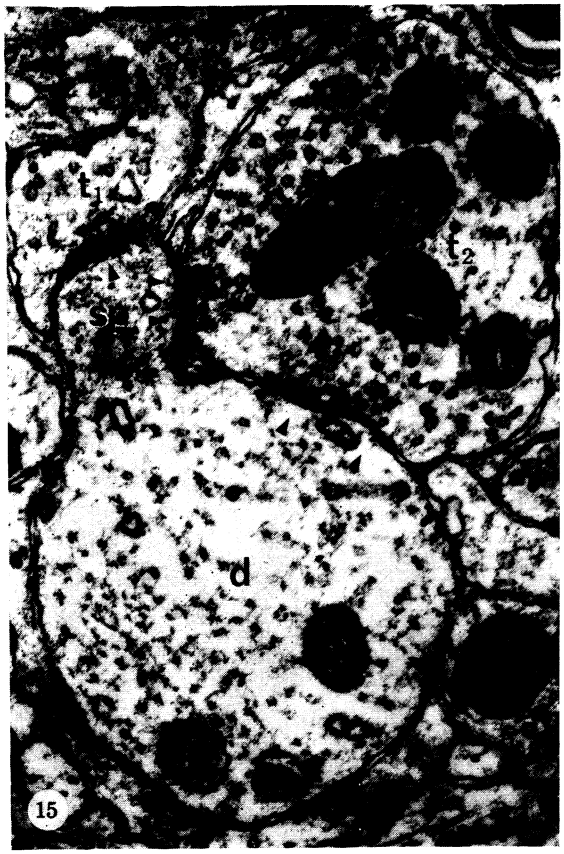
Figure 17. Detail of the somatic spine (sp) of figure 16 which shows that it receives a symmetrical synapse (two arrowheads). Note the darker flocculent cytoplasm in the spine. (Magn. × 32000.)

Figures 18 and 19. Serial sections of a varicose axon (a) containing large dense-cored vesicles. (Magn. × 18000.)

Figure 20. Example of a somatic spine. An axon terminal makes synapses on to both the spine and the cell soma (two arrowheads), the latter of these synapses being identifiable as symmetrical in type. (Magn. × 29000.)







FIGURES 11–15. For description see opposite.

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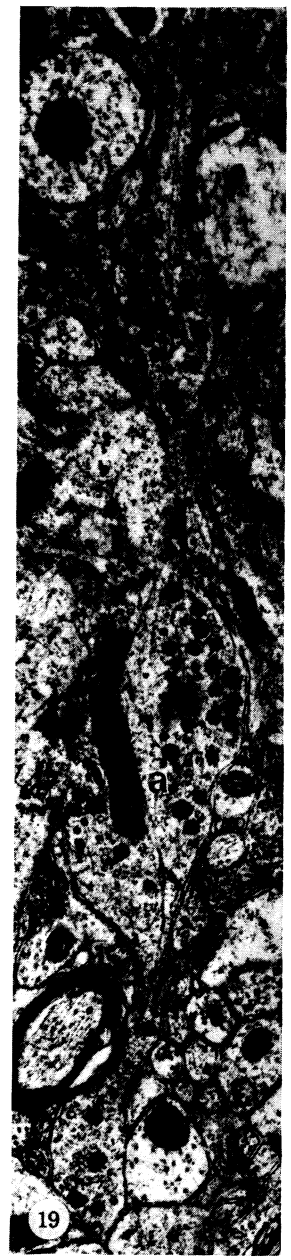
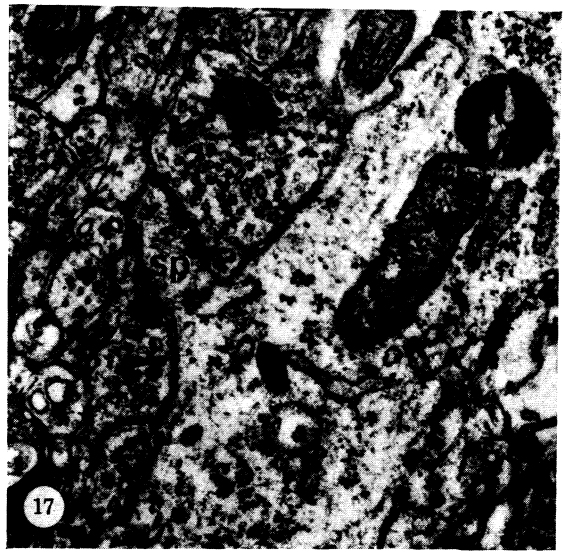
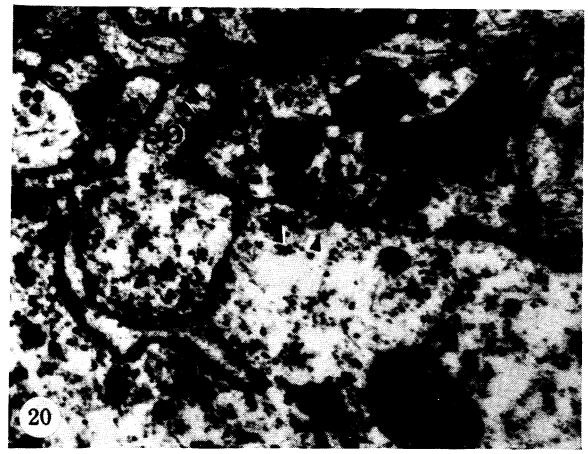
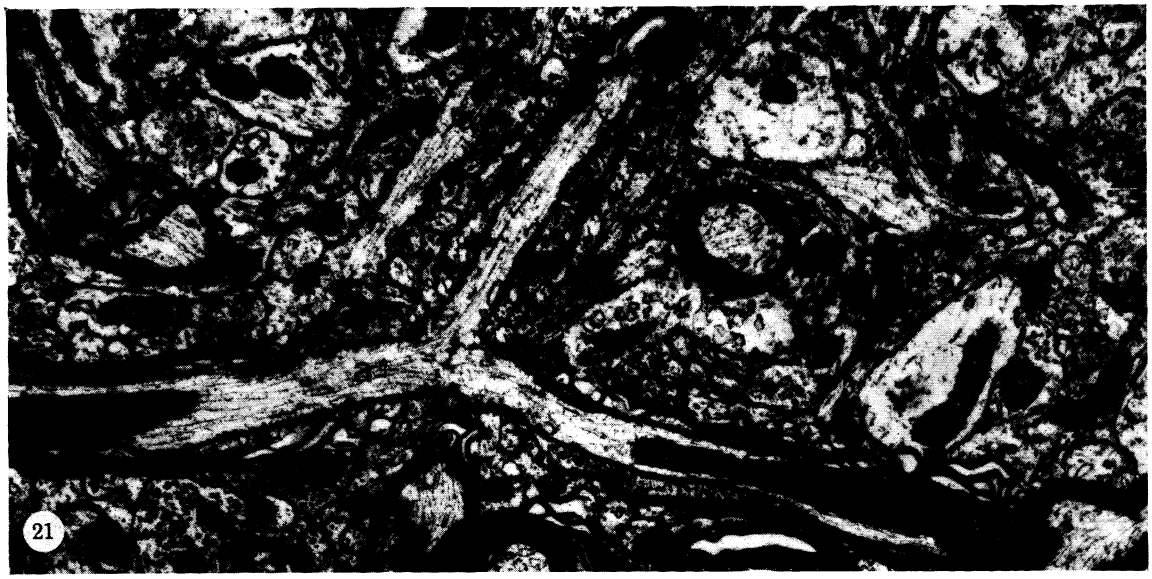
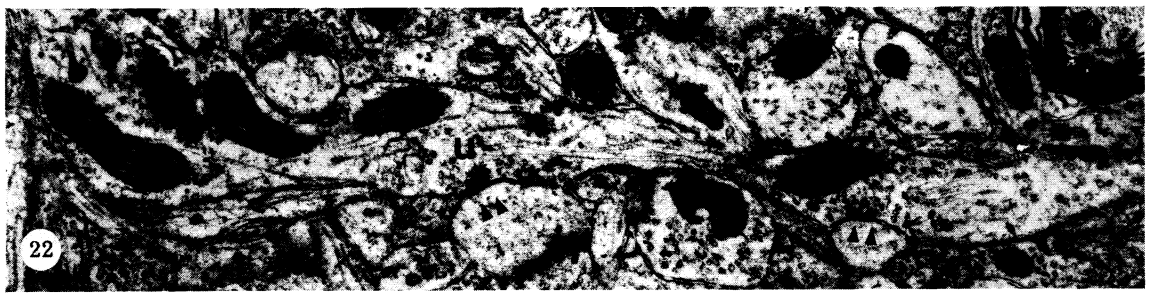


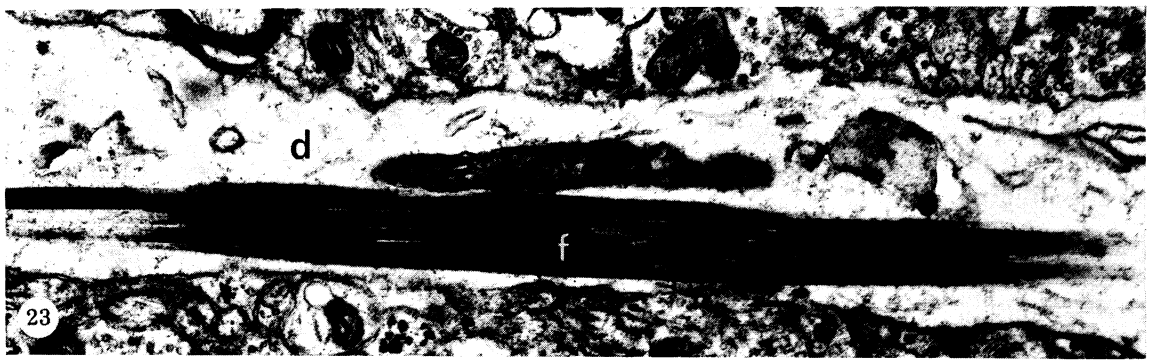


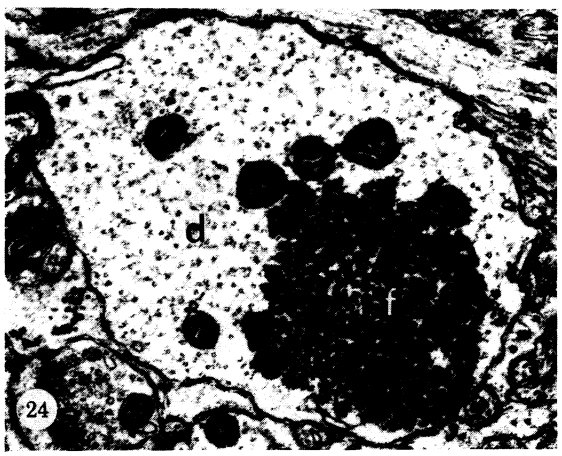


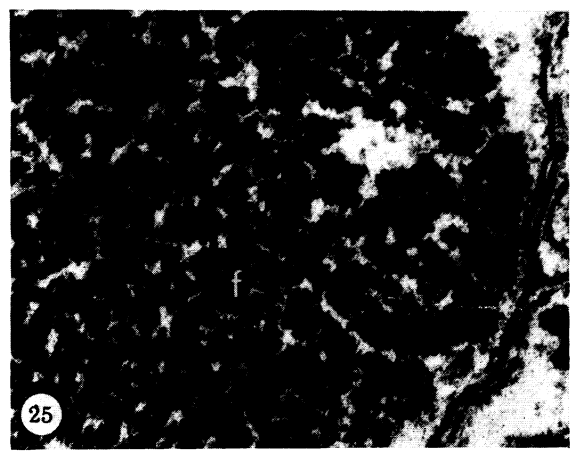
FIGURES 16–20. For description see page 132.



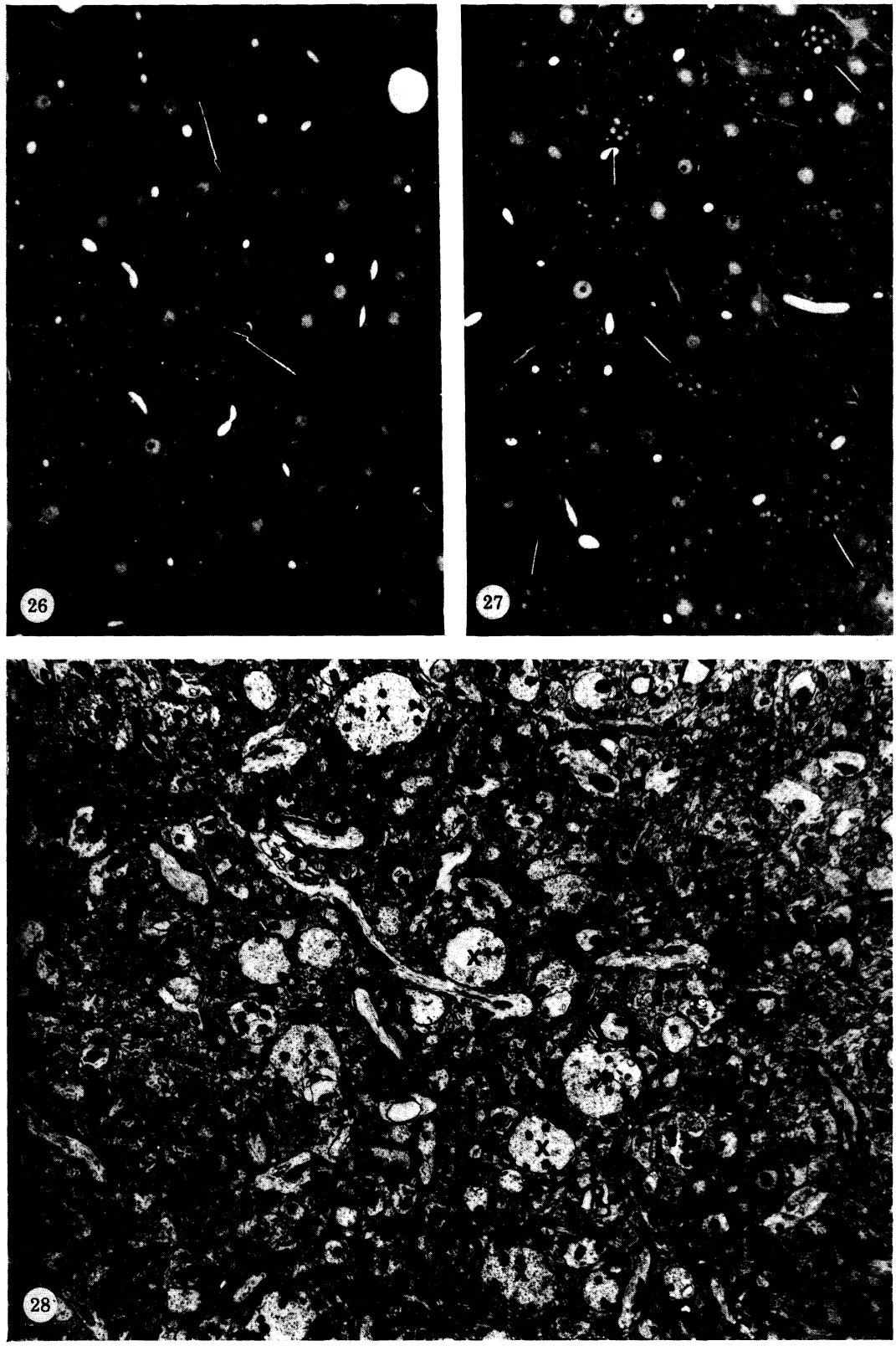








FIGURES 21–25. For description see page 133.



FIGURES 26 and 27. Light micrographs of 'thick' sections taken parallel to the pial surface in layers II and IV of motor cortex respectively. In layer II the apical dendrites, which are cut in transverse section and appear as small white circles (examples indicated by small arrows) are evenly distributed, whereas in layer IV they occur in groups (examples indicated by arrowheads). (Magn. × 220.)

FIGURE 28. Electron micrograph of a similar section through layer IV parallel to the pial surface showing a bundle of apical dendrites cut in transverse section (x). (Magn. × 6000.)

of vesicle formation or discharge (Gray 1961; Andres 1964; Westrum 1965; Kanaseki & Kadota 1969; Gray & Willis 1970; Gray & Pease 1971). Although often no contents are visible, in some examples the cytoplasm of an adjacent profile is invaginated into one of these coated pits; figures 36 and 37, plate 10 show this happening between an axon terminal and a dendrite and it appears that part of the cytoplasm of the axon terminal is being taken up by the dendrite. Such a coated pit has also been seen in continuity with the plasma membrane of a myelinated axon within its myelin sheath (figure 38). This process appears to be the same as that involved in the phagocytosis of degenerating axons and axon terminals by neurons and glia.

Phosphotungstic acid staining

The motor cortex was also studied in material block-stained with ethanolic phosphotungstic acid (method 1). As well as staining synaptic thickenings and the spine apparatus as described in other sites (figures 39 and 40), this method stained specifically at least some subsurface cisternae (figure 34), cilia arising from both neurons and glia (figure 45) and nucleoli (figure 43). The undercoating of axon initial segments and nodes of Ranvier, cisternal organs and degenerating axon terminals were also specifically stained by the ethanolic PTA and are described elsewhere (Sloper & Powell 1973). Comparison of nucleoli stained with ethanolic PTA and in normal material showed that ethanolic PTA stained the pars granulosa less heavily in relation to the other parts of the nucleolus than did the routine method (figures 43 and 44). The central filaments of cilia were densely stained by ethanolic PTA and in addition a short length of membrane undercoating was stained which extended under the plasma membrane of the cilium for approximately the first 0.25 μm and was slightly flared away from the central tubules at the base of the cilium (figure 45). A similar undercoating may also be seen in cilia stained by the normal method (figure 42). Preosmication of the blocks (method 2) partially inhibited the staining of the dense plates of the spine apparatus by ethanolic PTA (figure 41). As a control, unstained sections from unosmicated, unstained blocks were examined (method 3); none of the structures described above were naturally electron dense and therefore the density was due to staining by the ethanolic PTA.

Discussion

The motor cortex and area 3*b* of the somatic sensory cortex of the monkey are basically very similar to each other when seen under the electron microscope and are very similar to other areas of the neocortex described in various species (Colonnier 1968; Szentágothai 1969; Jones & Powell 1970*a–c*; Peters & Kaiserman-Abramof 1970; Garey 1971; Peters 1971).

Description of plate 6

Figure 21. Horizontal myelinated axon (a) in layer IV of the motor cortex giving off a vertical branch at a node of Ranvier. (Magn. × 9000.)

Figure 22. Horizontal unmyelinated axon (u) in layer IV of somatic sensory cortex which makes four 'en passage' synapses, two of which are clearly of the symmetrical type (two arrowheads). (Magn. × 18000.)

Figure 23. Bundles of parallel fibrils (f) in a dendrite (d). (Magn. × 29000.)

Figure 24. Similar bundle of fibrils in a dendrite cut in transverse section. (Magn. × 29000.)

Figure 25. Higher magnification of the fibrils of figure 24. (Magn. × 90000.)

The motor cortex has the same laminar pattern as these sensory cortical areas, although the deep layers are thicker, and the same features may be used to recognize the different laminae with the electron microscope. This degree of similarity is perhaps surprising considering the differences between the areas apparent in light microscopic sections stained by the Nissl method and in particular layer IV in the motor cortex is inconspicuous in such sections whereas in sensory cortical areas it is well developed. With the electron microscope the prominent presence of stellate cells studded with synapses in layer IV of sensory cortical areas has been emphasized but these are also prominent in layer IV of the motor cortex although they spread more into layers III and V; the overall impression given is that the components that make up the distinct layer IV of the sensory cortical areas have become more spread out and intermingled with the adjacent parts of layers III and V in the motor cortex but they are still present. The types of neuron present in the other laminae also appear qualitatively very similar in motor and somatic sensory cortices, although pyramids in particular were generally larger in the motor cortex. This qualitative impression of similarity was confirmed by a quantitative comparison of the neuronal populations in motor and somatic sensory cortices (Sloper 1973*a*; Sloper *et al.* 1979).

Synaptic relationships in the motor cortex resemble very closely those in sensory cortical areas. Dendritic spines are a prominent feature of the neuropil and receive the majority of synapses and the combinations of asymmetric and symmetrical synapses they receive are the same as in sensory areas. In particular symmetrical axon terminals were never found to give the only synapse on to a dendritic spine although they do so on to spines on axon initial segments (Sloper & Powell 1973) and probably also on to those on pyramidal somata. As in sensory areas, the majority of axon terminals in the motor cortex are small and fairly dark with spherical vesicles and asymmetric membrane thickenings; a minority are slightly larger and paler and have flattened vesicles with symmetrical membrane specializations. Jones & Powell (1970*a*) described large pale axon terminals with round vesicles and asymmetric thickenings in layers IV and I of the somatic sensory cortex and thought that these represented the terminals of the thalamo-cortical afferents. Similar terminals are prominent in layer IV of both the motor and somatic sensory cortices of the monkey and correspond in distribution to the thalamo-cortical projection in this species. The feature of early degenerating thalamo-cortical terminals in experimental studies of these areas also correspond to those of these terminals (Sloper 1973*b*). Occasional axon terminals containing large dense-cored vesicles were identified by Lund & Lund (1970) in the visual cortex of the rat. Similar terminals are occasionally found in the motor cortex and their appearance resembles that of terminals in the neocortex which take up 5-hydroxytryptamine (Descarries, Beaudet & Watkins 1975) and so these terminals may be part of the diffuse aminergic projection to the neocortex.

The differences that were apparent between the motor and somatic sensory cortices were mainly the same as those seen with the light microscope. There was a clear difference in the fibre plexus of layer I of the two areas seen by both light and electron microscopy and the greater number of fibres in the motor cortex is considerably more than can be accounted for simply by the greater thickness of layer I there. The origin of this fibre plexus is unknown but following lesions involving layer I its fibres degenerate up to 5 mm from the lesion and this degeneration crosses architectonic boundaries, unlike that of other fibre systems (Jones & Powell 1969*a*; Fisken, Garey & Powell 1975). Cells from deeper layers of the cortex, particularly layers V and VI, are known to project to layer I (Szentágothai 1964) and this plexus may

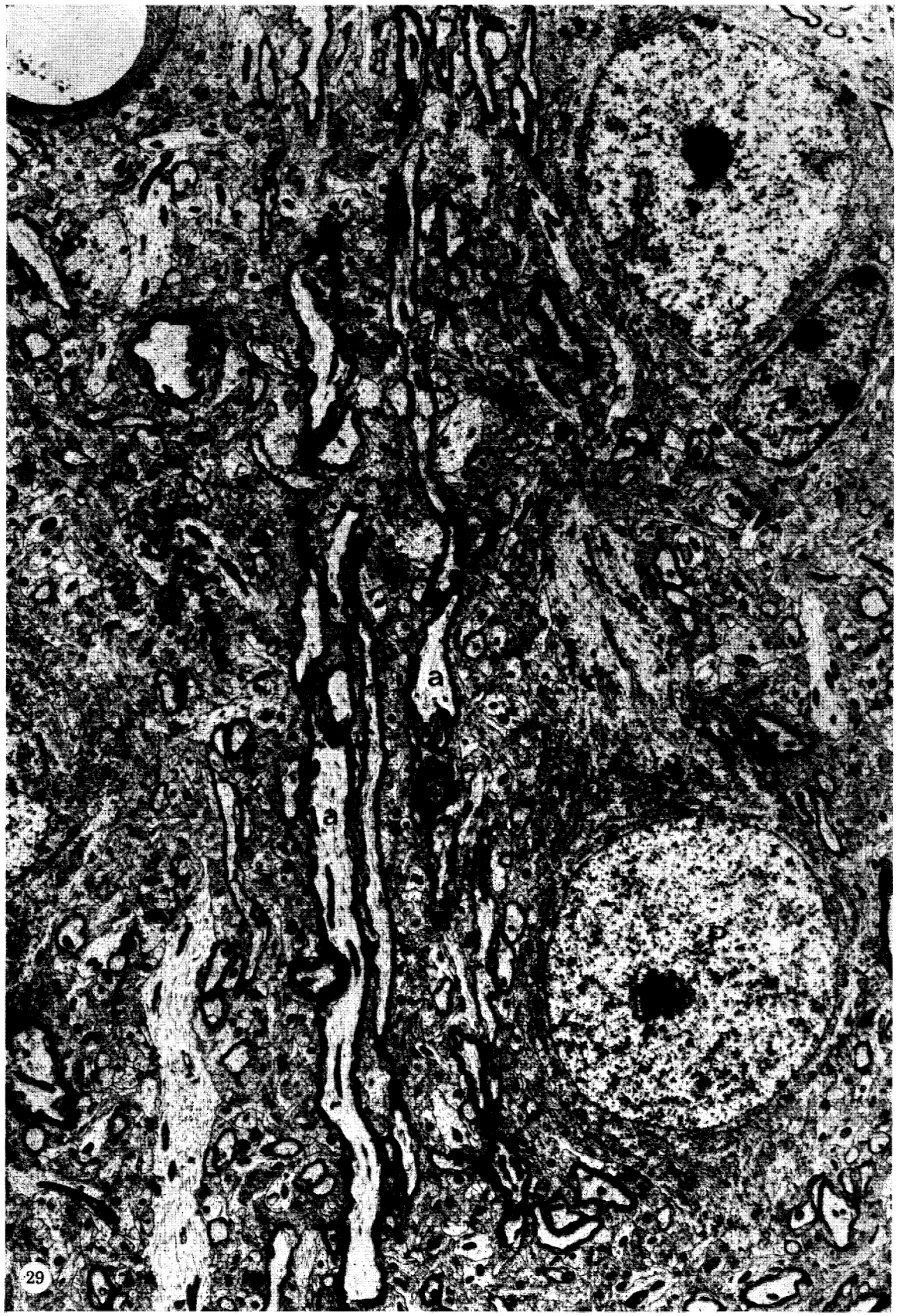


FIGURE 29. Layer V of motor cortex showing a group of myelinated axons (a) running vertically beside a pyramidal cell soma (P). The surface of the cortex is at the top of the figure. (Magn. × 3500.) N, neuronal cell soma; d, dendrite; G, glial cell.

(*Facing p.* 134)

Description of plate 9

Figure 30. Two subsurface cisternae (sc) in a large dendrite (d), both of which are closely related to the same mitochondrion. Note that both come into close contact with axonal profiles (a and t) containing flattened vesicles. Profile t also makes a symmetrical synapse on to the dendrite. (Magn. × 29 000.)

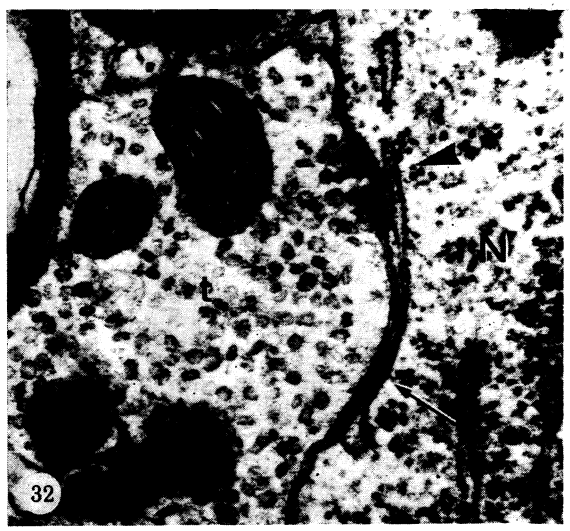
Figure 31. Higher magnification of part of figure 30 showing the subsurface cistern coming into close contact with the non-synaptic part of an axon terminal (large arrowhead) which is making a symmetrical synapse on to the dendrite. Note the way the cistern separates from the dendritic membrane opposite the synaptic membrane specialization and the lack of synaptic vesicles in the axon terminal opposite the cistern. Note also the electron dense material in the extracellular cleft between the axon terminal and dendritic plasma membrane opposite the cistern; there is no similar extracellular material where the cistern is opposite the adjacent profiles (arrows). (Magn. × 67 000.)

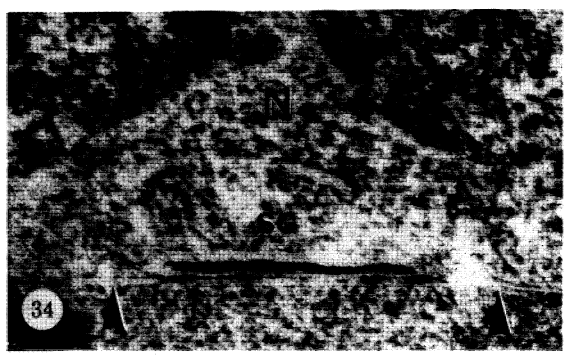
Figure 32. Subsurface cistern in a neuronal cell soma (N). The lower part of the cistern (arrowed) shows the normal appearance of a cistern opposed to the non-synaptic part of a symmetrical type axon terminal (t), whereas the upper part of the cistern (large arrowhead) appears to be partially attached to a synaptic membrane complex, a rare finding. (Magn. × 53 000.)

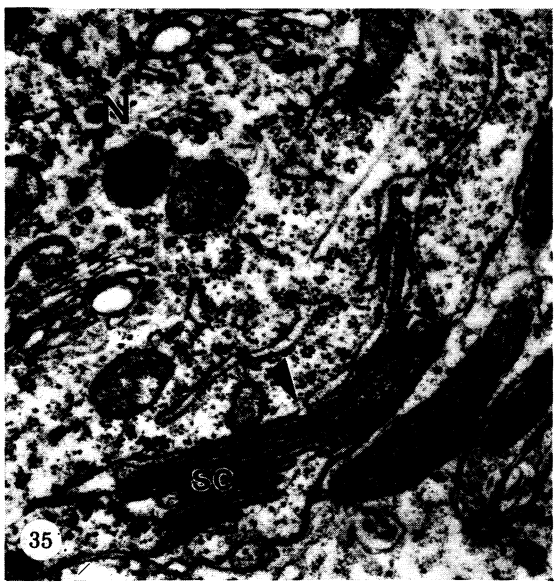
Figure 33. Higher magnification of the subsurface cistern shown in figure 32. Note the dense material both between the subsurface cistern and the neuronal plasma membrane and in the extracellular cleft between the neuronal plasma membrane and that of the axon terminal. This figure also illustrates the close similarity between the membrane specializations associated with these subsurface cisternae and those of a symmetrical synapse. (Magn. × 92 000.)

Figure 34. Subsurface cistern in the soma of a small neuron stained with E-PTA. The position of the unstained cell membrane is indicated by the large arrowhead and the edge of the nucleus(n) is shown. (Magn. × 47 000.)

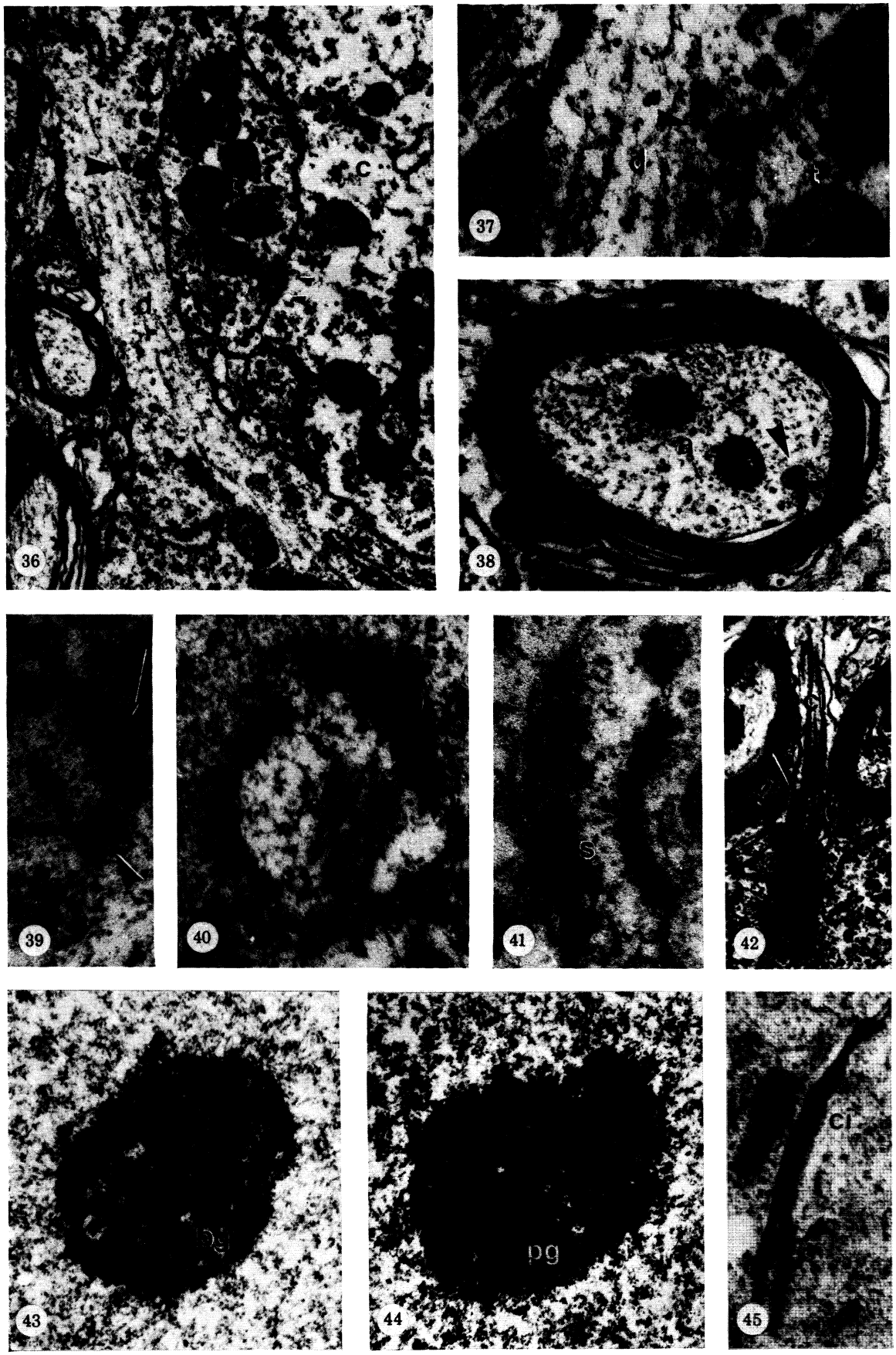
Figure 35. Complex subsurface cistern in a neuronal cell soma. Note the difference in appearance of the stacks of cisternae to the left and right of the large arrowhead. (Magn. × 29 000.)







FIGURES 30–35. For description see opposite.



FIGURES 36–45. For description see opposite.

represent their axons. However, although the deep layers are more developed in the motor cortex, the number of cells through the depth of the cortex is no greater in motor than in somatic sensory cortex so this may not account for the greater number of axons in the motor cortex plexus. It might also be expected that the cells in the motor cortex would be larger and give rise to axons of greater diameter, but the size distributions of axons in the two plexuses are very similar. There are however more synapses per cell in the motor cortex (Cragg 1967) and it may be that the difference in these fibre plexuses is a reflection of the more extensive axonal arborizations that this implies. There is also evidence that this plexus of fibres in layer I may arise in part from non-specific nuclei in the thalamus (Jones 1975) and it is possible that the difference in the density of the fibre plexuses reflects differing degrees of development of these thalamic nuclei in relation to different parts of the neocortex. The fact that this fibre plexus crosses architectonic boundaries would tend to support this suggestion.

Bundles of apical dendrites have been described in layer IV of both visual and somatic sensory cortices (Fifkova 1970; Peters & Walsh 1972) and the appearances described are very similar to those in the motor cortex. The distribution of apical dendrite bundles in the depth of the motor cortex corresponds to that of the thalamo-cortical afferents and degenerating thalamo-cortical axon terminals are found associated with the apical dendrites more frequently than in the neuropil between the bundles (Sloper 1973*b*). Apical dendrites in layer II are evenly spread but pyramids in layers II and III generally occur in groups and the occurrence of deeper apical dendrites in bundles may be a consequence of their having to pass upwards between these more superficial cell groups. Whether the bundles of apical dendrites or the cell groups are simply a natural consequence of the three-dimensional packing of the cortex or whether they have a particular functional significance remains to be determined.

Description of plate 10

Figure 36. Dendrite (d) with a coated pit (arrowhead) apparently engulfing a portion of the adjacent axon terminal (t) which makes a synapse on to an adjacent cell soma (c). (Magn. × 29000.)

Figure 37. Higher power of figure 36 showing the cytoplasm of the axon terminal extending into the coated pit (arrowhead) and apparently being pinched off by the dendrite. (Magn. × 67000.)

Figure 38. Coated pit (arrowhead) in continuity with the plasma membrane of a myelinated axon (a) inside its myelin sheath and containing electron dense material. (Magn. × 45000.)

Figure 39. Synaptic membrane complex (arrow), spine apparatus (s) and desmosome (arrowhead) stained with ethanolic PTA. Note the presynaptic dense projections (small arrow) of the presynaptic membrane complex the unstained plasma membranes of both axon terminal and spine and the dense material both in the synaptic cleft and beneath the postsynaptic membrane. In contrast to the synaptic complex the desmosome has no presynaptic projections. (Magn. × 67000.)

Figure 40. Spine apparatus stained with ethanolic PTA in a spine which is largely surrounded by a synaptic membrane complex. (Magn. × 53000.)

Figure 41. Spine and spine apparatus (s) stained with PTA *following* pre-osmification. Note that the plasma membranes are stained and that the dark staining of the dense plates of the spine apparatus and the synaptic membrane complex is inhibited. (Magn. × 53000.)

Figure 42. Cilium (ci) in a neuron prepared conventionally. Note the undercoating beneath the cell membrane where it extends up the shaft of the cilium (arrowhead). (Magn. × 29000.)

Figures 43 and 44. Nucleoli of neurons stained with ethanolic PTA and normal techniques respectively. Note the paler staining of the pars granulosa (pg) in relation to the other parts of the nucleolus in the nucleolus stained with ethanolic PTA (figure 43) compared with that stained normally. (Magn. × 24000 and × 21000 respectively.)

Figure 45. Cilium stained with ethanolic PTA. Note the dark staining of the membrane undercoating in the initial part of the cilium (arrowhead) (cf. figure 42). (Magn. × 29000.)

Spines are a dominant feature of the synaptic organization of the neocortex and their possible significance has been discussed by several authors (e.g. Jones & Powell 1969*b*; Diamond, Gray & Yasargil 1970). In this study it was not infrequent, particularly in serial sections, to find that a single axon terminal of either the asymmetric or symmetrical type made a synapse on to a spine and also on to the shaft of the dendrite giving rise to that spine, usually by way of a separate membrane specialization. A similar situation also occurs in the thalamus (Harding & Powell 1977). It would be difficult to determine whether this arrangement has any particular functional significance of itself but it must be taken into account in considering the possible functions of spines. In particular it is difficult to see how a spine in this situation could serve to isolate its input from the dendritic shaft when the same axon terminal also makes a synapse on to the shaft directly, although possibly it could do so for another terminal with a synapse on to the same spine.

Subsurface cisternae are a well recognized feature of neurons and have a variety of structures of differing complexities (Rosenbluth 1962*b*; Siegesmund 1968; Jones & Powell 1970*a*). The observations made here relate to the type of cistern having a single dense area of membrane fusion which is often seen to open out into a sac of endoplasmic reticulum. Observations of two different kinds have led to the conclusion that cisternae of this type are related to symmetrical axon terminals. First, where the dense membranes of these cisternae are closely apposed to the plasma membrane of the cell there is a specific membrane complex consisting of thickening of the membranes of both the soma and the symmetrical axon terminal and there is dense granular material both between the membranes and between the cistern and the cell membrane. Although dense material has been described between the cistern and the membrane of the soma (Siegesmund 1968) opposite other types of profile, the full membrane complex has only been observed in association with symmetrical axon terminals. The second line of evidence is the statistical association of cisternae and symmetrical terminals. The fused membranes of these cisternae may extend beyond the region opposite the symmetrical terminal itself so in single sections they may appear to be only opposite other profiles. It is also possible that some cisternae with this type of structure are not related to symmetrical terminals although they may either have been or would have become so. To overcome these difficulties a comparison was made of the relationship to cisternae of asymmetric and symmetrical axon terminals making synapses on to large stellate cell somata, a site where both types of terminal are present in approximately equal numbers. This showed clearly that the cisternae were specifically related to symmetrical rather than asymmetric terminals. These subsurface cisternae therefore have both a statistical and a specific structural relationship to symmetrical axon terminals.

The exact relationship of the cisternae to symmetrical axon terminals is of importance in that the cistern does not occur beneath the synaptic complex but opposite a non-synaptic part of the terminal. Although such a cistern may be related to a terminal without a synapse being present in the section the possibility that in such cases the terminal makes a synapse on to the cell or dendrite in an adjacent section has not been excluded. The position of the cistern at a site away from the synaptic membrane complex itself suggests that its function may not be directly related to synaptic transmission. Rosenbluth (1962*b*) has suggested that subsurface cisternae in general may be concerned with the transport of substances to and from the plasma membrane and the association of mitochondria with cisternae suggests that they perform an active metabolic role. In relation to these symmetrical axon terminals it is

possible that they are concerned in the transport of some trophic factor between the pre- and postsynaptic structures and the linking of synaptic activity to the metabolism and growth of the neuron. However, when fully developed the membrane complex associated with these cisternae differs from a symmetrical synapse only in the presence of the cistern and the absence of a local aggregation of synaptic vesicles. In some examples the membrane specializations are less well developed and in a few they are absent; these factors, together with the relationship of the cisternae to the endoplasmic reticulum and mitochondria, suggest that these cisternae may be involved in the synthesis of new synaptic membrane complexes. The presence of a fully developed synaptic zone in addition in some examples is in no way against this suggestion since a characteristic feature of these symmetrical axon terminals in the neocortex is the frequent occurrence of more than one membrane complex between a single axon terminal and cell soma. In support of this suggestion subsurface cisternae are present early in development, both in Xenopus retinal ganglion cells (Grillo & Rosenbluth 1972) and in the neocortex of one day old rats (Siegesmund 1968); the monkeys used in this study were not fully mature and it would be of interest to compare them with very young and fully adult animals. It is therefore possible that, following apposition of a symmetrical type preterminal bouton to a cell soma, a subsurface cistern is induced in the soma at that site and this synthesizes or delivers the components which make up the synaptic membrane complex. It may also be of interest in this respect that the dense material of both cistern and synaptic complexes stains specifically with ethanolic PTA. It has been shown that subsurface cisternae are induced by the apposition of an isolated postsynaptic membrane thickening both in the olfactory bulb (Pinching & Powell 1972) and the neocortex (Sloper 1973*c*) but it is also possible that the cisternae are already present but inactive before the presence of symmetrical-type boutons; this could explain the cisternae found opposite other types of profile, particularly in young animals. Price & Powell (1970) noted the occurrence of similar cisternae in relation to reciprocal synapses in the olfactory bulb; although they described them as being related to the presynaptic component of the asymmetric synapse, these cisternae may also be considered to be postsynaptic to the symmetrical part of the reciprocal synapse which would make them analogous to those described here. Open sacs have also been described in spinal motoneurons beneath boutons containing flattened vesicles but these boutons appear to show no membrane specializations (Conradi 1969; McLaughlin 1972). Subsurface cisternae have, however, also been described in dorsal root ganglion and acoustic ganglion cell somata (Rosenbluth 1962*a*, *b*), both of which receive no axo-somatic synapses and the more complex types of cistern in the cortex are not related to synapses. However there is no reason to expect all subsurface cisternae to perform the same function, particularly in view of differences in their structure, and it may well be that their function in relation to these synapses is a specific example of a more general function.

The relationship of the cisternal organ to symmetrical axon terminals making synapses on to axon initial segments appears to be the same as that of the subsurface cistern to them in the cell soma (Sloper 1973*c*). The cisternal organ comes into close apposition with the plasma membrane of the initial segment opposite the non-synaptic parts of symmetrical terminals and the membrane in the region of apposition may show the same specializations. Both cisternal organs and subsurface cisternae are also structurally similar, consisting of membranous sacs and dense regions which in both cases stain specifically with ethanolic-PTA (Sloper & Powell 1973). The spine apparatus also consists of dense plates which stain specifically with

ethanolic-PTA and which alternate with membranous sacs; these are connected to the reticulum of the cell (Peters & Kaiserman-Abramof 1970) and the relationship of the spine apparatus to Type I or asymmetric synapses both on to spines and the shafts of dendrites is well known (Gray 1959; Jones & Powell 1970*a*). There is thus a remarkable parallelism between these three organelles in both structure and relationships and it therefore seems reasonable to suppose that they may perform similar functions in relation to the different types of synapse and different sites.

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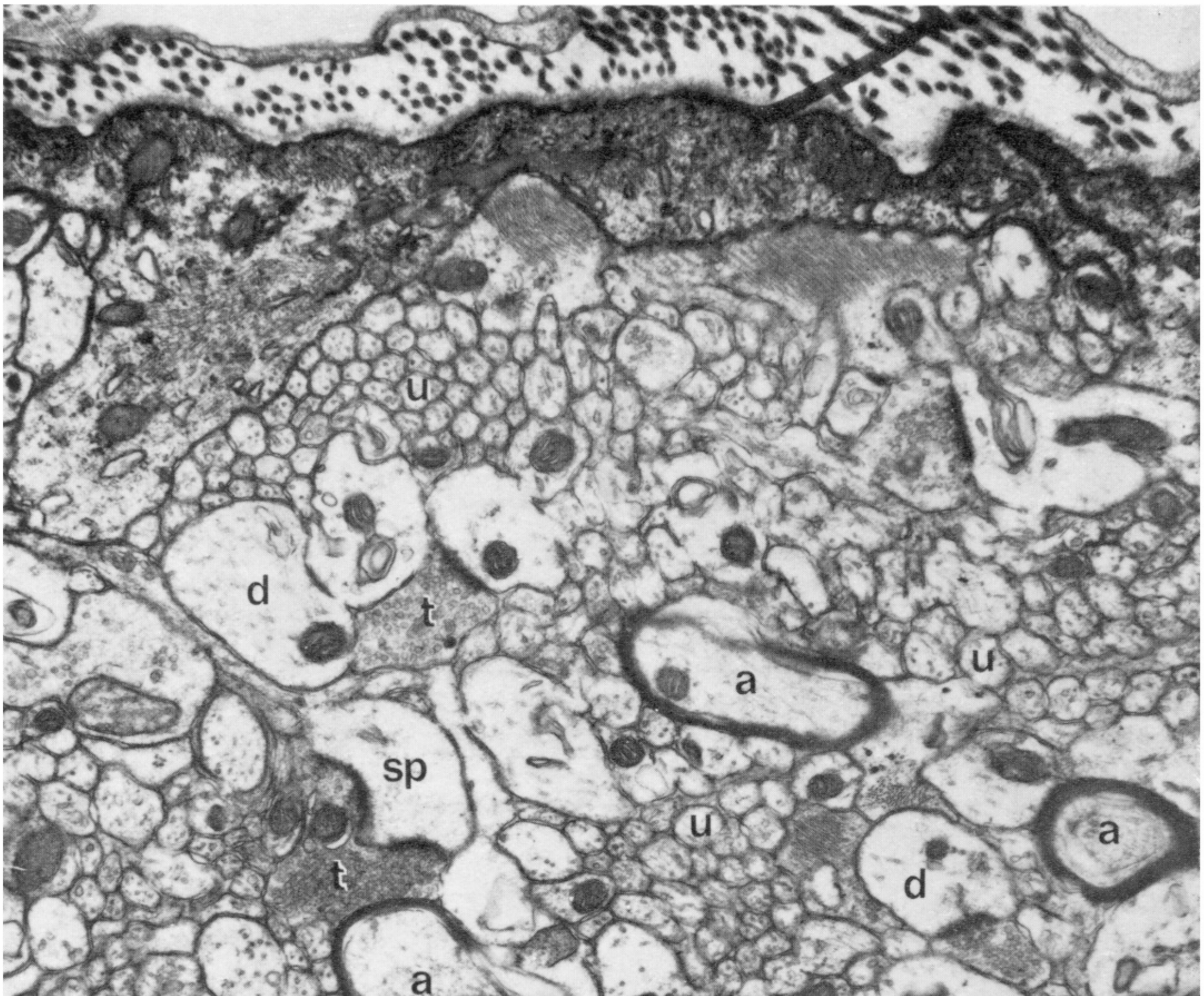


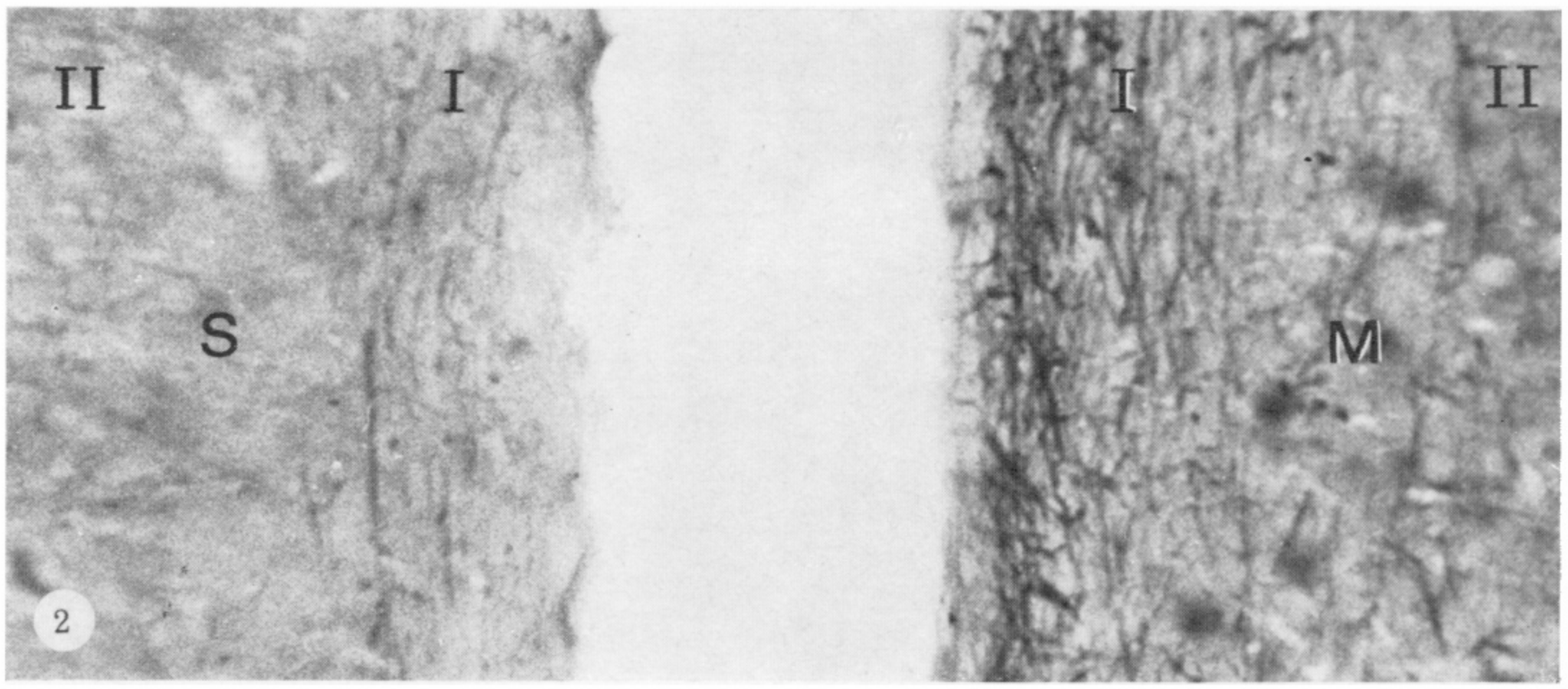
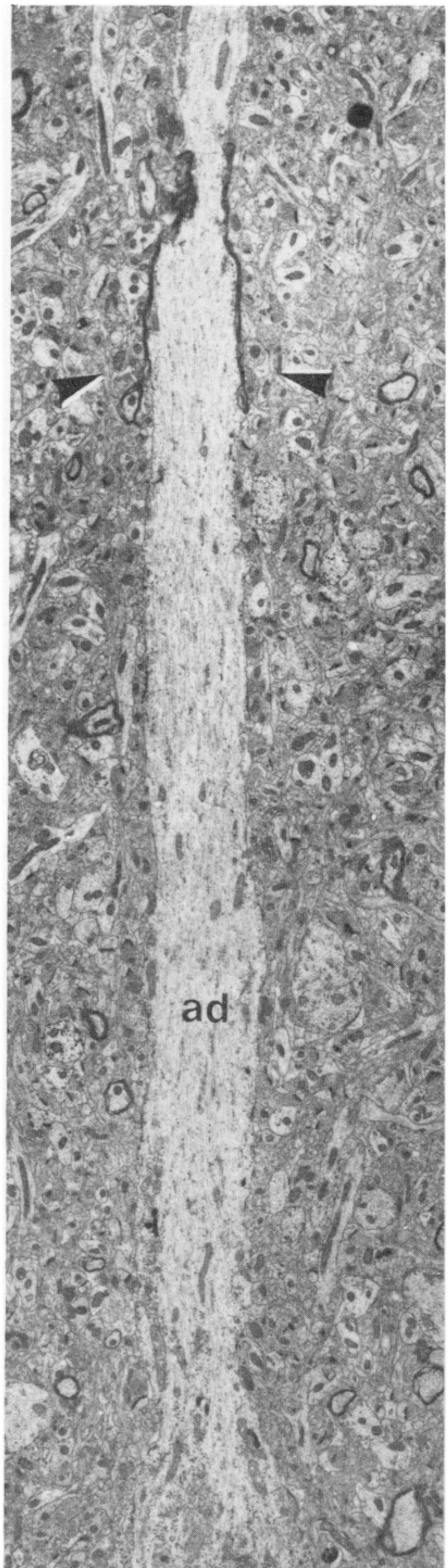


FIGURE 1. Electron micrograph showing the superficial part of layer I of the motor cortex with the pial surface at the top. Note the myelinated axons (a) which form part of the plexus of myelinated axons in this layer. There are also many small unmyelinated axons (u) in addition to a spine (sp), small dendrites (d) and axon terminals (t). (Magn. × 20000.)

FIGURE 2. Light micrograph showing the superficial parts of both somatic sensory cortex (area 3*b*) (S) and motor cortex (M) in the walls of the central sulcus, stained by Weil's method to show myelinated axons. Note the marked difference in density of staining of the fibre plexuses in the two cortical areas which were immediately adjacent on the same section as shown. (Magn. × 150.)



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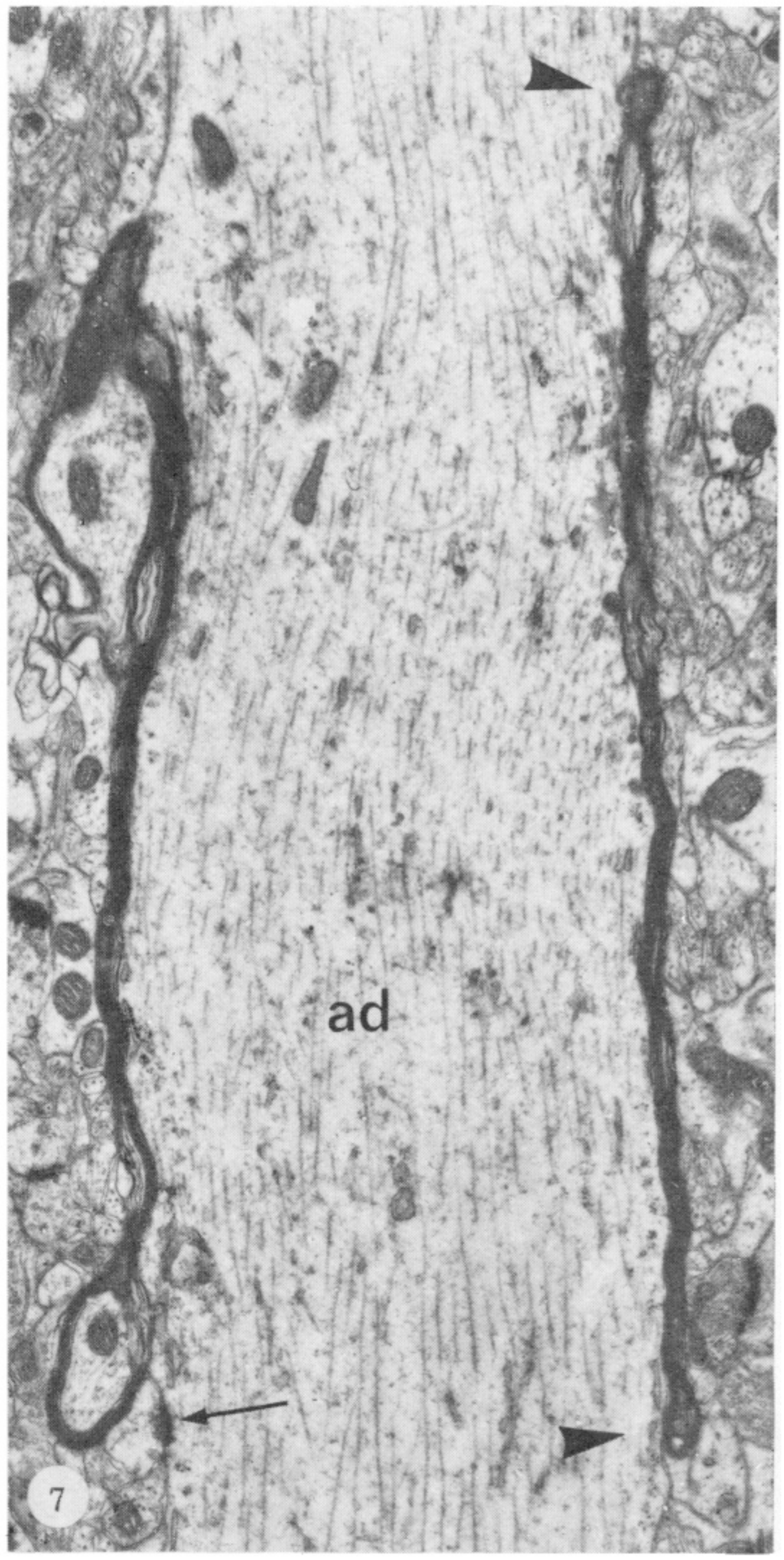

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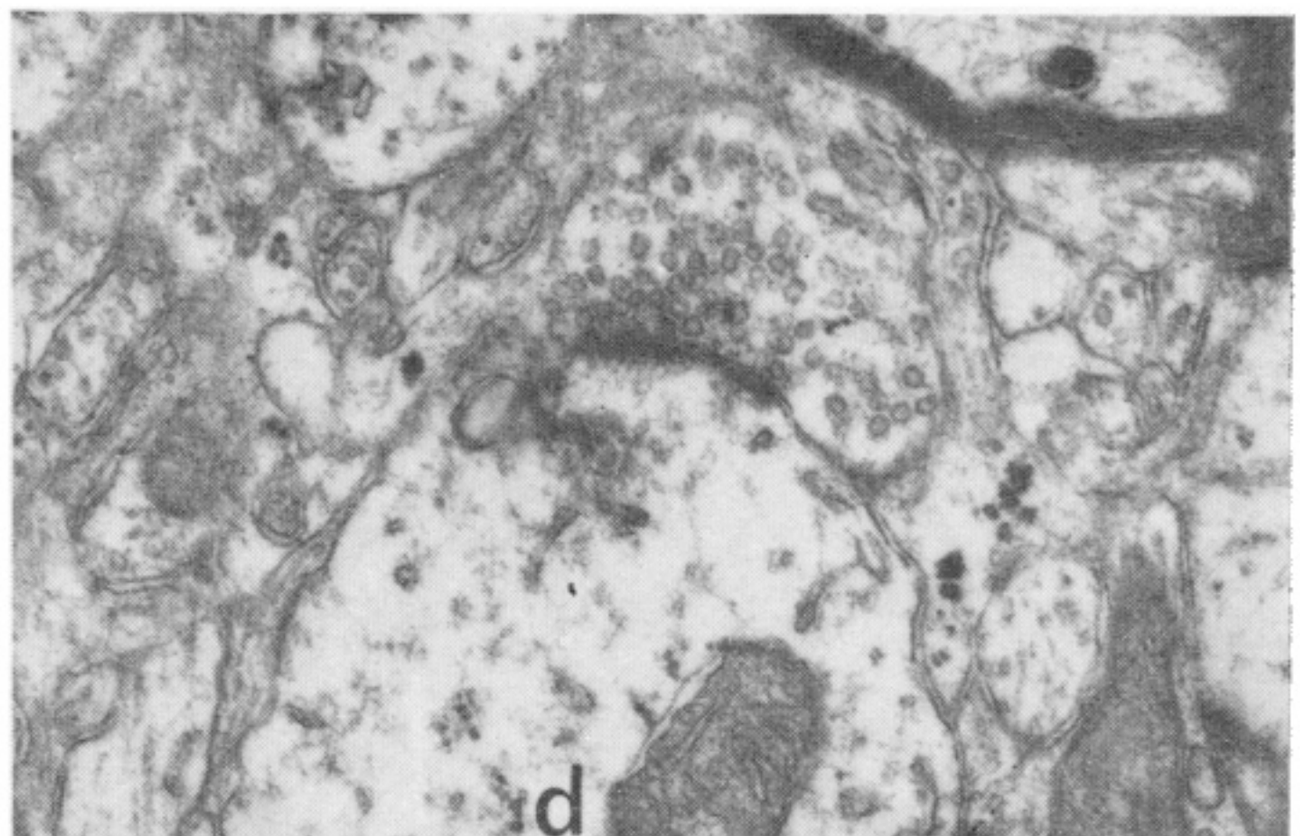

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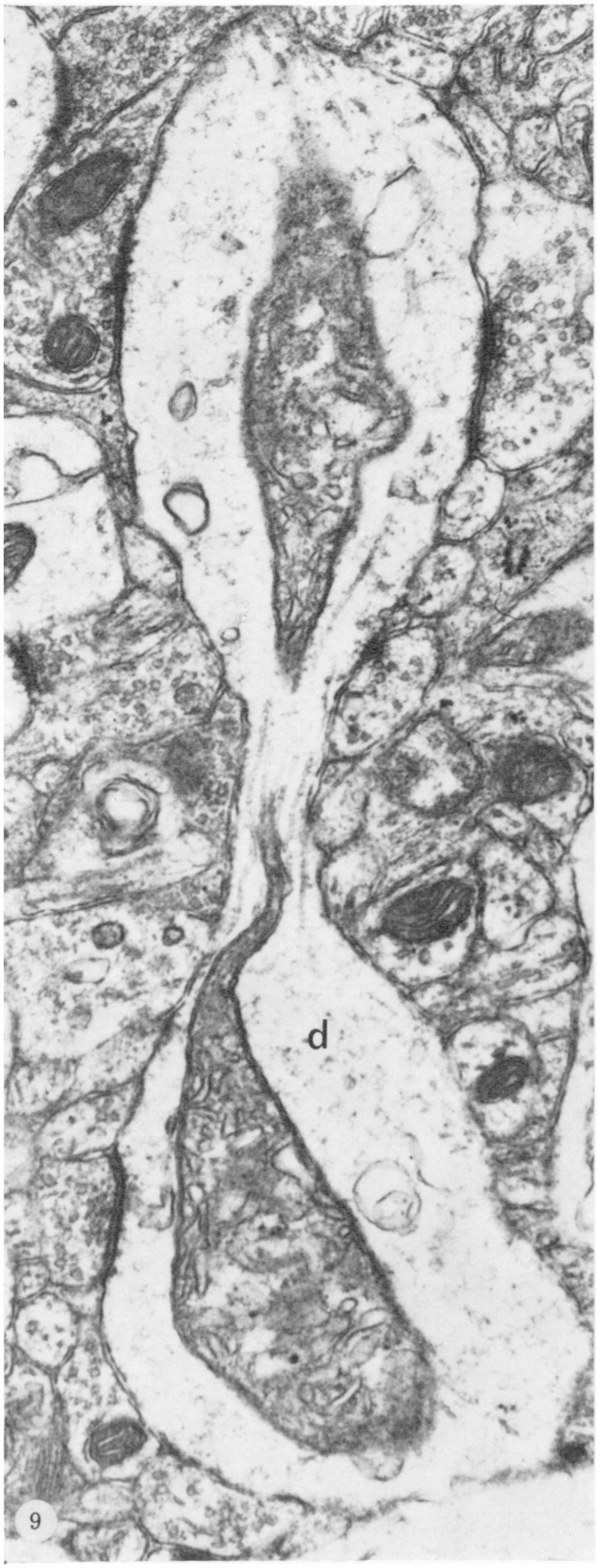
FIGURES 6–8. For description see opposite.



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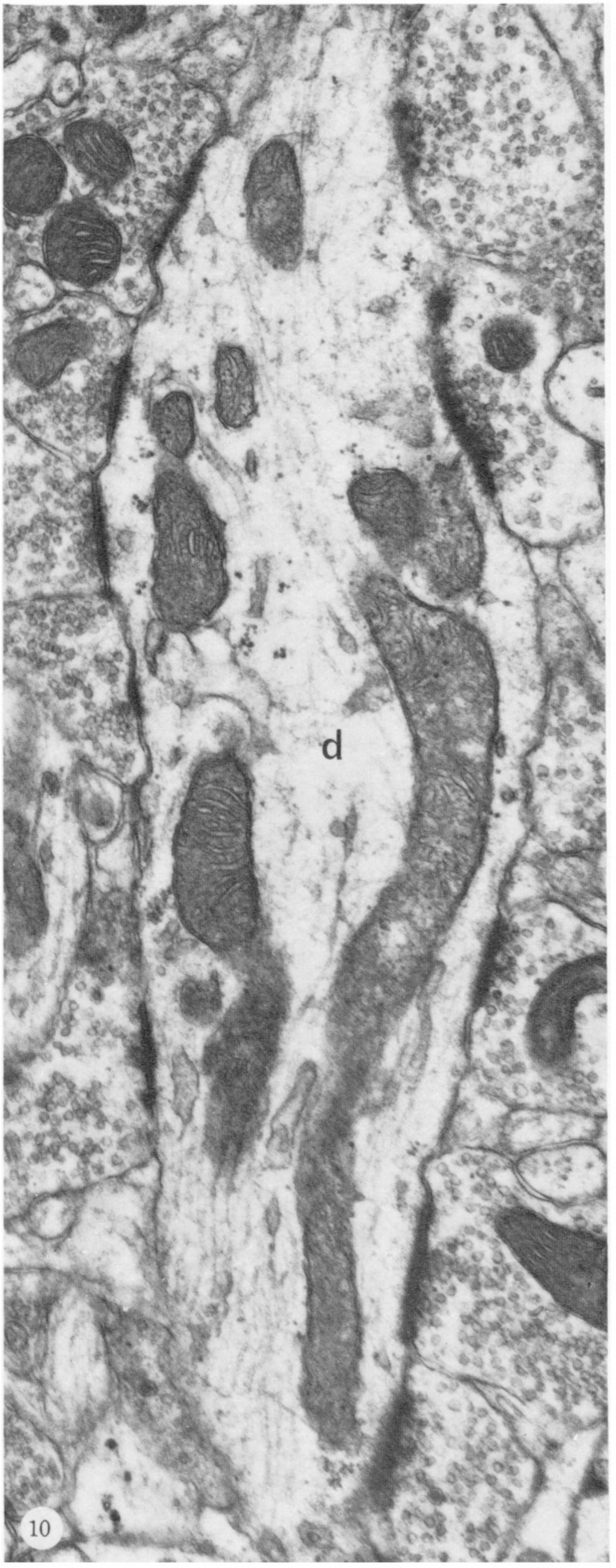

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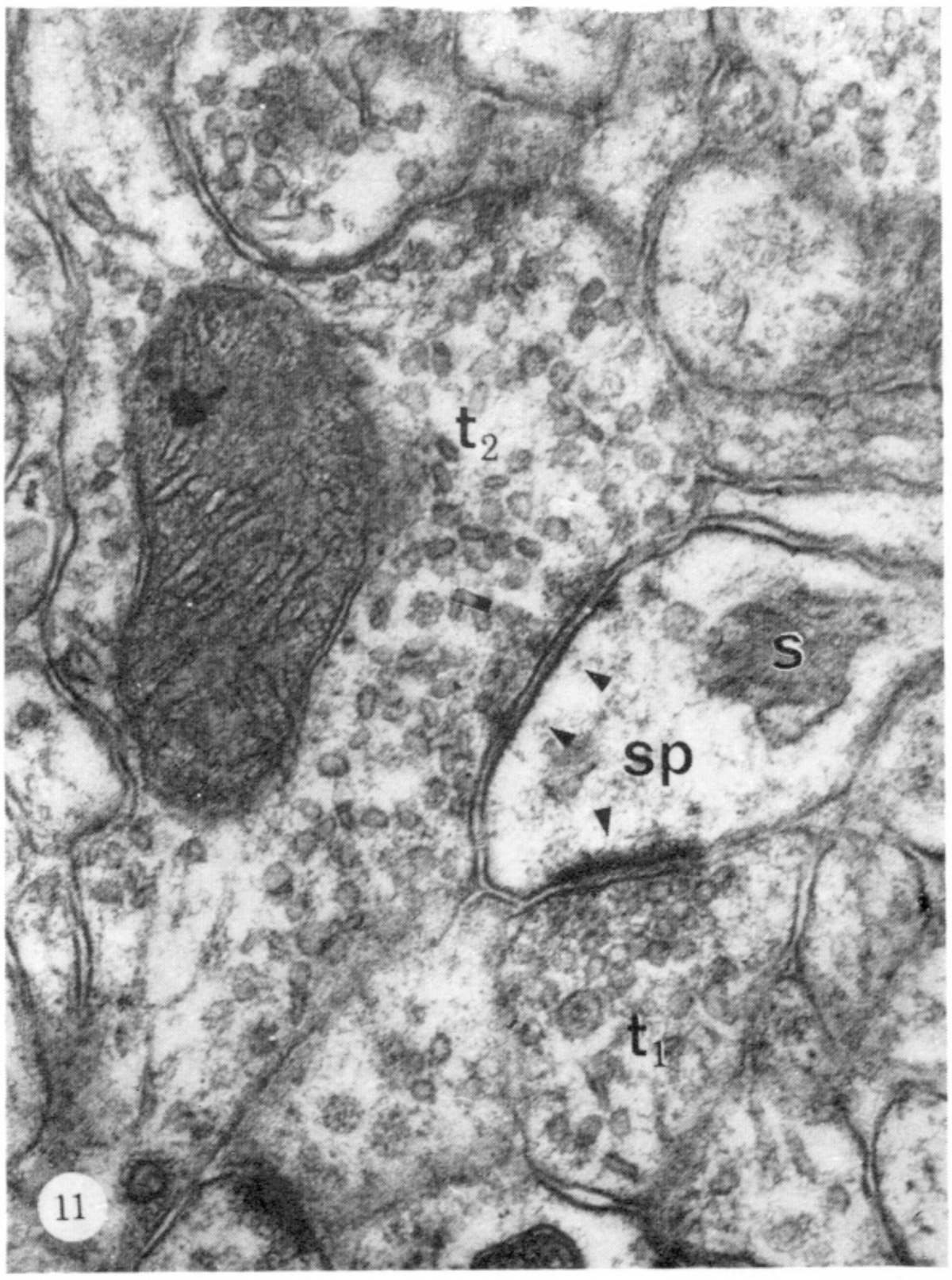
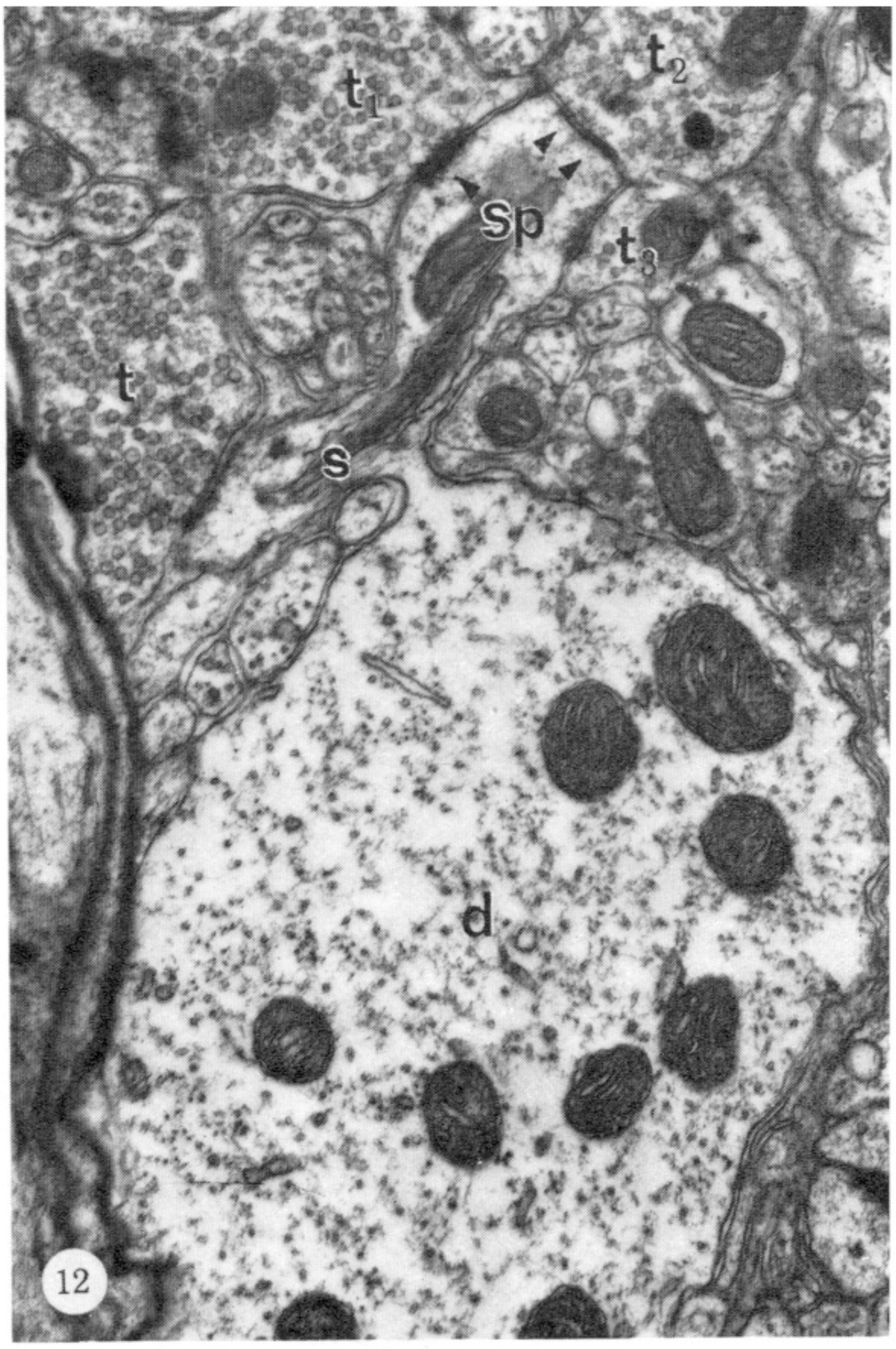
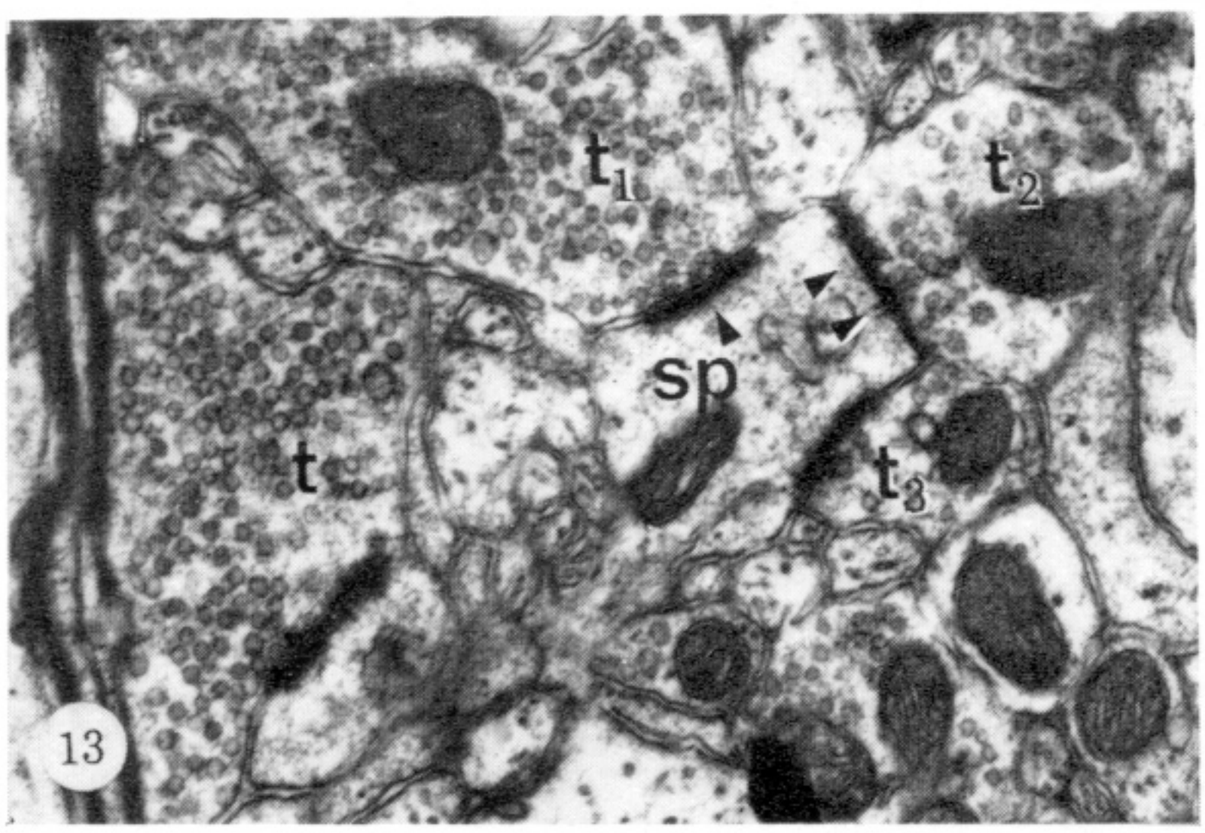
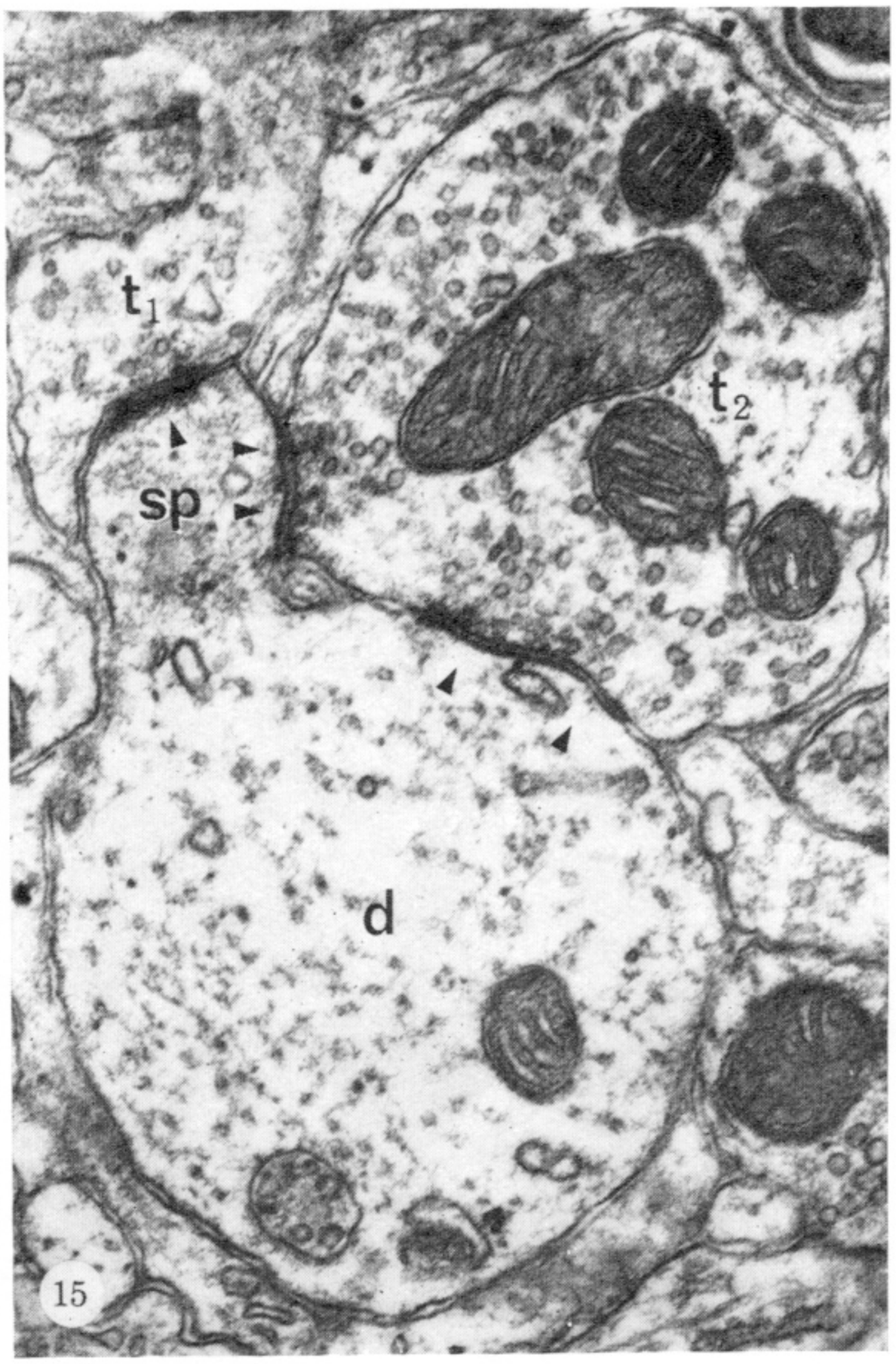
FIGURE 9. Example of the type of varicose dendrite (d) having a markedly varicose shape, clear cytoplasm and a moderate density of synapses. Layer I of motor cortex. (Magn. × 32000.)

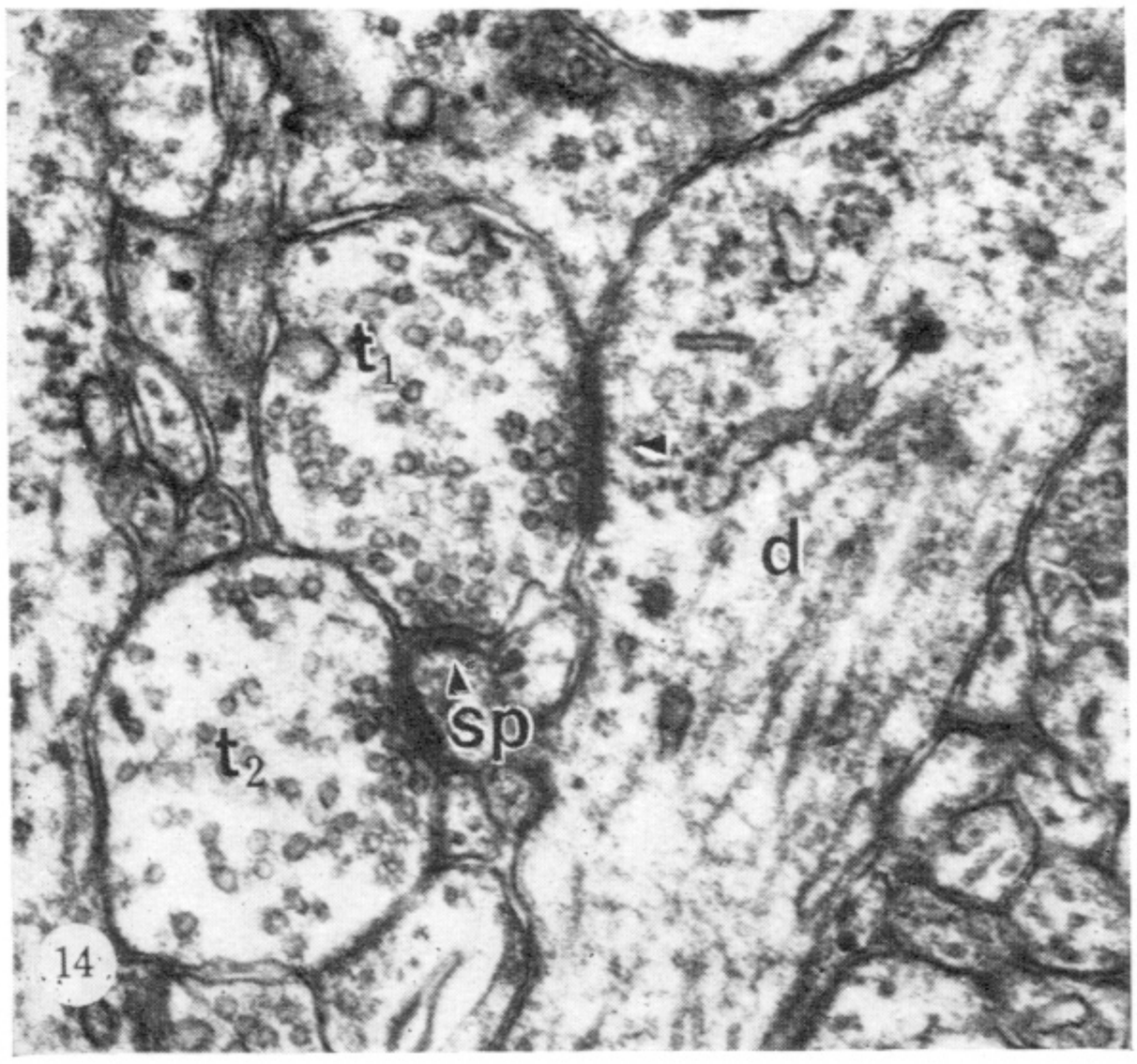
FIGURE 10. Example of the type of varicose dendrite having a less obviously varicose shape but containing a high density of organelles and receiving many synapses. Layer III of motor cortex. (Magn. × 29000.)



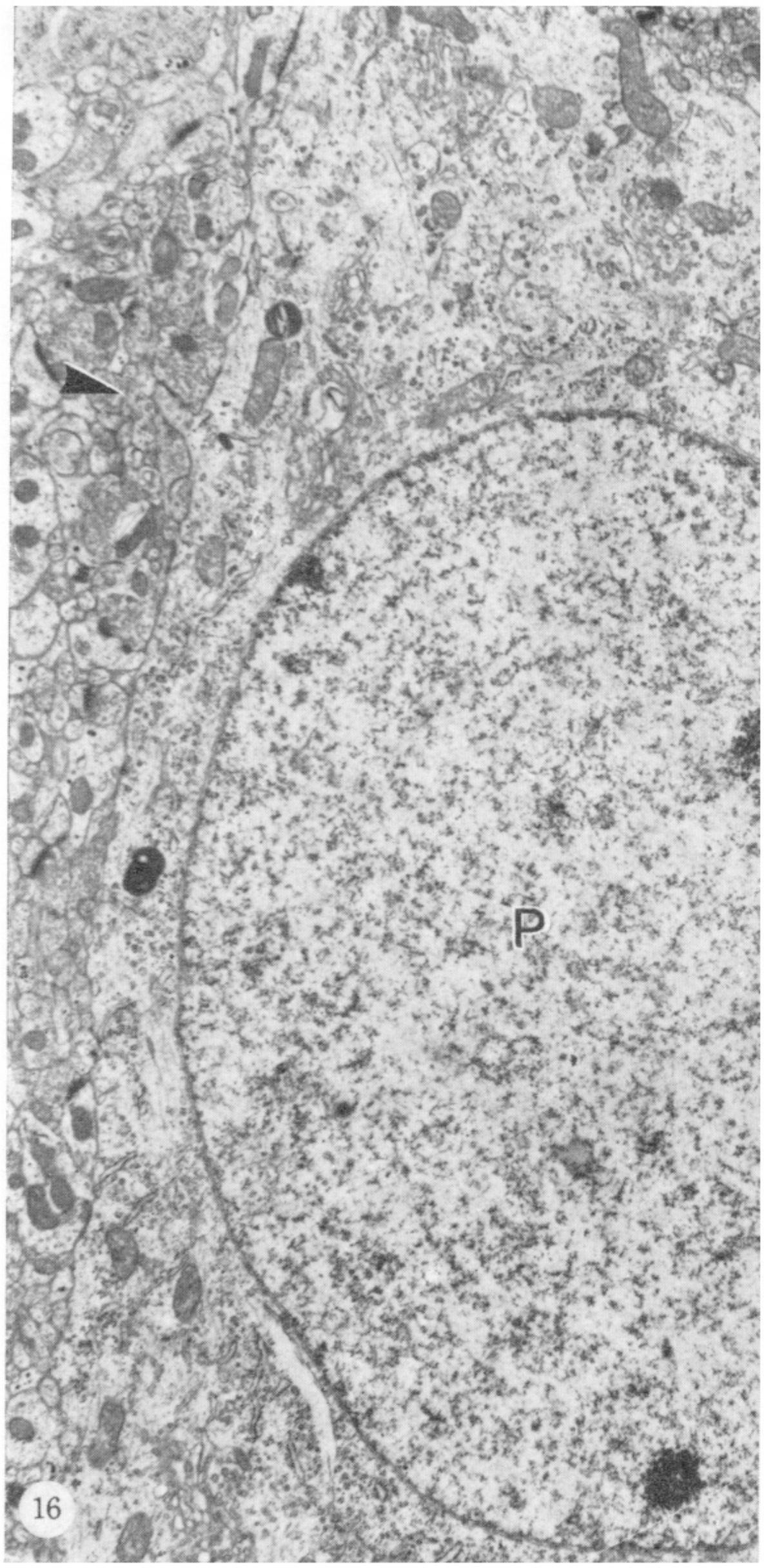








FIGURES 11–15. For description see opposite.



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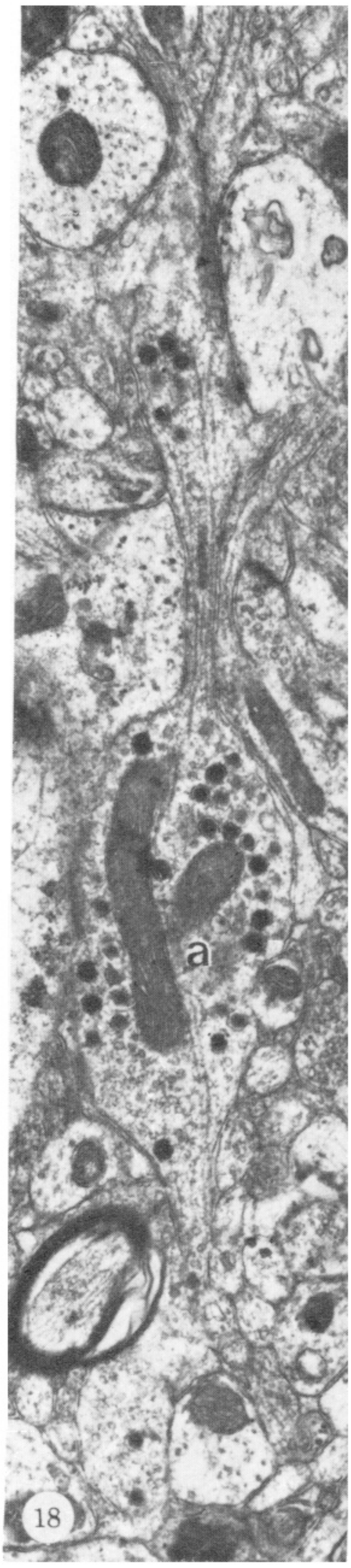

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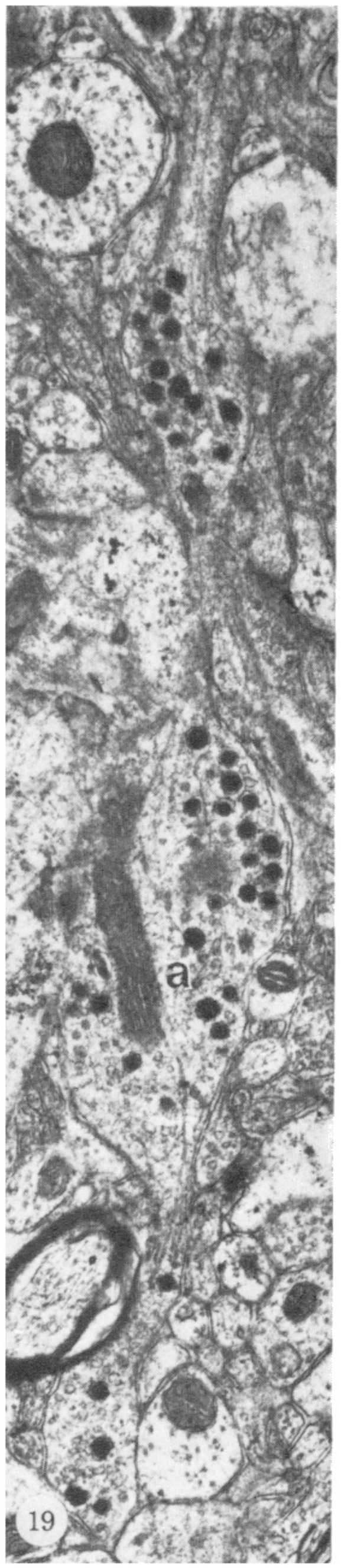

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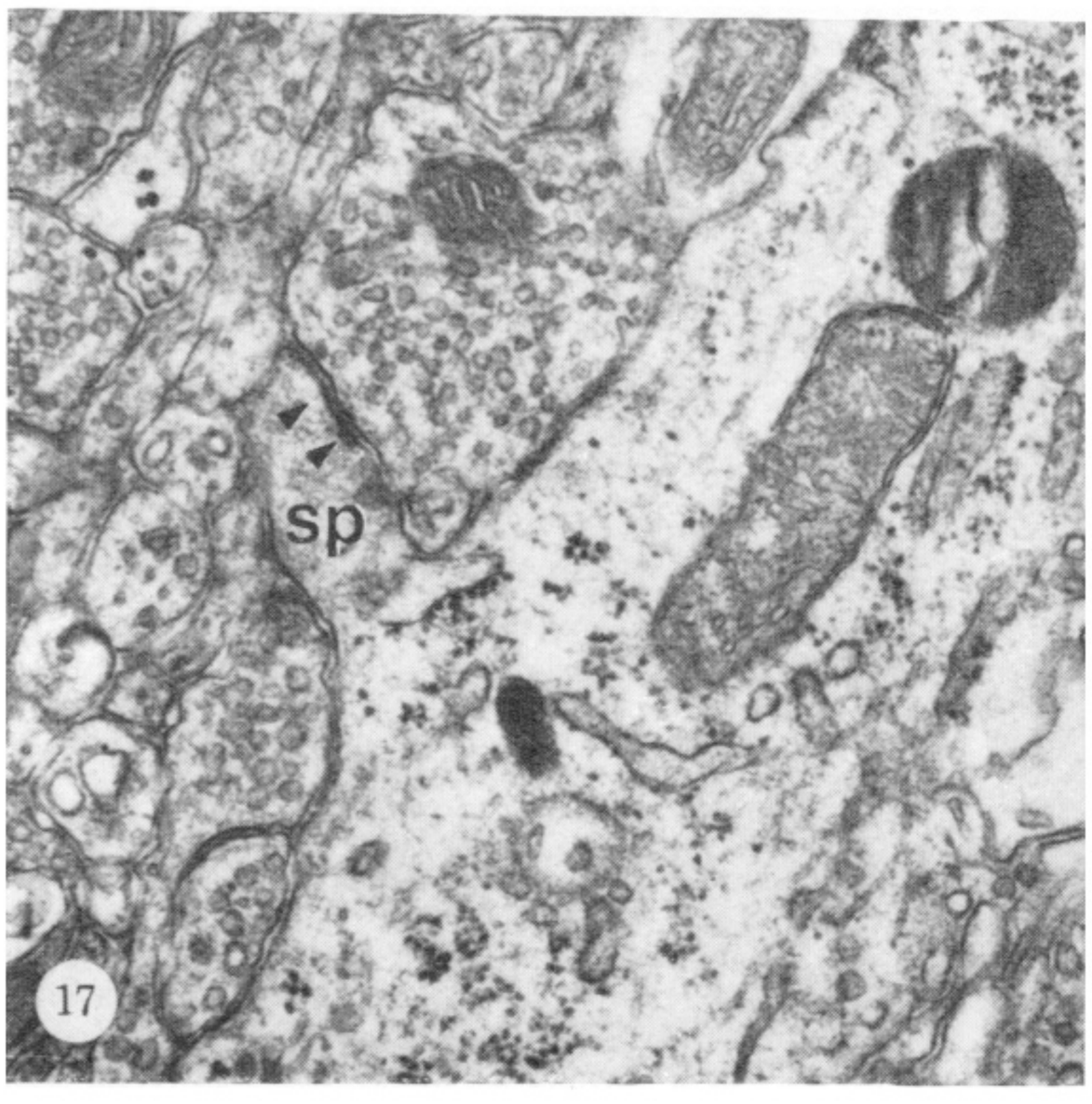

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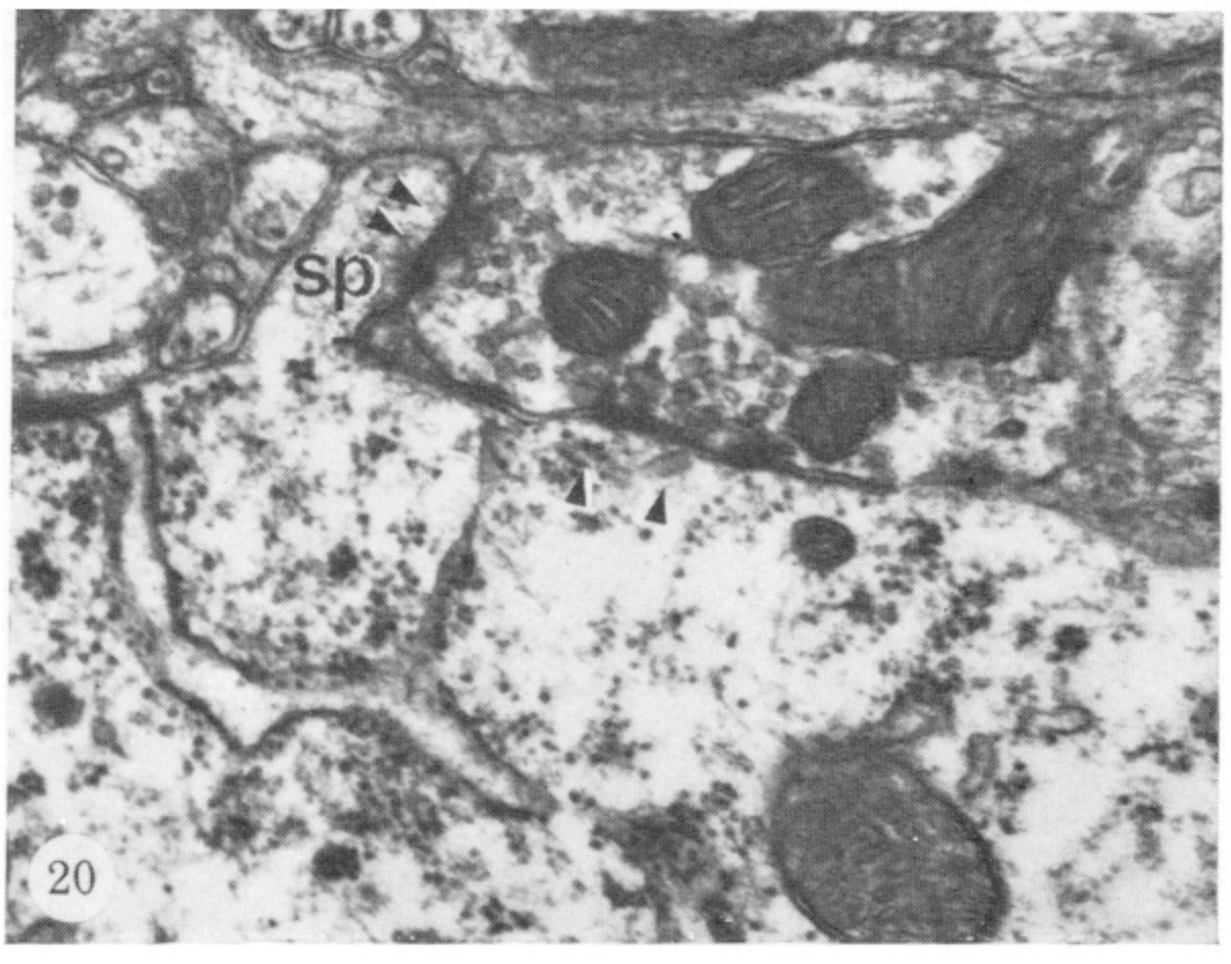

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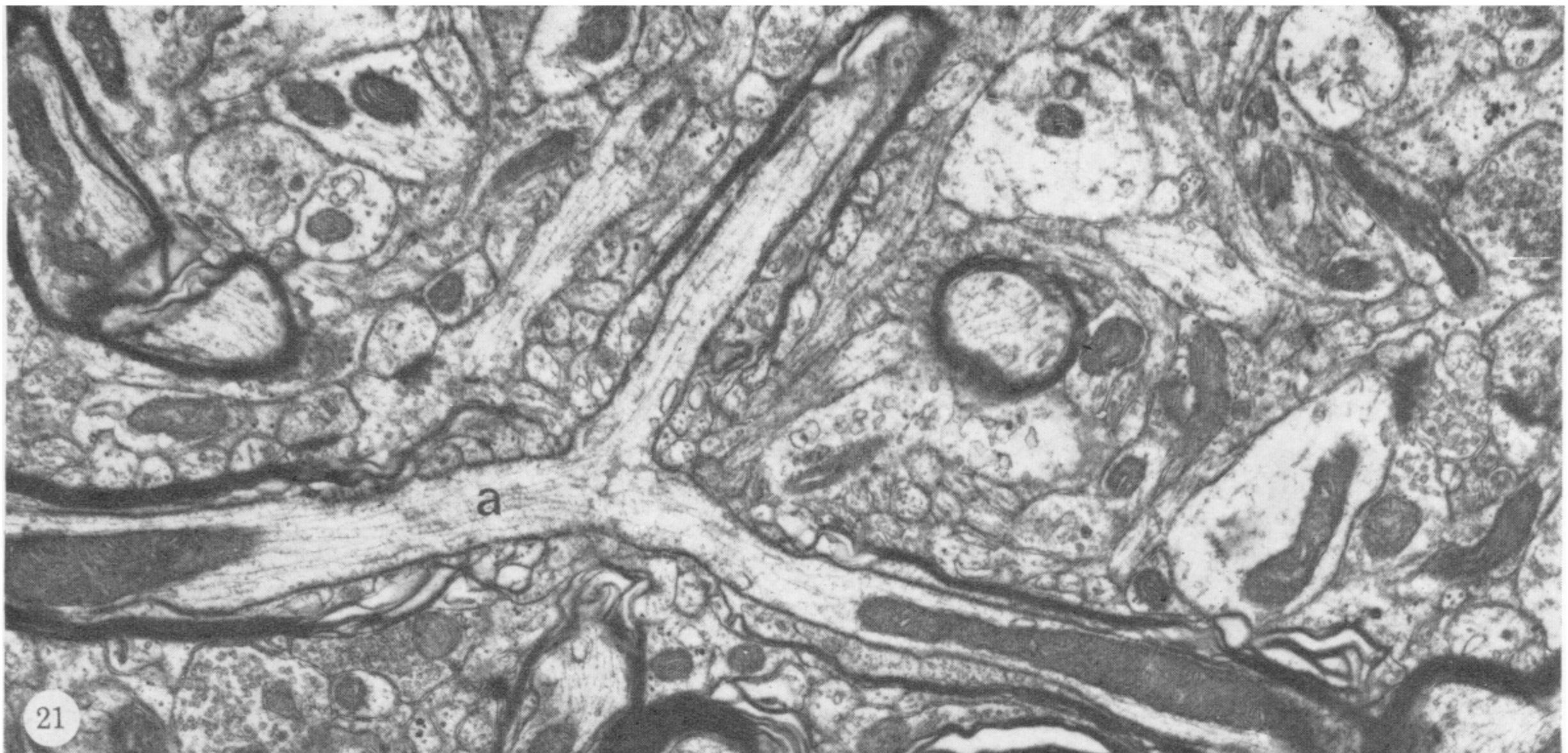
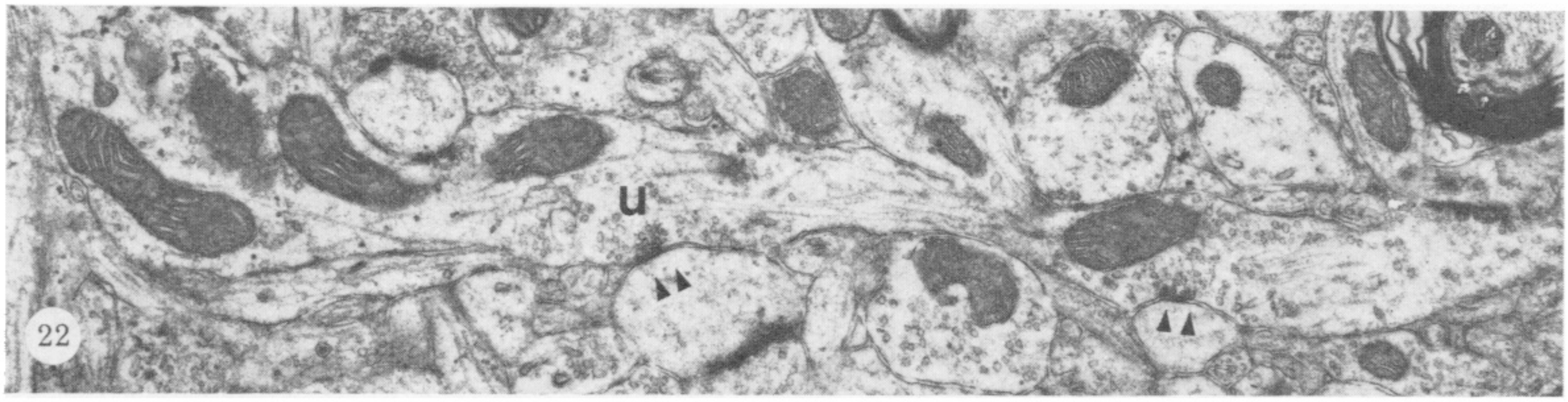
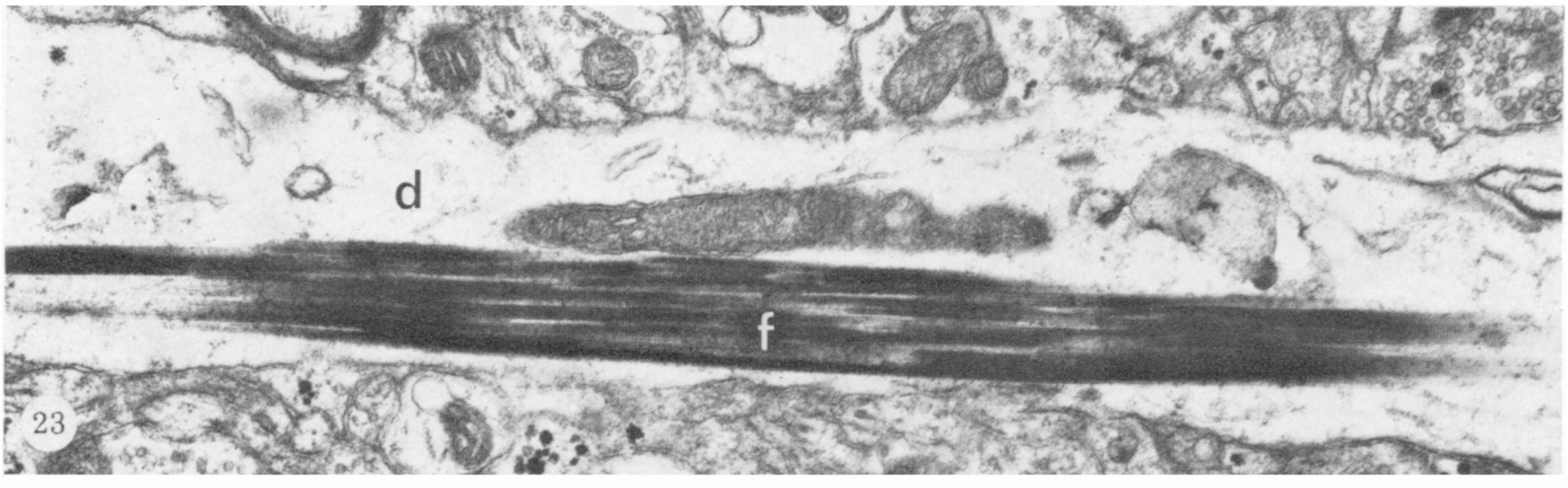
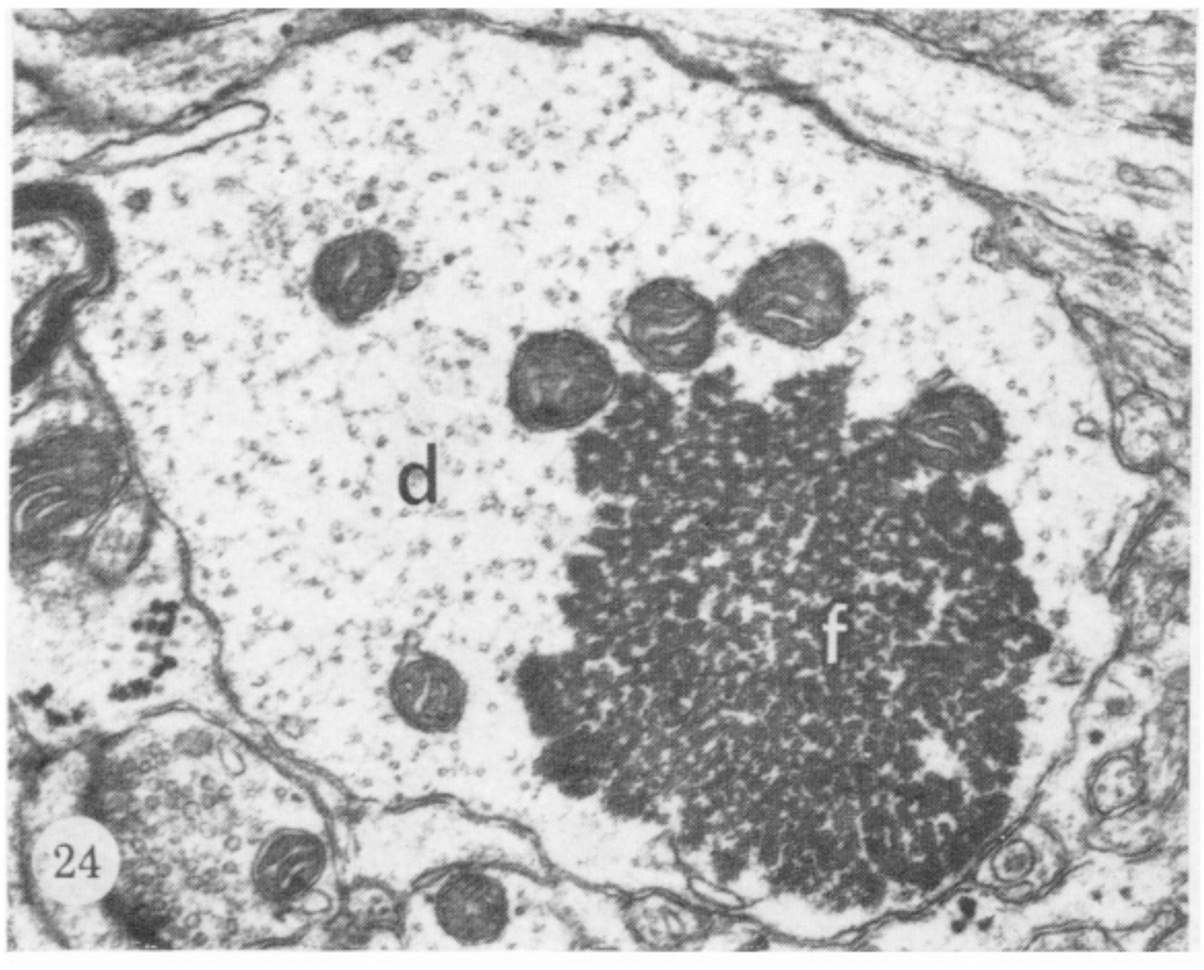
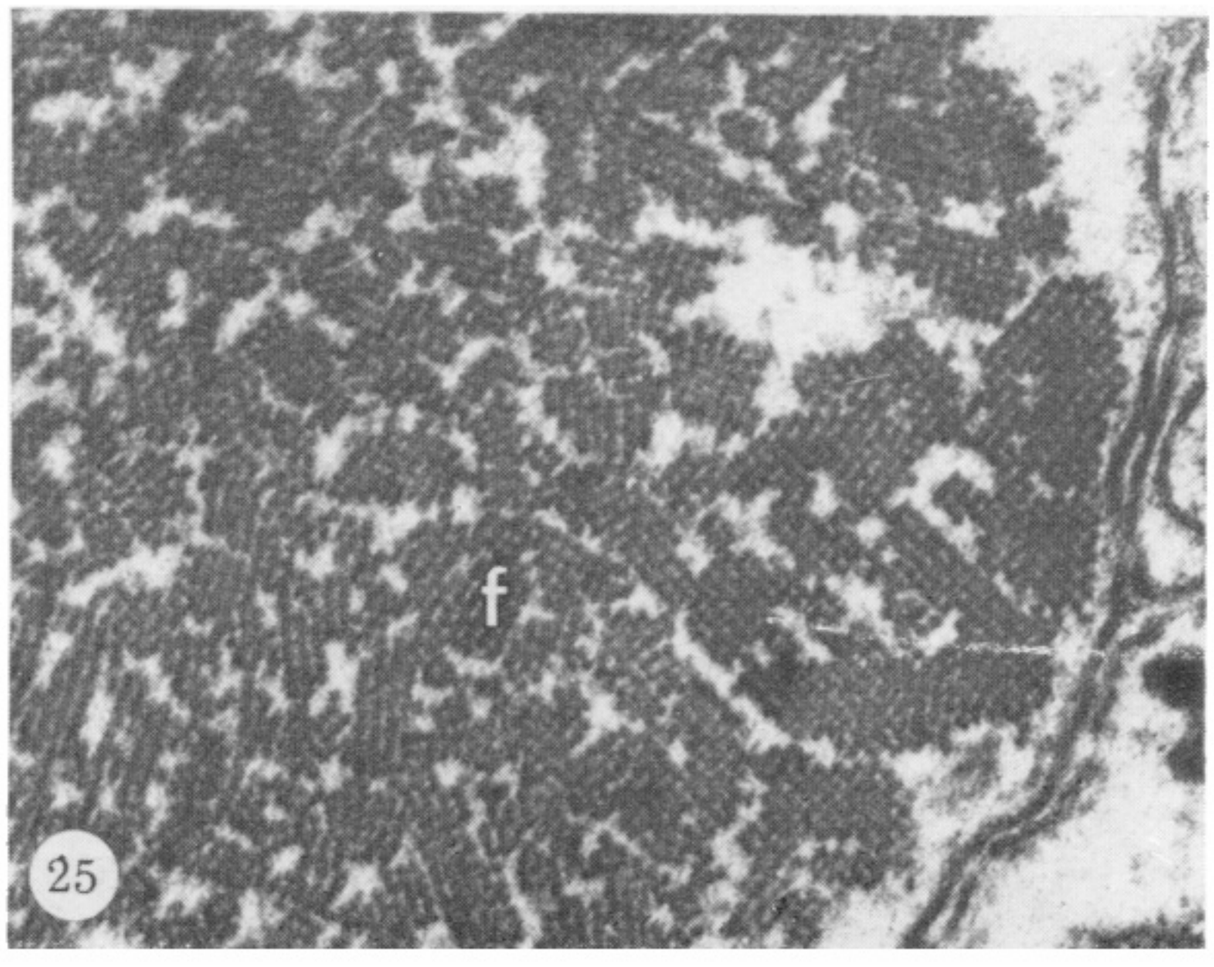
FIGURES 16–20. For description see page 132.



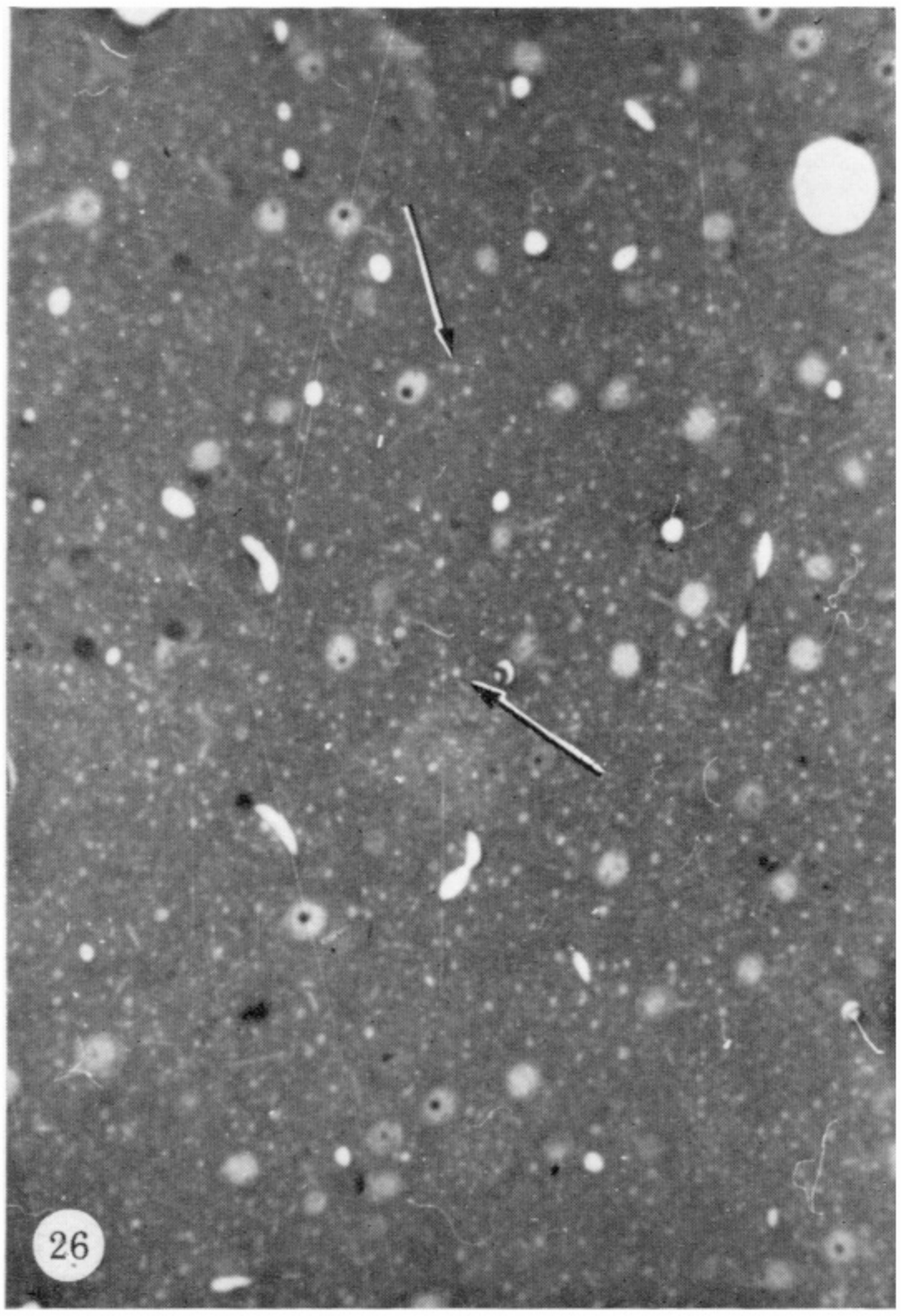


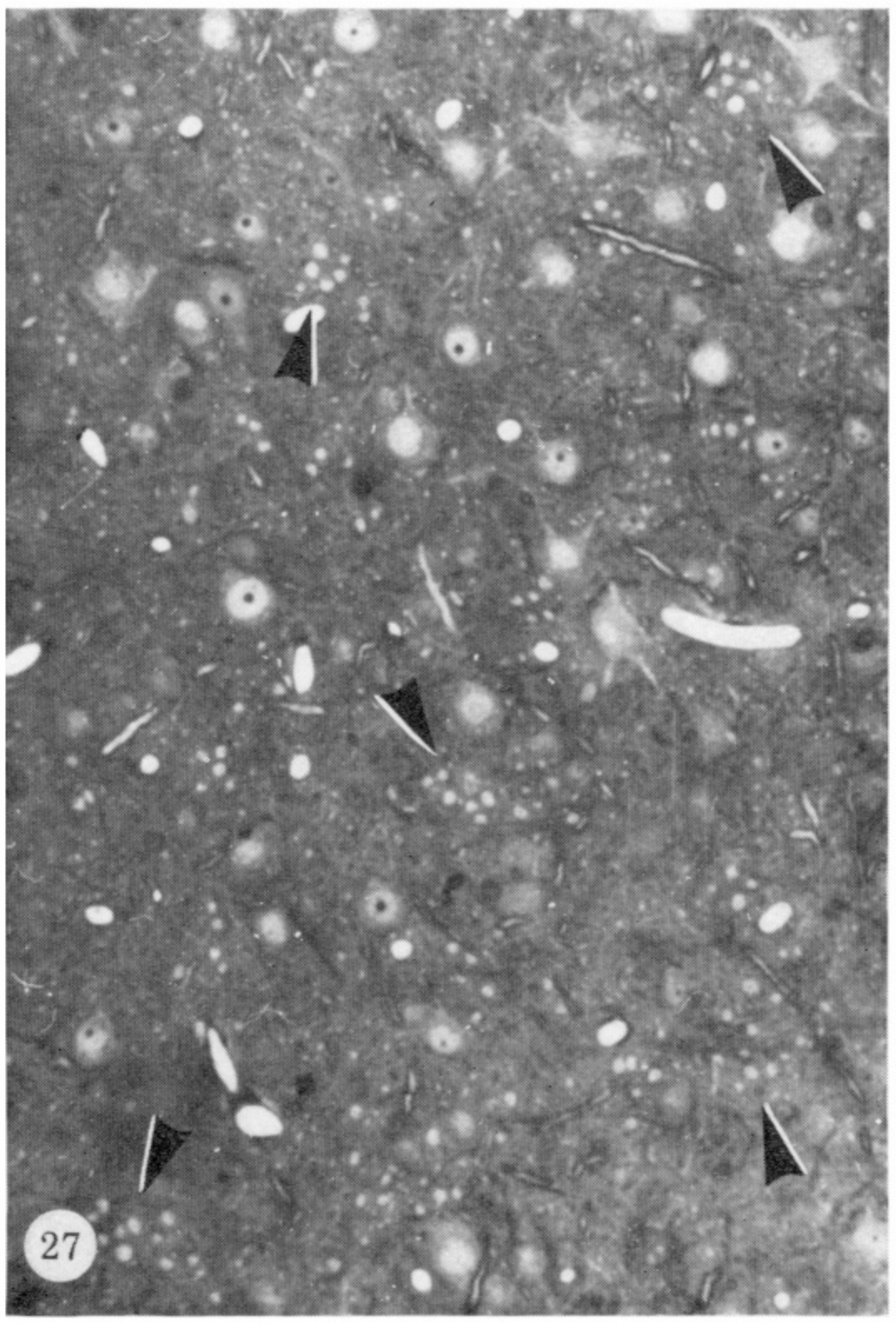


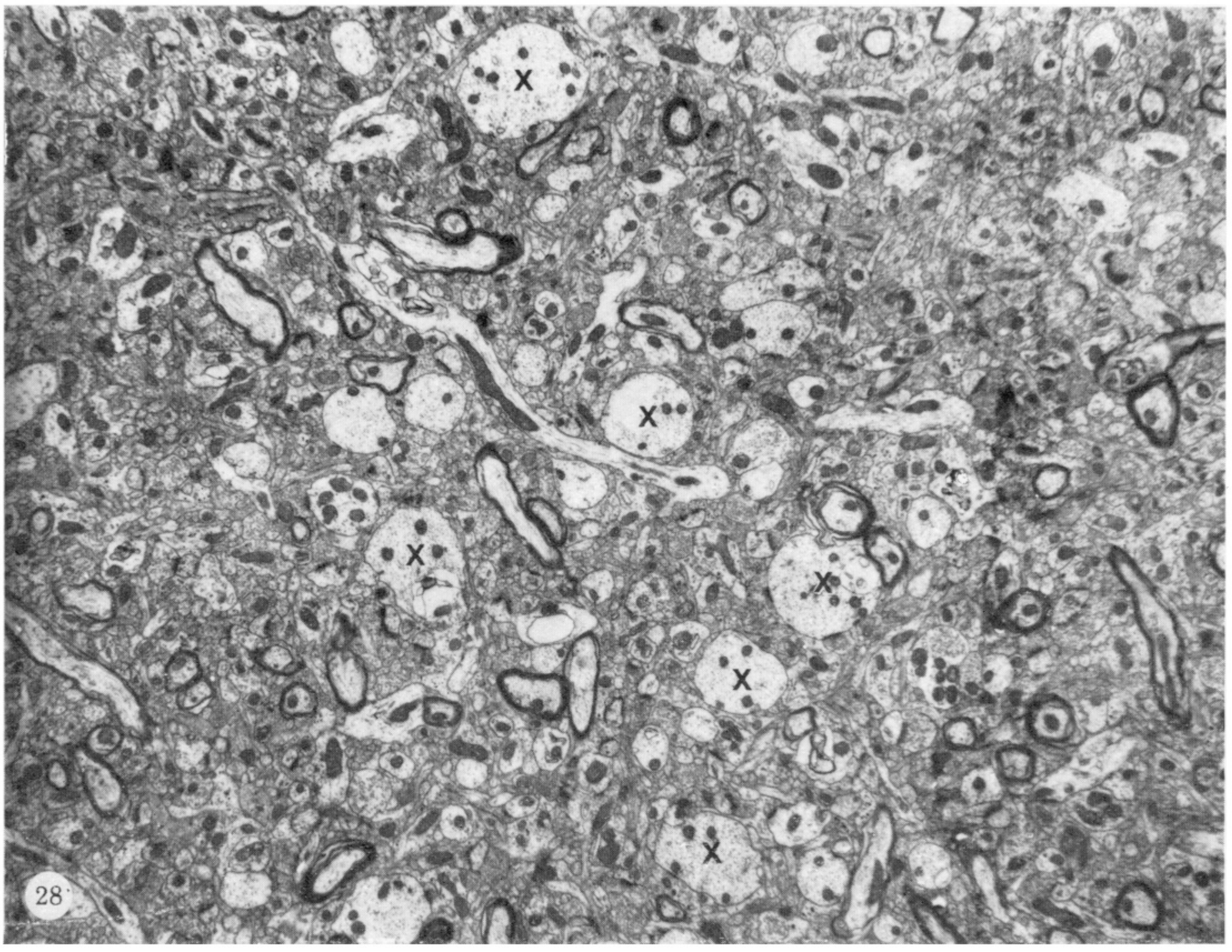




FIGURES 21–25. For description see page 133.







FIGURES 26 and 27. Light micrographs of 'thick' sections taken parallel to the pial surface in layers II and IV of motor cortex respectively. In layer II the apical dendrites, which are cut in transverse section and appear as small white circles (examples indicated by small arrows) are evenly distributed, whereas in layer IV they occur in groups (examples indicated by arrowheads). (Magn. × 220.)

FIGURE 28. Electron micrograph of a similar section through layer IV parallel to the pial surface showing a bundle of apical dendrites cut in transverse section (x). (Magn. × 6000.)

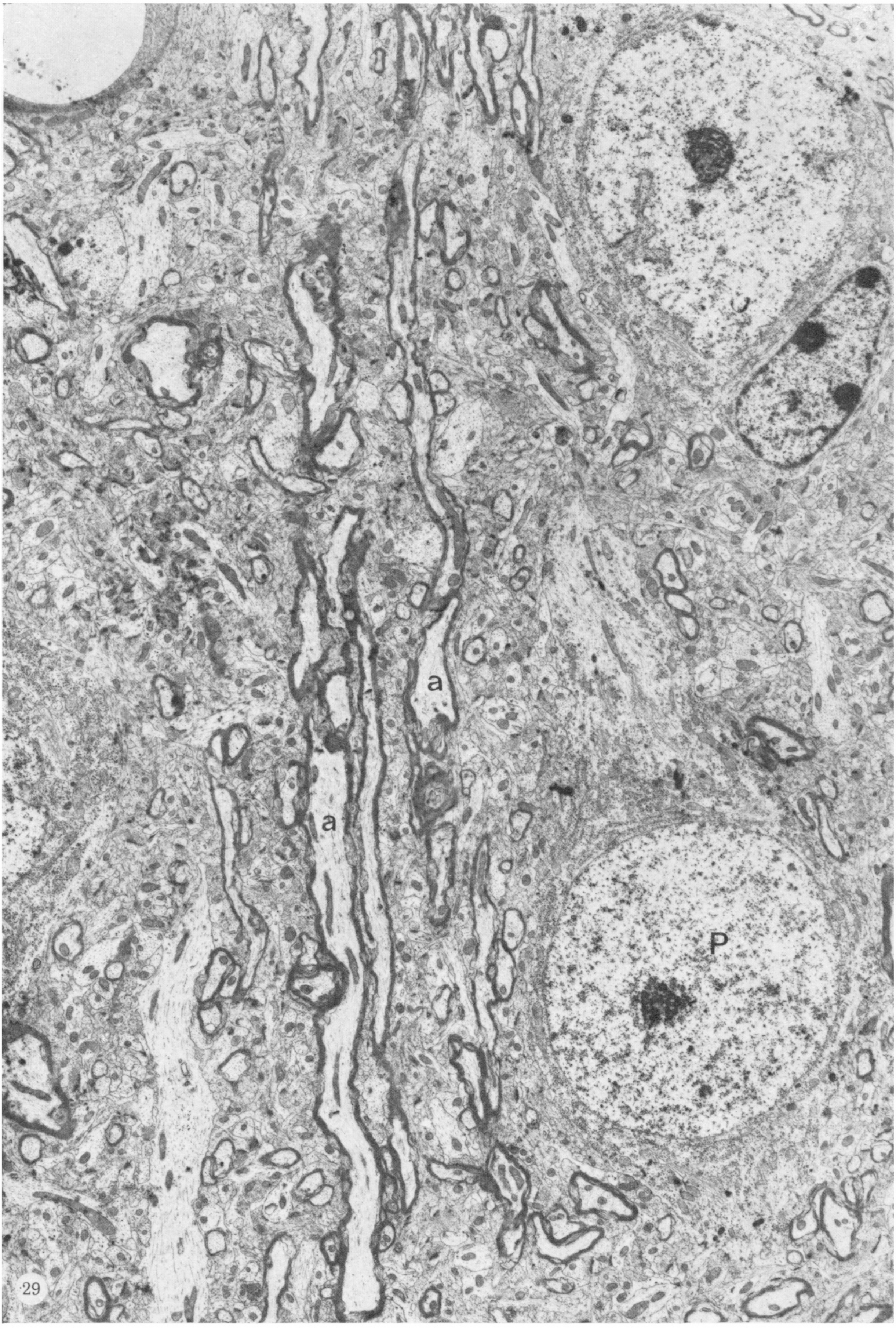
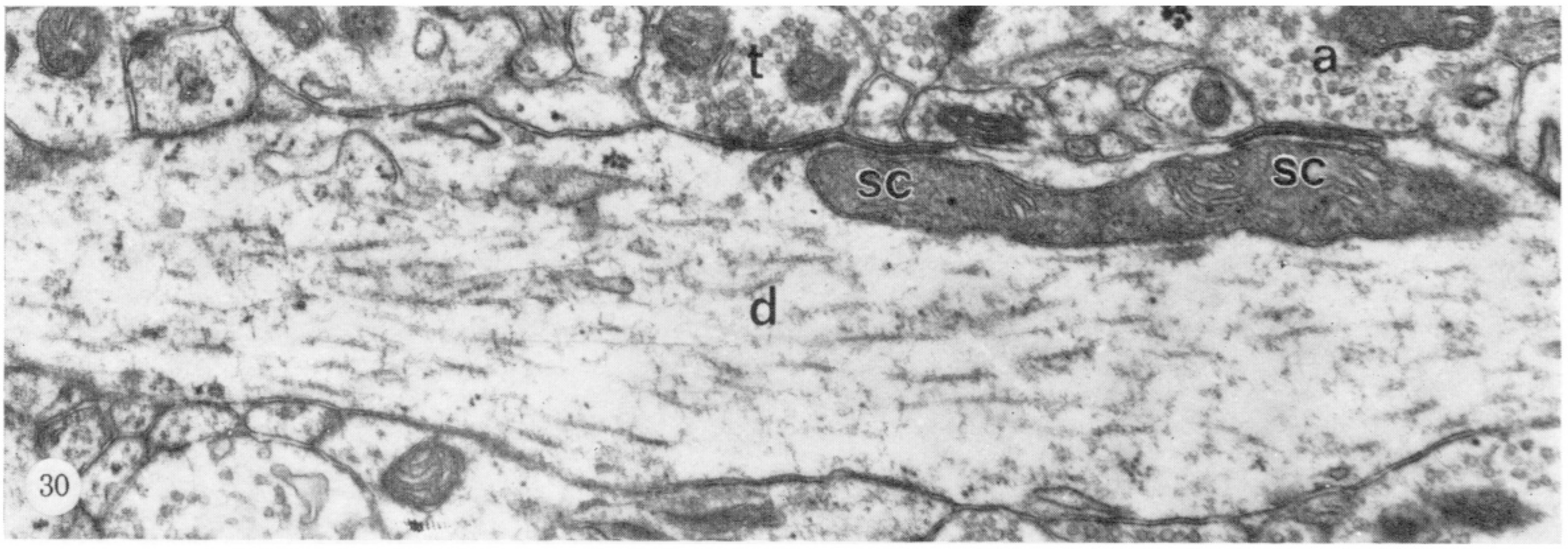
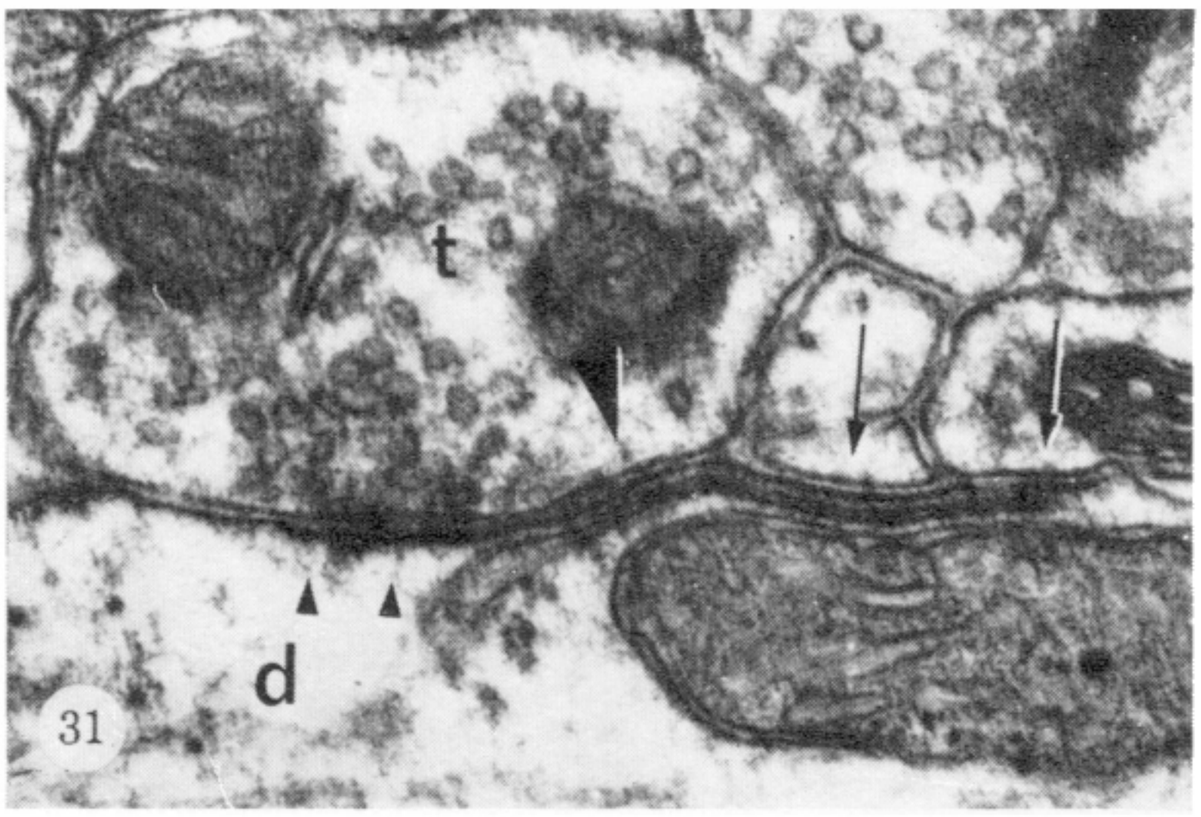
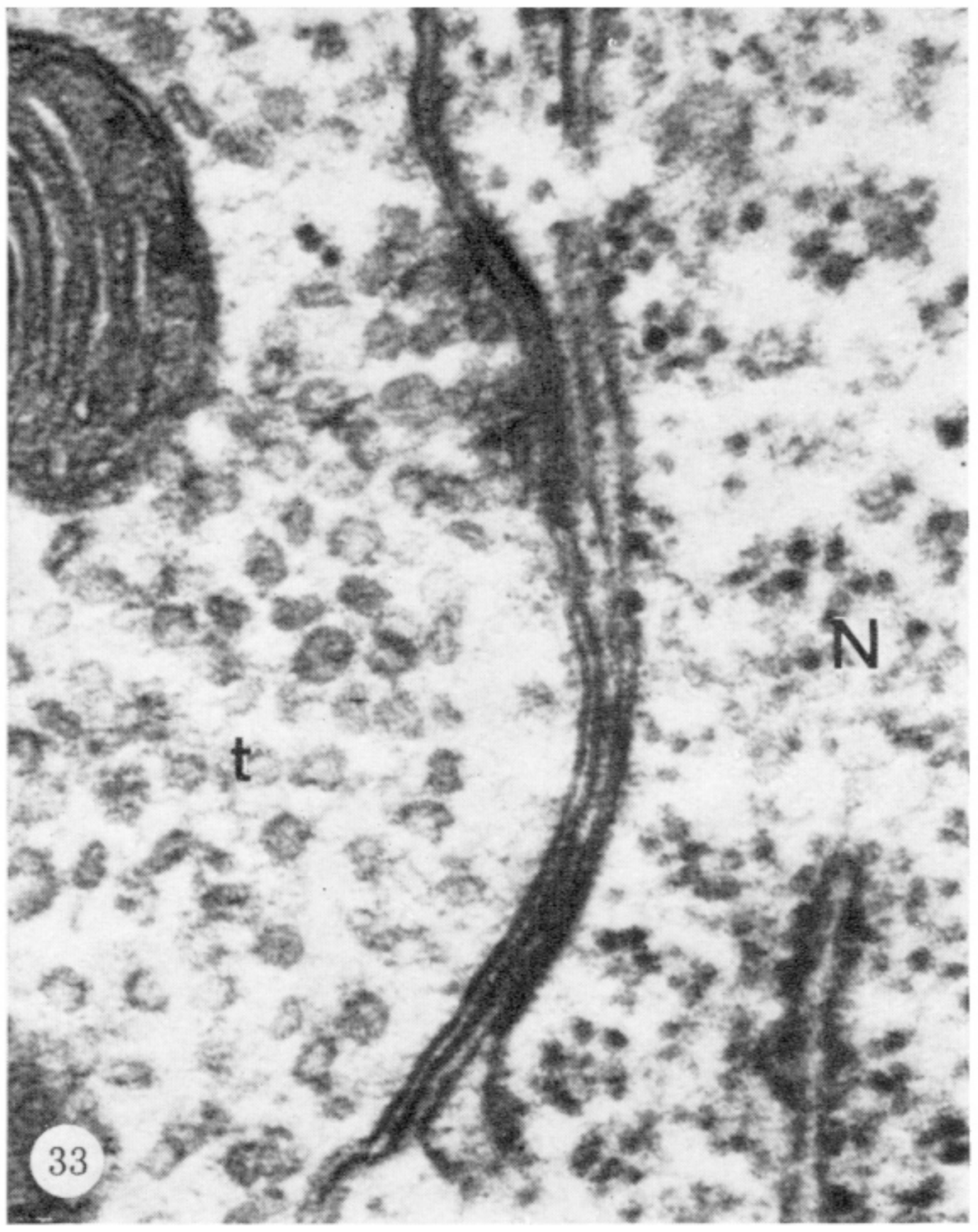
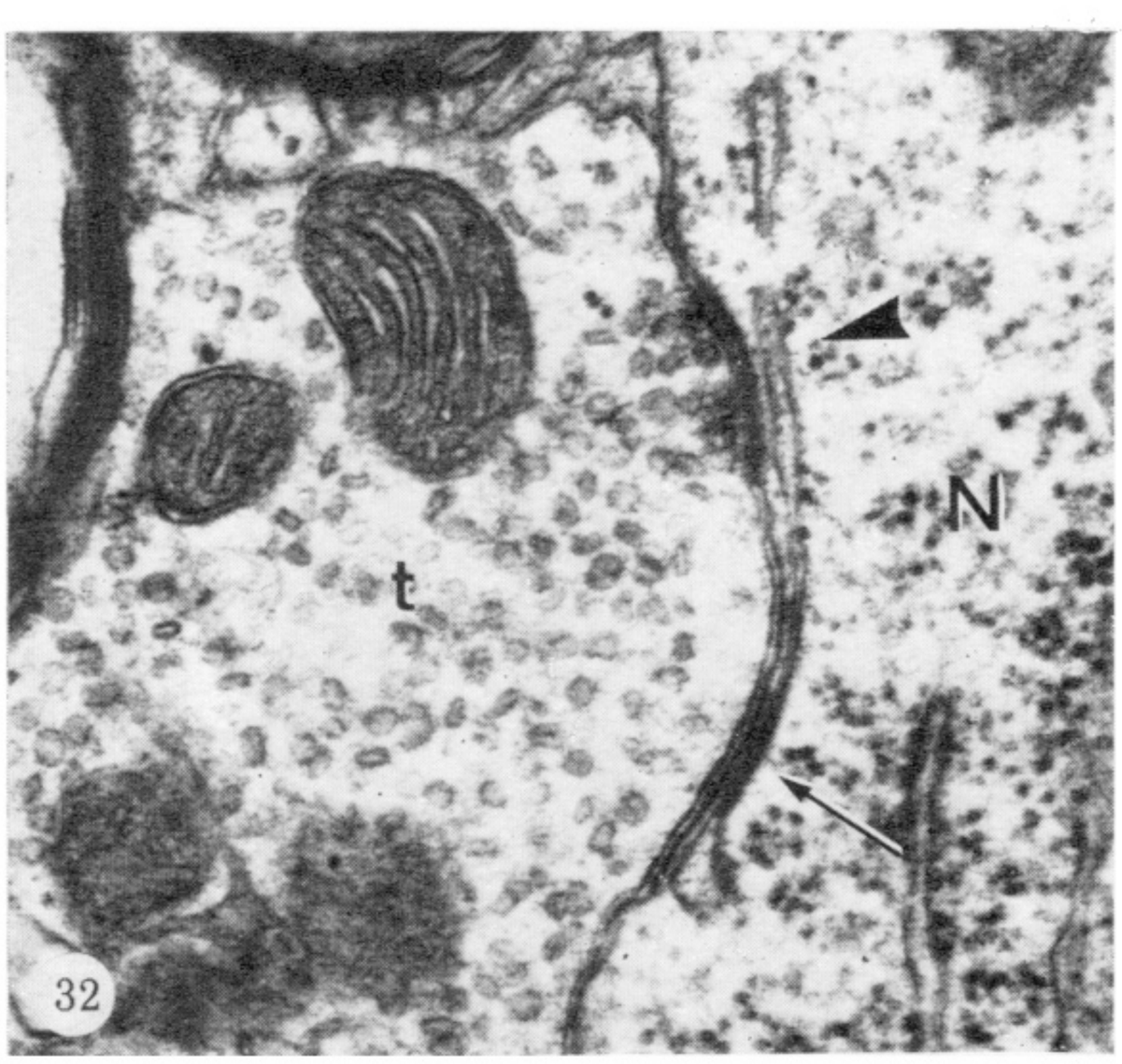


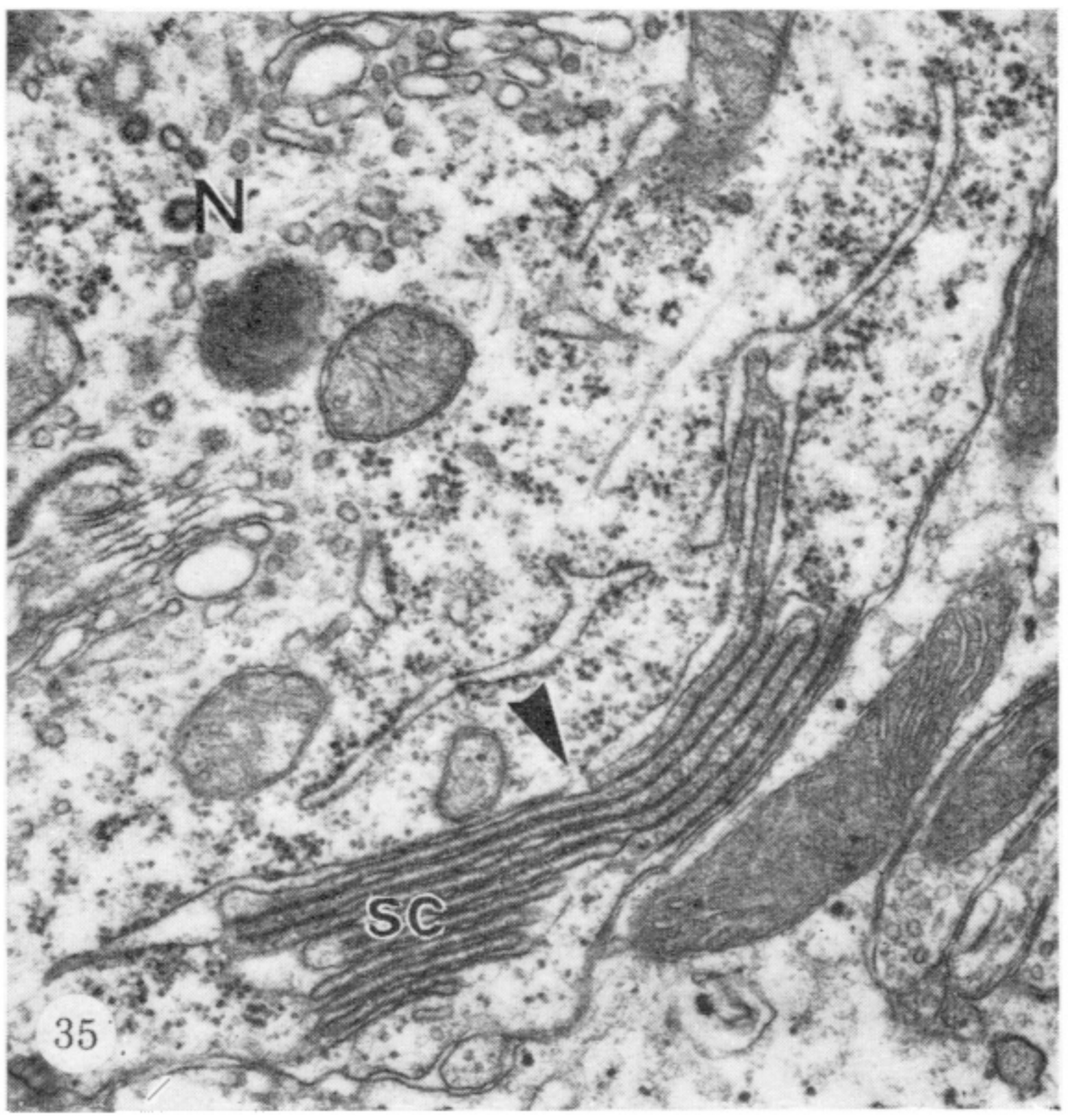
FIGURE 29. Layer V of motor cortex showing a group of myelinated axons (a) running vertically beside a pyramidal cell soma (P). The surface of the cortex is at the top of the figure. (Magn. × 3500.) N, neuronal cell soma; d, dendrite; G, glial cell.

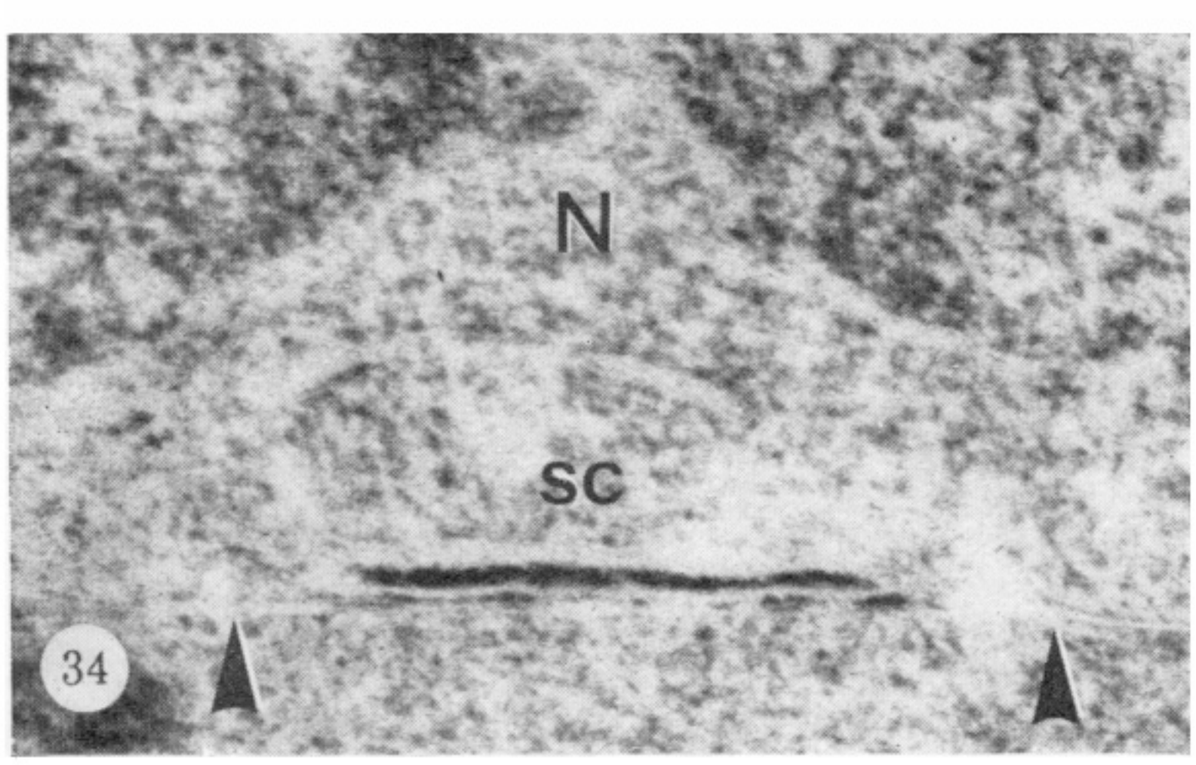




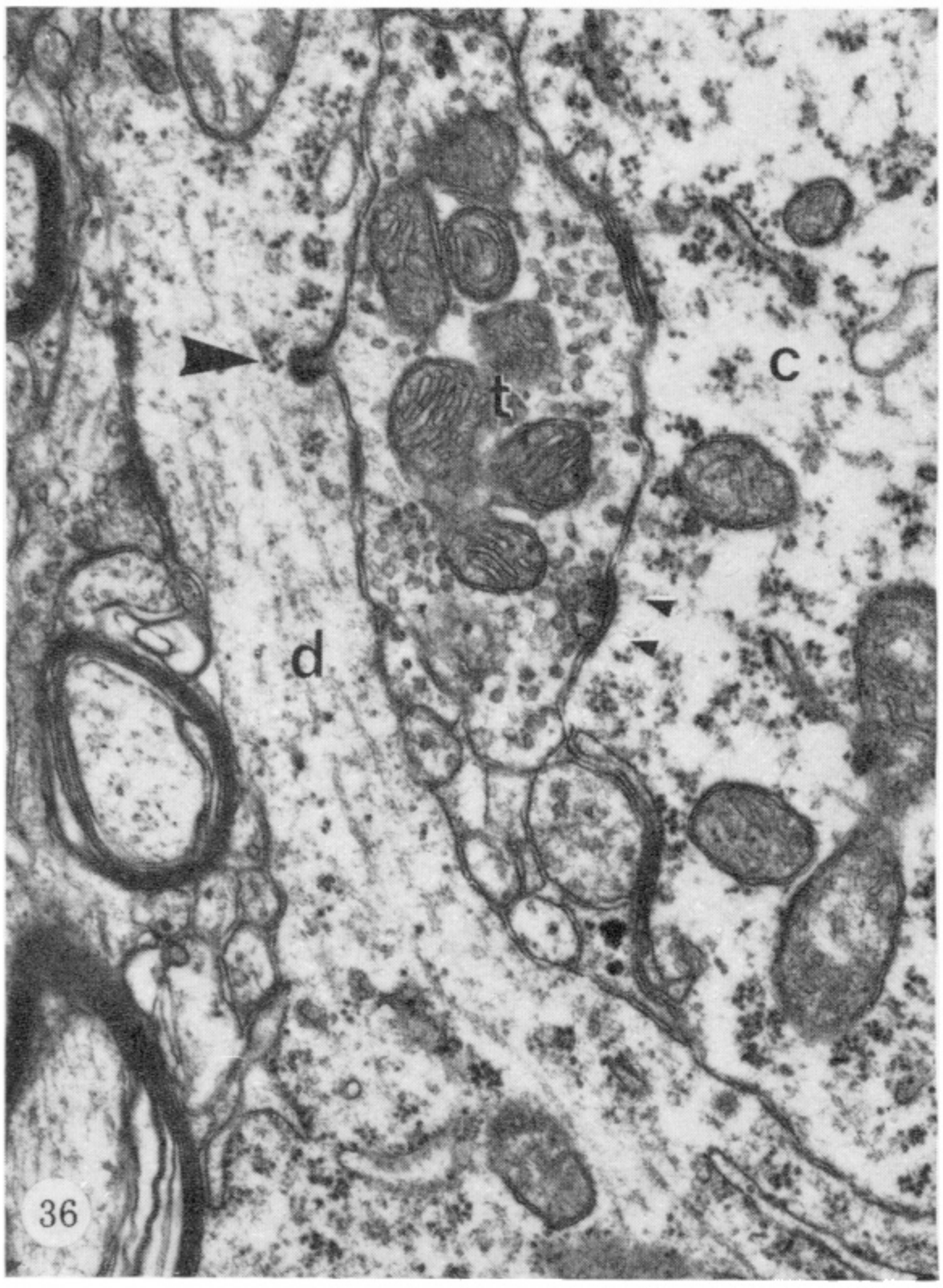








FIGURES 30–35. For description see opposite.



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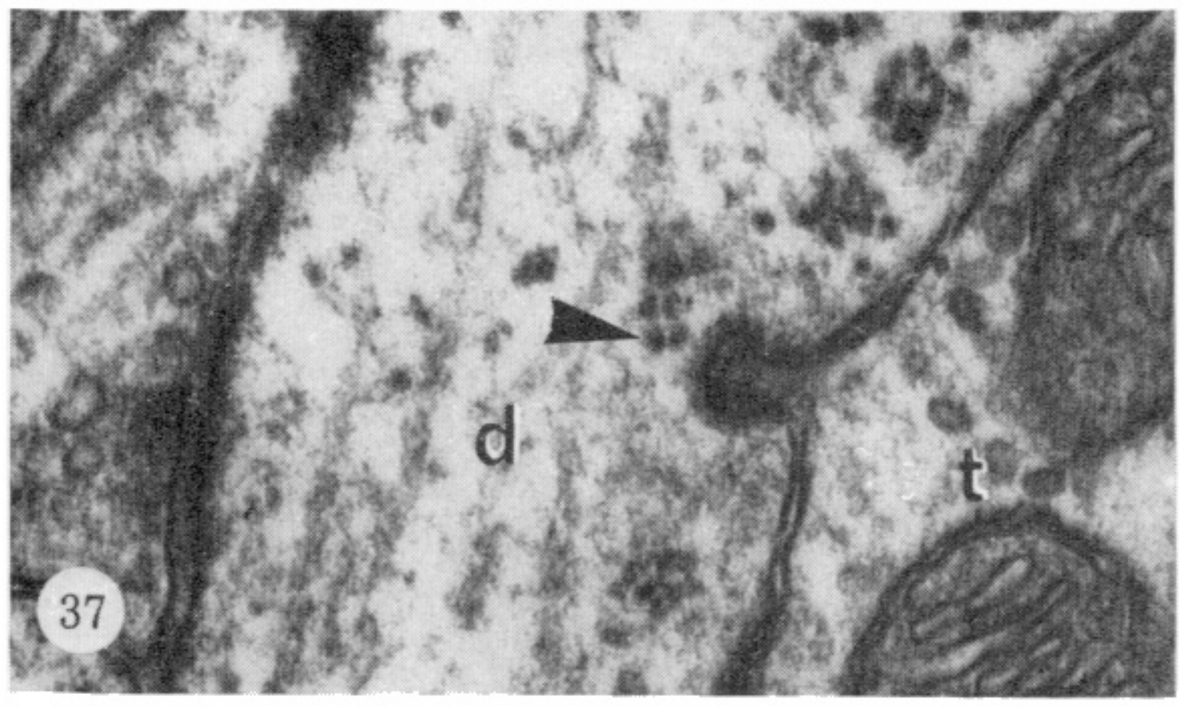

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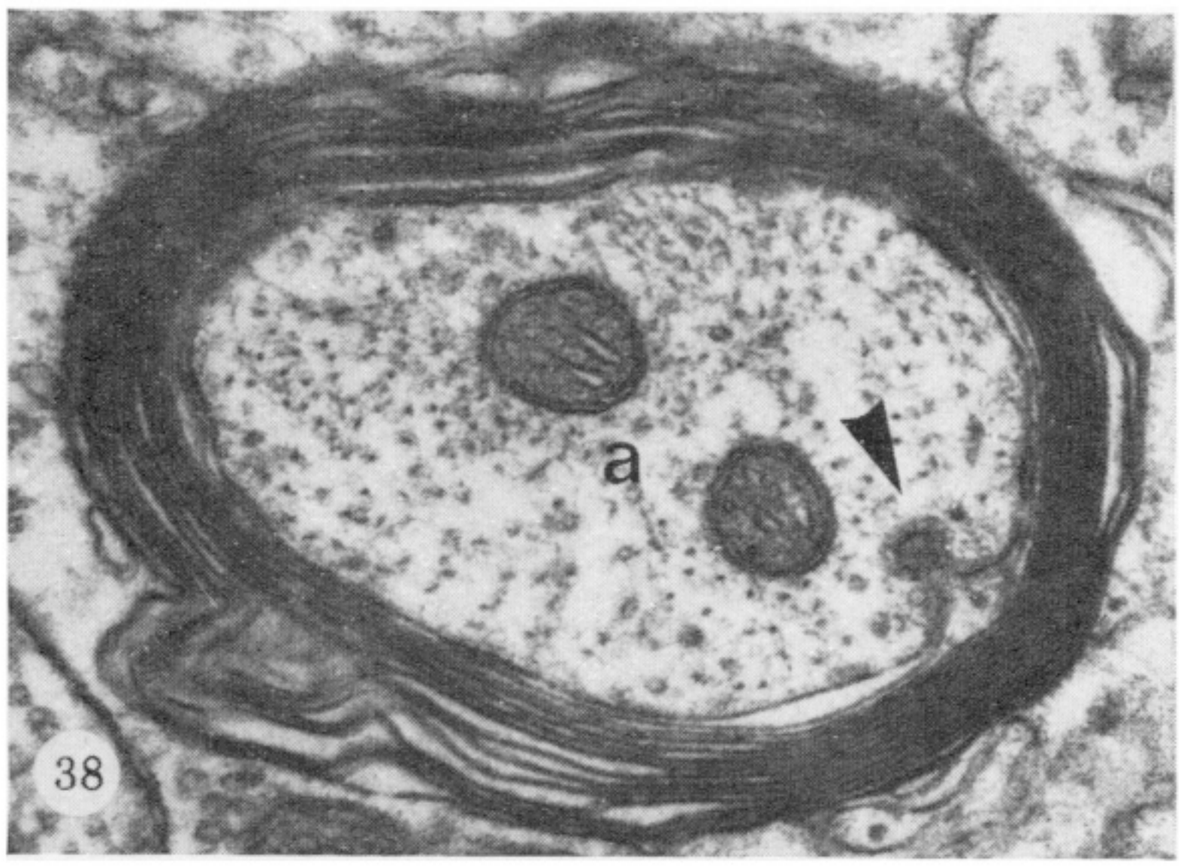

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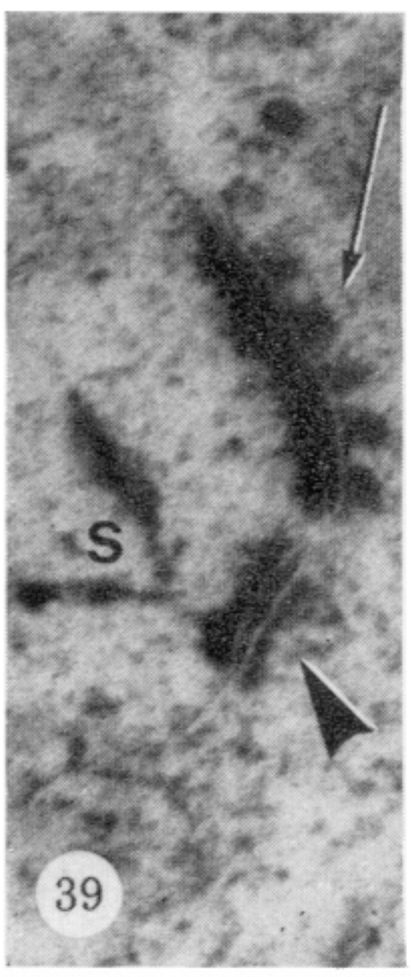

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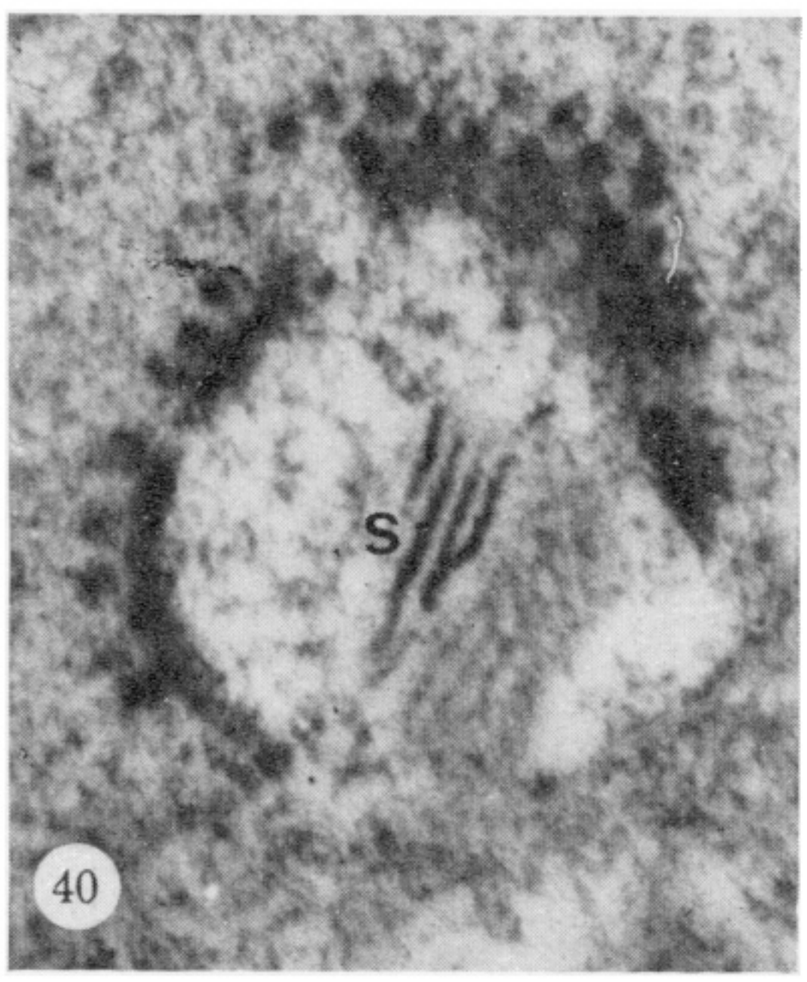

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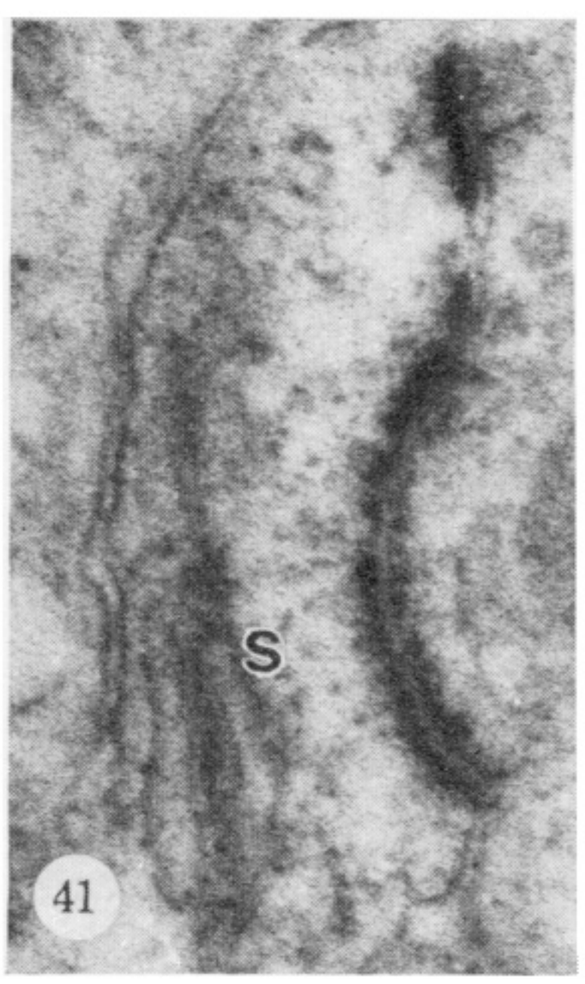

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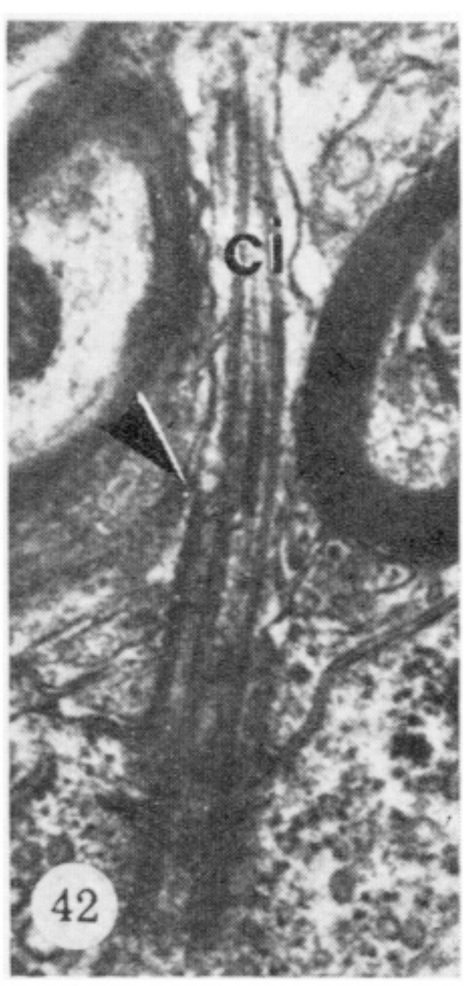

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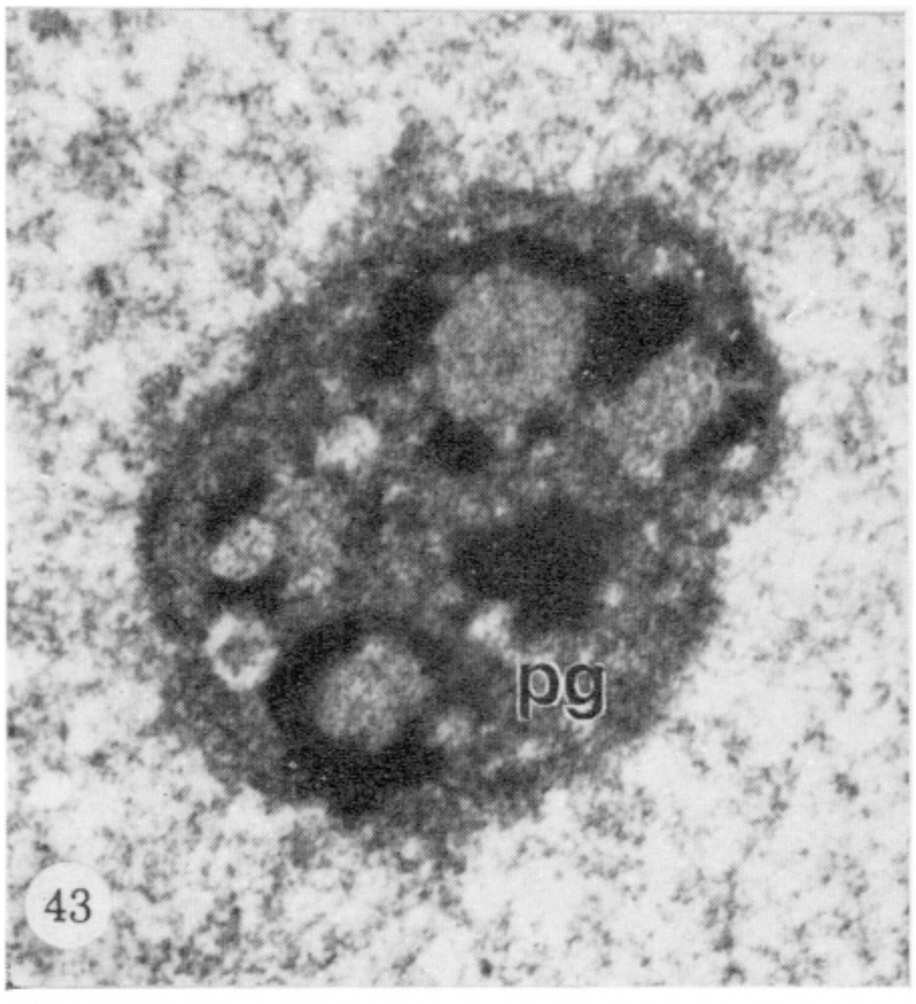

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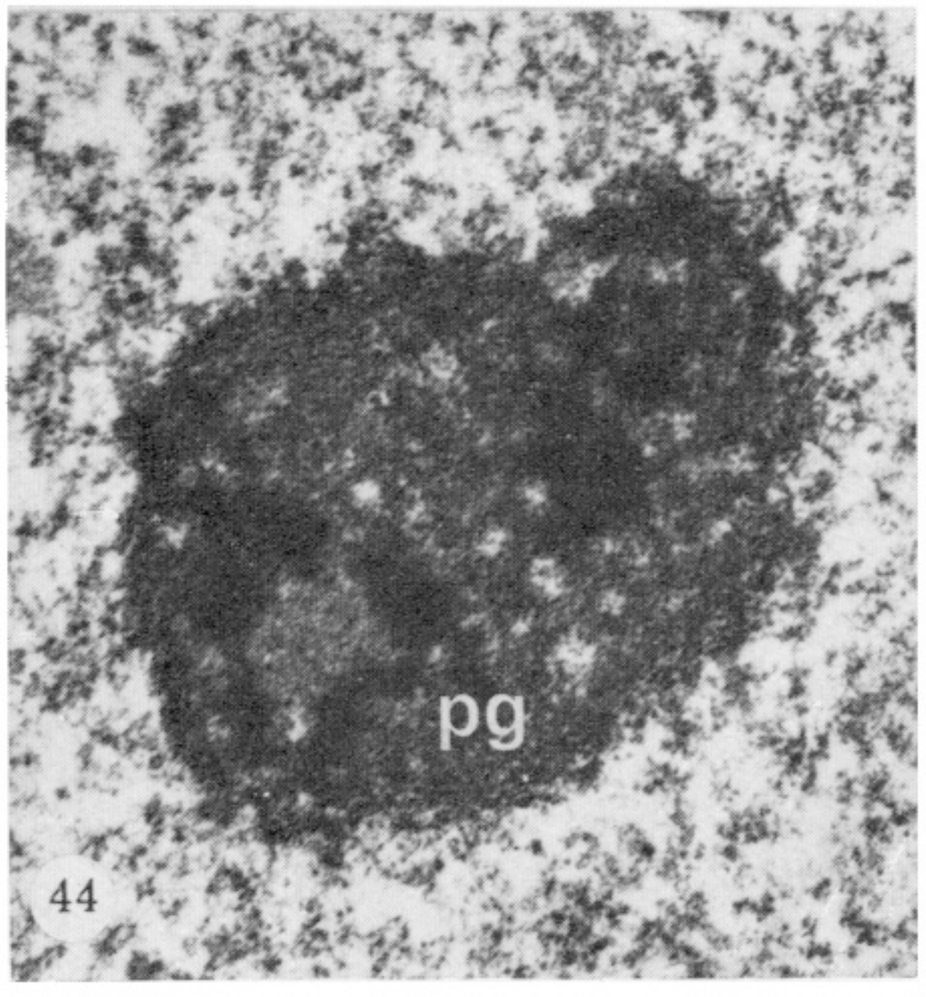
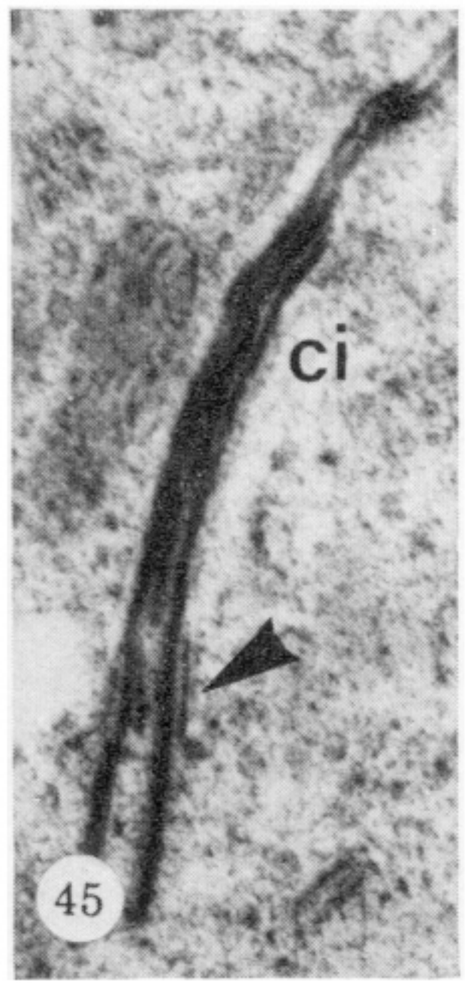


44



45

FIGURES 36–45. For description see opposite.